

Review

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Germline predisposition to soft tissue sarcoma

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Abstract

Soft tissue sarcoma (STS) most often occurs sporadically, but can also arise in the setting of a germline cancer predisposition syndrome (CPS). There is significant diversity amongst STS diagnoses as these tumors exhibit a variety of histologies, occur in all age groups, and can occur in any location in the body. This diversity is also reflected in the many known associated germline cancer predisposition associations. Some STS diagnoses, such as anaplastic rhabdomyosarcoma, are associated with high heritability and other STS, such as Ewing sarcoma, are notably absent from known CPS. Recognizing when a STS is more likely to be hereditary can influence clinical management. Individuals diagnosed with STS due to CPS may be at risk for other malignancies and should undergo additional surveillance for early detection. Additionally, family members should undergo genetic testing as they also may be at risk to develop STS and other CPS-associated malignancies. Some underlying cancer predisposition diagnoses may have implications for the treatment of a concurrent malignancy as in the case of PARP inhibitor therapy in the setting of homologous recombination deficiency. This review summarizes current knowledge of selected STS and their associations with CPS.

Keywords: Genetic, soft tissue sarcoma, Li-Fraumeni syndrome, cancer predisposition syndrome

INTRODUCTION

Soft tissue sarcoma (STS) most often arises sporadically, but can occur in the setting of a cancer



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Table 1. Summary of STS with and without cancer predisposition associations. Bolded are those that are discussed within the current review

Sarcomas associated with known predispositions	Sarcomas without known cancer predisposition association
Rhabdomyosarcoma	Desmoplastic small round cell tumor
Malignant peripheral nerve sheath tumor	Undifferentiated round cell sarcoma
Liposarcoma	Angiomatoid fibrous histiocytoma
Desmoid type fibromatosis	Congenital/infantile fibrosarcoma
Malignant rhabdoid tumor (extrarenal)	Dermatofibrosarcoma protuberans
Gastrointestinal stromal tumor	High/low grade endometrial stromal sarcoma
	Epithelioid hemangioendothelioma
	Epithelioid sarcoma
	Inflammatory myofibroblastic tumor
	Low-grade fibromyxoid sarcoma
	Solitary fibrous tumor
	Synovial sarcoma
	Clear cell sarcoma
	Tenosynovial giant cell tumor
	Ewing sarcoma*

*Ewing sarcoma is included in this review because preliminary data suggests a possible cancer predisposition association.

predisposition syndrome (CPS). Research into the etiology of STS has largely been in somatic tumorigenesis and suggests that STS do not all share the same etiology^[1-3]. As with other cancers, such as breast cancer, STS can be caused by a multitude of single gene pathogenic variants as well as polygenic variants. A 2016 study identified that 1% of all sarcoma are due to *TP53* pathogenic variants and 20% are due to rare polygenic variants^[4].

Germline genetic testing is relevant in the STS patient population due to implications for treatment and accompanying familial risk. Facilitating germline genetic testing and/or referral to genetic counseling in select patients at higher risk can help to provide access to the diagnosis of a CPS, which may be underutilized in this population because of nuances in identifying the right candidates for referral and/or testing. [Table 1](#) provides an overview of the STS discussed within this review and those outside the scope of this review. This review summarizes current knowledge about germline predisposition and STS, and includes specific recommendations about germline testing provided in [Table 2](#).

RHABDOMYOSARCOMA

Rhabdomyosarcoma (RMS) is associated with multiple CPS with the embryonal subtype being more frequently associated with genetic predisposition than the alveolar subtype. Most pediatric patients with RMS do not have a family history of cancer, but an increased risk for embryonal RMS has been reported in pediatric patients who have a first-degree relative with cancer, and among those who have a relative diagnosed with cancer at less than 30 years of age [not due to Li-Fraumeni syndrome (LFS)]^[14]. RMS diagnosed in childhood and adolescence is more likely to be associated with a cancer predisposition than adult-onset RMS.

Cancer predisposition association: LFS, DICER1 syndrome, RASopathies, Constitutional Mismatch Repair Deficiency, Rubenstein-Taybi and Beckwith-Wiedemann syndrome

Table 2. Description of soft tissue sarcoma subtypes with gene associations, cancer predisposition associations, location associations, and testing recommendations for patients diagnosed with the tumor type

