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## Prospects and Pitfalls of Personalizing Therapies for Sarcomas: From Children, Adolescent and Young Adults (AYA) to the Elderly

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### Abstract

Sarcomas represent a heterogeneous class of tumors that affect all ages, from children, adolescents, and young adults to the elderly. Within this panoply of tumor subtypes lies the opportunity to bring to bear a vision of personalized medicine in which the fast-paced evolution from the 'one gene, one test, one drug' approach to a comprehensive 'panomic,' multiplex, multianalyte method coupled with advances in bioinformatics platforms can unravel the biology of this disease. The increasingly enlarging repertoire of novel agents provides innumerable prospects in precision medicine. Personalized therapy covers the entire spectrum of cancer care, from risk factor assessment through prevention, risk reduction, therapy, follow-up after therapy, and survivorship care. Challenges remain in implementing the science of precision medicine in the clinic, including providing comprehensive multidisciplinary care and overcoming regulatory and economic hurdles, which must be facilitated within the collaborative framework of academia, industry, federal regulators, and third-party payers.

### Keywords

sarcoma; personalized therapy; immunotherapy; targeted therapy; precision medicine; next-generation sequencing; mutations; adolescents and young adults; AYA; bone sarcoma; soft tissue sarcoma; mTOR inhibitor; genetics; orphan disease; rare cancer; pediatric sarcoma; basket trials; unusual responders

### Introduction

Sarcomas represent a heterogeneous class of tumors that affect humans at all stages of life, from children, adolescents and young adults to the elderly. The diversity of sarcomas offers panoply of opportunities in the era of personalized therapy and precision medicine. The 'omics' revolution has opened up infinite avenues to unravel the complex and diverse

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biology of sarcomas. Cancer ‘omics’ refers to the in-depth attempt to decipher aberrations at multiple levels, including the DNA sequence (copy number alterations, somatic mutations, and rearrangements), the epigenome (DNA methylation and histone modification patterns), and the transcriptome (gene or microRNA expression changes) [1]. The current era is moving away from the ‘one gene, one test, one drug’ approach to comprehensive pan-omic multiplex and multianalyte analyses [1, 2]. The fast pace of evolution in this “pan-omic” technology coupled with recent advances in bioinformatics and analytics has enhanced the ability of scientists to unravel the ‘driver’ aberrations in sarcomagenesis. These aberrations, when ‘actionable,’ can be exploited as ‘druggable’ targets for novel developmental therapeutics or for re-aligning an already FDA-approved drug that has pharmacological inhibitory properties against a particular biomarker. Moreover, the increasingly enlarging repertoire of targeted agents provides myriad prospects in our attempt to target patients with sarcoma with molecularly matched therapies or personalized immunotherapy.

Cancers in general and sarcomas in particular present a complex problem, with their multiple molecular pathways of complex network signaling involved [3]. Sarcomas span across the age spectrum, from children, adolescents and young adults to the elderly. Given that sarcomas are conventionally categorized into more than 50 subtypes, the ‘omic’ era is yielding information that offers 50<sup>50</sup> different probabilities.

Personalized medicine is based on the principle that comprehensive sequencing is available for a patient’s tumor and the tumor is matched to molecularly targeted therapies or immunotherapies at the right combination to the right patient [2, 4–6]. We are rapidly evolving from the sequential phases of discovery, hypothesis generating, and generation of evidence of various levels. Over the last decade, unprecedented advances in the discovery of disease-specific genetic alterations and in the successful translation of mechanism-based targeted therapies have improved the outcome for patients with sarcoma and other cancer types.

Recent approaches, such as the use of patient-derived xenografts, attempt to overcome the limitations associated with cell line-based research by recapitulating the 3-dimensional, ‘plastic’ interaction among neoplastic tissue, stroma, and other cells in the micro-environment [7, 8]. Moreover, in the appropriate context, the addition of immunology-based personalized therapy, which is being integrated into the care of many patients with cancer, offers huge potential in sarcoma treatment. This review outlines some of the prospects from this exciting opportunity in personalized medicine and the pitfalls that need to be overcome in order to make personalized medicine for sarcoma a reality.

