Danish guidelines for management of non-APC-associated hereditary polyposis syndromes

Anne Marie Jelsig 1*, John Gåsdal Karstensen 2,3, Niels Jespersen 2, Zohreh Ketabi 4, Charlotte Lautrup 5, Karina Ranlund 6, Lone Sunde 6, Karin Wadt 1, Ole Thorlacius-Ussing 7,8 and Niels Qvist 9,10

Abstract

Hereditary Polyposis Syndromes (HPSs) are a group of rare, inherited syndromes characterized by the presence of histopathologically specific or numerous intestinal polyps and sometimes extra-intestinal manifestations. HPSs is associated with an increased risk of cancer in and outside the gastrointestinal (GI)-tract and timely diagnosis is important in order to offer specific organ-targeted surveillance programs with the purpose of reducing morbidity and mortality. The classification of HPS has traditionally been based on the histopathology of the removed polyps as presented in Fig. 1. Some HPSs have been known for decades, but the possibility of sequencing many genes in a very short time (Next Generation Sequencing (NGS)), has revealed several genes now known to be associated with HPSs, and genetic testing is therefore a part of the diagnostic pipeline for patients with (or suspected of having) a HPS. Both autosomal dominant and autosomal recessive inheritance is seen.

Keywords: Cancer, Polyposis, Genetics, Hereditary, Surveillance, Management, Guideline

Background

Hereditary Polyposis Syndromes (HPSs) are a group of rare, inherited syndromes characterized by the presence of histopathologically specific or numerous intestinal polyps and sometimes extra-intestinal manifestations. HPSs is associated with an increased risk of cancer in and outside the gastrointestinal (GI)-tract and timely diagnosis is important in order to offer specific organ-targeted surveillance programs with the purpose of reducing morbidity and mortality. The classification of HPS has traditionally been based on the histopathology of the removed polyps as presented in Fig. 1.

Some HPSs have been known for decades, but the possibility of sequencing many genes in a very short time (Next Generation Sequencing (NGS)), has revealed several genes now known to be associated with HPSs, and genetic testing is therefore a part of the diagnostic pipeline for patients with (or suspected of having) a HPS. Both autosomal dominant and autosomal recessive inheritance is seen.

Genetics diagnostics and genetic counselling

Genetic testing includes gene-panel screening using NGS with genes known to be related to polyposis syndromes. As of 2020, the panel should include the genes listed in Fig. 1. The finding of causative monoallelic (autosomal dominant) or biallelic (autosomal recessive) germline pathogenic variations (PVs) is crucial in order to make an accurate diagnosis which in turn is the prerequisite for tailoring the optimal surveillance program for each patient. Additionally, detecting a genetic cause also makes prenatal diagnosis, including preimplantation diagnosis (PGT), possible in some cases. Somatic mosaicism should be considered in patients with a clinically convincing HPS, where standard genetic analyses of blood does not identify the cause.
How to manage HPS?
There is a high demand for guidelines addressing questions like: how many and what types of polyps should cause concern? When should a patient be referred for genetic counselling? How should we manage patients and their families when detecting (or not detecting) a PV in an HPS gene? In order to address these questions, the Danish Society of Medical Genetics and the Danish Society of Surgery appointed a group of experts in the field in 2017. This paper is a summarized version of this work and guidelines, approved by the two societies in 2020. The guideline points out referral criteria for genetic work-up and counselling (Fig. 2) and suggests surveillance programs for HPS-patients with or without a known genetic etiology. APC-associated polyposis and PTEN-hamartoma-tumor syndrome are not included in the work. The working group agreed on general recommendations (Suppl. Table 1) and more specific surveillance for each HPS (Suppl. Table 2).

**General considerations of surveillance and prophylactic GI-operations**

Endoscopic investigations are the core of surveillance. There is no evidence for recommending prophylactic intestinal resections in any of the HPSs, which are described here, but some patients may have a massive polyp burden in part(s) of the GI-tract, making endoscopic surveillance challenging; gastrointestinal resection is indicated in some patients. In the case of colorectal cancer (CRC), a subtotal or total colectomy should be considered, but taking the polyp burden, age and comorbidity into consideration. If (large) polyps causes complications such as invagination and/or bleeding, segmental resections with or without peroperative enteroscopy should be performed. After surgery surveillance must be resumed.

