CCR PEDIATRIC ONCOLOGY SERIES

Cancer Screening Recommendations and Clinical Management of Inherited Gastrointestinal Cancer Syndromes in Childhood

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Abstract

Hereditary gastrointestinal cancer predisposition syndromes have been well characterized, but management strategies and surveillance remain a major challenge, especially in childhood. In October 2016, the American Association for Cancer Research organized the AACR Childhood Cancer Predisposition Workshop in which international experts in care of children with a hereditary risk of cancer met to define surveillance strategies and management of children with cancer predisposition syndromes. In this article, we review the current literature in polyposis syndromes that can be diagnosed in childhood and may be associated with an increased incidence of gastrointestinal neoplasms and other cancer types. These disorders include adenomatous polyposis syndromes (*APC* and *MUTYH*), juvenile polyposis coli (*BMPR1A* and *SMAD4*), Peutz–Jeghers Syndrome (*STK11/LKB1*), and PTEN hamartoma tumor syndrome (PHTS; *PTEN*), which can present with a more limited juvenile polyposis phenotype. Herein, the panel of experts provides recommendations for clinical diagnosis, approach to genetic testing, and focus on cancer surveillance recommendations when appropriate during the pediatric period. We also review current controversies on genetic evaluation of patients with hepatoblastoma and indications for surveillance for this tumor. Childhood cancer risks and surveillance associated with disorders involving the mismatch repair genes, including Lynch syndrome and constitutional mismatch repair deficiency (CMMRD), are discussed elsewhere in this series. *Clin Cancer Res; 23(13); e107–e14. ©2017 AACR.*

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Introduction

The hereditary gastrointestinal cancer syndromes have traditionally been divided into two categories: those associated with a substantial number of gastrointestinal polyps [e.g., familial adenomatous polyposis (FAP)] and those that predominantly present with a cancer phenotype and a smaller number of polyps (e.g., constitutional mismatch repair deficiency syndrome). As part of the AACR workshop on pediatric cancer predisposition, the gastrointestinal committee considered these two groups of disorders and their associated childhood cancer risks separately, with the latter disorders discussed in the article by Tabori and colleagues in this *CCR* Pediatric Oncology Series (1). Here, we review polyposis disorders that can be diagnosed in childhood and may be associated with an increased incidence of pediatric malignancies, including hepatoblastoma and brain tumors. We summarize the current literature and provide recommendations for diagnosis and cancer surveillance when appropriate during the pediatric period (Table 1).

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Table 1. Cancer surveillance recommendations in the pediatric age range

Syndrome	Gene	Inheritance pattern	Tumor risk	Pediatric surveillance	Frequency
FAP	*APC*	Autosomal dominant	Colorectum	Flexible sigmoidoscopy or colonoscopy	Starting at age 10–15; annually until surgery.
			Thyroid	Cervical palpation	Starting at age 15–19; annually.
			Liver (hepatoblastoma)	Abdominal ultrasonography and serum AFP (see discussion)	Starting early infancy; every 4–6 months until age 7.
			Desmoid	Annual physical examination Abdominopelvic MRI (for individuals with positive family history of desmoids)	Following colectomy or other surgery; 1–3 years, then lengthen time frame to 5–10 years.
			Medulloblastoma	Annual physical examination	Starting at childhood; annually.
Attenuated FAP			Colorectum	Colonoscopy	Starting at age 15–19; every 3 years until adenomas arise, then yearly.
MUTYH-associated polyposis	*MUTYH*	Autosomal recessive	Colorectum	Colonoscopy	No childhood surveillance recommended Starting at age 18; every 2 years.
			Gastric/duodenum	Upper gastroduodenal endoscopy	Starting at age 25–30; every 1–5 years.
Peutz–Jeghers syndrome	*STK11* (*LKB1*)	Autosomal dominant	Gastric/duodenum	Upper gastroduodenal endoscopy	Starting at age 8, baseline; every 3 years if polyps are found. In absence, repeat at age 18.
			Stomach	Gastroduodenal endoscopy	Starting at age 8; every 2–3 years.
			Small bowel	Capsule endoscopy	Starting at age 8; every 2–3 years.
			Ovary and cervix	Annual physical examination	Starting at childhood; annually.
			Testes	Annual physical examination	Starting at childhood; annually.
Juvenile polyposis	*BMPR1A* and *SMAD4*	Autosomal dominant	Colorectum	Colonoscopy	Starting at age 12–15; every year until no polyps are found, then lengthen interval to every 3 years.
			Stomach	Gastroduodenal endoscopy	Starting at age 15; every 1–2 years.
			Small bowel	Capsule endoscopy	Starting at age 15; every 1–2 years.