Group	STS type	Germline gene associated	% of tumor associated with PGV	Location commonly seen	Genetic testing recommendations
ES	Ewing sarcoma	DNA repair defect genes	Unknown	Unknown	No testing based on this diagnosis, consider based on family history ^[5]
RMS	Embryonal RMS	<i>DICER1, NF1, TP53, RASopathies</i>	10%	Female reproductive tract is the most common site of RMS in <i>DICER1</i> , no other associations with anatomic locations have been noted in other CPS	Testing recommended for all genitourinary sarcoma ^[6] Testing for other ERMS can be considered, particularly if family history or features of NF1 are present
	Alveolar RMS	<i>TP53</i>	3%	Unknown	No testing recommended based on this tumor, consider testing based on family history
	Anaplastic RMS	<i>TP53</i>	73%	Unknown	Yes, all anaplastic RMS warrant genetic testing ^[7]
MPNST	Malignant peripheral nerve sheath tumor	<i>NF1</i>	22%-52%	Unknown	Yes, all MPNST warrant genetic testing or evaluation by a medical geneticist for clinical NF1 criterion ^[8]
LPS	Liposarcoma	<i>TP53</i>	Unknown	Head and neck; pleomorphic myxoid liposarcoma	No testing recommended based on this diagnosis, consider based on previous cancer history and family history ^[9]
LMS	Leiomyosarcoma	<i>TP53, RB1, FH</i>	3%-10%	Unknown	BRCA testing may be considered for uterine LMS patients for treatment planning, and other cases based on family history ^[10]
DTF	Desmoid-type fibromatosis	<i>APC</i>	5%-15%	Abdominal	Yes, all diagnoses of DTF warrant testing ^[11]
MRT	Malignant rhabdoid tumor (extrarenal)	<i>SMARCB1, SMARCA4</i>	Up to 34% (<i>SMARCB1</i>) Unknown (<i>SMARCA4</i>)	Unknown	Yes, all diagnoses of MRT warrant testing ^[12]
GIST	Gastrointestinal stromal tumor	<i>SDH</i> genes, <i>NF1, KIT, PDGFRa</i>	32% of wild-type GIST	Stomach	Yes, all wild-type GIST or those with a family history ^[12,13]

RMS: Rhabdomyosarcoma; MPNST: malignant peripheral nerve sheath tumors; LMS: leiomyosarcoma; DTF: Desmoid-type fibromatosis; MRT: malignant rhabdoid tumors; GIST: Gastrointestinal stromal tumors.

Risk for predisposition: Up to 7.7% (unselected RMS - higher in certain subtypes or locations)

Sarcoma subtype with most significant predisposition risk: Embryonal and anaplastic.

A 2020 study on an unselected pediatric RMS cohort from the Children’s Oncology Group (COG) reported pathogenic variants after exome sequencing in 615 individuals with RMS. Importantly, this group included both alveolar RMS (ARMS) and embryonal RMS (ERMS) histologies. Germline pathogenic variants associated with CPS were identified in 7.3% (45 out of 615) of RMS patients. Of these 45 patients, 33 patients were identified to have germline pathogenic variants in genes associated with RMS development: *TP53* ($n = 11$), *NF1* ($n = 9$), *HRAS* ($n = 5$), *DICER1* ($n = 2$) and mismatch repair genes ($n = 3$). The other variants occurred in genes without known associations with RMS, with *BRCA2* ($n = 6$) being the most common. Of the patients identified with a

predisposition, 35 patients had ERMS (35 out of 347) and five patients had ARMS (5 out of 167). For the FOXO1 fusion-positive ARMS patients ($n = 66$), no pathogenic variants were identified, nor were there autosomal recessive disorders identified as a cause for pediatric RMS^[15]. A 2021 study of RMS comprised of a cohort from a COG intermediate risk group trial and an unselected risk group cohort reported that 7.7% and 6.6% were identified to have a CPS, respectively. The frequency and types of pathogenic variants were comparable to the abovementioned 2020 study, however pathogenic germline or likely pathogenic variants were identified in 3.8% (4 out of 105) patients with FOXO1 fusion-positive ARMS^[16].

LFS is the cancer predisposition most strongly associated with RMS development. In another RMS study, three of 13 children with nonalveolar RMS diagnosed under age three were found to have *TP53* variants and none of those over age three were identified to have *TP53* variants^[17]. Building on this study, 15 pediatric patients with anaplastic RMS underwent evaluation for *TP53* germline variants. Of these patients, 73% (11 out of 15) were identified to have a *TP53* germline variant. All of these patients were under age seven, and 45% (5 out of 11) were diagnosed under age three^[7]. In a 2015 study of LFS, 86 patients developed 105 STS. Of these STS, 29% were RMS. In 13 cases of RMS for which pathologic data were available, all of the patients were diagnosed with ERMS with anaplasia^[18].