**HAMARTOMATOUS polyposis syndromes**

**Peutz-Jeghers syndrome**

Peutz-Jeghers syndrome (PJS) is characterized by the presence of hamartomatous Peutz-Jeghers polyps in the GI-tract and mucocutaneous pigmentation (MPs) especially on the lips and buccal mucosa. MPs typically present in childhood and tend to fade after puberty. The polyps are mainly found in the small intestines and 50–75% of patients experience GI symptoms before 20 years of age, with invagination as the most common complication [1]. PJS is inherited
in an autosomal dominant manner and STK11 is the only gene known to be associated with the condition. An age dependent increased risk of cancer in the GI-tract as well as various extra-intestinal cancers are well documented (Table 1) [9]. Surveillance is comprehensive and should start in childhood (see Supp Table 2) [10].

Management of patients with a solitary Peutz-Jeghers-polyp or isolated MPs Patients with a solitary Peutz-Jeghers polyp should be referred to a clinical genetics department for STK11 analysis. Endoscopy with gastroscopy, colonoscopy and video capsule enteroscopy could be performed in order to rule out PJS. If both genetic and endoscopic work-up is negative, PJS is unlikely

---

**Referral criteria for genetic work-up and counseling**

Number of polyps is the **cumulative number**

### a: Hamartomatous polyps (including Peutz-Jeghers – and juvenile polyps)

- a personal history of 1 or more Peutz-Jeghers polyp(s)
- a personal history of 2 or more juvenile polyps
- a family history of Peutz-Jeghers Syndrome or Juvenile Polyposis Syndrome
- a history of 1 or more hamartomatous polyps and one or more extraintestinal manifestation(s), e.g. macrocephaly, mucocutaneous pigmentation, telangiectasias, epistaxis, thoracic aortic dilation, trichilemmomas, papilomatous lesions, acral keratoses, breast-, thyroid-, and/or endometrial cancer

### b: Adenomas

- a personal history of >25 colorectal adenomas
- a personal history of >10 colorectal adenomas before 50y
- a history of 3 adenomas in a person before 30y
- a family history of one of the adenomatous polyposis syndromes
- a personal or family history of adenomas and extraintestinal manifestations suggesting HPS e.g. desmoid tumors, papillary thyroid cancer, epidermal cysts, osteomas, café-au-lait spots or dental abnormalities

### C: Serrated

- a personal history of five or more serrated polyps/lesions proximal of the rectum
- a personal history of >20 serrated polyps located at any site in colon or rectum

---

Fig. 2 Referral criteria for genetic work-up and counseling. Number of polyps is the cumulative number.
| Syndrome                | Site of cancer                  | Cumulative lifetime risk or frequency among carriers | Age of debut |
|-------------------------|---------------------------------|-----------------------------------------------------|--------------|
| **Peutz-Jeghers Syndrome** [2] | Colon/rectum                    | 39%                                                 | 42-46y       |
|                         | Stomach                         | 29%                                                 | 30-40y       |
|                         | Small bowel                     | 13%                                                 | 37-42y       |
|                         | Breast                          | 32-54%                                              | 37-59y       |
|                         | Ovarian                         | 21%                                                 | 28y          |
|                         | Cervix (adenoma malignum)       | 10%                                                 | 34-40y       |
|                         | Uterus                          | 9%                                                  | 43y          |
|                         | Pancreas                        | 11-38%                                              | 41-52y       |
|                         | Testicular (sertoli cell tumour) | 9%                                                  | 6-9y         |
|                         | Lung                            | 7-17%                                               | 47y          |
| **Juvenile Polyposis Syndrome** | Colon/rectum                   | 38% [3]                                             | 36.0 (48) (median) |
|                         | Gastric                         | 21% [2]                                             | 44.0 (48)    |
| **POLE-associated polyposis** [4] | Colon/rectum                 | 28% (M), 21%(F) For p.Leu424VAL: 97% (M), 92% (F) | 50.2 (49) (mean) |
|                         | Uterus                          | ?                                                   | ?            |
|                         | Ovaries                         | ?                                                   | ?            |
|                         | Pancreas                        | ?                                                   | ?            |
|                         | Malignant melanoma              | ?                                                   | ?            |
| **POLD1-associated polyposis** [4] | Colon/rectum                 | 90% (M), 82% (F)                                   | 39.7 (49) (median) |
|                         | Uterus                          | ?                                                   | ?            |
|                         | Breast cancer                   | ?                                                   | ?            |
|                         | Ovarian                         | ?                                                   | ?            |
|                         | Lymphoma                        | ?                                                   | ?            |
|                         | Bladder                         | ?                                                   | ?            |
| **AXIN2-associated polyposis** | Colon/rectum                 | 13/35 individuals                                   | 36–80+       |
| **MUTYH- associated polyposis** [5] | Colon/rectum                 | 80–90%                                              | 48.0 (median) |
|                         | Duodenum                        | 4%                                                  | 61.0         |
|                         | Ovaries                         | 6–14%                                               | 51.0         |
|                         | Bladder                         | 6–8% (females), 6–25% males)                       | 61.0         |
|                         | Melanoma                        | ?                                                   | ?            |
|                         | Breast                          | ?                                                   | ?            |
|                         | Uterus                          | 3%                                                  | 51.0         |
| **NTHL1-associated polyposis** [6] | Colon/rectum                 | 16/29 individuals                                   | 61.0 median, (33-73y) |
|                         | Breast                          | 9/15 female individuals                             | 48.5 (38-63y) |
|                         | Uterus                          | 5/15 Uterus (precancerous and cancerous)            | 57.0 (6-74 y) |
|                         | Duodenum                        | ?                                                   | ?            |
| **CMMRD** [7]           | Colon/rectum                    | 59/146 individuals                                  | 8.48y        |
|                         | Duodenum                        | 18/149 individuals                                  | 11.42y       |
|                         | Hematologic malignancies        | ?                                                   | ?            |
|                         | Brain tumors                    | ?                                                   | ?            |
| **GREM1-associated mixed polyposis** | CRC                           | ?                                                   | ?            |
| **Serrated Polyposis Syndrome** [8] | CRC                           | 15–35%                                              | 53.9 (median) |
and the patient (and family members) should not be subjected to further investigations or follow-up. Isolated MPs suggestive of PJS should be managed as described by Latchford et al. [11].

