MILKEN INSTITUTE

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Uterine Leiomyosarcoma

A Giving Smarter Guide

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Foreword

Uterine leiomyosarcoma (uLMS) is a rare but highly aggressive cancer that presents unique challenges to patients. Unlike more common cancers, uLMS lacks reliable early detection methods, has few effective treatment options, and has alarmingly high recurrence rates. For patients, a diagnosis comes as an unexpected and life-altering revelation, often after surgery for what they and their doctors thought was a benign condition.

Despite these hurdles, there is reason for optimism. The field of precision oncology has experienced unprecedented progress in recent years, from advances in molecular tumor profiling to targeted therapies to breakthroughs in immunotherapy using a patient's own cells. However, these innovations have yet to fully extend to rare cancers such as uLMS. The lack of dedicated funding for research and infrastructure has left the uLMS field lagging, with patients often searching for better solutions.

This *Giving Smarter Guide* outlines the most pressing gaps in uLMS treatment and research and identifies targeted investment opportunities for philanthropists to drive accelerated progress in the field. By fostering stakeholder collaboration, supporting high-risk, high-reward research, and breaking down institutional silos, philanthropists can have an outsized impact on the field of uLMS.

The history of cancer research shows that bold investments in underfunded areas can yield transformative breakthroughs. By acting now, philanthropists can catalyze a future where innovation rather than uncertainty defines rare cancers such as uLMS, leading to improved outcomes and hope for people affected by these diseases.

Pete Briger
Briger Foundation for Oncology Research

Executive Summary

This *Giving Smarter Guide* aims to clearly outline the current state of research, clinical practice, and treatment approaches for uLMS and identify critical areas where philanthropy can significantly advance scientific knowledge and improve patient outcomes. It highlights emerging trends, key stakeholders, funding patterns, significant barriers to progress, and targeted opportunities where philanthropists can drive meaningful advancements. We want to give funders actionable insights, enabling them to strategically invest in areas with the greatest potential to transform uLMS research and patient care.

Uterine leiomyosarcoma (uLMS) is a rare and aggressive gynecologic cancer that originates in the smooth muscle layer of the uterus. It typically affects perimenopausal women between the ages of 45 and 60. uLMS often presents similarly to benign uterine fibroids, which are extremely common, affecting an estimated 70–80 percent of women during their lifetime. As a result, clinicians often presume that uterine masses are benign and monitor them conservatively or remove them surgically without heightened concern for malignancy. This high fibroid prevalence leads to missed opportunities in recognizing uLMS. Unlike fibroids, however, uLMS is malignant and has a tendency for rapid growth, recurrence, and metastasis. Due to its aggressive behavior, uLMS generally has a poor prognosis, especially if diagnosed after metastasis has occurred.

The molecular changes underlying uLMS development are complex, involving several alterations to individuals' genetic, epigenetic, metabolic, and immune features. This biological heterogeneity has made it challenging for researchers and clinicians to draw broad conclusions about uLMS and develop effective therapies.

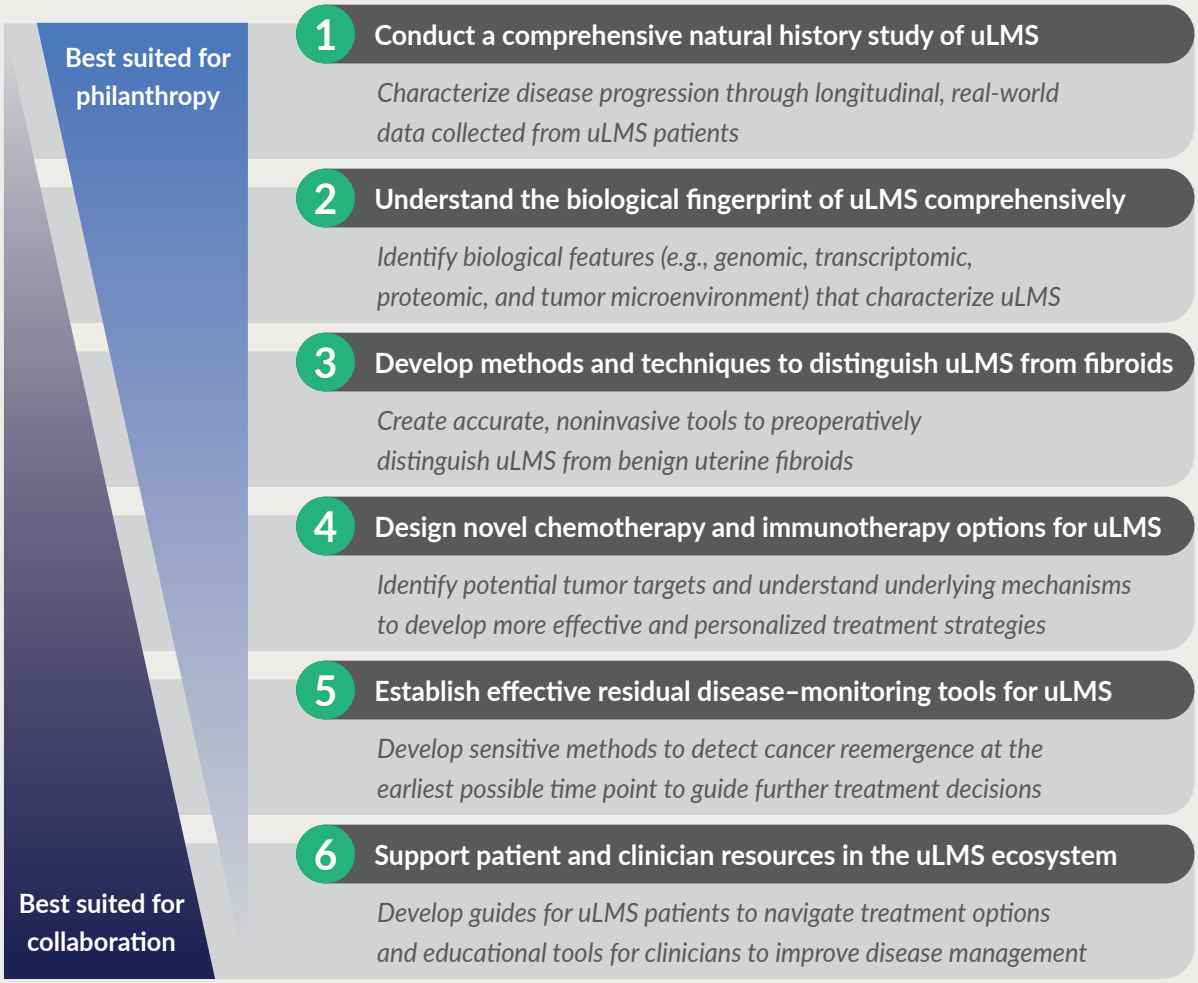
Clinicians generally first treat uLMS by surgical resection of the tumor, but no Food and Drug Administration (FDA)–approved targeted therapies are available specifically for uLMS. Clinical trials have explored various combinations of conventional chemotherapy agents. Most have extended patients' lives only slightly, if at all. Oncologists typically do not recommend radiotherapy due to the presence of other sensitive pelvic organs, leaving very few options for clinicians to help these patients.

Looking toward the future, researchers are exploring and developing various potential immunotherapies across many cancers, some of which could apply to uLMS. Taken together, the uLMS field shows an urgent need for progress to understand the disease's biology and mechanisms, advance diagnostics and monitoring strategies, and develop novel therapeutics that can address this rare cancer.

Advancing research and clinical care for uLMS will require significant and sustained funding. Our assessment suggests that the field needs philanthropic investment to improve the funding landscape. Despite recent increased federal support across biomedical research, uLMS remains significantly underfunded compared to other gynecologic cancers affecting women. From 2014 to 2024, endometrial cancer, which occurs just a few inches from where uLMS occurs, received over $885 million in funding from the National Institutes of Health (NIH). In stark contrast, uLMS research was allocated only $9.5 million over the past decade. Even after normalizing for disease incidence, uLMS receives far less funding than other gynecologic cancers. To improve diagnosis and treatment, financial investment in uLMS research must increase.

Overview of Key Opportunities in uLMS Research and Care

To inform the opportunities highlighted in this *Giving Smarter Guide*, we thoroughly reviewed the current landscape, emerging research trends, and clinical applications. By integrating expert input, we developed a set of high-priority opportunities that remain largely overlooked or insufficiently supported in uLMS research and clinical care. We ordered the opportunities based on their relative readiness and fit for philanthropic action, with those at the top representing the most immediately actionable and specifically suited for philanthropy. The opportunities not as specifically suited for philanthropy would benefit from collaborative funding that uses additional sources such as federal or industry funding. Subsequent sections will provide a deeper dive into each opportunity, outlining the unmet need and presenting models for how funding could accelerate progress in that area. If pursued, these opportunities would build on earlier strides and catalyze significant advances in uLMS research and care.



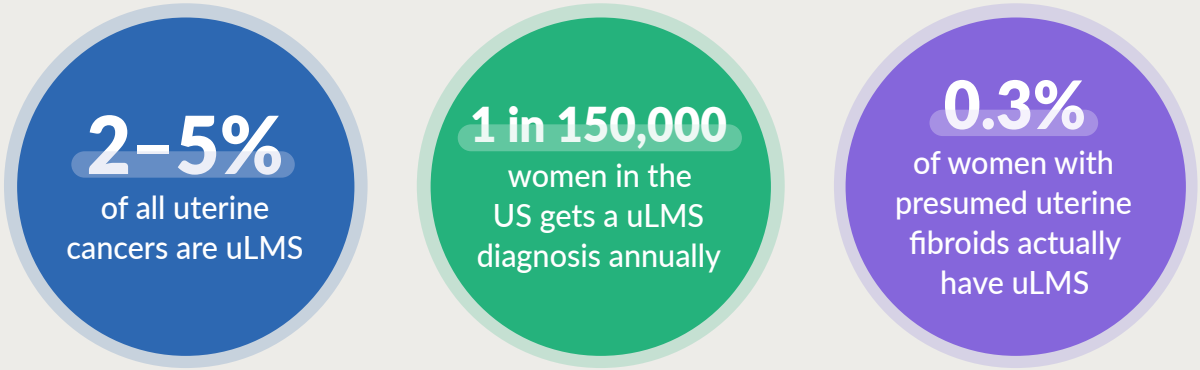
Background

Disease Insights and Epidemiology

Uterine leiomyosarcoma (uLMS) is a rare and aggressive form of gynecologic cancer that originates in the smooth muscle tissue of the uterus. It commonly presents around the ages of 45 to 60 during perimenopause (when women transition to menopause), with a peak incidence rate between the ages of 50 and 54. Clinicians often discover uLMS incidentally in women they are treating for benign uterine masses, called uterine fibroids, through surgical removal. Both symptomatic uterine fibroids and uLMS result in vaginal bleeding, an increase in pelvic size, abdominal pain and pressure, and bowel and bladder dysfunction, which makes distinction between a relatively benign condition and a deadly one exceptionally challenging.

Unlike the benign fibroids, uLMS is a high-grade malignancy, meaning that it can grow and spread quickly. The prognosis for uLMS is the least favorable among all soft tissue sarcomas. uLMS has a high rate of recurrence and metastasis, with the most common metastatic site being the lungs. The five-year survival rate for patients with uLMS ranges from 25 percent to 76 percent, and patients diagnosed with metastatic disease at the outset have survival rates closer to 10–15 percent. **Figure 1** summarizes key metrics associated with disease incidence.

Figure 1 • uLMS by the Numbers



Source: Byar and Fredericks (2022), NORD (2018), Mao et al (2015)

Types of Uterine Cancer

Cancers that develop in the uterus are classified into two types: carcinomas and sarcomas.

Uterine carcinomas are more common and can be treatable depending on the stage; they can occur in the cervix, which is the lower portion of the uterus right above the vagina, or in the endometrium, which is the innermost layer of the uterus.

On the other hand, uterine sarcomas are rare and aggressive in nature; typically, uterine sarcomas develop in the myometrium, which is the muscle layer of the uterus, or from connective tissue nearby, including the endometrium. See **Figure 2** for relevant anatomy.

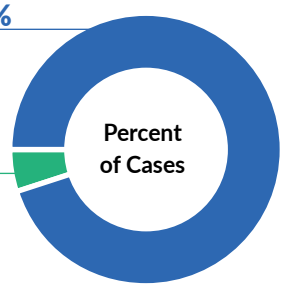
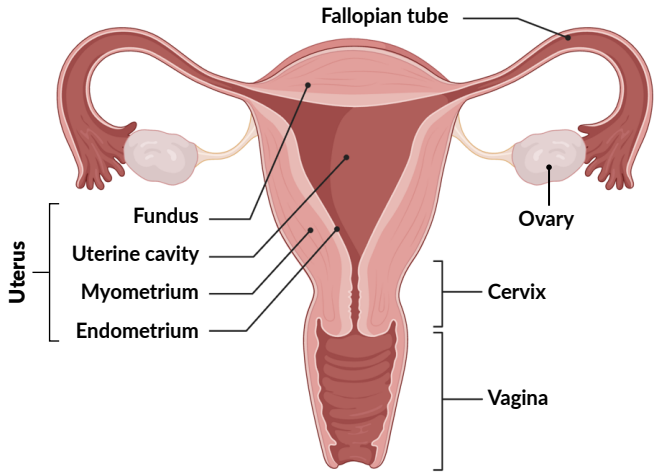


Figure 2 • Overview of the Female Reproductive System



Source: BioRender (2025)

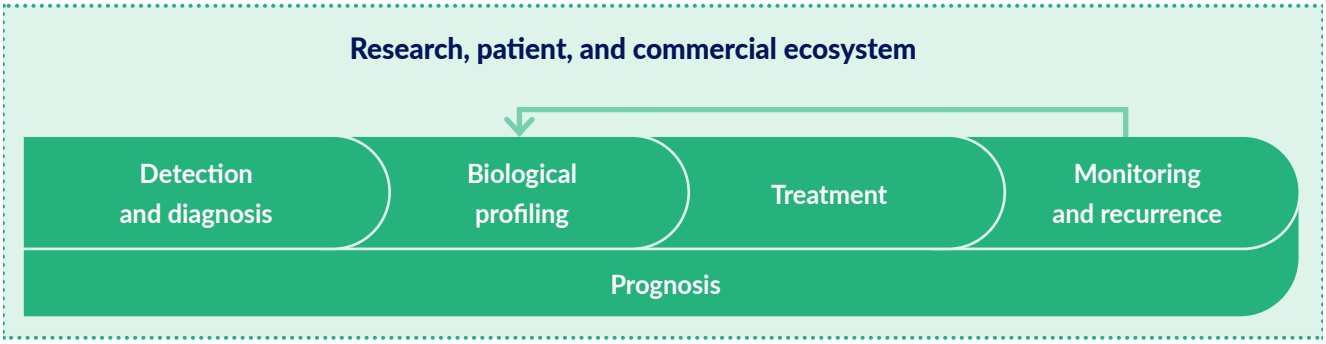
Uterine sarcomas can be further broken down into subtypes:

Leiomyosarcoma (LMS)	The most common type of uterine sarcoma. Starts in the myometrium and comprises up to ~50% of uterine sarcomas.
Endometrial stromal sarcoma (ESS)	The second most common type. Starts in the supporting connective tissue of the endometrium. Can be low or high grade, depending on the tumor's growth and spread.
Adenosarcoma	A rare subtype (~5% of uterine sarcomas) where normal gland cells mix with stromal cells, which support connective tissue. Tends to be low grade.
Undifferentiated sarcomas	A rare subtype that can start in the endometrium or in the myometrium. Tends to be high grade.

Smooth muscles are ubiquitous throughout the body, and as such, LMS can originate outside the uterus, such as the intestines, stomach, bladder, and blood vessels. uLMS is the largest subtype of LMS, comprising 40% of cases.

Illustrative Patient Journey

While every patient has a personal and unique journey, they share commonalities that draw them together. The diagnosis of a rare cancer in the prime of life creates specific challenges that many face. Understanding this journey can help us better target key points in the course of the disease, uncover critical touchpoints and stakeholders, and identify opportunities to improve patient outcomes through philanthropic initiatives.



Detection and Diagnosis

A patient's journey with uLMS often begins before diagnosis when learning about uterine fibroids, which are so common and considered so harmless that clinicians often recommend minimal follow-up. However, clinicians may surgically remove a problematic fibroid, and when they profile the tumor after the procedure, uLMS is typically diagnosed.

Imagine a postmenopausal woman who notices a growing lump in her pelvic area, accompanied by bloating, nausea, frequent urination, and persistent back pain. As these symptoms worsen and abnormal vaginal bleeding begins, she visits her gynecologist. Initial imaging (ultrasound or MRI) reveals a uterine mass, usually diagnosed as a benign fibroid. For many women with fibroids, clinicians typically use a watch-and-wait approach, but they pursue hysterectomy when symptoms become severe, when fibroids rapidly grow, or when nonsurgical treatments fail. After surgery, the removed tissue undergoes detailed microscopic examination by a pathologist. Here, unexpected signs emerge: abnormal cellular structures, rapid cell division, and unique cell death patterns—all hallmarks of cancer. Clinicians overturn the initial assumption of a benign fibroid, and the patient receives a diagnosis of uLMS or potentially another aggressive uterine sarcoma subtype.

This diagnosis brings a heavy psychological and emotional burden to the patient and her family, initiating a period of uncertainty. Some patients are relatively fortunate that the tumor is contained within the uterus, but for many others, the cancer has already spread to the abdomen or lungs by the time it's detected.

Biological Profiling

In certain rare but promising scenarios, clinicians process the patient's tumor immediately following hysterectomy to develop deeper biological insights. Typically, after a hysterectomy, clinicians discard uterine tissue or chemically preserve it in ways that limit further biological analysis. Fortunately, in this illustrative case, the patient's gynecologist has preserved cancerous tissue sample with future molecular studies in mind. By partnering with a biobank, the patient's family ensures the tissue remains available for advanced analyses. This preservation allows a sarcoma specialist, who is often affiliated with an academic research lab, to perform sophisticated molecular analyses.