Another CPS association with RMS is *DICER1* syndrome. The majority of *DICER1*-associated RMS are embryonal and occur within the genitourinary tract, though they can occur elsewhere^[6,19]. A 2020 retrospective review of *DICER1*-associated sarcomas identified 86 patients with sarcoma. Of these 86 patients reported, 24 (28%) ERMS or RMS not otherwise specified were reported in patients with germline *DICER1*-pathogenic variants. Most tumors (17/24 = 71%) occurred in the genitourinary tract, but some sites were unknown ($N = 5$), one occurred in the head and neck region, and the last in the pelvis. Of the RMS subtypes reported in the literature associated with *DICER1* germline variants, none were alveolar^[20]. Other authors have shown that *DICER1* variants, either somatic or germline, occur almost ubiquitously across all uterine embryonal RMS^[21]. The majority of *DICER1*-associated RMS have been reported in the female genitourinary tract, but an association with ERMS outside of this body system is emerging^[22,23].

RMS is also a component of the conditions caused by activation of the RAS pathway. These RASopathies include Costello syndrome (*HRAS*), Neurofibromatosis type 1 (*NF1*), and Noonan syndrome (*KRAS*, *NRAS*, *RAF1*, *BRAF*, *PTPN11*, *SOS1*, *SHOC2*, *MEK1*). The majority of RMS reported in patients with these conditions have been ERMS, but ARMS, botryoid, pleomorphic, mixed and spindle cell histologies have been reported^[24]. Other CPS such as Rubenstein-Taybi (*CREBBP* or *EP300*), Beckwith-Wiedeman syndrome (BWS) (multiple mechanisms of inheritance) and Constitutional Mismatch Repair Deficiency Syndrome (CMMRD) (*MSH2*, *MSH6*, *MLH1*, *PMS2*, *EPCAM*) have also been reported to cause RMS. In a study on individuals with Rubenstein-Taybi, two individuals out of 724 were diagnosed with RMS^[25]. A study on CMMRD identified two patients with RMS, and confirmed that embryonal tumors belong in the CMMRD tumor spectrum^[26]. Genetic testing for these conditions is often triggered by associated physical features. BWS is associated with a 5%-10% risk for cancers in childhood, and RMS occurs in approximately 0.5% of cases. There is evidence of genotype/phenotype association with those with BWS due to uniparental disomy and imprinting-control-region 2 methylation having the greatest risk for cancer^[27]. BWS has multiple causes and only sequencing of *CDKN1C*, which accounts for 5% and 40% of isolated and familial cases of BWS, is included in common clinically available multi-gene panel tests^[28]. Additional testing is needed to identify other causes such as imprinting defects or uniparental disomy. These tests only need to be included in the genetic workup of an RMS case if there are other features of BWS.

In conclusion, CPS has been identified in up to 8% of RMS. The most common RMS subtypes driven by germline pathogenic variants are of embryonal and/or anaplastic histology, with up to 73% of anaplastic RMS harboring a germline *TP53* pathogenic variant (replication studies are ongoing). Fusion-positive ARMS is rarely associated with CPS. The majority of RMS cancer predisposition has been studied in the pediatric and adolescent young adult (AYA) population (until age 25). Adults diagnosed with RMS may also be at risk for cancer predisposition, even more so in the presence of a family history of cancer; however, more research is needed in this older population.

MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

Malignant peripheral nerve sheath tumors (MPNST) occur sporadically or are in association with CPS, notably neurofibromatosis type 1 (NF1). MPNST can also occur as a consequence of previous radiation therapy in about 10% of patients without known CPS^[29,30].

Cancer predisposition association: Neurofibromatosis type 1.

Risk for predisposition: 22%-52%.

Sarcoma group with most significant predisposition risk: Not available.

In 1986, the first published study to evaluate the risk of an underlying NF1 diagnosis in patients with MPNST identified 62 patients with NF1 out of 120 total patients with MPNST (52%)^[31]. An additional report in 1998 identified 150 patients with MPNST, 34 of whom had NF1 (24%)^[32]. The first published MPNST longitudinal study in 2001 included 54 pathologically confirmed MPNST. Of those patients, 15 had an underlying diagnosis of NF1 (28%). Patients with NF1-associated MPNST were significantly younger than their sporadic counterparts^[8]. A 2006 study expanded the analysis of MPNST to include prognostic factors and the natural history of MPNST. A total of 205 patients with MPNST were included, and after clinical evaluation for NF1, 46 patients were diagnosed with NF1-associated MPNST (22%). This study confirmed previous findings that showed NF1-associated MPNST were diagnosed at younger ages and for the first time reported these patients presented with larger tumors. Based on this finding, it was suggested that inferior outcomes in NF1-associated MPNST may be due to the larger tumor size at presentation^[33]. A 2012 study reported on outcomes in 175 patients with MPNST diagnosed over the course of 15 years. In total, approximately 57 patients with NF1 were included in this study (32%). The authors noted a decreased disease-specific survival in patients with NF1 compared to those with sporadic MPNST^[30].

