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Biology-guided precision medicine in rare cancers: Lessons from sarcomas and neuroendocrine tumours

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A B S T R A C T

Rare cancers, which collectively account for almost 25 % of all malignancies, are poorly understood in terms of their aetiology and pathogenesis and are infrequently the focus of translational and clinical research to improve their diagnosis and treatment. Consequently, those affected have comparatively few treatment options, and their prognosis is worse than that of patients with more common entities. Here we review two relevant groups of rare cancers, bone and soft-tissue sarcomas and neuroendocrine tumours (NET), to illustrate recent efforts towards individualised, biology-guided clinical management to improve long-term outcomes. Specifically, we address how comprehensive, multi-layered molecular analyses, including the assessment of predisposing hereditary factors, and innovative imaging approaches can improve the diagnosis of these diseases, allow for better prognostic assessment, and provide new targets for pharmacologic and, in the case of NET, nuclear medicine interventions, whose clinical value must be determined in controlled trials optimally tailored to the particular patient population most likely to benefit. Furthermore, we describe the importance of multidisciplinary collaboration in dedicated reference centres for rare cancers and the increasingly acknowledged potential of networking across institutions at a national and international level. Finally, we illustrate the value of a learning health system based on the systematic collection and sharing of the biological and clinical profiles of patients with rare cancers to achieve continuous cross-fertilisation of scientific and clinical efforts, making the vision of stratified precision medicine in these long-overlooked diseases a reality.

1. Introduction

Rare cancers are malignant neoplasms with an incidence of less than six per 100,000 cases per year (https://www.rarecancerseurope.org). Comprising about 200 different diseases, they account for 24 % of all cancer cases [1]. The five-year overall survival rate for patients with rare cancers is only 48.5 %, which is in sharp contrast to 63.4 % for patients with more common cancers [2]. The reasons for these poor outcomes are multifaceted and primarily include delays in diagnosis at the patient, general practitioner, and medical specialist level; the absence of expert care; the scarcity of new treatments, including molecularly targeted approaches; and the lack of scientific evidence to guide clinical decision making [3,4]. Thus, rare cancer patients often face hurdles in terms of histopathologic and molecular diagnostic accuracy and selection of and adequate access to optimal imaging, which, together with a lack of expertise in the clinical management of particular entities, may lead to suboptimal treatment. Furthermore, biologically defined subgroups exist even in rare cancers, like in common malignancies. The resulting small patient numbers complicate the design and execution of clinical trials and the attraction of interest from pharmaceutical companies – a challenge increasingly addressed in recent years by cross-institutional, sometimes nationwide, collaboration and histology-independent basket trials [5–9]. To highlight different clinical implications of the biological understanding of rare cancers, we will first discuss sarcomas as an example of tumours with heterogeneous molecular aberrations that have important consequences for diagnosis and classification as well as personalised pharmacologic treatment options. Second, we will address neuroendocrine tumours (NET), focusing on theranostics and radioactive precision treatment. Finally, many rare cancers have no known causative external factors, unlike more common entities. This suggests that genetic predisposition, including familial cancer syndromes, contributes disproportionately to rare cancers, which we again discuss using

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sarcomas and NET as examples.

2. Examples of rare cancers

2.1. Sarcomas

2.1.1. Epidemiology and clinical presentation

Sarcomas are the largest and most heterogeneous category of rare cancers [10]. They can be divided into bone sarcomas and soft-tissue sarcomas (STS), of which gastrointestinal stromal tumours (GIST) are the largest group and are often seen as a distinct subset. Sarcomas are heterogeneous not only because of the many subtypes but also due to their differences in biology, anatomic location, and age of onset [11,12]. They each account for 11 % of cancers in children < 15 years [13] and adolescents and young adults (AYA) aged 15–29 years [14], but only 1 % overall in adults ≥ 18 years [15].

STS encompasses approximately 80 entities defined by the World Health Organization (WHO) classification based on distinctive morphologic, immunohistochemical, and molecular features [16–18]. Adult-type soft-tissue and visceral sarcomas, excluding GIST, are rare tumours with an estimated incidence of 4–5/100,000/year in Europe [1]. The most common subtypes are liposarcoma and leiomyosarcoma (LMS), each with an incidence < 1/100,000/year, while most histotypes have an incidence < 0.2/100,000/year. Primary bone sarcomas account for < 0.2 % of malignant neoplasms across all ages [1]. The overall incidence rate ranges from 0.8 to 0.9/100,000/year, with individual subtypes such as osteosarcoma having an incidence of 0.3/100,000/year. Osteosarcomas and Ewing sarcomas frequently occur in the second and third decades of life, whereas conventional chondrosarcomas are diagnosed later.

