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Peutz-Jeghers Syndrome

Synonym: PJS

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Summary

Clinical characteristics

Peutz-Jeghers syndrome (PJS) is characterized by the association of gastrointestinal (GI) polyposis, mucocutaneous pigmentation, and cancer predisposition. PJS-type hamartomatous polyps are most common in the small intestine (in order of prevalence: jejunum, ileum, and duodenum) but can also occur in the stomach, large bowel, and extraintestinal sites including the renal pelvis, bronchus, gall bladder, nasal passages, urinary bladder, and ureters. GI polyps can result in chronic bleeding, anemia, and recurrent obstruction and intussusception requiring repeated laparotomy and bowel resection. Mucocutaneous hyperpigmentation presents in childhood as dark blue to dark brown macules around the mouth, eyes, and nostrils, in the perianal area, and on the buccal mucosa. Hyperpigmented macules on the fingers are common. The macules may fade in puberty and adulthood. Recognition of the distinctive skin manifestations is important especially in individuals who have PJS as the result of a *de novo* pathogenic variant as these skin findings often predate GI signs and symptoms. Individuals with PJS are at increased risk for a wide variety of epithelial malignancies (colorectal, gastric, pancreatic, breast, and ovarian cancers). Females are at risk for sex cord tumors with annular tubules (SCTAT), a benign neoplasm of the ovaries, and adenoma malignum of the cervix, a rare aggressive cancer. Males occasionally develop large calcifying Sertoli cell tumors of the testes, which secrete estrogen and can lead to gynecomastia, advanced skeletal age, and ultimately short stature, if untreated.

Diagnosis/testing

The diagnosis of PJS is based on clinical findings. Identification of a heterozygous pathogenic variant in *STK11* by molecular genetic testing confirms the diagnosis and allows for testing of at-risk relatives.

Management

Treatment of manifestations: Routine endoscopic surveillance with polypectomy decreases the frequency of emergency laparotomy and bowel loss resulting from intussusception. Small-bowel imaging includes video

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capsule endoscopy (VCE), CT enterography, and/or magnetic resonance enterography (MRE). Balloon-assisted enteroscopy allows for removal of deep small-bowel polyps. Occasionally intraoperative enteroscopy and enterotomy is needed for removal of large distal small-bowel polyps. Intussusception and malignancies should be treated in the standard manner.

Prevention of primary manifestations: Although not specifically studied in individuals with PJS, prophylactic mastectomy to decrease the risk of breast cancer could be considered based on family history or other clinical factors. Similarly, there is no prospective data on gynecologic prophylactic surgery for the elevated gynecologic cancer risk in females with PJS.

Surveillance: In children and adolescents: colonoscopy and upper endoscopy at age eight years; if negative, follow up at age 18 years. If polyps are detected repeat every one to three years based on size, number, and histopathology of polyps. Small-bowel surveillance by MRE or VCE every one to three years beginning at age eight years. Examination for precocious puberty in females annually beginning at age eight years. Testicular examination and examination for feminizing changes in males annually beginning at age ten years.

In adults: Colonoscopy, upper endoscopy, and small-bowel examination by MRE or VCE every two to three years beginning at age 18 years; clinical breast examination in women every six months beginning at age 30 years; mammogram and breast MRI in women annually beginning at age 30 years; pelvic examination and pap smear in women annually beginning at age 18 to 20 years. Pancreatic imaging with endoscopic ultrasound or MRI/MRCP annually beginning at age 30 to 35 years.

Evaluation of relatives at risk: If the pathogenic variant in the family is known, offer molecular genetic testing to at-risk relatives so that morbidity and mortality can be reduced by early diagnosis and prevention of disease through appropriate surveillance and consideration of prophylactic measures in affected family members. If the family variant is not known, offer clinical diagnostic evaluations to all at-risk family members, who will benefit from early treatment and appropriate surveillance.

Genetic counseling

PJS is inherited in an autosomal dominant manner. The majority of individuals diagnosed with PJS have an affected parent; however, many individuals with PJS represent apparently simplex cases. The exact proportion of individuals who have PJS as the result of a *de novo* pathogenic variant is unknown. If a parent of the proband is affected and/or is known to have the *STK11* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Once the *STK11* pathogenic variant has been identified in an affected family member, predictive testing for at-risk family members, prenatal testing, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Peutz-Jeghers syndrome (PJS) **should be suspected** in individuals with the following:

- Two or more PJS-type hamartomatous polyps of the gastrointestinal (GI) tract.
- Characteristic mucocutaneous pigmentation and hyperpigmented macules (periorbital, lips, fingers, nose, toes, and anus)
- Gynecomastia in males as a result of estrogen-producing Sertoli cell testicular tumors
- History of intussusception, especially in a child or young adult

PJS-type GI polyps. The sine qua non of PJS diagnosis is the hamartomatous GI polyp, which is histopathologically characterized by distinctive interdigitating smooth muscle bundles in a characteristic

arborizing (branching tree) appearance throughout the lamina propria. Small-bowel polyps are typically pedunculated and demonstrate a lobular architecture. The overlying epithelium is typically nondysplastic, although dysplasia can occur. In the stomach, PJS polyps may be indistinguishable from juvenile or hyperplastic polyps. In the large intestine, PJS polyps resemble mucosal prolapse polyps. Their lobular architecture and desmin-positive smooth muscle fiber favor the diagnosis of PJS [Rosty 2018]. Pseudo invasion of misplaced crypts is an innate property of the PJS hamartoma, which may reflect the role of *STK11* in cell polarity [Tse et al 2013].