Although MPNST is most frequently associated with NF1, it has been reported in other CPS. In 2012, the North West Regional Genetic Register reported on the incidence of MPNST in 12 CPS. MPNST was reported in three cases of schwannomatosis (two with confirmed SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1 [*SMARCB1*] pathogenic variants causing rhabdoid tumor predisposition syndrome), two cases of neurofibromatosis type 2 (NF2), and three cases of LFS. MPNST was remarkably absent from other common CPS like hereditary breast and ovarian cancer (HBOC) syndrome and Lynch syndrome^[34]. While MPNST has been rarely reported in association with rhabdoid tumor predisposition syndrome^[35,36], investigation of rhabdoid tumor predisposition syndrome amongst unselected cohorts of MPNST has not been reported. MPNST risk in individuals with NF2 remains controversial. MPNST has occurred in patients with NF2 in the absence of radiation, but recent studies have supported that an increased risk for MPNST should only be counseled if that patient has undergone prior radiation therapy^[37,38]. MPNST is not frequently encountered in LFS, but because of the significant cancer risk in the setting of a germline *TP53* pathogenic variant, MPNST diagnosis remains a

possibility in the LFS population.

In conclusion, MPNST is most highly associated with NF1. Other CPS have been reported in association with MPNST, though other factors (such as radiation) and previous medical history (such as a diagnosis of a rhabdoid tumor) are clinically relevant to distinguish whether genetic testing should be expanded beyond NF1.

EWING SARCOMA

There is a notable absence of Ewing sarcoma risk in CPS^[39,40]. Case reports of familial Ewing sarcoma are rare, and no single gene explanations for heritability have been identified^[41,42]. Predispositions to Ewing sarcoma linked to a family history of cancer (mainly brain and prostate) have been postulated but no causative germline pathogenic variant has been identified^[43].

Cancer predisposition association: DNA repair genes.

Risk for predisposition: 3%.

Sarcoma group with most significant predisposition risk: Not available.

A 2017 study on 175 patients with Ewing sarcoma underwent germline genetic testing to investigate for CPS^[5]. A total of 23 pathogenic/likely pathogenic variants were identified in 13.1% (23 out of 175) of the patients. Of these identified variants, one was in the *TP53* gene, and several were in genes thought to only be associated with autosomal recessive inheritance, such as Fanconi Anemia Complementation Group M (*FANCM*)^[5]. There was a diversity of variants across several genes, though there was a highly enriched clustering of variants within the DNA double-stranded repair pathway. A hypothesis provided by the authors suggested that pathogenic variants in DNA repair genes may lead to the development of DNA breaks and subsequent translocations ultimately causing tumorigenesis of translocation associated Ewing sarcoma^[5]. In a study of germline variants in pediatric cancers, 3% (5 out of 46) patients with Ewing sarcoma had a cancer predisposition. Of note, three of the patients within this cohort were also represented in the above-referenced 2017 study. However, when restricted to genes associated with an autosomal dominant risk for cancer, only 3% of EWS patients have germline pathogenic variants. This may be incidental, and no specific genes have been found to be consistently associated with EWS.

There are additional case reports of germline pathogenic variants in individuals with Ewing sarcoma. This includes BRCA1-associated RING domain 1 (*BARD1*), Partner and Localizer of BRCA2 (*PALB2*), and *NF1*^[44-46]. Individuals with germline pathogenic variants in *RB1* have rarely been reported to have Ewing sarcoma^[47,48].

In conclusion, Ewing sarcoma risk has not been identified within a singular CPS, but may exist in the group of DNA repair genes and their associated pathways. Many of the reported germline pathogenic variants associated with Ewing sarcoma are in autosomal recessive associated syndromes, such as Fanconi Anemia. It is currently unknown whether those pathogenic variants lead to the development of Ewing sarcoma.

LIPOSARCOMA

Liposarcoma has some associations with CPS, notably LFS. A 2015 study identified that 12% of STS diagnosed in LFS patients were liposarcoma^[18], but additional studies are needed to determine the frequency

Table 3. Review of case reports in the literature on cancer predisposition and liposarcoma

