





# Guidelines for the management of patients with Polyposis – a guide for medical staff

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### Intestinal polyposis

Polyposis patients have unique needs, which are not best met through a conventional model of care. They have many social and family concerns that need sensitive handling. As their families grow up, they need access to advice and experience in managing various challenging periods, particularly in teenagers who have the added burden of coping with potential or known polyposis.

Everyone in the family needs emotional support and help from a multidisciplinary team. This is most effectively co-ordinated by the Polyposis Registry staff within a specialist centre.

Points to Remember:

- 1. Not all patients with multiple polyps have a polyposis syndrome
- 2. A family is at risk, not just an individual
- 3. Care is multidisciplinary and involves a registry, surgeons, endoscopists, pathologists, geneticists, and specialist nurses, all of whom must be familiar with the many varied presentations and problems of these rare patients

Polyposis can be categorised according to polyp histology:

- Adenoma FAP, MAP, PPAP (and recently described NTLH1, MSH3)
- Hamartoma JPS, PJS, PHTS (Cowden's syndrome, Bannayan-Riley-Ruvalcaba syndrome)
- Serrated serrated polyposis syndrome
- Mixed HMPS

## Familial adenomatous polyposis (FAP)

#### Management of a new patient

Confirm diagnosis by colonoscopy with dye-spray and histopathology. Consider:

- 1. Pathology review if performed elsewhere
- 2. Obtain detailed family pedigree through Registry, who will help notify atrisk individuals where possible
- 3. Counsel regarding genetic testing and if patient wishes to proceed, obtain consent for DNA testing, draw blood, monitor processing for use with at risk individuals
- 4. Discuss initial treatment (see below)

#### The background to treatment

- 1. Affected individuals will develop cancer if left untreated
- 2. Polyposis patients are at risk of cancer of the colon and rectum, the duodenum and stomach. Other sites may be affected but this is rare
- 3. The major problem areas are:
  - the large bowel
  - the upper gastrointestinal tract
  - desmoid disease

#### Endoscopic

- 1. Very rarely, with an extremely attenuated phenotype, endoscopic management can be considered. This is the exception rather than the rule.
- 2. For those with an extremely high risk of desmoid, surgery may be deferred for as long as possible and endoscopic therapy performed as part of a planned delaying strategy. Patient selection for this should be discussed in the Registry MDT.

#### Surgery

- 1. A permanent stoma should not be considered unless there is a low rectal cancer, sometimes when there is desmoid disease or when the anal sphincter is compromised.
- 2. In practice the choice lies between:
  - colectomy with ileo-rectal/distal sigmoid anastomosis
  - restorative proctocolectomy

#### Colectomy with ileorectal anastomosis

Advantages:

• low risk operation, good functional result

Disadvantages:

rectum remains at risk of cancer, 6-12 monthly surveillance of rectum needed postoperatively

Indication:

- low density polyposis phenotype (<500 polyps in colon)
- low density genotype (ie NOT codon 1250-1450)
- <20 rectal polyps (all of which are endoscopically manageable)
- concurrent desmoid disease
- palliative operation

Follow-up after treatment:

- 6-12 monthly flexible sigmoidoscopy
- Aim for endoscopic management of polyps
- If rectal polyps confluent, consider conversion to ileo-anal pouch

#### Restorative proctocolectomy

Advantages:

• minimises colorectal cancer risk

Disadvantages:

- bigger operation with more complications and poorer function
- temporary ileostomy usually used
- pouch surveillance required (cuff and pouch body polyps commonly develop)
- cancer, however, is uncommon and highest area of risk is the cuff/pouch anal anastomosis

Indication:

- conversion from ileo-rectal anastomosis in patients with rectal adenomas that are a cause for concern
- high density polyposis phenotype (>500 polyps overall) regardless of age
- > 20 rectal polyps (or <20 if not endoscopically manageable)
- mutation in the mutation cluster region (codon 1250- 1450)
- some patients with rectal cancer

Follow-up after treatment:

- annual flexible examination of pouch
- chromoendoscopy and NBI are helpful to identify adenomas in the ileoanal pouch
- aim for endoscopic management of cuff and pouch body polyps
- if pouch polyposis advanced, pouch excision may be required
- annual bloods (FBC, renal function, LFTs, folate, ferritin, B12)

#### Subclinical dehydration

This is common after colorectal surgery. It may often present with non-specific symptoms such as fatigue. There should be a low threshold for a trial of St Mark's electrolyte mix.