### **Personalized Therapy and Precision Therapy**

Personalized therapy for sarcoma covers the gamut of cancer care, from risk factor assessment through prevention, risk reduction, therapy, follow-up after therapy, and survivorship. Personalized therapy provides comprehensive multidisciplinary research-based care by not only medical and pediatric oncologists, surgeons, radiation oncologists, and pathologists but also geneticists, immunologists, basic science and translational scientists, and bioinformaticians [2, 4] (Figure 1). Comprehensive care should happen within the intimate collaborative framework among academia (which does the research), industry

(which has the drugs), the National Cancer Institute and National Institutes of Health (which provides the funding), the Food and Drug Administration (FDA; which provides the regulatory oversight and approves or disapproves the drugs or trials) and, most important, third-party payers (which ultimately pay for any effort to turn the idea of personalized medicine into reality).

The premise of personalized medicine for sarcoma seems direct and clear cut. The tumor is sequenced through cutting-edge sequencing methods; the underpinning of the driver aberrations is analyzed, interpreted and deciphered; the avenues for pharmacological inhibition are identified; and the data are presented to the treating oncologist for incorporation into the patient's therapy [5]. However, logistical issues, sequencing availability, clinical trial openings, accessibility of agents for pharmacological inhibition, economics, ethical issues, and other challenges need to be addressed to move personalized therapy into the clinic. These steps have to be done and these challenges addressed efficiently to be practically and seamlessly executed across the age spectrum from pediatrics to the elderly.

### Hallmarks of Sarcoma

One of the greatest advances in the last two decades is achieving more precise understanding of the complex biology of cancer [9] [10]. The seminal papers on the classic hallmarks of cancer— which include sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, enabling of replicative immortality, induction of angiogenesis, and activation of invasion and metastasis—are fully applicable to all types of sarcomas [9, 10]. Underlying these cancer hallmarks are genome instability, which generates the genetic diversity that expedites their acquisition, and inflammation, which fosters multiple hallmark functions [10]. These features, which are exemplified fully in sarcomas, should form the guiding principle in understanding the biology of a particular sarcoma subtype. These hallmarks should be interpreted in the context of collective definition and diagnosis of a sarcoma. Targeting the hallmarks of cancer should also form the basis for therapy that may include chemotherapy, surgery, radiotherapy, mechanism-based molecularly targeted therapy, and immunotherapy. Our understandings of the hallmarks of cancer in sarcoma are still evolving; the next decade should provide deeper understanding of the biology of these tumors and their interplay with the host.

### Sequencing and Molecular Profiling

A decade ago, molecular profiling fell within the realm of major academic centers and did not much involve community oncology groups. Now, with exponential increases in the commercial availability of next-generation multiplex sequencing, this discipline has moved from academic centers to private industry. Some of the industry-based companies are CLIA certified, and community oncologists are increasingly basing the medical decisions for their patients with relapsed cancer on company reports. Many motivated patients find out about these companies and self-request the sequencing services and some present to major cancer centers with disc drives containing whole-genomic data but no biomedical analytics or reports. Clinicians are faced with unique challenges when such data are presented without a validated approach [11, 4]. Even major academic centers may not have the resources to

quickly analyze data generated from different platforms into clinically useful information to implement personalized cancer therapy.

### The Expanding Landscape of Sarcomas and Moving away from ‘One Size Fits All Approach’

While more common cancers, such as non-small cell lung cancer (NSCLC; *EGFR* mutation, *KRAS* mutation, *BRAF* mutation, *EML4-ALK*- or *ROS1* rearrangement, *RET* aberrant) and breast cancer (*Her2/Neu*, ER+/PR+) are increasingly being treated according to a biomarker-driven approach, the ‘one size fits all’ approach is still the standard of care for sarcoma patients. Except for gastrointestinal stromal tumor (GIST), targeted agents are reserved for patients with metastatic sarcoma. In the future and moving away from the ‘one size fits all’ approach, biomarker-driven individualized therapy should be the norm. The oncology community is increasingly recognizing and the industry is accepting that there are diverse sarcoma subtypes, and various companies are open to developing drugs for even rare subsets of an orphan disease. Very good clinical evidence of effective biomarker-related molecularly targeted therapy is already available for several types of sarcoma (Table 1). This catalogue of actionable sarcoma biomarkers with clinical evidence of pharmacological inhibition is poised to grow exponentially in the near future.

