

FAMILIAL ADENOMATOUS POLYPOSIS (COLORECTAL CANCER)

PREFERRED MODEL OF CARE AND CRITERIA FOR REFERENCE CENTRES

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PREFERRED MODEL OF CARE AND CRITERIA FOR REFERENCE CENTRES

A. Type of cancer

Familial adenomatous polyposis (FAP)

B. Short description of the cancer

FAP (Familial adenomatous polyposis) is an autosomal dominant disorder characterised by the development of hundreds to thousands of colorectal adenomatous polyps and the inevitable occurrence of colorectal adenocarcinoma if the colon is not removed. FAP is a colon cancer predisposition syndrome, responsible for 1% or less of the CRC cases. It is characterized by hundreds to thousands of precancerous colonic polyps development, beginning at a mean age of 16 years (range 7-36 years). By age 35 years, 95% of individuals with FAP have polyps. The mean age of colon cancer diagnosis in untreated individuals is 39 years (range 34-43 years).

However, attenuated forms of FAP also exist. Attenuated familial adenomatous polyposis (AFAP) is characterized by multiple adenomas (<100) in most affected family members, with a later age of disease onset (with cancer occurring on average 15 years later than classical FAP).

Specific clinical/pathological features to FAP patients include cutaneous lesions (lipoma, fibromas, sebaceous and epidermoid cysts), desmoid tumors, osteomas, occult radiopaque jaw lesions, dental abnormalities, pigmented ocular fundic lesions (congenital hypertrophy of the retinal pigment epithelium). Moreover, there is an increased incidence of hepatoblastoma in male infants of families with FAP. Gardner Syndrome is an association of osteomas, desmoid tumors and adenomatous polyposis. Turcot Syndrome is an association of cerebellar medulloblastoma and adenomatous polyposis.

(A)FAP is a genetically determined condition that occurs in 1 of 5-10 000 births. FAP is mostly due to a mutation in the APC gene on chromosome 5q. Transmission of mutations in the APC gene is autosomal dominant even if 30-40% of cases are « de novo », meaning they arise in the affected individual without clinical or genetic evidence of (A)FAP in the parents. However, once a mutation occurred de novo, it can be transmitted to the next generation. Additionally, biallelic mutations in the MutYH gene were reported in (A)FAP cases without an APC germline mutation. The syndrome associated with biallelic MutYH mutations is called MAP (MutYH-associated polyposis). MAP is difficult to differentiate clinically from FAP or AFAP but tends to present later with mean and median ages in the mid-50s, although younger diagnoses have been documented. MAP is essentially a recessively inherited disorder.

C. Model of care pathway suggested for adult patients with Familial Adenomatous Polyposis (FAP)

Model of care pathway	Preferred model
1. <u>Model 1: Reference Centres exclusively (from diagnosis to follow-up).</u> Once there is a suspicion of Familial Adenomatous Polyposis or Familial Adenomatous Polyposis has been diagnosed, the patient should be referred to a Reference Centre. A network with other Reference centres or with specific experts working in other centres is encouraged.	
2. <u>Model 2: Shared care between Reference Centres and peripheral hospitals.</u> Part of the care pathway (e.g. diagnosis, MOC, surgical treatment, ..) is performed in the Reference Centre and for another part of the care pathway (e.g. chemo therapy, radiation therapy, follow-up, ..) the patient is referred (back) to the regional hospital	X



D. Phase(s) of the clinical pathway for which Reference Centres are required

All FAP patients should be discussed and examined in Reference Centres, who can let part of the follow-up be done in a ‘peripheral centre’ according to the guidelines.

Reference Centres are those who have access to specific expertise to guide all the aspects of the disease:

Genetics, Gastroenterology (endoscopy), Surgery, Imaging, Pathology, Paediatric Gastroenterologist, Oncology

Some specific interventions, such as restorative total proctocolectomy with pouch construction and ileal pouch-anal anastomosis should be done in a Reference Centre.

	Phase of the Clinical Pathway	Reference Centre	Peripheral centre
1	MOC	X	
2	Diagnostic confirmation (AP and/or medical imaging)	X	
3	Comprehensive AP diagnosis	X	
4	Therapeutic modalities	X	
5	Follow-up	X	X

Multidisciplinary Oncological Consult

Genetic counselling of FAP patients and their family members should be performed in a centre for human genetics or in a familial cancer clinic (including oncologist, geneticist,...) and can occur in several contexts: at the time of diagnosis of FAP, at the time a FAP patient is considering reproductive options, at the time the FAP patient is having his or her children to be screened, and at the time that an at-risk person is considering genetic testing.