These assessments can reveal unique, patient-specific characteristics of her cancer, potentially guiding personalized therapeutic strategies. With appropriate resources and funding, this specialist might even use advanced research models, such as patient-derived organoids (three-dimensional cell cultures) or patient-derived xenografts (human tumor tissue implants into mouse models), to better understand the cancer's biology and behavior. Although promising, this precision medicine approach is not yet standard clinical practice for uLMS patients.

Treatment

After diagnosis, the patient's gynecologist usually refers her to a sarcoma specialist at a large academic cancer center. Given the rarity of uLMS, specialized expertise is limited (~50 sarcoma specialists within the US), often requiring travel to distant centers. At these centers, interdisciplinary teams manage treatment, typically beginning with chemotherapy combinations such as trabectedin and doxorubicin. Even when patients appear disease-free, specialists often recommend adjuvant treatment—additional therapy to reduce recurrence risk.

Beyond standard chemotherapy, targeted immunotherapy treatments exist but are significantly less accessible. These immunotherapies (such as PD-1 inhibitors like pembrolizumab or nivolumab) are FDA-approved but not specifically for uLMS and thus must be prescribed off-label, leading to challenges with cost and insurance coverage. Additionally, determining the patient's eligibility for these therapies requires prior biomarker testing of tumor tissue. Participation in clinical trials offers another avenue for patients to access potentially beneficial investigational therapies.

Monitoring and Recurrence

Following initial treatment, the patient enters a critical period of regular monitoring due to the high risk of recurrence and aggressive nature of uLMS. Regular imaging, including CT scans or X-rays, helps detect the presence or recurrence of cancer early. Additionally, newer liquid biopsy methods (blood tests like Signatera) provide sensitive detection of tumor-derived biomarkers that might indicate recurrence earlier and less invasively.

The psychological burden at this stage is immense; patients often feel anxious, viewing recurrence as a constant threat. In uLMS, recurrence often happens within two years after initial diagnosis and treatment. If the cancer returns, it commonly affects the lungs, abdomen, liver, lymph nodes, or bone. At this stage, achieving a cure becomes significantly more challenging. Surgical removal of recurrent tumors might still be an option, but treatment plans become highly individualized.

Prognosis

The concept of prognosis runs through all stages of the uLMS patient journey, from initial diagnosis to recurrence. Prognosis is difficult to predict accurately, primarily due to the absence of comprehensive natural history studies and reliable predictive biomarkers. Several factors influence prognosis, including the tumor's genetic profile, evolution, treatment response, and additional understudied or unknown elements. Unfortunately, due to the aggressive nature of uLMS, rapid recurrence, and treatment resistance, survival rates remain discouragingly low. There is an urgent need to better understand these factors to improve patient outcomes.

Research, Patient, and Commercial Ecosystem

An extensive ecosystem supports the entire patient journey. It includes research institutions, biotech and pharmaceutical companies, and patient advocacy organizations. Basic and translational research labs, along with industry stakeholders, develop cutting-edge diagnostic tools, biological profiling technologies, and novel therapeutic options. Clinical trials assessing these investigational treatments rely on funding from government, biotech, and pharmaceutical entities, which play critical roles in later-stage development and commercialization. Patient advocacy groups provide essential support, community, and resources. They actively fundraise for research, connect patients with specialist care, and advocate for policy changes to improve outcomes for rare cancer patients. This comprehensive support ecosystem highlights areas where philanthropic investment could lead to outsized improvements for uLMS patients.

The subsequent sections of this report provide a deep dive into unmet needs, summarizing available peer-reviewed literature, current knowledge, and strategic philanthropic opportunities to drive advancements in uLMS. Note that because uLMS is rare, some research presented here may include data from leiomyosarcomas more broadly (which originate from smooth muscle tissues throughout the body) or draw comparisons with advances made in more common gynecologic cancers.

Comprehensive Review of Opportunities to Transform the Field of uLMS

Opportunity 1

Conduct a Comprehensive Natural History Study of uLMS

Natural history studies are essential tools in biomedical research, systematically documenting how a disease progresses over time without experimental intervention. In oncology, these studies generate longitudinal data, including clinical features, imaging, pathology, treatment responses, and outcomes, that enable researchers to understand disease behavior, refine diagnostic and prognostic tools, and design better clinical trials.

For rare cancers specifically, a well-designed natural history study could illuminate the typical patterns of recurrence and progression. Such knowledge is critical for improving prognostication and evaluating ongoing risk. This, in turn, helps clinicians and researchers more accurately weigh the risks and benefits of emerging therapies and trial designs. An additional consideration for rare cancers is that patient populations are small, and randomized controlled trials are often impractical, making natural history studies even more crucial. They offer a noninterventional yet rigorous pathway to develop the foundational knowledge needed for therapeutic innovation.

Despite advances in cancer research, the natural history of uLMS remains poorly characterized. Researchers extrapolate current staging and treatment guidelines from other malignancies, such as endometrial cancer or general soft tissue sarcomas. Such staging and guidelines do not adequately reflect the unique biology, spread patterns, and clinical course of uLMS. Clinicians stage uLMS using the 2009 International Federation of Gynecology and Obstetrics (FIGO) system and the American Joint Committee on Cancer (AJCC) staging system.

However, the FIGO system and AJCC staging system have limitations. The FIGO system, for instance, was originally developed for endometrial cancer and emphasizes lymph node metastasis as indicative of stage. While lymph nodes are commonly involved in endometrial cancer, they are less frequently involved in uLMS, which typically spreads within the abdominal cavity. Thus, the existing staging systems do not adequately stratify uLMS patients into clinically meaningful groups. Investment in a dedicated natural history study of uLMS could lay the foundation for creating more accurate, disease-specific staging systems that better guide prognosis and treatment decisions.

Natural history studies also offer regulatory advantages. For rare diseases, the FDA and other agencies increasingly accept external control data and real-world evidence to accelerate approvals, provided the data are robust, comprehensive, and well annotated. A uLMS natural history dataset could serve as a future comparator arm for single-arm therapeutic trials, thus de-risking clinical development pathways and enabling more efficient drug approvals.

To maximize impact, researchers must thoughtfully design any natural history study for uLMS. A multi-institutional partnership helps capture sufficient sample size and demographic diversity. The study should use standardized case report forms for clinical features, imaging, pathology, molecular profiling, treatment history, patient-reported outcomes, and longitudinal follow-up. Researchers should prospectively collect data wherever possible, supplementing it with real-world evidence such as electronic health records, billing data, and archival tissue analyses. Essential partnerships with major sarcoma centers, patient advocacy organizations, and clinical research networks would facilitate enrollment and ensure long-term patient engagement. Researchers must establish robust data governance structures to ensure data quality, privacy, and accessibility for the broader research community.

Philanthropy is uniquely positioned to help establish natural history studies. A tactical philanthropist would begin by convening a scientific advisory board of leading uLMS experts to design the study framework, define key clinical and biological endpoints, and standardize data collection protocols. Philanthropists could then fund major sarcoma centers in initiating patient enrollment and ensuring consistent, high-quality data capture across institutions. Investors would direct additional funds toward building a centralized, secure, and accessible data repository with rigorous quality control systems to harmonize clinical, imaging, pathological, and molecular data streams. To sustain the effort, philanthropists could fund operational staff such as research coordinators responsible for longitudinal patient follow-up, a critical component of any successful natural history study. Dissemination would also be a key pillar, with philanthropists enabling interim data releases and the establishment of open-access data-sharing policies to accelerate discovery across the broader research community.

Initial philanthropy could unlock future investment from government grants and industry partnerships once the infrastructure is in place, creating a sustainable platform for future research. By undertaking and supporting a comprehensive natural history study, philanthropists can build a shared knowledge base that empowers downstream clinicians, researchers, and industry stakeholders.

Opportunity 2

Understand the Biological Fingerprint of uLMS Comprehensively

uLMS, like other cancers, has both shared and unique biological "fingerprints"—features that make it recognizable as uLMS across all cases and distinguish each patient's tumor at an individual level. Techniques to characterize each tumor and establish its fingerprint are crucial for early detection, personalized treatment (precision medicine), and improved diagnosis and prognosis. These techniques include:

Sequencing: Reading the tumor's genetic code

Immunohistochemistry: Assessing which proteins demonstrate changes in expression or localization by viewing protein patterns under a microscope

Flow cytometry: Assessing physical and chemical characteristics of cells using a laser-based lab test that characterizes cells at the single-cell level

Epigenetic profiling: Checking for chemical tags on DNA that influence how genes are expressed

Metabolomic testing: Analyzing the mix of small chemicals produced from metabolism in and around tumor cells

Table 1 highlights the common biological features identified through these techniques, offering insights into the distinct characteristics of uLMS.

Table 1 • Common Biological Findings in uLMS, LMS, and Associated Domains

Biological Domain	Description	Commonly Associated Findings
Genomic	Genetic material (DNA)	• Mutations in *TP53*, *RB1*, *ATRX*, *PTEN*, *MED12* • DNA copy number variations, including complex chromosomal rearrangement in LMS
Transcriptomic	RNA sequences and amounts	• Impaired DNA damage response and telomere maintenance pathways in LMS, resulting in inappropriate cell division and chromosomal instability
Chromosomal abnormalities	Deviation in the number or arrangement of chromosomes	• Deletion of certain stretches of DNA in LMS tumor cells causes loss of important cell death regulation and leads to poor prognosis
Epigenetic	Modifications of DNA that don't change DNA sequence itself	• DNA hypomethylation (fewer chemical tags that help protect the DNA) in uLMS tumors, increasing the tendency to mutate further • High microRNA expression in uLMS tumors, which is highly correlated with clinical outcomes
Metabolomic	Presence and levels of the chemical inputs and outputs of cellular processes	• Lower levels of select metabolites suggest that LMS disrupts the balance of chemicals that control cell health and stress (redox state)

Source: Milken Institute analysis of relevant literature (2025)

Researchers have typically based uLMS characterization on which gene mutations occur in the tumor. Genes frequently mutated in uLMS include *TP53*, *RB1*, *ATRX*, *PTEN*, and *MED12* (detailed in **Table 2**). In the context of cancer generally, mutated genes are classified as either tumor suppressors or oncogenes. Tumor suppressor genes, under normal circumstances, regulate cell division and prevent uncontrolled cell or tissue growth, but when tumor suppressor genes mutate, they may become inactivated, which leads to unregulated cell growth and, potentially, to cancer. Conversely, proto-oncogenes promote controlled cell growth in normal circumstances, and when mutated or overexpressed, they can drive uncontrolled cell division that can lead to cancer. Fusion oncoproteins, which result from chromosomal rearrangements, are rare but can also contribute to cancer development or progression. Fusion oncoproteins do occur in some uLMS cases but are poorly understood. Together, these genetic disruptions disturb the normal regulation of cell proliferation, survival, and differentiation.

Table 2 • Tumor Suppressor and Oncogenes Often Mutated in uLMS, and Their Functions When Not Mutated

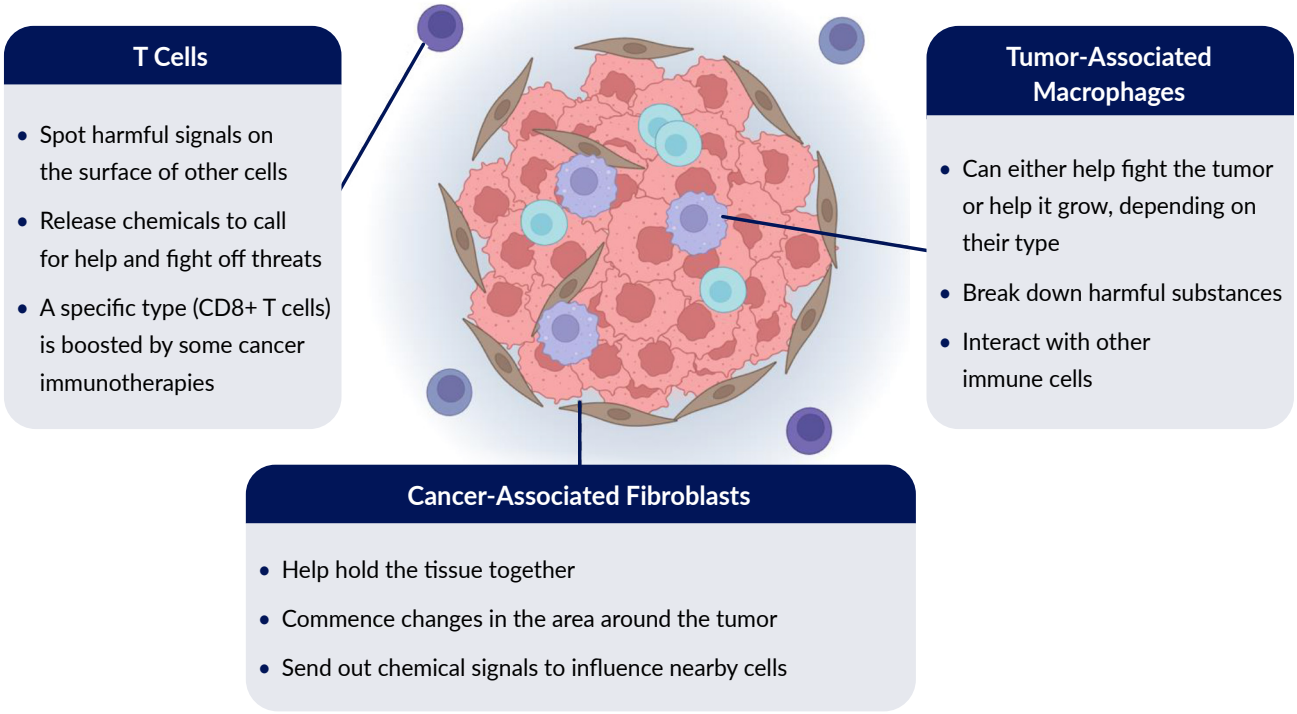
Gene Type	Gene	Functionality
Tumor suppressor	*TP53*	Regulates cell division to prevent inappropriate proliferation
	RB1	Regulates cell cycle progression
	ATRX	Regulates chromatin structures
	PTEN	Prevents excessive cell growth and division
Oncogene	*MED12*	Maintains normal cell signaling and regulates cell growth

Source: Milken Institute analysis of relevant literature (2025)

Across many cancers, the tumor microenvironment profoundly influences prognosis and treatment efficacy. The tumor microenvironment, or the local environment immediately surrounding the tumor, consists of cancer cells, immune cells, fibroblasts, and other tissue-resident cells, alongside extracellular molecules and proteins like growth factors and metabolites. As in other cancers, the microenvironment of uLMS prevents immune cells (including, importantly, T cells) from infiltrating and destroying the tumor. This barrier against immune cells protects the tumor from the patient's own immune cells, which might otherwise destroy the tumor, and from immunotherapies, which consist of immune cells engineered to attack specific tumors. The tumor microenvironment thus reduces immunotherapy effectiveness.

uLMS tumors often contain an abundance of tumor-associated macrophages, cells that modulate the local immune responses depending on signals and surrounding conditions. Cells called cancer-associated fibroblasts in uLMS further promote tumor growth, immune suppression, invasion into surrounding tissues, and metastasis. **Figure 3** illustrates the uLMS tumor microenvironment.

Figure 3 • Cell Types in the uLMS Tumor Microenvironment



Source: Milken Institute analysis of relevant literature (2025); figure created on BioRender.

The mechanisms driving recurrence and metastasis in uLMS remain poorly understood, presenting an opportunity for targeted clinical and mechanistic studies that philanthropy could support. Insights from other cancers may guide this research. In endometrial cancer, recurrence and metastasis are influenced by molecular profiles, hormone activity (e.g., estrogen, prolactin), pro-inflammatory adipocytokines, and altered microRNA expression. Cervical cancer studies have identified intermediate-risk factors (e.g., large tumors) and high-risk factors (e.g., lymph node involvement), with high-risk factors linked to a 35–40 percent recurrence rate and worse survival. These benchmarks may help identify similar risk factors in uLMS.

Despite insights from numerous studies of the underlying biology of uLMS, many critical questions remain unanswered, which hampers the development of a comprehensive biological fingerprint for uLMS. For instance, while a specific type of fingerprinting called metabolomic fingerprinting has advanced other cancer diagnostics, researchers have conducted few metabolomic studies in uLMS. In addition, uLMS tumors have substantial heterogeneity, making their biology different from patient to patient. This heterogeneity underscores the urgent need for deeper biological characterization of uLMS tumors, both broadly and at the individual patient level, to facilitate precision medicine applications. Additionally, few studies have focused on the uLMS tumor microenvironment.

Understanding the underlying biology of specific cancers has significantly informed and advanced the diagnosis, treatment, and overall knowledge of various tumor types, including colon, breast, and lung cancers. For instance, extensive genomic profiling in breast cancer has led to clearly defined subtypes of breast cancer–based hormone receptor expression. These definitions, in turn, have facilitated the development of targeted therapies for the separate subtypes, which has dramatically reduced recurrence rates and mortality in breast cancer patients. In contrast, uLMS currently lacks such well-defined biological profiles.

Philanthropy can advance efforts to map the biological fingerprint of uLMS. Given the disease's rarity and biological complexity, dedicated philanthropic funding can accelerate high-impact studies that otherwise struggle to secure traditional research support. Philanthropy could fund multiomic profiling initiatives, including genomic, transcriptomic, epigenetic, and metabolomic analyses, to build a comprehensive picture of uLMS biology and answer some of the field's outstanding questions, as highlighted in **Table 3**. It could support centralized efforts to collect, annotate, and share tumor tissue and clinical data across multiple centers, establishing a large, high-quality biobank critical for biological discovery.

Philanthropy could also help researchers apply cutting-edge technologies such as single-cell sequencing, spatial transcriptomics, and spatial metabolomics to better understand tumor heterogeneity and microenvironmental influences. It could foster collaboration by supporting consortium-based studies, where multiple institutions work together to integrate and harmonize biological data at scale. Philanthropy could also fund the development of robust uLMS model systems to experimentally probe its biology. These models allow researchers to study how tumors might respond to specific therapies. This way, before advancing to clinical trials, researchers can identify promising drugs that exploit individual tumor vulnerabilities.