However, with an explosion of data a rare disease will be segregated into rarer subsets [12–14]. For instance, taking the case of *KIT*-negative, *PDGFR*-negative GIST (“wild-type” GIST), the prevalence of other known aberrations has increased with at least 10 different subsets in wild-type GIST [15, 14]; these aberrations include *BRAF* mutation (3%), *KRAS* mutation (1%), *PIK3CA* mutation (1%), succinate dehydrogenase germline mutations (5–7.5%), *IGF1R* overexpression in succinate dehydrogenase-deficient GIST, and *NF1*-related GIST (Recklinghausen disease) (<1%). This poses a challenge to the clinician when selecting drugs to treat a particular patient, and a small biomarker-driven trial, including an N=1 trial, may need to be conducted even within these rare subtypes as proof-of concept studies [14]. This may require novel statistical methods to generate high-level evidence [16, 17].

### Generating Levels of Clinical Evidence in Precision Medicine

With the surge of known biomarkers of and targets for sarcoma, the next major step in precision medicine is to generate high levels of evidence for treating a particular type of sarcoma that is driven by a biomarker or gene. Several proof-of-concept studies recently demonstrated survival gains in specific subsets of biomarker-driven cancers, including common cancers such as NSCLC. Given the rarity and heterogeneity of sarcomas, generating a high level of clinical evidence in precision medicine for these tumors has its own challenges. Few targeted drugs are approved for sarcomas (except for GIST), so a shared structure with an algorithmic approach may be needed to explore the relevance of actionable (‘druggable’) molecular aberrations. This ‘discovery and generating evidence’ phase may range from ‘gold standard’ randomized phase 3 trials to case reports to preclinical evidence in the same tumor type or, when the aberration is so infrequent, another tumor type.

As illustrated in Figure 1, once the sarcoma is diagnosed using conventional pathologic techniques and scans, the tissue undergoes thorough molecular profiling that includes a panomic approach, data from which is analyzed by robust bioinformatics algorithms. These results are discussed by a multidisciplinary team (the ‘molecular tumor board’) that takes into account the genomic aberrations in the context of a particular sarcoma subtype and whether any level of evidence exists to treat the sub-type of sarcoma. This would be followed by a molecularly matched therapy which requires ready accessibility to a rich pipeline of drugs. Once therapy is initiated the ideal approach is to follow up on patients for safety, efficacy, toxicity, and response; if acquired resistance develops, the tissues are biopsied and analyzed to identify biomarkers to overcome resistance. Every effort has to be made to track the data of molecularly matched therapy in patients, whether they are on or off protocol. Given the rarity of various sarcoma subtypes, an automated online, open access registry or database that is constantly updated with input from published literature, clinicians, and even patient-reported outcomes is clearly needed. This data system should provide information to enable clinicians to predict the appropriate therapy (eg, imatinib for *KIT*-mutant GIST) and contraindications (eg, anti-EGFR monoclonal antibody therapy for *KRAS*-mutated colorectal cancer [CRC]).

Below are outlined the levels of evidence that need to be built in a continuous manner, by type of source.

- I. Phase 3 Studies.** This is the strongest level of evidence available for a particular tumor subtype. For example, Demetri et al. [18] described a phase 3 trial that was designed to assess the efficacy and safety of regorafenib in patients with metastatic or unresectable GIST progressing after failure with imatinib and sunitinib treatment. Patients were randomly allocated to receive regorafenib (n=133) or matching placebo (n=66). The median progression-free survival time was 4.8 months (interquartile range 1.4–9.2) for regorafenib and 0.9 months (0.9–1.8) for placebo (hazard ratio 0.27, 95% CI 0.19-0.39,  $p < 0.0001$ ) [18]. This trial formed the basis of the FDA approval of regorafenib in GIST patients. Such evidence from a randomized phase 3 trial for a particular biomarker driven disease would be considered gold standard.
- II. Phase 1 or 2 Studies.** While these are early phase trials, the data generated from them are critical for generating a good level of evidence. For example, in a phase 1 clinical trial, the cyclin-dependent kinase inhibitor flavopiridol was shown to potentiate doxorubicin efficacy in advanced sarcomas [19]. In addition, disease control was seen (8 of 12 patients had stable disease at >12 weeks) in well- or dedifferentiated liposarcoma, a disease with CDK4 amplification [19]. A phase 2 trial of the CDK4 inhibitor PD0332991 revealed a favorable progression-free rate in patients with CDK4-amplified and RB-expressing well- and dedifferentiated liposarcoma [20]. Among 29 evaluable patients at 12 weeks, the progression-free survival rate was 66% (90% CI 51-100%) [20].
- III. Retrospective Studies and Registry Data.** For example, trabectedin can bind to DNA and displace transcription factors. To explore the antitumor effect in translocation-related sarcoma subtypes, a retrospective pooled analysis conducted

