

Practice Guideline

Clinical Guidelines for Diagnosis and Management of Juvenile Polyposis Syndrome in Children and Adults—Secondary Publication

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Abstract

Juvenile polyposis syndrome (JPS) is a rare disease characterized by multiple hamartomatous polyps within the gastrointestinal tract. *SMAD4* or *BMPRIA* is known as a causative gene of JPS. Approximately 75% of newly diagnosed cases have an autosomal-dominantly inherited condition, whereas 25% are sporadic without previous history of polyposis in the family pedigree. Some patients with JPS develop gastrointestinal lesions in childhood and require continuous medical care until adulthood. JPS is classified into three categories according to phenotypic features of polyp distributions, including generalized juvenile polyposis, juvenile polyposis coli, and juvenile polyposis of the stomach. Juvenile polyposis of the stomach is caused by germline pathogenic variants of *SMAD4* with a high risk leading to gastric cancer. Pathogenic variants of *SMAD4* are also associated with hereditary hemorrhagic telangiectasia-JPS complex, inducing regular cardiovascular survey. Despite growing concerns regarding the managing JPS in Japan, there are no practical guidelines. To address this situation, the guideline committee was organized by the Research Group on Rare and Intractable Diseases granted by the Ministry of Health, Labor and Welfare involving specialists from multiple academic societies. The present clinical guidelines explain the principles in the diagnosis and management of JPS with three clinical questions and corresponding recommendations based on a careful review of the evidence and involve incorporating the concept of the Grading of Recommendations, Assessment, Development, and Evaluation system. Herein, we present the clinical practice guidelines of JPS to promote seamless implementation of accurate diagnosis and appropriate management of pediatric, adolescent, and adult patients with JPS.

Keywords

juvenile polyposis syndrome, child, adult, *SMAD4*, *BMPRIA*

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Introduction

Juvenile polyposis syndrome (JPS) is a rare disease characterized by the presence of hamartomatous polyposis throughout the gastrointestinal tract. Some patients with JPS develop gastrointestinal lesions in childhood, require continuous medical care until adulthood, and sometimes have serious complications that significantly reduce their quality of life. The germline variants of the causative genes of JPS may be identified by cancer gene panel tests to identify effective drugs. Novel diagnostic and therapeutic endoscopic procedures, such as small video capsule endoscopy (VCE) and balloon-assisted enteroscopy, have been developed in recent years. However, because of the diversity of the clinical features and low incidence of this disease, there have been no Japanese guidelines for diagnosis, treatment, and surveillance. Medical management of patients and their relatives with this disease may be required as a result of cancer genome medicine or as a part of the characteristics of the disease, and it is difficult to apply overseas guidelines directly to Japanese patients in terms of cost, clinical applicability, and the medical health insurance system. Therefore, there is a need to develop seamless clinical practice guidelines for children and adults in Japan.

In 2017, as a project of “Research group to improve the medical standard and equalize the treatment of benign multi-

ple tumors of the gastrointestinal tract” (representer, Ishikawa H.), which was the research on rare and intractable diseases granted by the Ministry of Health, Labor and Welfare, a working group was established to develop “Clinical Guidelines for Diagnosis and Management of Juvenile Polyposis Syndrome in Children and Adults.” The committee members included specialists in internal medicine, gastroenterology, surgery, pediatric gastroenterology, pediatric surgery, pathology, genetics, genetic counseling, and nursing. From 2019, the Japanese Society for Hereditary Tumors, the Gastrointestinal Polyposis Study Group of the Japanese Gastroenterological Association, and the Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition continued to work on the preparation of the guidelines with the cooperation of other organizations. In 2020, the “Research group for establishing a seamless medical care system from children to adults in the gastrointestinal hamartoma predisposition diseases” (representer, Nakayama Y.), granted by the Ministry of Health, Labor and Welfare as research on rare and intractable diseases, published the clinical guidelines in the Journal of Hereditary Tumors in Japanese[1]. Herein, we present an English version of the clinical practice guidelines for JPS with permission from the Japanese Society of Hereditary Tumors and the Editor-in-Chief of the Journal of the Anus, Rectum and Colon.

Table 1. Quality of Evidence.