For MutYH: mutation analysis of the partner of a MAP patient or MutYH heterozygous carrier is recommended in case parents wish prenatal testing.

Diagnostic confirmation

The diagnosis of attenuated FAP (AFAP) is suspected when more than 10 adenomas are found in one patient during colonoscopy. If more than 100 adenomas are found, clinical diagnosis of FAP can be made.

Genetic testing is required for definitive diagnosis in following cases:

1. > 100 colorectal adenomas
2. First-degree relatives (10 yr or older) of patients with FAP
3. > 20 cumulative colorectal adenomas (suspected attenuated FAP)
4. First-degree relatives (10 yr or older) of patients with attenuated FAP



Clinical genetic testing is available for the APC and the MutYH gene. The finding of germline mutations in these genes has important implications for the patient and his/her relatives. Individuals who inherit a deleterious APC mutation (dominant) have a very high likelihood of manifesting colonic adenomas; penetrance has been estimated to be 50% by the age of 15 years and 95% by the age of 35 years. The medical goal in patients with FAP is to prevent colon cancer.

- If a mutation is found, all first degree relatives should undergo genetic testing. Genetic testing should be offered to at risk children from the age of 10 years. If gene carrier status is confirmed, full colonoscopy and an upper endoscopic exam should be performed.
- If no mutation is found, all at risk relatives should undergo endoscopic screening.

Multidisciplinary consult between different experts (pediatric gastroenterologists, gastroenterologists, surgeons, geneticists...) is necessary. The work-out of these patients and family members should be done in a centre with expertise in pediatric gastroenterology, in upper and lower gastrointestinal endoscopy (the first with a side-viewing endoscope), and in restorative total proctocolectomy and ileal pouch-anal anastomosis.

- Complexity and new approaches
Endoscopy, Pathology, Genetics and Molecular Biology
- Facilities and equipment required
Endoscopy, Genetic Counselling, Molecular Biology Laboratory
- Professional expertise required both to perform the diagnostic procedure and to interpret the results

Expert GI-Endoscopist

Histological confirmation of polyps as adenomas is required to distinguish FAP from other forms of polyposis, including hamartomatous polyposis, lymphoid hyperplasia and lymphomatous polyposis. Histological confirmation of a diagnosis of hepatoblastoma is required before treatment. Because of the rarity of this type of liver tumour and the need for special immunohistochemistry, diagnosis has to be made, or confirmed, in a Reference Centre and this will commonly be asked by the clinical team of the Reference Centre before making a therapeutic decision.

As a result of the characterization of the causative gene (APC or MutYH), predictive genetic testing can be offered to family members in FAP kindreds. Multidisciplinary consultation including clinical geneticists and psychosocial supports (available in the 8 Centres of Human Genetics) may help at risk individuals who will choose genetic testing to understand the implication of the test for the patient and his/her relatives.



Comprehensive AP diagnosis

- Complexity and new approaches

In about 70-90% of FAP cases and families truncating germline mutations in the APC gene are found, depending on the range of molecular techniques applied in the analysis. Techniques relying on PCR amplification, including sequencing, will miss a significant minority of mutations (deletions and rearrangements that involve the PCR primer binding sites are found in about 10% of the patients). Therefore, the optimal mutation detection strategy should include a combination of the traditional PCR-based methods (like sequencing) and a method to detect large deletions and rearrangements (such as MLPA, multiplex-ligation dependent probe amplification). If no mutation in the APC gene is shown and in case of a recessive inheritance pattern, mutation analysis of the MutYH gene is performed. In about 20% of the patients with adenomatous polyposis without an APC mutation, biallelic MutYH mutations are identified (representing about 1.4% of all adenomatous polyposis patients). Genetic testing of both MutYH and APC genes are available in different Centres of Human Genetics in Belgium.

- Facilities and equipment required

Genetic counselling of FAP patients and their family members should be performed in a centre for human genetics or in a familial cancer clinic and the possibility for psychosocial support. The laboratory offering the molecular test should be equipped to detect point mutations as well as intra-genic rearrangements.

- Expertise required both to perform the cell or tissue sampling and to interpret the results

Sampling of the surgical specimens and microscopic analysis require, at least for hepatoblastoma, a reference pathologist whose laboratory will have the necessary immunohistochemical tools. Again, histological analysis of the surgical specimen has to distinguish FAP from other type of polyposis. A diagnosis of adenomas can be made by a general centre but the other types of polyps are less frequent and may require a reference pathologist.

Therapeutic modalities

- Complexity, new therapeutic strategies

FAP is a monogenic disorder due, for the most part, to mutations within the APC gene. At present time, there is no gene targeted therapies for this monogenic disease. Thus, there is not per se a curative treatment. FAP leads to colorectal cancer and other extra-colonic cancers (see above) and benign tumours (see above; i.e. osteomas). Each cancer or benign tumours must be managed by each organ-related medical specialities within the frame of a multi-disciplinary approach specific to FAP patients.

