Sarcomas Associated With Genetic Cancer Predisposition Syndromes: A Review

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Sarcoma • Hereditary • Cancer predisposition syndrome • Cancer genetics

ABSTRACT
Sarcomas are rare mesenchymal malignancies that demonstrate great clinical and biological heterogeneity. A variety of sarcomas develop in the context of well-defined heritable cancer predisposition syndromes, associations that are often overlooked, given the rarity and diversity of sarcomas and the equivalent relative infrequency of cancer genetic syndromes. This review describes in detail selected heritable cancer predisposition syndromes that are known to be associated with sarcomas. Beyond the molecular and clinical features that define each syndrome, disparities in clinical presentation, natural history, and treatment of syndrome-associated compared with otherwise histologically identical sporadic sarcomas will be described. The clinical approach to selected sarcoma subsets with a view to identifying possible associations with these syndromes will then be described. Although the treatment of the majority of sarcomas will not differ significantly between sporadic cases and those associated with predisposition syndromes, knowledge of features such as unique anatomic sites of affliction or excess toxicities with particular cytotoxic therapies can facilitate alterations in therapeutic strategies to maximize efficacy and minimize toxicity. In addition, recognition of cancer genetic predisposition syndrome will allow patients and their relatives to undertake appropriate genetic counseling and testing, as well as screening, surveillance, and interventional measures, as needed. Situating sarcomas within the genetic endowment of particular patients—specifically that which confers a higher risk of malignancy—will enable clinicians to better manage the patient as a whole, complementing the great efforts currently routinely undertaken to genomically characterize somatic tumor changes with a view to achieving the dream of personalized medicine. The Oncologist 2016;21:1002–1013

Implications for Practice: Sarcomas are uncommon malignancies that often occur sporadically but can also arise in the setting of a recognized heritable cancer predisposition syndrome. Identification of such associations when present can facilitate refinement and optimization of treatment strategies for the sarcoma so as to minimize toxicity and maximize efficacy. Discerning genetic predisposition can also facilitate institution of genetic counseling, as well as screening or surveillance schema for both the patient and his or her relatives, if required. Vigilance for these syndromes has the potential to significantly enhance the quality and comprehensiveness of sarcoma clinical management.

INTRODUCTION
Sarcomas are neoplasms of mesenchymal origin that comprise only 1% of adult malignancies, but a significantly greater proportion (15%) of childhood cancers [1]. Sarcomas are extraordinarily heterogeneous, comprising more than 70 distinct histological subtypes, with additional layers of biologic variability conferred by differences in genetic complexity and driver molecular aberrations, as well as particularities in clinical factors such as age of onset and anatomic site of affliction. These differences translate into great diversity in treatment regimens and outcomes that have rendered transformative progress in the overall management of sarcomas challenging. In the setting of localized disease, complete surgical excision, coupled in some instances with adjuvant radiation, can be curative, with two thirds of patients surviving more than 5 years [2]. In advanced disease, however, prognosis is dismal, with median survival of approximately 1 year [3], speaking to the critical need for early detection to ensure optimal outcomes.