Many sarcomas occur in the extremities, while others arise in the peritoneum, visceral organs such as the uterus, and the head and neck region. In addition, as a particular group of mesenchymal tumours, GIST live up to their name and arise in the gastrointestinal tract with a predilection for the stomach. These tumours originating from the interstitial cells of Cajal have an incidence of approximately 1/100,000/year. They are defined as a separate sarcoma subtype requiring unique treatment due to their distinctive biological characteristics with gain-of-functions mutations in the *KIT* and *PDGFRA* receptor tyrosine kinase genes [19].

2.1. .2. Treatment

The mainstay of curative sarcoma treatment is surgery, which is generally sufficient for low-grade tumours [15,20]. However, high-grade sarcomas metastasise in 40–50 % and have local relapse rates that have led to the standard introduction of perioperative radiotherapy in extremity STS. Furthermore, neoadjuvant chemotherapy for high-risk STS seems to reduce the risk of recurrences and improves survival [21–23], whereas standard adjuvant chemotherapy does not. In retroperitoneal sarcomas, the added value of preoperative radiotherapy has not been demonstrated for most histologies [24]. Once metastasised, the median survival of STS patients is only 18 months, with a wide variety due to the aggressiveness of the disease and its drug sensitivity [25–28]. With few exceptions, chemotherapy is the backbone of systemic treatment options.

Unlike most so-called non-GIST STS, GIST is a highly chemoresistant tumour. The therapeutic breakthrough in this disease happened in 2000 when the first positive results were achieved with the introduction of the tyrosine kinase inhibitor (TKI) imatinib. This oral drug, which must be taken continuously, and subsequent TKI have led to a prolongation of median survival from less than one year to more than five years, making GIST a shining example of the potential of biology-guided therapies in solid tumours [19]. Interestingly, this disease mainly occurs in older individuals, with a median age of about 65 years at diagnosis, and it is not uncommon for patients today to die with, rather than from, GIST. Young adults may present with GIST, more often without an activating *KIT* or *PDGFRA* mutation, and the presence of specific syndromes should be investigated in such a situation.

2.1. .3. Entry points for molecularly informed precision sarcoma medicine

From a molecular genetic perspective, sarcomas can be classified into two main groups, (i) those driven by simple alterations such as balanced chromosomal rearrangements or point mutations, and (ii) those exhibiting genomic instability and complex karyotypes.

2.1. .3.1. Balanced rearrangements. These changes include, in particular, chromosomal translocations, which occur in approximately 20 % of all sarcomas and are often pathognomonic and therefore of diagnostic value. Thus, for a number of subtypes, detecting a specific fusion gene resulting from an underlying chromosomal rearrangement is part of the standard workup to support the histopathologic diagnosis [29,30]. Many of these entities occur primarily in children and AYA patients, e.g., Ewing sarcoma, synovial sarcoma, alveolar rhabdomyosarcoma, desmoplastic small round cell tumour, alveolar soft part sarcoma, myxoid liposarcoma, and clear cell sarcoma (Table 1).

From a therapeutic point of view, it is important that these sarcomas have a broad spectrum of sensitivity to conventional cytotoxic drugs [15,20,31–33]. Ewing sarcoma and alveolar rhabdomyosarcoma are highly susceptible subtypes. In contrast, desmoplastic small round cell tumour, which is often treated according to chemotherapy schedules for Ewing sarcoma, is characterised by a high rate of secondary drug resistance and worse outcome, possibly due to extensive acquired DNA copy number changes [34], and alveolar soft part sarcoma and clear cell sarcoma are almost uniformly refractory to chemotherapy.

