Genetic predisposition in sarcomas: clinical implications and management

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Summary

Recent studies indicate up to 20% of sarcomas may be associated with predisposition genes, and this number will probably increase as genetic testing becomes more available. Evidence on the management of patients with sarcoma and genetic predisposition remains, however, scarce. This review compiles available research on genetic predisposition syndromes associated with sarcoma and sarcoma treatment within such syndromes, addressing key gaps in knowledge. We explore the current evidence on how genetic predisposition may influence treatment decisions and clinical management, focusing on surgery, radiotherapy, systemic treatment, and surveillance. Evidence-based recommendations are currently not available for most syndromes, and we have therefore included pragmatic advice for clinicians. Unanswered questions and unmet needs are also identified, underscoring the importance of multidisciplinary input from specialists such as geneticists, radiologists, surgeons and oncologists. The review stresses the need for future research to improve clinical outcomes for patients with sarcoma and genetic predisposition.

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Introduction

Sarcomas form a diverse group of mesenchymal tumours, encompassing over 80 malignant subtypes broadly categorised as either 'bone' or 'soft tissue' sarcomas.[1] Many subtypes are defined as 'ultra-rare', with an incidence of ≤1 per 1,000,000.[2] While sarcomas comprise approximately 1% of adult malignancies, they account for up to 15% of childhood cancers.[1,3] The most common individual soft tissue subtypes, which primarily affect adults and comprise over 50% of soft tissue sarcomas, include leiomyosarcoma, liposarcoma, undifferentiated pleomorphic sarcoma and gastrointestinal stromal tumour (GIST).[4] Osteosarcomas and Ewing sarcomas are the most common bone tumours affecting children and young adults, while chondrosarcoma is most common in adults.[5] Approximately 20% of sarcomas are defined by characteristic translocations, such as SYT-SSX fusions in synovial sarcoma

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and EWSR1-translocations in Ewing sarcoma. These 'translocation-associated sarcomas', typically arising in younger adults, are contrasted with 'complex karyotype' sarcomas.[6] Sarcomas can arise anywhere, with soft tissue sarcomas predominantly occurring in the extremities, visceral, retroperitoneal and intra-abdominal sites.[4] Ewing sarcomas typically arise in extremity bones, while osteosarcomas are more common in younger patients' extremities, increasing in axial sites with age.[5] In addition to the number of subtypes and their rarity, sarcoma exhibits considerable heterogeneity in natural history, treatment response and prognosis, making research and clinical management challenging.

Germline pathogenic variants in multiple genes confer an increased risk for development of several cancer types, including sarcoma. An expanding number of genes, and predisposition syndromes, are emerging as associated with sarcoma. Recent studies suggest up to 20% of sarcomas, may be linked to alterations in cancer predisposition genes.[7,8] Individuals with pathogenic variants in established, highly penetrant genes, such as *TP53*, are often offered participation in surveillance programs to improve early cancer detection and survival.[9,10] Evidence of surveillance efficacy and recommendations, however, are lacking for many sarcoma-associated predisposition syndromes. Furthermore, the implications of genetic predisposition in the clinical management and treatment of sarcomas are even less well defined. Consequently, patient care can vary greatly, even between highly specialized referral centers. This complex and challenging field is one of growing importance given the emergence of therapies that can target the underlying mechanisms of genetic predisposition.

Following an educational session on genetic predisposition in patients with sarcoma at the European Society of Medical Oncology (ESMO) international congress 2023, a working group of experts was established to review and summarise the current evidence relating to clinical management of individuals with sarcoma and a predisposition syndrome. This work has been conducted in advance of a planned global meeting to address this topic and its most contentious aspects.

Methods

A multidisciplinary group of international experts in the field of genetic predisposition in sarcoma was convened to develop this narrative review. Each expert drafted sections based on their specific expertise, conducted targeted, non-systematic literature reviews, and integrated key findings into their sections. The sections were combined and circulated among the working group for feedback and revisions, to enable an accurate and cohesive consensus review. While highly relevant, the approach for diagnosis of sarcoma-associated predisposition syndromes, psychological support for patients and families, or recommendations for individuals with these syndromes *who have not developed a sarcoma* are not discussed as these topics were deemed to be beyond the scope of this review.

Search strategy and selection criteria

Targeted, non-systematic literature reviews were conducted by field experts for each section. Search terms and strategies were individualised to each section. Articles published in English from inception of the PubMed database to December 2024 were included.

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Cancer predisposition syndromes

The observation that certain neoplastic phenotypes clustered in families was first made in the sixteenth century[11] but it was not until the 1980s and 1990s that the genetic basis of the first cancer predisposition syndromes were elucidated.[12] Such syndromes are caused by alterations in oncogenes and tumour suppressor genes, many of which are involved in DNA stability.[13] Over the past 40 years, sarcomas have provided a fertile field for identification of important biological pathways in cancer including these. Li-Fraumeni Syndrome (LFS), caused by germline pathogenic variants in the tumour suppressor *TP53*, exemplified this, with almost 25% of its tumours being sarcomas.[14] In 1990, Malkin and colleagues and Srivastava and colleagues investigated the emerging clinical syndrome using a candidate gene approach.[15,16] The observations that somatic mutations in *TP53* occur in almost half of all cancers, that *Trp53* transgenic mice carrying mutant *TP53* alleles develop a wide spectrum of malignancies, and screening of LFS families, complemented by extensive studies of the biology of p53, all led to the discovery of its pivotal role in this syndrome.[15,17–25]

Individuals with cancer predisposition syndromes may be at risk of a large variety of different cancers occurring in various age groups, although some syndromes predispose to one tumour type only.[26] Most syndromes are associated with an increased risk of certain core tumour types, such as osteosarcoma, soft tissue sarcomas, breast cancer, adrenocortical carcinoma, and choroid plexus carcinoma in *TP53* pathogenic variant carriers or breast and ovarian cancer in *BRCA1/2* pathogenic variant carriers.[11] With expansion of genetic testing, next generation sequencing of tumour specimens,[27] and dedicated research, it is increasingly recognized that the spectrum of tumours observed in individuals with cancer predisposition syndromes may be wider than initially described.[27–30] Furthermore, disease penetrance and tumour risk may be more variable than first established.[28] With the increasing use of DNA sequencing outside established testing criteria, the diagnosis of cancer predisposition

syndromes is now emerging in individuals with less striking personal and family histories.[8,31] Furthermore, it is estimated that 8% of individuals being screened using tumour profiling will have an actionable, causal germline variant identified.[32] Of particular importance, tumour genomic profiling bypasses the decision to test germline causes based on syndrome identification.