#### Chemoprevention

"Chemoprevention" with NSAIDs is not advocated for the management of colorectal adenomas in FAP. If they are to be used, the case should be discussed and agreement obtained at the Polyposis Registry MDT before initiation.

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# Upper Gastrointestinal Surveillance

(from age 25 years)

- In patients with FAP treated by colectomy, upper gastrointestinal cancer is a major cause of death
- Both side-viewing and forward viewing endoscopy may be required
- There are no data to support the use of chemoprevention agents to prevent upper GI tract cancers
- Gastric adenomas are becoming an important clinical problem. Data regarding optimal management and surveillance is awaited.

#### Duodenum

There are five stages of duodenal disease:

Spigelman Stage	Points	Recommendation
0&1	0—4	5 yearly endoscopy
Ш	5—6	3 yearly endoscopy
III	7—8	Annual endoscopy+/- endoscopic therapy
IV	9—12	Annual endoscopy. Consider need for surgery and/or endoscopic therapy

NB: Annual OGD advised for any patient with stage IV at any time, regardless of any downstaging achieved; may also be considered for downstaged stage III disease.

The Spigelman stage can be calculated using the table below:

No. of polyps	1 - 4	5 - 20	>20
Size of polyps	1–4mm	5–10mm	>10mm
Histology	Tubular adenoma	Tubulovillous adenoma	Villous adenoma
Dysplasia	mild	moderate	Severe
Points to be allocated	1	2	3

#### Ampulla

The ampulla is staged separately from the non-ampullary duodenum. It is classified as minor or major disease:

	Polyp	Histology	Dysplasia	Frequency
Major	>1cm	Villous features	Moderate or severe	Annual exams
Minor	<1cm	Tubular adenoma	Mild	3 yearly exams

#### **Ampullary Disease**

Minor disease should be monitored endoscopically. If major disease is identified, referral for EUS and surgical evaluation should be considered.

Biopsy of the ampulla should be performed if macroscopically abnormal and a biopsy away from the papillary orifice can be performed. Patients should be counselled regarding a small risk of pancreatitis from ampullary biopsy.

Desmoids are non-metastasising tumours originating from myofibroblasts, which occur in approximately 15% of patients with FAP. They are an important cause of morbidity and mortality. 70% of FAP associated desmoids are intra-abdominal and occur predominately in the small bowel mesentery. They can grow rapidly and may infiltrate locally leading to small bowel, ureteric and vascular obstruction. The natural history of desmoid disease is extremely variable and their unpredictable nature may make management difficult.

#### Presentation

The typical patient presents with a desmoid 2-3 years following colectomy and complains of abdominal swelling and/ or pain, or symptoms arising from complications.

#### Treatment algorithm for FAP-associated desmoid tumours

The algorithm on the following page applies to clinically relevant solitary desmoid tumours. In the case of multiple tumours the balance of treatment needs to be adjusted towards pharmacological management and away from surgery, particularly in individuals at known high-risk of developing further or recurrent tumours (e.g. 3' germline *APC* mutation, strong family history).

In individuals unable to tolerate sulindac consider switching to raloxifene 120mg once a day. If the patient has any problems tolerating this dose try 60mgs bd. This is preferred to toremifene or tamoxifen because of reduced risk of uterine carcinoma, cataracts and fractures.

# Algorithm for the treatment of FAP associated desmoids as used at St Mark's



#### Protocol for adrenal incidentaloma in FAP



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#### Management of "at-risk" relatives

- 1. At-risk relatives need to be identified and where possible, informed of their risk and offered screening. The Polyposis Registry team will help facilitate this.
- 2. Where predictive testing is possible, to be considered at age 12-14 years. All genetic testing and result giving should be done by the Polyposis Registry team. If a predictive DNA test is negative, a full explanation of the meaning of this result must be given before the patient can be discharged.
- 3. If the causative mutation in the family is unknown, entry into a clinical screening programme is needed. Five-yearly colonoscopy with chromoendoscopy is advised, from age 14-15 years. This person should not be discharged from the screening programme. The need for ongoing screening should be reviewed at age 50 years (or discuss at Polyposis MDT if earlier discharge considered). The person should be notified in the event that a predictive DNA test becomes available.