Note: Individuals with PJS also develop many other polyps; polyps showing adenomatous changes frequently arise in the colon and may cause confusion with familial adenomatous polyposis. The histology of gastric PJS polyps can be similar to gastric hyperplastic polyps, thus highlighting the importance of a GI pathologist in the review of polyp histology and knowledge of the clinical context [Rosty 2018].

Establishing the Diagnosis

The clinical diagnosis of PJS **is established** in a proband with one of the following [Beggs et al 2010]:

- Two or more histologically confirmed PJS-type hamartomatous polyps
- Any number of PJS-type polyps detected in an individual who has a family history of PJS in at least one close relative
- Characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in at least one close relative
- Any number of PJS-type polyps in an individual who also has characteristic mucocutaneous pigmentation

The molecular diagnosis of PJS **is established** in a proband with suggestive findings and a heterozygous pathogenic variant in *STK11* identified by molecular genetic testing (see Table 1).

Note: Identification of a heterozygous *STK11* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **single-gene testing, multigene panel**, and **comprehensive genomic testing** depending on the phenotype.

Single-gene testing. Sequence analysis of *STK11* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications. Sequence analysis and gene-targeted deletion/duplication analysis can be done simultaneously to decrease turn-around time.

Note: If no *STK11* pathogenic variant is identified, testing of an alternate DNA source (e.g., buccal cells) for somatic mosaicism should be considered [Butel-Simoes et al 2019]. To date, seven individuals with somatic mosaicism have been identified [Jelsig et al 2021].

A multigene panel that includes *STK11* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included and the sensitivity of multigene panels vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

More comprehensive genomic testing (when available) including exome sequencing and genome sequencing may be considered if single-gene testing (and/or use of a multigene panel that includes *STK11*) fails to confirm a diagnosis in an individual with features of PJS. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Peutz-Jeghers Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
STK11	Sequence analysis [3]	~80%-85% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	~15%-20% [4, 5, 7]
Unknown	NA	<1% [4, 8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Wu et al [2020]
5. In individuals without a pathogenic identified, sequence analysis and deletion/duplication testing of an alternate DNA source (e.g., buccal cells) for somatic mosaicism should be considered. To date, seven individuals have been identified with somatic mosaic *STK11* pathogenic variants.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Includes larger deletions, such as whole-gene deletions of *STK11* and smaller intragenic deletions [De Rosa et al 2010, Borun et al 2015].
8. Of 25 individuals who had PJS but did not have a detectable *STK11* pathogenic variant, one had a heterozygous pathogenic variant of the DNA repair enzyme MUTYH that was not observed in 1015 controls [Alhopuro et al 2008]. Of note, pathogenic variants in *MUTYH* ordinarily cause an autosomal recessive form of adenomatous polyposis coli.

Clinical Characteristics

Clinical Description

Peutz-Jeghers syndrome (PJS) is characterized by the association of gastrointestinal (GI) polyposis and mucocutaneous pigmentation. The risk for GI and extraintestinal malignancies is significantly increased. Distinct benign and malignant gonadal and gynecologic tumors can also be seen. Variable expressivity is common; for example, some affected individuals in families with PJS may have only polyps or perioral pigmentation.

GI polyposis. PJS-type hamartomatous polyps can occur anywhere in the GI tract but occur most commonly in the small intestine. The density of polyps is greatest in the jejunum, followed by the ileum, then the duodenum. Polyps also occur in the stomach and large bowel. Polyps have also been reported in the renal pelvis, urinary bladder, ureters, lungs, nares, and gallbladder.

Adenomas also appear with increased prevalence throughout the GI tract.

The malignant potential of PJS-type hamartomatous polyps is unknown; however, the polyps can cause significant complications including bowel obstruction, rectal prolapse, and/or severe GI bleeding with secondary anemia requiring multiple emergency laparotomies and bowel resections. The age of onset of symptoms from polyps is variable, with some children developing symptoms within the first few years of life. The risk of intussusception was estimated to be 44% by age ten years and 50% by age 20 years [van Lier et al 2011a]. Intussusception risk increases with polyp size ≥15 mm [Latchford et al 2019]. One small single-center retrospective study concluded that endoscopic management of small-bowel polyps in PJS using balloon assisted endoscopy (BAE) – or when needed, laparoscopically assisted double-balloon endoscopy – decreased the occurrence of urgent laparotomy [Belsha et al 2017].

Significant interfamilial variability in the age at which polyps first appear is observed, suggesting that the natural history of polyps in a family may be a predictor of severity for offspring. Increasingly, case series have demonstrated a younger onset of GI pathology either through diagnostic testing or evaluation based on a positive family history. These data have prompted recommendations to begin surveillance at a younger age to detect and remove GI polyps, decrease risk of malignancy, and reduce complications of bowel obstruction [Wagner et al 2021, NCCN 2021]. Increasingly, the literature demonstrates the efficacy and safety of BAE and polypectomy in children with PJS.

Mucocutaneous pigmentation. Melanocytic macules (MM) are rarely present at birth; they become pronounced in most children before the fifth year, but then may fade in puberty and adulthood. Children often present with dark blue to dark brown mucocutaneous MM around the mouth, eyes, and nostrils, in the perianal area, and on the buccal mucosa. Hyperpigmented MM on the fingers are also common. In one series, 94% of individuals with PJS had perianal MM, 73% had MM that affected the digits, 65% had MM on the buccal mucosa, and 21% had MM at other sites [Utsunomiya et al 1975].