Emergence of new genetic predisposition syndromes associated with sarcoma

After discovery of the *TP53*-LFS association, a host of genes have been causally linked to susceptibility to a variety of sarcomas. This list has recently been extended to at least 100 genes.[33] Recent efforts have investigated the role of genes associated with risk of other cancer types, such as breast and bowel cancer, in contributing to the risk of sarcoma. Ballinger et al. examined the distribution amongst sarcoma patients of pathogenic variants in 72 cancer genes.[31] It is notable that >20% of sarcoma patients belong to families with clinically relevant familial cancer patterns. In that study, 5% of sarcoma patients carried pathogenic or likely pathogenic variants in genes such as *APC, MLH1, MSH2, MSH6, PMS2, BRCA1, BRCA2* and *PTEN*, as well as more established sarcoma-associated genes like *TP53* and *SDHB*. Practically, this substantially extends the list of clinically important genetic causes that should be considered in the sarcoma population, and for which there are both established risk management and therapeutic implications.[34] Notably, such variants also occur in the general population, and the identification of a pathogenic variant in a sarcoma patient does not necessarily implicate a causal association.

The clinical impact of common variation is an emerging theme in cancer risk management. Over the past 20 years, genome-wide approaches to discover novel pathways have identified common variants at multiple coding and non-coding loci that associate with cancer risk.[35] These account for a greater proportion of cancer risk at the population level than rare variation, and the combination of these variants (polygenic risk) may increase an individual's risk for cancer to levels comparable with dominant or recessive monogenic causes. There have been a few recent studies in osteosarcoma and Ewing sarcoma, both of which identified novel loci linked to increased risk for these diseases.[36,37] Confirmation of a biological role for these newly described associations will represent a fertile area for research into sarcoma. In general, it will be some time before common variants play a role in defining clinical risk for sarcoma patients.

More recently still, the development of whole genome approaches (WGS) has permitted in principle a genome-wide approach to identifying novel rare genetic contributions to sarcoma risk. Using WGS in a large population of unselected sarcoma patients, Ballinger et al. recently reported pathogenic variants in known sarcoma or cancer genes in 6.6% of patients.[7] Using a robust case:control statistical design adapted from genome wide association studies, they also identified the contribution of two novel pathways, involving the shelterin and centrosome complexes. Variants in the centrosome complex genes appear linked to nerve sheath tumours and GISTs. Variants in the shelterin complex of genes appear associated with an increased risk of melanoma and thyroid cancers, as well as sarcomas. The clinical relevance of these new findings remains to be defined, but increases the explanatory yield amongst sarcoma patients to 8.6%. This trend will likely increase with further research.

Genetic predisposition syndromes associated with sarcoma

Table 1 presents a selection of predisposition syndromes associated with sarcomas. This includes syndrome names, genes, inheritance patterns, associated sarcomas, and other malignancies. While the lifetime risk of sarcoma is undefined for many syndromes, some predisposition syndromes, such as LFS, Rothmund-Thomson syndrome, neurofibromatosis type 1, and retinoblastoma, are associated with a moderate to high lifetime risk of sarcoma (5–50%).[3] In predisposition syndromes associated with risk of other cancer types, such as Lynch syndrome or BRCA1/2 mutations carriers, the risk of sarcoma appears to be lower compared to other associated malignancies, but remains to be precisely quantified. This table may serve as a reference for clinicians managing sarcoma and furthermore highlights associated malignancies to be aware of in the long-term follow-up of an individual with sarcoma, or potential predisposition syndromes to be considered if managing an individual with sarcoma with a significant personal or family history.

Germline genetic testing prior to sarcoma management

For selected patients who develop a soft tissue sarcoma (STS) or osteosarcoma before the age of 46 years, the ESMO-EURACAN-GENTURIS (European Society for Medical Oncology; European Reference Network for Rare Adult Solid Cancers; European Reference Network for Genetic Tumour Risk Syndromes) clinical practice guidelines (CPG) for STS and bone sarcoma propose that germline *TP53* testing should be offered, preferably before initiating treatment.[5,38] Germline testing is recommended for STS and osteosarcoma patients who have at least one first or second-degree relative with a *TP53*-related tumour before the age of 56 or a STS (especially within a previously irradiated volume) or osteosarcoma and a history of another *TP53*-associated tumour that has arisen before the age of 46.[39]

TP53 pathogenic variants are present in up to 5% of osteosarcoma patients and frequently arise de novo.[40] It has been proposed that TP53 genetic testing could be