Quality of evidence at the start of the evaluation	Systematic review, meta-analysis, randomized controlled trial = “high” Cross-sectional study, cohort study, case-control study = “low” Case series, case report = “very low”
When to lower the grade*	There are very serious limitations to the quality of the research. There are significant inconsistencies in the results. The directness of the evidence is somewhat or considerably uncertain. Data are inaccurate or inconsistent. Publication bias is highly likely.
When to raise the grade*	The degree of effect is large. There is a dose-response gradient. Possible confounding factors weaken the true effect.
Defining the quality of evidence about research on outcomes in general	
A: “High”	It is certain that the estimate of the effect is virtually identical to the actual effect.
B: “Moderate”	Confidence in the estimate of the effect is moderate.
C: “Low”	Confidence in the estimate of the effect is limited.
D: “Very low”	The estimate of the effect is quite uncertain.

*If the degree of effect is large or if it is considered difficult to conduct a randomized controlled trial because PJS is a rare disease, the grade can be increased.

Table 2. Strength of Recommendations.

1. Strong recommendation	Implementation is recommended “do it” Implementation is recommended “do not do it”
2. Weak recommendation	Implementation is proposed “probably do it” Implementation is proposed “probably do not do it”

1. Developing the Guidelines

When the guidelines were developed, the concept of evidence-based medicine (EBM) was emphasized and a project to promote the distribution of the EBM guideline development guide[2] and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[3] system were used. The guidelines included detailed explanations of the JPS and clinical questions and recommendations.

1.1. Collecting the evidence

On the basis of the identified key clinical issues and each clinical question (CQ), evidence was extracted using P (Patients), I (Intervention), C (Control or Comparison), and O (Outcome) as search keywords. We searched PubMed from January 1998 to December 2018, and the Internet version of the Central Journal of Medicine was searched from inception until December 2018.

1.2. Evaluating the articles and defining the quality of evidence

Articles selected for use in the guidelines were classified based on the study design (clinical practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, cohort studies, case-control studies, cross-sectional studies, case series, case reports, and re-

views). As JPS is a rare disease, case reports and case series were included in the systematic review. A structured abstract was developed for each article to evaluate the risk of bias. The overall evidence was determined using the systematic review method (Table 1), and the overall level of evidence for each CQ is listed from A to D.

1.3. Defining the strength of the recommendation

The strengths of these recommendations are listed in Table 2. Decisions were made upon agreement among committee members after careful consideration of the (i) quality of evidence and (ii) balance of benefits and harms (balance between disadvantages such as patient burden, cost, and benefits acquired by implementing the recommended practice). The consensus was formed by voting according to the GRADE grid method[4], and a decision was made when more than 70% of the votes were in favor.

1.4. Public comments

A draft of the guidelines was published on the website, and public comments were solicited from the members of the Japanese Society for Hereditary Tumors; the Japanese Gastroenterological Association; the Japanese Society of Gastroenterology; the Japan Gastroenterological Endoscopy Society; the Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition; and the Japanese Society of Pedi-

atric Surgery. Further revisions were made based on public comments, and the Japanese version was published in 2020[1].

2. Detailed Explanations of Juvenile Polyposis Syndrome

2.1. Overview

JPS is characterized by multiple juvenile hamartomatous polyps in the entire gastrointestinal (GI) tract[5,6]. Approximately 75% of cases are inherited in an autosomal dominant manner, whereas the rest are sporadic cases without a family history[7]. JPS is caused by *SMAD4* or *BMPRIA* germline variants. Both genes encode signaling proteins that suppress cell proliferation through the transforming growth factor (TGF)- β pathway and are tumor suppressor genes that regulate cell proliferation and apoptosis[8,9]. In JPS, hamartomatous polyps are characterized by cystic dilatation of typical glandular ducts, stromal edema, and inflammatory cell infiltration in the mucosal lamina propria[10].

2.1.1. Clinical features

GI bleeding due to the prolapse of the entire or partial polyp, intestinal intussusception due to the enlargement of the polyp, and protein-losing gastroenteropathy sometimes occur[7]. JPS may be associated with anomalies such as intestinal rotation, Meckel's diverticulum, hydrocephalus, cleft palate, cardiovascular malformations, polydactyly, psychomotor retardation, and cryptorchidism[10]. In JPS patients complicated with hereditary hemorrhagic telangiectasia (HHT), epistaxis, telangiectasia of the skin mucosa, and arteriovenous fistula in the lungs, liver, and brain occur. Malignant tumors may develop in the GI tract, as described below.

2.1.2. Disease frequency

The incidence is approximately 1 in 100,000 to 160,000, which is slightly more common in males (61%), and the mean age of onset is 18.5 years[10,11].