Histologically, increased melanocytes are observed at the epidermal-dermal junction, with increased melanin in the basal cells. No malignancy risk is associated with MM. In sporadic cases, MM is often the first diagnostic clue to PJS. *STK11* molecular analysis has been recommended in children with characteristic PJS freckling even in the absence of additional clinical criteria [Latchford et al 2019].

Gonadal tumors. Females with PJS are at risk for ovarian sex cord tumors with annular tubules (SCTATs) and mucinous tumors of the ovaries and fallopian tubes. Symptoms include irregular or heavy menstrual periods and, occasionally, precocious puberty due to hyperestrogenism. PJS-related SCTATs are bilateral multifocal small tumors with focal calcification and a typically benign course [Wagner et al 2021]. In contrast, sporadic SCTATs are large, unilateral, and associated with a 20% risk of malignancy.

Males occasionally develop large cell calcifying Sertoli cell tumors of the testes derived from sperm cord cells. These tumors may secrete estrogen and can lead to gynecomastia, advanced skeletal age, and ultimately short stature, if untreated. Multifocal calcifications are typically seen on testicular ultrasound. Aromatase inhibitors help reverse the hormonal effects of Sertoli cell tumors including reduction of gynecomastia and slowing of linear bone growth and bone age [Crocker et al 2014].

Malignancy. Individuals with PJS are at increased risk for intestinal and extraintestinal malignancies. A meta analysis of 583 individuals with PJS found an overall cancer risk of 83% by age 70 years [Ishida et al 2016]. A cohort study of 336 individuals with PJS reported an overall cancer diagnosis of 55% by age 60 years [Chen et al 2017].

Table 2. Cumulative Risk of Cancers in Peutz-Jeghers Syndrome

Cancer Site	General Population Risk	Peutz-Jeghers Syndrome	
		Risk	Mean Age at Diagnosis
Colorectal	5%	39%	42-46 yrs

Table 2. continued from previous page.

Cancer Site	General Population Risk	Peutz-Jeghers Syndrome	
		Risk	Mean Age at Diagnosis
Stomach	<1%	29%	30-40 yrs
Small bowel	<1%	13%	37-42 yrs
Breast	12.4%	32%-54%	37-59 yrs
Ovarian (mostly SCTAT)	1.6%	21%	28 yrs
Cervix (adenoma malignum)	<1%	10%	34-40 yrs
Uterine	2.7%	9%	43 yrs
Pancreas	1.5%	11%-36%	41-52 yrs
Testicular (Sertoli cell tumor)	<1%	9%	6-9 yrs
Lung	6.9%	7%-17%	47 yrs

Adapted from Syngal et al [2015]
SCTAT = sex cord tumor with annular tubules

Colorectal and gastric cancers can arise from adenomas that are commonly found in individuals with PJS. The incidence of cancer increases markedly after age 50 years. Colorectal cancer (28% by age 60) was the most common cancer reported by Chen et al [2017] in individuals with PJS.

Breast cancer can occur at early ages in women with PJS. The breast cancer risk in women with PJS may approach that of women who have a pathogenic variant in *BRCA1* or *BRCA2*. Early-onset breast cancer has been reported in multiple families with PJS.

Ovarian cancer. In an Italian series of 61 females with PJS, three had ovarian cancer, one of which was a malignant SCTAT [Resta et al 2013]. In a Dutch series of 69 females with PJS, two females had malignant Sertoli cell ovarian tumors and one had ovarian small cell cancer [van Lier et al 2011b].

Cervical cancer. Minimal deviation adenocarcinoma (adenoma malignum) is a rare well-differentiated adenocarcinoma of the uterine cervix. Presenting symptoms include bleeding or a mucoid, watery vaginal discharge. Histologic diagnosis can be difficult on small pathologic samples and a core biopsy or endo-cervical curettage is often necessary.

The current risk for gynecologic cancer in females with PJS is estimated to range from 18% to 50% by age 50 years [Wagner et al 2021].

Testicular cancer. Malignant transformation of Sertoli cell tumors is unusual. In a series including 64 males with PJS, one testicular seminoma was reported [van Lier et al 2011b].

Pancreatic cancer is among the top causes of cancer death in the US and Europe with a dismal five-year survival after diagnosis. Recent advances in the detection of early pancreatic adenocarcinoma amenable to curative surgical resection and identification of premalignant lesions by endoscopic ultrasound and MRI/MRCP have supported surveillance in high-risk individuals including individuals with PJS [Korsse et al 2013, Goggins et al 2020].

Genotype-Phenotype Correlations

Data on genotype-phenotype correlation related to *STK11* pathogenic variants are conflicting. Genotype-phenotype correlations have been extensively reviewed [Daniell et al 2018].

Variants that predict premature protein truncation are thought to predispose to a more severe phenotype. Amos et al [2004] found that individuals who had pathogenic *STK11* variants that predicted premature truncation and those who tested negative for pathogenic variants had similar ages of onset for first-reported polyps or polypectomy, and those with missense variants had later onset for these symptoms. Salloch et al [2010] similarly found that persons with pathogenic *STK11* variants that predicted premature truncation had more GI surgeries, a higher polyp count, and an earlier age of first polypectomy.

Pathogenic variants affecting protein kinase domain XI coded by exon 7 correlated with a 90% (9/10) incidence of GI polyp dysplasia [Wang et al 2014].

