SUMMARY

Background: Hereditary gastrointestinal polyposis syndromes account for about 1% of all cases of colorectal cancer and are associated with a broad spectrum of extracolonic tumors. The early detection and accurate classification of these syndromes are essential, since effective methods for surveillance and treatment are available.

Methods: This review article is based on a selective literature search, the author’s own work, and evidence-based guidelines and recommendations.

Results and Conclusions: The diagnosis is initially suspected on the basis of the endoscopic findings and polyp histology. Because different syndromes can resemble each other phenotypically, e.g., autosomal dominant familial adenomatous polyposis and autosomal recessive MUTYH-associated polyposis, molecular genetic studies are important for differential diagnosis and for assessing the risk of recurrence. Identification of the familial mutation in an affected patient is a prerequisite for predictive testing in asymptomatic persons at risk and sometimes enables prognostication. In recent years, the rate of detection of mutations has risen by 10% to 30%, and clinically relevant genotype-phenotype correlations have been described for juvenile polyposis syndrome. Except in cases of mild adenomatous polyposis, phenotypic overlap among the hamartomatous polyposes often causes difficulties in differential diagnosis. Thus, in unclear cases, a pathologist with special expertise in gastrointestinal disorders should be consulted for the evaluation of polyp tissue. Aside from the monogenic polyposes, there are many other types of polyposis that are non-hereditary or of unknown cause, including the hyperplastic and mixed polyposis syndromes. Risk-adapted surveillance programs have been established for the more frequently occurring polyposes.

The occurrence of a few isolated colonic polyps is a frequent, age-related phenomenon (e1–e3). The number of polyps required for a diagnosis of polyposis has not been clearly defined and depends on the prevalence of the polyp type in the general population, on the location of the polyps, and on the patient’s age.

Gastrointestinal polyposis syndromes include numerous entities, some of which are clinically and genetically well characterized; in the case of others, research into their causes and delineation of their phenotypes has only just begun (Table 1, eTable 1) (1–5, e4). The known monogenic forms are precancerous and are responsible for approximately 1% of all colorectal carcinomas (CRC); after hereditary nonpolyposis colon cancer (HNPCC, Lynch syndrome) they are the most frequent cause of hereditary cancer of the colon.

Recognition and correct differential diagnosis of the polyposis syndromes is essential, because on the one hand polyposis patients have a high lifetime risk of gastrointestinal and extraintestinal carcinoma and their first-degree relatives a high risk of recurrence of the syndrome; on the other hand, endoscopic screening as an effective instrument in preventing cancer is available. Polyposis syndromes may be encountered in patients of any age and can vary greatly in their clinical manifestations, even within a family.

Initial symptoms usually relate to stool abnormalities (blood and/or mucus in the stool, diarrhea, constipation) and nonspecific abdominal complaints. Specialized interdisciplinary centers should be involved in the diagnosis and coordination of surveillance (Box 1).

The Institute for Human Genetics at the University of Bonn has been engaged in the molecular genetic diagnostics and research of hereditary gastrointestinal tumor syndrome for 20 years and has access to one of the largest patient cohorts in the world. On the basis of a selective literature search in PubMed and our own work, this review article will summarize the most recent research results and their clinical implications.