2.1.3. Causative genes

SMAD4 (SMAD family member 4) is a gene located on the long arm of chromosome 18 (18q21.2). *BMPRIA* (bone morphogenetic protein receptor, type 1A) is a gene located on the long arm of chromosome 10 (10q23.2). The frequency of identification of pathogenic variants in *SMAD4* or *BMPRIA* genes is approximately 60%[12-14], and pathogenic variants are found in 17%-35% and 17%-25% of *SMAD4* and *BMPRIA* genes, respectively[12,13].

Patients with pathogenic variants of *SMAD4* show gastric lesions more frequently than those with pathogenic variants of *BMPRIA* (approximately 70% of patients with *SMAD4* pathogenic variants and approximately 10% of patients with *BMPRIA* pathogenic variants). Approximately 20% of patients with an *SMAD4* pathogenic variant have HHT, which

is called combined JPS/HHT syndrome[14,15].

2.2. Diagnosis

2.2.1. Diagnostic criteria

The diagnosis of JPS was established in a proband with any one of the following clinical features[11]:

1. Five or more juvenile polyps in the colon.
2. Multiple juvenile polyps in the whole GI tract (more than two organs).
3. Juvenile polyps of any number and family history of juvenile polyps.

2.2.2. Endoscopic findings (Figure 1)

Polyps are found throughout the GI tract, but the frequency is higher in the colon (98%), followed by the stomach (14%), jejunum (7%), and duodenum (7%)[9-11]. Polyps are subclassified according to the site of occurrence: generalized juvenile GI polyposis, juvenile polyposis coli, and juvenile polyposis of the stomach. Among them, juvenile polyposis of the stomach is the most common in Japan[16]. The number of polyps varies from a few to 300, and the size varies from several millimeters to several centimeters[17]. Color tone is erythematous, and the macroscopic type is sessile in small polyps and semipedunculated to pedunculated in large ones. The surface is smooth, lobulated, villous, edematous, and shiny[17-20], sometimes with white exudate. The surrounding mucosa is also normal, but some polyps are tall and dense and produce excessive mucus, giving them the appearance of stalactite columns. Magnifying endoscopy with crystal violet shows a sparse distribution of mildly large round pits, asteroid pits, and tubular pits. Narrow-band imaging shows sparse open glandular orifices with dense capillaries around them. Endoscopic ultrasound shows cystically dilated glandular ducts as hypoechoic areas.

2.2.3. Pathological findings (Figure 2)

The mucosal lamina propria is the main locus of the lesions, showing cystic dilatation of the glandular ducts without atypia, interstitial edema, and inflammatory cell infiltration[8]. The superficial epithelium is shed with increased capillaries and erosion. Pathologically, it is classified as a hamartomatous polyp.

2.2.4. Genetic testing

The genetic diagnosis of JPS is made by the identification of a pathogenic germline variant in *SMAD4* or *BMPRIA* genes. Genetic testing is useful for confirming the proband of the disease and for differential diagnosis. However, approximately 40% of patients with JPS do not have pathogenic variants in their genes.

2.2.5. Differential diagnosis

Peutz-Jeghers syndrome, Cowden syndrome/PTEN hamartomatous syndrome, tuberous sclerosis, inflammatory polyposis, serrated polyposis syndrome, Cronkhite-Canada syndrome, and hereditary mixed polyposis syndrome should be