from data from 81 patients with translocation-related sarcoma treated in eight phase II trials with trabectedin showed that the tumor control rate (overall response rate plus stable disease) was 59% (95% CI 48–70%) [21]. However, this type of evidence has its limitations with its inherent selection bias and retrospective nature. Follow-up phase III trials need to be conducted for validity.

- IV. Case Reports.** For extremely rare subtypes of sarcoma, evidence from a case report could be considered in the absence of a prospective trial or retrospective data. For example, Butrynski et al. [22] reported that a patient with anaplastic lymphoma kinase (ALK) aberrant inflammatory myofibroblastic tumor responded to the ALK inhibitor crizotinib (PF-02341066, Pfizer), whereas in a patient without the ALK translocation, no clinical response occurred [22]. This information provided evidence for an extremely rare tumor but one that is genetically defined. In another report, a patient with *BRAF V600E*-mutated GIST resistant to imatinib was treated successfully with the BRAF inhibitor dabrafenib [23]. Personalized medicine is not restricted to targeted agents and includes a tailored approach to a specific disease in an appropriate setting. As an illustration, a case of desmoplastic small round cell tumor metastatic to the liver that was not amenable to chemotherapy or targeted therapy was successfully treated with radioembolotherapy with yttrium-90 microspheres [24].
- V. Evidence from Other Tumor Types.** This type of evidence is tricky. It remains to be tested in trials if a clinical success story of a pharmacological inhibition for a particular tumor type would be applicable to another tumor type with the same genomic aberration. For instance, the dramatic effectiveness of vemurafenib as a single agent in *BRAF V600E* melanoma or papillary thyroid cancer has not translated to *BRAF V600E* mutant CRC [25–27]. However, it was shown in preclinical models that EGFR is a mechanism of resistance to BRAF inhibition and that the combination of BRAF and EGFR inhibition could overcome the resistance. Based on this evidence, the single-agent clinical trial for CRC was amended to include cetuximab for CRC patients [28]. Hence, any data that are tracked is reasonable as long the knowledge is applied quickly to adapt to clinical practice as for or against a particular therapy.
- VI. Evidence in Genetic Disease:** For example, tuberous sclerosis complex (TSC) is caused by an aberrant *TSC1* gene which results in up-regulation of the mTOR pathway. mTOR inhibitors, like everolimus, are effective against this disease [28]. The fact that *TSC1* aberrations could be also seen as somatic mutations in different cancers could form the biological rationale for mTOR inhibitors being a possible therapeutic option.
- VII. Preclinical Evidence:** A preclinical level of evidence, if compelling, can be used if no other type of evidence exists. In the absence of therapy that could improve patient survival, preclinical evidence may be used as low-level evidence for that disease. For instance, Ewing's sarcoma cell lines harboring the *EWSRI-FLII* gene translocation was shown to be markedly sensitive to poly(ADP-ribose) polymerase (PARP) inhibition as a single agent [29] or in combination with temozolomide [30].



**VIII Mechanistic Evidence:** Even if there is no preclinical evidence, the molecular tumor board could, after reviewing all available input, consider suggestions based on mechanistic evidence. This is the lowest possible level of evidence.