The phenotype is variable and overlaps with FAP. The duodenum appears to have a different phenotype with older age onset and less ampullary disease and fewer polyps.

Although there are some similarities with FAP, it is inherited in a recessive manner.

#### Treatment

The major problem areas are:

- the large bowel
- the upper gastrointestinal tract
- the vastly extended family in this recessively inherited condition

#### Homozygotes and compound heterozygotes (affected)

- Dye spray colonoscopy at time of diagnosis
- Side-viewing upper GI endoscopy starting age 35 years

#### Follow-up

- Management of the colon should be the same as FAP and according to polyp burden. Delayed surgery may well be possible in MAP
- Side viewing upper GI endoscopy surveillance repeated according to Spigelman staging as for duodenal disease in FAP

Genetic screening is currently performed on partner and 1st degree relatives. Children should be called for counselling at age 18-21 years. It is important to differentiate between obligate carriers' risk and those that are at-risk of MAP.

#### Heterozygotes (carriers)

Spouse/partner should be tested in order to determine any risk to current or future children.

There are no data to support a significantly increased risk of CRC above population risk and therefore colonoscopy surveillance is not routinely warranted. Advise to enrol in the national BCSP and be alert for bowel symptoms.

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- 1. Peutz Jeghers syndrome is very rare
- 2. Not all patients are easily recognisable (rarely, patients with Peutz Jeghers syndrome may not have conspicuous perioral pigmentation, or pigmentation may have faded as the patient ages)
- 3. Some people with freckles around the mouth do not have Peutz Jeghers syndrome
- 4. There are two main management issues:
  - risk of intussusception from small bowel polyps
  - high risk of cancer

#### Treatment of intestinal polyps

- 1. Most colonic, gastric and duodenal polyps can be managed endoscopically
- 2. Small bowel polyps may be managed by either double balloon enteroscopy or need laparotomy and on-table enteroscopy. For most, DBE is adequate and possible but if polyps are particularly large, numerous or distributed throughout the small bowel, then a surgical approach may be required. Such cases should be discussed at the Polyposis Registry MDT and imaging reviewed.

#### Follow-up

- 1. Cancer is common in patients with Peutz Jeghers syndrome
- 2. Screening should be according to the management guidelines (see over)
- 3. In families where the mutation has not yet been identified, counselling for diagnostic genetic testing should be performed

#### Management:

#### **Recommended investigations**

- Consider haemoglobin yearly
- OGD and colonoscopy from age 8 years. If normal repeat age 18 years and up to 3 yearly thereafter
- Capsule endoscopy 3 yearly, starting age 8 years
- Females should be referred to their local breast screening unit for breast screening. Currently NICE advocate annual mammography age 40-60. Annual mammography may be considered age 30-39 years. >60 years, screening as per population screening programme
- Cervical smear according to national programme
- Be alert that any clinical abnormality raises the question of malignancy

#### Recommended polyp management

- There are no size criteria for intervention with polypectomy for polyps in the stomach, duodenum and colorectum
- DBE or laparotomy and intra-operative enteroscopy for small bowel polyps >2 cm, or for symptomatic smaller polyps. In children, other factors such as height and weight trajectories may need to be taken in to consideration

#### Management of at-risk relatives

- If predictive testing not possible, at-risk relatives should be examined for typical mucocutaneous pigmented lesions and undergo pan-enteric GI screening, using the same guideline as GI surveillance for affected individuals. Whether this needs to be repeated is not clear and should be discussed with the patient.
- If predictive testing is possible, testing in infancy allows for appropriate identification of symptomatic polyps (particularly small bowel) before clinical surveillance is initiated

- 1. Juvenile polyposis is very rare
- 2. There is an increased risk of gastric and colorectal cancer
- 3. Small juvenile polyps may be misclassified as inflammatory
- 4. Patients may present at any age
- 5. Extra-intestinal abnormalities occur in some patients, such as features of hereditary haemorrhagic telangiectasia (HHT) (e.g. epistaxis, pulmonary AV fistulae, intracerebral haemorrhage)