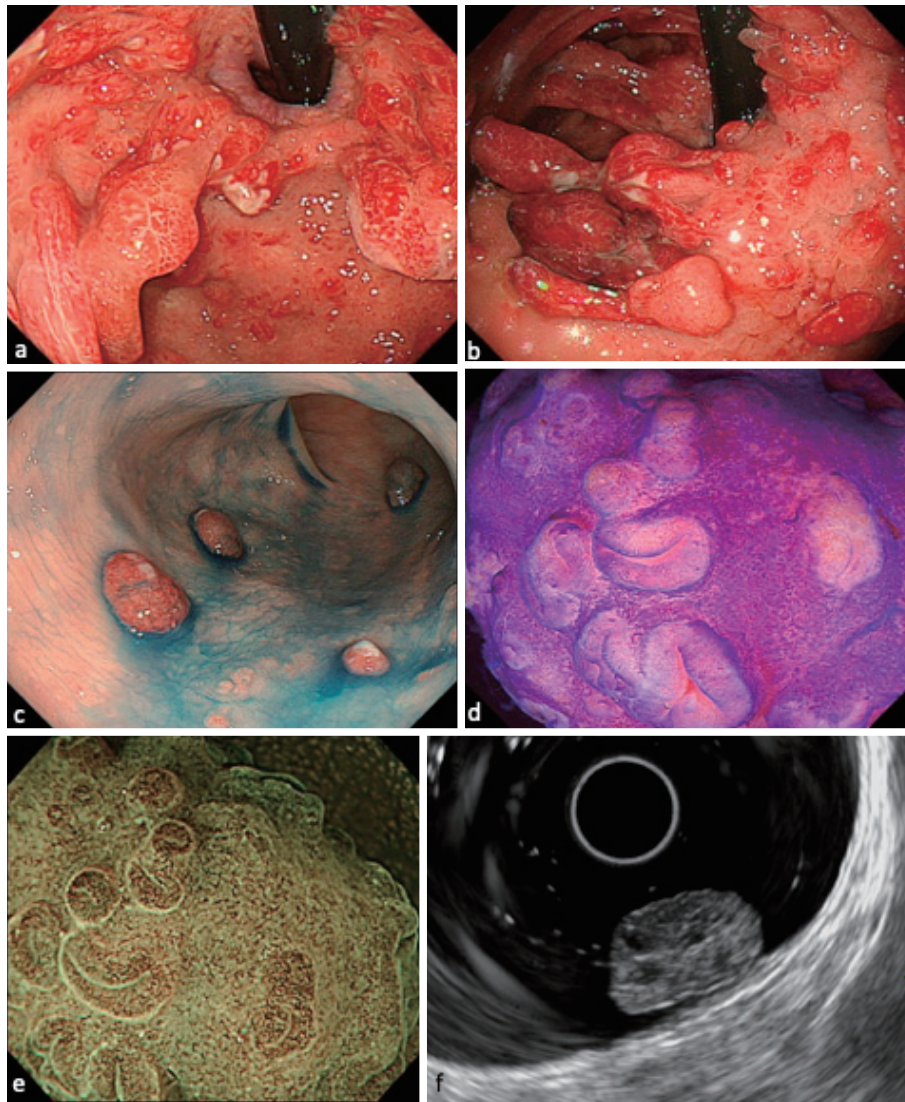


Figure 1. Endoscopic findings of the stomach (a, b) and colon (c, d, e, f) in JPS.

Multiple erythematous polyps are located from the cardia to the upper part of the gastric body. The surface of the polyps is covered with mucus (a, b). Erythematous semipedunculated polyps are seen in the colon (c). Crystal violet staining and narrow-band imaging show normal glandular ductal openings on some surfaces, but in most areas, no glandular structures can be observed (d, e). Ultrasound endoscopy reveals a small hypoechoic area that appears to be an enlarged glandular duct (f).

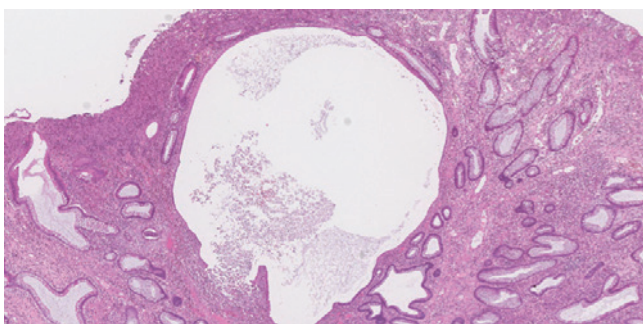


Figure 2. Histological findings of colonic lesions in JPS.

differentiated.

2.3. Treatment and surveillance

2.3.1. Treatment

There is no curative treatment. Endoscopic resection is recommended for symptomatic polyps, and surgical resection is recommended for patients with invasive carcinoma, intestinal intussusception, refractory anemia, and hypoproteinemia[7,8]. Endoscopic resection is also recommended for polyps larger than 5 mm to prevent intestinal intussusception and cancer. In addition, polyps in JPS overexpress cyclooxygenase 2 (COX2) compared to sporadic juvenile polyps[21].

The efficacy of nonsteroidal anti-inflammatory drugs as chemoprevention is unclear. Patients with *SMAD4* pathogenic variants should be aware of HHT-related vascular lesions.