Abbreviation: AFP, alpha-fetoprotein.

The diagnosis of a polyposis disorder in childhood generally occurs in two distinct ways. First, an at-risk child who has a close relative with a prior diagnosis of a polyposis disorder is referred for genetic evaluation. It is critical that the pathogenic mutation underlying the disorder is first identified in the relative with the disorder, so that familial mutation testing is possible and efficient in the child and other relatives. Occasionally, the child is referred to a gastroenterologist first, and colonoscopy maybe performed prior to definitive genetic testing. According to most professional organizations, genetic testing in children is recommended at the time that medical actions would be initiated (2, 3). Thus, we recommend that genetic testing begin 1 year prior to the age that these actions start. This recommendation for timing of genetic testing assumes that the child has ongoing access to health care, and the health system can effectively track patients over time. However, it is important to note that these ideal circumstances do not apply across many countries and health care systems.

The second way in which children are evaluated for the polyposis disorders is when they present with some symptom or medical complication of the disorder. A number of these disorders can be associated with *de novo* mutations in a child with no family history of the disorder. These conditions can involve multiple different organ systems, thus a child might be referred for a genetic evaluation with non-gastrointestinal problems, for example, pigmentary changes in the retina seen in *APC*-related FAP; gastrointestinal manifestations, such as bloody stools, leading to identification of colonic or upper gastrointestinal polyps; or the occurrence of desmoid tumors or hepatoblastoma. As described in the sections below, the specific pathologic features of the polyps are often critical in determining the likely underlying genetic disorder. It is critical to obtain a detailed pathology report from prior procedures as well as the description of the findings and number of polyps. These features will aid in determining the genes that should be considered for genetic testing, and to clarify the clinical diagnosis.

The process and methods in genetic testing are undergoing radical change. Previously, genes were tested one by one using a Sanger-based sequencing method. A second methodology, multiplex ligation–dependent probe amplification (MLPA) or array hybridization, was used to detect single- or multi-exon insertions or deletions that may comprise up to 40% of disease alleles in some genes, for example, *STK11*.

Next-generation sequencing methodologies are becoming predominant, and many laboratories offer hereditary colon cancer and polyposis panels that simultaneously test all of the genes described in this article (including mismatch repair genes). Panel analysis may report sequence changes, and alternatively, a separate comparative genomic hybridization (CGH) or single-nucleotide polymorphism (SNP) array test may provide insertion/deletion information. Compared with single-gene tests, panel testing is more efficient, lowers the cost, and is useful when insufficient clinical data are available to differentiate among the disorders.

However, the larger the panel, the greater the likelihood of identifying variants of uncertain significance (VUS), with some reports of hereditary cancer panels in adults yielding more than one VUS per test report (4). Also, larger panels represent a greater challenge in genetic counseling in children, because the results can include the incidental diagnosis of an adult-onset disorder in a pediatric patient. Thus, if the child presents with unique

features of a single polyposis disorder, for example, congenital hypertrophy of the retinal pigment epithelia associated with FAP, it is still appropriate to order a directed test for that gene, comprehensive *APC* testing, to assure high specificity with fewer variants or unanticipated findings. If there is concern for somatic mosaicism, it should be noted that Sanger-based tests are less sensitive for detecting a child who is mosaic for a mutation in the gene in question compared with next-generation sequencing tests that include deep coverage of the gene.

FAP

Introduction

FAP is an autosomal dominant cancer predisposition syndrome caused by pathogenic variants in the *APC* gene, which is most strongly associated with an increased risk for colorectal cancer (5). Birth incidence is between one in 9,000 to 18,000 (6, 7). Individuals with classic FAP typically start developing polyps in late childhood to teen years, although polyps have been reported as young as 8 months old (8). Unless the colon is removed, these polyps eventually become malignant, with an average age of 39 years (range, 34–43 years) at the time of colorectal cancer diagnosis (9). Colorectal cancer occurs most often in adulthood but is occasionally seen in childhood or adolescence (10). Individuals with FAP are also at risk for the development of other gastrointestinal complications including duodenal, jejunal, and gastric polyps, with the duodenum being the second most common location of cancer after the colon and rectum (11).