### Unusual Responders and N=1 Trials

Unusual responders to targeted therapy present a unique opportunity to unravel retrospectively the genomic, proteomic, or immunological basis of sensitivity. Deciphering the basis of response and resistance mechanisms by studying these cases in depth may benefit both current and future patients with the same aberration. In one study, genome sequencing identified loss-of-function mutation in *TSC1* as a basis for everolimus sensitivity in bladder cancer [31]. In another pilot study, two advanced Ewing's sarcoma cases were studied in depth to analyze the resistance and response mechanisms to Insulin like growth factor type 1 receptor (IGF1R) inhibitor therapy [32]. Both patients initially responded to IGF1R therapy. Morphoproteomic analysis revealed that the mTOR pathway was activated at the time of resistance. They were treated again in another combination trial with IGF1R and mTOR inhibitor. They started to respond again to combined IGF1R and mTOR inhibition. One patient continued to respond to the combination therapy, whereas the other developed resistance. It was shown that the ERK pathway was activated in the patient in whom resistance to this combination emerged [32, 33]. These data suggested that therapy with IGF1R inhibitor may need to be combined with MAPK kinase pathway and mTOR inhibitors [34]. Although just two cases were described in this study, it provided important information on the intricate resistance mechanisms and broke the usual linear picturization of signaling pathways [34, 35].

Serendipitous observations by clinicians, which when analyzed in depth, may provide better understanding of the biology of a disease [36]. Such observations may be used to leverage biomarker-driven trials in the future with similar biomarkers or drugs. In addition, several sarcoma patients enrolled in phase 1 clinical trials may have an exceptional response to a random new agent [37]. Comprehensive exploratory studies should be carried out with such patients and may provide novel insights into the targeted therapies of that disease. For instance, chondrosarcomas are notorious for their resistance to conventional types of chemotherapy. In a phase 1 trial of the pro-apoptotic agent recombinant human Apo2L/TRAIL (dulanermin), which is based on the ligand for death receptors (DR4 and DR5), a patient with refractory chondrosarcoma had an unusual response to dulanermin: after 62 months of experimental therapy, the patient developed some new nodules of resistant disease [38]. An exploratory morphoproteomic study of the resistant tumor specimen detected DR4 in the patient's tumor as the basis of sensitivity and the emergence of several prosurvival proteins (phosphorylated (p)-NF- $\kappa$ Bp65 (Ser 536), p-STAT3 (Tyr 705), p-ERK 1/2 (Thr 202/Tyr 204), p-mTOR (Ser 2448), FASN, and Bcl-2) as plausible mechanisms of resistance [38].

### Tumors Defying Histologic Characterization

Tumors with ambiguous histologic and uncertain immunohistochemical characterization are difficult to diagnose and treat. Several types of sarcoma present as a diagnostic and therapeutic challenge and defy conventional histopathological characterization. In such

cases, clinical next-generation sequencing technology may help in uncovering genomic aberrations that drive sarcomagenesis, which in turn may help inform clinicians of the pathways that may be vulnerable to pharmacological inhibition. For instance, CLIA-certified next-generation sequencing was performed for a patient with a malignant spindle cell neoplasm/sarcoma refractory to standard chemotherapy [39]. The sequencing uncovered a *KIAA1549-BRAF* mutation resulting from a tandem duplication event in the background of a homozygous deletion of *PTEN* as a driving genomic aberration. The patient had a radiological and clinical response to combination targeted therapy that fortuitously targeted *KIAA1549-BRAF* and *PTEN* loss by simultaneous RAF kinase inhibition (sorafenib), mTOR inhibition (temsirolimus), and VEGF (bevacizumab)-targeted therapy [39]. Another model for orphan diseases is to generate data by a panomic approach and publish them in an open-access domain for the benefit of both current and future patients [11].

### **Prospective Matching in Histology-Independent Clinical Trials or Basket Trials**

Basket trials are biomarker-directed umbrella trials that are histology-independent clinical trials. Patients with different tumor types with the same aberration are enrolled into a phase 2 trial of a targeted therapy that affects that aberration. Cohorts are enrolled and the results are analyzed for efficacy, futility, and safety for that particular tumor type [40]. The trials are adaptively designed to expand to include tumor types with that aberration that respond and tumor types that shut down and do not respond. For instance, the NCT01524978 BRAF umbrella trial enrolls *BRAF V600*-mutant patients with tumor types other than melanoma. This unique strategy was recently commissioned by several major pharmaceutical companies as customized clinical trials enrolling groups of patients according to their molecular aberration. Results from these trials may not by themselves lead to FDA approval, but their exploratory nature may provide functional clinical validation of targets across multiple tumor types in one basket trial [41].