Clinical differential diagnosis

Most polyposis syndromes can be confidently distinguished on the basis of the number and distribution of polyps in the gastrointestinal tract, and, especially, on the basis of polyp type (Figures 1 and 2) (5, e5). The
<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene*3</th>
<th>Incidence</th>
<th>Mutation identified (%)</th>
<th>Mode of inheritance</th>
<th>No. of polyps</th>
<th>Distribution of polyps</th>
<th>Polyp histology</th>
<th>Pene- trance (%)</th>
<th>Lifetime risk of CRC (%) (untreated)</th>
<th>Other symptoms</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predominantly adenomatous</strong></td>
<td></td>
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</tr>
<tr>
<td>Classical familial adenomatous polyposis (FAP)</td>
<td>APC</td>
<td>1 : 10 000</td>
<td>80–90</td>
<td>AD</td>
<td>100 to &gt;5000</td>
<td>Large bowel, duodenum, (stomach)</td>
<td>Adenoma</td>
<td>~100</td>
<td>100</td>
<td>Desmoids, osteomas, CHRPE, epidermoid cysts, hepatoblastoma, medulloblastoma</td>
<td>Mutation detection rate rises with severity of disease</td>
</tr>
<tr>
<td>Attenuated FAP (AFAP)</td>
<td>APC</td>
<td>&lt;1 : 10 000</td>
<td>20–30</td>
<td>AD</td>
<td>10–100</td>
<td>Large bowel, duodenum, (stomach)</td>
<td>Adenoma</td>
<td>~100</td>
<td>80–100</td>
<td>Rare</td>
<td>On a continuous spectrum with classical FAP</td>
</tr>
<tr>
<td>MUTYH-associated polyposis (MAP)</td>
<td>MUTYH</td>
<td>&lt;1 : 10 000</td>
<td>15–20*4</td>
<td>AR</td>
<td>20 to hundreds</td>
<td>Large bowel, duodenum, (stomach)</td>
<td>Adenoma</td>
<td>~100</td>
<td>80–100</td>
<td>Increased incidence of extra-intestinal malignancies, rarely sebaceous gland tumors</td>
<td>Low risk of recurrence in offspring (AR)</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer (HNPCC)</td>
<td>MLH1, MLH2, MSH6, PMS2</td>
<td>1 : 500?</td>
<td>60–80</td>
<td>AD</td>
<td>0 to &gt;30</td>
<td>Large bowel</td>
<td>Adenoma</td>
<td>~80</td>
<td>~80</td>
<td>Endometrial carcinoma, gastric carcinoma, sebaceous gland tumors, etc.</td>
<td>If few adenomas, HNPCC is an important DD for AFAP/ MAP</td>
</tr>
<tr>
<td>Birt–Hogg–Dubé syndrome (BHD)*4</td>
<td>BHD (FLCN)</td>
<td>Rare</td>
<td>80–90</td>
<td>AD</td>
<td>Several, multiple</td>
<td>Large bowel</td>
<td>Adenoma</td>
<td>High</td>
<td>High</td>
<td>Specific skin tumors, renal tumors, pulmonary cysts (pneumothorax)</td>
<td>Not usually associated with gastrointestinal polyps</td>
</tr>
<tr>
<td><strong>Predominantly hamartomatous</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Peutz–Jeghers syndrome (FJS)</td>
<td>STK11 (LKB1)</td>
<td>1 : 150 000</td>
<td>90</td>
<td>AD</td>
<td>&lt;20</td>
<td>Small bowel, large bowel, stomach</td>
<td>PJ polyps</td>
<td>High</td>
<td>40</td>
<td>Mucocutaneous/ perianal hyperpigmentation, ovarian tumors (SCTAT), breast cancer</td>
<td>Pigmentations often fade over the course of life; colorectal adenomas are also frequent</td>
</tr>
<tr>
<td>Juvenile polyposis syndrome (JPS)</td>
<td>SMAD4, BMPR1A</td>
<td>1 : 16 000–1 : 100 000</td>
<td>60</td>
<td>AD</td>
<td>~ 5 to hundreds</td>
<td>Small bowel, large bowel, stomach</td>
<td>Juvenile polyps</td>
<td>&gt;90</td>
<td>20–70</td>
<td>SMAD4 mutation carriers: hereditary hemorrhagic telangiectasia (HHT) in ~ 20%, gastric polyps and gastric cancer</td>
<td>Polyps often histologically misinterpreted, in case of doubt refer to expert pathologist</td>
</tr>
<tr>
<td>Juvenile polyposis of infancy</td>
<td>BMPR1A + PTEN</td>
<td>Very rare</td>
<td>100</td>
<td>AD*5</td>
<td>Numer- ous</td>
<td>Small bowel, large bowel, stomach</td>
<td>Juvenile polyps</td>
<td>High</td>
<td>?</td>
<td>Symptomatic in first years of life, symptoms of JPS and BRRS</td>
<td>Often fulminant course with high mortality</td>
</tr>
<tr>
<td>Cowden syndrome (CS)</td>
<td>PTEN</td>
<td>1 : 200 000</td>
<td>80</td>
<td>AD</td>
<td>Multiple</td>
<td>Small bowel, large bowel, stomach</td>
<td>3P, HP, lipomas, ganglioneuromas, etc.</td>
<td>~100</td>
<td>Low</td>
<td>Mucocutaneous tumors, breast cancer, endometrial carcinoma, thyroid cancer, other hamartomatous tumors</td>
<td>Colorectal hamartomas manifest late and are not the main focus for the diagnosis</td>
</tr>
</tbody>
</table>

*1 Hereditary gastrointestinal polyposis syndromes

*2 Synonyms in parentheses; *3 Mutation detection rate, when diagnostic criteria are fulfilled; *4 In APC-mutation-negative patients; *5 Only sporadic cases reported to date

**Note:** HNPCC and BHD are not themselves polyposis syndromes, but are included in the DD of polyposis syndromes.

**Additional Notes:**
- **JP:** juvenile polyps; **HP:** hyperplastic polyps; **P.J.:** Peutz–Jeghers; **BRRS:** Bannayan–Ruvalcaba–Riley syndrome; **CHRPE:** congenital hypertrophy of the retinal pigment epithelium; **CRC:** colorectal carcinoma; **SCTAT:** sex cord tumors with annular tubules; **AD:** autosomal dominant; **AR:** autosomal recessive; **?, unknown at present; DD:** differential diagnosis.
- According to recent studies, BHD is not associated with intestinal polyps (e37, e38).
- Dtsch Arztebl Int 2010; 107(10): 163–73
initial diagnostic workup is therefore always based on the endoscopic and histological findings, together with any extraintestinal manifestations (eFigure, Box 2) and the family history. Because several polyp types may occur, it is important to examine a large enough number of polyps to get a clear idea of which is the predominant type. The process of classification should be guided by the current histological classification of gastrointestinal polyps (e6). Clinical diagnostic criteria have been developed for most of the hereditary polyposes (Box 3), and these can be accessed at GeneReviews (www.geneclinics.org), for example.