Additional extracolonic manifestations of FAP include desmoid tumors that can cause significant morbidity and mortality. Desmoid tumor growth is most often abdominal and can be provoked by surgery. It is further complicated by a high rate of recurrence (12). Nuchal fibromas, sometimes referred to as Gardner-associated fibroma (GAF), are associated with FAP and can be present early in life. For those children initially presenting with GAF, directed testing for *APC* mutations should be offered. In desmoid tumors, evaluation of somatic *CTNNB1* mutation status in the tumor can aid in distinguishing between sporadic tumors and those associated with germline *APC* mutations and FAP, because somatic *CTNNB1* mutations are more likely to be identified in sporadic tumors (13). Other benign findings can provide a clue to FAP diagnosis, including congenital hypertrophy of the retinal pigment epithelium (CHRPE) or pigmented ocular fundus lesions of FAP (POFL; ref. 14), extranumerary teeth/dental anomalies, osteomas, epidermal cysts, and soft-tissue tumors (15).

Children with FAP are at risk of developing hepatoblastoma (0.3%–1.6%), with most cases occurring before the age of 3 years (16, 17). Notably, up to 10% of patients with hepatoblastoma have an underlying *APC* mutation and may not have a family history of FAP (16). Similar to desmoid tumors, molecular testing for somatic mutation or in-frame deletions, particularly exon 3, in *CTNNB1* can be helpful in distinguishing sporadic tumors from those potentially associated with a germline mutation in *APC* (18). An increased risk for central nervous system (CNS) tumors (<1% overall risk), particularly medulloblastoma, is also present in childhood. *APC* germline mutations are associated with WNT-activated medulloblastoma (19). The risk for papillary thyroid carcinoma (2%–7% lifetime risk) increases in the second to third decade of life (11), with the cribiform-morula variant commonly associated with germline *APC* mutations and being found more frequently in females (20, 21).

Individuals carrying pathogenic variants in *APC* with extracolonic features including osteomas and soft-tissue tumors are said to have Gardner syndrome. Turcot syndrome is an older term used to describe individuals with FAP and CNS tumors. Overlap in these clinical descriptions, however, has led to the broader, preferred description of *APC*-associated polyposis instead of the potentially misleading labels of Turcot or Gardner in a patient with an *APC* mutation.

Genetics

Molecular genetic testing is able to identify pathogenic variants, most often loss-of-function sequence variants (nonsense and frameshift mutations; rare deletions) in approximately 90% of individuals with classic FAP. Approximately 75% to 80% of individuals with FAP have an affected parent (9). Of the remaining, individuals with a *de novo* pathogenic variant, approximately 20% may have somatic mosaicism (22). Somatic mosaicism contributes to the lack of a molecular diagnosis in some individuals. Mutations in the 1B promoter region of the *APC* gene are less frequent (23). Given that a molecular diagnosis may be missed in up to 10% of individuals, a baseline colonoscopy in the teenage years can be considered in patients with clinical suspicion for FAP, such as a CHRPE or POFL finding, or the cribriform-morula variant of papillary thyroid cancer, and no identifiable *APC* pathogenic variant. The main differential diagnoses for *APC*-related adenomatous polyposis are recessive conditions, especially *MUTYH* polyposis (24), and also *MSH3*- and *NTHL1*-associated disorders (25, 26), although these are unlikely to present in childhood.

Genotype–phenotype correlations

Studies have been performed to examine genotype–phenotype correlations, but the correlation between genotype and management decisions remains controversial (27). Attenuated FAP (AFAP), however, caused by pathogenic variants in the 5′ and distal 3′ portion of the *APC* gene as well as mutations in exon 9, has a later clinical presentation and lower polyp burden than classic FAP (28). There is an increased risk for desmoid tumors in carriers of germline mutations between codons 543 and 713 and 1310 and 2011 (29). No region in the *APC* gene specifically correlates with the development of hepatoblastoma in FAP families, as mutations throughout the gene have been described in these children (30).