**Juvenile polyposis syndrome**

Juvenile Polyposis Syndrome (JPS) is characterized by the presence of few to over a 100 hamartomatous juvenile polyps in the GI-tract, mostly in the large intestine and stomach. A subgroup of patients with JPS and a PV in SMAD4 may have symptoms of hereditary hemorrhagic telangiectasia (HHT) as well as an increased risk of aortic aneurisms [12]. The phenotypic spectrum is broad and there is significant intra- and interfamilial variability in expressivity. JPS is inherited in an autosomal dominant manner. The distinction between patients – especially children – with solitary or few juvenile polyps from juvenile polyposis can be difficult, but for patients with only one juvenile polyp the risk for having JPS is low [13]. The risk of CRC and gastric cancer is increased with the risk of gastric polyposis, gastric cancer being highest in SMAD4 carriers [14].

The clinical approach may vary depending on the clinical picture. For SMAD4 carriers surveillance for HHT should start at 12 years, while the starting point for screening for aortopathy is less clear.

**Autosomal dominant adenomatous polyposis syndromes**

**POLE-associated polyposis**

PVs in the exonuclease domains of POLE (exon 9–14) were described in adult patients with colonic polyps and/or early-onset CRC in 2013 [15, 16]. Since then, additional cases have been reported [17, 18]. Still, data regarding the phenotypic characteristics, penetrance and estimation of cancer risk are limited. Café-au-lait pigmentation may be part of the phenotypic spectrum and are important to discover, as this manifestation can be suggestive of a more aggressive phenotype.
Several PVs have been reported with c.1270C > G, p.Leu424Val, (NM_006231.3) as the most frequent. Other pathogenic missense variants seem to be associated with a more severe phenotype with cancer including medulloblastoma) and CRC [19, 20]. There is an increased risk of CRC, and a high frequency of extraintestinal cancer has been investigated in a prospective study from 2019 [23] which found no evidence of an adenomatous polyposis phenotype in monoallelic carriers. Carriers of a PV who have a first-degree relative with MAP have up to a 5-fold increased risk of CRC [24], while carriers in general have an over 3-fold increased risk. It is debated whether the finding of one PV in an individual should result in genetic testing of relatives (cascade-testing) as recommendations are contradictory [2, 25]. It is recommended that siblings of a patient with MAP are tested for the PV(s) in the family. Spouses of patients with MAP and spouses of patients, who are heterozygous carriers of a PV should be offered genetic screening of MUTYH.