Syndrome/condition	Gene	Disease inheritance	Sarcomas	Other malignancies and associated musculoskeletal conditions	PMID references
Li-Fraumeni	*TP53*	AD	Bone and soft tissue sarcomas - osteosarcoma most frequently associated.	Adrenal carcinoma, choroid plexus carcinoma, brain, breast, colorectal, leukemia, lung, prostate and other malignancies.	27496084
Retinoblastoma	*RB1*	AD	Bone and soft tissue sarcomas - LMS most frequently associated.	Retinoblastoma and epithelial cancers.	30382615, 19066271
Familial adenomatous polyposis (FAP)	*APC*	AD/sporadic	Desmoid tumours	Gastrointestinal, thyroid and CNS tumours, hepatoblastoma.	16642469, 27401891
Neurofibromatosis type1 (a 'RASopathy')	*NF1*	AD	MPNST RMS GIST	Plexiform neurofibromas, gliomas including optic pathway glioma, juvenile myelomonocytic leukaemia and phaeochromocytoma.	30382615, 28230061
GIST: Carney Stratakis	*SDHA, SDHB, SDHC, SDHD*	AD	GIST (multifocal)	Paraganglioma. Pulmonary chondroma.	30382615, 27401891, 33737510
GIST predisposition	*KIT*	AD	GIST (multifocal)	Interstitial cell of Cajal (ICC) hyperplasia.	30382615, 33737510
GIST predisposition	*PDGFRA*	AD	GIST (multifocal)	Inflammatory fibroid polyps.	30382615, 33737510
Tuberous sclerosis	*TSC1, TSC2*	AD	PEComa Chordoma	Hamartomas and renal angiomyolipoma. Renal cell carcinoma.	16642469, 34319396
POT1 tumour predisposition	*POT1*	AD	Angiosarcoma Other bone and soft tissue sarcomas reported	Familial glioma, melanoma, colorectal cancer.	30382615, 32987645, 39820259
Paget disease of bone	*TNFRSF11A, TNFRSF11B, SQSTM1, PDB4, ZNF687*	AD/unclear	Osteosarcoma Chondrosarcoma Fibrosarcoma	Giant cell tumours.	30382615, 28752905
Mazabraud	*GNAS1*	Sporadic	Bone sarcomas including osteosarcoma, chondrosarcoma	Fibrous dysplasia. Intramuscular myxomas.	30653046 31275685
McCune Albright	*GNAS1*	Sporadic	Osteosarcoma	Fibrous dysplasia.	30382615
Werner	*RECQL2*	AR	Osteosarcoma	Meningiomas.	30382615, 16642469
Bloom	*RECQL3*	AR	Osteosarcoma RMS	Leukemia, lymphoma, skin tumours.	30382615, 16642469,
Rothmund-Thomson and RAPADILINO	*RECQL4*	AR	Osteosarcoma	Skin tumours.	30382615,
Multiple hereditary exostoses (multiple osteochondromas)	*EXT1, EXT2*	AD	Chondrosarcoma	Osteochondromas.	30382615, 32253147
Endochondromatosis: Maffucci	*IDH1, IDH2*	Embryonic mosaicism	Chondrosarcoma Osteosarcoma Fibrosarcoma Vascular sarcomas	Multiple endochondromas. Soft tissue haemangiomas. Multiple malignancies including pancreatic and hepatic adenocarcinoma, mesenchymal ovarian tumours, brain tumours and leukaemia.	22147000, 3805090, 20661403, 32253147, 32144835
Endochondromatosis: Ollier disease	*IDH1, IDH2*	Embryonic mosaicism	Chondrosarcoma	Multiple endochondromas. Multiple malignancies including hepatocellular carcinoma, glioma, leukaemia, juvenile granulosa cell tumours	22147000, 32253147
Beckwith-Wiedemann	(epi)genetic 11p15 alteration	Embryonic mosaicism/AD	RMS	Wilms tumour, hepatoblastoma, adrenal carcinoma.	30382615, 16642469
Constitutional mismatch repair	*PMS2, MLH1, MSH2, MSH6*	AR	RMS	Haematological malignancies, brain tumours, embryonal tumours, gastrointestinal tumours and polyps.	27401891
Basal cell nevus (Gorlin-Goltz)	*PTCH1, PTCH2, SUFU*	AD	RMS LMS	Basal cell carcinomas, brain, adrenal and odontogenic tumours, lymphoma.	30382615, 34494262
Nijmegen breakage	*NBN*	AR	RMS	Lymphoma, medulloblastoma, glioma.	30382615, 16642469
DICER1	*DICER1*	AD	RMS Gynaecological adenosarcomas	Pleuropulmonary blastoma, Sertoli-Leydig cell tumour, anaplastic sarcoma of the kidney, Cystic nephroma.	36354292, 33135284
Costello (a 'RASopathy')	*HRAS*	AD	RMS	Neuroblastoma, bladder cancer.	30382615, 27401891, 39287844

(Table 1 continues on next page)

Syndrome/condition	Gene	Disease inheritance	Sarcomas	Other malignancies and associated musculoskeletal conditions	PMID references
(Continued from previous page)					
Noonan (a 'RASopathy')	Multiple genes including *PTPN11* (50%), *SOS1, CREBBP, RAF, RIT1, KRAS* and others	AD	RMS Angiosarcoma	Tenosynovial giant cell tumour of bone. Multiple malignancies, varying based on gene involved, including leukaemia.	27401891, 23312968
Multilineage mosaic RASopathies	*HRAS, KRAS*	Embryonic mosaicism	RMS (urogenital)	Skin cancer, Wilms tumour, bladder cancer	39287844
Mosaic variegated aneuploidy	*BUB1B, CEP57, TRIP13*	AR	RMS	Wilms tumour and haematological malignancies.	30382615, 27401891
Familial rhabdoid predisposition	*SMARCB1/INI1*	AD	Malignant rhabdoid tumour	Medulloblastoma, choroid plexus tumours.	16642469
Hereditary leiomyomatosis and renal cell cancer	*FH*	AD	LMS (Uterine)	Leiomyomatosis. Renal cell cancer.	30382615
BRCA related cancer predisposition	*BRCA1, BRCA2*	AD	To be defined - bone and soft tissue sarcomas	Breast, ovarian, pancreatic, stomach, prostate and other cancers.	27498913, 35077220
Lynch	*MLH1, MSH2, MSH6, PMS2, EPCAM*	AD	Bone and soft tissue sarcomas - pleomorphic soft tissue sarcomas most frequent	Colorectal and non-colorectal tumours including endometrial, ovarian, upper urinary tract, gastric, small intestine, biliary duct cancers and glioblastoma.	37301271, 39742560

AD, autosomal dominant; AR, autosomal recessive; MPNST, malignant peripheral nerve sheath tumour; GIST, gastrointestinal stromal tumour; RMS, rhabdomyosarcoma; LMS, leiomyosarcoma; TGCT, tenosynovial giant cell tumour. [a]It is to be noted that the subtypes of sarcoma and other malignancies associated with each syndrome may extend beyond those included in this table.

Table 1: **A selection of predisposition syndromes associated with sarcomas.**[a]

indicated for all patients with osteosarcoma, regardless of family history.[41] Counselling and testing of all children, adolescents and young adults diagnosed with a soft tissue sarcoma has also been proposed.[42]

With advances in our understanding of established syndromes and the emergence of new syndromes, identification of patients at risk and those who may benefit from screening is increasingly complex. This necessitates a redefinition of which cases should be offered genetic counselling, including whether this should be offered to all sarcoma patients. Further refinement of the criteria indicating who should undergo screening is a priority for future research.