An intriguing element in the care of patients with sarcoma centers on their association, in a fraction of cases, with heritable cancer predisposition syndromes (Table 1). Ever since the preeminent German pathologist Heinrich von Recklinghausen described and systematically characterized the multiple neurofibromas of the syndrome we now call neurofibromatosis type 1 in the 1880s [4], a great deal has been learned about this and many other heritable cancer predisposition
<table>
<thead>
<tr>
<th>Inherited syndrome</th>
<th>Inheritance</th>
<th>Genes</th>
<th>Chief clinical features</th>
<th>Associated sarcomas</th>
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</thead>
<tbody>
<tr>
<td>FAP</td>
<td>AD</td>
<td>APC at 5q21-22</td>
<td>Thousands of colonic adenomatous polyps with colon cancer at age &lt;40 years, osteomas, hepatoblastomas</td>
<td>Desmoid tumors</td>
</tr>
<tr>
<td>Beckwith-Wiedemann</td>
<td>Sporadic/AD</td>
<td>CDK4/11C, KCNQ1OT1, LIT1, IGF2, and H19</td>
<td>Overgrowth syndrome: macroglossia, omphalocele, hemihypertrophy, gigantism</td>
<td>Embryonal RMS</td>
</tr>
<tr>
<td>Bloom</td>
<td>AR</td>
<td>RECQL3 on 15q26.1</td>
<td>Progeroid syndrome: growth retardation, sun sensitivity, telangiectasias, and other skin changes</td>
<td>Osteosarcoma, embryonal RMS</td>
</tr>
<tr>
<td>Carney-Stratakis</td>
<td>AD</td>
<td>SDHB at 1p36, SDHC at 1q21, SDD at 11q23</td>
<td>Dyad of paraganglioma and GIST</td>
<td>GIST</td>
</tr>
<tr>
<td>Constitutional mismatch repair syndrome</td>
<td>AR</td>
<td>PSM2 at 7p/q22.1</td>
<td>Predisposition to hematologic malignancies, CNS tumors, gastrointestinal tumors and polyps, and other embryonic tumors</td>
<td>Embryonal RMS</td>
</tr>
<tr>
<td>Costello</td>
<td>AD</td>
<td>HRAS at 11q15 / 12p12.1</td>
<td>RASopathy: coarse facies, short stature, cardiac anomalies, developmental delay, and congenital myopathy</td>
<td>Embryonal RMS</td>
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<td>Familial GIST</td>
<td>AD</td>
<td>KIT, PDGFRA at 4q12</td>
<td>Multifocal GISTs in setting of interstitial cells of Cajal hyperplasia</td>
<td>GIST</td>
</tr>
<tr>
<td>Familial pleuropulmonary blastoma (DICER 1 syndrome)</td>
<td>AD</td>
<td>Dicer1 at 14q23.13</td>
<td>Predisposition to pleuropulmonary blastomas and other dysplastic/malignant lesions</td>
<td>Embryonal RMS</td>
</tr>
<tr>
<td>Familial rhabdoid predisposition syndrome</td>
<td>AD</td>
<td>SMARCB1/INI1 at 22q11.33</td>
<td>Renal or extrarenal malignant rhabdoid tumors, CNS tumors</td>
<td>Malignant rhabdoid tumor</td>
</tr>
<tr>
<td>Gorlin syndrome/nevoid basal cell carcinoma syndrome</td>
<td>AD</td>
<td>PTCH at Xp11.23 / 9q22</td>
<td>Multiple basal cell carcinomas, odontogenic keratocysts, palmar/plantar pits, calcification of the falx cerebri, rib abnormalities</td>
<td>Embryonal RMS</td>
</tr>
<tr>
<td>Hereditary retinoblastoma</td>
<td>AD</td>
<td>RB1 at 13q14.2</td>
<td>Retinoblastoma, often bilateral and in early childhood (&lt;5 years age)</td>
<td>Osteosarcomas, STS</td>
</tr>
<tr>
<td>HLRCC</td>
<td>AD</td>
<td>FH at 1q42</td>
<td>Cutaneous and uterine leiomyomas, type 2 papillary RCC</td>
<td>Uterine leiomyosarcoma</td>
</tr>
<tr>
<td>LFS</td>
<td>AD</td>
<td>TPS3 at 17p13.1, CHEK2 at 22q12</td>
<td>Predisposition to early onset of multiple cancers, most commonly premenopausal breast cancer, STS, CNS tumors, osteosarcomas, adrenocortical carcinomas, and leukemias</td>
<td>Osteosarcomas, RMS, STS</td>
</tr>
<tr>
<td>Mosaic variegated aneuploidy</td>
<td>AR</td>
<td>BUB1B at15q15</td>
<td>Intrauterine growth restriction, microcephaly, predisposition to cancer (Wilms tumor, hematologic malignancies).</td>
<td>Embryonal RMS</td>
</tr>
<tr>
<td>Multiple osteochondromas</td>
<td>AD</td>
<td>EXT1 at 8q24, EXT2 at 11p11</td>
<td>Multiple osteochondromas</td>
<td>Chondrosarcomas</td>
</tr>
<tr>
<td>NF1</td>
<td>AD</td>
<td>NFI at 17q11.2</td>
<td>Café-au-lait spots, neurofibromas, iris hamartomas (Lisch nodules), optic gliomas, skeletal abnormalities</td>
<td>MPNST, GIST, RMS</td>
</tr>
<tr>
<td>Nijmegen breakage syndrome</td>
<td>AR</td>
<td>NBS1 at 8q21.3</td>
<td>Chromosomal instability syndrome associated with microcephaly, growth retardation, immunodeficiency, and tumor predisposition</td>
<td>Embryonal RMS</td>
</tr>
</tbody>
</table>
syndromes. Although the initial characterization of these syndromes involved careful clinical observation and annotation only, epochal advances in molecular biology and bioinformatics have enabled us to interrogate these syndromes to a much greater degree of genetic detail and depth, refining our understanding and classification of these syndromes at every step. For example, Li-Fraumeni syndrome was first defined in 1969 based on the observation of early onset cancers transmitted in autosomal-dominant fashion in four families [5]; germline mutation of TP53 was discovered to be the genetic aberration responsible for this syndrome more than 20 years later [6]. The clinical and genetic features of this syndrome continue to be refined to this day, with a recent publication reporting a long and detailed follow-up of more than 300 affected TP53 mutation carriers, suggesting significant updates to clinical criteria for diagnosis and putative clinical implications of mutational subtypes [7].

Although there are ample data detailing the clinical and genetic features of individual syndromes, as well as well-defined therapeutic strategies for individual sarcoma subtypes, there are no guidelines, as far as we know, to aid clinicians in evaluating for familial syndromes or cancer predisposition when managing sarcoma patients. Accurate identification of such syndromes through both clinical evaluation and targeted specific investigations allows clinicians to adapt their therapy to the particular needs of patients with genetic predisposition, if any, and plan appropriate genetic counseling and surveillance for the patients and their relatives.

In this review, we aim to describe the most common cancer predisposition syndromes associated with sarcomas (Table 2) and suggest a sound and clinically practical approach to the question of inherited cancer predisposition when treating sarcomas. Although we recognize the existence of many more benign soft-tissue tumors than malignant ones, and a significant number of nonheritable tumor-associated syndromes, they are beyond the scope of this review; we shall focus only on malignant mesenchymal tumors arising in the setting of recognizably heritable cancer predisposition syndromes.

**Table 1. (continued)**

<table>
<thead>
<tr>
<th>Inherited syndrome</th>
<th>Inheritance</th>
<th>Genes</th>
<th>Chief clinical features</th>
<th>Associated sarcomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noonan syndrome</td>
<td>AD</td>
<td>PTPN11 at 12q24, SOS1 at 2-22</td>
<td>RASopathy associated with dysmorphic facies, short stature, neck webbing, cardiac anomalies, deafness, and bleeding diathesis</td>
<td>Embryonal RMS, giant cell tumor of bone, granular cell tumor, PVNS</td>
</tr>
<tr>
<td>Rothmund-Thomson syndrome II</td>
<td>AR</td>
<td>REQL4 at 8q24.3</td>
<td>Characterized by poikiloderma, as musculoskeletal (short stature, radial defects, and hypoplastic patellae) and organ abnormalities (esophageal atresia, cataracts, and myelodysplasia)</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Rubinstein-Taybi</td>
<td>AD</td>
<td>CREBBP at 16p13.1</td>
<td>Multiple congenital anomalies, developmental delay, microcephaly, and dysmorphic features</td>
<td>Embryonal RMS, LMS</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>AD</td>
<td>TSC1 at 9q34, TSC2 at 16p13.3, TSC3 at 12q22-24.1</td>
<td>Hamartomas of multiple organs, angiomyolipomas, other renal tumors (cysts and RCCs), lymphangiomylomatosis, and angiofibromas</td>
<td>PEComa tumor (Pacoima), chordomas</td>
</tr>
<tr>
<td>Werner</td>
<td>AR</td>
<td>WRN at 8p11.2-12</td>
<td>Progeroid syndrome with tight atrophic skin and bird-like facies, early onset atherosclerosis, diabetes, and osteoporosis</td>
<td>Osteosarcoma, embryonal RMS</td>
</tr>
</tbody>
</table>