**Risk of cancer in heterozygotes with pathogenic MUTYH variants**

The risk for colorectal adenomas in monoallelic carriers of pathogenic MUTYH-variants has been investigated in a prospective study from 2019 [23] which found no evidence of an adenomatous polyposis phenotype in monoallelic carriers. Carriers of a PV who have a first-degree relative with MAP have up to a 5-fold increased risk of CRC [24], while carriers in general have an over 3-fold increased risk. It is debated whether the finding of one PV in an individual should result in genetic testing of relatives (cascade-testing) as recommendations are contradictory [2, 25]. It is recommended that siblings of a patient with MAP are tested for the PV(s) in the family. Spouses of patients with MAP and spouses of patients, who are heterozygous carriers of a PV should be offered genetic screening of MUTYH.

**NTHL1-associated polyposis**

NTHL1-associated polyposis (or NTHL1-tumour syndrome) was described for the first time by Weren et al. in 2015 in patients with adenomatous polyposis in the lower GI-tract [26]. As of January 2020, reports of 34 patients with NTHL1-associated polyposis have been published [6, 26–32]. Development of NTHL1-associated polyposis is caused by biallelic PVs in NTHL1 and the inheritance pattern is autosomal recessive. Most patients are homozygous for the recurrent PV, NTHL1, c.268C > T, p.Gln90* (NM_002528).

There is a high frequency of CRC in the published cases, but also of breast- and duodenal cancer suggesting a broader cancer predisposition syndrome [32–39]. Thus, the phenotypic spectrum of this syndrome is still emerging.

**Constitutional mismatch repair deficiency syndrome**

Constitutional mismatch repair deficiency syndrome (CMMRD) is a distinct childhood cancer predisposition syndrome characterized by an increased risk of a broad spectrum of malignancies, and GI-polyposis in both the upper and lower GI-tract. Often café-au-lait spots and other findings that mimic neurofibromatosis type 1 are detected. The patients carry biallelic PVs in the MMR genes (MLH1, MSH2, MSH6 and PMS2) and thus the inheritance pattern is autosomal recessive. More than half of the patients known with CMMRD have bi-allelic PVs in PMS2 [33]. Recommendations for GI-surveillance are listed in Suppl.Table 2. Suggested surveillance for other
malignancies is described by the European Consortium of CMMRD [34].

**MSH3- and MLH3-associated polyposis**

**MSH3**: As of January 2020, a total of four individuals from two families have been reported with biallelic PVs in *MSH3* [35]. The inheritance pattern is autosomal recessive and the associated phenotype is characterized by the presence of colorectal adenomatous polyposis. Polyposis was accompanied by benign and malignant lesions in the GI-tract and extracolonic manifestations such as duodenal adenomas, thyroid adenomas, gastric cancer and astrocytoma.

**MLH3**: Olkinuora et al. [36] reported five patients from four families to be homozygous for PVs in *MLH3*. The patients had 50–200 adenomatous polyps (age range 48–52 years). One of three female patients had breast cancer at age 52, and the male patient had CRC at age 48.

**Other polyposis syndromes**

**GREM1-associated mixed polyposis**

**GREM1**-associated Mixed Polyposis (previously Hereditary Mixed Polyposis syndrome) is an extremely rare condition with an unknown incidence. The condition was first described by Whitelaw et al. in 1997 [37] in an Ashkenazi Jewish family with mixed GI-polyposis and CRC. A genetic cause was reported in 2012 by Jaeger et al, who detected a 40 kb duplication upstream of **GREM1** [38]. Since then other duplications have been reported [21, 39, 40]. The mode of inheritance is autosomal dominant and the condition is caused by upstream **GREM1** duplications [40]. The histopathology of the polyps is variable and includes atypical juvenile polyps and/or hyperplastic polyps as well as adenomas and serrated adenomas, and there is a phenotypic overlap with other syndromes, although the phenotypic description is limited. CRC occurs with an increased frequency in adulthood [41].

**Serrated polyposis syndrome**

Serrated Polyposis Syndrome (SPS) (previously named Hyperplastic Polyposis Syndrome) Is a condition characterized by numerous serrated polyps in the colon. Although the prevalence is unknown, the syndrome is probably more common than anticipated. In fecal occult blood test-based screening cohorts 1:111–1:238 individuals were diagnosed [42, 43].

SPS is commonly grouped with the HPSs but does not appear to be inherited in a simple Mendelian fashion. Some studies link PVs in **RNF43** to SPS; however, studies of larger cohorts suggest that **RNF43** only explains a small proportion of cases [44, 45]. Individuals with SPS have an increased risk of CRC, and relatives have a recognized substantial risk of developing CRC, but the risk is not well defined [46].