Sarcoma-associated predisposition syndrome summary:

- Whole genome sequencing and genome-wide association studies have identified new genetic variants and pathways linked to sarcoma risk. Over 20% of apparently sporadic sarcoma patients belong to families with clinically relevant familial cancer patterns. This extends the list of genetic causes to consider, and emphasizes the importance of comprehensive genetic screening.
- Germline *TP53* testing should be considered for selected patients who develop STS or osteosarcoma before the age of 46, especially if they have a family history of TP53-related tumours.
- New risk management and therapeutic strategies will be required as the clinical relevance of emerging variants is defined.

Surgery in patients with genetic predisposition to cancer

Soft tissue

Surgeons frequently play a pivotal role in suspecting a cancer predisposition syndrome. When identified, the surgical approach should consider each syndrome's characteristics. In syndromes with risks of subsequent cancers and potential for tumour promotion in regions of radiation (e.g., LFS or retinoblastoma), local treatment should follow the same surgical principles as sporadic cases. The addition of (neo)adjuvant radiotherapy in high-risk sarcomas, however, may be offset by employing larger margins when feasible. This strategy is typically discussed in a sarcoma multidisciplinary tumour board (MDT) setting.

Certain cancer predisposition syndromes cause multiple synchronous tumours of the same subtype, where complete surgery could be excessively mutilating. In such situations, the surgical strategy aims to be conservative, addressing only symptomatic or at-risk tumours, such as multiple GISTs associated with germline mutations (*SDHA-D, KIT, PDGFRA, NF1*).[43] Similarly, patients with familial adenomatous polyposis (FAP) who have undergone major gastrointestinal resections tend to develop multiple intra-abdominal desmoid tumours, often underestimated by imaging. The standard frontline strategy for desmoid tumours is active surveillance, with medical treatment initiated for symptoms or when progression poses potential complications. Surgical interventions have limited indications.[44]

Conversely, malignant peripheral nerve sheath tumours (MPNST) are the leading cause of mortality in neurofibromatosis type 1 patients, where the lifetime risk approaches 10%. Anticipating surgery at the precancerous stage becomes crucial, considering the high mortality risk. Precancerous lesions like plexiform neurofibromas and atypical neurofibromatous neoplasms of unknown biological potential (ANNUBP) require less aggressive resection than MPNST, with better outcomes. However, determining the optimal timing for surgery remains challenging, particularly with the emergence of new systemic treatments for plexiform neurofibromas, and necessitates MDT input.[45,46]

Tuberous sclerosis complex (TSC) syndrome is characterized by hamartomas and benign tumours in various organs, including bilateral kidney angiomyolipomas, malignant perivascular epithelioid cell tumours (PEComa) and chordomas. TSC syndrome requires organ-sparing surgery if possible, with follow-up for early percutaneous treatment for growing contralateral tumours.[47]

Lynch Syndrome is associated with germline mutations in DNA mismatch repair (MMR) genes (*MLH1, MSH2, MSH6, PMS2*) and associated tumours exhibit microsatellite instability (MSI).[48] As described in the systemic treatment section below, MMR-deficient tumours show exceptional responses to immune checkpoint inhibitors (ICI), including in the neo-adjuvant setting.[49,50] Although MMR-deficient sarcomas are rare,[51] the exceptional responses seen raise the question of whether morbid surgery could be spared in these patients. Further evidence will be required to determine this.

Bone

Bone sarcomas can arise in syndromes associated with various malignant tumours, such as LFS and hereditary retinoblastoma. The importance of MDT meetings before deciding on the extent of surgery has been described above. Some autosomal recessive syndromes like Werner, Bloom, and Rothmund Thomson syndromes, involving the RECQL family of genes, also have a higher risk of developing various malignant tumours, including osteosarcoma and rhabdomyosarcoma.[12]

Hereditary multiple exostoses (HME), also called multiple osteochondromas, is an autosomal dominant disease caused by *EXT1* or *EXT2* mutations.[52] It is characterized by the formation of multiple benign cartilage-capped bone tumours on the bone surface. These tumours can lead to skeletal deformities and, in some cases, malignant transformation. Up to 5% of osteochondromas can become malignant (mainly secondary peripheral chondrosarcomas, grade 1), and require surgical R0 resection. Lifelong clinical and/or radiological follow-up is advised.[1]

Enchondromatosis, or Ollier disease, is a rare non-hereditary condition caused by postzygotic somatic mosaic *IDH1* or *IDH2* pathogenic gene variants.[52] It is characterized by the presence of multiple enchondromas. The overall incidence of chondrosarcoma is up to 40%, with an increased risk of developing chondrosarcoma when the lesions are located in the pelvis. Surgery is indicated for skeletal deformities or signs of malignant transformation. Lifelong clinical and magnetic resonance imaging (MRI) follow-up is also advised.[53] Enchondromatosis accompanied by soft tissue haemangiomas is referred to as Maffucci syndrome. This related disorder is also caused by postzygotic somatic mosaic variants in *IDH* genes and carries a higher risk of developing chondrosarcomas, up to 50%,[53] and vascular sarcomas.[54]

Surgery summary:

- Treatment strategy decisions should be made collaboratively in a multidisciplinary setting within expert sarcoma centers/networks.
- The surgical approach for STS patients with a cancer predisposition syndrome should be customized according to the specific genetic condition. For example, in TP53-related sarcomas, employing larger margins during surgery can help avoid adjuvant radiotherapy.
- Early intervention is crucial for precancerous lesions in syndromes like neurofibromatosis type 1.
- In Lynch Syndrome, the potential role of ICI in sparing morbid surgery warrants consideration.
- Syndromes like hereditary multiple exostoses and enchondromatosis require lifelong follow-up and may necessitate surgical resection for malignant transformation.