Abbreviations: AD, autosomal dominant; APC, adenomatous polyposis coli; AR, autosomal recessive; CNS, central nervous system; FAP, familial adenomatous polyposis; FH, fumarate hydratase; GIST, gastrointestinal stromal tumor; HL RCC, hereditary leiomyomatosis and renal cancer; LFS, Li-Fraumeni syndrome; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; NF1, neurofibromatosis type 1; PDGFR A, platelet-derived growth factor receptor A; PEComa, perivascularepithelioid cell tumor; PVNS, pigmented villonodular synovitis; RCC, renal cell carcinoma; RMS, rhabdomyosarcoma; STS, soft-tissue sarcoma; TSC1, tuberous sclerosis complex 1.

**HEREDITARY CANCER PREDISPOSITION SYNDROMES ASSOCIATED WITH SARCOMAS**

**Li-Fraumeni Syndrome**

Li-Fraumeni syndrome (LFS) is an autosomal dominant disorder associated with germline loss-of-function mutations in TP53, one of the cell’s chief bulwarks to the development of neoplasia, whose loss of function as a tumor suppressor is implicated in >50% of all cancers. In the classic clinical definition of this syndrome, the proband had to have a sarcoma diagnosis before 45 years of age [5]; subsequent modifications of this criteria have allowed for any of the multiple cancers associated with LFS to afflict the proband, namely, sarcoma, brain tumor, premenopausal breast cancer, adrenocortical carcinoma, leukemia, or bronchoalveolar lung cancer [7]. Approximately 80% of families meeting classic LFS criteria harbor germline TP53 mutations. A key issue with using such criteria is that diagnosis of the syndrome predates diagnosis of the primary malignancies, with no opportunity for preventive intervention; thus, obtaining a complete family history in every patient with a new diagnosis of sarcoma is critical. Based on data from the International...
Table 2. Clinical and genetic features of selected sarcoma histological subtypes associated with genetic predisposition syndromes

<table>
<thead>
<tr>
<th>Inherited syndrome (mode of inheritance)</th>
<th>Clinical features of inherited syndrome</th>
<th>Demographic</th>
<th>Unique clinical features of the sarcoma (compared with sporadic cases)</th>
<th>Associated gene(s)</th>
<th>Other associated malignant tumors</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIST</td>
<td>Dyad of paraganglioma in conjunction with GIST</td>
<td>1% of GIST almost exclusively in pediatric population</td>
<td>Stomach or small-bowel GIST</td>
<td>SDH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carney-Stratakis (AD)</td>
<td></td>
<td>&lt;1% of GIST</td>
<td>Multifocality of GIST, ICC hyperplasia</td>
<td>KIT or PDGFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial GIST</td>
<td></td>
<td>&lt;1% of GIST 7% of NF1 develop GIST</td>
<td>Intestinal GIST, multifocal, indolent biology</td>
<td>NF1</td>
<td>MPNST</td>
<td></td>
</tr>
<tr>
<td>NF1 (AD)</td>
<td></td>
<td>2 of 7 criteria: Six or more café-au-lait spots or hyperpigmented macules, axillary or inguinal freckles (&gt;2 freckles), two or more typical neurofibromas or one plexiform neurofibroma, optic nerve glioma, two or more iris hamartomas (Lisch nodules), sphenoid dysplasia or typical long-bone abnormalities such as pseudoarthrosis, first-degree relative with NF1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td></td>
<td>Location similar to sporadic, age younger than general population</td>
<td>Sarcomas, premenopausal breast cancer, brain tumors, adrenocortical carcinomas, leukemia</td>
<td>TP53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFS (AD)</td>
<td>Proband diagnosed with sarcoma age &lt;45 years, first-degree relative with any cancer age &lt;45 years, any first- or second-degree relative with any cancer age &lt;45 years or sarcoma any age</td>
<td>13% of LFS develop osteosarcoma</td>
<td>Location similar to sporadic, age younger than general population</td>
<td>Sarcomas, premenopausal breast cancer, brain tumors, adrenocortical carcinomas, leukemia</td>
<td>TP53</td>
<td>Sarcomas, premenopausal breast cancer, brain tumors, adrenocortical carcinomas, leukemia</td>
</tr>
<tr>
<td>Hereditary retinoblastoma (AD)</td>
<td>Malignant retinal tumor presenting age &lt;5 years</td>
<td>Location similar to sporadic, age younger than general population</td>
<td>Sarcomas, premenopausal breast cancer, brain tumors, adrenocortical carcinomas, leukemia</td>
<td>RB1</td>
<td>STS, melanoma, brain tumors, breast cancer</td>
<td>Genetic testing of families as more intensive surveillance leads to less morbid therapy; mosaicism possible</td>
</tr>
<tr>
<td>RTS II</td>
<td>Poikiloderma is hallmark; the rash spreads to extremities and buttocks, and then enters chronic lifelong phase. Other features include skeletal dysplasia, sparse eyebrows/lashes, short stature, cataracts, and dental abnormalities</td>
<td>32% of RTS II patients develop osteosarcoma, at a mean age of 11 years</td>
<td>UPS BCC and SCC MDS/AML lymphoma; gastric carcinoma</td>
<td>REQL4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued)
### Table 2. (continued)