#### Treatment of intestinal polyps

- 1. Endoscopic therapy is usually sufficient to control the large bowel, gastric and duodenal polyps. Small bowel polyps are rare
- 2. Colectomy and gastrectomy may be necessary in severe cases
- 3. Most care is individualised to the circumstances, evidence and experience being limited

#### Follow-up

- 1. Colonoscopy, 1-3 yearly from age 15 years, according to polyp burden
- 2. Upper GI endoscopy 1-3 yearly depending on polyp burden. Initiate from age 18 for *SMAD4* mutation carriers and age 25 years for *BMPR1A* mutation carriers (advanced UGI disease nearly always confined to those with *SMAD4* mutations)
- 3. CVS (auscultation of the heart) examination in clinic
- 4. Extra-intestinal abnormalities of clinical significance should be managed appropriately
- 5. If the causative mutation is unknown, an affected individual should be counselled regarding diagnostic genetic testing

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#### **JPS/HHT** overlap

This may be seen in patients with a germline *SMAD4* mutation. All patients with an identified *SMAD4* germline mutation should be screened by:

- 1. One-off CT chest (with IV contrast) to exclude arteriovenous malformations (AVMs) age 16 yrs
- 2. One-off transthoracic echo to look for aortic root aortopathy and structural abnormalities
- 3. One-off capsule endoscopy to detect angioectasias (but may need repeating if iron deficiency anaemia is diagnosed)

Those with identified AVMs should referred to Professor Claire Shovlin, HHT clinic at Hammersmith hospital

#### Management of "at-risk" relatives

- 1. If predictive testing is possible, this should be offered age 12-14 years (earlier if symptomatic)
- If predictive testing not possible, the individual can be offered endoscopic screening by colonoscopy, starting at age 15 years. If normal this can be repeated 5 yearly. If a colonic juvenile polyposis phenotype is found then UGI tract endoscopy should be initiated

#### Definition

- 1. 5 or more serrated spectrum polyps proximal to the sigmoid colon, of which at least one must be >10mm in size **OR**
- 2. any number of serrated spectrum polyps in a first degree relative of someone with serrated polyposis **OR**
- 3. more than 20 serrated spectrum polyps throughout the colon (excluding rectum)

The serrated polyp spectrum comprises hyperplastic polyps, sessile serrated lesions and traditional serrated adenomas.

#### Management

- 1. Most patients can be managed endoscopically
- 2. Colonoscopy is performed with the aim to resect lesions >5mm. There is a clearance phase where the burden of disease is controlled, which may require procedures as frequently as 3-6 monthly. Once clearance is achieved, 1-2 yearly dye spray surveillance colonoscopy is offered
- 3. Surgery may be required for endoscopically unmanageable disease; SPS being diagnosed at the time of a new diagnosis of colorectal cancer arising whilst on surveillance or for patient choice. Choice of surgery will depend on the phenotype but colectomy with ileo-rectal anastomosis usually suffices
- 4. If combined adenomas and serrated spectrum polyps are identified, consider genetic screening of the *MutYH* and *GREM1* genes

#### At-risk relatives

First degree relatives have an increased risk of SPS and colorectal cancer. They should be offered 5-yearly colonoscopic screening age 25-70 years. If polyps are identified, colonoscopy interval is adjusted accordingly.

This is extraordinarily rare and one of the PTEN hamartomatous tumours syndromes (PHTS). The intestinal phenotype shows marked variation. There is now some evidence of an increased risk of gastrointestinal malignancy in individuals with a clinical diagnosis of Cowden's Syndrome, or those who have a *PTEN* mutation but it is difficult to quantify the magnitude of risk.

The intestinal tract is not the major clinical problem in PTHT

#### Management

- 1. Surveillance colonoscopy frequency should be individualised but current recommendations are at age 35 and 55 years. A role for upper GI endoscopy is not well established but may be considered
- 2. For the newly diagnosed, they should be referred to their regional genetics centre through which the screening for the other manifestations of Cowden's Syndrome can be coordinated by the local appropriate specialist services

Please contact the Polyposis Registry for current guidelines.

#### For more information please contact:

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