Preprints.org

Review

Not peer-reviewed version

Guidelines on Management of Hereditary Polyposis Syndromes in Pediatric Patients: Agreement, Disagreement and Where it Matters

Taina Hudson * , Claudia Phen , Isabel Rojas , Shlomi Cohen , Warren Hyer , Thomas Attard

Posted Date: 16 February 2024

doi: 10.20944/preprints202402.0861.v1

Keywords: hereditary; pediatric polyp; polyposis; cancer; syndromes

Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 February 2024 doi:10.20944/preprints202402.0861.v1

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Review

Guidelines on Management of Hereditary Polyposis Syndromes in Pediatric Patients: Agreement, Disagreement and Where it Matters

Taina Hudson DO [1,*], Claudia Phen MD [2], Isabel Rojas MD [2], Shlomi Cohen MD [3], Warren Hyer MD [4] and Thomas Attard MD [1]

[1] Department of Gastroenterology, Children's Mercy Hospital and Clinics, Kansas City, MO, USA
[2] Department of Gastroenterology, University of Texas Southwestern Medical Center, Dallas, TX, USA
[3] Department of Gastroenterology, Sackler Faculty of Medicine, Tel Aviv University, Israel
[4] Department of Gastroenterology, Chelsea and Westminster Hospital, London, UK
* Correspondence: Thudson4@kumc.edu

Abstract: Hereditary polyposis syndromes are rare but potentially devastating conditions which require multidisciplinary care from an early age. Societal guidelines serve as the framework for disease diagnosis, surveillance and treatment. Guidelines are based on expert opinion and ideally are evidence-based; however, recommendations may vary among different societies and can result in discordant care. This paper aims to summarize key differences in management based on societal guidelines for pediatric polyposis syndromes and identify some of the factors which may contribute to divergence in care.

Keywords: hereditary; pediatric polyp; polyposis; cancer; syndromes

1. Introduction

Polyposis syndromes are defined by clinical characteristics including polyp type and burden and presence of extra-intestinal manifestations; these syndromes confer an increased lifelong risk of malignancy. A genetic mutation may confirm the clinical diagnosis. Although the most common polyposis syndromes are inherited in an autosomal dominant pattern, incomplete penetrance and de novo mutations are common in up to 40–50% of patients, making absence of a family history relatively common.

Societal guidelines are the mainstay for the diagnosis and management of a variety of disorders. However, there may be different recommendations among societies in part due to the background of its authors. Limited experience with rare diseases often leads to heavy reliance on guidelines for clinical management; hence, a high level of agreement amongst guidelines is ideal. Patients with chronic, rare diseases often transition between different providers at various institutions which can result in further discontinuity and heterogeneity in care.

We conducted a literature review of management guidelines for the three most common pediatric polyposis syndromes: Juvenile Polyposis Syndrome (JPS), Peutz-Jeghers syndrome (PJS) and Familial Adenomatous Polyposis syndrome (FAP). The aim of this review is to (1) identify key areas of discordance and concordance among existing societal guidelines for management and surveillance (2) investigate the evidence behind differing recommendations, if available, and (3) identify knowledge gaps to inform further research in the care of pediatric patients with hereditary polyposis syndromes.

2. Methods

A comprehensive literature search limited to the English language was performed on electronic databases (Medline, CINAHL, EMBASE) in March 2023. The following MeSH subject headings and search terms were used: "hereditary polyposis syndrome", "juvenile polyposis syndrome," Peutz-Jeghers syndrome," and "familial adenomatous polyposis syndrome" combined with ""practice

© 2024 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 February 2024 doi:10.20944/preprints202402.0861.v1

guideline," "position paper," and "consensus statement." The search was limited to articles published between 2010 and 2023. Duplicate articles were removed. Full text articles were then reviewed for inclusion and exclusion criteria. The inclusion criteria were as follows: (1) medical guideline or position paper, (2) published by a major international society, (3) publication date between 2010 and March 2023, (4) included recommendations on all three syndromes, and (5) produced in the English language. The exclusion criteria were as follows: (1) articles not in English, (2) publications that did not include recommendations on all three syndromes, and (3) surgical guidelines. From this, eligible articles were manually identified that included management of pediatric age patients. Cited literature within the guidelines was reviewed in face-to-face discussion (Figure 1).