**Requirements and role of molecular genetic diagnosis**

Demonstration of a causal mutation in leukocyte DNA is essential for the differential diagnosis (e.g. among the various adenomatous polyposis syndromes), assessment of the risk of recurrence (autosomal dominant versus autosomal recessive inheritance), and predictive testing of asymptomatic persons at risk. Using predictive genetic testing allows preventive measures to be restricted to those members of a family who are actually mutation carriers.

The role of molecular genetic findings in treatment decisions, on the other hand, is limited because identification of a germline mutation rarely allows any estimation of the likely course of the disease. Moreover, even if no mutation can be demonstrated, the patient with polyposis still needs to be treated appropriately, so any necessary measures should be initiated even before testing for mutation is complete.

A suspected diagnosis based on clinical and histological features is a requirement for rational, targeted testing for mutation, which is always first carried out on a person who is already ill—the so-called index patient. Failure to identify a mutation does not invalidate a clinically definite diagnosis (6), but only demonstration of a mutation makes it possible to perform predictive testing of at-risk relatives who are clinically healthy (Figure 3).

The more typical the clinical and histological features of the polyposis, the more likely it is that a mutation will be identified. When the diagnostic criteria are not fulfilled, the mutation detection rate drops markedly (7, 8). With the introduction of multiplex ligation-dependent probe amplification (MLPA), it is now possible to identify large genomic deletions affecting the whole gene or individual exons. This has increased the mutation detection rate by 10% to 30% (Table 1).

**Familial adenomatous polyposis**

Familial adenomatous polyposis (FAP) is the most common colorectal polyposis. With more than 100 colorectal adenomas and early manifestation during adolescence, the classical form is usually not difficult to diagnose. Without treatment, the risk of CRC is almost 100% (9, 10, e7) (Box 3). In about 80% of families a heterozygous germline mutation in the tumor suppressor gene APC is demonstrated. FAP is inherited in an autosomal dominant pattern, so children of a person affected by FAP have a 50% risk of the disease. In some patients a de novo mutation is seen.

In 10% to 15% of de novo mutations a somatic APC mosaicism may be present (11, e8). The clinical significance of mosaicism is that predisposed children may be more severely affected than the parent, and in an apparently new (sporadic) case there may be a clinically normal parent who carries the mutation in mosaic form and may, unnoticed, develop adenomas.

FAP with a mild disease course is usually designated “attenuated FAP” (AFAP) (Box 3), but even here without treatment the risk of CRC is still very high. This patient group is clinically poorly defined and genetically heterogeneous. An APC mutation is found in only 20% to 30% of index patients. The diagnostic criteria are a smaller number of polyps (<100) andmanifestation at a later age (12). However, the severity of disease in polyposis can in the end be understood as a biological continuum and the dichotomous classification into classical versus attenuated should be seen more as marking the phenotypic extremes than as distinct nosological entities.

Benign fundic gland polyps develop in over 50% of FAP patients; gastric carcinoma, however, is rare (incidence 0.6%) (e9, e10). The incidence of duodenal adenomas is up to 90%; the lifetime risk of developing duodenal carcinoma is around 5% (e11).

In some patients typical extraintestinal manifestations are seen: in addition to osteomas or epidermoid cysts, about 10% of patients develop desmoids, which can grow aggressively (e12). The benign pigment changes in the retina—so-called congenital hypertrophy of the retinal pigment epithelium (CHRPE)—have largely lost their diagnostic significance. The most frequently described extraintestinal malignant tumors are hepatoblastoma, medulloblastoma, and thyroid carcinoma; because their incidence is very low (1% to 2%), there is no consensus about specific preventative measures (13, e13). Gardner syndrome and Turcot syndrome are phenotypic variants of FAP, not separate syndromes.

Genotype–phenotype correlations regarding the severity of colorectal polyposis and the occurrence of extraintestinal manifestations have been known for a

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**Internet addresses**

Clinical diagnostic criteria: www.geneclinics.org
Guidelines for early recognition: www.nccn.org
Portal for rare diseases: www.orphanet.de
Polyposis self-help group: www.familienhilfe-polyposis.de

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**Table 1**

<table>
<thead>
<tr>
<th>BOX 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Internet addresses</strong></td>
</tr>
<tr>
<td>Clinical diagnostic criteria: <a href="http://www.geneclinics.org">www.geneclinics.org</a></td>
</tr>
<tr>
<td>Guidelines for early recognition: <a href="http://www.nccn.org">www.nccn.org</a></td>
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<td>Polyposis self-help group: <a href="http://www.familienhilfe-polyposis.de">www.familienhilfe-polyposis.de</a></td>
</tr>
</tbody>
</table>
MUTYH-associated polyposis

MUTYH-associated polyposis (MAP) is the most important differential diagnosis of APC-associated FAP (e16–e18). This autosomal recessive polyposis syndrome is caused by biallelic mutations in the MUTYH gene (previously called the MYH gene). The MUTYH protein is a component of the base excision repair system of the cell, which corrects DNA point mutations caused by oxidative stress. Loss of function of the protein leads to an accumulation of somatic mutations in other genes, e.g. the APC gene, and hence in particular to the development of adenomas.