<table>
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<tr>
<th>Inherited syndrome (mode of inheritance)</th>
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<th>Associated gene(s)</th>
<th>Other associated malignant tumors</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Werner syndrome</td>
<td>Phenotype that mimics premature aging; prematurely aged appearance in 2nd and 3rd decades. Bilateral cataracts, scleroderma-like skin changes, short stature, premature graying, and loss of scalp hair</td>
<td>Largest number in Japan; frequency strongly influenced by local founder mutations and consanguinity; 7.7% of Werner syndrome develop osteosarcoma</td>
<td></td>
<td>WRN</td>
<td>Thyroid carcinoma, melanoma, STS, hematolymphoid malignancies</td>
<td>WRN encodes a DNA helicase</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>Multiple osteochondromas, with at least 2 osteochondromas in the juxta-epiphyseal region of long bones observed radiographically</td>
<td>First 2 decades of life</td>
<td></td>
<td>EXT1 or EXT2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STS</td>
<td>Proband diagnosed with sarcoma age &lt;45 years, first-degree relative with any cancer age &lt;45 years, any first- or second-degree relative with any cancer age &lt;45 years or sarcoma any age</td>
<td>11%–17% of LFS develop STS</td>
<td></td>
<td>TP53</td>
<td>Sarcomas, premenopausal breast cancer, brain tumors, adrenocortical carcinomas, leukemia</td>
<td>UPS</td>
</tr>
<tr>
<td>NF1 (AD)</td>
<td>2 of 7 criteria: Six or more café-au-lait spots or hyperpigmented macules, axillary or inguinal freckles (&gt;2 freckles), two or more typical neurofibromas or oneplexiform neurofibroma, optic nerve glioma, two or more iris hamartomas (Lisch nodules), sphenoid dysplasia or typical long-bone abnormalities such as pseudoarthrosis, first-degree relative with NF1</td>
<td>50% of MPNSTs are NF1-associated; 10% of NF1s develop MPNST</td>
<td>Conflicting data on prognostic impact of NF1 on MPNST (possibly associated with inferior prognosis compared with sporadic MPNST)</td>
<td>NF1</td>
<td>GIST</td>
<td>MPNST</td>
</tr>
</tbody>
</table>
Aggressive fibromatosis

The percentage of intra-abdominal disease among FAP-associated desmoid tumors is 80%, compared with 5% for sporadic desmoid tumors. Intra-abdominal disease is associated with significant morbidity, usually related to bowel obstruction. Inherited syndrome

Clinical features of inherited syndrome

Demographic

7.5% of desmoid tumors have FAP; 15% of FAP will develop desmoid tumors; average age at diagnosis: 32 years

Associated gene(s)

Table 2.

Type II papillary RCC
Leiomyosarcoma

FH

1.5% of leiomyosarcomas in patients aged 45 years

Abbreviations: AD, autosomal dominant; AML, angiomyolipoma; APC, adenomatous polyposis coli; BCC, basal cell carcinoma; FAP, familial adenomatous polyposis; FH, fumarate hydratase; GIST, gastrointestinal stromal tumor; ICC, intrahepatic cholangiocarcinoma; LFS, Li-Fraumeni syndrome; MDS, myelodysplastic syndrome; MPNST, malignant peripheral nerve sheath tumor; NF1, neurofibromatosis type 1; PDGFR, platelet-derived growth factor receptor A (PDGFRA), a group that, unsurprisingly, displays decreased sensitivity to the tyrosine kinase inhibitor that targets these two oncoproteins, imatinib. In the pediatric population, rhabdomyosarcoma has also been noted to occur 20 times more frequently among NF1-affected children compared with

Neurofibromatosis Type 1

Also known as von Recklinghausen’s disease, neurofibromatosis type 1 (NF1) is an autosomal dominant disorder affecting 1 in 3,000 live births, making it the most common human cancer predisposition syndrome. It is most distinctively characterized by the development of widespread nerve sheath tumors, termed neurofibromas, and multiple areas of cutaneous hyperpigmentation, or café-au-lait spots. Other clinical features include axillary freckling, optic gliomas, iris hamartomas (Lisch nodules), bone dysplasia, and positive family history; the diagnosis of NF1 is made when any two of these seven clinical criteria are met. The syndrome is genotypically defined by loss-of-function mutations to the NF1 gene encoding the tumor suppressor neurofibromin, which leads to untrammeled mitogenic signaling down the mitogen-activated protein kinase (MAPK) pathway. Patients with NF1 syndrome have an 8%–13% lifetime risk of developing malignant peripheral nerve sheath tumor (MPNST), an aggressive, genetically complex soft-tissue sarcoma that comprises 2% of all sarcomas [16]. NF1 syndrome has also been associated with the development of gastrointestinal stromal tumors (GISTs), the mesenchymal tumor deriving from the interstitial cells of Cajal that line the gastrointestinal tract. Data from a Swedish cancer registry showed that 7% of NF1 patients develop GIST; NF1-associated GISTs comprise approximately 1.5% of all GIST cases [17]. These GISTs are often associated with an indolent biology and have a predilection for the small bowel. They are part of approximately 10% of GISTs not mutated for either cKIT or platelet-derived growth factor receptor A (PDGFRA), a group that, unsurprisingly, displays decreased sensitivity to the tyrosine kinase inhibitor that targets these two oncoproteins, imatinib. In the pediatric population, rhabdomyosarcoma has also been noted to occur 20 times more frequently among NF1-affected children compared with
children without NF1, with the urogenital system being the most commonly affected anatomic site [18].