### **Drug Repurposing: Teaching the old dog's new tricks strategy**

Drug repurposing is the process in which new therapeutic indications are identified for already existing drugs on the market [42]. This strategy may be of great relevance in sarcomas given their diversity and rarity. In assessments of more than 25 different IGF1R inhibitors at different stages of clinical development [43, 35] Ewing's sarcoma was the subtype that clearly responded in many of the clinical trials [44, 45]. When combined with mTOR inhibitor, the response rate was more than 25% [46]. Unfortunately, because Ewing's sarcoma is considered an orphan disease and responses are rare (although dramatic in small subsets of patients), there has not been enough interest from pharmaceutical companies to develop this approach further and many of the inhibitors have been shelved, akin to a baby being thrown out with the bathwater [47]. In this case a common drug such as metformin that has interactions with the IGF1R pathway may be a potential for drug repurposing [48]. In addition it may be worthwhile to study of pasireotide (SOM230) in patients with Ewing sarcoma as it blocks IGF-1 action. Pasireotide is currently US FDA approved for Cushing's disease [49].



## Personalized immunotherapy for Sarcomas

There has been some evidence of clinical activity with interleukin-2 and interferon in sarcomas in the past, and several vaccine studies have shown clinical benefit in sarcoma. Recent unprecedented advances in immunology research have led to a deeper understanding of the concepts of immune responses and immunological therapy. Autologous cell transfer and chimeric antigen receptors that target overexpressed antigens in specific types of sarcoma are definitely worth exploring in sarcoma. In a clinical trial to evaluate the ability of adoptively transferred autologous T cells transduced with a T-cell receptor (TCR) directed against NY-ESO-1 to mediate tumor regression, objective responses were seen in four out of six patients with synovial sarcoma in addition to partial response lasting for 18 months.[50] NY-ESO-1 is a cancer/testis (CT) antigen that is expressed in 80 % of synovial sarcomas in addition to being expressed ubiquitously in myxoid/round cell liposarcoma [51].

An exciting strategy would be to combine targeted therapy with immune therapy. GIST preclinical models have shown a synergistic effect of CTLA4 blockade combined with imatinib [52]. In fact, two clinical trials are currently exploring this strategy for GIST (NCT01643278) and solid tumors, including sarcomas (NCT01738139). In addition, several early phase clinical trials, like the study of autologous, activated dendritic cells for intratumoral injection in combination with BCG and interferon (NCT01882946), are recruiting patients with sarcoma.

## Personalized Patient-Derived Xenografts/Mouse Avatars for Sarcoma

Given the rarity and the intra- and inter-tumoral heterogeneity of sarcomas, there are major limitations to translating cell line-based work as it does not recapitulate the Darwinian evolution/adaptation tumor dynamics [53, 41, 7]. To overcome these hurdles, a recent pilot project demonstrated the use of tumor tissue engrafted into immune-deficient mice, termed ‘TumorGrafts’ (Champions Oncology, Inc., Baltimore, MD), as a solution to find real-time, personalized models for patients with advanced sarcoma [8]. In that study, tumors from 29 patients with sarcoma were implanted into immune-deficient mice and drug sensitivity tests were performed on these mouse avatars. The preliminary results showed an engraftment rate of 76% in addition to an association between TumorGraft results and patient clinical outcome in 13 of 16 (81%) engrafted mice. Although this technology has been reported for many other carcinoma tumor types, such as breast cancer, adenoid cystic cancer, and CRC [54–56], and it is consuming, expensive, and not pragmatic for day-to-day practice, the results showed that for advanced sarcoma patients with few treatment options, this mouse avatar (‘xenopatient’) approach is promising [8].

## Challenges and Pitfalls in implementing therapies across the age spectrum

Some of the major hurdles in implementing clinical targeted personalized therapy for sarcoma, including platform selection, logistical issues regarding tissue acquisition, and the availability of genome-driven trials, remain to be surmounted. In addition to ethical issues, reimbursement by third-party payers for non-FDA-approved therapy is a major hurdle in the implementation of precision medicine.