Publication	Age at diagnosis (years)	Type of liposarcoma	Location	Previous cancer history	Germline variant
Francom et al. ^[9]	11	Pleomorphic myxoid liposarcoma	Left facial mass	Yes, anaplastic medulloblastoma at age 5	<i>TP53</i>
Sinclair et al. ^[49]	15	Pleomorphic myxoid liposarcoma	Right perineal mass	No	<i>TP53</i>
Debelenko et al. ^[50]	5	Atypical lipomatous tumor/well-differentiated liposarcoma	Right antecubital fossa	No	<i>TP53</i>
	6	Atypical lipomatous lesion, favor atypical intramuscular lipoma over low-grade liposarcoma	Right thigh	No	Presumed <i>TP53</i>
Zare et al. ^[51]	34	Pleomorphic myxoid liposarcoma	Right chest wall	Yes, Primary mediastinal large B-cell lymphoma	<i>TP53</i>
Sui et al. ^[52]	49	Well-differentiated liposarcoma	Wall of lower esophagus	No	Presumed <i>TP53</i>
Poli et al. ^[53]	20	Myxoid liposarcoma	Upper right eyelid	No	<i>TP53</i>
Sadri et al. ^[54]	61	Dedifferentiated liposarcoma	Left perinephric space	Yes, breast cancer and leiomyosarcoma	<i>CHEK2</i>
Yozu et al. ^[55]	74	Pleomorphic liposarcoma	Right buttock	Yes, metachronous colon cancer and sebaceous neoplasms	<i>MSH2</i>

of LFS and other germline pathogenic variants in newly diagnosed liposarcoma.

Cancer predisposition association: LFS and other DNA repair genes.

Risk for predisposition: Unknown.

Sarcoma subtype with most significant predisposition risk: Pleomorphic myxoid liposarcoma.

Predisposition to liposarcoma has not been systematically studied, but multiple case reports describe individuals with liposarcoma and CPS (outside of hereditary retinoblastoma). [Table 3](#) includes a summary of the relevant case reports published about liposarcoma and CPS.

An increased risk to develop liposarcoma may be associated with germline pathogenic variants in *RB1*^[48,56]. This greatest risk is thought to begin approximately 10 years after hereditary retinoblastoma diagnosis. In a 2013 study of hereditary retinoblastoma cases, three male patients developed liposarcoma. These tumors were found in the head and neck, trunk, and spermatic cord and all were noted to be well-differentiated^[57]. Other studies on secondary malignancies in hereditary retinoblastoma have not identified any patients with liposarcoma^[58].

In conclusion, risks for a CPS in individuals diagnosed with liposarcoma are unknown. Of the case reports summarized in the literature, 55% (5 out of 9) were diagnosed with liposarcoma as their first diagnosis and 45% had a previous history of cancer. Liposarcoma may be associated with hereditary retinoblastoma, so careful attention to previous cancer diagnoses is warranted when caring for patients with liposarcoma. It is possible that CPS is underdiagnosed due to the low incidence of this STS in the adult population and the lack of other suspicious personal history warranting genetic testing.

LEIOMYOSARCOMA

Leiomyosarcoma (LMS) has a definite association with cancer predisposition, but there remains a lack of details about germline contribution despite extensive work studying somatic variants. Studies have shown that maternal breast cancer diagnoses may be associated with an increased risk for offspring to develop LMS, but these studies did not control for the possibility that a family could have a predisposition such as LFS or HBOC^[59]. Familial LMS is rare, but has been reported in siblings^[60]. Because of the overall rarity of LMS, it is understudied at a population level and the total heritability of LMS by either common or rare genetic variants has not been reported.

Cancer predisposition association: LFS, hereditary retinoblastoma, *FH* tumor predisposition syndrome.

Risk for predisposition: Unknown.

Sarcoma subtype with most significant predisposition risk: Unknown.

Individuals diagnosed with hereditary retinoblastoma due to germline pathogenic variants in *RB1* are thought to have between a 31%-41% increased risk to develop sarcoma in the 50 years after their retinoblastoma diagnosis^[61]. In studies of hereditary retinoblastoma, a consistent risk for LMS continues to be reported. Interestingly, despite a significant association between radiation dose and sarcoma risk, LMS has predominantly occurred outside of the radiation field^[62,63]. A 2019 study reported on increased sarcoma diagnoses in a hereditary retinoblastoma cohort of 952 patients who previously underwent radiation as treatment for their retinoblastoma. The median year of retinoblastoma diagnosis in this cohort was 1968. Of the 124 STS reported in this cohort, 16% (21 of 124) were diagnosed with LMS. The risk to develop LMS in this cohort started in the fourth decade and mainly occurred in the pelvis and abdomen^[56]. In a 2011 study, eight out of 525 females with hereditary retinoblastoma developed uterine LMS. Another patient in this cohort developed cutaneous LMS of the trunk^[64]. In a 2013 study of 1927 hereditary retinoblastoma patients, 152 developed secondary malignancies. Of these patients, 20% (31 out of 152) developed LMS, confined mostly to the bladder, retroperitoneum, and uterus. LMS diagnoses in this cohort made up 67% of the total STS diagnoses^[57]. Consistent with other studies, LMS is a frequent diagnosis amongst individuals with hereditary retinoblastoma^[48,57,65].