The colorectal phenotype of MAP resembles that of attenuated FAP (15). Usually from 20 to a few hundred adenomas occur; the mean age at diagnosis is 45 years, with a range between 12 and 68 years. As with attenuated FAP, without treatment the lifetime risk of CRC is up to 100% (e19). According to a current multicenter study of 276 patients with MAP, there is a 17% risk of duodenal polyposis, and the lifetime risk of duodenal carcinoma is around 4%. Extraintestinal malignancies occur significantly more frequently than in the general population and show a certain overlap with HNPCC. However, no dominant tumor type was found (e20). Desmoids were not observed.

Because of the mode of inheritance, the obligate heterozygote children of a patient with MAP and a non-consanguineous partner have only a small risk of developing MAP (about 1%). The CRC risk of heterozygous carriers is still under debate. Recent systematic studies in large patient populations estimate the relative risk at 1.5 to 2.1 in relation to the general population (e19, e21, e22).

Mutation-negative adenomatous polyposis

In about 50% of families the cause of adenomatous polyposis remains unexplained. In these cases milder forms of the disease dominate, and extracolonic manifestations are rare. The family history often shows no abnormalities or is nonspecific. In some patients the failure to find a mutation is explained by diagnostic difficulties or misdiagnoses. In cases where there are fewer than 30 colorectal adenomas, HNPCC should be considered in the differential diagnosis. Besides this, adenomas are also observed in other polyposis syndromes. In the remaining cases, APC mutations that are unidentifiable or uninterpretable by routine diagnostic methods or mutations in yet unknown genes are the probable explanation. In the latter scenario a monogenic or multifactorial etiology is a possibility.

Peutz–Jeghers syndrome

Peutz–Jeghers syndrome (PJS) is a rare hamartomatous polyposis (Box 3). Peutz–Jeghers polyps occur particularly in the small intestine and have characteristic long time (14, e14). However, these are statistical relationships that can give no reliable prediction of the course of the disease in an individual patient. In addition, mosaic findings and splice mutations can lead to deviations from the expected phenotype (11, e15).
histological features. The frequent synchronous occurrence of adenomas can, however, lead to misidentification. The typical perioral pigmentation are rarely present at birth, but usually present before the 5th birthday; they often fade in the course of life (3, e23) and are nonspecific. The differential diagnosis includes in particular the Carney complex and Laugier–Hunziker syndrome (e24).

Age at manifestation is very variable; some patients develop symptoms as early as in the first year of life. Complications in children include acute abdomen due to invaginations or obstructive ileus, and chronic bleeding with secondary anemia. Up to 30% of patients have undergone laparotomy before their 10th birthday (e25).

PJS predisposes not only to CRC but to a broad spectrum of benign and malignant extracolonic tumors which include breast cancer, pancreatic cancer, and endocrinologically active benign sex cord tumors with annular tubules (SCTAT) in the ovaries. The cumulative lifetime risk of developing carcinoma is estimated at 70% to 90% (1).

PJS is caused by germline mutations in the STK11 gene (LKB1 gene). In about 30% of families there is a large deletion of the gene; the mutation detection rate in clinically confirmed PJS has now risen to over 90% (7).

Juvenile polyposis syndrome
Solitary juvenile polyps are the most frequent polyps seen in children and adolescents, and are usually harmless (3, e26). The rare juvenile polyposis syndrome (JPS) only comes under consideration when certain clinical criteria are fulfilled (Box 3). This is often a sporadic disease entity. In about 60% of families with a clinically confirmed diagnosis, mutations of the SMAD4 or BMPRIA genes can be identified (8).

The disease can become manifest even during early childhood with chronic gastrointestinal bleeding or exudative enteropathy accompanied by delayed development. In case of early onset and severe manifestation, the rare juvenile polyposis of infancy should be considered, which is caused by large microdeletions that include the BMPR1A and PTEN genes (e27).

Recently, significant genotype–phenotype relationships were described: gastric polyposis, gastric carcinoma, and clinical symptoms of hereditary hemorrhagic telangiectasia (Osler–Rendu–Weber disease) occur almost exclusively in carriers of an SMAD4 mutation (8, e28).

Correct diagnosis of juvenile polyps is challenging, because of morphological similarities with hyperplastic polyps, lymphocytic infiltrates, and dysplastic components; for this reason, in a sizeable proportion of cases in which JPS is later genetically confirmed, it is initially wrongly identified as ulcerative colitis or hyperplastic polyposis (1, e29). In doubtful cases, therefore, a second opinion from a pathologist specializing in gastrointestinalology is decisive (8) (Box 1). The delineation of JPS from Cowden and Cronkhite–Canada syndrome can be difficult and is usually done on the basis not of histology but of the extraintestinal tumor spectrum and.

**Box 2**

Extraintestinal symptoms that can indicate gastrointestinal polyposis
- Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
- Osteoma in the jaw area
- Perioral pigmentation
- Multiple epidermoid cysts
- Multiple (sub)cutaneous lipomas
- Sebaceous gland tumors (adenoma, epithelioma, carcinoma)
- Hepatoblastoma and medulloblastoma
molecular genetics (2, 4) (Table 1, eTable). Cowden syndrome, which is due to mutations in the PTEN gene, is usually grouped together with its allelic variant, Bannayan–Ruvalcaba–Riley syndrome, which manifests in childhood, under the name PTEN hamartoma tumor syndrome (PHTS). However, colorectal polyps are not the main symptom of PHTS and have at worst a low potential for malignancy (16).