Table 3 • Selected Set of Outstanding Questions Regarding uLMS Biology and Related Implications for the Field

Selected Outstanding Questions in uLMS Biological Fingerprinting	Implications for the Field
Do the spatial properties of cells and associated markers inform clinical outcomes in uLMS?	Recent developments in spatial transcriptomics and metabolomics will enable scientists to pinpoint RNA expression and metabolites in specific locations within tissues in uLMS.
Do uLMS tumors arise *de novo* or evolve from preexisting benign leiomyomas, and what factors influence this process?	Knowing how uLMS tumors form will provide crucial information for cancer prevention and early detection methods.
How do hormonal factors, such as estrogen and progesterone receptor expression, contribute to uLMS initiation and progression? Do they predict therapeutic response?	Hormonal factors (like estrogen in breast cancer) contribute to effective personalized uLMS treatment plans with specific targeted therapies.
How does the tumor microenvironment influence uLMS progression and aggressiveness?	Understanding the uLMS tumor microenvironment will provide critical information about factors that might influence immune evasion, metastasis, and overall tumor growth.
Are there molecular signatures and signaling pathways that facilitate metastasis in uLMS?	Defining the molecular signatures associated with metastasis in uLMS will improve prognosis by providing valuable information about metastatic potential, which can inform better patient treatment strategies.
How do the primary tumor and recurrence differ in their biology?	Understanding the molecular and cellular differences between primary and recurrent tumors could guide surveillance strategies, identify mechanisms of resistance, and help develop therapies that target recurrent disease more effectively.

Source: Milken Institute analysis of relevant questions from the uLMS literature (2025)

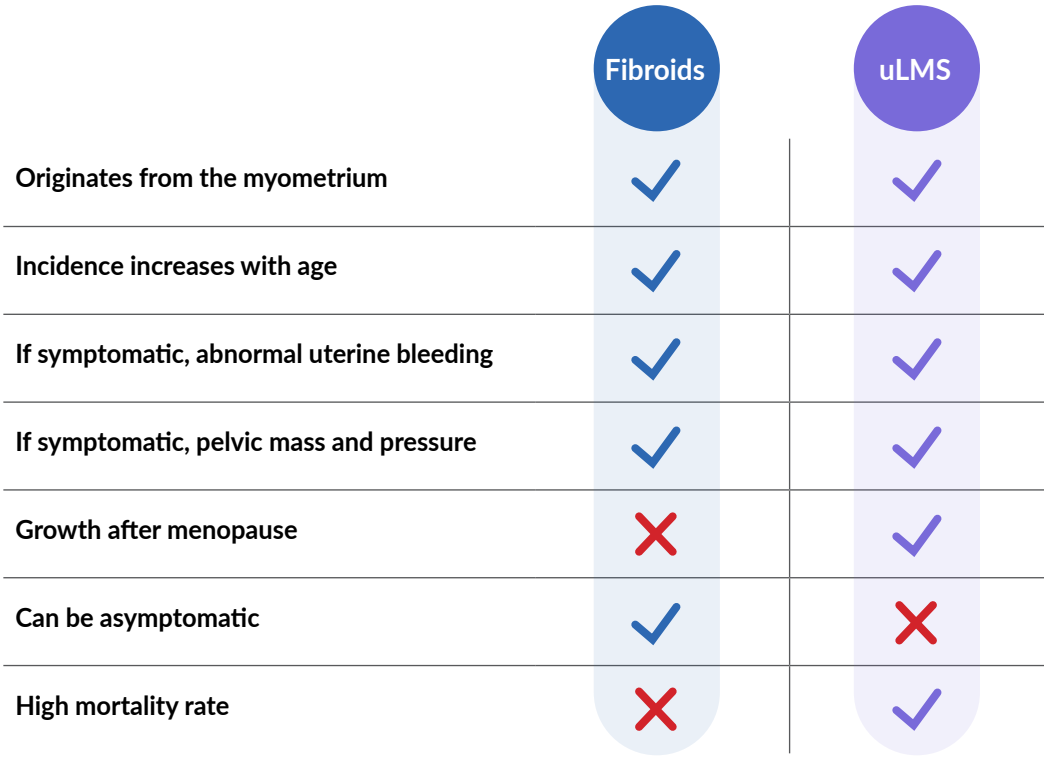
Opportunity 3

Develop Methods and Techniques to Distinguish uLMS from Fibroids

Diagnosis of uLMS is particularly difficult due to the commonality of uterine fibroids (also known as uterine leiomyomas), which are *benign* cell growths that arise from the uterus's smooth muscle. Nearly 80 percent of women experience these fibroids at some point during their lifetimes.

Accurately differentiating uterine fibroids from cancerous uLMS is essential but challenging because both conditions share similar symptoms (**Figure 4**). Current diagnostic methods, such as MRI, ultrasound, endometrial sampling, and blood-based biomarkers, cannot reliably distinguish between benign fibroids and malignant tumors. MRI scans specifically fail to detect key cancer indicators like genetic mutations or cellular abnormalities.

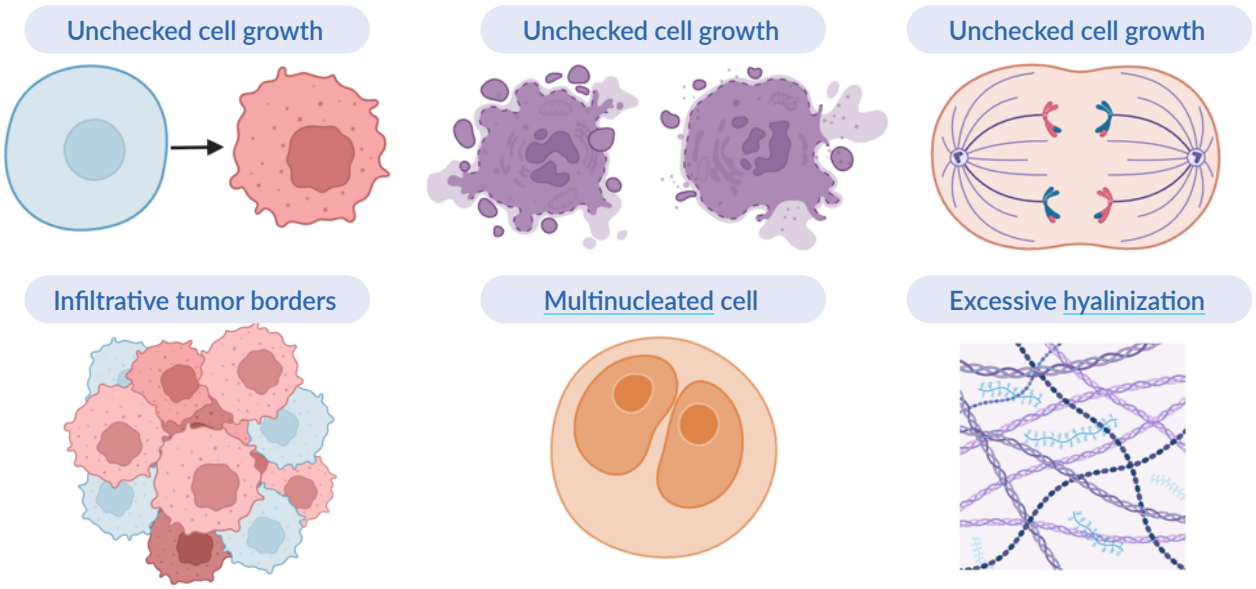
Figure 4 • Comparison of Uterine Fibroids and uLMS Highlighting the Limitations in Preoperative Diagnosis



Source: Adapted from Yang et al. (2024)

Currently, uLMS diagnosis typically occurs after a woman receives a hysterectomy due to fibroid presence, followed by biopsy analysis. However, biopsies can miss tumor cells, leading to false benign diagnoses. Routine biopsies of the myometrium, the uterine layer where uLMS originates, are invasive; procedure feasibility depends heavily on tumor location and depth, making hysterectomy the standard procedure. Clinicians can diagnose uterine masses as uLMS by identifying certain cellular characteristics that contribute to the tumor's aggressive nature. This includes high cellular replication, increased cell death, and abnormal cellular appearance (**Figure 5**).

Figure 5 • Characteristics Seen in uLMS Cells



Source: Milken Institute analysis of relevant literature (2025); figure created on BioRender.

Early and accurate identification of uLMS is critical for optimal patient outcomes because early intervention in any cancer is associated with better survival rates, reduced treatment side effects, and lower health-care costs. While early detection generally improves prognosis, uLMS often recurs even when diagnosed early, so its overall prognosis remains poorer than most cancers, even with early detection.

Several strategies can improve the preoperative detection of uLMS (**Table 4**). One effective approach involves enhancing existing imaging methods with artificial intelligence (AI). AI can detect early cancer signs when paired with standard diagnostics, and the uLMS field could benefit from techniques successfully developed for other cancers (e.g., breast cancer), where AI can accurately identify subtle abnormalities and mitigate false-positive diagnoses.

Table 4 • Current and Emerging Technologies in uLMS Diagnosis

	Modality	Proposed Improvements	Selected Past and Current Research (uLMS or Other Cancers)
Preexisting Technologies	**Histology**	Train AI to detect histological indicators of uLMS	• Train AI to identify abnormal rates of cell division
	MRI	Augment with AI to find patterns that distinguish uLMS and fibroids	• Use AI to detect complex patterns associated with uLMS • Enhance early detection of breast cancer via AI identification of tumors on MRI • Train AI to detect malignant prostate cancer in MRIs
	Liquid biopsy	Use biomarkers that distinguish uLMS from fibroids	• Monitor levels of plasma tumor DNA to detect mutations in LMS • Explore whether tumor DNA levels in blood plasma are associated with treatment outcomes
Potential New Technologies (implementation contingent on confirmation of hypothesized differences between uLMS and fibroids)	**Protein profiling**	Identify key protein signatures that identify uLMS	• Quantify proteins in tumors to inform appropriate treatment options for endometrial sarcoma • Use proteogenomics to detect differences in cellular pathways, gene regulation, and tumor immunity in endometrial carcinoma
	Shear wave elastography	Determine tissue stiffness and behavior of uLMS tumors	• Measure stiffness of tumor versus noncancerous tissue in breast cancer • Assess tissue stiffness to detect fibroids
	Nanosensors	Detect distinct biomarkers in uLMS	• Use novel nanotubes to detect biomarkers in ovarian cancer patient serum • Use nanotubules to detect biomarkers of cancer in uterine wash fluid

Source: Milken Institute analysis of relevant literature (2025)

Liquid biopsy, the practice of analyzing fluids such as blood or urine to identify circulating tumor cells or genetic material, also holds promise as an improved diagnostic tool for uLMS. This noninvasive and cost-effective method has been effective in other gynecologic cancers, such as endometrial cancer. Also in development are nanoparticle sensors that can detect patterns of multiple biomarkers in blood samples. Paired with machine-learning analysis of the biomarkers, these sensors could help clinicians determine not only presence or absence of uLMS but also disease severity, treatability, and therapy responsiveness.

Philanthropy can transform the field by funding research to improve the preoperative detection of uLMS. Specifically, philanthropy could support AI models trained on rare uLMS imaging and pathology datasets, prospective biobanks to fuel biomarker discovery, and pilot studies testing novel liquid biopsy or nanosensor technologies. Early investment can de-risk these innovations, generate critical proof-of-concept data, and encourage broader funding from government grants. Partnerships with diagnostic companies, imaging firms, and biotechnology start-ups could further accelerate progress by bringing technical expertise, platforms, and pathways for clinical implementation. By accelerating the discovery of sensitive and specific diagnostic tools, philanthropy can meaningfully improve early detection and improve outcomes for women with or at risk for uLMS.

Opportunity 4

Design Novel Chemotherapy and Immunotherapy Options for uLMS

Chemotherapy

Chemotherapy is a form of cancer treatment that uses powerful drugs to kill cancer cells or slow their growth. These medications are typically delivered by injection, taken orally as pills, or applied topically, depending on the cancer's type and location. uLMS is highly chemoresistant, meaning that it often does not respond well to standard chemotherapy treatments and relapse is common even after initial tumor shrinkage. **Figure 6** describes the mechanisms of chemotherapeutic drugs often used to treat uLMS.

Figure 6 • Common Chemotherapy Drugs Used to Treat uLMS

Chemotherapy	Mechanism
Doxorubicin	Disrupts DNA replication and DNA repair
Docetaxel	Prevents cell division
Gemcitabine	Disrupts DNA synthesis and replication
Trabectedin	Disrupts DNA repair
Ifosfamide	Disrupts DNA replication

Source: Milken Institute analysis of relevant literature (2025)

Doxorubicin is the standard of care for uLMS patients. Over the past few decades, several clinical trials have aimed to improve chemotherapy efficacy in treating LMS. **Table 5** details these clinical trials.

Table 5 • Chemotherapeutic Clinical Trials Involving LMS Patients

Clinical Trial	Treatment	Comparator	Phase	Setting	Primary Endpoint	Outcome
NCT00061984	**Doxorubicin + Ifosfamide**	Doxorubicin	3	1st line	Overall survival	Negative
NCT01168791	**Evofosfamide + Doxorubicin**	Doxorubicin	3	1st line	Progression-free survival	Negative
NCT02451943	**Olaratumab + Doxorubicin**	Doxorubicin	3	1st line	Overall survival	Negative
ISRCTN07742377	**Gemcitabine + Docetaxel**	Doxorubicin	3	1st line	Progression-free survival	Negative
NCT01514188	**Aldoxorubicin**	Doxorubicin	2b	1st line	Progression-free survival	Negative
NCT02997358	**Trabectedin+ Doxorubicin**	Doxorubicin	3	1st line	Progression-free survival	Positive
NCT01343277	**Trabectedin**	Dacarbazine	3+	3rd+ line	Overall survival	Positive
NCT01327885	**Eribulin**	Dacarbazine	3+	3rd+ line	Overall survival	Positive

Source: Milken Institute analysis of relevant literature (2025)

Despite the numerous chemotherapies and combinations used to treat uLMS, patients have exhibited low response rates to those therapies. uLMS tumors tend to develop chemotherapy resistance, such that progression-free survival lasts for only a few months. Recent research indicates that uLMS cells may establish chemotherapy resistance by several mechanisms, including limiting the drug accumulation within tumor cells, enhancing the tumor cells' DNA repair pathways, and reducing the tumor cells' ability to undergo cell death. Each of these resistance strategies is mediated by distinct molecular pathways within uLMS cells and contributes to the overall therapeutic challenge of effectively treating uLMS with conventional chemotherapy. By designing new therapeutics that can target these resistance mechanisms and combining existing chemotherapies in novel ways, clinicians can treat uLMS patients more effectively.

A promising strategy to improve chemotherapy in uLMS is to combine chemotherapy drugs with small molecules that target DNA repair pathways. uLMS tumors often have DNA repair defects, so therapies that induce DNA damage while blocking repair, such as PARP or DNA-PK inhibitors, are more effective than others against uLMS. These agents prevent cells from repairing chemotherapy-induced DNA damage, pushing cancer cells toward death. PARP inhibitors are already approved for several cancers, and preclinical studies show that pairing PARP inhibitors or DNA-PK inhibitors with low-dose chemotherapy suppresses LMS growth in model systems. Underscoring this approach's potential is an ongoing Phase 2 trial (NCT04076579) testing trabectedin, a chemotherapy, with olaparib, a PARP inhibitor, in advanced sarcomas, including uLMS.

Philanthropists can help advance new chemotherapeutic strategies for uLMS, particularly in early-stage, high-risk projects that might not yet attract commercial investment. Philanthropy could support preclinical research designing novel chemotherapeutic agents that better target resistance mechanisms and initiatives that attach chemotherapies to antibodies or nanoparticle carriers to improve drug delivery to tumor cells and minimize toxicity to healthy tissues. Philanthropists can also accelerate early-stage combination therapy studies, such as pairing chemotherapy with DNA repair inhibitors like PARP or DNA-PK inhibitors, to exploit vulnerabilities in uLMS tumors.

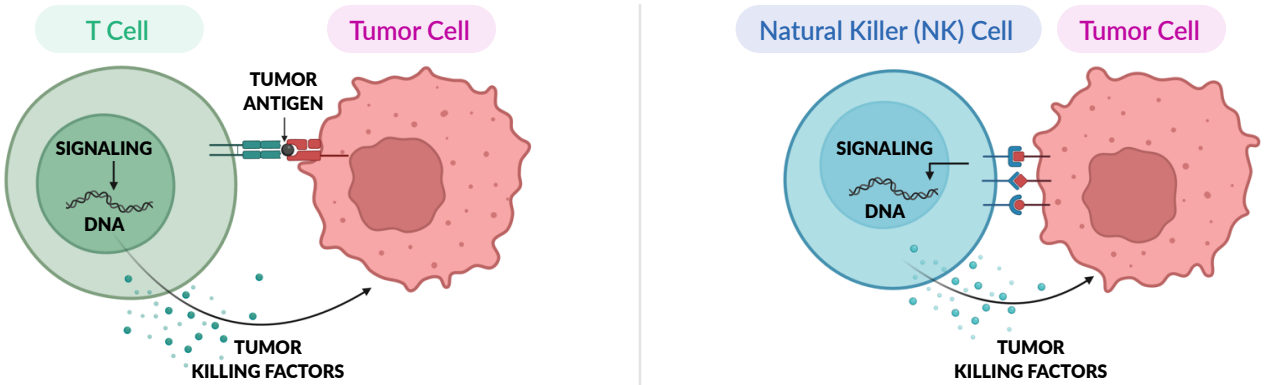
To maximize impact, philanthropists could fund critical proof-of-concept data in academic settings through exploratory studies, early animal model testing, and biomarker identification efforts. Once researchers establish early efficacy and safety signals, they could better position these projects to attract larger grants from federal agencies like the National Cancer Institute (NCI) for formal clinical trial development. At this stage, researchers could also leverage partnerships with biotech companies and venture capital investors, particularly to transition from preclinical findings to first-in-human trials. Industry engagement could provide expertise in drug formulation, manufacturing, and regulatory navigation, ensuring promising therapies can move efficiently through development. By strategically funding these early stages and facilitating handoffs to federal and private-sector partners, philanthropists can de-risk innovation, accelerate timelines, and create a sustainable ecosystem for new chemotherapy options for uLMS patients.