Since, sarcomas span across the age spectrum a targeted therapy trial from adults provide some insight in children. However, the biology of childhood sarcoma seems different than adults and a major challenge is to identify targets and validate them. The next step is to identify the correct doses and formulations of novel agents [57]. A majority of sarcomas affect the adolescent and young adult (AYA) population (15–39 years) whose survival has historically lagged behind the young children and older adults not only in sarcomas but also across all tumor types [58, 59]. Some of the major reasons cited for the absence of improvement in survival are lack of participation in clinical trials, diversity and complexity in disease biology, lack of tissue availability for translational research in tissue banks, in addition to lack of consistent in treatment approaches across centers [60]. These AYA sarcoma patients pose further challenges medically, economically and socially that compound implementation of personalized medicine [60]. These challenges are being increasingly recognized and extensive task forces have been created to address these issues across major cancer centers and co-operative groups.

## Conclusion

The assortment of sarcoma subtypes lends itself to a tantalizing array of myriad avenues to make personalized medicine a reality, but there are many challenges that need to be overcome that span scientific, clinical, ethical, regulatory, economic, social and statistical domains. A collaborative environment needs to be forged with multi-institutional online networks that can integrate discovery in real time to hypothesis generation to action. The unprecedented advances in garnering genomic information and the availability of targeted therapies provide a new paradigm in investigational sarcoma therapeutics. An integrated multidisciplinary systematic approach conducted efficiently with intimate collaboration has the potential to translate the hope of personalized medicine for sarcoma into a reality.

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### Compliance with Ethics Guidelines

### Conflict of Interest

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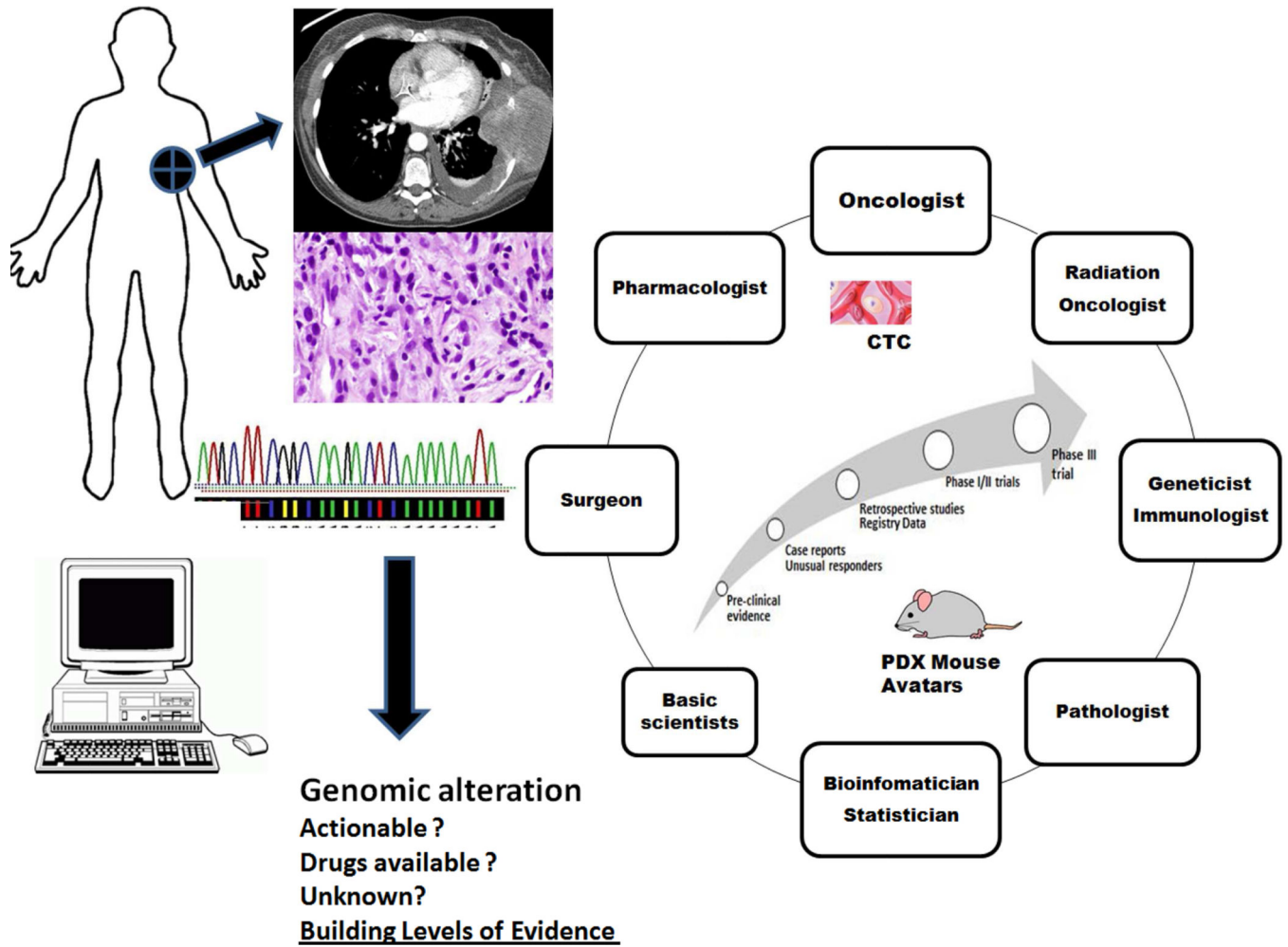
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**Fig. 1. Personalized Therapy or Precision Medicine Paradigm**