The variable and, even for sensitive subtypes, difficult-to-predict effect of conventional chemotherapy in individual cases raises the question of novel therapeutic strategies that exploit entity-defining fusion genes as targets. While the concept of targeting tumour-specific genetic features is very attractive, one difficulty is that the fusion genes mentioned above encode aberrant transcriptional regulators that, unlike cancer drivers with pharmacologically tractable enzymatic activity, evade established methods of direct inhibition. This finding has sparked interest in secondary functional dependencies that exist in the context of these "undruggable" fusions. Such context-dependent vulnerabilities include, e.g., (i) mutant *PIK3CA*, which occurs in 15–20 % of all myxoid liposarcoma cases [35,36]; (ii) the MET receptor tyrosine kinase aberrantly expressed in alveolar soft part sarcoma and clear cell sarcoma downstream of the corresponding fusion genes [37,38]; and (iii) the sensitivity of alveolar soft part sarcoma, an entity with very few mutations, to immune checkpoint inhibitors, in particular in combination with certain antiangiogenic TKI, possibly due to immunogenicity of the pathognomonic *ASPSCR1*::*TFE3* fusion [39]. An interesting new strategy may be to focus on elements of the machinery controlling the stability of a sarcoma-driving fusion protein, as recently demonstrated for the TRIM8 ubiquitin ligase in preclinical Ewing sarcoma models [40]. Finally, there are balanced rearrangements that affect tyrosine kinase signalling pathways established as drug targets and are thus

Table 1
Examples of sarcomas whose diagnosis is supported by the detection of entity-specific fusion genes.

Diagnosis	Translocation (s)	Fusion gene (s)
Ewing sarcoma	t(11;22)(q24;q12)	*EWSR1*::*FLI1*
	t(21;22)(q22;q12)	*EWSR1*::*ERG*
Synovial sarcoma	t(X;18)(p11;q11)	*SS18*::*SSX1*
	t(X;18)(p11;q11)	*SS18*::*SSX2*
Alveolar rhabdomyosarcoma	t(2;13)(q36;q14)	*PAX3*::*FOXO1*
	t(1;13) (p36;q14)	*PAX7*::*FOXO1*
Desmoplastic small round cell tumor	t(11;22)(p13;q11)	*EWSR1*::*WT1*
Alvolar soft part sarcoma	t(X;17)(p11;q25)	*ASPSCR1*::*TFE3*
Myxoid liposarcoma	t(12;16)(q13;p11)	*FUS*::*DDIT3*
	t(12;22)(q13;q12)	*EWSR1*::*DDIT3*
Clear cell sarcoma	t(12;22)(q13;q12)	*ATF1*::*EWSR1*
	t(2;22)(q33;q12)	*CREB1*::*EWSR1*

directly druggable. Clinically validated examples include *ALK* fusions in inflammatory myofibroblastic tumour [41], *COL1A1*::*PDGFB* in dermatofibrosarcoma protuberans [42], and various alterations of *NTRK* family members that can be detected – mostly at very low frequency, but in certain entities such as infantile fibrosarcoma also very commonly – in a broad spectrum of STS across age groups [43].

2.1. .3.2. Point mutations. The most prominent example of STS driven by point mutations is GIST, which in the vast majority of cases have somatically acquired activating variants in either the KIT or PDGFRA receptor tyrosine kinases [19]. The approval of the selective TKI imatinib in 2001 has revolutionised oncology by transforming a previously fatal disease into one with long-lasting partial response and stable disease within a year. Subsequently, other TKI were approved, namely sunitinib and regorafenib as second- and third-line therapy, respectively. However, almost all patients develop resistance to these agents, usually due to secondary kinase mutations [44]. A major limitation of imatinib, sunitinib, and regorafenib is that they target the inactive conformation of KIT and PDGFRA; therefore, their efficacy against secondary mutations in the kinase activation loop is attenuated. Neither sunitinib nor regorafenib inhibit the full spectrum of secondary *KIT* mutations, and other factors such as extensive clonal heterogeneity also contribute to acquired resistance [45].

To overcome these limitations, two next-generation TKI have been developed [46]. Ripretinib, a broad-spectrum KIT/PDGFRA inhibitor, was recently approved by the United States Food and Drug Administration (FDA) for the treatment of adult patients with advanced GIST who previously received three or more TKI, including imatinib. Avapritinib, a so-called type I inhibitor that targets the active kinase conformation, was approved for by the FDA the treatment of adults with unresectable or metastatic GIST who have a *PDGFRA* exon 18 mutation, including the most common and imatinib-resistant *PDGFRA* D842V variant. The European Medicines Agency approval is limited to patients with *PDGFRA* D842V-mutant GIST.

Below, we discuss how the discovery and understanding of resistance mutations have yielded new treatment options for GIST patients by looking at the clinical development of ripretinib and avapritinib.