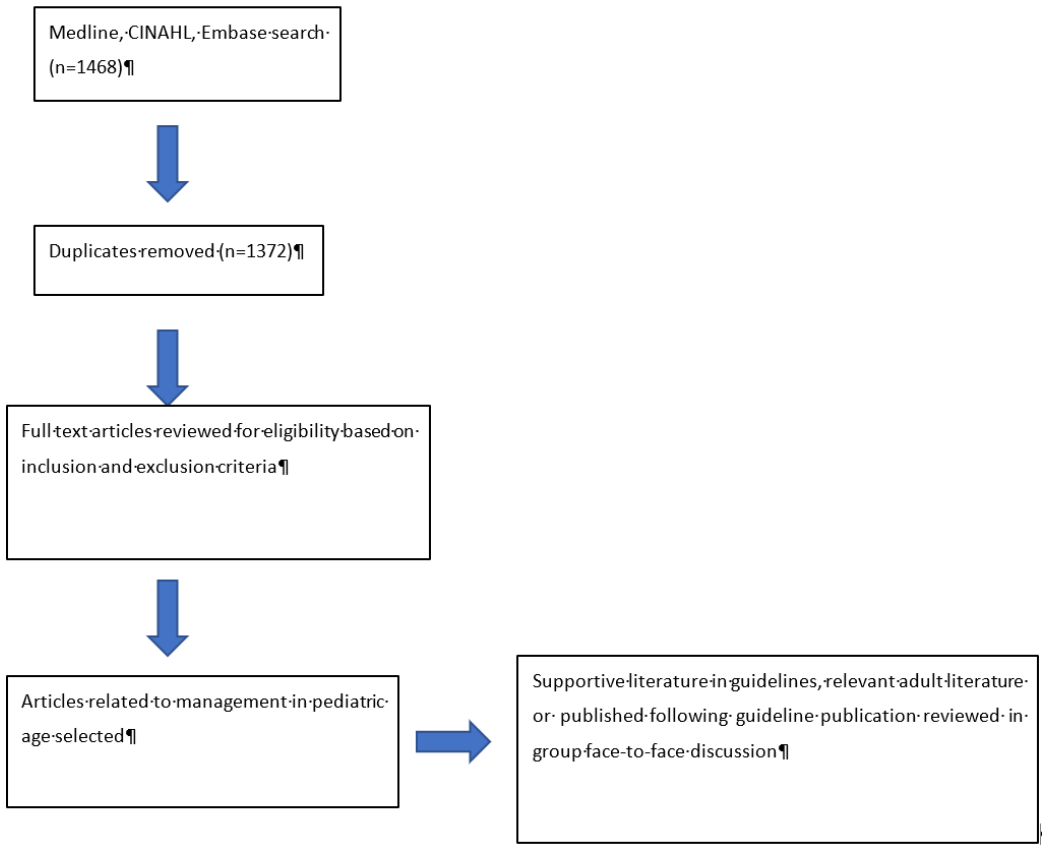

Figure 1. Study methods.

Societal guidelines were categorized by major professional society. Extracted data from each guideline was divided into the following specific management domains: genetic testing, gastrointestinal/endoscopic screening and surveillance recommendations, and extraintestinal screening and surveillance recommendations. Recommendations were individually tabulated, and results were collated to identify areas of discordance (Table 1) which were then reviewed in detail by the authors. Full text articles of guidelines that appeared to be relevant were independently reviewed and discussed by authors to assess for inclusion. Points of discrepancy were discussed by the authors as a group as well as reasoning for possible discrepancies and future directions. We summarize the specific areas of discordance for each of the three polyposis syndromes in Table 1 followed by rationale for key recommendations and supporting literature.