In a study of 297 individuals with PJS, the type or site of the *STK11* pathogenic variant did not influence cancer risk [Lim et al 2004]. A review of 419 affected individuals found that the variant type and site within the functional domains of the expressed protein did not affect cancer risk [Hearle et al 2006a]. The risk for small-bowel intussusception was not influenced by *STK11* variant status [Hearle et al 2006b]. PJS phenotype did not vary between individuals with large deletions and those with other *STK11* variants [Daniell et al 2018].

Penetrance

To date all reported individuals with pathogenic variants in *STK11* have shown clinical manifestations.

Nomenclature

The following terms have also been used for PJS:

- Polyp and spots syndrome
- Inherited hamartomatous polyps in association with mucocutaneous melanocyte macules
- Hutchinson Weber-Peutz syndrome
- Perioral lentiginosis (sometimes used inappropriately as a synonym for PJS)

Prevalence

Birth prevalence has not been reliably established; estimates range widely, from 1:25,000 to 1:280,000 [Tchekmedyian et al 2013].

PJS can occur in any racial or ethnic group.

Genetically Related (Allelic) Disorders

One individual with a pathogenic nonsense variant of *STK11* was diagnosed with gonadotropin-independent precocious puberty [Massa et al 2007]. Another individual with a 29-base pair deletion of exon 1 of *STK11* was diagnosed with juvenile polyposis coli (see Juvenile Polyposis Syndrome) [Sweet et al 2005]. These findings could reflect clinical heterogeneity or incomplete diagnosis of Peutz-Jeghers syndrome, in which a wide range in the numbers and types of polyps can be seen.

Differential Diagnosis

Table 3 summarizes the differential diagnosis of Peutz-Jeghers syndrome (PJS).

Table 3. Autosomal Dominant Genetic Cancer Syndromes Showing Signs and Symptoms that Overlap with Peutz-Jeghers Syndrome

Gene(s)	Syndrome	Clinical Features	
		Overlapping	Distinguishing
BMPR1A *SMAD4*	Juvenile polyposis syndrome (JPS) [1]	GI polyps usually by age 20 yrs: hamartoma +++; adenoma + Cancers: CRC; gastric; upper GI; pancreatic	In JPS: juvenile polyp histology different from PJS: hamartomas w/nl epithelium w/a dense stroma, an inflammatory infiltrate & smooth surface w/dilated, mucus-filled cystic glands in the lamina propria; HHT in those w/*SMAD4*-JPS [3]; no pigmentary abnl (MM); no ovarian or testicular tumors
15q15.3q22.1 duplication [2] *BMPR1A* *SMAD4*	Hereditary mixed polyposis syndrome (HMPS) (OMIM 601228)	Polyps: juvenile hamartoma +; adenoma +; serrated + Cancers: CRC	In HMPS: no pigmentary abnl; no ovarian or testicular tumors
PTEN	*PTEN* hamartoma tumor syndrome (PHTS)	Polyps: hamartoma +++; adenoma +; ganglioneuroma + Cancers: breast; CRC	In PHTS: different pigmentary abnl - freckles of glans penis & keratoses; extraintestinal manifestations more pronounced than intestinal polyposis: trichilemmoma, lipomas, macrocephaly, breast fibrosis; thyroid, kidney, & endometrial cancer
PRKAR1A	Carney complex (CC)	Polyps: ± adeno Hyperpigmented lesions: facial +; mucosal + Cancers: large-cell calcifying Sertoli cell tumor	In CC: myxomas of heart, skin, breast, oropharynx, & female genital tract; thyroid nodules; acromegaly; thyroid cancer, primary pigmented nodular adrenocortical disease, & schwannomas
APC	Familial adenomatous polyposis (See *APC*-Associated Polyposis Conditions.)	Polyps: adenoma +++ Cancers: CRC; GI	In FAP: desmoid tumors, osteomas, CHRPE, brain tumors; no ovarian or testicular tumors
EPCAM *MLH1* *MSH2* *MSH6* *PMS2*	Lynch syndrome	Polyps: adenoma + Cancers: CRC; gastric; ovarian	In Lynch syndrome: sebaceous adenoma; addl cancers incl endometrial, renal pelvis & ureter; no testicular tumors

CC = Carney complex; CHRPE = congenital hypertrophy of the retinal pigment epithelium; CRC = colorectal cancer; FAP = familial adenomatous polyposis; GI = gastrointestinal; HHT = hereditary hemorrhagic telangiectasia; JPS = juvenile polyposis syndrome; MM = melanocytic macules; PJS = Peutz-Jeghers syndrome

1. The term "juvenile" refers to the type of polyp, not the age of onset of polyps.

2. HMPS can be caused by either a *BMPR1A* pathogenic variant or a duplication of 15q15.3q22.1 that leads to increased expression of *GREM1* [Jaeger et al 2012]. Some families with mixed hereditary polyposis syndrome have *SMAD4* pathogenic variants [Valle et al 2019].

3. JPS may occur with hereditary hemorrhagic telangiectasia (HHT); or the combined entity of JPS-HHT. The JPS-HHT overlap syndrome has been reported in 22% of individuals with JPS due to a *SMAD4* pathogenic variant (*SMAD4*-JPS) [Aretz et al 2007]. In a cohort 41 families with *SMAD4*-JPS, nearly all affected individuals had overlap syndrome [O'Malley et al 2012].