Since the mutational profile of LMS was studied more extensively than germline predisposition to LMS, a unique finding of “BRCAness” in LMS tumors was identified. Growing data indicate that uterine LMS may be described as BRCA-related cancer^[10]. Somatic *BRCA2* variants occur in 8% of uterine LMS and recent data suggest *BRCA1* promoter methylation and homologous recombination deficiency mutational signatures may also contribute to tumorigenesis^[10,66]. Investigations into the frequency of *BRCA1/2* germline pathogenic variants in this population are warranted, and further evidence is needed to determine whether individuals with *BRCA* inactivation respond to PARP inhibitors as the use of PARP inhibitors is an exciting avenue to explore potential personalized therapy options for patients with LMS. It has been suggested that all uterine LMS should undergo germline testing for *BRCA1/2* to assist with treatment decisions^[10].

FH tumor predisposition syndrome (FTPS) predisposes primarily to benign leiomyoma (cutaneous and uterine) and renal cell carcinoma. There is evidence that FTPS is associated with a risk to develop uterine LMS. In a 2006 study of uterine LMS, 67 patients (diagnosed less than 45 years old) were screened to determine the frequency of *FH* pathogenic variants. A novel germline missense *FH* variant was identified in one patient, suggesting that 1.5% (1 out of 67) of uterine LMS have FTPS. Other data sets have not identified similar rates of predisposition in uterine LMS cohorts^[2,10]. A study identified three individuals out of 182

with FTPS, who developed cutaneous LMS^[67]. There are recent changes to diagnostic criteria for LMS, and lesions previously called LMS may in fact be atypical smooth-muscle neoplasms/leiomyomas thus older cohorts estimating the proportion of FTPS patients with LMS may not be truly accurate^[68]. The true prevalence of CPS, specifically in FTPS, may need to be re-evaluated in LMS given the potential overestimate of an LMS diagnosis in previous cohorts.

LMS in LFS is well-recognized, but genetic testing for cancer predisposition in LMS patients is not routinely performed; therefore, the true prevalence of germline *TP53* pathogenic variants in LMS remains unknown^[69,70]. In limited datasets, including Brazilian datasets, LMS may develop in 5%-10% of patients with clinically diagnosed LFS (unpublished data). In a 2015 study on LFS, 86 patients develop 105 STS. Of these STS, 25% were LMS^[18].

In a 2018 study characterizing the molecular profile of 49 patients with LMS, the authors identified three (6.1%) patients with pathogenic germline variants (one in *TP53* and two in *RB1*). The authors did not specify the location of the LMS nor whether the patients had any previous history of cancer^[2]. A 2020 study prospectively sequencing uterine sarcomas identified four patients with possible germline pathogenic variants. Two of these patients were diagnosed with high grade uterine LMS and were found to have MSH6 and MSH2 loss of protein expression via IHC. Neither were confirmed to have germline pathogenic variants in these DNA repair genes, but no additional somatic variants were identified to explain their tumor phenotype. Two additional patients were identified to have germline pathogenic variants in *TP53*, one was previously known to have LFS. In total, four of 107 (3.7%) patients had a possible CPS in a majority uterine LMS cohort^[10]. In a 2017 study that included 500 patients with metastatic cancers of many lineages, paired whole exome sequencing was performed. Two of the 23 (8.6%) total LMS patients were identified to have germline pathogenic variants in *RB1* and *APC*^[71].

In conclusion, additional prospective, longitudinal data are needed to determine the frequency of CPS amongst individuals diagnosed with LMS. Germline pathogenic variants in *TP53*, *RB1*, and other genes have been reported to cause LMS. A careful review of previous medical history and family history is helpful to determine eligibility for genetic counseling and germline genetic testing.

DESMOID-TYPE FIBROMATOSIS

Desmoid-type fibromatosis (DTF) occurs sporadically and in association with Familial Adenomatous Polyposis (FAP) caused by germline pathogenic variants in the *APC* gene. The two etiologies (sporadic and FAP) are associated with mutually exclusive mutations. Most DTF have somatic variants in the *CTNNB1* gene (β -catenin), and a small minority of DTF without somatic variants in *CTNNB1* are diagnosed in individuals with FAP^[72]. DTF without *CTNNB1* (or Wnt pathway activation) or *APC* variants have not been reported^[73]. To date, no other cancer predispositions have been identified to cause DTF.

Cancer predisposition association: FAP.

Risk for predisposition: 5%-15%.

Sarcoma subtype with most significant predisposition risk: NA.