Specific management of FAP patients includes **prevention and surveillance of FAP patients and families** (Diagnosis relies on positive APC gene testing or, in 20% of patients which are negative for APC gene testing, FAP positive clinical and endoscopic criteria) and **prophylactic surgery**.

Prevention and surveillance of FAP patients relies on National and International recommendations. There are not only general recommendations for all FAP patients, but also specific recommendations for families presenting with a high prevalence of extra-colonic cancer such as hepatoblastoma or Turcot Syndrome.

Patients with positive FAP clinical and endoscopic criteria who are negative for gene testing should be considered at very high risk patients for CRC and extra-colonic patients and should be enrolled in the same screening and surveillance program than FAP patients with positive gene testing.

Many FAP are actually attenuated FAP (AFAP) (diagnosis suspicion should be raised if patient presents with 20 consecutive adenomas on surveillance colonoscopies)



FAP can be diagnosed before cancer occurs or at the time of diagnosis of cancer. When FAP patients present with cancer, medical and surgical management of FAP-related cancers remain similar to medical and surgical management of sporadic cancer, although more extensive surgery is often recommended, because of high risk of metachronous cancer.

In FAP patients, colonoscopic screening should start at the age of 10 if the mutation in the APC gene is present. The goal is to detect dysplasia. Definitive prophylactic surgical treatment is usually recommended at the end of puberty, before the risk of developing colorectal cancer. The classical procedure required for this syndrome is a total proctocolectomy, excising the entire colon and rectum in order to completely eliminate the inevitable risk of colorectal cancer. The reconstruction is done by performing an ileo-anal anastomosis with the construction of an ileal pouch, usually a J-pouch, which is then sutured to the anal canal. In order to avoid the consequences of pelvic complications of this procedure, as anastomotic fistula, a protective and temporary ileostomy may be constructed. Laparoscopic procedures should be offered whenever possible. Closure of the ileostomy is then performed 8-10 weeks later.

In the attenuated form of the syndrome (AFAP), the rectum may be preserved from polyps and the risk of cancer is lower and delayed. In this setting, a less aggressive surgical procedure may be discussed. A total colectomy, leaving the rectum in place, with an ileo-rectal anastomosis is then performed. The main advantages of this second procedure are the avoidance of a temporary ileostomy placement, a better functional outcome and less effect on future fertility. This option requires a surveillance of the remaining rectum by a lifelong 6-months follow-up rectoscopy.

- Facilities and equipment required

Appropriate management of FAP patients for the prevention and surveillance of gastro-intestinal (GI-) cancer requires expertise in diagnostic and therapeutic endoscopy.

The recognition and management of GI FAP lesions requires a high –volume of FAP patients. For example, in the upper GI tract, the Spiegelman classification of duodenal adenoma that eventually guides the endoscopic or surgical management of duodenal adenoma is sometimes difficult to establish. Another example for the lower GI tract is the appropriate evaluation of patients for prophylactic surgery. All classical FAP patients should undergo total colectomy with ileo-anal anastomosis. However, some FAP patients eligible for prophylactic surgery should be evaluated for colectomy with ileo-rectal anastomosis (rectal sparing surgery).

Upper GI endoscopic ultrasound (EUS), Endoscopic Retrograde Cholangio-Pancreatography (ERCP), Lateral Duodenoscopy, Capsule Endoscopy and Double-Balloon Endoscopy should be available in tertiary centres dedicated to the management of FAP patients.

- Expertise required to perform the treatment

Expertise in endoscopic polypectomy and mucosectomy of duodenal adenomas, and more specifically, expertise and experience in the endoscopic removal of the ampulla (Vater papilla) (Endoscopic ampullectomy) is highly recommended.

Surgical team with expertise in laparoscopic and open colorectal surgery, especially with expertise in total proctocolectomy with ileo-anal pouch reconstructive surgery.

- Para-medical expertise required

As major partners involved in genetic counseling, trained psychologists, nurses and social workers are recommended to communicate with families facing or experiencing a genetic diagnosis (parents' concerns for their children, age-appropriate language, childhood testing).

Dietician and stoma nurse are also required.



Follow-up

Patients with FAP are at risk for extracolonic malignancies, including duodenal ampullary cancer, thyroid carcinoma, hepatoblastoma and central nervous system tumours. Desmoid tumours affect 10-20% of patients with FAP and are an important cause of morbidity and mortality because, due to prophylactic colectomy, life expectancy of patients with FAP is increasing.