Systemic treatment in patients with cancer predisposition syndromes

Genetic predisposition syndromes may influence systemic treatment decisions. Sarcomas arising in affected individuals may have different responses to certain therapies, standard treatment options may be limited by previous chemotherapy exposure from a prior cancer, and treatment regimens may be modified if radiotherapy is being avoided (for example, in LFS). The risk of late effects related to the genetic predisposition might be a concern and considered in decision making. Sarcomas may be encountered as secondary or new primary neoplasms in childhood cancer survivors,[55] in particular those with mutations in homologous recombination genes treated with alkylating agents.[56] While unproven, this increased risk may also apply to individuals treated after the age of 18 years. Managing a sarcoma patient with a predisposition syndrome, therefore, crucially requires shared decision making with the patient to balance possible benefits and risks, such as how the probability of cure is affected by the use or avoidance of certain drugs, or how certain treatments may increase the risk of developing secondary tumours.

We review below how common genetic predisposition syndromes may affect systemic treatment decisions.

Li-Fraumeni syndrome

The impact of germline *TP53* pathogenic variants on systemic treatment decisions are not currently clear and affect all TP53-related malignancies, not just sarcomas. In clinical practice, prior malignancies and treatments, such as anthracycline use, often influences therapeutic decisions. Mutated *TP53* may also confer potential for increased therapeutic efficacy. Mice bearing loss-of-function mutations develop tumours that rapidly regress upon genetic restoration of the *TP53* gene, suggesting potential for drugs that restore wild-type function. However, few drugs have reached the stage of clinical trials and mutant p53 proteins remain "undruggable".[57] Systemic treatments could also serve as cancer-preventative agents. Metformin to improve cancer-free survival, for example, is under investigation in a randomised phase 2 trial in adults with LFS.[58]

Tuberous sclerosis complex

Malignant PEComas, in *TSC1* or *TSC2* mutation carriers, exhibit minimal benefit with conventional chemotherapy. TSC mutations lead to loss of function with subsequent mTOR pathway activation, which can be targeted using mTOR inhibitors such as sirolimus, everolimus and nab-sirolimus.[59] In a phase 2 study with nab-sirolimus for locally advanced, unresectable or metastatic PEComa, an encouraging response rate of 39%, median progression free survival of 10.6 months and median overall survival of 40.8 months were reported.[60] Nab-sirolimus is now approved by the FDA for advanced PEComa.

Neurofibromatosis type 1 (NF1)

Plexiform neurofibromas in NF1 patients are pre-malignant lesions in patients with NF1, linked with substantial morbidity and potential to progress into MPNST. Until recently, surgery was the only treatment. *NF1* mutations lead to activation of the RAS/MAPK and PI3K/AKT/mTOR signalling pathways. The MEK1/2 inhibitor selumetinib, approved by the FDA and EMA for paediatric patients with inoperable plexiform neurofibromas, targets the activation of the RAS/MAPK pathway.[46] Selumetinib's efficacy in MPNST was investigated in the phase 2 SARC031 trial (NCT03433183), however early outcomes are less encouraging (Kim et al., Connective Tissue Oncology Society (CTOS) 2022). Other MEK inhibitors are under investigation (NCT03962543; NCT03231306).

NF1 is also associated with development of GISTs which typically do not respond to imatinib due to the absence of activating mutations in *KIT* and *PDGFRA*. There is no standard systemic treatment and current ESMO GIST guidelines (2021) recommend avoiding imatinib or adjuvant treatment for NF1-related GIST.[61] In terms of alternative therapies, a long-term response in one patient was reported in a phase 1 study of binimetinib and pexidartinib.[62] A case of NF1-associated metastatic GIST also showed a partial metabolic response to regorafenib on FDG PET/CT (fluorodeoxyglucose positron emission tomography/computed tomography) after six cycles, and over 15 months, of treatment.[63]

SDH-deficient GIST

The succinate dehydrogenase (SDH) enzyme complex consists of four subunits: SDHA, SDHB, SDHC and SDHD. Germline mutations in any of these subunits increases the risk of developing SDH-deficient GISTs, which can also arise sporadically by epigenetic silencing of the SDHC promoter.[64] While evidence on systemic treatment is limited, SDH-deficient GIST appear to have different treatment sensitivities. These tumours show resistance to imatinib and similar to NF1-related GIST, ESMO guidelines do not recommend imatinib or adjuvant treatment for SDH-deficient GIST.[61] SDH-GIST, however, may have some sensitivity to drugs such as sunitinib and regorafenib. Recent studies have shown promising disease control rates in two trials: a phase 2 trial of temozolomide (Burgoyne et al., CTOS 2023, NCT03556384) and a trial of the BCR-ABL1 tyrosine kinase inhibitor olverembatinib (Qiu et al., ASCO 2024, NCT03594422).[65] Additionally, a study evaluating the combination of temozolomide with INBRX-109, an antibody targeting human death receptor 5, is ongoing (NCT03715933).

Genetic syndrome related based therapy

Several cancer predisposition syndromes have genetic defects that correlate with tumour-agnostic treatment efficacy. A few select examples are detailed below. Evidence for these therapies is largely confined to the setting of advanced disease. If sarcoma with advanced disease arises in a syndrome such as these, considering directed therapies where evidence exists may be appropriate.

Mismatch repair deficiency cancer syndromes including Lynch syndrome

Pembrolizumab is FDA-approved for MSI-H/dMMR solid tumours, including sarcomas, that are pre-treated and have no valid alternative treatment options.[66] Responses to checkpoint inhibition have been observed in Lynch syndrome related and MSI-H/dMMR sarcomas.[29,67–69] In children with dMMR tumours, Constitutional Mismatch Repair Deficiency (CMMRD) due to bi-allelic pathogenic variants in *MLH1, MSH2, MSH6,* or *PMS2* should be considered. Durable response with ICI in sarcomas associated with CMMRD have been reported.[70,71] Although MSI-H/dMMR tumours are exquisitely sensitive to ICI, many patients develop resistance and disease progression. ICI

indications and strategies in dMMR sarcomas, such as the use of multi-agent regimens, are therefore evolving.[72] Given the low incidence of sarcomas associated with dMMR (~1%)[51] or Lynch syndrome in particular, and the lack of sarcoma-specific trials, learning from outcomes in the more prevalent non-sarcoma tumour groups associated with Lynch Syndrome will be beneficial.