**Hereditary mixed polyposis syndromes**

The vague term ‘hereditary mixed polyposis syndrome’ (HMPS) unites a collection of polyposis syndromes showing a mixture of various types of polyp. In some patients mutations of the PTEN or the BMPRIA gene are demonstrated. These cases should be seen respectively as variants of Cowden syndrome and JPS and treated accordingly (4).

The nosological status of the remaining cases remains unclear. Misinterpretation of histological findings is a possibility, but on the other hand, in five families an association with a locus on chromosome 15 has been described, indicating a possible new genetic disposition (e30).

**Hyperplastic polyposis**

Small hyperplastic polyps are the most frequent type of polyp and have no potential for malignancy. Hyperplastic polyposis (HP), by contrast, is a rare, usually sporadic disease entity that remains poorly defined, and little is known about its genetic basis (17, 18). Diagnostic criteria are taken to be more than 20 to 30 colorectal hyperplastic polyps, more than 1 cm in size and with a pronounced proximal localization (eTable, Box 3).
So far the only published data relate to a few large, clinically heterogeneous patient groups, some of whom had a markedly increased risk of CRC. The data vary between studies by anything from 0 to more than 50% and are likely to be strongly biased. In 84% of patients various types of polyp were diagnosed. As to pathogenesis a sequence of HP—serrated adenoma—CRC has been postulated. Larger case numbers and consistent inclusion criteria will be needed for clarification of the etiology of this polyposis.

**Other gastrointestinal forms of polyposis**

Alongside those already mentioned, there exist numerous rare syndromes that accompany the development of multiple polyps in the gastrointestinal tract (18, 19) (Table 2). Some are probably not heritable, while in the case of others the genetic aspects have not yet been elucidated, as for instance the various intestinal ganglioneuromatoses, which appear in isolation or as an accompanying symptom of known genetic syndromes. Lymphoproliferative diseases and intestinal angiomatoses can usually be easily identified (e31); other forms require a more comprehensive workup and interdisciplinary collaboration between specialists. Since some entities are associated with severe complications and a poor prognosis, and since the treatment options can be different for different syndromes, the outcome of the differential diagnosis has clinical consequences.

**Prevention**

In patients with fewer than 10 colorectal adenomas and no relevant family history, the extent of risk-adjusted colonoscopic surveillance should be guided by the current ‘Colorectal carcinoma’ S3 guideline of the German Society for Digestive and Metabolic Diseases (Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten) (20) or the US recommendations (21, e32) (Table 2).

For the more frequent polyposis syndromes, specific surveillance programs have been established (Table 3) (www.nccn.org). Some of the recommendations disagree, however, and for very rare syndromes it is difficult to validate effectiveness (2, 13, e33, e34).

The efficiency of early and frequent colonoscopy to prevent CRC is well proven in FAP (e35). Besides that, endoscopic surveillance of the upper gastrointestinal tract and appropriate treatment of desmoids is decisive for the prognosis (e12). A European team of experts recently proposed recommendations for prevention of MAP (13). In respect of extraintestinal malignancies, specific preventive measures do not seem to be justified (e20).

In juvenile polyposis syndrome, because of the significant genotype–phenotype relationships, gastric endoscopies could perhaps be reduced in future in patients with a BMPR1A mutation. In carriers of the SMAD4 mutation, however, the occurrence of symptoms of hereditary hemorrhagic telangiectasia must be considered. For PJS, the start and extent of a surveillance program have yet to be validated. In the

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**TABLE 2**

<table>
<thead>
<tr>
<th>Colonoscopic/histological finding</th>
<th>Recommended colonoscopy interval</th>
<th>Evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small rectal hyperplastic polyps</td>
<td>Once every 10 years or screening as in general population</td>
<td>3b</td>
</tr>
<tr>
<td>1 or 2 low-risk adenomas*2</td>
<td>Every 5(–10) years</td>
<td>2b</td>
</tr>
<tr>
<td>3–10 low-risk adenomas or any high-risk adenomas*3</td>
<td>Every 3 years</td>
<td>1b</td>
</tr>
<tr>
<td>&gt;10 synchronous adenomas</td>
<td>Every &lt;3 years</td>
<td>3b</td>
</tr>
<tr>
<td>Incompletely removed adenomas</td>
<td>Every 2–6 months</td>
<td>3b</td>
</tr>
</tbody>
</table>

*No indication of colorectal polyposis in personal or family history
*2 Low-risk adenomas are tubular adenomas <1 cm; no high-grade dysplasia
*3 High-risk adenomas are adenomas >1 cm or histologically advanced adenomas (tubulovillous, villous, high-grade dysplasia)
CASE ILLUSTRATION

This female patient had a medulloblastoma diagnosed in her posterior cranial fossa at the age of 13 years. For 3 years after surgery a shunt was needed to relieve occlusive hydrocephalus. At the age of 34 the patient experienced constipation and hematochezia. Colonoscopy showed a stenosing rectal tumor and numerous colorectal polyps. Analysis of the proctocolectomy specimen led to diagnosis of a rectal adenocarcinoma (pT2, pN1, G2) and >500 adenomas; adjuvant radiotherapy and chemotherapy followed.