Constitutional MMR deficiency (CMMRD) – a rare childhood cancer predisposition syndrome caused by biallelic pathogenic variants in *MLH1*, *MSH2*, *MSH6*, or *PMS2* – should also be considered in the differential diagnosis of PJS. Similar to PJS, CMMRD is associated with colorectal polyps and duodenal and gastric cancer. Unlike PJS, CMMRD is associated with a diverse malignancy spectrum in childhood and adolescence, T-cell

lymphoma gliomas, and pigmentary features similar to neurofibromatosis type I (nearly all affected individuals have café au lait macules), (See Lynch Syndrome, Lynch Syndrome Variants.)

Unexplained hamartomatous mixed polyposis. In a study of 49 unrelated persons with unexplained hamartomatous mixed polyposis, Sweet et al [2005] determined that 22% had various germline pathogenic variants.

- Of 14 individuals with juvenile-type polyposis: two had pathogenic variants in *ENG*, a gene associated with hereditary hemorrhagic telangiectasia; one had a hemizygous deletion encompassing *PTEN* and *BMPR1A*; and one had a *SMAD4* pathogenic variant.
- Of 23 individuals with hyperplastic/mixed polyposis, two had *PTEN* pathogenic variants.
- Of nine individuals with an unknown hamartomatous polyposis, pathogenic variants were seen in *STK11* (4 individuals), *BMPR1A* (2), and *SMAD4* (1).

Oral pigmented lesions. The differential diagnosis of oral pigmented lesions includes the following:

- Laugier-Hunziker syndrome (LHS), characterized by the presence of perioral, digit, and nailbed lentiginosis (small, well-demarcated; dark-brown to blue-black in color). This condition usually develops in adults and the hyperpigmentation is progressive. LHS has not been associated with any known exposure and has not been reported to occur in families. LHS is diagnosed by the absence of diseases associated with mucocutaneous pigmentation such as underlying PJS and Addison's disease [Sputa-Grzegrzolka et al 2020].
- A fixed drug reaction
- A normal feature, especially in African Americans [Sputa-Grzegrzolka et al 2020]

Rare tumors. The differential diagnosis of some of the rare tumors observed in PJS includes:

- Sex cord tumors with annular tubules (SCTAT); 50% are associated with PJS; the remainder may occur as an isolated finding.
- Calcifying Sertoli tumors of the testes and adenoma malignum of the cervix in women; these may also occur as an isolated finding or in other disorders.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and need for clinical follow up in an individual diagnosed with Peutz-Jeghers syndrome (PJS), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Peutz-Jeghers Syndrome

System/Concern	Evaluation	Comment
Gastrointestinal polyps/cancer	• Colonoscopy • Upper endoscopy • Small-bowel exam by MRE or VCE	Beginning at age 8 yrs or earlier if symptomatic
Breast cancer (females)	Clinical breast exam	Beginning at age 18 yrs
	Breast MRI & mammogram	Beginning at age 30 yrs

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Gynecologic cancer (females)	Exam for precocious puberty	Beginning at age 8 yrs
	• Pelvic exam for uterine & ovarian cancer (typically SCTAT) • Pap smear for cervical cancer (typically adenoma malignum)	Beginning at age 18-20 yrs
Testicular cancer (males)	• Testicular exam • Exam for feminizing changes in males • Testicular ultrasound exam if clinically indicated	Beginning at age 10 yrs
Pancreatic cancer	Pancreatic imaging w/endoscopic ultrasound or MRI/MRCP ideally performed at center of expertise	Beginning at age 30 yrs
Genetic counseling	By genetics professionals [1]	To inform patients & their families re nature, MOI, & implications of PJS in order to facilitate medical & personal decision making

MOI= mode of inheritance; MRCP = magnetic resonance cholangiopancreatography; MRE = magnetic resonance enterography; PJS = Peutz-Jeghers syndrome; SCTAT = sex cord tumors with annular tubules; VCE = video capsule endoscopy

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Polyps. Once the burden of gastrointestinal (GI) polyps has been established by endoscopy and imaging studies, prophylactic polypectomy of polyps larger than one centimeter is performed. This strategy has two goals:

- To decrease the sequelae of large polyps including bleeding, anemia, obstruction, and intussusception
- To reduce the risk for cancer by the malignant transformation of PJS-type polyps

The luminal polyp-related complications arise in childhood whereas cancer in PJS is typically seen in adulthood. Some evidence indicates that routine endoscopy and intraoperative enteroscopy with polypectomy decreases the frequency of emergency laparotomy and bowel loss. From St Mark's PJS registry of 51 affected individuals who underwent surveillance endoscopies, none had emergency surgical interventions and no GI luminal cancers were diagnosed [Latchford et al 2011]. In surveillance endoscopies in affected individuals by age 18 years, 17/28 had large gastroduodenal or colonic polyps (>1 cm). These studies demonstrate that endoscopic surveillance and polypectomy in PJS is safe and effective.

Until recently, distal small-bowel polyps that are beyond the reach of conventional endoscopy have been difficult to manage. In the past, barium contrast upper-GI series with a small-bowel follow through has been recommended. However, recent advances allow better diagnosis and eradication of small-bowel polyps, often without laparotomy and with a decrease in the radiation burden related to prior dependence on CT scan imaging [Belsha et al 2017].

- Video capsule endoscopy (VCE) allows for better visualization of the small-bowel polyps than barium x-rays and is recommended as a first-line surveillance procedure. In children, the capsule can be deployed in the duodenum after upper endoscopy. The results of the small-bowel imaging studies direct the endoscopic removal of polyps. See Note.
- Magnetic resonance enterography (MRE) is a reliable procedure for the detection of larger small-bowel polyps with similar sensitivity to VCE, and avoids the radiation exposure of CT enterography. CT and MR enteroclysis are alternative procedures but are less well tolerated. See Note.
- Balloon-assisted enteroscopy (BAE) can remove distal small-bowel polyps with or without laparotomy [Gao et al 2010]. The efficacy and safety of BAE for small-bowel polyp management in PJS has been established in children with PJS [Korsse et al 2012]. BAE and polypectomy decrease the need for

intraoperative enteroscopy and enterotomy, which should be reserved for affected individuals with large and distal small-bowel polyps beyond the reach of BAE.