Cancer screening protocols

The National Comprehensive Cancer Network (NCCN) has published surveillance recommendations for individuals carrying a pathogenic variant in *APC*, which we endorse. Recommendations include flexible sigmoidoscopy or colonoscopy every year beginning between age 10 and 15 years until surgery is warranted. For those with AFAP, colonoscopy can begin in the late teens and continue every 2 to 3 years until adenomas are detected, at which time frequency is increased to every 1 to 2 years. Surgical options include total abdominal colectomy with ileorectal anastomosis (TAC/IRA), total proctocolectomy with end ileostomy (TPC/EI), and total proctocolectomy with ileal pouch-anal anastomosis (TPC/IPAA). Decisions are made based on clinical circumstances as well as personal choice. In those with desmoid-region mutations associated with milder polyp disease, surgery is best delayed and should ideally be a single-stage procedure (31).

Following colectomy, upper endoscopy is recommended starting at age 20 to 25 years. Annual thyroid examinations should begin in the late teen years, and annual thyroid ultrasounds can be considered. Annual abdominal palpation should be done to screen for desmoid tumors. The American College of Gastroenterologists states that periodic abdominal imaging is not generally of benefit (32). However, members of the workshop commented that in families with a positive family history of desmoid tumors, abdominopelvic MRI 1 to 3 years following colectomy and then every 5 to 10 years may be considered to evaluate for the development of desmoid tumors. Screening for CNS tumors is currently based on physical examination given the relatively low risk of medulloblastoma (3). The American College of Gastroenterology recommend screening from birth to 7 years for hepatoblastoma in FAP. However, there has been substantial controversy as to the value of implementing hepatoblastoma screening. This topic is discussed in greater detail at the end of this article.

Entering into adulthood, the risk for CNS tumors and thyroid cancer persists. In addition, the risk for small bowel, pancreatic, bile duct, and stomach cancers increases in adulthood. Chemoprevention options to decrease the development of polyps have also been investigated, including use of anti-inflammatory drugs and resistant starch (33). However, whether such interventions prevent the development of cancer remains to be demonstrated. Thus, there are no specific chemoprevention strategies with regard to cancer risk that can be recommended at this time.

Genetic counseling considerations

The timing of testing children at risk for FAP is controversial (34). Consideration of genetic testing before age 10 depends on whether medical management would change (i.e., perhaps earlier if hepatoblastoma surveillance will be utilized), family preference, and clinician practice. In addition, the burden of living with FAP has many psychosocial consequences (35). Misperceptions may be passed from generation to generation; for example, families may believe ostomy bags after surgery are required. Families have been living with FAP longer as the medical advances to prevent by prophylactic surgery and/or treat the manifestations of the condition has been available. Comprehensive genetic counseling with follow-up is essential to help families address misconceptions, utilize appropriate coping strategies, and incorporate informed decision making about genetic testing into care. Long-term psychologic follow-up is also essential, and communication between the genetic counselor and mental health therapist may benefit the family, so that the mental health therapist has an improved understanding of the challenges of living with FAP.

MUTYH-Associated Polyposis

Introduction

MUTYH-associated polyposis (MAP) is a recessively inherited polyposis syndrome due to biallelic mutations in the base excision repair gene *MUTYH* (36, 37). Individuals with MAP generally present with an attenuated polyposis phenotype (usually between 10 and 100 adenomatous polyps) and have an increased lifetime risk for colorectal cancer, of approximately 60% as compared with the general population (approximately 6%; refs. 32, 38). In addition, <5% of individuals with MAP develop extracolonic manifestations, including duodenal adenomas and carcinomas (32, 38). Genetic testing for MAP is indicated for individuals with at least 10 adenomatous polyps before the age of 60 in the absence of a clear dominant inheritance pattern with negative *APC* mutation analysis (32). The majority of colorectal cancer in MAP presents during adulthood, although cases have been described during childhood (24). Overall, the risk for cancer during childhood is extremely low.

Genetics

MUTYH sequence variants have been described in 308 cases in the Leiden Open Variation Database (LOVD; ref. 39). The most frequently observed *MUTYH* pathogenic missense variants are p.Y179C and p.G396D, which are found in up to 70% of Caucasian individuals with MAP (40). *MUTYH* encodes a DNA glycosylase involved in DNA oxidative damage repair, and associated polyps and tumors have a C:G>A:T transversion phenotype, which is relatively uncommon in sporadic colorectal cancer (36, 41, 42). Controversy remains regarding whether monoallelic carriers have an increased risk for colorectal cancer in adulthood (43). Germline monoallelic *MUTYH* mutations have been identified in children diagnosed with Ewing sarcoma, medulloblastoma, B-lineage acute lymphoblastic leukemia, and high-grade glioma (44, 45), but their contribution to childhood cancer etiology has not been established.