Homologous recombination pathway syndromes including BRCA

BRCA-related malignancies have been observed to be sensitive to poly (ADP-ribose) polymerase (PARP) inhibitors.[73] While *BRCA* is most frequently associated with breast and ovarian cancer, a range of tumours can develop, including sarcomas.[74] Ballinger and colleagues identified enrichment of pathological variants in *BRCA2* genes in 3.6% of 1162 sarcoma patients tested.[31] Durable responses to PARP inhibitors in sarcomas with *BRCA* alterations are reported, although available literature is largely limited to somatic *BRCA2* alterations found in uterine leiomyosarcoma.[75,76] BRCA2 loss-of-function may increase sensitivity to platinum-based treatment.[77] In children with *BRCA1/2* or *PALB2* associated tumours, Fanconi anaemia due to bi-allelic variants in these genes should be ruled out.

Systemic treatment summary:

- Genetic predisposition syndromes can influence systemic treatment decisions, affecting both the treatments employed and treatment-related decisions.
- Syndromes such as Neurofibromatosis type 1 and SDH-deficient GIST require tailored therapies and typically do not respond to imatinib.
- dMMR syndromes (e.g., Lynch Syndrome) show high sensitivity to ICI, suggesting potential alternatives to traditional systemic approaches.
- As knowledge on the biology of tumours arising in specific genetic backgrounds increases, the impact on systemic treatment decisions will grow.

Radiotherapy in patients with genetic predisposition

Radiotherapy response, toxicity and repair in sarcoma

Radiotherapy (RT) is recommended when the balance between tumour control and normal tissue complication probabilities are favourable. In sarcoma patients with genetic predisposition syndromes there are certain specific considerations:

Potential inherent radio-resistance

TP53 mutations have been associated with increase radio-resistance and inferior tumour control in paediatric type rhabdomyosarcoma and Ewing sarcoma compared to *TP53* wild type. This may necessitate changes in treatment strategy to improve local control.[78] Factors such as tissue type, concomitant chemotherapy exposure, radiation dose and *TP53* variant type may all influence the actual risk. Comprehensive analysis of radiation dose–response is currently lacking.

Increased normal tissue radiosensitivity

Some syndromes are associated with increased normal tissue toxicities. DNA repair disorders, including sarcoma-associated Bloom and Werner syndromes, may exhibit hyper-sensitivity to DNA-damaging agents like radiotherapy and chemotherapy.[79,80] An illustration of genetic predisposition related RT hypersensitivity includes Phelan-McDermid syndrome (PMS), a global developmental disorder associated with *SHANK3* genomic deletions or structural changes. Development of sarcomas is not an association. Radiosensitivity was studied after increased radiosensitivity was identified in a child with a rhabdoid tumour and PMS.[81] When compared to healthy volunteers and breast and rectal cancer patients, all but two patients with PMS showed increased radiosensitivity. A number of radiosensitivity assays are under investigation which, if prospectively validated, may be useful to inform radiosensitivity risk and RT decisions in genetic predisposition syndromes.[82–84]

Risk of radiation-induced malignancy

In a large registry study of over 600,000 cancer patients, 9% developed a second solid cancer. Of 42,294 patients who received RT and developed a second cancer, 8% were estimated to be related to RT (i.e., post-RT second primary cancer (SPC)).[85] In a series of 322 patients with LFS who developed malignancies, 19 (30%) of 64 patients who had undergone RT developed 26 SPC within a radiation field within 10 years (range 2–26 years).[86] Most neoplasms were sarcomas occurring within three years of RT. As in the context of radiation resistance, the tissue type irradiated, concomitant chemotherapy exposure, radiation dose and *TP53* variant may all contribute in determining actual risk.

Radiotherapy use and risk in sarcomas with genetic predisposition

RT in patients with hereditary sarcomas has to be considered carefully, as potential risks vary between syndromes. If alternative curative treatment modalities are available, avoidance of RT can be considered.[87] If RT is required as a part of standard multi-modal treatment, proven to achieve cure, the potential benefit often outweigh the risks. When considering RT, total dose, fractionation dose, fraction number and the irradiation volume should be limited whenever possible to spare normal tissues.[81,88] Novel approaches have also been developed that could help determine suitability for RT and inform RT dosing, including a gene expression based radiosensitivity index[84] and a genome-based

model for adjusting RT dose.[82,83] Highly conformal RT techniques, such as proton beam therapy (PBT), can be of benefit in sarcoma-associated predisposition syndromes.[81,88,89] In studies, PBT plans were adjusted to minimal gross tumour volume and were safe in terms of acute and chronic toxicities.[89] Though tumour control was often achieved using RT,[81,90] some patients developed SPCs during follow up.[88–90]

SPCs can be induced by ionizing radiation but can also develop spontaneously as patients with predisposition syndromes are prone to develop SPC. In patients with retinoblastoma, up to 40% of SPC occurred outside the radiation volume, indicating that tumour predisposition or other treatments might play a central role.[3,91] In patients with LFS, RT-induced sarcomas were reported to arise less frequently than previously expected.[90] Regarding RT for SPC, decisions are largely multidisciplinary and case specific. For SPC in previously irradiated areas, The European Society for Radiotherapy and Oncology and the European Organisation for Research and Treatment of Cancer consensus guidelines on re-irradiation provide considerations for decision making and indicate re-irradiation can be considered for new malignancies for patients when other options are limited.[92] Within the LFS community, fear and resistance are associated with RT, although it might not be substantiated by recent literature. While balancing risks and benefits, the need for optimal treatment of the current sarcoma should always prevail.

Radiotherapy summary:

- In patients with genetic predisposition related sarcomas, who may have increased risk of adverse effects including secondary malignancies, radiotherapy should be restricted to individuals where alternative effective treatment options are not available. Alternative treatment modalities may need to be explored to mitigate these risks.
- Tailoring radiotherapy approaches based on genetic predisposition is crucial. Techniques such as highly conformal proton beam therapy may reduce normal tissue toxicity while effectively controlling tumours and should be considered.