Table 1. Areas of discordance among guidelines.

Polyposis Syndrome	Management Domain
JPS	Initial timing of upper GI tract screening
PJS	Timing of genetic screening

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 February 2024 doi:10.20944/preprints202402.0861.v1

FAP	Frequency of small bowel surveillance
	Ideal size of polyp removal for elective polypectomy
	Number of adenomas to trigger genetic screening
	Recommendations on routine screening for hepatoblastoma
	Ideal method for initial lower endoscopic evaluation

3. Results

We reviewed clinical practice guidelines for major gastrointestinal, genetics, and oncology societies. After inclusion and exclusion criteria were applied, the following societal guidelines were included in our final analysis:

- American Association for Cancer Research (AACR)[1]
- American College of Gastroenterology (ACG)[2]
- European Society of Gastrointestinal Endoscopy (ESGE)[3]
- European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[4–6]
- National Comprehensive Cancer Network (NCCN)[7]

It is worth noting that agreement regarding most aspects of the reviewed guidelines exists and our focus was to identify and analyze areas of discordance. The key discrepancies noted are in the realms of genetic screening and intestinal and extraintestinal screening.

We observed that release of guideline publications was infrequent and often with little to no pediatric gastroenterology representation across all guidelines aside from ESPGHAN (Table 3). The authorship among remaining guidelines was comprised of adult oncologists, colorectal surgeons, and genetics counselors. Furthermore, recommendations were based heavily on adult studies with limited pediatric data.

3.1. Juvenile Polyposis Syndrome

3.1.1. Timing of initial upper endoscopic evaluation

Table 2. Recommendations on timing of initial upper endoscopic evaluation.

Society	AACR	ACG	ESGE	ESPGHAN	NCCN
Recommendations	EGD at age 15, then every 1-2 years	EGD at 12 years; annually if polyps, every 2-3 years if no polyp identified	EGD at 18 years in individuals with *SMAD4* mutation, 25 years with *BMPR1A* mutation	Not required in childhood or teenage years, unless unexplained anemia or upper GI symptoms	EGD at 15 years, annually if polyps, every 2-3 years if no polyps identified

3.1.2. Evidence behind differing recommendations:

JPS is caused by a germline mutation in *SMAD4* or *BMPR1A* in 40-60% of patients, with 25% presenting with a de novo mutation and the remainder with negative genetic testing.[8] JPS has variable penetrance and heterogeneity in disease presentation with a need for further genotype-phenotype correlations.

Patients with a pathogenic *SMAD4* mutation are also more likely to have significant gastric polyposis and an increased risk of gastric cancer, anemia and hereditary hemorrhagic telangiectasia (HHT) in contrast to *BMPR1A* carriers.[6,8,9] Despite the known increased risk of gastric cancer with

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 February 2024 doi:10.20944/preprints202402.0861.v1

SMAD4 mutations, there are variable recommendations regarding initiation of upper endoscopic surveillance (range 12 to 25 years of age, Table 2) with only ESGE guidelines delineating recommendations based on this known genotype-phenotype correlation.

	Knowledge Gaps
Juvenile Polyposis Syndrome	• Further genotype-phenotype correlations are needed for the two separate entities of juvenile polyposis (positive and negative disease-causing variant), which may require different surveillance and management strategies. • Ideal timing and frequency of upper endoscopic surveillance in patients with JPS due to *SMAD4* mutation

3.2. *Peutz-Jeghers Syndrome*

3.2.1. Genetic Screening of at-risk individuals

Table 3. Recommendations on genetic screening for Peutz Jeghers.