**Polyposis with unknown etiology**

In some patients with a significant number of adenomas in the L-GI-tract, both with and without a family history of polyposis, the etiology is not identified by gene analysis. These patients/families may have the diagnosis of “polyposis of unknown etiology” although there is no clear definition of the term “polyposis”. The definition seen in Table 2 can be used as guidance.

Few publications have focused on this group of patients, and these are likely influenced by selection bias. Cancer occurrence has been reported in relatives, both in the colon and in the U-GI tract, but the inclusion criteria in these studies differ from those listed in Table 2 [47–49]. The National Comprehensive Cancer Network (NCCN) suggests surveillance/management guided by the phenotype of the patient and by the family history [2].

**Conclusion**

In recent years, HPSs have been identified due to the development in genetic technologies. Patients with these syndromes should be offered surveillance in order to reduce mortality and morbidity, and genetic analysis is crucial in the diagnostic pipeline. Long-term follow-up studies are needed in order to obtain evidence but are complicated by the small number of patients, lack of population-based data and risk of ascertainment bias. The guidelines presented will have to undergo revision as knowledge increases and new polyposis syndromes are identified.

**Abbreviations**

CMMRD: Congenital mismatch repair deficiency; CRC: Colorectal cancer; FAP: Familial adenomatous polyposis; FDR: First-degree relative; HHT: Hereditary hemorrhagic telangiectasia; HPS: Hereditary polyposis syndrome; MP: Mucocutaneous pigmentations; JPS: Juvenile polyposis syndrome; L-GI: Lower gastrointestinal tract; MAP: **MUTYH**-associated polyposis; PJS: Peutz-Jeghers syndrome; PV: Pathogenic variant; U-GI: Upper gastrointestinal tract; SPS: Serrated Polyposis Syndrome; VCE: Videocapsule endoscopy

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s13053-021-00197-8.

**Additional file 1: Supplementary Table 1**: General recommendations for management of the Hereditary Polyposis Syndromes.

**Additional file 2: Supplementary Table 2**: Surveillance strategies for each Hereditary Polyposis Syndrome.

**Acknowledgements**

Not applicable.
Authors’ contributions
John Gasdal Karstensen: literature search on hamartomatous polyposis, discussion of guidelines. Niels Jespersen, literature search on adenomatous polyposis syndromes, discussion of guidelines. Zohre Ketabi, literature search on the gynecological aspects of the syndrome, discussion of guidelines. Charlotte Lautrup, literature search on adenomatous polyposis syndromes and serrated polyposis syndromes, discussion of guidelines Karina Ranlund, literature search on adenomatous polyposis syndromes and serrated polyposis syndromes, discussion of guidelines. Lone Sundé, literature search on adenomatous polyposis syndromes, polyposis without known etiology, discussion of guidelines Karin Wadt, literature search on adenomatous polyposis syndromes, discussion of guidelines. Ole Thorlacius-Ussing, literature search on adenomatous polyposis syndromes, discussion of guidelines. Niels Qvist, literature search on hamartomatous polyposis, discussion of guidelines. Anne Marie Jelsig, literature search on hamartomatous polyposis, writing the final draft of the paper, figures and tables. The author(s) read and approved the final manuscript.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that there is no conflict of interest.

Author details
1Department of Clinical Genetics, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark. 2Danish Polyposis Registry, Gastrounit, Hvidovre Hospital, Hvidovre, Denmark. 3Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. 4Department of Gynecology and Obstetrics, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark. 5Department of Clinical Genetics, Aalborg University Hospital, Aalborg, Denmark. 6Department of Clinical Genetics, University Hospital of Southern Denmark, Vejle Hospital, Vejle, Denmark. 7Department of Gastrointestinal Surgery, Aalborg University Hospital, Aalborg, Denmark. 8Research Unit for Surgery, Odense University Hospital, Odense, Denmark. 9University of Southern Denmark, Odense, Denmark.