Hereditary Retinoblastoma Syndrome
Hereditary retinoblastoma syndrome is an autosomal dominant condition caused by a germline mutation in the RB1 gene, a tumor suppressor that regulates cell-cycle progression and modulates the transcription of a large number of target genes involved in apoptosis, autophagy, and chromosomal stability, among other roles [19]. Hereditary retinoblastoma is genotypically defined by a germline mutation in the tumor suppressor RB1, with a “second hit” causing inactivation of both alleles and the development of malignancy. This most often occurs before 1 year of age, in the embryonic retina of both eyes, occurring with a penetrance of approximately 90%. Approximately 13% of patients with unilateral disease, however, also carry a germline mutation in RB1 [20]. Long-term survivors have a significantly increased risk of second primary nonocular malignancies, comprised primarily of bony tumors, soft-tissue sarcomas, and melanomas, with leiomyosarcomas and osteosarcomas accounting for more than half of these second primary tumors [21]. Notably, up to 40% of these second primary neoplasms occur outside the radiation field, speaking to the multiple factors beyond radiation for the primary retinoblastoma, including alkylator chemotherapy and underlying genetic susceptibility, as causes for the second malignancy. Indeed, there is ample molecular evidence for an association with hereditary retinoblastoma with defects in the RB1 pathway, providing a mechanistic biological explanation for the association of sarcomas with this syndrome beyond radiation-associated etiology [22, 23]. Patients presenting with newly diagnosed sarcoma thus need to be screened for personal history of childhood cancers like retinoblastoma. The age of presentation in hereditary retinoblastoma survivors varies; bone sarcomas usually develop in survivors between the 1st and 2nd decade of life, whereas soft-tissue sarcomas can arise between 10 and 50 years after retinoblastoma diagnosis [24]. Survivors of hereditary retinoblastoma also have elevated risks of epithelial tumors of bladder, lung, and breast [25], so diagnosis of sarcomas synchronously or metachronously with these cancers should trigger an evaluation for hereditary retinoblastoma.

GIST Predisposition Syndromes
Familial GIST syndromes, unsurprisingly, involve aberrations in the genes pathogenically linked to the development of GIST. Approximately 80% of sporadic GISTs are mutated for the cKIT oncoprotein; there are now more than 20 kindreds reported with germline KIT mutations and associated familial GIST, inherited in an autosomal dominant fashion [26]. In addition to being predisposed to developing GIST, patients may develop pigment changes of the skin, urticaria pigmentosa, myenteric plexus hyperplasia, and dysphagia. There have also been several reported kindreds of GIST in patients with germline mutations of PDGFR, a gene mutated in approximately 10% of sporadic GISTs [27]. Another form of familial GIST can arise the setting of Carney-Stratakis syndrome, which clinically manifests as a dyad of paragangliomas and GISTs, arising from a germline mutation in one of the subunits of succinate dehydrogenase (SDH), a mitochondrial enzyme complex critical to cellular metabolism [28]. SDH-deficient GISTS as a group form approximately half of the 10% of GISTS not mutated for cKIT or PDGFR, with the majority of pediatric GISTS (comprising <5% of all GISTS) being SDH-deficient [29]. A proportion of these GISTS in children and young adults are associated with pulmonary chondromas and/or paragangliomas, referred to as the Carney triad, a nonheritable syndrome not to be confused with Carney-Stratakis syndrome. There are currently no data to suggest that familial GISTs should be managed any differently than sporadic GISTS.

Familial Adenomatous Polyposis
Familial adenomatous polyposis is primarily an inherited colorectal cancer syndrome characterized by the development of hundreds to thousands of adenomas throughout the large bowel. The autosomal-dominant syndrome is caused by germline mutation of adenomatous polyposis coli (APC). This tumor suppressor is involved in modulating the levels of β-catenin, a protein involved in mitogenic signaling. The penetrance of familial adenomatous polyposis (FAP) is nearly 100%, with virtually all patients developing colorectal cancer by the 4th decade of life, if not detected early through surveillance endoscopy and treated with prophylactic surgery. Patients with FAP are also predisposed to developing other neoplasms, including desmoid tumors or aggressive fibromatosis. These sarcomas of intermediate malignant potential that, although not associated with the development of widely metastatic disease, are locally invasive and predisposed to repeated local recurrences that can lead to morbidity and mortality. The absolute lifetime risk of developing desmoid tumors in FAP is 15% [30]. A Dutch study of more than 500 patients revealed the incidence of FAP among patients with desmoid tumors to be 7.5%, with 85% of these FAP-associated desmoids diagnosed in the setting of known FAP [31]. FAP-associated desmoids differ from sporadic desmoids both genetically and phenotypically. Unlike APC-mutated FAP-associated desmoids, sporadic desmoids are most often the result of mutations in the β-catenin gene, CTNNB1. Up to 80% of FAP-associated desmoids arise intra-abdominally, as opposed to only 5% of sporadic desmoids, the majority of which arise extra-abdominally, in part explaining the increased morbidity of FAP-associated desmoids compared with those arising sporadically, as well as their status as one of the leading causes of death in FAP [32]. The morbidity of such FAP-associated intra-abdominal or mesenteric desmoids is often prominent, leading to interventions like surgery and systemic therapy. This is distinct from extra-abdominal desmoids, which can often be managed expectantly, especially if disease bulk and anatomical factors are favorable [33].

Tuberous Sclerosis Complex
Tuberous sclerosis complex is an autosomal dominant multisystem disorder that almost invariably affects the central nervous system. Epilepsy occurs in 80%–90% of patients and is often difficult to control; almost half of patients will have some degree of intellectual disability [34]. The main genetic defect involves loss-of-function germline mutations of tumor suppressor genes tuberous sclerosis complex 1 (TSC1) and TSC2, critical negative regulators of the mTOR signaling pathway. These genes
encode proteins that inhibit the RAS family GTPase Rheb, the
avtivator of the mechanistic target of rapamycin 1 complex, a
key regulator of protein synthesis. This syndrome is also
associated with several abnormal proliferations, including
intracranial tumors (subependymal nodules and subependy-
mal giant cell astrocytomas) and a range of extracranial
tumors, including angiomylipomas (AMLs) of the kidney,
clear cell “sugar” tumor of the lung, and lymphangioleiomyo-
matosis (LAM) of the lung [35]. These extracranial tumors can
be subsumed under the pathological category perivascular
epithelioid cell tumor (PEComa). These are histopathologically
well-defined entities that appear to be driven by mTOR pathway
overactivity, for which use of mTOR pathway antagonists has
shown satisfactory responses and improvements in outcomes
[36, 37]. Their incidence is approximately 200 cases worldwide
per year, and they can arise from almost any organ. Most
PEComas other than AML and LAM are sporadic, with only a
small subset associated with the TSC [38].