2.1. .3.3. Genomic instability and complex karyotypes. Several soft-tissue and bone sarcomas do not have “simple” genomes dominated by a single driving fusion gene or point mutation but rather exhibit multiple genomic gains and losses [16–18]. Entities with such complex karyotypes include, e.g., undifferentiated pleomorphic sarcoma, leiomyosarcoma, well-differentiated and dedifferentiated liposarcoma, and osteosarcoma [47–49]. As with sarcomas driven by balanced genomic rearrangements, sensitivity to conventional cytotoxic drugs varies, and no reliable predictive parameters exist beyond the underlying histology. Given this limitation and the overall unsatisfactory results of drug therapy for advanced-stage patients, the question of novel therapeutic strategies based on molecular profile also arises in genomically complex sarcomas.

In several cases, these entities’ “chaotic” karyotypes contain individual DNA copy number alterations that are clinically actionable. These include, e.g., amplification of the long arm of chromosome 12 in patients with well-differentiated and dedifferentiated liposarcoma, which has diagnostic value due to its universal occurrence in this entity and is associated with aberrant activity of the CDK4 cell cycle kinase and the MDM2 ubiquitin ligase targeting TP53 for proteasomal degradation, which are candidate drug targets being explored, either alone or in combination, in controlled clinical trials [50,51]. Another example is genomic imbalances associated with constitutive activation of the PI3K-AKT-mTOR axis, e.g., *PTEN* deletions, which occur in more than 50 % of patients with LMS [52–54].

In addition to detecting individual targetable sarcoma drivers in complex sarcoma genomes, an alternative or even combinatorial strategy might be to therapeutically exploit specific aspects of genomic instability itself. For example, comprehensive genomic analyses have revealed that many patients with extensively pretreated leiomyosarcoma, chordoma, and osteosarcoma exhibit a genomic profile reminiscent of the genomic imprint of disrupted DNA repair via homologous recombination [53,55–58]. Whether such a “BRCAness” signature, as in certain epithelial cancers, represents a therapeutic liability by determining sensitivity to PARP inhibition needs to be systematically investigated and is the subject of current clinical trials. However, positive case reports in certain entities, e.g., chordoma [56], versus the widespread refractoriness of osteosarcomas to these agents indicate that the druggability of deficient homologous recombination is a complicated matter and also determined by the tissue context in which it occurs. Other composite biomarkers, not limited to a single gene or molecular alteration, that may gain importance for the treatment of sarcomas include high tumour mutational burden, detected, e.g., in angiosarcomas of the head, neck, face, and scalp regions, and B-cell-rich tertiary lymphoid structures, which appear to be associated with sensitivity to immune checkpoint inhibition [59–62].

2.1.3. .4. Targets for emerging cellular sarcoma therapies. Recently, approaches for adoptive cellular therapies of sarcomas have been developed for the first time. These involve the administration of patient-derived T lymphocytes transduced ex vivo with a T-cell receptor directed against antigens presented on tumour cells in the context of specific HLA molecules. Particularly immunogenic epitopes include CTAG1B (also called NY-ESO-1) and MAGEA4, which are highly expressed in patients with synovial sarcoma and myxoid/round cell liposarcoma, making these entities currently prime candidates for exploration of cellular therapies [63,64].

2.1.4. Strategies for nominating and validating new targets for molecularly informed precision sarcoma medicine

The most important tool to evaluate new therapeutic strategies based on insight into disease biology and thus level the way from empirical to pathogenesis-oriented sarcoma medicine is, of course, clinical trials. These are associated with particular challenges in sarcomas, especially to avoid "lumping" of biologically distinct subtypes and thus not to miss important clinical signals due to unstratified administration of uniform, “one-size-fits-all” treatment [8].