Received: 2 June 2021 Accepted: 14 September 2021

Published online: 07 October 2021

References
1. Hinds R, Philip C, Hyer W, Fell JM. Complications of childhood Peutz-Jeghers syndrome: implications for pediatric screening. J Pediatr Gastroenterol Nutr. 2004;39(2):219–20. https://doi.org/10.1097/00005156-200408000-00027.
2. Syngal S, Brand RE, Church JM, Giardiello FM, Hapel HL, Burt RW. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223–62; quiz 63. https://doi.org/10.1038/ajg.2014.435.
3. Briosrens LA, van Hattem A, Hylind LM, Iacobuzio-Donaleh C, Romans KE, Avilbund J, et al. Risk of colorectal cancer in juvenile polyposis. Gut. 2007;56(7):965–7. https://doi.org/10.1136/gut.2006.116913.
4. Buchanan DD, Stewart JR, Clendenning M, Rosty C, Mahmood K, Pope BJ, et al. Risk of colorectal cancer for carriers of a germ-line mutation in POLE or POLD1. Genet Med. 2016;18(9):1073–9. https://doi.org/10.1038/gim.2016.150.
5. Nielsen M, Ingeberg T, Brand R. MUTHY polyposis. 2012 Oct 4 [updated 2019 Oct 10]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK107219/.
6. Grollemen JE, de Vooer RM, Elayed FA, Nielsen M, Weren RDA, Palles C, et al. Mutational signature analysis reveals NTHL1 deficiency to cause a multistumor phenotype. Cancer Cell. 2019;35(2):256–66 e5. https://doi.org/10.1016/j.ccell.2018.12.011.
7. Wimmer K, Krazt JP, Yasen HF, Caraballo S, Colas C, Entz-Wohle N, et al. Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium ‘care for CMMRD’ (C4MMDR4), J Med Genet. 2014;51(6):355–65. https://doi.org/10.1136/jmedgenet-2014-102284.
8. Bleijenberg AG, JE IU, van Herwaarden YJ, Caraballo S, Pellissi M, Jung G, et al. Personalised surveillance for serrated polyposis syndrome: results from a prospective 5-year international cohort study. Gut. 2020;69(1):112–21. https://doi.org/10.1136/gutjnl-2019-318134.
9. Heafer N, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJ, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006;12(10):3209–15. https://doi.org/10.1158/1078-0432.CCR-06-0083.
10. Goggins M, Overbeek KA, Brand R, Syngal S, Del Chiaro M, Bartsch DK, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the pancreas screening (CAPS) consortium. Gut. 2020;69(1):17–17. https://doi.org/10.1136/gutjnl-2019-319352.
11. Latchford A, Cohen S, Auth M, Scallon M, Viala J, Daniels R, et al. Management of Peutz-Jeghers Syndrome in children and adolescents: a position paper from the ESPGHAN polyposis working group. J Pediatr Gastroenterol Nutr. 2019;68(3):442–52. https://doi.org/10.1097/MPG.0000000000002248.
12. Tseekakirikul P, Milewicz DM, Miller DT, Lacro RV, Regalado ES, Rosales AM, et al. Thoracic aortic disease in two patients with juvenile polyposis syndrome and SMAD4 mutations. Am J Med Genet A. 2013;161A(1):185–91. https://doi.org/10.1002/ajmg.a.35659.
13. Jelsig AM, Brugaard K, Hansen TP, Qvist N, Larsen M, Bojesen A, et al. Germline variants in Hamartomatous polyposis syndrome-associated genes from patients with one or few hamartomatous polyps. Scand J Gastroenterol. 2016;51(9):1118–25. https://doi.org/10.1080/00365521.2016.1174880.
14. Blatter R, Tschupp B, Arlet S, Bernstein I, Colas C, Evans DG, et al. Disease expression in juvenile polyposis syndrome: a retrospective survey on a cohort of 221 European patients and comparison with a literature-derived cohort of 473 SMAD4/BMPR1A pathogenic variant carriers. Genet Med. 2020;22(9):1524–32. https://doi.org/10.1038/s41436-020-0262-1.
15. Palles C, Cazier JB, Howarth KM, Domingo E, Jones AM, Broderick P, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet. 2013;45(2):136–44. https://doi.org/10.1038/ng.2003.
16. Valle L, Hernandez-Illan E, Bellido F, Alza G, Castillo E, Castillejo M, et al. New insights into POLE and POLD1 germline mutations in familial colorectal cancer and polyposis. Hum Mol Genet. 2014;23(13):3506–12. https://doi.org/10.1093/hmg/ddu58.
17. Bellido F, Pineda M, Alza G, Valdes-Mas R, Navarro M, Puente DA, et al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. Genet Med. 2016;18(4):325–32. https://doi.org/10.1038/jmg.2015.75.
18. Rosner G, Gluck N, Carmi S, Bercovich D, Fliss-Issakov N, Ben-Yehoyada M, et al. POLD1 and POLE gene mutations in Jewish cohorts of early-onset colorectal cancer and of multiple colorectal adenomas. Dis Colon Rectum. 2018;61(9):1073–9. https://doi.org/10.1097/DCR.0000000000001150.
19. Lindsay H, Scallon S, Reuther J, Voicu H, Rednam SP, Lin FY, et al. Germline POLE mutation in a child with hypermutated medulloblastoma and features of constitutional mismatch repair deficiency. Cold Spring Harbor Mol Case Stud. 2019;5(3):a004499. https://doi.org/10.1101/cms.a004499.
20. Wimmer K, Beiken A, Nustede R, Rapperger T, Lamotte B, Ure B, et al. A novel germline POLE mutation causes an early onset cancer prone syndrome mimicking constitutional mismatch repair deficiency. Familiar Cancer. 2017;16(1):67–71. https://doi.org/10.1007/s10689-016-9925-1.
21. Rohlin A, Rambech E, Krist T, Torgnen T, Eiergard F, Lundstam U, et al. Expanding the genotype-phenotype spectrum in hereditary colorectal cancer by gene panel testing. Familiar Cancer. 2017;16(2):195–203. https://doi.org/10.1007/s10689-016-9934-0.
22. Rivera B, Pereira J, Sanchez E, Villapun M, Sanchez-Tome E, Mercadillo F, et al. A novel AXIN2 germline variant associated with attenuated FAP without signs of olligondontia or ectodermal dysplasia. Eur J Hum Genet. 2014;22(3):423–6. https://doi.org/10.1038/ejhg.2013.146.