Hereditary Leiomyomatosis and Renal Cell Carcinoma
Hereditary leiomyomatosis is an autosomal dominant syn-
drome, characterized predominantly by the development of
cutaneous and uterine leiomyomatosis, as well as renal tumors,
most distinctively papillary renal cell carcinoma (RCC) in a
fraction of patients, one of the more aggressive forms of
renal cancer. The underlying genetic aberration is a germline
mutation in the fumarate hydratase (FH) gene, which encodes
the tricarboxylic acid cycle enzyme that converts fumarate to
malate, an important step in oxidative phosphorylation and
cellular energetics. Loss of function of fumarate hydratase
leads to a shift to aerobic glycolysis and accumulation of
fumarate, which leads to overactivity of hypoxia-inducible
factor-1α and increased transcription of its target genes such
as vascular endothelial growth factor [39]. The development of
uterine leiomyosarcoma has only been reported very in-
frequently among hereditary leiomyomatosis and renal cancer
(HLRCC) patients [40]. A Finnish study of early onset uterine
leiomyosarcoma showed that 1.5% of seemingly sporadic,
nonsyndromic cases of uterine leiomyosarcoma evaluated
harbored FH germline mutations [41]. Among HLRCC patients,
the majority of families with RCCs—and the only cases of
uterine leiomyosarcoma—have been reported in Finland [42,
43]. A genome-wide linkage-analysis study failed to find
evidence for a genetic modifier for RCC risk [42]. This apparent
clustering is thus probably explained by differences in
recruitment methodology across various reported series,
predisposing to ascertainment bias, in addition to chance
variation in the prevalence of rare diseases between
different small cohorts.

Management of Specific Sarcomas Accounting for
Possibility of Inherited Cancer Predisposition
The optimal family history for in the evaluation of any new
patient with cancer is the three-generation pedigree used in
genetic counseling. It is recognized, however, that such a
comprehensive evaluation is logistically challenging in a busy
clinical oncology practice. Consistent with recent American
Society of Clinical Oncology guidelines for collection and use of
cancer family history for oncology care providers [44], we
would advocate a minimum adequate family history as family
history of cancer in first- and second-degree relatives. For each
relative with cancer, minimum data required are the type of
primary cancer, the age at diagnosis of each primary cancer,
and whether the relative is along the maternal or paternal
lineage.

As a general rule, the primary treatment of patients whose
sarcoma arises as part of an inherited cancer predisposition
syndrome does not differ significantly from that of the same
sarcoma arising sporadically. For the vast majority of sarcomas,
surgical extirpation with adequate margins remains the
cornerstone of care. That being said, there should be a
heightened concern for the short- and long-term toxicity of
cytotoxic agents (chemotherapy and radiotherapy) in the
treatment of patients with particular syndromes (LFS and
hereditary retinoblastoma syndrome), the value of which
needs to be framed against each individual patient’s prognosis
in totality. The recognition of particular genotype-phenotype
correlations can certainly facilitate surveillance, diagnosis, and
therapy of the patient’s sarcoma, as well as other manifesta-
tions of the syndrome, both neoplastic and otherwise. Clearly,
early apprehension of particular syndromes with well-defined
inheritance will facilitate appropriate genetic counseling to
guide fertility and surveillance protocols both for the patient
and his or her relatives.

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individual patient’s prognosis in totality.

GIST
In spite of its relative cytogenetic and genomic simplicity, as
well as its status as the archetypal oncogene-addicted tumor,
GIST represents a molecularly complex family of tumors,
rather than a uniform biological entity [45]. Validated clinic-
opathologic risk factors, such as size, mitotic rate, anatomic origin,
and tumor rupture, are more important than genotype in
diagnosing the treatment of patients with particular syndromes
(LFS and hereditary retinoblastoma syndrome), the
value of which needs to be framed against each
individual patient’s prognosis in totality.

PDGFRα-mutant
GISTs (10%) are generally associated with more favorable
growth in totality. KIT is the
gene most commonly mutated, affecting 80% of GIST patients.
In primary disease, KIT-mutant GISTs can have varying prog-
oses, but are generally imatinib-sensitive. PDGFRα-mutant
GISTs (10%) are generally associated with more favorable
prognosis compared with KIT-mutant GISTs [43]. However, the
PDGFRα exon 18 d842V mutation, affecting approximately
half of GIST cases mutated for PDGFRα, confers imatinib
resistance—these patients should not receive imatinib. The
10% of GIST patients wild-type for KIT and PDGFRα dem-
strate an evolving complexity, with the best characterized
groups being the MAPK-pathway mutated and SDH-deficient
GISTs. These GISTs are also generally predisposed to indolent
biologies and relative imatinib resistance, although these data necessarily accrue from very small patient series [47]. Imatinib-resistant KIT-mutated GIST is almost always driven by secondary mutations in KIT, for which second-line therapies have varying activities depending on the nature of the secondary mutation. The utility of genotype-directed therapy in this setting is limited by clonal heterogeneity and ongoing evolution of the resistant tumors.

Patients with GIST should have a history and physical examination to evaluate for signs and symptoms of functional gastrointestinal symptoms, cutaneous signs or thoracic lesions, suggestive of familial GIST or Carney-Stratakis syndrome. The treatment for GIST in the setting of these syndromes would not be different from that as described for sporadic GIST.

Osteosarcoma
Osteosarcomas are the most common primary bone tumor. They are genomically complex tumors, defined pathologically by their characteristic feature of laying down new bone or osteoid. There are two peaks in incidence, the first in the 2nd and 3rd decades of life, arising in the long bones most commonly the distal femur, and the second in the 6th and 7th decades of life, in this setting more commonly secondary to an environmental insult, such as chronic inflammation (e.g., secondary to Paget’s disease of bone) or radiotherapy for cancer.