2.3.2. Risk of carcinogenesis and surveillance

Although juvenile polyps are considered hamartomatous polyps with a low risk of carcinogenesis, polyps in JPS have traditionally been suggested to be potentially malignant. Some polyps in JPS have been reported to become adenomas, leading to carcinogenesis, whereas others have been reported to become carcinomas directly without adenomas[16]. The latter mechanism may be due to the repeated erosion of the superficial layer of juvenile polyps, which promotes cell turnover of regenerative cells and leads to carcinogenesis. The lifetime risk of gastrointestinal cancer in JPS is estimated to be 9%-68%, the risk of colorectal cancer (17%-22% by age 35 years and 68% by age 60 years; mean age of onset, 34 years) is the most common, and gastric cancer (risk, 30%; mean age of onset, 58 years) is more common in cases with *SMAD4* pathogenic variants[9-11,22]. In addition, small intestinal and pancreatic cancers are rarely observed.

Therefore, in JPS, periodic surveillance is necessary considering the risk of carcinogenesis[10]. Surveillance of the stomach and large intestine should be started at the age of 12-15 years, and total colonoscopy is recommended annually if polyps consistent with JPS are found or every 2-3 years if not. Although the risk of small bowel cancer is low, balloon endoscopy, capsule endoscopy, and CT enterography are recommended in the presence of polyps consistent with JPS and in cases where small bowel bleeding or protein-losing gastroenteropathy is suspected. There are no recommended surveillance methods for the other organs.

2.4. Risk assessment of patient's relatives of the proband

Genetic testing of relatives for the presence of applicable variants should be considered if *SMAD4* or *BMPRIA* pathogenic variants are known in the proband. In addition, adequate genetic counseling is important in this case. If the causative pathogenic variants have not been identified, patients should be evaluated for JPS diagnostic criteria to identify relatives who may benefit from early diagnosis and treatment.

When performing genetic testing in children, follow the "Guidelines for Genetic Testing and Diagnosis in Medicine" (February 2011 <http://jams.med.or.jp/guideline/genetics-diagnosis.html>). If it is possible to obtain the informed assent of the individual, explain the procedure sufficiently according to the individual's ability to understand and obtain consent. If the subject is a minor or otherwise incapable of consent, the test should be performed with the consent of a guardian. As the patient grows, it is necessary to provide step-by-step explanations and support for understanding the disease and genetic testing while respecting the "right to

know" and the "right not to know." Concurrently, several genetic counseling should be conducted based on parental cooperation, considering the relationship between siblings and other family members.

2.5. Medical expense subsidy system

JPS is certified as the Specific Pediatric Chronic Diseases in Japan. Pediatric patients can receive financial support for medical costs from a government-funded and medical aid project for children with chronic diseases.

3. Clinical Questions and Recommendations

CQ1

Main CQ1: How Do We Make a Definitive Diagnosis in a Case of Suspected JPS?

Sub-CQ1-1: In asymptomatic cases with a family history of JPS, should genetic testing (pre-onset diagnosis [risk-bearing individuals]) or endoscopy, laboratory tests (anemia and hypoalbuminemia), and fecal occult blood tests be performed to diagnose JPS? Which tests should be performed and when?

Main CQ1: Gastrointestinal endoscopy is strongly recommended for patients suspected of JPS, with symptoms such as gastrointestinal bleeding, in addition to family history.

Evidence Level B

Recommendation Level 1 Strong

Sub-CQ1-1: Gastrointestinal endoscopy is weakly recommended in asymptomatic JPS cases at the age of 12-15 years.

Evidence Level B

Recommendation Level 2 Weak

Explanation

The diagnosis of JPS by endoscopy is determined by satisfying one of the following clinical diagnostic criteria: 1) five or more juvenile polyps in the colon, 2) multiple juvenile polyps in the whole GI tract (more than two organs), or 3) juvenile polyps of any number, with a family history of juvenile polyps[23]. Upper GI endoscopy and total colonoscopy are essential for definitive diagnosis, leading to pathological evaluation by biopsy. In addition, VCE and balloon endoscopy have been reported to be effective in detecting small bowel lesions[24].

Regarding the recommended age and interval for starting endoscopic evaluations for JPS, endoscopy should be performed at the age of 12-15 years in cases of suspected JPS, and regular endoscopic evaluations should be performed every 1-2 years after definitive diagnosis[25].