23. El Hachem N, Abadie C, Longy M, Colas C, Fert-Ferrer S, Leroux D, et al. Endoscopic phenotype of Monoallelic carriers of MUTYH gene mutations in the family of polyposis patients: a prospective study. Dis Colon Rectum. 2019;62(4):470–5. https://doi.org/10.1010/dcr.000000000001323.

24. Win AK, Dowty JG, Cleary SP, Kim H, Buchanan DD, Young JP, et al. Risk of colorectal cancer for carriers of mutations in MUTYH, with and without a family history of cancer. Gastroenterology. 2014;146(1):281–91.e1–5.

25. van Leeuwen ME, Roos VH, van Hooft JE, Dekker E, Joeris P, Kaminski MF, et al. Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy. 2019;51(9):877–95. https://doi.org/10.1055/a-0965-0605.

26. Weren RD, Lietsman MJ, Kets CM, de Knok MJ, Verwiel ET, Spruijt L, et al. Validation of recently proposed colorectal Cancer susceptibility gene NTHL1 germline mutations in the family of polyposis patients: a prospective study. Dis Colon Rectum. 2019;62(4):470–5. https://doi.org/10.1010/dcr.000000000001323.

27. Rivera B, Castellsague E, Baj I, van Kempen LC, Foulkes WD. Biallelic NTHL1 repair-deficiency proposed by the European consortium “care for CMMR-D”. Guidelines for surveillance of individuals with constitutional mismatch repair deficiency. Gastroenterology. 2014;50:987–997.e2–5.

28. Belhadj S, Quintana I, Mur P, Munoz-Torres PM, Alonso MH, Navarro M, et al. A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatosous polyposis and colorectal cancer. Nat Genet. 2015;47(6):688–71. https://doi.org/10.1038/ng.3287.

29. Rivera B, Casteil-Sauge E, Baj I, van Kempen LC, Foulkes WD. Biallelic NTHL1 mutations in a woman with multiple primary tumors. N Engl J Med. 2015;373(20):1985–6. https://doi.org/10.1056/NEJMct1506878.

30. Belhadj S, Quintana I, Mur P, Munoz-Torres PM, Alonso MH, Navarro M, et al. NTHL1 biallelic mutations seldom cause colorectal cancer, serrated polyposis or a multi-tumor phenotype, in absence of colorectal adenomas. Sci Rep. 2019;9(1):5020. https://doi.org/10.1038/s41598-019-45281-1.

31. Fossta F, Kontopoulos E, Apostolou P, Fragiaki M, Andoulakis N, Yannoukakos D, et al. Clinical phenotype associated with biallelic NTHL1 germline mutations. Clin Genet. 2018;94(6):588–9. https://doi.org/10.1111/cge.13444.