Note: (1) VCE was preferred by individuals and detected more large polyps than MRE [Urquhart et al 2014]. (2) In three individuals, MRE detected polyps >15 mm that were not detected by VCE [Gupta et al 2010].

Intussusception should be treated in a standard manner.

Malignancies should be treated in a standard manner. Conservative management of gonadal tumors in males and females is appropriate.

Prevention of Primary Manifestations

Although not specifically studied in females with PJS, prophylactic mastectomy may be considered to manage the increased risk for breast cancer based on the family history or other clinical factors. Prophylactic hysterectomy and bilateral salpingo-oophorectomy to prevent gynecologic malignancy in women may be considered. In some disorders with a high risk for malignancy (e.g., Lynch syndrome), evidence supports this strategy [Schmeler et al 2006]. As the benefits of surveillance and prophylactic surgery have not been established, all females with PJS should be offered expert breast and gynecologic care at an established center in the framework of a study or registry [Wagner et al 2021].

Surveillance

Surveillance guidelines for PJS have evolved. With accumulation of clinical data demonstrating a high incidence of polyp-associated complications in young individuals with PJS and the greater availability of endoscopic expertise and pediatric-sized endoscopes, the trend is to begin endoscopic surveillance at age eight years. Some recommend beginning surveillance at age five years [Goldstein & Hoffenberg 2013, NCCN 2021].

Table 5a. Recommended Surveillance Guidelines for Children and Adolescents with Peutz-Jeghers Syndrome

System/Concern	Evaluation	Frequency
Gastrointestinal polyps/cancer	Colonoscopy & upper endoscopy	• If the baseline endoscopy at age 8 yrs is negative, rpt at age 18 yrs. • If polyps are detected at baseline, endoscopy every 1-3 yrs based on size, number, & histopathology
	Small-bowel exam by MRE or VCE	• Every 1-3 yrs beginning at age 8 yrs • Or frequency based on findings; repeat at least by age 18 yrs. [1]
Gynecologic cancer	Exam for precocious puberty in females	Annually beginning at age 8 yrs
Testicular cancer	• Testicular exam • Exam for feminizing changes in males • Testicular ultrasound exam if clinically indicated	Annually beginning at age 10 yrs

MRE = magnetic resonance enterography; VCE = video capsule endoscopy
1. Latchford et al [2019]

Table 5b. Recommended Surveillance Guidelines for Adults with Peutz-Jeghers Syndrome

System/Concern	Evaluation	Frequency
Gastrointestinal polyps/cancer	• Colonoscopy • Upper endoscopy • Small-bowel exam by MRE or VCE	Every 2-3 yrs beginning at ~18 yrs [1]

Table 5b. continued from previous page.

System/Concern	Evaluation	Frequency
Breast cancer (women)	Clinical breast exam	2x/yr beginning at age 30 yrs
	Mammogram & breast MRI	Annually beginning at age 30 yrs
Gynecologic cancer	• Pelvic exam for uterine & ovarian cancer (typically SCTAT) • Pap smear for cervical cancer (typically adenoma malignum)	Annually beginning at 18-20 yrs
Pancreatic cancer	Pancreatic imaging w/endoscopic ultrasound or MRI/MRCP ideally performed at center of expertise	Annually beginning at ~30-35 yrs
Lung cancer	Provide education about symptoms & smoking cessation. No other specific recommendations.	
Testicular cancer	Testicular ultrasound exam if clinically indicated	Annually beginning at age 10 yrs

Modified from NCCN [2021] and Wagner et al [2021]
MRCP = magnetic resonance cholangiopancreatography; MRE = magnetic resonance enterography; SCTAT = sex cord tumors with annular tubules; VCE = video capsule endoscopy
1. Shorter intervals may be indicated depending on polyp size, number, and pathology.

Agents/Circumstances to Avoid

No agents that increase the risk for polyps or malignancy in individuals with PJS have been described.

Due to the increased risk for cervical, lung, and pancreatic cancer in individuals with PJS, smoking should be avoided.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures.

If the pathogenic variant in the family is known, it is appropriate to offer molecular genetic testing for the familial *STK11* pathogenic variant to at-risk relatives.

- Morbidity and mortality can be reduced in those individuals identified to have the family-specific pathogenic variant by means of early diagnosis, treatment, and surveillance (see Surveillance).
- Relatives in whom the familial pathogenic variant is not identified (and who do not meet clinical diagnostic criteria for PJS) should not be considered as requiring PJS surveillance [Wagner et al 2021].

If the pathogenic variant in the family is not known, it is appropriate to offer:

- Clinical diagnostic evaluations to identify those family members who will benefit from early treatment;
- Surveillance as outlined in Surveillance to all first-degree relatives whether or not they meet diagnostic criteria.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this rare disorder.