Although the involvement of pathogenic variants in the germline of *SMAD4* and *BMPRIA* has been suggested as the cause of JPS, genetic testing should be considered an auxiliary diagnosis because the positive rate of genetic mutations

in JPS is approximately 20%-30% in both cases[11,26-28]. Kohda et al. reported that *BMPRIA* pathogenic variants could also be detected by next-generation sequencing (NGS) in genetically confirmed JPS patients[29]. Therefore, NGS is expected to be used to diagnose pathogenic variants easily and accurately in the definitive diagnosis of JPS-suspected cases and at-risk individuals. Some studies have reported an association between the germline variants of *SMAD4* and the frequency of gastric lesions and HHT[30,31]. In a study of immunostaining for *SMAD4* in gastric lesions of JPS, *SMAD4* expression disappeared in 70%-80% of cases, suggesting that *SMAD4* immunostaining may be effective as a screening test[32,33]. Patients with *SMAD4* pathogenic variants have also been reported to have various complications such as pulmonary arteriovenous malformation, aortic arch dilatation, protein-losing enteropathy, and immunodeficiency[34-36]. However, no genotype-phenotype correlation was found for GI lesions of JPS, suggesting that genetic testing is not clinically significant in patients diagnosed with JPS. For the genotype-phenotype correlation of extra-gastrointestinal lesions, please refer to CQ-3.

CQ2

Main CQ2: How should surveillance and treatment of gastrointestinal polyps and malignant tumors of the gastrointestinal tract be performed in JPS?

Sub-CQ2-1: What is the recommended method and frequency of surveillance for gastrointestinal polyps and gastrointestinal malignancies in JPS?

Sub-CQ2-2: What is the recommended treatment for polyps with JPS? (What are the indications for endoscopic, surgical, and drug treatment?)

Main CQ2: Endoscopy is strongly recommended for the surveillance of GI polyps and malignant tumors with JPS.

Evidence Level C

Recommendation Level 1 Strong

Sub-CQ2-1: It is strongly recommended to perform both upper and lower GI endoscopy every 1-3 years, although the correspondence differs according to the number of polyps and phenotypes such as gastric and colonic localized type.

Evidence Level C

Recommendation Level 1 Strong

Sub-CQ2-2

(1) Polypectomy or partial resection of the GI tract with multiple polyps is weakly recommended.

(2) Prophylactic gastrectomy is weakly recommended in gastric localized JPS with refractory iron deficiency anemia and/or hypoalbuminemia because of the high incidence of gastric cancer and the difficulty in preoperative diagnosis of cancer.

Evidence Level B

Recommendation Level 2 Weak

Explanation

There are no reports of comparative studies on the surveillance of GI polyps and GI malignancies in JPS, and the evaluation was based on case reports, case series reports, and recommendations in overseas guidelines.

A review of reported cases of JPS in the Japanese population showed that gastric cancer occurred in 29% of cases with juvenile polyposis of the stomach, and colorectal cancer occurred in 26% of cases with juvenile polyposis coli (colorectal localized type). Malignancies occur in 86% of all JPS cases, and the lifetime onset risk is 73% and 51% for gastric and colorectal cancer, respectively[16]. In addition, it should be noted that the median diagnostic age of malignancy is relatively young, with 41 (23-80) years for gastric cancer and 36 (17-80) years for colorectal cancer. Similar results have been reported from European countries and the United States, and the American College of Gastroenterology practice guidelines[11] recommend annual lower GI endoscopy and every 1 to 3 years of upper GI endoscopy as surveillance starting at 12 years, but surveillance should be started earlier in symptomatic cases. It has also been pointed out that JPS with a pathogenic variant of the *SMAD4* gene has a higher degree of gastric lesions and is more likely to become malignant than JPS with a *BMPRIA* pathogenic variant[31].

Surgery is the mainstay of treatment for patients with advanced cancers. Endoscopic resection of polyps larger than 5 mm is recommended, but endoscopic resection is difficult for diffusely localized polyps. In addition, prophylactic gastrectomy should be considered in patients with gastric localized JPS with refractory iron deficiency anemia and/or hypoalbuminemia because of the high incidence of gastric cancer and the difficulty in preoperative diagnosis of cancer.

We found no supporting evidence for drug-induced polyp reduction.

CQ3: How Should Surveillance and Treatment of Extra-gastrointestinal Lesions Be Performed in JPS?

(1) Genetic testing for *SMAD4* is weakly recommended for the surveillance of extra-gastrointestinal lesions in JPS because the complication of HHT is important information.