Follow-up of patients after total proctocolectomy :

- Upper gastrointestinal screening with both end-viewing and side-viewing instruments, because a side-viewing endoscope is better suited for visualization of the papilla. The Spigelman classification of duodenal polyposis should be used to determine the surveillance interval.
- Polypectomy of duodenal polyps (if indicated) and ampullectomy or biopsy of an abnormal papilla should be performed.
- Yearly surveillance with lower endoscopy is recommended because patients who have undergone total proctocolectomy remain at risk for the development of adenomas in the ileal pouch.
- Palpation of the thyroid is recommended yearly.
- Children at risk for FAP should be examined every 6 months
- No surveillance is recommended for desmoid tumors.
- If indicated chemoprevention with celecoxib should be started.

Follow-up of gene carriers or at risk family members with uninformative genetic testing :

- Surveillance of the colon with colonoscopy should be performed
- Surveillance for extra-intestinal tumors should be carried out as described previously.

Follow-up should be done in a centre with expertise in pediatric gastroenterology, in lower gastrointestinal endoscopy and in upper GI endoscopy with a side-viewing endoscope. The gastroenterologist should be aware of the possibility of extra-intestinal tumours and the existence of chemoprevention. Preferably the same physician should see the patient to notice the evolution of the lesions in time.

E. General and specific criteria for Reference Centres

Human Resources and dedicated team

Multidisciplinary team of experts: Gastroenterologists-endoscopists, paediatric gastroenterologist with experience in FAP, radiologists, geneticists, pathologists, colorectal surgeons, gastroenterologist who obtained a certificate showing specific expertise in oncology or a medical oncologist experienced in the treatment of GI cancer, intensive care doctors and nurses, stoma nurses, psychologists, dieticians.

Required facilities and equipment

GI-endoscopy, abdominal and GI Radiology and interventional Radiology, Pathology, Genetics, Genetic counselling, Molecular Biology, Surgery, ICU, Chemotherapy facilities, Paediatric Gastroenterologist with experience in FAP.



Patient centred care

Inclusion of all FAP patients and their families in the FAPA Registry (Familial Adenomatous Polyposis Association). The FAPA is member of the InSight Group (International Society for Gastrointestinal Hereditary Tumours) and participates regularly to international meetings for FAP and Lynch registries. FAPA has also collaborations with STOET (Stichting Opsporing Erfelijke Tumoren) in the Netherlands.

Minimal volume of patients

Centres of excellence for FAP should have experience with laparoscopic restorative proctocolectomy and ileoanal pouch anastomosis. As decision making regarding surgical procedure (laparoscopic ileo-anal pouch anastomosis versus laparoscopic ileo-rectal anastomosis) is complex in a young population (desmoids, fecundity, lifetime cancer risk), this should be done in a Reference Centre.

More than 10 ileo-anal pouches should be performed annually and experience of at least 50 ileo-anal pouch reconstructions should have been documented in a Reference Centre for FAP and UC (Ulcerative Colitis) indications combined.

Centres should be accredited also for pancreas surgery (duodenal polyps) and oncologic surgery for desmoid tumours.

Quality Assurance

The physician should be able to determine in conjunction with a multidisciplinary team the preferred therapy, should have knowledge and experience of FAP and extra-intestinal tumours. A minimum number of procedures to achieve and maintain competence is necessary. Physicians should adhere to the guidelines and a database (number of new patients, endoscopic investigations, surgery, follow-up) should be sent to the FAPA Registry.

Adherence to quality control in endoscopy (evaluation of number of procedures, completeness, adverse drug reactions, complications,...) is necessary, just as surgical expertise and adherence to quality control in surgery (number of procedures, outcome,...).

Genetic testing laboratories provide major medical services to clinicians requesting a test, patients from whom the sample was collected, or referral laboratories. Therefore, the accreditation in compliance with International Organization for Standardization (ISO) 15189 becomes in Belgium and for the beginning of 2014 an obligation for assuring laboratory quality in the Centres of Human Genetics.

Research and other scientific activities

Each Centre of Human Genetics has developed close relationships with a biobank, especially those funded by the "Plan Cancer/Kankerplan" available in the several academic and non-academic hospitals.

Educational activities: Teaching and dissemination

One of the objectives of FAPA is to sensitize patients as well as doctors regarding FAP and Lynch Syndrome to increase the knowledge about these 2 syndromes improving the detection of at risk persons and the follow-up of the patients. This is done by the distribution of info brochures, the organization of info days for the patients, personal contacts (via mail or phone contact), info stands at medical congresses, sending of Newsletters and distribution of guidelines for professionals...

These educational activities of the FAPA are shared by Reference Centres.