CHAPTER

2 Diagnosis

2.1 Suggestive findings

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

- Two or more PJS-type intestinal polyps
- Mucocutaneous macules
- Gynecomastia in males as a result of estrogen-producing Sertoli cell testicular tumors
- History of intussusception, especially in a child or young adult

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 gastrointestinal pathologist in reviewing polyp histology.

PJS-type intestinal polyps. The sine qua non of PJS diagnosis is the hamartomatous gastrointestinal polyp, which is histopathologically characterized by distinctive interdigitating smooth muscle bundles in a characteristic arborizing (branching tree) appearance throughout the lamina propria, particularly of small bowel polyps, and lobular organization, particularly of colonic crypts. 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].

2.2 Establishing the diagnosis

The diagnosis of PJS **is established** in a proband with one of the following, based on a European consensus statement [Beggs et al 2010]:

- Two or more histologically confirmed PJS-type hamartomatous polyps
- Any number of PJS-type polyps detected in one 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

Identification of a heterozygous pathogenic variant in *STK11* by molecular genetic testing (see Table 1) also establishes the diagnosis based on diagnostic criteria from the Mayo Clinic [Riegert-Johnson et al 2008].

Molecular testing approaches can include **single-gene testing**, use of a **multi-gene panel**, and more **comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *STK11* is performed first and followed by gene-targeted deletion/

duplication analysis. Sequence analysis and gene-targeted deletion/duplication analysis of *STK11* may also be performed concurrently to reduce turnaround time.

- **A multi-gene panel** that includes *STK11* and other genes of interest (see Differential Diagnosis) may also be considered.
- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered if serial single-gene testing (and/or use of a multi-gene 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 more information on comprehensive genome sequencing click here.

Note: (1) The genes included and the sensitivity of multi-gene panels vary by laboratory and over time. (2) Some multi-gene panels may include genes not associated with the condition discussed in this GeneReview; thus, clinicians need to determine which multi-gene panel provides the best opportunity to identify the genetic cause of the condition at the most reasonable cost. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing based tests.

Table 1: Molecular genetic testing used in Peutz Jeghers syndrome

Gene[1]	Proportion of PJS attributed to pathogenic variants in this gene	Proportion of probands with a pathogenic variant[2] detectable by this method	
		Sequence analysis[3]	Gene-targeted delection/duplication analysis[4]
STK11	94-96%[5]	~81%[6]	~15%[7]
Unknown[8]	NA		

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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.

4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that may be used 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.

5. In a large Dutch study, 73 (96%) of 76 individuals with PJS had an *STK11* pathogenic variant [van Lier et al 2010]. In another study 65 (94%) of 69 individuals with PJS had an *STK11* pathogenic variant, including 20 (87%) of 23 familial cases and 45 (97.8%) of 46 sporadic cases [Resta et al 2013].

6. van Lier et al [2010], Resta et al [2013]

7. Includes larger deletions, such as whole-gene deletions of *STK11* and smaller intragenic deletions [Le Meur et al 2004, 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.