(2) Periodic cardiovascular examination is weakly recommended for JPS with a germline pathogenic variant of *SMAD4*.

Evidence Level D

Recommendation Level 2 Weak

Explanation

The development of malignant tumors is an important complication of JPS, and the lifetime risk of all malignant tumors in JPS (up to 70 years of age) was reported to be 86.2% in the Japanese population[16]. By contrast, extra-gastrointestinal lesions associated with JPS include HHT, central nervous system disease, and cardiovascular disease. In particular, JPS cases with variants in the *SMAD4* gene

have been found to have a high incidence of HHT (combined JPS/HHT). However, it is unclear how surveillance and treatment should be performed. We then summarize the current state of knowledge of CQ.

In extra-gastrointestinal lesions in JPS, the JPS/HHT complex was observed in 71%-81% of JPS cases with germline pathogenic variants in the *SMAD4* gene[37,38]. Conversely, JPS/HHT complex cases have been reported to have pathogenic variants in *SMAD4*[39]. Therefore, *SMAD4* may be useful in predicting the presence of HHT in some JPS cases. By contrast, one case report showed that *SMAD4* with a pathogenic variant had a mixture of adenomatous components[30], and another study showed that *SMAD4* without a pathogenic variant presented HHT[40]. Other extra-gastrointestinal lesions, epilepsy, developmental retardation, facial abnormalities, hypothyroidism, rheumatoid arthritis, bile duct hamartoma, gallbladder polyps, and cardiovascular diseases (hypertension, patent foramen ovale, atrial septal aneurysm, and cerebral infarction) have also been reported[41,42].

Because it was reported that JPS with pathogenic variants of *SMAD4* has aortic involvement as a subset of HHT (23%)[43], the international guidelines for hereditary GI cancer syndromes, including JPS, recommended annual cardiovascular examinations[11]. The prognosis of HHT is generally good, but cardiovascular lesions may lead to serious complications. Thus, periodic cardiovascular examinations should be considered in JPS patients with pathogenic variants of *SMAD4*. HHT lesions in the JPS/HHT complex cases, including cardiovascular lesions (aortic and coronary aneurysm, aortic dilatation, and mitral valve dysfunction), pulmonary vascular lesions (arteriovenous malformation [AVM]), intracranial vascular lesions (AVM), cutaneous and nasal vascular lesions (epistaxis, hemangioma, and telangiectasia), and hepatic vascular lesions (hepatic artery dilatation and AVM) were reported.

In conclusion, the information obtained by genetic testing of *SMAD4* for the JPS/HHT complex and routine cardiovascular testing for pathogenic variants in *SMAD4* as surveillance for extra-gastrointestinal lesions may be beneficial for JPS patients. Moreover, because there are no reports of adverse events from both tests, we recommend performing them. Other surveillance of JPS extra-gastrointestinal lesions could not be manifestly recommended due to the lack of scientific evidence. However, in this systematic literature search, there were no randomized controlled trials or interventional studies on the surveillance of JPS extra-gastrointestinal lesions, and the evidence level was downgraded because of the lack of scientific evidence (evidence level D). Meanwhile, we could not find literature on the treatment of extra-gastrointestinal lesions in JPS and could not clearly recommend any treatments based on scientific evidence. Therefore, we decided not to prepare a flowchart

for the diagnosis and treatment of juvenile polyposis in this study.

Appendix

Members of the working committee who created and evaluated the “Clinical Guidelines for Diagnosis and Management of Juvenile Polyposis Syndrome in Children and Adults” are listed below.

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Conflicts of Interest

Prior to the preparation of these clinical guidelines, all members of the Guidelines Committee declare any conflict of interest. T.M. received payment for lectures from Mitsubishi Tanabe Pharma Co.; EA Pharma Co., Ltd.; Janssen Pharmaceutical K.K.; AbbVie GK. and KYORIN Pharmaceutical Co., Ltd.; grants from Mitsubishi Tanabe Pharma Co. and NIPPON KAYAKU CO., LTD. M.A. received payment for lectures from AstraZeneca Co., Ltd. N.T. has received grants from Taiho Pharmaceutical Co., Ltd. H.I. has received grants from Taiho Pharmaceutical Co., Ltd. and Yakult Honsha Co., Ltd. The other authors declare no conflict of interest.

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The authors have no ethical conflicts to disclose.

Disclaimer

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