Immunotherapy

Immunotherapies are cancer treatments that harness the immune system to target and destroy tumor cells specifically, unlike chemotherapy and radiation, which harm both healthy and cancerous tissues. This targeted approach can significantly improve patient outcomes and quality of life and, in some cases, cure patients. Driven by the promise of immunotherapy, R&D investment in immunotherapies has outpaced chemotherapy and radiation over the past 14 years, leading to greater efficacy and expanded clinical use. Recent approvals include Tecelra for metastatic synovial sarcoma and Tecentriq for metastatic alveolar soft part sarcoma, both of which are rare cancers.

Immunotherapies work by either enhancing the tumor-killing ability of immune cells like T cells and natural killer (NK) cells or by increasing their numbers. These cells identify cancer through receptors that bind to tumor-specific antigens, triggering the release of factors that destroy the tumor (see **Figure 7**).

Figure 7 • Schematics of T-cell– and NK-Cell–Mediated Killing of Tumor Cells



Source: Milken Institute analysis of relevant literature (2025); figure created on BioRender.

Tumors often evade the patient's immune system by taking advantage of checkpoint proteins, which normally act as immune system brakes. Tumors produce signals that activate these checkpoints on T cells, tricking immune cells and telling them to stand down. Immune checkpoint blockade therapies prevent this hijacking, restoring T-cell function and allowing them to continue identifying and killing cancer cells. Other approaches include chimeric antigen receptor (CAR) T cell and CAR NK cell therapies, which genetically enhance immune cell function, and tumor-infiltration lymphocyte (TIL) therapy, which boosts the number of tumor-targeting T cells. Cancer vaccines can work before cancer occurs by training immune cells, such as antigen-presenting cells, to recognize molecular hallmarks of cancer before they develop. See **Table 6** for a detailed comparison of immunotherapy modalities: their targets, benefits, and limitations.

Table 6 • Description of Immunotherapy Modalities Across Cancers

Therapy	Description	Approved Indications	Target	Advantages	Disadvantages
Immune checkpoint blockades (e.g., nivolumab, pembrolizumab)	Removes the baseline "brakes" from the immune system, empowering it to attack cancer	Many types of cancers, such as lung, skin, kidney, bladder, and colon cancer	Immune checkpoints	• Long-lasting effects • Fewer side effects than chemotherapy • Works well in some patients with certain tumor types	• Improved therapeutic outcomes in about a third of patients • Needs immune cells already in the tumor
CAR T cell therapy (e.g., tisagenlecleucel, axicabtagene ciloleucel)	Modifies a patient's T cells in a lab, then reintroduces them into the patient's body to better kill cancer cells	Blood cancers like leukemia and lymphoma	Patient's own T cells	• Very good at killing blood cancers • Long-lasting in the body	• Doesn't work well for solid tumors • Complex and expensive to make
TIL therapy (e.g., lifileucel)	Takes immune cells from a tumor, multiplies them in a lab, and introduces them back into the patient's body	Melanoma (a type of skin cancer)	Patient's own tumor-specific T cells	• High efficacy ceiling in solid tumors • Low risk of severe side effects	• Needs immune cells in tumor • Expensive to produce
CAR NK cell therapy	Similar to CAR T but uses a different immune cell type called NK cells	Still being studied; not yet FDA-approved	NK cells from patient or a donor	• Can be made from donor cells, reducing burden on the patient • Fewer side effects than CAR T	• Doesn't work well for solid tumors • Doesn't last long in the body • Costly
Bispecific T cell engagers (BiTEs)	Uses special antibodies to connect cancer cells and T cells together	Certain blood cancers, such as leukemia and lymphoma	Tumor markers and T cells	• Very strong response in blood cancers • Can target more than one cancer marker at a time	• Can cause serious side effects • Kills healthy immune cells too • Ineffective against solid tumors
Cancer vaccines (e.g., sipuleucel-T)	Trains the immune system to recognize and attack cancer using a modified version of the cancer	Human papillomavirus-related cancers, prostate cancer, melanoma	Patient's immune cells (antigen-presenting cells)	• May help prevent cancer from coming back • Fewer side effects	• Only effective in cancers where the same cancer markers are consistent across many patients

Source: Milken Institute analysis of relevant literature (2025)

Immunotherapy has worked well for some cancers but not for uLMS to date. In two clinical trials, patients with advanced uLMS didn't benefit much from immune checkpoint inhibitor drugs like nivolumab or pembrolizumab, even when combined with chemotherapy. Other types of immunotherapy, like CAR T cell therapy, NK cell therapy, cancer vaccines, or TILs, have not yet been tested in uLMS. This shows a clear need to develop immunotherapies designed for this cancer and to better understand how the immune system interacts with uLMS tumors.

Despite challenges, clear and actionable opportunities exist to improve outcomes for uLMS patients through targeted investment. Philanthropy can advance immunotherapy for uLMS by targeting early-discovery efforts that are often too high risk for traditional funding sources. Specifically, philanthropy can support foundational research to better characterize uLMS tumor–immune interactions, fund development of next-generation immunotherapies (such as multiantigen CAR T/NK cell therapy, bispecific antibodies, or immune-modulating agents), and enable more predictive preclinical models that faithfully recapitulate the immune environment of uLMS tumors. Early-stage investment can generate the critical biological insights, early proof-of-concept data, and biomarker identification needed to de-risk later-stage therapeutic development.

To maximize impact, philanthropy could focus on exploratory studies and preclinical work in academic and nonprofit research settings. Once researchers establish early immune targets, therapeutic candidates, or preclinical validation, their projects could become competitive for federal grants (e.g., NCI Cancer Moonshot, Rare Cancers Research Program) to fund translational development and early-phase clinical trials. Philanthropy can also foster partnerships with biotech and venture capital groups at the translational stage, when lead candidates are ready for Investigational New Drug–enabling studies or early human testing. Industry partnerships at this stage could provide manufacturing scale-up, regulatory guidance, and commercialization pathways. By strategically funding early discovery and bridging the translational gap, philanthropy can accelerate promising immunotherapy approaches for uLMS into the clinic and ultimately improve patient outcomes.

Opportunity 5

Establish Effective Residual Disease–Monitoring Tools for uLMS

Liquid biopsies are noninvasive tests that, unlike traditional methods such as imaging or serum markers, detect minimal residual disease (MRD), or the harmless trace amounts of cancer cells that circulate through the bloodstream even after successful treatment. Liquid biopsies can monitor treatment efficacy by detecting how many cancer cells remain and for how long, and they can detect cancer recurrence or progression if cancer cell count rises. These tests analyze circulating tumor-derived markers such as circulating tumor cells, extracellular vesicles and proteins, cell-free DNA (cfDNA), and circulating tumor DNA (ctDNA), which enter the bloodstream when cells die. ctDNA, specifically, originates from tumor cells and could signal that the cancer has recurred sooner than symptom onset, when the patient or their care team might begin to suspect recurrence.

Liquid biopsies offer a personalized, sensitive, and specific approach to disease monitoring. Clinicians can compare results against known tumor markers to guide treatment decisions. Repeated MRD testing can track treatment response by measuring changes in ctDNA or tumor protein levels over time.

While MRD testing is standard in blood cancers, researchers and practitioners are now exploring and implementing it in solid tumors. Adoption in rare solid cancers, including LMS, remains limited but promising, with ongoing research supporting its potential for recurrence monitoring. **Table 7** outlines MRD methodologies and companies offering or developing these tests, across cancer indications.

Table 7 • MRD Methodologies and Assays Across Cancer Indications

MRD Methodology	Description	Commercially Available Products (Company)
Next-generation sequencing	Detects mutations in ctDNA; often used in combination with polymerase chain reaction–based approaches to confirm presence of mutations	• Signatera (Natera) • RaDaR (Inivata)* • FoundationOne Tracker (Foundation Medicine) • Strata Sentinel (Strata Oncology)* • SureSeq (Oxford Gene Technology) • PhaseED-Seq (Foresight) • NeXT Personal (Personalis)
Flow cytometry	Detects cell surface markers in a sample; primarily used for hematological cancers but might be relevant in LMS because it tends to spread through the bloodstream rather than through the lymphatics	• DuraClone (Beckman Coulter) • ARUP Laboratories • CellNetix • Labcorp
Epigenetics-based strategies	Includes two main epigenetics-based MRD strategies: (1) detecting where DNA has been modified by bonding to a chemical group called methyl group, and (2) fragmentomics, which analyzes cfDNA characteristics including fragment length and breakpoint motifs	• Galleri (GRAIL) • Shield (Guardant Health) • Bladder EpiCheck (Nucleix) • Adela*

*Denotes methods that have not yet been commercialized

Source: Milken Institute analysis of relevant literature and commercially available products (2025)

Liquid biopsies alone may be insufficient for MRD detection in solid tumors, which tend to shed fewer tumor markers into the bloodstream than blood cancers do. As a result, combined monitoring approaches are often more effective for solid tumors. For rare solid cancers such as uLMS, MRD testing is further complicated by tumor heterogeneity and the lack of well-defined biomarkers, making it difficult to develop sensitive and specific tests that can consistently identify the presence or growth of uLMS tumors.

MRD testing also carries inherent limitations. Like any binary test, false positives can lead to unnecessary treatments, while false negatives risk missing the disease recurrence. The absence of standardized thresholds across testing platforms means that test results for the same person can vary between companies, and there are currently no clear clinical guidelines for when to use MRD testing or how to interpret positive results in asymptomatic patients.

Additionally, not all hospitals are equipped to perform these tests in house, and reliance on external labs to perform and interpret the tests can introduce logistical barriers and financial burdens, particularly in rare cancers.

Since no MRD tests are currently approved for uLMS, researchers are exploring new strategies, particularly ones that leverage the tumor's unique genomic, epigenomic, and metabolic profiles. Rather than adapting assays designed for other cancers, developing a uLMS-specific test panel will be more effective. Combining traditional MRD tests with emerging tools and techniques and innovative technologies could improve detection.

Philanthropists have several concrete ways to advance this opportunity in combination with industry and federal agencies. First, philanthropy could fund early-stage discovery research to identify circulating biomarkers uniquely associated with uLMS, such as specific mutations, methylation patterns, or metabolite signatures, that can be incorporated into MRD assays. Second, it could support the development and validation of uLMS-specific MRD test panels in small pilot cohorts, providing proof-of-concept data necessary to attract further funding. Once researchers establish promising assays, philanthropy could also help academic centers and companies collaborate on larger prospective validation studies, potentially in partnership with federal agencies. Further downstream, philanthropy could help create biobanks of longitudinal blood samples from uLMS patients who have undergone initial treatment and are now disease-free, enabling MRD threshold refinement and improving test sensitivity and specificity over time.

Opportunity 6

Support Patient and Clinician Resources in the uLMS Ecosystem

Build a Patient Playbook to Navigate Turnkey Treatment Options for uLMS

After receiving a uLMS diagnosis, patients often turn to a range of available resources, such as advocacy groups that connect them with fellow patients, caregivers, and even global clinical experts. While these resources offer valuable support, there is currently no comprehensive, centralized guide, or "patient playbook," that compiles all available information in one place and systematically walks patients through the critical treatment and care decisions they will face.

Cutting-edge treatments, such as immunotherapy, are still in the exploratory phase for uLMS and might not be widely available through standard clinical care. However, for many patients, time is not a luxury, and they can't wait decades until the FDA approves the therapies. With the right knowledge and guidance, some patients might be able to pursue experimental therapies through clinical trials or expanded access programs. Similarly, although minimal residual disease (MRD) testing is not yet routinely available for uLMS, some biotech companies offer experimental MRD assays. Select patients might be able to access these assays on an individual (N=1) basis if they are informed about these opportunities.

Such a playbook is aspirational for uLMS and rare cancers more broadly, especially given that researchers still do not fully understand many aspects of the disease. But patients urgently need such a playbook, as its absence places them and their families at a significant disadvantage. Without a playbook, patients often remain unaware of critical

information such as optimal or experimental treatment options or even practical steps, like requesting that clinicians preserve live tissue samples so the patient can choose further biological profiling to understand the potential nature of their disease or donate the tissue for research.

Because uLMS is so rare, even leading institutions vary widely in how they treat and handle these cases. Practices like storing viably frozen tissue, flash-frozen tumor samples, or presurgical blood are not standardized, and clinicians often do not routinely do them, even at top-tier cancer centers. These early procedural choices, if not proactively considered, can severely limit future options for therapeutic decision-making.

Moreover, select patients might be able to access cutting-edge options such as comprehensive biological profiling, experimental therapeutics, or noncommercial MRD assays on a case-by-case basis (e.g., by establishing relationships with companies or researchers developing them), but patients often overlook these options simply because they are unaware of them. A centralized resource would enable patients to benefit directly from all potential options, including experimental ones, empowering them to advocate more effectively for the best possible care.

Despite existing efforts, support systems for uLMS patients remain fragmented. Streamlining these resources could greatly improve the patient experience. For example, multiple programs facilitate tumor donation, ranging from pan-cancer to uLMS-specific initiatives (**Table 8**), and various organizations, blogs, and foundations aim to connect and support the uLMS community (**Table 9**).

Table 8 • Existing Organizations Facilitating Tumor Sample Donation and Further Analysis

Organization	Description
LMSproject by Count Me In	LMSproject by Count Me In is a nonprofit initiative and cancer research study open for LMS. • Patients can share their cancer samples, clinical information, and experiences, which many studies can then use. • Count Me In generates cancer datasets that link clinical, genomic, molecular, and patient-reported data. • Developing a robust dataset can accelerate our understanding of different cancers.
Rare Cancer Research Foundation (RCRF)	RCRF is a nonprofit that helps patients donate their tissue directly to researchers. • Researchers have limited access to samples from rare cancers, making these diseases difficult to study and treat. Therefore, RCRF hopes to promote scientific discoveries by closing that gap. • RCRF has already contributed to 65+ rare cancer research models, which can accelerate new therapy development.
Cancer Cell Line Factory (CCLF) by the Broad Institute	CCLF converts any tumor sample, including those from rare cancers such as uLMS, into next-generation models such as organoids and cell lines, which researchers can use for further investigation. • The models advance studies in cancer biology, accelerate drug discovery, and help identify novel therapeutic targets.

Source: Milken Institute analysis of relevant organizations (2025)

Table 9 • uLMS Patient-Specific Resources

Resource	Description
Leiomyosarcoma Support & Direct Research Foundation (LMSDR)	LMSDR supports LMS patients and research by contributing to patient registries, tissue banks, and cell lines. • They educate and support patients and offer advocacy and awareness. LMSDR also funds uLMS research specifically.
National Leiomyosarcoma Foundation (NLMSF)	NLMSF offers many resources for LMS patients. • They inform patients about insurance, financial assistance, transportation and lodging, mentoring programs, and virtual coping and grief support groups.
LMSeAlerts	LMSeAlerts is a free online newsletter organized through LMSDR with news about LMS, clinical trial updates, research project information, and other resources. • Patients can subscribe to the newsletter through the LMSDR website.
LMS Boot Camp	This boot camp is a video crash course about LMS basics created by LMSDR. • This video series provides step-by-step guidance, including how to access doctors and discuss treatment options, and information about surgery, chemotherapy, radiology, coping with the disease, and other issues associated with LMS.
LMS Community Blog	This blog, organized by LMSDR, features articles written by LMS patients, caregivers, doctors, and researchers. • Blog posts discuss survivor stories, clinical trials, community events, and other topics as a way for people to voice their experiences with LMS.
LMSDR Facebook Group	This Facebook group has over 5,300 LMS survivors and caregivers. • This group gives members a chance to connect with other patients and caregivers and to share posts in a closed, confidential space.
Sarcoma Alliance	The Sarcoma Alliance is an international sarcoma advocacy organization that educates and supports people affected by sarcoma. • It hosts patient care initiatives, including support groups, advocacy, conferences, and grants to help patients receive second opinions.

Source: Milken Institute analysis of available resources (2025)

A patient playbook could serve as a one-stop resource. It could include an accessible explanation of uLMS and what the diagnosis means, a curated overview of available treatment options including emerging and experimental therapies, practical guidance on navigating care such as how to seek second opinions or enroll in clinical trials, insights into new technologies such as MRD testing, and tips on organizing care and communicating effectively with a medical team. A patient playbook empowers individuals by delivering structured, reliable, and up-to-date information so they do not have to assemble fragmented data independently. It supports confident, informed decision-making at each key point in a patient's treatment journey.

While philanthropists could invest in developing and disseminating a centralized patient playbook, the effort and funding required to create it are relatively modest compared to other major research initiatives. This inexpensive opportunity primarily requires leadership and collaboration among the uLMS patient, advocacy, and clinical communities. The creation of a patient playbook is best suited for a coordinated community effort.

Create Continuing Education Opportunities for Gynecologists to Manage uLMS Effectively

Given the high prevalence of uterine fibroids and the rarity of uLMS, gynecologists need to have the most current and comprehensive information on uLMS. Continual education on the latest research is critical for delivering optimal patient care. A clear example lies in the historical use of power morcellation, a procedure that pulverized uterine tumors inside the abdominal cavity. This procedure dispersed tumor tissue, promoting metastases, which significantly increased mortality rates in uLMS patients. Fortunately, clinician awareness, training, and FDA intervention have sharply reduced the use of power morcellation.

Challenges diagnosing and managing uLMS highlight the need for improved physician education. Training can come through existing platforms and resources that target gynecology groups (**Table 10**), or the community can create entirely new educational initiatives. Providing gynecologists with efficient, accessible methods to stay current on uLMS detection and diagnosis advancements can significantly improve patient outcomes. **Table 10** highlights examples of such methods, including online courses, forums, conferences, and journals.