2.1.4. .1. Entity-specific interventional trials. One entity where the concept of individualised therapy tailored to disease biology has been pioneered is GIST. The main reasons are that its molecular pathogenesis has been known for a long time, that a very large proportion of cases are driven by mutant *KIT* and *PDGFRA*, and that GIST are comparatively common. Therefore, numerous entity-specific studies could be performed, leading to a steady improvement of therapy and a dramatic improvement of outcomes for GIST patients. To date, five TKI have been approved for the treatment of GIST. While imatinib remains the standard of care for cases caused by *KIT* exon 9 and 11 mutations, sunitinib is used in the second-line setting and also targets imatinib-resistant *KIT* mutations in other exons. Regorafenib is a less selective, “dirtier” agent approved for third-line treatment. Although TKI have revolutionised GIST treatment, a significant challenge is that over time, almost all patients develop resistance to the individual agents, mostly due to secondary kinase mutations [19]. Two new agents approved in 2020, avapritinib and ripretinib, are distinct from first-generation GIST therapies. Avapritinib was approved for the treatment of tumours driven by *PDGFRA* exon 18 mutations, including the most common D842V variant, which are generally resistant to imatinib [65]. Ripretinib has a different mode of action than the other four agents, is active against *KIT* and *PDGFRA* mutations, and was recently approved for fourth-line therapy of adults with advanced GIST previously treated with three or more TKI, including imatinib [66]. The different target selectivities and modes of

action of these agents also entail distinct toxicity profiles, which must be taken into account in therapeutic decision making.

2.1.4. .2. Basket trials. For the study of molecular alterations occurring in smaller subsets of different entities, so-called basket trials have become of great importance, which enroll patients across multiple histologies and are based on the assumption that the presence of a particular molecular profile is associated with sensitivity to a specific therapy tailored to that constellation [67]. This concept particularly relates to sarcomas because (i) it accounts for their rarity and diversity, (ii) the sarcoma community has been involved in the development of basket trials at an early stage, and (iii) histology-independent protocols have established therapeutic targets significant to relevant subsets of sarcomas.

An example of a successful basket trial in which most categories were intended for sarcoma subtypes is the CREATE (Cross-tumoral Phase 2 With Crizotinib) study by the European Organisation for Research and Treatment of Cancer (EORTC). CREATE was an international, biomarker-driven, single-arm, non-randomised, open-label phase 2 trial designed to assess the efficacy and safety of crizotinib in alveolar soft part sarcoma, inflammatory myofibroblastic tumour, clear cell sarcoma, and alveolar rhabdomyosarcoma [68]. These subtypes were selected because their underlying fusion genes were thought to lead, directly or indirectly, to activation of the ALK and/or MET receptor tyrosine kinases inhibited by crizotinib. The primary end-point in all cohorts was the objective response rate. The ALK cohort included a total of 20 patients with advanced inflammatory myofibroblastic tumour, an STS subtype that, in approximately half of the cases, has balanced rearrangements of the *ALK* gene, predominantly translocations with variable fusion partners, resulting in the overexpression of chimeric ALK protein with constitutive kinase activity. Of 12 patients with *ALK* fusions, six (50 %) achieved an objective response to crizotinib, compared with only one of seven (14.3 %) cases without *ALK* alteration [69]. Continued follow-up after the primary analysis showed a further increase in the objective response rate to 66.7 % [70]. Overall, this substudy demonstrated the feasibility of establishing a new therapeutic target even in ultra-rare cancers such as inflammatory myofibroblastic tumour based on an understanding of disease biology and effective multicenter collaboration across national borders. The value of CREATE trial as a model of a biomarker-driven approach to evaluate individualised therapies in non-GIST STS was also demonstrated in alveolar soft part sarcoma and clear cell sarcoma. However, crizotinib proved to be less effective in these subtypes, which were selected based on the aberrant expression of *MET* downstream of the pathognomonic *ASPSCR1*::*TFE3* and *EWSR1*::*ATF1* fusions. The alveolar soft part sarcoma cohort included 48 patients with metastatic or locally advanced disease who had a response rate of only 4.4 % [71]. In the 34-patient clear cell sarcoma cohort, which was in almost 75 % chemo-naïve, a partial response was observed in only one of 26 evaluable patients (3.8 %) [72]. These results underscore the challenge discussed above of finding therapeutic targets in sarcomas driven by aberrant transcriptional regulators. Of note, the presence of individual targets was not assessed before initiation of treatment, and truly molecularly guided basket studies are even more attractive, with the key requirement that the turnaround time to the result of molecular analysis should be short.

Finally, recent basket studies of the small-molecule inhibitors larotrectinib and entrectinib have shown that rearrangements of NTRK receptor tyrosine kinase family members are promising therapeutic targets in several STS subtypes, including quadruple (*KIT*, *PDGFRA*, *SDH*, and *BRAF*)-negative GIST [46,73–76]. As in other solid tumours, the frequency of these alterations is very low in most subtypes, except for infantile fibrosarcoma, where *NTRK* fusions therefore also have diagnostic value. The sarcoma community has responded to this encouraging development by nominating *NTRK*-rearranged STS as an "emerging entity" in the new WHO classification and developed recommendations for the diagnosis and clinical management of these tumours [17,43].