One year later the patient attended for genetic counseling asking about the risk of recurrence of the disease in her daughters, aged 9 and 11 years. The patient's father died of colon cancer at the age of 43; medical records were no longer available.

Because of the patient’s history and the family history, mutation screening of the \( APC \) gene was performed and a stop mutation in exon 5 was identified. This provided molecular genetic proof of the clinically suspected diagnosis of familial adenomatous polyposis (FAP), and at-risk persons in the family were offered predictive genetic testing.

In both children the mutation was ruled out in two independent blood tests, so they could be excluded from the FAP related intensive surveillance program. The patient's 27-year-old sister had undergone colonoscopy a few months before which had shown no abnormalities, and as expected she did not carry the mutation either. The 30-year-old sister does carry the mutation and the following colonoscopy revealed hundreds of polyps. The 31-year-old brother refused predictive testing.

### TABLE 3

**Surveillance recommendations in patients with gastrointestinal polyposis syndromes**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Colonoscopy</th>
<th>EGD</th>
<th>Small bowel</th>
<th>Complementary examinations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start (age)</td>
<td>Intervals (years)</td>
<td>Start (age)</td>
<td>Intervals (years)</td>
<td>Start (age)</td>
</tr>
<tr>
<td>FAP</td>
<td>10–12</td>
<td>1–2</td>
<td>30(^a)</td>
<td>3(^a)</td>
<td>n.p.</td>
</tr>
<tr>
<td>AFAP</td>
<td>18–20(^a)</td>
<td>1–2</td>
<td>30(^a)</td>
<td>3(^a)</td>
<td>n.p.</td>
</tr>
<tr>
<td>MAP</td>
<td>18–20</td>
<td>1–2</td>
<td>25–30(^a)</td>
<td>3(^a)</td>
<td>n.p.</td>
</tr>
<tr>
<td>PJS</td>
<td>8–20</td>
<td>2–3</td>
<td>8–12</td>
<td>2–3</td>
<td>8–12</td>
</tr>
<tr>
<td>JPS</td>
<td>10–15</td>
<td>1–3</td>
<td>10–15</td>
<td>1–3</td>
<td>?</td>
</tr>
<tr>
<td>CS</td>
<td>50</td>
<td>10(^a)</td>
<td>n.p.</td>
<td>n.p.</td>
<td>n.p.</td>
</tr>
</tbody>
</table>

\( US \), ultrasonography; \( EGD \), esophagogastroduodenoscopy; \( FAP \), familial adenomatous polyposis; \( AFAP \), attenuated FAP; \( MAP \), MUTYH-associated polyposis; \( PJS \), Peutz–Jeghers syndrome; \( JPS \), juvenile polyposis syndrome; \( CS \), Cowden syndrome; \( HP \), hyperplastic polyposis; ? , no consistent recommendations at present; n.p., no preventive screening measures recommended at present

\(^a\) In patients, carriers, and first-degree relatives

\(^b\) Until the first adenoma is shown, rectosigmoidoscopy is sufficient in classical FAP

\(^c\) But always before a colectomy

\(^d\) More frequently when adenomas are shown

\(^e\) According to Schmiegel et al. 2004, first colonoscopy at age 15, and if no abnormalities are found, colonoscopy every year from age 20