Society	AACR	ACG	ESGE	ESPGHAN	NCCN
Recommendations	No recommendations	Individuals with perioral or buccal pigmentation and/or 2 or more histologically characteristic gastrointestinal polyps should undergo genetic screening	No recommendations	Predictive genetic testing at 3 years in asymptomatic at-risk child, earlier if symptomatic	No recommendations

Evidence behind differing recommendations:

Early presentation of polyp related complications in PJS is common with median age of first episode of intussusception between 10-15 years of age and 15-30% of patients requiring surgery before the age of 10 years.[5,10] The rationale for timing of genetic testing is to identify individuals at risk, however there is significant variation in age at first screening (Table 3). Of all guidelines, only ACG and ESPGHAN make recommendations regarding genetic screening. Given intussusception and obstruction can be the initial presentation of PJS as early as 14-16 months of age, a recommendation to test at age 3 may still fail to identify this subgroup of at-risk patients .[11,12]

Lastly, the practical significance of ACG's divergence in recommendations for screening individuals with perioral or buccal pigmentation and/or characteristic gastrointestinal polyps is unclear as [12,13] even with a high index of suspicion, mucosal freckling is absent in more than 10% of patients with PJS,[1] and may be harder to detect in dark-skinned individuals leading to delay in diagnosis.

3.2.2. Small Intestinal Surveillance

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 February 2024 doi:10.20944/preprints202402.0861.v1

Table 4. Recommendations on small intestinal surveillance.

Society	AACR	ACG	ESGE	ESPGHAN	NCCN
Age for gastroduodenal surveillance	EGD at 8, 18 years	EGD at 8, 18 years	EGD at 8, 18 years	EGD at 8 years	EGD in late teen years
Frequency gastroduodenal surveillance	Every 3 years if polyps present. If no polyps, repeat at 18 years	Every 3 years if polyps present. If no polyps present, repeat at 18 and then every 3 years or earlier, if symptoms occur	Every 1–3 years if polyps present. If no polyps present, repeat at 18 and then every 1-3 years	Every 3 years	Every 2-3 years
Age for small bowel surveillance	VCE at 8 years	VCE at 8,18 years	MRI or VCE at 8 years	VCE at 8 years	CTE, MRE or VCE at 8-10 years
Frequency small intestinal surveillance	Every 2-3 years	Every 3 years if polyps present. If no polyps present, repeat at 18 and then every 3 years or earlier, if symptoms occur	Every 1-3 years based on phenotype	Every 3 years	Follow up based on findings. If no polyps present, repeat at 18 years and then every 2-3 years

Evidence behind differing recommendations:

The role of small bowel surveillance in children with PJS, achieved with a combination of upper endoscopic evaluation and video capsule endoscopy (VCE), is to identify and remove polyps at risk of intussusception and obstruction. For clarity, we divide small bowel surveillance into the categories of gastroduodenal and small intestinal surveillance.

There are several points of variation in small bowel surveillance recommendations from age of screening initiation to frequency (Table 4). Some guidelines recommend less frequent surveillance in the absence of polyps. Discrepancy in recommendations is likely due to lack of robust literature on the risk of polyp development to progression to obstruction in individuals with PJS who have negative endoscopic screening at 8 years of age.

Given the ambiguity in polyp progression and the relatively high risk of obstruction by age 18, a more conservative approach with more frequent small bowel surveillance utilizing the same modality may have greater potential to reduce polyp-related morbidity.[5,10,13,14] Further studies are needed regarding development of small intestinal polyps following a negative initial EGD.

3.2.3. Recommended size of polyp for removal during elective polypectomy

Table 5. Recommendations on ideal size for elective polypectomy.

Society	AACR	ACG	ESGE	ESPGHAN	NCCN
Small bowel polyps	No recommendations	No recommendations	>15-20mm (or smaller if symptomatic)	>15-20mm (or smaller if symptomatic)	>10mm or smaller if symptomatic
Gastroduodenal and colonic polyps	No recommendations	>5-10mm	No recommendations	No recommendations	>3mm

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 February 2024 doi:10.20944/preprints202402.0861.v1

Evidence behind differing recommendations:

As mentioned previously, the role of polypectomy in PJS patients is to decrease polyp-related morbidity and mortality associated with intussusception and obstruction. As noted in Table 5, divergence in recommendations exists in two realms: size and location of the polyp at time of elective polypectomy with only ESGE and ESPGHAN making recommendations for size of small intestinal polyps to remove. The discordance in guidelines regarding timing of elective polypectomy is understandable given the multiple, poorly defined factors that could influence polyp-related morbidity in a pediatric patient.