Other

Several animal models of PJS have been generated using *STK11* knockout mice [Wei et al 2005]. Gastrointestinal hamartomatous polyposis in *STK11*$^{+/-}$ mice mimics human PJS polyps with the unique smooth muscle arborization. In these animal models, upregulation of cyclooxygenase-2 (COX-2) in polyp tissue was noted [Rossi et al 2002]. Overexpression of COX-2 in human PJS hamartomas and PJS-associated cancers has also been detected [McGarrity et al 2003, Wei et al 2003]. COX-2 inhibition in mice using celecoxib suppresses polyp growth [Udd et al 2004]. Polyp burden in *STK11* (*Lkb1*) heterozygous (+/–) knockout mice was reduced by 86% among mice who had developed polyps and were then treated with celecoxib, a Cox inhibitor.

Selective COX-2 inhibitors have been used to inhibit premalignant adenoma formation. To date, however, no clinical trials in the US are studying efficacy of COX-2 inhibitors in reducing polyp formation in individuals with PJS. Increased cardiovascular and cerebrovascular adverse events with selective COX-2 inhibitors limit their use.

Observation of hyperactivation of mTOR in hereditary hamartoma syndrome and a variety of cancers suggests that mTOR inhibitors may be useful in the management of PJS [van Veelen et al 2011]. A significant reduction in tumor burden in *STK11*+/– mice treated with rapamycin was reported compared with that in mice without rapamycin treatment [Wei et al 2009]. Treatment begun before the onset of polyposis resulted in more dramatic reduction than treatment begun after onset. In another study in *STK11*+/– mice oral rapamycin intake was associated with a significant reduction in microvessel growth in polyps as well as in tumor burden [Robinson et al 2009].

In addition, in two small trials in persons with tuberous sclerosis complex, treatment with rapamycin induced regression of the astrocytomas [Franz et al 2006] and reduced facial angiofibroma [Hofbauer et al 2008]. Whether rapamycin would decrease polyp growth in PJS has not been documented in human studies. The mTOR inhibitor, everolimus, caused partial regression of a pancreatic cancer in an individual with PJS. Induction of apoptosis in colon polyps was also noted [Klümpen et al 2011]. These findings suggest that mTOR inhibitors are an option to investigate for management of polyposis in PJS. A Phase II trial was initiated in Utah and the Netherlands with a goal of recruiting 15 participants to evaluate chemoprevention with everolimus. The trial was stopped due to low enrollment and poor tolerance of everolimus after only two participants could be recruited [de Brabander et al 2018].

Poffenberger et al [2018] demonstrated that selective deletion of STK11 in T-cells reproduced the PJS phenotype in mice. PJS polyps in experimental mice and human were characterized by intense immune cell infiltration and increased levels of inflammatory cytokines (interleukin 6) and enhanced STAT3 signaling, providing new potential therapeutic targets for PJS.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Peutz-Jeghers syndrome (PJS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- The majority of individuals diagnosed with PJS have an affected parent. In large series, 60%-78% of individuals with PJS had affected relatives [van Lier et al 2010a, Resta et al 2013].
- Many individuals diagnosed with PJS represent apparently simplex cases (i.e., a single affected family member).
  - In the series noted above, 17%-40% of probands represent apparently simplex cases. In a separate study, between 30% and 45% of probands represent simplex cases [Daniell et al 2018]. In the absence of sufficient parental clinical and molecular data, the proportion of these individuals who have PJS as the result of a *de novo* pathogenic variant cannot be determined.
  - In a study of 38 individuals with PJS, 11 of 26 probands had the disorder as the result of a *de novo* pathogenic variant [Wu et al 2020].
- If the proband appears to be the only affected family member, recommendations for the evaluation of parents of a proband include:
  - Molecular genetic testing if an *STK11* pathogenic variant has been identified in the proband;
  - Examination of the buccal mucosa and skin of the digits and genital area for hyperpigmented macules; upper and lower gastrointestinal endoscopy; mammography; bimanual pelvic examination and ovarian ultrasound examination (females); and testicular examination (males).
- If the pathogenic variant identified in the proband is not identified in either parent, neither parent has clinical findings consistent with PJS, and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
  - Parental mosaicism has been reported in PJS. Somatic mosaicism can have variable effects on severity of the phenotype depending on which tissues have the *STK11* pathogenic variant [Jelsig et al 2021]; a parent with somatic and germline mosaicism for a *STK11* pathogenic variant may be mildly/minimally affected [Butel-Simoes et al 2019].
- The family history of some individuals diagnosed with PJS may appear to be negative because of failure to recognize the disorder in family members or early death of the parent (and other relatives) before the onset of symptoms. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation has been performed on the parents of the proband and/or molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents.

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. PJS is marked by a wide range of phenotypic expression in family members with the same *STK11* pathogenic variant. Epigenetic modifications, the effects of modifying genes, environmental, and other factors are known to influence the development of PJS-related manifestations in heterozygous individuals [Daniell et al 2018].
- If the proband has a known *STK11* pathogenic variant that cannot be detected in the leukocyte DNA of either parent and both parents are clinically unaffected, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental mosaicism [Butel-Simoes et al 2019].
- If the genetic status of the parents is unknown but they are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for PJS because of the possibility of parental mosaicism.

Offspring of a proband

- Each child of an individual with PJS and an identified *STK11* pathogenic variant has a 50% chance of inheriting the *STK11* pathogenic variant. (The offspring of individuals who are mosaic for an *STK11* pathogenic variant are also at risk of inheriting an *STK11* pathogenic variant.)
- The risk to the offspring of a proband with a clinical diagnosis of PJS, a negative family history, and no identified *STK11* pathogenic variant is unknown.