Philanthropists can seed pilot programs or fund professional societies. However, given the need's relatively modest scale and the traditional mechanisms already available, this effort would be most appropriately led by the professional and clinical communities themselves. Meaningful progress will depend on collective action and professional commitment.

Table 10 • Resources for Continued Clinician Education in Gynecology and Gynecologic Oncology

Type	Resource	Description
Online courses	American College of Obstetricians and Gynecologists	Three free online courses available to all health-care practitioners (in partnership with the Centers for Disease Control and Prevention) that focus on prevention and early diagnosis of uterine, ovarian, and lower anogenital tract cancer
Educational forums and materials	The Foundation for Women's Cancer	Educational materials, courses, and webinars to support gynecologic cancer patients, caregivers, and survivors; resources that spread awareness and knowledge of gynecologic cancer symptoms, risk factors, prevention, and early detection
Conferences	Society of Gynecologic Oncology	Annual educational and scientific gathering for professionals who treat and care for patients with gynecologic cancer
	International Gynecologic Cancer Society	Meeting for leading experts in all disciplines involved in gynecologic oncology to discuss research, hold collaborative workshops, and experience educational sessions
Journals	*International Journal of Gynecological Cancer*	A primary educational and informational publication about the detection, prevention, diagnosis, and treatment of gynecologic malignancies for gynecologists, oncologists, pathologists, and research scientists
	Gynecologic Oncology	An international journal that publishes clinical and investigative articles about female reproductive tract tumors, discussing etiology, diagnosis, and treatment

Source: Milken Institute analysis of available resources (2025)

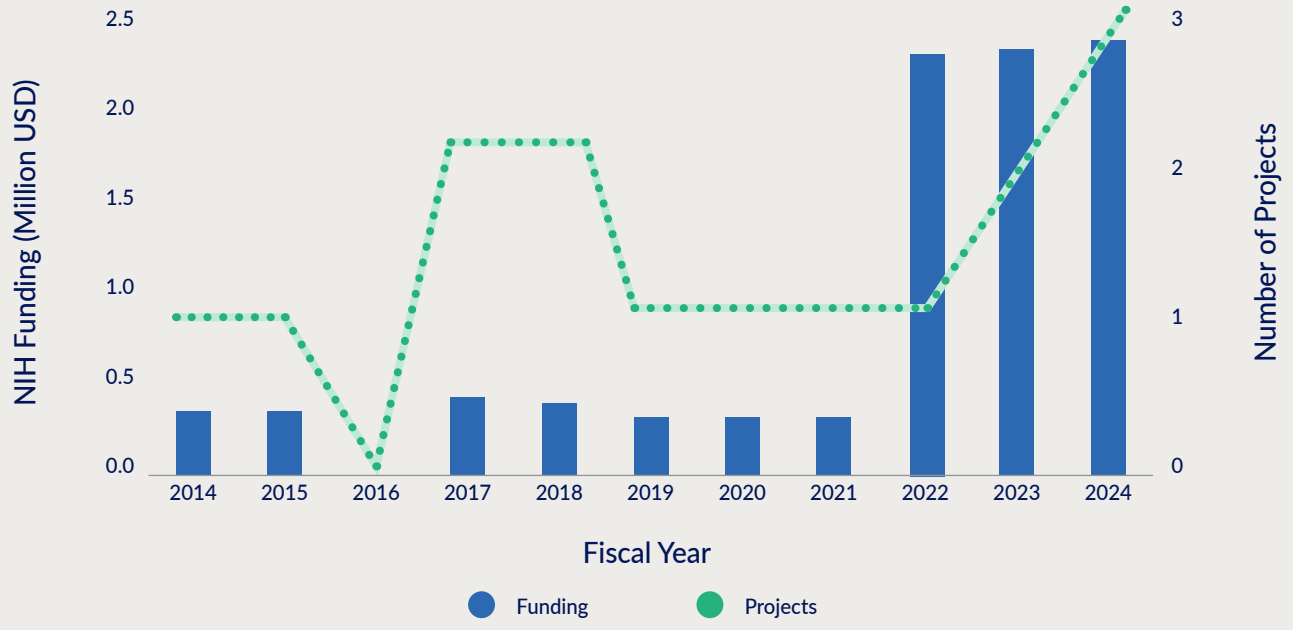
Funding and Investment Landscape

This section reviews historical and current funding trends in the uLMS field, from scientific research to commercial development. We want to equip philanthropists with a clear understanding of the current funding landscape, highlighting the types of projects that are receiving support, identifying critical gaps in investment, and uncovering opportunities where targeted funding could have the greatest impact.

US Government Funding for uLMS from NIH

Between fiscal years 2014 and 2024, the federal government allocated approximately $9.5 million to uLMS research, as reported in the NIH Research Portfolio Online Reporting Tool (NIH RePORTER) (**Figure 8**). Since 2022, annual NIH funding for uLMS research increased significantly, with average annual funding rising from $314,000 (2014–2021) to $2.3 million (2022–2024) due to the initiation of the Specialized Program of Research Excellence (SPORE) in LMS, led by the University of Michigan. The SPORE is a multi-institutional project, including international collaboration, that focuses on LMS (including uLMS) genetic vulnerabilities, disease epidemiology, and biomarker identification.

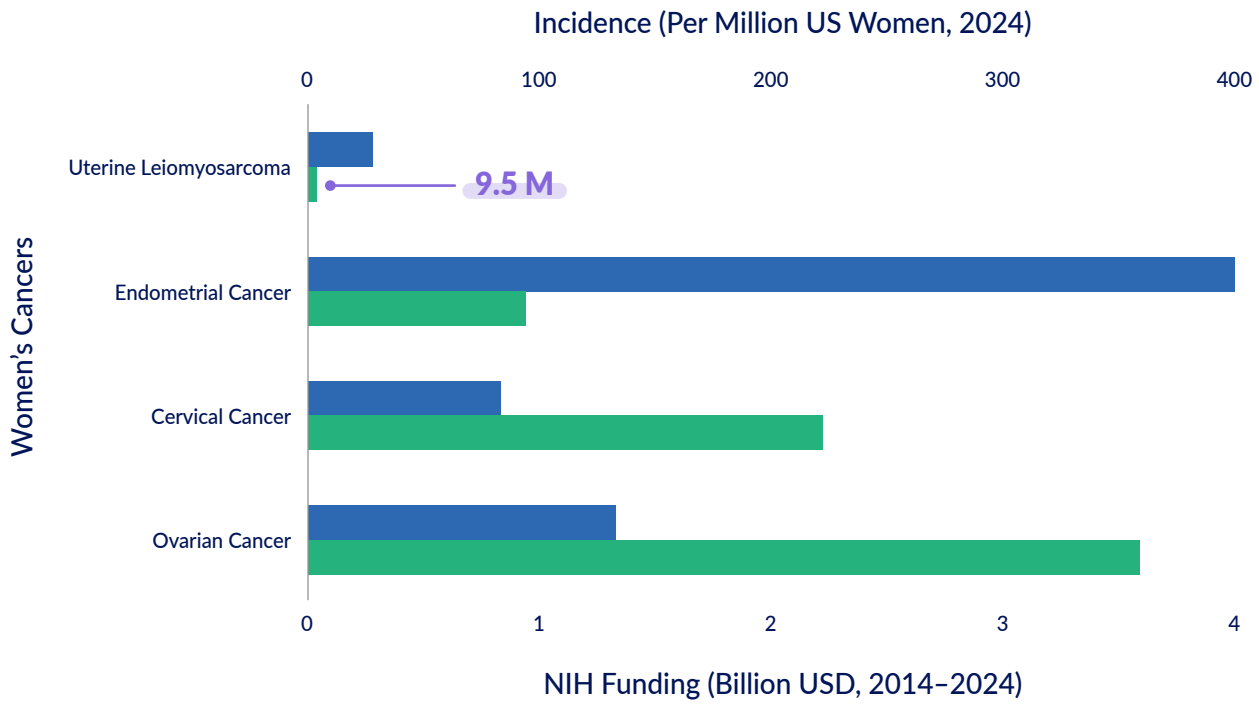
Figure 8 • Annual NIH-Funded uLMS Research by Funding Amount and Number of Projects from 2014 to 2024



Source: Milken Institute analysis of funding from NIH RePORTER (2025)

Despite the increase in NIH funding, uLMS remains an underfunded disease compared to other cancers affecting women. From 2014 to 2024, endometrial cancer, a cancer that takes place a few inches away from the myometrium in the endometrium, received over $885 million in NIH funding (**Figure 9**). In contrast, uLMS research received only $9.5 million over the past decade, highlighting a significant funding gap. Although uLMS has a lower incidence rate than other women's cancers, a comparison of public funding normalized by incidence shows that uLMS continues to receive disproportionately low support ($1.2 million per incidence in 1 million women) relative to ovarian ($30.6 million), cervical ($28.0 million), and endometrial cancer ($2.2 million). Accelerating our understanding of uLMS to improve diagnosis and treatment requires greater financial investment in uLMS research.

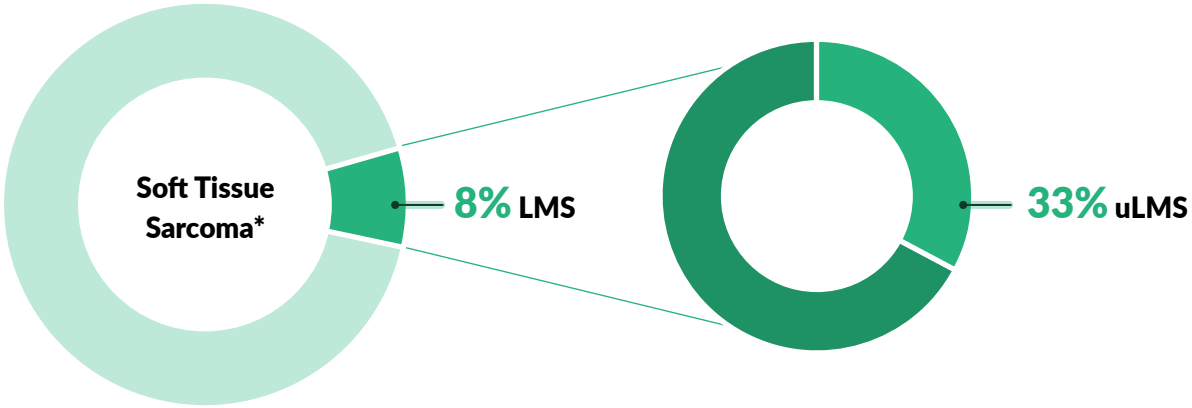
Figure 9 • NIH Funding for Women's Cancers Compared to Incidence Rate per Million US Women in 2024



Source: Milken Institute analysis of funding from NIH RePORTER (2025)

Focusing on sarcomas, from 2014 to 2024, only 4 percent of the total funding for sarcoma research ($9.3 billion) related to soft tissue sarcomas ($360 million). Among soft tissue sarcoma research, approximately 8 percent ($29 million) was allocated to LMS research (**Figure 10**). uLMS is one of the most common LMS types and the only organ-specific form to receive distinct NIH funding. Research funding for uLMS accounts for about 3 percent of the total soft tissue sarcoma funding, or one-third of the total LMS research funding.

Figure 10 • Portion of NIH Funding for Soft Tissue Sarcomas Dedicated to LMS and uLMS, 2014–2024

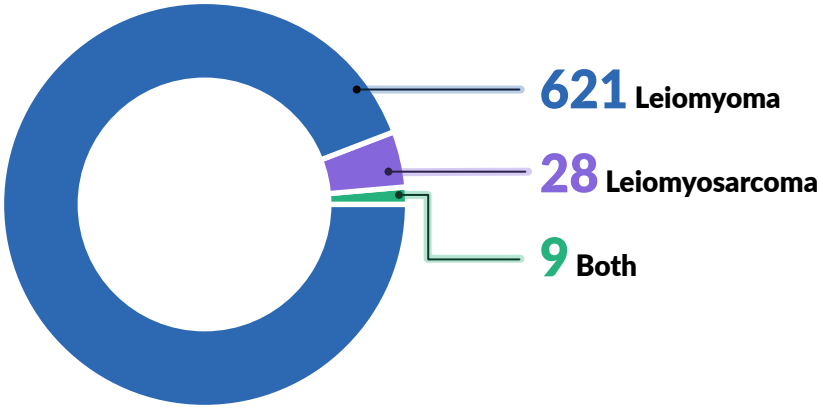


*Soft tissue sarcoma comprises the entire pie chart on the left.

Source: Milken Institute analysis of funding from NIH RePORTER (2025)

When comparing the number of NIH-funded projects from 2014 to 2024 for LMS, an aggressive form of cancer, and leiomyoma, a benign fibroid, only nine projects mention both conditions. Leiomyomas are a widespread condition (affecting up to 70–80 percent of women by age 50), and projects focusing on leiomyoma alone (621) vastly outnumber projects focusing on LMS alone (28) (**Figure 11**). This disparity highlights the limited funding for research on how uLMS may arise from, relate to, or be distinguished from leiomyomas.

Figure 11 • Number of NIH-Funded Projects from 2014 to 2024 for Leiomyoma, Leiomyosarcoma, or Both Conditions



Source: Milken Institute analysis of funding from NIH RePORTER (2025)

uLMS NIH Funding by Research Area

Understanding funding trends critically advances research in the field. Between FY 2014 and 2024, the NIH has directed most uLMS research funding (70.2 percent) toward therapeutics, largely through the SPORE project launched in 2022. Model systems research has 10 funded projects but received only 22.3 percent of NIH funding. Meanwhile, biomarkers research received just 7.5 percent of the allocated funds (**Table 11**).

Table 11 • NIH-Funded uLMS Research by Research Area

uLMS Research Area	Project Counts (% of total) (FY 2014–2024)	Total Funding (% of total) (FY 2014–2024)
Therapeutics*	3 (20.0)	$6,651,787 (70.2)
Model systems	10 (66.7)	$2,115,866 (22.3)
Biomarkers	2 (13.3)	$708,980 (7.5)
Total	**15 (100)**	**$9,476,633 (100)**

*The three projects in therapeutics are the SPORE projects from 2022 to 2024.

Source: Milken Institute analysis of funding from NIH RePORTER (2025)

LMS NIH Funding by Research Area

When analyzing NIH funding distribution across LMS research areas, therapeutics, model systems, and biomarkers are again major research categories (**Table 13**). NIH funding for LMS research also includes genomic analysis as the top-funded research category, receiving the highest share (49.4 percent) of total funding. This surge is primarily from a $13 million project that the Broad Institute has led since 2020. This project is developing a comprehensive LMS-related database (LMSproject) to bolster future research.

Table 12 • NIH-Funded LMS Research by Research Area

LMS Research Area	Project Counts (% of total) (FY 2014–2024)	Total Funding (% of total) (FY 2014–2024)
Genomic analysis	9 (24.3)	$14,255,336 (49.4)
Therapeutics *Drug discovery* *Targeting tumor-associated macrophages* *Atezolizumab*	6 (16.2) *3* *2* *1*	$8,424,289 (29.2)
Model systems	16 (43.2)	$4,365,846 (15.1)
Biomarkers	6 (16.2)	$1,772,106 (6.1)
Total	**37 (100)**	**$28,817,577 (100)**

Source: Milken Institute analysis of funding from NIH RePORTER (2025)

International Government Funding for uLMS

Conducting a systematic search for international government funding is a challenge because there is no comprehensive database like NIH RePORTER. We can identify some public funding sources through the acknowledgments and funding sections of published uLMS research papers. Notable international government funding sources include, but are not limited to, the National Institute for Health and Care Research (NIHR) and UK Research and Innovation in the United Kingdom, the National Health and Medical Research Council (NHMRC) in Australia, the Canadian Institutes of Health Research (CIHR), and the European Research Council (ERC) in the European Union. However, data on uLMS-specific projects remain scarce.

The SPORE project for uLMS is based in the US and features collaborations with various international institutions, including the Garvan Institute of Medical Research and the University of New South Wales in Australia and the University of Toronto in Canada. CIHR has also provided a $17,500 grant to support research identifying uLMS biomarkers. NHMRC funded a $504,000 project focusing on targeted therapy for ovarian cancer.

Some international government funding initiatives focus on fields related to uLMS, such as LMS and uterine leiomyoma, as shown in **Table 13**. This is not a comprehensive list, as not all international agencies provide funding information.

Table 13 • International Government Funding

Research Field	Country (Funding Agency)	Funded Project Counts (FY 2014–2024)	Total Funding (FY 2014–2024)
LMS	Canada (CIHR)	3	$749,000
	UK (NIHR)	1	$66,500
Uterine leiomyoma	Finland (ERC)	1	$2,600,000

Source: Milken Institute analysis of funding from international sources (2025)

Even when expanding the search to uLMS-related fields, such as leiomyoma, sustained and sufficient international government funding is minimal. This lack of funding hinders research efforts and significantly impairs advancements in disease understanding.

Nonprofit Private Source Funding for uLMS and Related Research Fields

Beyond public funding, many nonprofit organizations, including foundations and university-based research institutions, support vital research efforts. While no private funding sources are specifically dedicated to uLMS research, several foundations advance LMS research and treatment. Notable examples include the Leiomyosarcoma Support & Direct Research Foundation and the National Leiomyosarcoma Foundation. The LMSproject, launched by Count Me In, is building a patient database for LMS. Other foundations and initiatives support research in sarcoma and rare cancers. The Appendix summarizes key organizations that fund LMS, sarcoma, and rare cancer research in the United States, including their financial contributions (where available) and goals for cancer research (**Appendix Table A**).

Biotech and Pharmaceutical Investments in uLMS

Due to the rarity of uLMS, companies have limited financial motivation to develop treatments specifically for it. Yondelis (trabectedin) is the first FDA-approved treatment for advanced soft tissue sarcoma, a cancer category that includes uLMS. Initially approved in 2007 for medical use in the European Union, Yondelis later received US FDA approval in 2015. Yondelis is marketed by PharmaMar in Europe and by Janssen Pharmaceuticals (a subsidiary of Johnson & Johnson) in the United States.

Beyond Yondelis, several biotech and pharmaceutical companies are actively researching therapeutics for soft tissue sarcoma and LMS. **Table 14** lists companies currently investing in research for new LMS and soft tissue sarcoma treatments. We sourced this information from the companies' official websites.