Once a patient is diagnosed with conventional pathology tests and scans, the tissue undergoes molecular profiling that includes a ‘pan’-omic assessment, data from which is analyzed by robust bioinformatics algorithms. The results are discussed by a multidisciplinary team (the ‘molecular tumor board’) that takes into account the genomic aberrations in the context of a particular sarcoma subtype and whether evidence of therapeutic benefit at any level exists. This would be followed by molecularly matched therapy, which requires accessibility to a rich pipeline of drugs. Once therapy is initiated the ideal approach is to follow up on patients for safety, efficacy, toxicity, and response; if acquired resistance develops, the tissues are biopsied and analyzed to identify biomarkers to overcome resistance. Every effort has to be made to track the data of molecularly matched therapy in patients, whether they are on or off protocol. Patient-derived xenografts and circulating tumor cells may provide more data about resistance mechanisms and therapy sensitivity.

**Table 1**

Actionable sarcoma biomarkers with clinical evidence of pharmacological inhibition

Sarcoma Type	Actionable Biomarker	Clinical Evidence of Pharmacological Inhibition
Gastrointestinal stromal tumor	<i>KIT, PDGFR</i>	Imatinib (KIT, BCL, ABL, PDGFR) Dasatinib (KIT, PDGFR, ABL, SRC) Sunitinib (KIT, PDGFR, VEGFR, RET, FLT3) Sorafenib (KIT, VEGFR, PDGFR, BRAF inhibitor) Regorafenib (KIT, RET, VEGFR, BRAF, PDGFR)
Soft tissue sarcoma	<i>VEGFR</i>	Pazopanib (VEGFR, PDGFR, KIT)
Inflammatory myofibroblastic tumor	<i>ALK</i>	Crizotinib (ALK, ROS1, C-met)
Liposarcoma	<i>CDK4</i> amplification	CDK4 inhibitor
Giant cell tumor of bone	<i>RANKL</i> expression	Denosumab (RANK-L)
Angiosarcoma	<i>KDR, VEGF</i>	Sorafenib, bevacizumab (VEGF)
Solitary fibrous tumor	<i>IGF1R</i> pathway	
Perivascular epithelioid cell tumor (PECOMA)	<i>TSC1, TSC2</i>	Sirolimus, everolimus, temsirolimus
Lymphangioliomyoma	<i>TSC2</i>	Sirolimus, everolimus, temsirolimus
Tenosynovial giant cell tumor/pigmented villonodular synovitis	<i>CSF1R</i>	Imatinib (KIT, BCL, ABL, PDGFR, CSF1R)
Dermatofibrosarcoma protuberans	<i>PDGFR</i>	Imatinib, pazopanib
Endometrial stromal sarcoma	ER+, PR+	Anastrozole, letrozole
Clear cell sarcoma	<i>MET</i>	Cabozantinib (c-MET, VEGFR2)