Critical considerations regarding timing of polypectomy include growth rate of polyps, risk of obstruction, and risk from polypectomy. Two factors to consider related to the polyp itself include size and interval growth rate. Although there are no pediatric studies to date investigating the growth rate of PJS polyps, one adult study noted that the number of small bowel polyps >10mm, colorectal polyps and gastric polyps over 5mm in size as well as negative family history were independent predictors of growth rate of small bowel polyps.[15] In a separate study evaluating attributes of 37 intussusception-causing polyps in a small cohort of patients, a median size of 35 mm was reported, with a range of 15 – 60mm. Of these, three lesions were <20mm in diameter.[13]

Given the little that is known about interval polyp growth rate, a separate practice, termed the "clean sweep strategy," has evolved, which involves bulk removal of small, asymptomatic polyps. In support of this strategy, several adult and pediatric studies suggest that small intestinal surveillance with polypectomy of symptomatic and asymptomatic small intestinal polyps <1 cm, is feasible and decreases likelihood of intussusception and surgery, although it should be noted that screening intervals were variable.[16–19] However, these lower thresholds for polypectomy make it difficult to discern ideal size for polyp removal, particularly for asymptomatic patients.

Lastly, although serious endoscopic complications are uncommon, it is unclear if children are at higher risk of procedural complications than adults due to their smaller body habitus. One study of 63 pediatric patients who underwent a total of 766 procedures noted 2 perforations with excision of larger lesions (6 cm colonic polyp and 2 cm duodenal polyp),[14] although this may have been subject to endoscopist comfort and technique with polypectomy.

Polyp size and number clearly relate to risk of intussusception; however, non-polyp factors including mutation status, patient age and size, localization of the polyps and the related risks of polypectomy should be considered. Given the ambiguity in polyp progression coupled with high risk of obstruction, a more conservative approach with more frequent small bowel surveillance regardless of initial endoscopic findings should be considered. This in fact underscores the need for pediatric gastroenterologist involvement in the development of guidelines.

	Knowledge Gaps
Peutz Jeghers Syndome	• Further studies are needed to determine the ideal size of small bowel polyp for removal to prevent polyp-related complications in the pediatric population, with consideration of polyp and non-polyp related factors. • More information is needed on interval progression of small bowel polyps, particularly in those with negative screening at 8 years of age

3.3. Familial adenomatous polyposis syndrome

3.3.1. Recommendations for genetic testing in individuals not at risk for FAP

Table 6. Recommendations on number of adenomas to trigger genetic screening.

Society	**AACR**	**ACG**	**ESGE**	**ESPGHAN**	**NCCN**
Recommendations	No recommendations	Personal history of >10 cumulative colorectal	No recommendations	Identification of 1 adenoma	Personal history of ≥20 cumulative adenomas or

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 February 2024 doi:10.20944/preprints202402.0861.v1

	adenomas, family history of an adenomatous polyposis syndrome or a personal history of adenomas with FAP-type extracolonic manifestation	multifocal/bilateral CHRPE can consider testing if a personal history of any of the following: - between 10-19 cumulative adenomas[a] - desmoid tumor - hepatoblastoma - cribiform-morular variant of papillary thyroid cancer - unilateral CHRPE or meets critiera for serrated polyposis syndrome with at least some adenomas

[a] Age of onset, family history, personal history of colorectal cancer, and/or presence of other features may influence whether genetic testing is offered in these situations.