Table 14 • Biotech and Pharmaceutical Companies Investigating Treatments for uLMS, LMS, and Soft Tissue Sarcomas

Company (Country)	Name (Therapeutic)	Stage of Development	Indication
Intensity Therapeutics (United States)	**INT230-6** (chemotherapy)	Global Phase 3 (2024) NCT06263231	Metastatic soft tissue sarcoma
Lixte Biotechnology (United States)	**LB-100** (chemotherapy)	Phase 1/2 (2024) NCT05809830	Advanced soft tissue sarcoma
PharmaMar (Spain)	**Zepzelca (SaLuDo)** (chemotherapy)	Phase 2b/3 (2023) NCT06088290	Metastatic LMS
	Ecubectedin PM14 (chemotherapy)	Phase 1/2 (2024) NCT05146440	Soft tissue sarcoma
Cebiotex (Spain)	**CEB-01** (membrane implant)	Phase 1 (2024) NCT04619056	Soft tissue sarcoma
Polaris Pharmaceuticals (Taiwan)	**Pegargiminase ADI-PEG 20** (chemotherapy)	Phase 3 (2024) NCT05712694	Soft tissue sarcoma; LMS

Source: Milken Institute analysis of biotech and pharmaceutical pipelines (2025)

Conclusion

uLMS is a rare and aggressive cancer with limited diagnostic, monitoring, and treatment options, posing significant challenges for patients and the medical community. Unlike more common cancers, uLMS has not benefited from extensive research investment, leaving many critical questions about the disease unanswered. However, the field is at a pivotal moment, with emerging technologies and scientific insights offering new pathways for discovery.

Many uLMS research obstacles mirror those seen in other rare cancers. Philanthropists can accelerate progress through investment and strategic funding collaboration with federal agencies and the industry, driving natural history studies, early detection advancements, biological profiling, uLMS-specific monitoring, and targeted and effective therapy development.

Advancing any of the opportunities and unmet needs this report outlines will not only improve the understanding and treatment of uLMS but may also contribute to broader breakthroughs in sarcoma research and other rare cancers. Through investment, collaboration, and scientific rigor, we can transform the outlook for uLMS patients, ensuring they have access to high-quality, evidence-based care and promising new options throughout their journey.

Appendix

Giving Smarter Guide Research and Analysis Process

In 2025, the Milken Institute Science Philanthropy Accelerator for Research and Collaboration partnered with the Briger Foundation for Oncology Research to analyze understanding of uLMS. We assessed the landscape at various stages of the uLMS patient journey, which helped us identify priority unmet needs. We began by reviewing emerging research trends and clinical applications, consulting relevant academic literature, online lectures and webinars, and 40 key opinion leaders comprising scientists, clinicians, and biotech companies. This diverse perspective provided insights from bench to bedside, helping us identify opportunities for further philanthropic and research support.

NIH RePORTER Funding Landscape Methodology

We searched the NIH RePORTER database for fiscal years 2014 to 2024. Our search included projects if their title or abstract contained the term "uterine leiomyosarcoma." For comparison purposes, we performed additional searches using the terms:

- "Endometrial cancer," "cervical cancer," and "ovarian cancer" (to compare with other women's cancers)
- "Leiomyosarcoma" and "soft tissue sarcoma" (to compare with LMS and soft tissue sarcomas more broadly)
- "Leiomyoma" (to compare with uterine fibroids)

Figure Creation

We created scientific and medical figures for this document with BioRender.

Details of Private uLMS, LMS, and Rare Cancer Funding Initiatives

Table A • Private Funding for Initiatives in uLMS, LMS, and Rare Cancers

Type	Organization Name	Funding Contribution
LMS/uLMS specific	Leiomyosarcoma Support & Direct Research Foundation	LMSDR has supported research grants in LMS since 2006. It awarded $2 million from 2014 to 2025. Select recently funded projects (2024 and 2025) include: • Identification of neoantigens unique to LMS (with applications to vaccine design) • Phase 1/2 study of pexidartinib with pembrolizumab in advanced and metastatic LMS • Circulating tumor DNA for long-term surveillance of LMS patients • Distribution of novel human macrophage subsets in LMS • Comprehensive compendium of clinically relevant active chromatin domains in LMS
	National Leiomyosarcoma Foundation	NLMSF has supported research grants in LMS since 2002. Select recently funded projects (2023–2025) include: • AI for characterizing LMS • Immunomodulatory effects of P13k/mTOR inhibitors on the tumor microenvironment in LMS • Multiomic liquid biopsy for preoperative diagnosis of uLMS and benign leiomyoma • Activated telomere maintenance mechanisms in LMS

Table continued on following page

Type	Organization Name	Funding Contribution
Rare cancers/ Sarcomas	Sarcoma Foundation of America (SFA)	SFA has funded 200+ research grants, including 14 LMS and uLMS projects. Topics in LMS and uLMS (2024) include: • Novel immunotherapy combination strategies and predictive biomarkers for patients with uLMS • Therapeutic efficacy of eribulin in LMS through a better knowledge of its complex mechanism of action • A preclinical mouse model for targeted therapy in uLMS • Liquid biopsy in patients with uLMS • MicroRNA-based strategy for targeting uLMS
	JEDI Rare Cancer Foundation	The foundation has funded several initiatives, including: • $5 million to Case Western to launch CURE: The Rare Cancer Initiative • $100,000 to Columbia University to support sarcoma research in 2024
	Transformative Rare Cancer Initiative (TRACER) at Fred Hutch Cancer Center	Founded in 2024 with a $2.5 million grant, TRACER focuses on the following projects: • Development and characterization of patient-derived models of rare cancers • Molecular characterization of rare tumors • Use of AI and patient tissue to identify potential cancer therapies
	Bertarelli Rare Cancer Initiative	In 2019, Dona Bertarelli, cofounder of the Bertarelli Foundation, gifted $15 million to Harvard Medical School for rare cancer research.
	TargetCancer Foundation (TCF)	TCF has invested over $2 million in rare cancer research initiatives since 2009.
	Northwest Sarcoma Foundation	The Northwest Sarcoma Foundation has provided over $384,000 to sarcoma research since 2011.
General	Chan Zuckerberg Initiative (CZI)	CZI supported the Rare Cancer Research Foundation with $1 million in 2025 for data infrastructure, a patient-centered biobank, and patient community engagement.

Source: Milken Institute (2025)

Glossary

Adipocytokines:
group of proteins released by fat cells and circulating in the blood

Alveolar soft part sarcoma:
cancer originating in soft tissue such as muscle, nerves, or fat

Antigen:
molecule expressed by cells that can trigger an immune response

Antigen-presenting cells:
immune cells that activate immune cells such as T cells to tumor antigens

Breakpoint motifs:
specific DNA sequences associated with structural variations such as chromosomal deletions

Cell-free DNA (cfDNA):
DNA fragments circulating in the bloodstream often shed from cells

Cell matrix (or extracellular matrix):
noncellular network of proteins and carbohydrates surrounding and supporting cells and tissues

Chromatin immunoprecipitation sequencing:
technique combining DNA sequencing and chromatin immunoprecipitation to determine gene–protein interactions that regulate gene expression

Circulating tumor DNA (ctDNA):
subset of cfDNA originating from tumor cells

Copy number variation:
change in the number of copies of a DNA sequence

Differentiation:
process by which immature cells develop into specialized cells with distinct functions

DNA damage response:
DNA repair processes resulting from DNA damage including mismatch repair, base excision repair, nucleotide excision repair, homologous recombination, and nonhomologous end joining

DNA-PK:
protein kinases that help repair DNA damage

Estrogen receptor:
cellular receptors that bind estrogen and mediate processes such as reproductive health and immune function

Flow cytometry:
technique used to measure markers such as cell size, complexity, and surface markers

Fragmentomics:
study of DNA fragment size and distribution

Hematological cancers:
cancers arising from blood-forming tissues such as leukemia and lymphoma

Hyalinization:
process in which an acellular matrix replaces normal tissue, often caused by tumors

Hypomethylation:
fewer methylation events leading to greater propensity for mutations

Indication:
diseases that are approved for a given treatment

Karyotyping:
measurement of chromosome size, number, and shape

Lymphatic system:
circulatory system that drains lymph or extra fluid from tissues

Lymph node metastasis:
spread of cancer cells from the primary tumor site to lymph nodes

Mass spectroscopy:
technique to measure the type and concentration of metabolites using their mass and charge

Methylation:
addition of a methyl group to DNA that often reduces expression of a gene

Methylation bisulfite sequencing:
technique to detect DNA methylation

MicroRNA:
class of noncoding RNAs that bind to and silence other RNAs resulting in gene silencing

Multinucleated cell:
abnormal cell containing more than one nucleus

Natural killer (NK) cells:
immune cells that directly kill tumor or infected cells in an antigen-independent manner

Next-generation sequencing:
genetic sequencing strategy allowing rapid sequencing of large amounts of DNA

Nuclear magnetic resonance:
process to analyze the structure and contents of molecules

Oncogene:
mutated version of a proto-oncogene that can disrupt the cell cycle and contribute to cancer

Oxidation-reduction (redox):
chemical reaction involving electron transfer important for cancer cell survival

PARP:
proteins that help repair damaged DNA in cells

Peritoneum:
membrane lining the abdomen

Polymerase chain reaction:
echnique used to amplify specific DNA regions

Progesterone receptors:
cellular receptors that bind progesterone and mediate reproductive functions and cell growth

Progression-free survival:
time a cancer patient lives without disease worsening

Prolactin:
hormone produced by the pituitary gland that plays a role in lactation and other functions

Proto-oncogene:
gene that promotes cell cycle and division, which can become an oncogene if mutated

Response rate of therapies:
percentage of patients with at least a 30 percent reduction in tumor size after treatment

Senesce:
state of permanent cell cycle arrest

Stratification:
division of patient populations based on characteristics such as clinical features or molecular markers

T cells:
immune cells that directly kill tumor or infected cells in an antigen-dependent manner

Telomere:
region of repetitive DNA at chromosome ends that maintains chromosomal stability

Vesicles:
small sacs that transport substances either within or between cells

Bibliography

Abbou, Samuel, Kelly Klega, et al. "Circulating Tumor DNA Is Prognostic in Intermediate-Risk Rhabdomyosarcoma: A Report from the Children's Oncology Group." *Journal of Clinical Oncology* 41, no. 13 (February 1, 2023): 2382–2393. https://doi.org/10.1200/JCO.22.00409.

Abeshouse, Adam, Clement Adebamowo, et al. "Comprehensive and Integrated Genomic Characterization of Adult Soft Tissue Sarcomas." *Cell* 171, no. 4 (November 2, 2017): 950–65.e28. https://doi.org/10.1016/j.cell.2017.10.014.

Ahn, Jong Seok, Sangwon Shin, et al. "Artificial Intelligence in Breast Cancer Diagnosis and Personalized Medicine." *Journal of Breast Cancer* 26, no. 5 (October 17, 2023): 405–435. https://doi.org/10.4048/jbc.2023.26.e45.

Alshibany, Aisha, Maggie Zhou, et al. "Molecular Residual Disease (MRD) Detection Using Bespoke Circulating Tumor DNA (ctDNA) Assays in Localized Soft Tissue Sarcoma (STS): A Multicenter Study." *Journal of Clinical Oncology* 42, no. S16 (May 29, 2024): 11537. https://doi.org/10.1200/JCO.2024.42.16_suppl.11537.

American Cancer Society. "Breast Cancer Hormone Receptor Status: Estrogen Receptor." November 8, 2021. https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-hormone-receptor-status.html.

American Cancer Society. "Cancer Facts & Figures 2024." Accessed May 8, 2025. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/2024-cancer-facts-figures.html.

Angel, P., F. Wijovi, et al. "307P Hormonal Therapy vs Combination Chemotherapy in Metastatic Leiomyosarcomas: A Systematic Review." *Annals of Oncology* 34, no. S4 (November 2023): S1592. https://doi.org/10.1016/j.annonc.2023.10.428.

Arend, Rebecca C., Michael D. Toboni, et al. "Systemic Treatment of Metastatic/Recurrent Uterine Leiomyosarcoma: A Changing Paradigm." *The Oncologist* 23, no. 12 (August 23, 2018): 1533–45. https://doi.org/10.1634/theoncologist.2018-0095.

Baker-Rand, Holly, and Sarah J. Kitson. "Recent Advances in Endometrial Cancer Prevention, Early Diagnosis and Treatment." *Cancers* 16, no. 5 (March 1, 2024): 1028. https://doi.org/10.3390/cancers16051028.

Bartosch, Carla, Mariana Afonso, et al. "Distant Metastases in Uterine Leiomyosarcomas: The Wide Variety of Body Sites and Time Intervals to Metastatic Relapse." *International Journal of Gynecological Pathology* 36, no. 1 (January 2017): 31–41. https://doi.org/10.1097/PGP.0000000000000284.

Ben-Ami, Eytan, Constance M. Barysauskas, et al. "Immunotherapy with Single Agent Nivolumab for Advanced Leiomyosarcoma of the Uterus: Results of a Phase 2 Study." *Cancer* 123 no. 17 (April 25, 2017): 3285–90. https://doi.org/10.1002/cncr.30738.

Bertini, Ivano, Stefano Cacciatore, et al. "Metabolomic NMR Fingerprinting to Identify and Predict Survival of Patients with Metastatic Colorectal Cancer." *Cancer Research* 72, no. 1 (January 2, 2012): 356–64. https://doi.org/10.1158/0008-5472.CAN-11-1543.

Bento, Laiz, Rodolfo Correia, et al. "Performance of Eight-Color Dry Antibody Reagent in the Detection of Minimal Residual Disease in Chronic Lymphocytic Leukemia Samples." *Clinical Cytometry*, 98, no. 6 (April 6, 2020): 529–35. https://doi.org/10.1002/cyto.b.21875.

Boichuk, Sergei, Firuza Bikinieva, et al. "Inhibition of AKT-Signaling Sensitizes Soft Tissue Sarcomas (STS) and Gastrointestinal Stromal Tumors (GIST) to Doxorubicin via Targeting of Homology-Mediated DNA Repair." *International Journal of Molecular Sciences* 21, no. 22 (November 22, 2020): 8842. https://doi.org/10.3390/ijms21228842.

Bose, Sminu, Gary K. Schwartz, et al. "Novel Therapeutics in the Treatment of Uterine Sarcoma." *American Society of Clinical Oncology Educational Book* 42 (June 17, 2022): 900–909. https://doi.org/10.1200/EDBK_350541.

Bradley, Rosie, Jeremy Braybrooke, et al. "Trastuzumab for Early-Stage, HER2-Positive Breast Cancer: A Meta-Analysis of 13,864 Women in Seven Randomised Trials." *The Lancet Oncology* 22, no. 8 (August 2021): 1139–50. https://doi.org/10.1016/S1470-2045(21)00288-6.

Broz, Marina T., Emily Y. Ko, et al. "Metabolic Targeting of Cancer Associated Fibroblasts Overcomes T-Cell Exclusion and Chemoresistance in Soft-Tissue Sarcomas." *Nature Communications* 15, no. 1 (March 20, 2024): 2498. https://doi.org/10.1038/s41467-024-46504-4.

Burg, Lara, Maite Timmermans, et al. "Incidence and Predictors of Peritoneal Metastases of Gynecological Origin: A Population-Based Study in the Netherlands." *Journal of Gynecological Oncology* 31, no. 5 (September 2020): e58. https://doi.org/10.3802/jgo.2020.31.e58.

Byar, Katherine L., and Tricia Fredericks. "Uterine Leiomyosarcoma." *Journal of the Advanced Practitioner in Oncology* 13, no. 1 (January 19, 2022): 70–76. https://doi.org/10.6004/jadpro.2022.13.1.6.

Canadian Institutes of Health Research. "Detailed Information." Government of Canada. Accessed May 8, 2025. https://webapps.cihr-irsc.gc.ca/decisions/p/project_details.html?applId=506550&lang=en.

ChadTough Defeat DIPG Foundation. "Navigating the Disease." My DIPG Navigator. Accessed May 12, 2025. https://www.mydipgnavigator.org/about-dipg-dmg/navigating-disease/.

Chiorazzi, Michael, Jan Martinek, et al. "Autologous Humanized PDX Modeling for Immuno-Oncology Recapitulates Features of the Human Tumor Microenvironment." *Journal for ImmunoTherapy of Cancer* 11, no. 7 (July 2023): e006921. https://doi.org/10.1136/jitc-2023-006921.

Choi, Jungmin, Aranzazu Manzano, et al. "Integrated Mutational Landscape Analysis of Uterine Leiomyosarcomas." *Proceedings of the National Academy of Sciences* 118, no. 15 (February 16, 2021): e2025182118. https://doi.org/10.1073/pnas.2025182118.

Chudasama, Priya, Sadaf S. Mughal, et al. "Integrative Genomic and Transcriptomic Analysis of Leiomyosarcoma." *Nature Communications* 9, no. 1 (January 10, 2018): 144. https://doi.org/10.1038/s41467-017-02602-0.

Congressionally Directed Medical Research Programs. "Peer Reviewed Cancer." Military Health System. Last modified April 17, 2025. https://cdmrp.health.mil/prcrp/default.

Cosgrove, David O., Wendie A. Berg, et al. "Shear Wave Elastography for Breast Masses Is Highly Reproducible." *European Radiology* 22, no. 5 (December 31, 2011): 1023–32. https://doi.org/10.1007/s00330-011-2340-y.

Cuppens, Tine, Matthieu Moisse, et al. "Integrated Genome Analysis of Uterine Leiomyosarcoma to Identify Novel Driver Genes and Targetable Pathways." *International Journal of Cancer* 142, no. 6 (October 24, 2017): 1230–43. https://doi.org/10.1002/ijc.31129.

Cystic Fibrosis Foundation. "CF Peer Connect." Accessed May 7, 2025. https://www.cff.org/get-involved/cf-peer-connect.