Other family members. The risk to other family members depends on the status of the proband's first-degree relatives: if a relative is affected and/or is heterozygous for an *STK11* pathogenic variant, his or her family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Predictive testing for at-risk asymptomatic family members requires prior identification of the germline *STK11* pathogenic variant in the family. Because early detection of at-risk individuals who have an *STK11* pathogenic variant affects medical management – particularly surveillance (see Table 4) – testing of at-risk individuals (with informed parental assent) during childhood is considered beneficial [NCCN 2021, Wagner et al 2021].

Parents often want to know the genetic status of their children prior to initiating screening in order to avoid unnecessary procedures in a child who has not inherited the pathogenic variant. Special consideration should be given to education of the children and their parents prior to genetic testing. A plan should be established for the manner in which results are to be given to the parents and their children.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – Health Professional Version (part of PDQ®, National Cancer Institute). Limited data on the effects of a PJS diagnosis on family planning and quality of life are available [van Lier et al 2010b, van Lier et al 2012]

Other issues to consider. It is recommended that physicians ordering PJS molecular genetic testing and individuals considering undergoing testing understand the risks, benefits, and limitations of the testing prior to sending a sample to a laboratory. Referral to a genetic counselor and/or a center in which testing is routinely offered is recommended.

Genetic heterogeneity. Individuals with a clinical diagnosis of PJS who do not have a detectable *STK11* pathogenic variant may have a pathogenic variant(s) in a gene other than *STK11* and, consequently, have a disorder that is inherited in a different manner from *STK11*-related PJS (see Differential Diagnosis). Of 25 individuals who had PJS but did not have a detectable *STK11* pathogenic variant, one had a heterozygous pathogenic variant in *MUTYH* [Alhopuro et al 2008]. Of note, pathogenic variants in *MUTYH* ordinarily cause an autosomal recessive form of adenomatous polyposis coli.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *STK11* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing for PJS are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Collaborative Group of the Americas on Inherited Gastrointestinal Cancer (CGA-IGC)**
  www.cgaigc.com
- **MedlinePlus**
  Peutz-Jeghers syndrome
- **International Society for Gastrointestinal Hereditary Tumours (InSiGHT)**
  insight-group.org
- **Inherited Cancer Registry (ICARE)**
  www.inheritedcancer.net

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Peutz-Jeghers Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
STK11	19p13.3	Serine/threonine-protein kinase STK11	STK11 database	STK11	STK11

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Peutz-Jeghers Syndrome (View All in OMIM)

175200	PEUTZ-JEGHERS SYNDROME; PJS
602216	SERINE/THREONINE PROTEIN KINASE 11; STK11

Molecular Pathogenesis

STK11 encodes a serine/threonine-protein kinase (STK11), a multi-tasking tumor suppressor that has a role in apoptosis, cell cycle arrest, cell proliferation, cell polarity, and energy metabolism.

- STK11 activates *TSC2* through an AMP-dependent protein kinase [Corradetti & Guan 2006] leading to accumulation of mTOR, which is critical for protein translation. Loss of STK11 increased tumor cell metabolism via mTOR [Faubert et al 2014].
- STK11 expression was shown to cause apoptosis in epithelial cells [Marignani 2005].
- STK11 was reported to phosphorylate AMPK and several other members of the AMPK-related subfamily of kinases including the microtubule affinity-regulating kinases (MARKs) to regulate cell polarity [Tanwar et al 2012].
- Through activation of AMPK by phosphorylation, STK11 plays a role in energy metabolism [Udd & Mäkelä 2011].
- Loss of STK11 increased tumor-promoting cytokines with reduced expression of PD-1 ligand in mouse and human tumors [Koyama et al 2016].

More than 300 *STK11* pathogenic variants have been reported in persons with Peutz-Jeghers syndrome. All types of variants have been reported, from missense variants to whole-gene deletion.

Mechanism of disease causation. Loss of function

Cancer and Benign Tumors

Non-small cell lung cancer. Sporadic pathogenic variants in *STK11* are observed in one third of non-small cell lung cancers; *STK11* is the third most commonly mutated gene, following *p53* and *KRAS*. Demographically, *STK11* variants in lung tumors appear to be frequent in male smokers of northern European background and are associated with poorly differentiated tumors. In addition, *STK11* pathogenic variants are more frequently observed in association with concomitant activating *KRAS* pathogenic variants. Such digenic variants have been associated with a poorer prognosis compared to a *KRAS* pathogenic variant alone [Pécuchet et al 2017]. The high prevalence of *STK11* pathogenic variants in non-small cell lung cancers suggests that cigarette smoking could be particularly harmful for individuals with pathogenic variants in *STK11*. The presence of *STK11* pathogenic variants in these types of cancers may indicate a more aggressive tumor that has a poorer prognosis and is seen more often in smokers [Pécuchet et al 2017, Wang et al 2020].

Cervical cancer. Sporadic pathogenic variants in *STK11* are observed in at least 20% of cervical cancers [Wingo et al 2009]. Among the variants observed in tumors, half are single-nucleotide variants or small indels and the other half are large-fragment deletions in either one allele or both alleles. *STK11* inactivation in primary cervical tumors has been associated with accelerated disease progression. These results suggest that *STK11* is a major cervical tumor suppressor for sporadic cancers.

Chapter Notes

Author Notes

Dr Amos is a research scholar in the Cancer Prevention Research Institute of Texas supported by RR170048. Dr McGarrity is a gastroenterologist who partially specializes in the diagnosis and treatment of PJS. Dr Baker is a genetic counselor and medical geneticist who specializes in the recognition of hereditary cancer predisposition syndromes.

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