Genotype–phenotype correlations

Genotype–phenotype correlations have revealed that individuals with homozygous p.Y179C variants have more severe phenotypes than p.Y179C/pG396D compound heterozygotes or p.G396D homozygotes although still with cancer occurrence in adulthood (38, 46).

Cancer screening protocols

As colorectal cancer is rarely observed before 30 years of age in individuals with MAP, colonoscopy screening every 2 years beginning at 18 years of age is a generally accepted recommendation. Upper gastrointestinal endoscopy is advised to start even later, from the age 25 to 30 years (47).

Genetic counseling considerations

Because of the autosomal recessive inheritance pattern of MAP, transmission risk for children of an individual with MAP depends upon the *MUTYH* molecular status of the reproductive partner. Genetic counseling regarding reproductive options and genetic testing for partners should ideally be offered prior to conception. As medical management does not change until adulthood, genetic testing of children should ideally be postponed until adulthood, so that each individual can make their own informed decision about whether or not they would like to pursue genetic testing for MAP. In addition, the potential risk for cancer in individuals with heterozygous *MUTYH* variants (48) should be addressed.

Conclusions

Colonoscopy should start at the age of 18 years. Colon cancer during childhood and adolescence is extremely rare in MAP, and, therefore, surveillance for cancer in childhood is not recommended.

Peutz–Jeghers Syndrome

Introduction

Peutz–Jeghers syndrome (PJS) is an autosomal dominant polyposis syndrome, defined by multiple characteristic, hamartomatous gastrointestinal polyps and mucocutaneous freckling, particularly at the vermillion border of the lips (32, 49). The polyps exhibit a branching growth pattern with normal overlying epithelium, arborizing smooth muscle extending into the polyp, and cystic gland dilatation. Although polyps can appear to be invasive, most polyps lack dysplasia, which helps distinguish pseudoinvasion from malignancy. Polyps can be found anywhere in the gastrointestinal tract, most commonly in the small bowel and colon, but they can also be found at extraintestinal sites, including the respiratory and urinary tracts. Mucocutaneous pigmentation is reportedly found in over 90% of cases but fades with age, so it may not be apparent in adults. Distinctively, pigmentation often crosses the vermillion border and is found in the buccal mucosa, perianal region, hands and fingers, and/or is more densely clustered than common freckles. Polyps can cause bleeding, anemia, abdominal pain, intussusception, obstruction, or infarction.

Symptoms often arise in childhood, with intussuception occurring in 15% of patients by age 10 years and 50% by age 20 years (50). The possibility of intussusception in later childhood and adolescence should be explained to parents, along with the need for urgent management of acute abdominal pain. The diagnosis of PJS can be made with any one of the following: (i) two or more PJS polyps, (ii) any number of PJS polyps and a history of PJS in a close relative, (iii) characteristic mucocutaneous pigmentation in an individual with a history of PJS in a close relative, or (iv) any number of PJS polyps with characteristic mucocutaneous pigmentation (49). The differential diagnosis includes juvenile polyposis syndrome, hereditary mixed polyposis syndrome, *PTEN* hamartoma tumor syndrome, and Carney complex.

Patients with PJS are at increased lifetime risk for a wide variety of malignancies, including cancers of the gastrointestinal tract, pancreas, breast, testis, and ovary. Cancer risk increases with age, with about 1% to 2% risk by 20 years of age, more than 30% by 50 years, and more than 80% by 70 years (51, 52). Females with PJS are also at increased risk for developing less common tumors, including ovarian sex cord tumors with annular tubules (SCTAT), mucinous tumors of the ovary, and well-differentiated adenocarcinomas of the cervix. SCTAT have been reported in girls as young as 4 years of age (53). Boys with JPS may develop large-cell calcifying Sertoli cell tumors (LCCSCT) of the testes, which can be present bilaterally and malignancy is rare in young patients with bilateral tumors or in association with a genetic syndrome (54). Gonadal tumors in children may present with or without manifestations of elevated sex hormone levels, including precocious puberty or gynecomastia.