\(^f\) If only hamartomas are present, colonoscopy intervals as for the general population
**GLOSSARY**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allele:</strong></td>
<td>One of two or more alternative forms (variants) of a gene. Because of human diploidy (having two sets of chromosomes), all autosomal genes have two alleles (copies).</td>
</tr>
<tr>
<td><strong>Autosomal dominant:</strong></td>
<td>In the autosomal dominant mode of inheritance, carriers develop the disease if just one of the two copies (alleles) of a gene is damaged by mutation. The risk of recurrence in children of an affected person is therefore 50%. Autosomal dominant diseases typically appear in several generations of a family.</td>
</tr>
<tr>
<td><strong>Autosomal recessive:</strong></td>
<td>In the autosomal recessive mode of inheritance, carriers only develop the disease if both copies (alleles) of a gene are damaged by mutation. The risk of recurrence in siblings of an affected child is 25%. These diseases occur only sporadically or within a set of siblings in a family.</td>
</tr>
<tr>
<td><strong>Biallelic mutation:</strong></td>
<td>People affected by autosomal recessive diseases carry two mutations in the gene concerned, so both alleles are involved.</td>
</tr>
<tr>
<td><strong>CHRPE:</strong></td>
<td>(Congenital hypertrophy of the retinal pigment epithelium.) Benign pigmentation anomaly of the retina; occurs in a specific form in classical familial adenomatous polyposis (FAP), but similar changes are occasionally noted in the general population unrelated to FAP. Distinguishing the forms with certainty requires ophthalmological expertise.</td>
</tr>
<tr>
<td><strong>Codon:</strong></td>
<td>Three base pairs (nucleotides) of the protein-coding sequences of DNA which code for a particular amino acid.</td>
</tr>
<tr>
<td><strong>Exon:</strong></td>
<td>Protein-coding DNA sequences. Between exons there are often noncoding sequences, the introns.</td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Genetic or locus heterogeneity exists when mutations in various genes cause the same phenotype (disease characteristics).</td>
</tr>
<tr>
<td><strong>Heterozygosity:</strong></td>
<td>Possession by a person of two different alleles (copies) of a gene, e.g. mutation plus wild type.</td>
</tr>
<tr>
<td><strong>Homozygosity:</strong></td>
<td>Possession by a person of two identical alleles (copies) of a gene, e.g. wild type plus wild type, or mutation plus mutation. This has relevance particularly in diseases with an autosomal recessive mode of inheritance.</td>
</tr>
<tr>
<td><strong>HP—serrated adenoma—CRC sequence:</strong></td>
<td>Analogous to the adenoma–carcinoma development model, this sequence describes a pathogenetic hypothesis whereby colorectal cancer (CRC) develops from hyperplastic polyps that transform into serrated adenomas, an atypical variant of adenoma.</td>
</tr>
<tr>
<td><strong>Index patient:</strong></td>
<td>The sick or affected person through whom a genetic disease is identified in a family, and in whom the initial screening for a mutation in a particular gene may be carried out.</td>
</tr>
<tr>
<td><strong>Germline mutation:</strong></td>
<td>Mutation of the germ cells (oocytes or sperm), in contrast to other cells of the body (somatic cells). Germline mutations are passed on to offspring in a mendelian inheritance pattern, whereas somatic mutations are present only in the individual in whom they arise.</td>
</tr>
<tr>
<td><strong>MLPA method:</strong></td>
<td>(Multiplex ligation-dependent probe amplification.) A new semiquantitative molecular genetic method that makes it possible to look for large genomic deletions or duplications of individual exons or whole genes relatively easily.</td>
</tr>
<tr>
<td><strong>Monogenous:</strong></td>
<td>A characteristic or disease resulting from mutation of a single gene.</td>
</tr>
<tr>
<td><strong>Mosaic:</strong></td>
<td>Simultaneous occurrence of normal and genetically altered cells or cell lines in the same individual.</td>
</tr>
<tr>
<td><strong>De novo mutation:</strong></td>
<td>Mutation occurring for the first time in a person or in one of the germ cells from which this person developed. Particularly relevant in autosomal dominant diseases.</td>
</tr>
<tr>
<td><strong>Penetrance:</strong></td>
<td>Proportion of individuals carrying a mutation who develop clinical disease.</td>
</tr>
<tr>
<td><strong>Phenotype:</strong></td>
<td>Clinically visible expression (disease symptoms) of a genotype.</td>
</tr>
<tr>
<td><strong>Predictive testing:</strong></td>
<td>Investigation of a clinically healthy person for characteristics that would predispose him or her to diseases later in life. Such investigations might test for genetic mutations or for nongenetic characteristics (e.g. HIV infection).</td>
</tr>
<tr>
<td><strong>Somatic:</strong></td>
<td>Relating to somatic cells as opposed to germ cells. Somatic mutations are not passed on to offspring.</td>
</tr>
</tbody>
</table>
end, it comes down to protocols agreed with the affected individuals.

Future research
In mutation-negative polyposis, a genetic cause is possible because the occurrence of numerous polyps cannot be satisfactorily explained by exogenous factors. Knowledge of the underlying hereditary factors has major significance for our understanding of how gastrointestinal tumors arise and for counseling of the affected families. In addition to modern chip-based methods (SNP arrays), close collaboration between human geneticists, pathologists and gastroenterologists will be necessary for new genetic dispositions to be identified.

Practical diagnostic procedure
Colonoscopy is used to elucidate the cause of stool abnormalities, a suggestive family history, or specific extraintestinal findings. Referral for molecular genetic testing should be done in a targeted manner after appropriate endoscopic and histological workup has been carried out. If nosological doubt remains, obtaining a second opinion on the polyps from a pathologist with gastroenterological expertise is recommended, along with looking for extraintestinal symptoms and consulting with the testing laboratory, in order to rule out unnecessary investigations. Mutation testing requires about 10 mL uncooled EDTA blood (6). Detailed clinical information is important in order to determine the examination strategy and interpret the findings.

Diagnosis of a polyposis syndrome, and especially predictive testing, should always be accompanied by the offer of genetic counseling (22, e36). Predictive testing of minors should not be done until the results could lead to treatment or preventive measures such as screening in the immediate future (23, e37). The address of the nearest genetic counseling center will be found on the internet (24). National self-help groups exist for FAP and MAP (25).

KEY MESSAGES

- Many polyposis syndromes show great variability in the severity of disease; if untreated, they carry a high risk of gastrointestinal and extraintestinal malignancies.
- The initial diagnostic workup for polyposis always includes endoscopy, histology, family history, and a search for extraintestinal manifestations.
- Demonstration of a mutation is carried out in a targeted manner in a person with clinical symptoms and is prerequisite for predictive testing of asymptomatic persons at risk, which should be performed in the context of genetic counseling.
- The established risk-adjusted surveillance programs are an effective instrument of cancer prevention.
- Polyposis patients should be seen in regular intervals at a specialized interdisciplinary center.