In a 2006 study of DTF, 447 patients with desmoid tumors were evaluated to determine differences between sporadic and FAP-associated DTF. Of these patients, 70 had a diagnosis of FAP (15.4%). This study reported that the majority of FAP-associated DTF were abdominal and the majority of sporadic DTF were

extra-abdominal^[74]. In a 2011 study of DTF, 519 patients with DTF were evaluated and 39 patients were identified to have FAP (7.5%). An additional investigation identified that younger age of diagnosis (< 60 years old) and intra-abdominal location are significantly associated with a diagnosis of FAP^[75]. In a 2012 study of pediatric and adolescent DTF, 93 patients were included and 10 were found to have FAP (10.8%). All of these patients were younger than 21 years old^[76]. Other studies have confirmed similar rates of FAP diagnosis amongst patients with DTF^[77,78].

In conclusion, approximately 5%-15% of DTF are associated with underlying diagnoses of FAP. They are most often located in the abdomen and diagnosed at a younger age compared to sporadic desmoid tumors. DTF identified to have somatic *CTNNB1* gene mutations are unlikely to be due to underlying FAP.

MALIGNANT RHABDOID TUMOR (EXTRA-RENAL)

Malignant rhabdoid tumors (MRT) have significant genetic associations, specifically with the *SMARCB1* and *SMARCA4* genes. These tumors are commonly identified in the kidneys and the central nervous system, but can be seen in any soft tissue^[79]. Most research on predisposition to MRT has occurred when tumors are identified in the CNS, known as atypical teratoid/rhabdoid tumors (AT/RT). When MRTs occur in the familial setting, an underlying predisposition is likely.

Cancer predisposition association: Rhabdoid tumor predisposition syndrome.

Risk for predisposition: Up to 34%.

Sarcoma subtype with most significant predisposition risk: Atypical rhabdoid/teratoid tumor (AT/RT).

A 2010 study included 100 cases of MRTs for evaluation of underlying *SMARCB1* pathogenic variants. Of these patients, 17 had extrarenal MRTs and three of these patients were found to have an underlying *SMARCB1* germline pathogenic variant (17.6%). Six patients with multiple MRTs were included in the study, all had germline pathogenic variants in *SMARCB1*, and two of these patients had either multiple extrarenal tumors or an extrarenal tumor and renal tumor^[80]. In a 2011 retrospective study of 74 MRTs, including 26 extrarenal, 9 out of the 26 were identified to have a pathogenic germline variant in *SMARCB1* (34%)^[81]. The rates of germline pathogenic variants in AT/RT are similar to those in extrarenal sites, suggesting that germline variants are equally predisposed to various tumor locations^[81,82].

Pathogenic germline variants in SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4 (*SMARCA4*) have also recently been identified to cause MRTs^[83]. Unpublished data and personal communications have reported between 5%-15% of rhabdoid tumor predisposition syndrome is due to pathogenic variants in *SMARCA4*. It is unknown the proportion of extrarenal MRTs with *SMARCA4* germline variants^[84].

In conclusion, individuals presenting with extrarenal MRTs are at significant risk for rhabdoid tumor predisposition syndrome. It is most likely that individuals would have a *SMARCB1* germline pathogenic variant, but testing should also include *SMARCA4*. Individuals with multiple MRTs, including extrarenal, have a very high likelihood to have rhabdoid tumor predisposition syndrome.

GASTROINTESTINAL STROMAL TUMOR

Gastrointestinal stromal tumors (GIST) occur sporadically or in association with CPS. When familial GIST is identified, it is often associated with a cancer predisposition, but cancer predispositions can be diagnosed in apparently sporadic GIST. Gain-of-function somatic variants in *KIT* or *PDGFRa* (also written as *PDGFRA*) are the most common oncogenic driver genes in GIST, making up 75%-80% and < 10% of tumors respectively. There is a small subset (~15%) of GIST that are considered wild-type, negative for *KIT* or *PDGFRa* somatic variants^[85,86]. A portion of wild-type GIST are due to underlying cancer predispositions such as the hereditary paraganglioma and pheochromocytoma syndromes.

Cancer predisposition association: *KIT*, *SDH* genes, *NF1*, and *PDGFRa*.

Risk for predisposition: Unknown.

Sarcoma subtype with most significant predisposition risk: Gastric location.

Over 20 families have been reported with germline *KIT* pathogenic variants^[87]. Families with germline *KIT* variants may have other features beyond a risk to develop GIST, including dysphagia and hyperpigmentation. Reported variants in the *KIT* gene have been in exon 11, exon 13, and exon 17 - all are gain of function variants resulting in constitutional activation of *KIT*^[88-90]. Several families have been reported with germline *PDGFRa* variants^[87]. Much like germline *KIT* variants, individuals with germline *PDGFRa* may have other syndromic features beyond GIST risks, such as large hands^[91].