Evidence behind differing recommendations:

There is some consensus for predictive genetic testing of at-risk individuals with recommendations ranging from 10-14 years of age.[4,7,20] However, there is less clear consensus regarding threshold for genetic testing of individuals who are not deemed at risk for FAP (ie, those without a prior family history or presence of extraintestinal manifestations) as demonstrated in Table 6. Divergence in guideline recommendations for FAP is largely centered around number of adenomas that should prompt genetic testing of standard risk individuals. Recommendations for genetic testing range from identification of 1 lifetime adenoma (ESPGHAN recommendations) to 20 cumulative adenomas (NCCN recommendations). NCCN guidelines do note that consideration for genetic testing can occur in standard risk individuals with 10-19 cumulative adenomas depending on age of onset and personal history but without clear delineation of appropriate number of adenomas as they relate to patient age.

As increasing age is a known risk factor for the development of colonic adenomas, this divergence in recommendations may be a function of explicitly stated age parameters (ie, ESPGHAN criteria assuming pediatric age range while assuming non pediatric age range for ACG and NCCN guidelines). However, our literature review did not yield any evidence relating number of adenomas by age category to likelihood of FAP. As such, without further evidence, a more conservative approach with genetic testing upon identification of 1 adenoma in the pediatric patient should be considered.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 February 2024 doi:10.20944/preprints202402.0861.v1

3.3.2. Ideal method for initial lower endoscopic evaluation

Table 7. Recommendations on initial lower endoscopic evaluation.

Society	AACR	ACG	ESGE	ESPGHAN	NCCN
Recommendations	Flexible sigmoidoscopy or colonoscopy starting at 10-15 years and annually until surgery	Flexible sigmoidoscopy [a] or colonoscopy at puberty and then annually [4,7,20]	Colonoscopy at 12-14 years and then every 1-2 years	Colonoscopy at 12-14 years and then every 1-3 years	Flexible sigmoidoscopy or colonoscopy (preferred) at 10-15 years and then annually

[a] Flexible sigmoidoscopy is reasonable until an adenomatous polyp is found, after which full colonoscopy should be performed.

Evidence behind differing recommendations:

All guidelines apart from ESGE and ESPGHAN make recommendations that flexible sigmoidoscopy may be an adequate initial screening method for FAP given predominant rectal involvement in these patients. NCCN guidelines state that either method is adequate but colonoscopic evaluation is preferred. One important point of divergence in recommendations is ACG's recommendation to transition from sigmoidoscopy to colonoscopy for subsequent evaluations if adenomas are identified on initial evaluation.[2]

Although there is a tendency towards development of polyps in the distal colon, adenomatous polyps can also be generally distributed evenly throughout the colon.[2] Given that proximal colonic polyps have been reported in children without rectosigmoid involvement, the weight of evidence favors colonoscopy as the preferred method for initial lower endoscopic assessment.

3.3.3. Hepatoblastoma Screening in patients with known FAP

Table 8. Recommendations on routine hepatoblastoma screening.

Society	AACR	ACG	ESGE	ESPGHAN	NCCN
Recommendations	Abdominal US and serum AFP starting early infancy and every 4-6 months until 7 years	Abdominal US and serum AFP biannually until 7 years	No recommendations	Routine screening not recommended	High level evidence to support routine screening is lacking but may consider liver palpation, abdominal US and serum AFP every 3-6 months until 5 years

Evidence behind differing recommendations:

The association between hepatoblastoma and FAP has been well documented, with FAP patients having a 750 to 7500 times higher risk of developing hepatoblastoma than the general population.[21] Additionally, in a study of patients with presumably sporadic hepatoblastomas based on a negative

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 February 2024 doi:10.20944/preprints202402.0861.v1

family history of FAP and/or parents with negative colonoscopies, germline APC mutations were detected in up to 10% of patients.[21]