Dall, Genevieve, Cassandra J. Vandenberg,et al. "Targeting Homologous Recombination Deficiency in Uterine Leiomyosarcoma." *Journal of Experimental & Clinical Cancer Research* 42, no. 1 (May 4, 2023): 112. https://doi.org/10.1186/s13046-023-02687-0.

Dall, Genevieve V., Anne Hamilton, et al. "Interrogating the Genomic Landscape of Uterine Leiomyosarcoma: A Potential for Patient Benefit." *Cancers* 14, no. 6 (March 18, 2022): 1561. https://doi.org/10.3390/cancers14061561.

D'Ambrosio, Lorenzo, Nathan Touati, et al. "Doxorubicin plus Dacarbazine, Doxorubicin plus Ifosfamide, or Doxorubicin Alone as a First-Line Treatment for Advanced Leiomyosarcoma: A Propensity Score Matching Analysis from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group." *Cancer* 126, no. 11 (March 4, 2020): 2637–47. https://doi.org/10.1002/cncr.32795.

Dancsok, Amanda R., Dongxia Gao, et al. "Tumor-Associated Macrophages and Macrophage-Related Immune Checkpoint Expression in Sarcomas." *Oncoimmunology*, 9, no. 1 (April 12, 2020): 1747340. https://doi.org/10.1080/2162402X.2020.1747340.

Dancsok, Amanda R., Karama Asleh-Aburaya, et al. "Advances in Sarcoma Diagnostics and Treatment." *Oncotarget* 8, no. 4 (October 9, 2016): 7068–93. https://doi.org/10.18632/oncotarget.12548.

de Almeida, Bruna Cristine, Laura Gonzalez dos Anjos, et al. "Epigenetic Features in Uterine Leiomyosarcoma and Endometrial Stromal Sarcomas: An Overview of the Literature." *Biomedicines* 10, no. 10 (October 13, 2022): 2567. https://doi.org/10.3390/biomedicines10102567.

de Graaff, Marieke A., Marije A. J. de Rooij, et al. "Inhibition of Bcl-2 Family Members Sensitises Soft Tissue Leiomyosarcomas to Chemotherapy." *British Journal of Cancer* 114 (May 3, 2016): 1219–26. https://doi.org/10.1038/bjc.2016.117.

de Visser, Karin E., and Johanna A. Joyce. "The Evolving Tumor Microenvironment: From Cancer Initiation to Metastatic Outgrowth." *Cancer Cell* 41, no. 3 (March 13, 2023): 374–403. https://doi.org/10.1016/j.ccell.2023.02.016.

Dochez, Vincent, Hélène Caillon, et al. "Biomarkers and Algorithms for Diagnosis of Ovarian Cancer: CA125, HE4, RMI and ROMA, a Review." *Journal of Ovarian Research* 12, no. 1 (March 27, 2019): 28. https://doi.org/10.1186/s13048-019-0503-7.

Dong, Guizhi, Deguang Wang, et al. "Factors Related to Survival Rates for Breast Cancer Patients." *International Journal of Clinical and Experimental Medicine* 7, no. 10 (October 15, 2014): 3719–24. https://pubmed.ncbi.nlm.nih.gov/25419424/.

Dou, Yongchao, Emily A. Kawaler, et al. "Proteogenomic Characterization of Endometrial Carcinoma." *Cell* 180, no. 4 (February 20, 2020): 729–748.e26. https://pubmed.ncbi.nlm.nih.gov/32059776/.

Dou, Yongchao, Lizabeth Katsnelson, et al. "Proteogenomic Insights Suggest Druggable Pathways in Endometrial Carcinoma." *Cancer Cell* 41, no. 9 (September 11, 2023): 1586–1605.e15. https://doi.org/10.1016/j.ccell.2023.07.007.

Eglovitch, Joanne S. "FDA Officials Stress Natural History Studies in Supporting Rare Disease Drug Development." Regulatory Affairs Professionals Society. October 19, 2023. https://www.raps.org/news-and-articles/news-articles/2023/10/fda-officials-stress-natural-history-studies-in-su.

Emens, Leisha A., Pedro J. Romero, et al. "Challenges and Opportunities in Cancer Immunotherapy: A Society for Immunotherapy of Cancer (SITC) Strategic Vision." *Journal for ImmunoTherapy of Cancer* 12, no. 6 (June 2024): e009063. https://doi.org/10.1136/jitc-2024-009063.

Falcao, Raul Maia, Jorge Estefano Santana de Souza, et al. "Deep Multi-Omics Integration Approach Reveals New Molecular Features of Uterine Leiomyosarcoma." *Biochimica et Biophysica Acta—Molecular Basis of Disease* 1871, no. 3 (March 2025): 167632. https://doi.org/10.1016/j.bbadis.2024.167632.

Frank, M. L., S. D. Schäfer, et al. "Importance of Transvaginal Elastography in the Diagnosis of Uterine Fibroids and Adenomyosis." *European Journal of Ultrasound* 37, no. 4 (January 26, 2015): 373–78. https://doi.org/10.1055/s-0035-1553266.

Garzon, Simone, Antonio Simone Laganà, et al. "Secondary and Tertiary Ovarian Cancer Recurrence: What Is the Best Management?" *Gland Surgery* 9, no. 4 (August 26, 2020): 1118–29. https://doi.org/10.21037/gs-20-325.

George, Suzanne, César Serrano, et al. (2018). "Soft Tissue and Uterine Leiomyosarcoma." *Journal of Clinical Oncology* 36, no. 2 (December 8, 2017): 144–50. https://doi.org/10.1200/JCO.2017.75.9845.

Giuntoli, Robert L. II, Daniel S. Metzinger, et al. "Retrospective Review of 208 Patients with Leiomyosarcoma of the Uterus: Prognostic Indicators, Surgical Management, and Adjuvant Therapy." *Gynecologic Oncology* 89, no. 3 (June 2003): 460–69. https://pubmed.ncbi.nlm.nih.gov/12798712/.

Gordon, Erlinda Maria, Sant P. Chawla, et al. "Five-Year Results of a Phase 2 Trial Using Ipilimumab (I), Nivolumab (N), and Trabectedin (T) for Previously Untreated Advanced Soft Tissue Sarcoma (NCT03138161)." *Journal of Clinical Oncology* 40, no. 16 (June 2, 2022): 11573. https://doi.org/10.1200/JCO.2022.40.16_suppl.11573.

Gustafson, Daniel L., Dawn L. Duval, et al. "Canine Sarcomas as a Surrogate for the Human Disease." *Pharmacology & Therapeutics* 188 (August 2018): 80–96. https://doi.org/10.1016/j.pharmthera.2018.01.012.

Haince, Jean-François, Philippe Joubert, et al. "Metabolomic Fingerprinting for the Detection of Early-Stage Lung Cancer: From the Genome to the Metabolome." *International Journal of Molecular Sciences* 23, no. 3 (January 21, 2022): 1215. https://doi.org/10.3390/ijms23031215.

Hayashi, Takuma, Akiko Horiuchi, et al. "Molecular Approach to Uterine Leiomyosarcoma: LMP2-Deficient Mice as an Animal Model of Spontaneous Uterine Leiomyosarcoma." *Sarcoma* 2011, no. 1. (March 8, 2011): 476498. https://doi.org/10.1155/2011/476498.

Hayashi, Takuma, Akiko Horiuchi, Kenji Sano, et al. "Potential Role of LMP2 as Tumor-Suppressor Defines New Targets for Uterine Leiomyosarcoma Therapy." *Scientific Reports* 1, no. 1 (December 5, 2011): 180. https://doi.org/10.1038/srep00180.

Hayashi, Takuma, Akiko Horiuchi, et al. "Uterine Leiomyosarcoma Tumorigenesis in LMP2-Deficient Mice: Involvement of Impaired Anti-Oncogenic Factor IRF1." *Anticancer Research* 35, no. 9 (September 2015): 4665–79. https://ar.iiarjournals.org/content/35/9/4665.

Heinonen, Hanna-Riikka, Miika Mehine, et al. "Global Metabolomic Profiling of Uterine Leiomyomas." *British Journal of Cancer* 117, no. 12 (October 26, 2017): 1855–64. https://doi.org/10.1038/bjc.2017.361.

Hernando, Eva, Elizabeth Charytonowicz, et al. "The AKT-mTOR Pathway Plays a Critical Role in the Development of Leiomyosarcomas." *Nature Medicine* 13 (May 13, 2007): 748–53. https://doi.org/10.1038/nm1560.

Highfill, Steven L., Yongzhi Cui, et al. "Disruption of CXCR2-Mediated MDSC Tumor Trafficking Enhances Anti-PD1 Efficacy." *Science Translational Medicine* 6, no. 237 (May 21, 2014): 237ra67. https://doi.org/10.1126/scitranslmed.3007974.

Hirsch, Lukas, Yu Huang, et al. "Early Detection of Breast Cancer in MRI Using AI." *Academic Radiology* 32, no. 3 (October 30, 2024): 1218–25. https://doi.org/10.1016/j.acra.2024.10.014.

Hodgson, Ruth, Priya Bhave Chittawar, et al. "GnRH Agonists for Uterine Fibroids." *Cochrane Database of Systematic Reviews*, October 29, 2017. https://doi.org/10.1002/14651858.CD012846.

Istl, Alexandra C., Nerlyne Desravines, et al. "Treatment Patterns and Outcomes for Primary Uterine Leiomyosarcoma with Synchronous Isolated Lung Metastases: A National Cancer Database Study of Primary Resection and Metastasectomy." *Gynecologic Oncology Reports* 51 (February 2024): 101308. https://doi.org./10.1016/j.gore.2023.101308.

Jentzsch, Madlen, Sebastian Schwind, et al. "Clinical Challenges and Consequences of Measurable Residual Disease in Non-APL Acute Myeloid Leukemia." *Cancers* 11, no. 11 (October 23, 2019): 1625. https://doi.org/10.3390/cancers11111625.

Johnston, Andrew D., Jason P. Ross, et al. "Epigenetic Liquid Biopsies for Minimal Residual Disease, What's Around the Corner?" *Frontiers in Oncology* 13 (April 3, 2023): 1103797. https://doi.org/10.3389/fonc.2023.1103797.

Jung, Inha, Kyunghwa Han, et al. "Annual Trends in Ultrasonography-Guided 14-Gauge Core Needle Biopsy for Breast Lesions." *Korean Journal of Radiology* 21, no. 3 (February 11, 2020): 259–67. https://doi.org/10.3348/kjr.2019.0695.

Keeler, Elizabeth. "Uterine Fibroids and Cancer: Is There a Connection?" MD Anderson Cancer Center, August 1, 2024. https://www.mdanderson.org/cancerwise/uterine-fibroids-and-cancer--is-there-a-connection-.h00-159699912.html.

Khazaei, Masoud, Marzieh Sadat Hosseini, et al. "Nanosensors and Their Applications in Early Diagnosis of Cancer." *Sensing and Bio-Sensing Research* 41 (August 2023): 100569. https://doi.org/10.1016/j.sbsr.2023.100569.

Kim, Hakyoung, Won Kyung Cho, et al. "Significance of the Number of High-Risk Factors in Patients with Cervical Cancer Treated with Radical Hysterectomy and Concurrent Chemoradiotherapy." *Gynecologic Oncology* 157, no. 2, (March 2, 2020): 423–28. https://doi.org/10.1016/j.ygyno.2020.02.031.

Kim, Mijin, Chen Chen, et al. "Detection of Ovarian Cancer via the Spectral Fingerprinting of Quantum-Defect-Modified Carbon Nanotubes in Serum by Machine Learning." *Nature Biomedical Engineering* 6, no. 3 (March 17, 2022): 267–275. https://doi.org/10.1038/s41551-022-00860-y.

Kostov, Stoyan, Yavor Kornovski, et al. "New Aspects of Sarcomas of Uterine Corpus—a Brief Narrative Review." *Clinics and Practice* 11, no. 4 (November 22, 2021): 878–900; https://doi.org/10.3390/clinpract11040103.

Kris-Etherton, Penny M., Sharon R. Akabas, et al. "The Need to Advance Nutrition Education in the Training of Health Care Professionals and Recommended Research to Evaluate Implementation and Effectiveness." *The American Journal of Clinical Nutrition* 99, no. 5 (May 2014): 1153S–66S. https://doi.org/10.3945/ajcn.113.073502.

Liegl-Atzwanger, Bernadette, Ellen Heitzer, et al. "Exploring Chromosomal Abnormalities and Genetic Changes in Uterine Smooth Muscle Tumors." *Modern Pathology* 29, no. 10 (October 2016): 1262–77. https://doi.org/10.1038/modpathol.2016.107.

Lim, D., W. L. Wang, et al. "Old Versus New FIGO Staging Systems in Predicting Overall Survival in Patients with Uterine Leiomyosarcoma: A Study of 86 Cases." *Gynecologic Oncology* 128, no. 2 (February 2013): 322–26. https://doi.org/10.1016/j.ygyno.2012.11.009.

Lin, Szu-Ting, Hsiu-Chuan Chou, et al. "Proteomic Analysis of Proteins Responsible for the Development of Doxorubicin Resistance in Human Uterine Cancer Cells." *Journal of Proteomics* 75, no. 18 (October 22, 2012): 5822–47. https://doi.org/10.1016/j.jprot.2012.07.047.

Lippman, Sheri A., Marcella Warner, et al. "Uterine Fibroids and Gynecologic Pain Symptoms in a Population-Based Study." *Fertility and Sterility* 80, no. 6 (December 2003): 1488–94. https://pubmed.ncbi.nlm.nih.gov/14667888/.

Lee, Sung-Jong, Jeong-Hoon Bae, et al. "Clinical Characteristics of Metastatic Tumors to the Ovaries." *Journal of Korean Medical Science* 24, no. 1 (February 28, 2009): 114–19. https://doi.org/10.3346/jkms.2009.24.1.114.

Li, Jina, Gaoming Liu, et al. "Cervical Cancer Prognosis and Related Risk Factors for Patients with Cervical Cancer: A Long-Term Retrospective Cohort Study." *Scientific Reports* 12, no. 1 (August 17, 2022): 13994. https://doi.org/10.1038/s41598-022-17733-8.

Liu, Ming, Tianhao Mu, et al. "The Method of Minimal Residual Disease Detection with Circulating Tumor DNA and Its Clinical Applications in Colorectal Cancer." *Cancer Reports*, 8, no. 3 (March 4, 2025): e70167. https://doi.org/10.1002/cnr2.70167.

Machado-Lopez, Alba, Roberto Alonso, et al. "Integrative Genomic and Transcriptomic Profiling Reveals a Differential Molecular Signature in Uterine Leiomyoma versus Leiomyosarcoma." *International Journal of Molecular Sciences* 23, no. 4 (February 16, 2022): 2190. https://doi.org/10.3390/ijms23042190.

Mao, Jialin, Samantha Pfeifer, Xi Emily Zheng, Peter Schlegel, and Art Sedrakyan. "Population-Based Estimates of the Prevalence of Uterine Sarcoma Among Patients with Leiomyomata Undergoing Surgical Treatment." *JAMA Surgery* 150, no. 4 (2015): 368–70. https://jamanetwork.com/journals/jamasurgery/fullarticle/2107250.

Marino-Enriquez, Adrian, Jan Philipp Novotny, et al. "Hyper-Dependence on NHEJ Enables Synergy Between DNA-PK Inhibitors and Low-Dose Doxorubicin in Leiomyosarcoma." *Clinical Cancer Research* 29, no. 24 (December 15, 2023): 5128–39. https://doi.org/10.1158/1078-0432.CCR-23-0998.

Markowska, Anna, Włodzimierz Baranowski, et al. "Metastases and Recurrence Risk Factors in Endometrial Cancer—the Role of Selected Molecular Changes, Hormonal Factors, Diagnostic Methods and Surgery Procedures." *Cancers* 16, no. 1 (December 29, 2023): 179. https:/doi.org/10.3390/cancers16010179.

Markowski, Dominique Nadine, Mahboobeh Tadayyon, et al. "Cell Cultures in Uterine Leiomyomas: Rapid Disappearance of Cells Carrying MED12 Mutations." *Genes, Chromosomes and Cancer* 53, no. 4 (January 21, 2014): 317–23. https://doi.org/10.1002/gcc.22142.

Martin-Broto, Javier, Maria Lopez-Alvarez, et al. "Predictive Value of MRP-1 in Localized High-Risk Soft Tissue Sarcomas: A Translational Research Associated to ISG-STS 1001 Randomized Phase III Trial." *Molecular Cancer Therapies* 20, 12 (December 3, 2021): 2539–52. https://doi.org/10.1158/1535-7163.MCT-21-0315.

Memorial Sloan Kettering Cancer Center. "A Sensor Sniffs for Cancer, Using Artificial Intelligence." May 12, 2022. https://www.mskcc.org/news/sensor-sniffs-cancer-using-artificial-intelligence.

Merck. "FDA Converts to Full Approval Indication for KEYTRUDA® (pembrolizumab) for Certain Adult and Pediatric Patients with Advanced Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors." March 29, 2023. https://www.merck.com/news/fda-converts-to-full-approval-indication-for-keytruda-pembrolizumab-for-certain-adult-and-pediatric-patients-with-advanced-microsatellite-instability-high-msi-h-or-mismatch-repair-deficient/.

Meyer, Harris. "Talking with Patients About What Matters Most to Them: The Serious Illness Care Program." Better Care Playbook. Center for Health Care Strategies. August 13, 2024. https://www.bettercareplaybook.org/_blog/2024/12/talking-patients-about-what-matters-most-them-serious-illness-care-program.

Miceli, Valentina, Marco Gennarini, et al. "Imaging of Peritoneal Carcinomatosis in Advanced Ovarian Cancer: CT, MRI, Radiomic Features and Resectability Criteria." *Cancers* 15, no. 24 (December 13, 2023): 5827. https://doi.org/10.3390/cancers15245827.

Morello, Emanuela, Marina Martano, et al. "Biology, Diagnosis and Treatment of Canine Appendicular Osteosarcoma: Similarities and Differences with Human Osteosarcoma." *The Veterinary Journal* 189, no. 3 (September 2011): 268–77. https://doi.org/10.1016/j.tvjl.2010.08.014.