GIST predisposition understanding expanded in 2010 when authors evaluated wild-type GIST for germline pathogenic variants in the succinate dehydrogenase (*SDH*) genes (*SDHB*, *SDHC*, and *SDHD*). A total of 34 patients with wild-type GIST participated in the study, and none had a family history of paraganglioma. A single patient had a previous diagnosis of *NF1*. Four patients (12%) were identified to have germline pathogenic variants in *SDHB* ($N = 3$) and *SDHC* ($N = 1$) in this series of wild-type GISTs, and a total of five patients (14%) were identified to have a cancer predisposition^[92]. A 2011 study evaluated the proportion of GIST with *SDH* deficiency. A total of 1156 samples of GIST from various locations underwent IHC for *SDHB* expression, and 66 gastric GISTs were identified to have abnormal *SDHB* staining (66/756, 8.7%). The authors estimate that the true unselected proportion of *SDHB* deficient GISTs is around 7.5% after adjusting their analysis to unselect young onset GIST^[93]. A 2012 study evaluated *SDHA*-deficient GIST for germline variants in *SDHA*. A total of 33 wild-type GIST were included and four were identified to have *SDHA* pathogenic variants (12%)^[94]. A 2016 study evaluated 95 wild-type GISTs for *SDHB* expression, *SDH* gene sequencing, and *SDHC* methylation. Of these tumors, 84 were identified to be *SDH*-deficient and 31 were found to have a germline *SDH* pathogenic variant. An interesting finding was that 21 *SDH* deficient tumors had methylation of the *SDHC* promoter. This study further confirmed that *SDH* deficient tumors only occurred in the stomach^[95]. Approximately 1.5% of GIST are due to underlying *NF1* and also fall within the proportion of predisposition associated wild-type GIST^[96].

In conclusion, a significant portion of wild-type GIST are due to an underlying predisposition. Close attention to syndromic features and family history of other cancers (particularly paraganglioma and GIST) should assist providers to select patients most likely to have a predisposition. Since both *KIT* and *PDGFRa* are recurrently mutated in GIST, it is important to recognize the family history of GIST or other syndromic features to determine whether germline genetic testing is warranted. However, not all patients with predispositions causing GIST will have other features or family history and germline testing is indicated for all wild-type GIST.

OTHER STS

As outlined in [Table 1](#), there are other STS that do not have a defined cancer predisposition syndrome association. However, given the overall rarity of STS, the connection to STS development and germline variants may still need to be determined. If an individual presents with a STS that does not have a defined cancer predisposition association, referral to a genetic specialist may still be warranted. If that individual has had multiple tumors, has a family history of cancer, or has questions about their underlying etiology, referral may still be indicated. Close attention to personal and family history is essential for all caregivers.

CONCLUSIONS

A recurrent theme identified in this review was the lack of population level germline predisposition data amongst STS, thus prohibiting us from providing accurate cancer predisposition risk estimates for individual STS diagnoses. Due to the impact of diagnosing an individual with a CPS, such as offering surveillance for other cancer risks and providing predictive testing for family members, we advocate for continued research around genetic predisposition to STS. Providers treating patients for STS should pay close attention to previous medical histories, noting whether their patients have other cancer diagnoses, and family histories. However, not all cancer predispositions may be apparent in personal or family histories, so consideration of germline genetic testing or referral to a genetic specialist may be warranted in the absence of any concerning medical/family history depending on the STS diagnosis. Further, strong consideration should be given to STS associated with CPS as reviewed in [Table 2](#) by either performing germline genetic testing and/or referring to a genetic specialist. The field of STS and genetic predisposition continues to evolve as new discoveries are made providing greater insight into cancer risk, specifically within STS.

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Authors' contributions

Contributed to the conception and design, analysis, and draft of this work: Vagher J

Contributed to the conception and substantively revise this work: Kohlmann W, Schiffman JD

Substantively revised it: Dietz MS, Maese L

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Jennie Vagher: Consulting or Advisory Role: Invitae.

Wendy Kohlmann: Employment: BioFire Diagnostics.

Joshua Schiffman: Employment: PEEL Therapeutics, Leadership: PEEL Therapeutics, Stock and Other Ownership Interests: ItRunsInMyFamily.com, PEEL, Therapeutics, Honoraria: Affymetrix, Consulting or Advisory Role: N-of-One, Fabric Genomics.

Luke Maese: Honoraria: Jazz Pharmaceuticals, Consulting or Advisory Role: Jazz Pharmaceuticals.

Matthew Dietz: None.

Ethical approval and consent to participate

Not applicable.

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Not applicable.

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