2.1.4. .3. Observational registries and cohort studies. The recent past has shown that other study types, such as prospective observational registries and multi-arm cohort studies, also have the potential to improve therapy for rare cancers, as illustrated by the DRUP (Drug Rediscovery Protocol) [7,77], MASTER (Molecularly Aided Stratification for Tumor Eradication Research) [9,78], MoST (Molecular Screening and Therapeutics) [79], and TAPUR (Targeted Agent and Profiling Utilization Registry) [5] initiatives. Although except MoST, these studies were generally not designed for rare cancers, substantial numbers of such patients get enrolled in them because there is a significant unmet medical need and these trial designs can offer therapies to patients with rare cancers to which they would not otherwise have access. In addition, these and other similarly designed protocols have proven to be important "signal finding" endeavours from which interventional trials are increasingly emerging, including some that use composite biomarkers and evaluate combination therapies (ClinicalTrials.gov: NCT03127215, NCT04551521) [80]. In any case, progress in precision therapy of rare cancers, whether through interventional or registry studies, requires the consistent collaboration of multiple institutions in coordinated national networks or even international alliances such as the EORTC [81,82] and Cancer Core Europe [83].

2.2. Neuroendocrine tumours

2.2.1. Clinical presentation and outcome

Neuroendocrine tumours (NET) are a heterogeneous group of epithelial malignancies with a relatively indolent disease course. Primary tumours can arise from neuroendocrine cells at various anatomic sites, most commonly in the gastroenteropancreatic tract and lungs [84]. In recent years, the incidence and prevalence of NET have increased, most likely due to early detection, better awareness, and longer survival. The tumour now accounts for about 0.5 % of all newly diagnosed malignancies [85]. Patients with NET are often asymptomatic or experience non-specific symptoms, resulting in frequently missed diagnoses. Therefore, metastatic disease at the time of diagnosis is often seen [86]. Some tumour cells are classified as functional and can produce an excess of hormones such as insulin or glucagon. Because of clinical symptoms associated with the overproduction of hormones, patients with a functional tumour are more often diagnosed at an earlier stage of the disease. There is, however, an exception because small intestinal NET (SI-NET) have the ability to secrete various vasoactive peptides, the most prominent being 5-hydroxytryptamine (also known as serotonin), which are normally inactivated by the liver. Only in the presence of liver or retroperitoneal metastases this process is bypassed. Elevated serotonin can then lead to typical symptoms such as flushing, sweating, and diarrhoea, giving rise to the so-called carcinoid syndrome. This syndrome occurs in 30–40 % of patients with metastatic SI-NET [87]. Most NET are sporadic, but there is a predisposing hereditary syndrome in some cases, i.e., multiple endocrine neoplasia (MEN) type 1, von Hippel-Lindau syndrome, neurofibromatosis, and tuberous sclerosis. Familial clustering is also recognised [84].

In patients with local or locoregional disease, surgery is the cornerstone of all management strategies. Even in the case of metastatic disease, surgery of the primary tumour is often performed, although it is still a matter of debate whether prophylactic surgery in asymptomatic patients with metastatic NET should be considered standard practice [88,89]. Survival differs widely between the different locations of the primary NET, whereas patients with appendiceal NET have an excellent prognosis, the outcome of patients with pulmonary NET is rather poor. Apart from tumour localisation, tumour stage and grade are independent predictors of survival [85]. Despite these parameters, it is still challenging to predict the clinical course in individual patients.

2.2.2. Histologic diagnosis

NET are, as per definition, well-differentiated, and the majority of cells show diffuse overexpression of a G-protein-coupled somatostatin receptor (SSTR), most frequently subtype 2, on their surface. Furthermore, there is overexpression of the neuroendocrine markers synaptophysin and chromogranin [84]. On gross appearance, NET of the gastrointestinal tract are often well-circumscribed lesions in the submucosa or extending to the muscular layer, while those in the pancreas may be well-circumscribed, multinodular, or infiltrative. Although NET have similar characteristics on routine histologic evaluation, they have different pathogenesis and biology. The proliferation rate, assessed by mitotic count and Ki-67 labelling index, is of prognostic significance. The WHO classification, which considers the proliferative fraction of neoplastic cells, divides NET into three subgroups, i.e., grade 1 (G1), 2 (G2), and 3 (G3). While G3 tumours are more aggressive, 90 % of NET are G1 or G2 [90].

