Morbidity can be severe, and nearly 25% of affected individuals succumb by the age of 21.[34]

PS has a wide range of neoplasms, including meningiomas, genitourinary tumors, and breast tumors.[35] Most neoplasms associated with PS are benign, but some malignancies have been seen. It can be challenging to distinguish benign from malignant tumors in this disorder because some can have histologic features of both (C Ours, unpublished data).

PS is only associated with mosaic, activating *AKT1* (HGNC:391) variants, nearly always the NC_000014.9:g.104780214C>T c.49G>A p.(Glu17Lys) variant but occasionally the NC_000014.9:g.104780213_104780214delinsCT NM_001382430.1:c.49_50delinsAG p.(Glu17Arg) variant.[36] The molecular diagnosis requires testing of affected solid tissues because peripheral blood is uniformly negative.

Because of the rarity of the disorder and the wide range of tumors associated with PS, it has been difficult to develop robust data on the magnitude of the risk. Additionally, the heterogeneity of the observed tumors makes it difficult to develop specific tumor surveillance recommendations. Regular monitoring by clinicians caring for affected individuals is recommended at least annually for signs and symptoms of tumors. Expedited evaluations should be performed if concerning signs or symptoms arise.[4]

PIK3CA-related overgrowth spectrum

PROS describes a range of phenotypes characterized by the segmental overgrowth of 1 or more tissues including muscle, nerve, adipose, vascular, and brain. Vascular and lymphatic malformations, skin findings (eg, epidermal nevi and hyperpigmented macules), digital anomalies (eg, polydactyly and macrodactyly), renal anomalies, and differences on brain imaging (eg, hemimegalencephaly and cortical dysplasia) are also associated with this condition.[37] Previously described syndromes that are now considered part of PROS because of their common underlying genetic etiology include megalencephaly-capillary malformation syndrome, Klippel-Trenaunay syndrome, fibroadipose hyperplasia, and congenital lipomatous asymmetric overgrowth of the trunk, lymphatic, capillary, venous, and combined-type vascular malformations, epidermal nevi, skeletal, and spinal anomalies syndrome (CLOVES) among others.[38,39]

A diagnosis of PROS is confirmed via the identification of a pathogenic, activating variant in *PIK3CA* (HGNC:8975). Because most individuals with PROS have postzygotic, somatic variants in *PIK3CA*, molecular testing is complicated by mosaicism. Testing of an apparently affected tissue increases the chances of determining a molecular diagnosis, and the use of next-generation sequencing (NGS) with deep coverage is preferred for detecting a low-level variant.[40]

The most common benign tumor in individuals with PROS is a lipoma. Although there are reports of individuals with PROS having "hemangioma," these actually refer to capillary malformations, not vascular tumors. Two individuals with molecularly confirmed PROS have been reported with spinal neurofibromas (only 1 of which was confirmed histologically).[37] A small number of malignancies that have not been seen with enough frequency to consider surveillance have been reported in affected individuals with PROS. These malignancies include leukemia, retinoblastoma, rhabdomyosarcoma, astrocytoma, juvenile granulosa cell tumor, and borderline serous tumor.[3,41,42] The primary malignant tumor reported in PROS is Wilms tumor. In a recent meta-analysis, 6 affected individuals with PROS out of 483 affected individuals were reported to have Wilms tumor or nephrogenic rests. Of note, 5 of those individuals were diagnosed with CLOVES.[3] At this time, the data are insufficient to recommend standard Wilms tumor screening via quarterly abdominal imaging for affected individuals with PROS; however, a shared decision-making model for surveillance with families of affected individuals with a CLOVES phenotype can be considered.[22] It is currently not entirely understood why individuals with PROS do not have higher incidences of neoplasia.

Neurofibromatosis 1

Classical *NF1*-related neurofibromatosis 1 (NF1) presents with multiple café au lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, iris Lisch nodules, and plexiform neurofibromas. Cutaneous neurofibromas develop during adolescence and adulthood and about 10% of individuals develop malignant peripheral nerve sheath tumors.[43] The risk of breast cancer is also increased in women with this condition.[44]

Café au lait spots, typically ovoid in shape with well-defined borders, uniform in color and about 1 to 3 cm in size, are often present at birth and increase in number during the first few years of life. Freckling can be present in unusual, non-sun-exposed areas, including axilla and inguinal regions where skin rubs against skin. Congenital anterolateral tibial bowing is typically present at birth but can become more apparent upon ambulation. Diffuse plexiform neurofibromas of the face and neck rarely appear after the first birthday. Those on other parts of the body rarely develop after adolescence and typically remain stable throughout adulthood.[45] Deep nodular plexiform neurofibromas may be seen at any age; however, these are usually not symptomatic in childhood and often remain asymptomatic in adulthood. Benign cutaneous and subcutaneous neurofibromas are rare before late childhood and usually present in adults. Optic nerve gliomas in *NF1*-related neurofibromatosis are usually asymptomatic, and the majority of them can regress spontaneously.[46] Most individuals with *NF1*-related neurofibromatosis have normal intelligence; however, learning disabilities or behavioral problems occur in 50% to 80% of patients, intellectual disability in 6% to 7%, and autism spectrum in up to 30%.[47,48]

Mosaic or segmental *NF1*-related neurofibromatosis occasionally presents in the context of LO of an arm or leg in a child. This limb asymmetry is typically subtle, and