CHAPTER

1 Summary

1.1 Clinical characteristics

Peutz-Jeghers syndrome (PJS) is an autosomal dominant condition characterized by the association of gastrointestinal polyposis, mucocutaneous pigmentation, and cancer predisposition. Peutz-Jeghers-type hamartomatous polyps are most common in the small intestine (in order of prevalence: in the 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. Gastrointestinal polyps can result in chronic bleeding and anemia and also cause 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. Individuals with Peutz-Jeghers syndrome 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 (LCST) of the testes, which secrete estrogen and can lead to gynecomastia, advanced skeletal age, and ultimately short stature, if untreated.

1.2 Diagnosis/ testing

The diagnosis of Peutz-Jeghers syndrome is based on clinical findings. Identification of a heterozygous pathogenic variant in *STK11* by molecular genetic testing confirms the diagnosis and allows for family studies.

1.3 Management

Treatment of manifestations: Routine endoscopic surveillance with polypectomy decreases the frequency of emergency laparotomy and bowel loss resulting from intussusception. Diagnosis and management of small-bowel polyps is challenging. New advances in small-bowel imaging include video capsule endoscopy, CT enterography, and MR enterography. 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, the following could be considered based on family history or other clinical factors: prophylactic mastectomy to manage high risk for breast cancer and prophylactic hysterectomy and bilateral salpingo-oophorectomy after age 35 years or after child bearing has been completed to prevent gynecologic malignancy.

Surveillance: Protocols have been suggested for monitoring stomach, small and large bowel, breasts, testicles, ovaries, uterus, and pancreas by various procedures as early as birth and as frequently as once a year.

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.

1.4 Genetic counseling

Peutz-Jeghers syndrome is inherited in an autosomal dominant manner. However, approximately 45% of affected individuals have no family history of PJS; the exact proportion of cases caused by a de novo pathogenic variant is unknown as the frequency of subtle signs of the disorder in parents has not been thoroughly evaluated and molecular genetic data are insufficient. The risk to the offspring of an individual with a pathogenic STK11 variant is 50%. Once the STK11 pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.