Radiology: sarcoma surveillance and screening relating to a genetic predisposition

Imaging in patients with sarcoma and genetic predisposition aims to rule out local relapse, distant metastases, new sarcomas or second cancers. Whole-body imaging is therefore crucial, utilising techniques that cover a range of anatomical sites (bone and soft tissue including brain, breast and lung) and tissue types. Whole body (WB) MRI, for example, poses limitations in transverse coverage, potentially missing parts of the upper limbs. WB-MRI should be supplemented with dedicated imaging of the upper arm when indicated. WB-MRI also lacks the resolution to detect sub-centimetre pulmonary nodules, so non-contrast enhanced CT thorax may be required to exclude pulmonary metastases. The diverse tissue composition in sarcoma also poses challenge; for example, intramuscular metastases containing myxoid stroma are notoriously difficult to detect on CT. They often show minimal FDG uptake on FDG PET/CT but can be detected with MRI. Given the young age of patients with sarcoma with genetic predisposition, imaging modality choices must consider the cumulative effects of radiation and cancer risk from lifelong imaging.

Current recommendations and evidence for routine surveillance imaging for LFS

Routine surveillance is now recommended for LFS in many countries. Current American Association of Cancer Research (AACR) recommendations for screening are: Abdominal and pelvic ultrasound 3–4 monthly from birth to 18 years, then annually; brain MRI annually from birth (initially with contrast, then without if normal); WB-MRI annually from birth; and, for females, breast MRI annually from 20 to 75 years.[93] Combined imaging, biochemical and imaging surveillance has been shown to improve overall survival.[10,94] A prospective observational study with 11 years follow-up showed a 5-year overall survival of 88.9% in the surveillance group versus 59.6% in the non-surveillance group.[10] Outside of LFS, surveillance recommendations are undefined for many sarcoma-associated predisposition syndromes, especially for recently identified genes.

WB-MRI

The AACR guidance highlights that WB-MRI is only one component of surveillance on account of detection of only 20% of tumours in early studies, along with two of 59 patients with false positive scans and two with false negative scans.[10,93] Advances in WB-MRI since these studies have likely improved its effectiveness and it is notable that in the National Cancer Institute LFS cohort, non-MRI techniques did not lead to a diagnosis of prevalent cancer.[95,96] Contemporary WB-MRI protocols use morphological and functional imaging sequences which contribute to sensitivity but also specificity through better characterisation of findings. More recently a standardised approach to WB-MRI has been suggested (ONCO-RADS) which includes minimum technical parameters (sagittal STIR of the spine, axial diffusion weighted and Dixon MRI and axial FLAIR of the brain), structured reporting templates for standardised data collection and a 5-category assessment score which assigns likelihood of malignancy to direct management. Coverage from vertex to mid thighs/feet can be achieved in 30–45 min.[97] Recent artificial intelligence (AI) augmented acquisitions may substantially reduce these times.[98] Some centers also recommend double reporting of screening WB-MRI as sensitivity is paramount and consensus opinions on indeterminate

findings are advantageous. The economic and psychosocial impact of investigating indeterminate findings must be considered and should not be underestimated. In the SIGNIFY study, 15 of 44 individuals with LFS underwent investigations for abnormities on WB-MRI that transpired to be benign.[99]

Surveillance studies in predisposition syndromes

Several prospective studies have evaluated screening intervention for individuals with cancer predisposition syndromes.[9,100] Many focus on *TP53* but studies enrolling multiple syndromes are also available. Examples include the national Australian 'SMOC+' study: a Surveillance study in Multi-Organ Cancer prone syndromes, and the prospective study of children with cancer predisposition syndromes at St Jude Children's Research Hospital.[101,102] Individuals with sarcoma and a predisposition syndrome should be encouraged to enrol in available studies to help inform the specific utility of radiology, including radiological modalities, in sarcoma and individual predisposition syndromes.

Psychosocial effects of surveillance imaging

The term "scanxiety", introduced in 2011, describes anxiety and/or distress associated with an imaging test in post-cancer follow up. It is now commonly described, particularly in patient and public social media.[103] Although the survival benefits of screening are acknowledged,[10,94] the emotional cost should also be defined, and patients and their families supported appropriately.[104] That said, baseline WB-MRI screening of patients with LFS was found to be acceptable with high levels of satisfaction and low psychological morbidity,[105,106] however, the cumulative effects of lifelong imaging remain undefined.

Imaging summary:

- Surveillance imaging in sarcoma patients with genetic predisposition requires comprehensive protocols that encompass whole-body imaging capabilities, such as whole-body MRI (WB-MRI).
- Routine cancer surveillance is recommended for LFS but recommendations are undefined for many sarcoma-associated predisposition syndromes.
- Surveillance imaging can cause anxiety and distress among patients undergoing frequent imaging.