32. Groves A, Gleeson M, Spigelman AD. NTHL1-associate polyposis: first Australian case report. Familial Cancer. 2019;18(2):179–82. https://doi.org/10.1007/s10689-018-0107-0.

33. Broderick P, Dobbs SE, Chubb D, Kinnross D, Dunlop MG, Tomlinson I, et al. Validation of recently proposed colorectal Cancer susceptibility gene variants in an analysis of families and patients-a systematic review. Gastroenterology. 2017;152(1):75–7 e4. https://doi.org/10.1053/j.gastro.2016.09.041.

34. Altaraihi M, Gerdes AM, Wadt K. A new family with a homozygous nonsense variant in NTHL1 further delineated the clinical phenotype of NTHL1-associated polyposis. Hurn Genome Variation. 2019;6(1):46. https://doi.org/10.1038/s41439-019-0077-3.

35. McKenna DB, Van Den Akker J, Zhou AY, Ryan L, Leon A, O’Connor R, et al. Identification of a novel GREM1 duplication in a patient with multiple colon polypos. Familial Cancer. 2019;18(1):63–6. https://doi.org/10.1007/s10689-018-0009-6.

36. Lieberman S, Walsh T, Schechter M, Adar T, Goldin E, Beerli R, et al. Features of patients with hereditary mixed polyposis syndrome caused by duplication of GREM1 and implications for screening and surveillance. Gastroenterology. 2017;152(2):176–80.e1. https://doi.org/10.1053/j.gastro.2017.02.014.

37. Tomlinson I, Rahman N, Frayling T, Mangion J, Barfoot R, Hamoudi R, et al. Inherited susceptibility to colorectal adenomas and carcinomas: evidence for a new predisposition gene on 15q14-q22. Gastroenterology. 1999;116(4):769–769. https://doi.org/10.1016/S0016-5085(99)70061-2.

38. Bleijenberg AG, Je JJ, van Hervenaud YJ, Carbalal S, Pellise M, Jung G, et al. Personalised surveillance for serrated polyposis syndrome: results from a prospective 5-year international cohort study. Gut. 2020;69(1):112–21. https://doi.org/10.1136/gutjnl-2018-318134.

39. Jeg I, Bevan R, Senore C, Kaminski MF, Kuipers EJ, Mroz A, et al. Detection rate of serrated poly and serrated polyposis syndrome in colorectal cancer screening cohorts: a European overview. Gut. 2017;66(7):1225–32. https://doi.org/10.1136/gutjnl-2015-310784.

40. Yan HHH, Lai JCW, Ho SL, Leung WK, Law WL, Lee JFY, et al. RNF43 germline and somatic mutation in serrated neoplasia pathway and its association with BRAF mutation. Gut. 2017;66(6):1645–56. https://doi.org/10.1136/gutjnl-2016-318149.

41. Buchanan DD, Clandenberg M, Zhuker L, Stewart JR, Joseland S, Woodall S, et al. Lack of evidence for germline RNF43 mutations in patients with serrated polyposis syndrome from a large multinational study. Gut. 2017;66(6):1170–2. https://doi.org/10.1136/gutjnl-2016-312773.

42. Win AK, Walters RI, Buchanan DD, Jenkins MA, Sweet K, Frankel WL, et al. Cancer risks for relatives of patients with serrated polyposis. Am J Gastroenterol. 2012;107(5):770–8. https://doi.org/10.1038/ajg.2012.52.

43. Tieu AK, Edelstein D, Axelkund J, Romans KE, Broens LA, Wiley E, et al. Clinical characteristics of multiple colorectal adenoma patients without germline APC or MYH mutations. J Clin Gastroenterol. 2016;50(7):584–8. https://doi.org/10.1097/MCG.0000000000000416.

44. Kallenberg FGJ, Latchford A, Lips NC, Aalfs CM, Bastiaansen BAJ, Clark SK, et al. Duodenal adenomas in patients with multiple colorectal adenomas without germline APC or MUTYH mutations. Dis Colon Rectum. 2016;61(1):58–66. https://doi.org/10.1002/dcr.25968.

45. Girola M, Staqlj S, Prettiultini S, Mondini P, Rodice MT, Sala P, et al. Screening for mutations of the APC gene in 66 Italian familial adenomatous polyposis patients: evidence for phenotypic differences in cases with and without identified mutation. Hum Mutat. 1999;13(2):116–23. https://doi.org/10.1002/(SICI)1098-1004(1999132<116::AID-HUMU3>3.0.CO;2-2.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.