However, there is still insufficient evidence to support hepatoblastoma screening in individuals with known FAP or advise genetic screening for FAP in those with sporadic hepatoblastoma.[22] This aligns with the current ESPGHAN recommendations, which emphasize counseling over screening given the increased relative risk and exceptionally low absolute risk of hepatoblastoma in FAP patients.[44] Despite this, AACR and ACG guidelines recommend routine biannual screening for hepatoblastoma in patients with FAP with no specific recommendations from ESGE likely due to endoscopic focus of their guidelines. Interestingly, NCCN's recommendations to consider routine hepatoblastoma screening conflict with their recommendations to complete genetic testing by 10-12 years when colon screening is initiated.[7]

As screening for hepatoblastoma would imply need for genetic testing at an earlier age and exposure to repeat procedures, imaging, and lab draws without clear evidence of benefit, further studies evaluating the effect of early genetic testing on hepatoblastoma morbidity and mortality in patients with FAP is needed.

	Knowledge Gaps
Familial Adenomatous Polyposis Syndrome	• The correlation between number of adenomas in children required for diagnosis of FAP needs to be further evaluated • Further studies to support the need for full colonoscopy in children as initial screening method are needed • More studies evaluating the effect of early genetic testing on hepatoblastoma morbidity and mortality in patients with FAP

4. Conclusions

Discrepancies in societal guidelines may have greater clinical impact for relatively uncommon conditions such as pediatric polyposis syndromes. The most significant differences in societal recommendations for polyposis management have moderate or potentially high clinical impact. Our observations underscore the need to harmonize recommendations across subspecialist societies to optimize the attention and care for patients with a life-long condition that carries heavy burden of disease.

An important observation in our review is the common thread of poor-quality evidence in formulating the published guidelines and further study and investigation to answer the questions posed. This paper emphasizes the need for collaborative efforts and prospective, multicenter and registry-based studies to refine the quality of guidelines. The guidelines with the weakest level of evidence should serve as a premise for future studies that should be supported and prioritized for publication in societal journals.

Lastly, with the exception of ESPGHAN guidelines, the lack of pediatric gastroenterology input in societal guidelines for diseases of pediatric onset is especially concerning. The published guidelines from preeminent societies include a vast wealth of expertise from different specialist groups intimately familiar with the disease process who may or may not have had exposure to pediatric age-range patients. We feel professional societies must engage with rare disease-specific consortia and support efforts to create management guidelines for these patient groups.

In summary, pediatric polyposis syndromes are rare but potentially devastating life-long conditions that carry the burden of gastrointestinal complications and cancer predisposition within and outside the GI tract. A greater effort is needed to harmonize guideline recommendations across subspecialties, with consideration for pediatric gastroenterology input in future societal guidelines. This will be pivotal in minimizing the fragmentation in care as many will inevitably transition through different providers of diverse backgrounds and subspecialties. Further study and investigation is needed to answer the questions posed, and prospective-registry based collaboration is vital to fill in the gaps of care for our pediatric patients with polyposis syndromes.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 February 2024 doi:10.20944/preprints202402.0861.v1

Author Contributions: TH performed the literature search and synthesized and collated the data. TH, CP, IR, SC, WH and TA reviewed the collated data and supporting literature. TH, CP, IR wrote the manuscript draft which was critically reviewed by all authors. TH submitted the final manuscript.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