Genetics

More than 90% of patients with the strictly defined clinical diagnosis of PJS have loss-of-function mutations in the *STK11* (*LKB1*) gene, approximately equally split between sequence variants and deletions (55). Approximately 25% of individuals diagnosed with PJS have *de* novo *STK11* mutations.

Genotype–phenotype correlations

Genotype–phenotype associations have been suggested in small studies, but larger series have not found clear differences (51).

Cancer screening protocols

Consensus surveillance guidelines have been published (49) and endorsed by others (32). The surveillance strategy is designed to address polyps that may cause intestinal obstruction, as well as the detection of cancer, although gastrointestinal cancers are very rarely reported in childhood (56). Recommended surveillance includes upper gastrointestinal endoscopy, video capsule endoscopy, and colonoscopy, to be done at 8 years of age or sooner if symptomatic, although some recommend starting as early as 4 to 5 years of age (57). It is important to note that some older recommendations include imaging methodologies such as barium studies that require ionizing radiation. Given the desire to minimize the lifetime radiation exposure of these individuals at increased risk of cancer, we discourage such surveillance methodologies. If polyps are found, examinations should be repeated every 3 years. In the absence of polyps, subsequent endoscopy should be done at age 18. Although surveillance studies for gonadal tumors were not recommended (49), we recommend annual physical examination, looking for gynecomastia or testicular masses in boys, or precocious puberty in girls, as surgical or medical interventions may prevent the long-term consequences of hormonal abnormalities. Recommendations for adults include screening for breast and gynecologic cancer at 25 years of age, and for pancreatic cancer at 30 years.

Genetic counseling considerations

The increased use of large, multigene, hereditary cancer panels is identifying individuals with *STK11* pathogenic variants and expanding the clinical spectrum of PJS. It is important to the diagnostic evaluation for PJS to note that the pigmentary features of PJS may not always be present in an affected individual and may have been present in childhood but fade during adulthood. Pigmentary lesions may be present in less than the historically reported 90% of individuals with PJS. PJS has variable penetrance, but unless/until the mechanism for the variable penetrance is understood, any individual with PJS should be considered to have elevated cancer risk and should follow the recommended surveillance guidelines.

Juvenile Polyposis Syndrome

Introduction

Juvenile polyposis syndrome (JPS) is a familial polyposis syndrome, typically defined by the presence of five or more juvenile polyps in the colon, juvenile polyps in the extracolonic gastrointestinal tract, or any number of juvenile polyps in the colon and a family history of JPS (32, 58). Juvenile polyps are diagnosed histologically (rather than by the age of presentation). Juvenile polyps have hamartomatous features with dense stroma, cystic architecture with mucus-filled glands, prominent lamina propria, and inflammatory cell infiltration, and they lack of a smooth muscle core. They are often first identified while evaluating a child for rectal bleeding and/or anemia from gastrointestinal blood loss, abdominal pain or intussusception, or in some cases, as an asymptomatic, incidental finding. JPS is associated with anomalies of the vasculature (cardiac and CNS) in up to 30% of patients (59).

Although solitary juvenile polyps are the most common polyps found in childhood, they are not associated with an increased risk of cancer. In contrast, individuals with JPS are at substantially increased risk of colon cancer, as well as an increased risk for

cancer elsewhere in the gastrointestinal tract. The accuracy of estimates of risk are limited due to the small scale of most reports, but the relative risk (95% confidence interval) of colorectal cancer cancer is estimated to be 34% (14.4–65.7), with a cumulative lifetime risk of 39% (60). The risk of gastric cancer is reported to be 21% for those who have gastric polyps (58).

Genetics

JPS is inherited as an autosomal dominant disease, with about 75% of patients having a positive family history. Mutations in *BMPR1A* and *SMAD4* have been reported in 20% to 40% of patients with JPS (58). Both tumor suppressor genes are associated with the TGF-β signaling pathway. Multiple members of the workshop, however, report experiences of lower detection rates in these genes, particularly in children with juvenile polyposis without a family history.

Genotype–phenotype correlations

Generally, genotype associations with polyp phenotype and cancer incidence are unclear in JPS. However, *SMAD4* mutations are associated with features of hereditary hemorrhagic telangiectasia (HHT), a syndrome of vascular anomalies, including mucocutaneous telangiectasia and arteriovenous malformations in the brain, lung, gastrointestinal tract, and liver (61). As described below, this subset requires additional screening for these vascular complications. Interestingly, a restricted spectrum of *SMAD4* mutations cause Myhre syndrome, defined by developmental and short stature, athletic build, skeletal anomalies, joints stiffness, distinct facial features, and deafness (62).