NCI Staff. "FDA Approves Trabectedin to Treat Two Types of Soft Tissue Sarcoma." *Cancer Currents Blog*. National Cancer Institute, National Institutes of Health. December 4, 2015. https://www.cancer.gov/news-events/cancer-currents-blog/2015/fda-trabectedin-sarcoma.

Nixdorf, D., M. Sponheimer, et al. "Adapter CAR T Cells to Counteract T-Cell Exhaustion and Enable Flexible Targeting in AML." *Leukemia* 37 (April 27, 2023): 1298–1310. https://doi.org/10.1038/s41375-023-01905-0.

National Organization for Rare Disorders (NORD). "Uterine Leiomyosarcoma." Accessed June 11, 2025. https://rarediseases.org/rare-diseases/uterine-leiomyosarcoma/.

O'Flynn, Helena, Neil A. J. Ryan, et al. "Diagnostic Accuracy of Cytology for the Detection of Endometrial Cancer in Urine and Vaginal Samples." *Nature Communications* 12, no. 1 (February 11, 2021): 952. https://doi.org/10.1038/s41467-021-21257-6.

Ong, Matthew. "Gynecology's Deadly Surprise: Cancers Are Frequently Missed Prior to Routine Procedures." *The Cancer Letter* 44, no. 20 (May 18, 2018). https://www.cancerletter.com/the-cancer-letter/20180518_1/.

Orrantia-Borunda, Erasmo, Patricia Anchondo-Nuñez, et al. "Subtypes of Breast Cancer." In *Breast Cancer*, edited by H. N. Mayrovitz (Brisbane: Exon Publications, August 6, 2022). https://www.ncbi.nlm.nih.gov/books/NBK583808/.

Pancholi, Neha J. "Taking a BiTE Out of Cancer." *Cancer Research Catalyst* (blog). American Association for Cancer Research. November 14, 2023. https://www.aacr.org/blog/2023/11/14/bites-help-immune-system-destroy-cancer-cells.

Phillips, Carmen. "First Cancer TIL Therapy Gets FDA Approval for Advanced Melanoma." National Cancer Institute, National Institutes of Health. March 5, 2024. https://www.cancer.gov/news-events/cancer-currents-blog/2024/fda-amtagvi-til-therapy-melanoma.

Piras, Roberta, Emily Y. Ko, et al. "CircCsnk1g3- and CircAnkib1-Regulated Interferon Responses in Sarcoma Promote Tumorigenesis by Shaping the Immune Microenvironment." *Nature Communications* 13, no. 1 (November 25, 2022): 7243. https://doi.org/10.1038/s41467-022-34872-8.

Polito, Letizia, Giulia Calafato, et al. "Antibody Conjugates for Sarcoma Therapy: How Far Along Are We?" *Biomedicines* 9, no. 8 (August 8, 2021): 978. https://doi.org/10.3390/biomedicines9080978.

Przybyl, Joanna, Jacob J. Chabon, et al. "Combination Approach for Detecting Different Types of Alterations in Circulating Tumor DNA in Leiomyosarcoma." *Clinical Cancer Research* 24, no. 11 (May 31, 2018): 2688–99. https://doi.org/10.1158/1078-0432.CCR-17-3704.

Przybyl, Joanna, Magdalena Kowalewska, et al. "Macrophage Infiltration and Genetic Landscape of Undifferentiated Uterine Sarcomas." *JCI Insight* 2, no. 11 (June 2, 2017): e94033, 94033. https://doi.org/10.1172/jci.insight.94033.

Qi, Ting, Min Pan, et al. "Cell-Free DNA Fragmentomics: The Novel Promising Biomarker." *International Journal of Molecular Sciences* 24, no. 2 (January 12, 2023): 1503. https://doi.org/10.3390/ijms24021503.

Ranganathan, Keerthi, Neethu Sheri Kurian, et al. "Exploring the Clinical Utility of Liquid Biopsy with cfDNA in Cancer: A Systematic Review." *The Journal of Liquid Biopsy* 5 (March 20, 2024): 100150. https://doi.org/10.1016/j.jlb.2024.100150.

Raut, Chandrajit P., Marisa R. Nucci, et al. "Predictive Value of FIGO and AJCC Staging Systems in Patients with Uterine Leiomyosarcoma." *European Journal of Cancer* 45, no. 16 (August 3, 2009): 2818–24. https://doi.org/10.1016/j.ejca.2009.06.030.

Ravegnini, Gloria, Adrian Mariño-Enriquez, et al. "MED12 Mutations in Leiomyosarcoma and Extrauterine Leiomyoma." *Modern Pathology* 26, no. 5 (October 30, 2012): 743–49. https://doi.org/10.1038/modpathol.2012.203.

Research Link Australia. "Tailoring Targeted Therapy to DNA Repair-Defective High-Grade Serous Ovarian Cancer." Australia Research Data Commons. Accessed May 8, 2025. https://demo.researchlink.ardc.edu.au/view/grant?id=nhmrc/1062702.

Rizo, Jason A., Vakil Ahmad, et al. "Uterine Organoids Reveal Insights into Epithelial Specification and Plasticity in Development and Disease." *Proceedings of the National Academy of Sciences* 122, no. 5 (January 30, 2025): e2422694122. https://doi.org/10.1073/pnas.2422694122.

Rodrigues de Souza, Guilherme Moreno, Anderson Fernandes Carvalho, et al. "Main Phenotypes and Histological Types of Breast Cancer in Young Women Attended at a Reference Hospital in Women's Health in the City of São Paulo." *Breast Cancer Management* 9, no. 4 (September 28, 2020). https://doi.org/10.2217/bmt-2020-0021.

Rogel Cancer Center. "Leiomyosarcoma LMS SPORE." University of Michigan Health. Accessed May 8, 2025. https://www.rogelcancercenter.org/leiomyosarcoma-spore.

Rose, Maddison, Joshua T. Burgess, et al. "PARP Inhibitors: Clinical Relevance, Mechanisms of Action and Tumor Resistance." *Frontiers in Cell and Developmental Biology* 8 (September 8, 2020). https://doi.org/10.3389/fcell.2020.564601.

Saha, Anindo, Joeran S. Bosma, et al. "Artificial Intelligence and Radiologists in Prostate Cancer Detection on MRI (PI-CAI): An International, Paired, Non-Inferiority, Confirmatory Study." *The Lancet Oncology* 25, no. 7 (June 11, 2024): 879–87. https://doi.org/10.1016/S1470-2045(24)00220-1.

Shenasa, E., S. Thornton, et al. "96P Immune Biomarkers on Tissue Microarray Cores Support the Presence of Adjacent Tertiary Lymphoid Structures in Soft Tissue Sarcoma." *ESMO Open* 9, no. 2 (March 2024): 102485. https://doi.org/10.1016/j.esmoop.2024.102485.

Shimada, Yasuhiro, Tomoharu Naito, et al. "Establishment of a Patient-Derived Xenograft Mouse Model of Pleomorphic Leiomyosarcoma." *Journal of Toxicologic Pathology* 34, no. 1 (2021): 89–93. https://doi.org/10.1293/tox.2020-0061.

Siegenthaler, F., K. Lindemann, et al. "Time to First Recurrence, Pattern of Recurrence, and Survival After Recurrence in Endometrial Cancer According to the Molecular Classification." *Gynecologic Oncology* 165, no. 2 (March 8, 2022): 230–38. https://doi.org/10.1016/j.ygyno.2022.02.024.

Soerjomataram, Isabelle, Melissa S. Y. Thong, et al. "Most Colorectal Cancer Survivors Live a Large Proportion of Their Remaining Life in Good Health." *Cancer Causes & Control* 23, no. 9 (June 26, 2012): 1421–28. https://doi.org/10.1007/s10552-012-0010-2.

Stewart, Elizabeth A., and Shannon K. Laughlin-Tommaso. "Patient Education: Uterine Fibroids (Beyond the Basics)." UpToDate. Last modified July 25, 2024. https://www.uptodate.com/contents/uterine-fibroids-beyond-the-basics.

Subklewe, Marion. "BiTEs Better than CAR T Cells." *Blood Advances* 5, no. 2 (January 26, 2021): 607–12. https://doi.org/10.1182/bloodadvances.2020001792.

Subramanian, Ajay, Neda Nemat-Gorgani, et al. "Sarcoma Microenvironment Cell States and Ecosystems Are Associated with Prognosis and Predict Response to Immunotherapy." *Nature Cancer* 5, no. 4 (March 1, 2024): 642–658. https://doi.org/10.1038/s43018-024-00743-y.

Takehara, Kazuhiro, Natsumi Yamashita, et al. "Clinical Status and Prognostic Factors in Japanese Patients with Uterine Leiomyosarcoma." *Gynecologic Oncology* 157, no. 1 (January 23, 2020): 115–20. https://doi.org/10.1016/j.ygyno.2020.01.022.

Tan, K. H. X., L. Simonella, et al. "Quantifying the Natural History of Breast Cancer." *British Journal of Cancer* 109, no. 8 (October 1, 2013): 2035–43." https://doi.org/10.1038/bjc.2013.471.

Thies, K. A., Steck, S., et al. "Pathological Analysis of Lung Metastasis Following Lateral Tail-Vein Injection of Tumor Cells." *Journal of Visualized Experiments* 159 (May 20, 2020): e61270. https://doi.org/10.3791/61270.

Tirumani, Sree Harsha, Pamela Deaver, et al. "Metastatic Pattern of Uterine Leiomyosarcoma: Retrospective Analysis of the Predictors and Outcome in 113 Patients." *Journal of Gynecologic Oncology* 25, no. 4 (October 7, 2014): 306–12. https://doi.org/10.3802/jgo.2014.25.4.306.

Toulmonde, Maud, Nicolas Penel, et al. "Use of PD-1 Targeting, Macrophage Infiltration, and IDO Pathway Activation in Sarcomas: A Phase 2 Clinical Trial." *JAMA Oncology* 4, no. 1 (January 2018): 93–97. https://doi.org/10.1001/jamaoncol.2017.1617.

Toyohara, Yusuke, Kenbun Sone, et al. "Development of a Deep Learning Method for Improving Diagnostic Accuracy for Uterine Sarcoma Cases." *Scientific Reports* 12, no. 1 (November 16, 2022): 19612. https://doi.org/10.1038/s41598-022-23064-5.

Trinidad, Camille V., Ashley L. Tetlow, et al. "Reducing Ovarian Cancer Mortality Through Early Detection: Approaches Using Circulating Biomarkers." *Cancer Prevention Research* 13, no. 3 (March 4, 2020): 241–52. https://doi.org/10.1158/1940-6207.CAPR-19-0184.

US Cancer Statistics Working Group. "United States Cancer Statistics: Data Visualizations." US Department of Health and Human Services, Centers for Disease Control and Prevention, National Cancer Institute. Accessed July 2024. https://www.cdc.gov/cancer/dataviz.

US Department of Defense. "DoD Commits $500 Million for Women's Health Research, Supports Better Care for All Women." September 23, 2024. https://www.defense.gov/News/Releases/Release/Article/3913913/dod-commits-500-million-for-womens-health-research-supports-better-care-for-all/.

US Food and Drug Administration. "FDA Grants Approval to Atezolizumab for Alveolar Soft Part Sarcoma." December 9, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-approval-atezolizumab-alveolar-soft-part-sarcoma.

Vaisvila, Romualdas, V. K. Chaithanya Ponnaluri, et al. "Enzymatic Methyl Sequencing Detects DNA Methylation at Single-Base Resolution from Picograms of DNA." *Genome Research* 31, no. 7 (June 17, 2021): 1280–89. https://doi.org/10.1101/gr.266551.120.

van Oosterwijk, J. G., B. Herpers, et al. "Restoration of Chemosensitivity for Doxorubicin and Cisplatin in Chondrosarcoma In Vitro: BCL-2 Family Members Cause Chemoresistance." *Annals of Oncology* 23, no. 6 (June 2012): 1617–26. https://doi.org/10.1093/annonc/mdr512.

Weber, Evan W., Kevin R. Parker, et al. "Transient Rest Restores Functionality in Exhausted CAR-T Cells Through Epigenetic Remodeling." *Science* 372, no. 6537 (April 2, 2021): eaba1786. https://doi.org/10.1126/science.aba1786.

Wegienka, Ganesa, Donna Day Baird, et al. "Self-Reported Heavy Bleeding Associated with Uterine Leiomyomata." *Obstetrics & Gynecology* 101, no. 3 (March 2003): 431–37. https://doi.org/10.1016/s0029-7844(02)03121-6.

Welch, Danny R., and Douglas R. Hurst. "Defining the Hallmarks of Metastasis." *Cancer Research* 79, no. 12 (June 14, 2019): 3011–27. https://doi.org/10.1158/0008-5472.CAN-19-0458.

Winstead, Edward. "FDA Approves Engineered Cell Therapy for Advanced Synovial Sarcoma." National Cancer Institute, National Institutes of Health. August 27, 2024. https://www.cancer.gov/news-events/cancer-currents-blog/2024/fda-tecelra-synovial-sarcoma-mage-a4.

Wise, Lauren A., and Shannon K. Laughlin-Tommaso. "Epidemiology of Uterine Fibroids: From Menarche to Menopause." *Clinical Obstetrics and Gynecology* 59, no. 1 (March 2016): 2–24. https://doi.org/10.1097/GRF.0000000000000164.

Wong, Eric. "Breast Cancer Pathogenesis and Histologic vs. Molecular Subtypes." *McMaster Pathophysiology Review*, December 29, 2012. https://www.pathophys.org/breast-cancer/breastcancer-copy/.

World Trade Center Health Program. "Uterine Cancer Added to the List of World Trade Center (WTC)-Related Health Conditions." *Centers for Disease Control and Prevention*, January 17, 2023. https://www.cdc.gov/wtc/uterineCancer_20230118.html.

Wright, Lauri. "How New Competencies in Medical Training Can Elevate Nutrition Care—Bridging the Gap." *JAMA Network Open* 7, no. 9 (September 30, 2024): e2435406. https://doi.org/10.1001/jamanetworkopen.2024.35406.

Yaari, Zvi, Yoona Yang, et al. "A Perception-Based Nanosensor Platform to Detect Cancer Biomarkers." *Science Advances* 7, no. 47 (November 19, 2021): eabj0852. https://doi.org/10.1126/sciadv.abj0852.

Yang, Qiwei, Obianuju Sandra Madueke-Laveaux, et al. "Comprehensive Review of Uterine Leiomyosarcoma: Pathogenesis, Diagnosis, Prognosis, and Targeted Therapy." *Cells* 13, no. 13 (June 26, 2024): 1106. https://doi.org/10.3390/cells13131106.

Yoshida, Kosuke, Akira Yokoi, et al. "Aberrant Activation of Cell-Cycle–Related Kinases and the Potential Therapeutic Impact of PLK1 or CHEK1 Inhibition in Uterine Leiomyosarcoma." *Clinical Cancer Research* 28, no. 10 (May 13, 2022): 2147–59. https://doi.org/10.1158/1078-0432.CCR-22-0100.

Yuan, Hua, Yaxi Wang, et al. "Clinical Characteristics and Treatment Outcomes of Women with Recurrent Uterine Leiomyosarcoma." *Orphanet Journal of Rare Diseases* 19, no. 1 (October 25, 2024): 395. https://doi.org/10.1186/s13023-024-03415-3.

Zanoni, Daniella Karassawa, Snehal G. Patel, et al. "Changes in the 8th Edition of the American Joint Committee on Cancer (AJCC) Staging of Head and Neck Cancer: Rationale and Implications." *Current Oncology Reports* 21, no. 6, (April 17, 2019): 52. https://doi.org/10.1007/s11912-019-0799-x.

Zehra, Talat, Sharjeel Anjum, et al. "A Novel Deep Learning-Based Mitosis Recognition Approach and Dataset for Uterine Leiomyosarcoma Histopathology." *Cancers* 14, no. 15 (August 3, 2022): 3785. https://doi.org/10.3390/cancers14153785.

Zhang, Meng, Ruiping Li, et al. "Analysis of Prognostic Factors of Metastatic Endometrial Cancer Based on Surveillance, Epidemiology, and End Results Database." *Frontiers in Surgery* 9 (January 5, 2023): 1001791. https://doi.org/10.3389/fsurg.2022.1001791.

Zhang, Zhiying, Kaiwen Hu, et al. "A Patient-Derived Orthotopic Xenograft (PDOX) Nude-Mouse Model Precisely Identifies Effective and Ineffective Therapies for Recurrent Leiomyosarcoma." *Pharmacological Research* 142 (April 2019): 169–75. https://doi.org/10.1016/j.phrs.2019.02.021.

Zhou, Maggie, Nam Bui, et al. "Feasibility of Longitudinal ctDNA Assessment in Patients with Uterine and Extra-Uterine Leiomyosarcoma." *Cancers* 15, no. 1 (December 27, 2022): 157. https://doi.org/10.3390/cancers15010157.

Zhou, Shu, and Fang Peng. "Patterns of Metastases in Cervical Cancer: A Population-Based Study." *International Journal of Clinical and Experimental Pathology* 13, no. 7 (July 1, 2020): 1615–23. https://pubmed.ncbi.nlm.nih.gov/32782680/.

Zivanovic, Oliver, Mario M. Leitao, et al. "Stage-Specific Outcomes of Patients with Uterine Leiomyosarcoma: A Comparison of the International Federation of Gynecology and Obstetrics and American Joint Committee on Cancer Staging Systems." *Journal of Clinical Oncology* 27, no. 12 (March 2, 2009): 2066–72. https://doi.org/10.1200/JCO.2008.19.8366.

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Before joining the Milken Institute, Mawla worked as a management consultant at the Boston Consulting Group, where he led strategy projects for philanthropists, government agencies, and Fortune 500 health-care companies across the biopharmaceutical, medical device, health system, and payer sectors. He is skilled in navigating complex, cross-sector challenges and driving actionable outcomes through cross-functional collaboration. Mawla holds a bachelor's degree from Connecticut College and a PhD in neuroscience from the University of Michigan.

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