References

1. Achatz, M. I. *et al.* Cancer Screening Recommendations and Clinical Management of Inherited Gastrointestinal Cancer Syndromes in Childhood. *Clinical Cancer Research* **23**, e107–e114 (2017).
2. Syngal, S. *et al.* ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes. *American Journal of Gastroenterology* **2014**, 223–263 (2015).
3. Van Leerdam, M. E. *et al.* Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* **51**, 877–895 (2019).
4. Hyer, W. *et al.* Management of Familial Adenomatous Polyposis in Children and Adolescents: Position Paper from the ESPGHAN Polyposis Working Group. *J Pediatr Gastroenterol Nutr* **68**, 428–441 (2018).
5. Latchford, A. *et al.* Management of peutz-jeghers syndrome in children and adolescents: A position paper from the espghan polyposis working group. *J Pediatr Gastroenterol Nutr* **68**, 442–452 (2019).
6. Cohen, S. *et al.* Management of juvenile polyposis syndrome in children and adolescents: A position paper from the espghan polyposis working group. *J Pediatr Gastroenterol Nutr* **68**, 453–462 (2019).
7. Weiss, J. M. *et al.* NCCN Guidelines® Insights: Genetic/Familial High-Risk Assessment: Colorectal, Version 1.2021. *J Natl Compr Canc Netw* **19**, 1122–1132 (2021).
8. Mougenot, J, Olschwang, S, Peuchmaur, M. Intestinal Tumors. in *Walker's Pediatric Gastrointestinal Disease* 931–956 (2018).
9. Aytac E, Sulu B, Heald B, et al. Genotype-defined cancer risk in juvenile polyposis. *Br J Surg* **102**, 114–118 (2015).
10. Hinds, R., Philp, C., Hyer, W. & Fell, J. M. Complications of Childhood Peutz-Jeghers Syndrome: Implications for Pediatric Screening. *J Pediatr Gastroenterol Nutr* **39**, 219–220 (2004).
11. Zacharias, S. A. *et al.* Small Bowel Intussusception in a 16-Month-Old Child With Peutz-Jeghers Syndrome. *Clin Pediatr (Phila)* **57**, 745–748 (2018).
12. Boseto, F., Shi, E., Mitchell, J., Preddy, J. & Adams, S. Gastroduodenal intussusception due to Peutz-Jeghers syndrome in infancy. *Pediatr Surg Int* **18**, 178–180 (2002).
13. Van Lier, M. G. F., Mathus-Vliegen, E. M. H., Wagner, A., Van Leerdam, M. E. & Kuipers, E. J. High cumulative risk of intussusception in patients with peutz-jeghers syndrome: Time to update surveillance guidelines. *American Journal of Gastroenterology* **106**, 940–945 (2011).
14. Latchford, A. R., Neale, K., Phillips, R. K. S. & Clark, S. K. Peutz-Jeghers syndrome: Intriguing suggestion of gastrointestinal cancer prevention from surveillance. *Dis Colon Rectum* **54**, 1547–1551 (2011).
15. Ohmiya, N. *et al.* Management of small-bowel polyps in Peutz-Jeghers syndrome by using enteroclysis, double-balloon enteroscopy, and videocapsule endoscopy. *Gastrointest Endosc* **72**, 1209–1216 (2010).
16. Edwards, DP, Khosraviani, K, Stafferton, R. Long-term results of polyp clearance by intraoperative enteroscopy in the Peutz-Jeghers syndrome. *Dis Colon Rectum* **46**, 48–50 (2003).
17. Oncel, M., Remzi, F. H., Church, J. M., Connor, J. T. & Fazio, V. W. Benefits of 'clean sweep' in Peutz-Jeghers patients. *Colorectal Disease* **6**, 332–335 (2004).
18. Blanco-Velasco, G. *et al.* Safety and efficacy of small bowel polypectomy using a balloon-assisted enteroscope in pediatric patients with Peutz-Jeghers syndrome. *Revista de gastroenterologia de Mexico (English)* **83**, 234–237 (2018).
19. Li, B. R. *et al.* Primary experience of small bowel polypectomy with balloon-assisted enteroscopy in young pediatric Peutz–Jeghers syndrome patients. *Eur J Pediatr* **179**, 611–617 (2020).
20. Syngal, S. *et al.* ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *American Journal of Gastroenterology* **110**, 223–262 (2015).
21. Aretz S, Koch A, Uhlhaas S, et al. Should children at risk for familial adenomatous polyposis be screened for hepatoblastoma and children with apparently sporadic hepatoblastoma be screened fro APC germline mutations? *Pediatr Blood Cancer* **47**, 811–818 (2006).
22. Harvey JJ, Clark SK, Hyer W, et al. Germline APC mutations are not commonly seen in children wtih sporadic hepatoblastoma. *J Pediatr Gastroenterol Nutr.* **47**, 675–7 (2008).

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.