Cancer screening protocols

Cancer in JPS is thought to arise from adenomatous changes in juvenile polyps (32), and the risk of cancer (as well as anemia and obstruction) can be reduced with polypectomy. Guidelines recommending surveillance studies for those with JPS have been published in the literature and NCCN, which the panel endorses with minor modifications (18, 32). In addition to yearly physical examinations and complete blood counts, the panel recommends colonoscopy with polypectomy for polyps $\geq$5 mm beginning in childhood (age 12–15 years old) or earlier if symptoms occur. Subsequent colonoscopy should be performed annually until no colonic polyps are found, at which time colonoscopy can be deferred for up to 3 years. Existing guidelines vary in the age at which to start upper gastrointestinal surveillance, ranging from 12 years (32) to 25 years of age (63). The panel generally agrees with the NCCN guideline recommending starting upper gastrointestinal endoscopy at around age 15 years. The small bowel past the duodenum should also be assessed periodically by capsule endoscopy beginning at age 15, or earlier if there are unexplained symptoms or blood loss. For those with *SMAD4* mutations, screening for HHT should include MRI imaging of CNS vasculature and transcutaneous measurement of the oxgen saturation. If oxygen saturation is pathologic, chest radiography or transthoracic contrast cardiac echocardiography with agitated saline is indicated to assess pulmonary vasculature. As arteriovenous malformations (AVM) may develop with increasing age, repeat screening after negative results should be considered after puberty, before planned pregnancy, after pregnancy, and every 5 to 10 years (61).

Genetic counseling considerations

Individuals meeting clinical diagnostic criteria for JPS should be managed as though they have JPS; however, it is important to note the importance of exploring differential diagnoses in individuals with hamartomatous polyposis. Conditions such as PJS and PHTS both have clinical overlap with JPS, but surveillance protocols and implications vary significantly between the syndromes (64). In addition, PHTS has characteristic clinical features and a different tumor predisposition spectrum [discussed by Schultz and colleagues (65) elsewhere in this series]. When a young child is diagnosed with juvenile polyposis, consideration should be given for asymptomatic siblings/relatives to begin surveillance prior to the typical 12 to 15 years of age.

Hepatoblastoma and Other Pediatric Liver Malignancies

At least 80% of hepatoblastomas are not associated with a predisposition syndrome. However, multiple genetic syndromes have been described that predispose to hepatoblastoma, including overgrowth syndromes. These include Beckwith–Wiedemann syndrome (BWS), which confers a 2,280-fold relative risk; Simpson–Golabi–Behmel syndrome; and Sotos syndrome. The latter two syndromes are rare, and the association consists of case reports and small series. Surveillance for tumor development in BWS and other overgrowth syndromes is widely utilized, and consists of abdominal ultrasonography every 3 months until age 4 to screen for both hepatoblastoma and Wilms tumor [see the article by Kalish and colleagues (66) in this series], with additional recommendations implemented in some but not all centers, including periodic measurement of serum alpha-fetoprotein (AFP; every 3 months).

As described earlier, there is also an association of hepatoblastoma with FAP. There are widely varying practices regarding the need for surveillance for hepatoblastoma in FAP kindreds, as the risk is elevated but presumably not higher than 1% for *APC* mutation carriers. Many large centers, mostly in the United States and Canada, have incorporated screening for hepatoblastoma with strategies similar to early detection strategies for the overgrowth syndromes, whereas in Europe, most groups do not recommend screening considering the low incidence of hepatoblastoma in this population.

Constitutional trisomy 18 usually leads to death within the first 2 years of life, but it also carries a risk of hepatoblastoma and Wilms tumor, along with heart defects and other major anomalies. Metabolic genetic syndromes that lead to liver damage and cirrhosis, such as tyrosinemia type I, fumarylacetoacetate hydroxylase deficiency, and the glycogen storage diseases, also predispose to liver tumors in children, most notably hepatocellular carcinomas. However, hepatoblastomas have been observed in these syndromes, and those children undergo monitoring for their liver function and clinicians caring for these children should maintain a high level of awareness of the risk of liver tumor development (67).

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