2.2.3. Treatment of metastatic disease and SSTR-targeting radiolabelled peptides

As many patients present with metastatic disease at diagnosis [86], management strategies mainly focus on controlling symptoms and tumour growth rather than cure [91]. Patients with functional tumours are treated with systemic somatostatin analogues as first-line therapy to control their symptoms. Several guidelines consider a watchful waiting strategy appropriate in patients with non-functional NET to estimate the growth kinetics, considering anti-proliferative therapy only to be initiated when progressive tumour growth is objectively proven [91].

Given the overexpression of SSTR on the tumour cell membrane, a variety of SSTR-targeting peptides have been developed. The native ligand for SSTR is somatostatin (also known as growth hormone-inhibiting hormone), which has two variants consisting of 14 or 28 amino acids. The octapeptide octreotide was the first synthetic derivative introduced for the treatment of SSTR-overexpressing tumours, showing affinity mainly for SSTR subtype 2 but also having a much longer half-life than somatostatin of approximately 90 min as compared to two to three minutes, respectively.

Octreotide was derivatised to pentetreotide, allowing labelling the peptide with the radionuclide ^{111}Indium for molecular imaging using single-photon emission computed tomography (SPECT) and later SPECT/CT. After introducing ^{111}In-pentetreotide, a complete shift towards positron emission tomography (PET) tracers has occurred, demonstrating much faster tumour targeting and superior diagnostic accuracy than ^{111}In-pentetreotide. Being a small peptide, modifications affecting target affinity, pharmacokinetics, and pharmacodynamics was relatively straightforward. A variety of peptides with different affinities for the various SSTR subtypes have been developed and derivatised with tetraazacyclododecane-tetraacetic acid (DOTA) for convenient radiolabelling with the positron-emitting ^{68}Gallium for PET/CT imaging and subsequently studied. In patients with metastatic NET, the most commonly used peptides are ^{68}Ga-DOTA-TATE, which has a high affinity for the SSTR subtype 2, and ^{68}Ga-DOTA-TOC, targeting SSTR subtype 2 and moderately subtype 5. The less frequently used ^{68}Ga-DOTA-NOC analogue has a high affinity for SSTR subtypes 2, 3, and 5 [92]. The affinity of ^{68}Ga DOTA-TATE for SSTR type 2 is 100 times higher than that of ^{111}In-pentetreotide. PET/CT of these peptides is the imaging modality of choice in detecting, staging, and characterising NET