Approximately 10% of osteosarcomas are associated with genetic cancer predisposition syndromes [48]. The most prominent are LFS and hereditary retinoblastoma syndrome, a finding, when considered together with the known presence of defects in TP53 and RB function in sporadic osteosarcomas [49] speaks to the importance of these tumor suppressors in osteosarcomagenesis. Another group of syndromes associated with osteosarcomas is the DNA helicase mutation-related syndromes, autosomally recessive inherited syndromes where patients usually present with developmental and physical abnormalities; in this setting, osteosarcoma is usually diagnosed even earlier, in the 1st decade of life [50]. Otherwise, there are no known clinical differences in prognosis and treatment between osteosarcomas presenting in the setting of genetic predisposition or sporadically. Treatment comprises combination chemotherapy combined with complete surgical excision, with the extent of chemotherapy-induced tumor necrosis being prognostic for eventual outcomes. The utility of radiation therapy is limited, so the need for vigilance to avoid radiation is less prominent. Most patients who present with osteosarcoma will be in the adolescent and young adult age group (16–39 years old)—if the tumor arises in the setting of genetic cancer predisposition, these patients may benefit from genetic testing and subsequent surveillance. Thus, all patients should have a thorough family history and physical examination to exclude phenotypic presence of syndromes. Li Fraumeni may not present with any phenotypic features if there is no family history, so it may arguably be of value to refer all newly diagnosed osteosarcomas for genetic counseling to discuss the evaluation for germline TP53 mutation.

Rhabdomyosarcoma
Rhabdomyosarcomas are skeletal muscle tumors composed of several histologic variants, of which the most common in children and young adults is embryonal rhabdomyosarcoma (ERMS), followed by alveolar rhabdomyosarcoma (ARMS). ERMS is composed of cells with features of embryonal skeletal muscle cells. Up to 80% of cases arise in the 1st decade of life. The head and neck and genitourinary system are the main anatomic sites of involvement, with less than 10% of cases affecting the extremities. ARMS are highly cellular tumors containing a monomorphous population of primitive cells with features of arrested myogenesis [1]. Approximately 80% of ARMS are characterized by translocations that either juxtapose PAX3 (chromosome 2) or PAX7 (chromosome 1), with FOXO1 on chromosome 13, to generate chimeric fusion genes [51]. A very small subset of ERMS and ARMS are associated with inherited cancer predisposition syndromes. These include LFS, hereditary retinoblastoma syndrome, Beckwith-Wiedemann syndrome, and RASopathies such as Costello syndrome and neurofibromatosis type 1 [52]. The majority of syndromic rhabdomyosarcoma (RMS) has been ERMS, and those with morphologic features of ARMS often lack the PAX-FOXO1 translocations. Treatment of ERMS and ARMS is multimodal, often involving surgery, radiation, and multiagent chemotherapy according to clinicopathologic prognostication schema and therapeutic regimens developed by the Intergroup Rhabdomyosarcoma Study Group as part of the Children’s Oncology Group.

Soft-Tissue Sarcomas
As described, the general principles of therapy for soft-tissue sarcomas arising from the extremity, viscerum, retroperitoneum, or head and neck region apply equally to sporadic or inherited disease. In the absence of metastasis, the most critical element of treatment is complete surgical removal with adequate margins, with consideration of adjuvant radiation therapy to optimize local control [53]. The value of radiation however, needs to be balanced against the heightened risk of second malignant neoplasms in these patients, over and above their inherent increased risk for developing malignancy, which has been repeatedly demonstrated in patients with hereditary retinoblastoma syndrome and LFS [54, 55]. The role of adjuvant chemotherapy in completely resected soft-tissue sarcoma remains controversial. A meta-analysis evaluating 18 trials revealed absolute risk reductions in recurrence and death of 12% and 11%, respectively, with the use of adjuvant doxorubicin in combination with ifosfamide [56]; despite this, the most recently reported large randomized trial using the same combination involving 351 patients, two thirds of whom had extremity sarcoma, revealed no benefit in recurrence free survival or overall survival [2]. The weight of clinical opinion is generally against the widespread use of adjuvant chemotherapy in the treatment of localized sarcomas. In addition, DNA-damaging chemotherapy, especially alkylators, have been implicated in contributing to increased risk of second malignant neoplasms in hereditary retinoblastoma syndrome [57].

Pertaining to specific sarcomas, patients with MPNST should be evaluated clinically for signs of NF1 syndrome. Fluorodeoxyglucose-positron emission tomography has been studied to differentiate benign neurofibromas from MPNST in patients with NF1 with promising results; one study demonstrated reliable and replicable differentiation with relatively high specificity [58]. After curative treatment of an NF1-associated
MPNST, if feasible, consideration should be made for close clinicoradiologic monitoring with PET-CT to detect malignant transformation of neurofibromas earlier, to facilitate early intervention [59]. Patients with PVComa or angiomylipoma should be evaluated for clinical evidence of tuberous sclerosis complex. Patients with leiomyosarcoma should have clinical evaluation (cutaneous examination and thoracic examination) for hereditary leiomyomatosis with renal cell carcinoma.

After curative treatment of an NF1-associated MPNST, if feasible, consideration should be made for close clinicoradiologic monitoring with PET-CT to detect malignant transformation of neurofibromas earlier, to facilitate early intervention.

Soft-tissue sarcomas should be evaluated clinically for past personal history of, and treatment for any malignancy, to assess for the possibility of cancer predisposition syndromes such as LFS and hereditary retinoblastoma. If patients meet clinical criteria for these syndromes, genetic counseling should be initiated, and the appropriate confirmatory genetic tests should be instituted. Patients with desmoid tumors should have a clinical evaluation for history and features of FAP. In the Dutch study described earlier, the odds ratio for being associated with FAP when compared against extra-abdominal desmoids, was 4.8 for abdominal wall and 18.9 for intra-abdominal desmoids [31]. In the absence of a family history or clinical symptoms suggestive of FAP, we would suggest genetic counseling for evaluation of germline APC mutation in all patients under 60 years old with abdominal desmoids.