25. Familienhilfe Polyposis Coli e.V.: www.familienhilfe-polyposis.de.

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The Differential Diagnosis and Surveillance of Hereditary Gastrointestinal Polyposis Syndromes

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# The Differential Diagnosis and Surveillance of Hereditary Gastrointestinal Polyposis Syndromes

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## eTABLE

<table>
<thead>
<tr>
<th>Nonhereditary or genetically unelucidated gastrointestinal polyposis syndromes</th>
<th>Distribution of polyps</th>
<th>Polyp histology</th>
<th>Age at first manifestation (years)</th>
<th>Extraintestinal symptoms</th>
<th>Remarks</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic polyps</td>
<td>Large bowel (proximal &gt; distal)</td>
<td>Hyperplastic polyps, “ser-rated” adenomas</td>
<td>Usually &gt;50</td>
<td>None</td>
<td>As many polyps should be removed as possible and histologically examined</td>
<td>17</td>
</tr>
<tr>
<td>Hereditary mixed polyposis syndrome (HMPS)</td>
<td>Large bowel</td>
<td>Atypical juvenile polyps, hyperplastic polyps, (“ser-rated”) adenomas</td>
<td>Usually &gt;20</td>
<td>None</td>
<td>Some cases prove to be (atypical) JFP or CS</td>
<td>e30</td>
</tr>
<tr>
<td>Cronkhite–Canada syndrome</td>
<td>Entire gastrointestinal tract except esophagus</td>
<td>Hamartomatous, sometimes juvenile polyps</td>
<td>Usually &gt;50</td>
<td>Ectodermal anomalies (alopecia, onychodystrophy, hyperpigmentation)</td>
<td>High mortality due to malnutrition, gastrointestinal bleeding, infections, nausea, invagination, prolapse</td>
<td>18</td>
</tr>
<tr>
<td>Ganglioneuromatous polyposis</td>
<td>Entire gastrointestinal tract</td>
<td>Hamartomatous (benign proliferation of ganglion cells and surrounding stroma cells), sometimes also synchronous adenomas and juvenile polyps</td>
<td>Usually adult</td>
<td>Sometimes cutaneous lipomas, adrenal myelolipoma, goiter, pancreatic telangiectasia</td>
<td>Sometimes an accompanying symptom of MEN IIb, NF1, or CS</td>
<td>19</td>
</tr>
<tr>
<td>Lipomatous polyposis</td>
<td>Small and large bowel</td>
<td>Submucous lipomas, sometimes also synchronous adenomas</td>
<td>Usually &gt;40</td>
<td>None</td>
<td>Often asymptomatic, very rare, often initially misdiagnosed as FAP</td>
<td>18</td>
</tr>
<tr>
<td>Lymphoproliferative polyposis</td>
<td>Small bowel, large bowel, rarely stomach</td>
<td>Lymphomas, lymphoid hyperplasia</td>
<td>Usually adult</td>
<td>Dependent on underlying disease</td>
<td>Occurs with various lymphoproliferative diseases, more frequent in patients with immune deficiencies; often asymptomatic</td>
<td>18, e31</td>
</tr>
<tr>
<td>Intestinal leiomyomatosis</td>
<td>Small bowel, large bowel, rarely esophagus</td>
<td>Smooth muscle cell proliferation, vascular wall hyalinization, skeinoid fibers</td>
<td>Adult</td>
<td>Sometimes described in Alport syndrome; mucocutaneous pigmentation in some cases</td>
<td>Malignant transformation probably very rare</td>
<td>e42</td>
</tr>
<tr>
<td>Pneumatosis cystoides intestinais</td>
<td>Small bowel (especially terminal ileum) and/or large bowel</td>
<td>Sessile pseudopolyps: submucous/subserous gas-filled cysts</td>
<td>Often 30–50</td>
<td>Sometimes other underlying diseases (scleroderma, polyarthritis, lupus erythematosus, etc.)</td>
<td>Pneumoperitoneum frequent; conservative (medical) therapy usually sufficient; no treatment needed for asymptomatic patients</td>
<td>e43</td>
</tr>
<tr>
<td>Intestinal (hem)angiomatosis</td>
<td>Small bowel, also stomach, large bowel</td>
<td>Mucous and submucous (cavernous) hemangiomata</td>
<td>Variable</td>
<td>Dependent on underlying disease</td>
<td>Various underlying diseases, some cases have characteristic endoscopic findings</td>
<td>e44</td>
</tr>
<tr>
<td>Inflammatory (pseudo-)polyposis</td>
<td>Large bowel</td>
<td>Inflammatory pseudo-polyps</td>
<td>Variable</td>
<td>Correspond to underlying inflammatory disease</td>
<td>Frequent in chronic inflammatory bowel diseases (ulcerative colitis, Crohn’s disease); important DD: FJP</td>
<td>18</td>
</tr>
</tbody>
</table>
The Differential Diagnosis and Surveillance of Hereditary Gastrointestinal Polyposis Syndromes

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**eFigure:** Characteristic histological findings in polyposis syndromes

b) Prof. M. Stolte, Bayreuth
c) Prof. M. Stolte, Bayreuth
g) From: Pathol Res Pract 2008; 204: 431–47, with permission: Elsevier Ltd.
h) Prof. M. Stolte, Bayreuth
i) Prof. M. Stolte, Bayreuth