Multi-disciplinary and clinical genetics care	• Multi-disciplinary consultation and care is optimal with inclusion of specialists including clinical geneticists, radiologists, surgical oncologists, radiation oncologists, and medical oncologists. • Referral to, and shared care, with a clinical geneticist or hereditary cancer clinic, to direct surveillance strategies and risk modification management specific to the associated syndrome.
Sarcoma management approach	• Local management should be as per standard of care and as for a sporadic sarcoma, unless high level evidence to direct otherwise is available. • In multidisciplinary discussions, consideration of potential increased sensitivity to radiation and the risk of secondary malignancies should be given, opting for radiation-sparing management *if feasible.* For example, employing a larger surgical margin when technically feasible to ensure a clear margin, or if surgery or radiotherapy are being considered for concern of an involved margin, further surgery to achieve a clear margin may be preferable *if viable without significant morbidity.* • Patients receiving treatment for sarcoma should be counselled of secondary malignancy risk associated with the treatment according to their predisposition syndrome.
Surgery	• Surgical management strategies can be informed and modified in the setting of predisposition syndromes. Pre-operative discussion in a sarcoma MDT is optimal, and encouraged, to determine the best approach specific to the sarcoma and syndrome involved.
Radiotherapy	• In individuals with genomic predisposition related sarcomas with increased risk of adverse effects from radiation, radiotherapy decisions should be made after careful evaluation of the benefit and potential risks of radiotherapy and with multi-disciplinary input to evaluate if alternative management to avoid radiotherapy may be feasible.
Systemic treatments	• Genetic predisposition syndromes may influence sarcoma systemic treatment decisions in several ways in terms of the treatments employed and decisions related to treatment.
Radiological surveillance for sarcoma recurrence	• Consideration of cumulative radiation risk from imaging must be given, noting potential increased risk of additional malignancies and/or sensitivity to radiation. As such, adopting an imaging technique appropriate for the sarcoma but that considers cumulative radiation risk. For example, where appropriate and available, utilising a MRI in lieu of CT. • Frequency of surveillance imaging should also be pragmatic; it should be based on sarcoma risk, and standard care, but with consideration of cumulative radiation risk. • If whole body MRI is employed, inclusion of body areas which might be at risk, such as the upper arm in the case of a upper limb sarcoma, or where MRI may be suboptimal, such as for detection of sub-centimetre lung nodules, should be considered.
Long term care	• Awareness that familial cancer predisposition is an evolving field where new evidence is arising for predisposition syndromes. It is thus prudent to consult with a clinical geneticist, or review available literature, at regular intervals during a patient's long term follow up, for emerging evidence relating to the specific predisposition syndrome. • Psychological support and services should be offered with consideration of the known psychological morbidity associated with surveillance or screening imaging in familial cancer and genomic predisposition syndromes. • Clinicians should have a low threshold to investigate symptoms that may be pertain to a malignancy associated with a specific predisposition syndrome.
Surveillance related to predisposition syndrome	• Li-Fraumeni is a predisposition syndrome where routine surveillance and surveillance imaging is recommended and has been shown to improve overall survival. • Individuals should be encouraged to enrol in surveillance studies, where available, to help inform malignancy risk and the specific utility of radiology, including radiological modalities, in sarcoma and individual predisposition syndromes.

Table 2: **Clinical approach considerations for management of individuals with sarcoma and a genetic predisposition syndrome.**

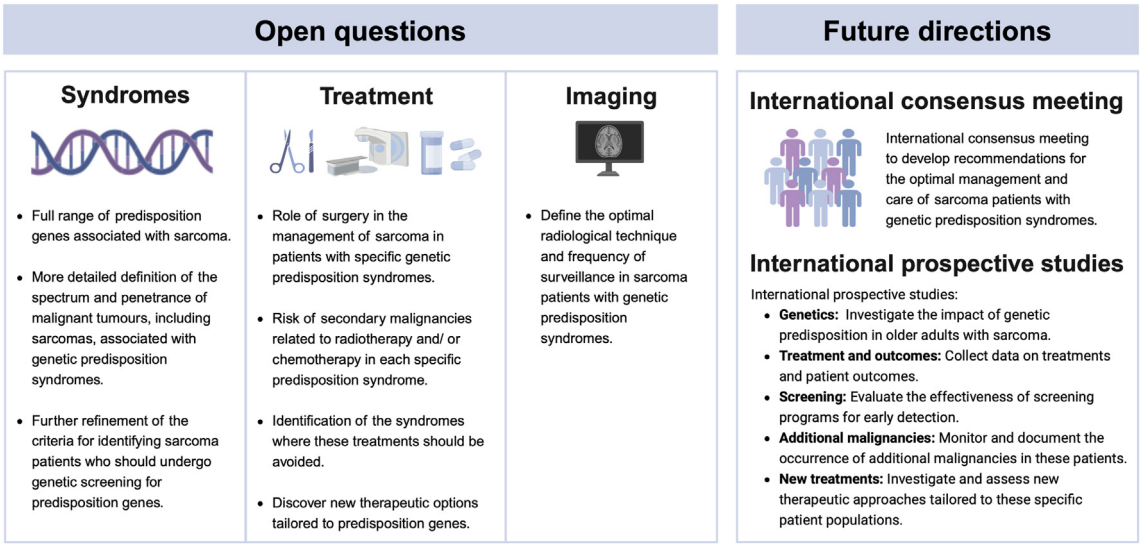

Fig. 1: Priorities for future research. Figure created with BioRender.com.

Balancing the clinical benefits with psychosocial impacts is crucial.
- Individuals with sarcoma and a predisposition syndrome should be encouraged to enrol in available studies.

Pragmatic approach to management and future directions

There is a growing number of sarcoma-associated predisposition syndromes with significant heterogeneity between syndromes in terms of risk of additional malignancies, and the type of associated malignancies. A 'one type fits all' approach is therefore unlikely to be appropriate for individuals with sarcoma and a genetic predisposition syndrome. High-level evidence is currently lacking for most syndromes and evidence-based recommendations on this topic are not currently possible with available literature. Table 2 summarises pragmatic considerations for clinicians who are managing these cases. Multidisciplinary management is essential, with specialists including clinical geneticists, radiologists, and surgical, radiation, medical and paediatric oncologists. As is typical in sarcoma, each entity is rare and as such, specific high-level evidence to guide management is unlikely to be available imminently. International expert consensus will likely be the first step in developing guidelines.

Outstanding questions

There are many unanswered questions and unmet needs for future research which are illustrated in Fig. 1. To inform recommendations and management there is a need for prospective studies and registries which include evaluation of screening interventions and treatment outcomes, and registration of additional malignancies.

Conclusions

In summary, an expanding number of genes, and predisposition syndromes, are emerging to be associated with sarcoma. High level evidence to base recommendations is not currently available for most syndromes and as such these are unmet clinical needs. Individuals with sarcoma and a predisposition syndrome should be managed pragmatically by a multi-disciplinary team, including a clinical geneticist or familial cancer syndrome service. International consensus working groups and studies may help enhance knowledge and improve the management of patients with genetic predisposition associated sarcomas.

Contributors

Conceptualisation: SS, KB, EC; Data curation: All authors; Formal analysis: All authors; Funding acquisition, investigation- N/A; Methodology- N/A; Project administration- SS, KB, EC; Resources, software- All authors; Supervision- SS; Validation, visualisation: All authors; Writing – original draft: All authors; Writing – review & editing: All authors.

All authors read and approved the final version of the manuscript. We confirm that more than one author has directly accessed and verified the underlying data reported in the manuscript (KB, EC). This work does not involve a commercial partnership.

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