**SARCOMA SUBTYPES NOT CLASSICALLY ASSOCIATED WITH INHERITED CANCER PREDISPOSITION**

In spite of the fact that the vast majority of individual sarcoma cases arise sporadically, quite a few histological subtypes, as thus far described, can arise within the context of one or several inherited cancer predisposition syndromes. A number of sarcoma subtypes, however, have not, to the best of our knowledge, been systematically or recurrently linked with any such syndromes. This may very well represent no more than the workings of chance—rarely diagnosed sarcoma subtypes not arising in rarely prevalent cancer predisposition syndromes. Yet there are several relatively more common sarcomas that are comparatively more conspicuous in their absence from the catalogs of sarcomas arising in the setting of cancer predisposition. These include liposarcoma, synovial sarcoma, angiosarcoma, and Ewing sarcoma.

Liposarcomas (LPS) are adipocytic malignancies that make up approximately 20% of soft-tissue sarcomas (STS). They comprise well-differentiated/dedifferentiated (WD/DD LPS; 64%), myxoid/round cell (MR LPS; 28%), and pleomorphic (8%) varieties [60]. WD/DD LPS most often arises in the retroperitoneum of adults in the 5th or 6th decade of life and is associated with amplification of the 12q14-15 chromosomal region, resulting in increased activity of *MDM2*, *HMG2*, and *CDK4*. MR LPS commonly afflicts the extremities of adults in the third and fourth decades of life and harbors gene fusions involving *DDIT3*, most commonly from the reciprocal translocation involving chromosomes 12 and 16 to generate the FUS-DDIT3 chimeric fusion protein. The majority of liposarcomas are predisposed primarily to repeated local recurrences and treated mainly with multiple surgical extirpations, where possible.

Synovial sarcomas, making up 6% of STS, predominantly affect young adults in the 3rd decade of life. They are associated with reciprocal translocations involving the X chromosome and chromosome 18, leading to the formation of an SS18-SSX oncogenic fusion protein [61]. They can arise from any anatomical site, although they most commonly occur in the extremities. These are aggressive malignancies that have a predilection for distant relapses after surgical resection, primarily in the lungs. Although more sensitive to chemotherapy than most soft-tissue sarcomas, responses are usually short-lived, and prognosis in the setting of advanced disease is generally poor.

Angiosarcomas, comprising 1%–4% of STS, primarily afflict adults in the 5th decade of life and beyond. These are tumors of endothelial origin that can arise from the multiple anatomic sites including head and neck, skin, heart, breast (most often in the postradiation therapy setting), bone, liver, or spleen, and in association with chronic lymphedema (Stewart-Treves syndrome) [62]. Angiosarcomas are genetically complex tumors with no well-characterized defining recurrent molecular aberrations. They are extremely aggressive biologically with dismal overall outcomes and few effective treatment options in the setting of advanced disease.

Ewing sarcoma or primitive neuroectodermal tumor, making up 6%–8% of primary malignant bone tumors, has a peak incidence in the 2nd decade of life. These are small, round blue cell tumors whose cell of origin is unknown, defined by chromosomal translocation giving rise to EWSR1-ETS fusion proteins that drive the malignant phenotype. Ewing sarcomas are exquisitely sensitive to chemotherapy and radiation therapy, with satisfactory cure rates achieved by using intensive multimodal therapy in the setting of localized disease [63].

To the best of our knowledge, there are no specific defining features linking the members of sarcoma subtypes not classically associated with hereditary cancer predisposition. They include both genetically simpler sarcomas characterized by specific recurrent molecular aberrations (chromosomal translocations, mutations, and amplifications) and usually simple karyotypes, as well as genetically complex sarcomas with nonspecific genetic alterations and complex unbalanced karyotypes. There is no doubt that the members of this group of sarcomas will continually change as we progressively refine the taxonomy of sarcomas in ways that are more biologically and therapeutically meaningful and as we improve the techniques used to evaluate and annotate patients with inherited cancer predisposition.

**CONCLUSION**

The clinical management of sarcomas can be very heterogeneous, deriving from the numerous biologically distinct entities that are subsumed within this group, each with
different natural histories and varying sensitivities to antineo-
plastic therapy—the oncologist treating sarcomas will need to be
aware of the many different sarcoma subtypes and their
disparate therapeutic strategies. The association of particular
sarcomas with various heritable cancer predisposition
syndromes adds yet another layer of complexity to this
already-formidable matrix. Yet as we hope we have shown,
apprehension of these associations will be critical for the
optimal management of the patient, both specific to the
treatment of the sarcoma, as well to his or her overall health
state and wellbeing. As we continue to make exponential
inroads into cancer genomics and bioinformatics, it is likely
that these relationships will only become more muddled and
complicated, with the same qualitative genetic aberration
confering different risks of sarcoma and other diseases
depending on multiple other factors. It will be critical for us as
a community to effectively grapple with such burgeoning
complexity and resolve new data in real time with the dictates
of clinical medicine, so that our patients with this rare
malignancy can enjoy the best care science and medicine has
to offer.

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For Further Reading:

Implications for Practice:
Mutations in the gene-encoding β-catenin, CTNNB1, are highly prevalent in sporadic desmoid tumors, yet whether mutation status and/or type predict outcome is not certain. In contrast to recently published studies from other groups, we did not detect a significant difference in recurrence risk according to either the CTNNB1 mutation status or the specific mutation. Accordingly, the impact of CTNNB1 mutation status in the treatment algorithm of these enigmatic tumors is uncertain at present. However, with the acquisition of further data, and as the efforts to target β-catenin as a therapy mature, knowledge of the CTNNB1 mutation status may eventually permit a much more rational, individualized treatment approach to desmoid tumors.