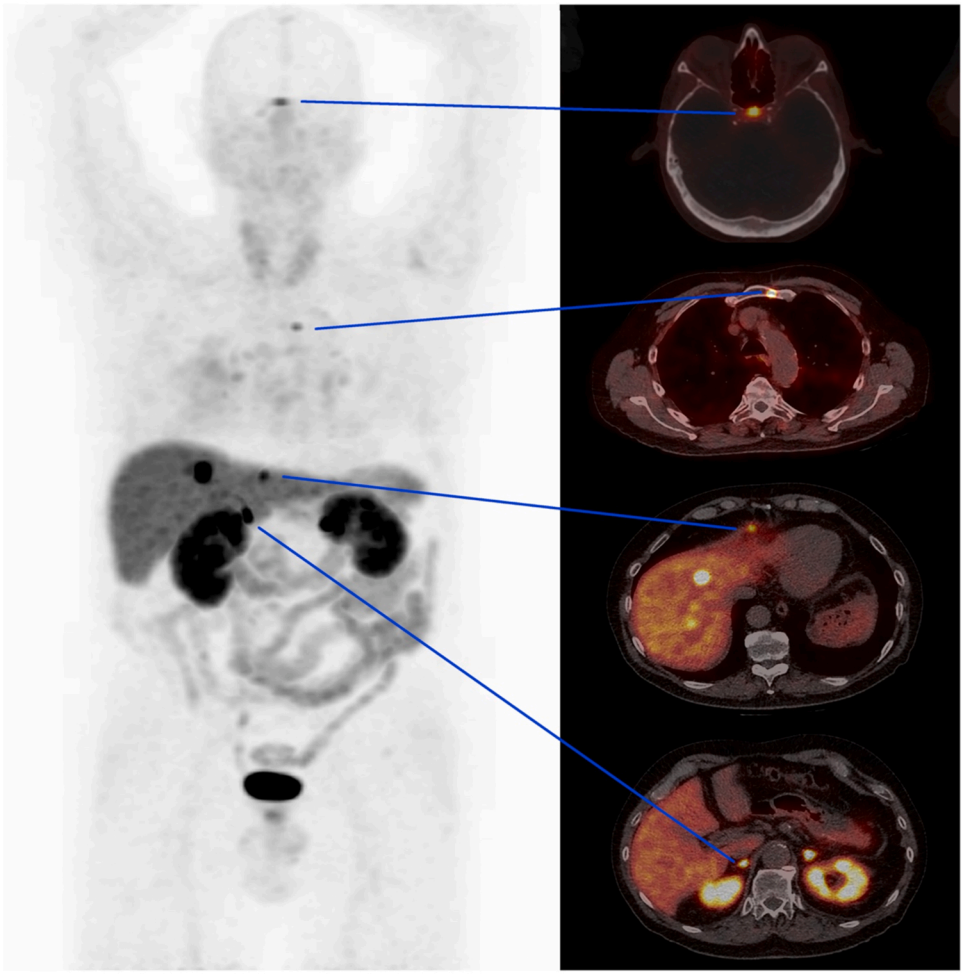

Fig. 1. 70-year-old male with a history of partial pancreatectomy for NET G2, now referred for follow-up with ^{68}Ga-DOTATOC PET/CT. Left panel: Maximum intensity projection (MIP) of ^{68}Ga-DOTATOC PET/CT. Right panel: Transverse cross-sectional PET/CT images at various levels. Blue lines connect areas of ^{68}Ga-DOTATOC uptake on MIP with the same lesion on the corresponding transverse section. Upper blue line: Physiological uptake in the hypophysis. Second blue line: Bone metastasis in the sternum. Third blue line: Two metastases in the liver. Bottom blue lines: Physiological uptake in the right adrenal gland.

(Fig. 1) [93,94]. Further to the radiolabelling of somatostatin analogues with gamma and positron emitters for diagnostic imaging, the same compounds have been radiolabelled with beta-emitting radionuclides such as ^{177}Lu and ^{90}Y for radioligand therapy (RLT). This resulted in the theranostic concept of PET/CT imaging to assess receptor expression and select patients with sufficient expression to be offered treatment with the beta-emitting compound. Equally important, using molecular imaging-based patient selection prevents the exposure of patients with limited or absent receptor expression to high doses of radiation. Treating the latter group is futile because of the lack of target, while side effects such as renal and haematologic toxicity remain. In the randomised phase 3 trial NETTER-1 in patients with advanced NET, ^{177}Lu-DOTA-TATE demonstrated markedly longer progression-free survival and a significantly higher response rate than the control group treated with high-dose somatostatin analogue. Additionally, treatment with ^{177}Lu-DOTA-TATE resulted in a significant quality-of-life benefit for patients with progressive midgut NET compared to standard of care [95]. Very recently, it was reported that ^{177}Lu-DOTA-TATE did not improve overall survival [96]. This was attributed to a high cross-over rate of patients in the control arm to RLT after progression. ^{177}Lu-DOTA-TATE is now available as an approved therapy in the United States and Europe. Currently, second and higher-line treatments are based on several modalities and include liver-directed therapies, RLT, chemotherapy, kinase inhibitors, or the mTORC1 inhibitor everolimus in the case of non-functional, advanced, and progressive NET as well as pancreatic NET (pNET) [84]. Unfortunately, no biomarker is available that predicts response to everolimus or all other therapies [97].

2.2.4. *Potential entry points for molecularly informed treatment*

To move towards precision medicine, the genomic landscape of NET has been increasingly investigated over the past years, intending to unravel the molecular events underlying NET development, facilitating the identification of novel therapeutic targets and rational treatment strategies and improving prognosis. Using whole-exome analysis, Jiao et al. discovered mutations in mTOR pathway genes in 15 % of pNET patients [98]. Recently, whole-genome sequencing of primary pNETs revealed genomic events of pathogenetic relevance and associated with tumour progression [99]. The mutational landscape of sporadic pNET, described by Scarpa et al., shows alterations in *DAXX*, *ATRX*, and mTOR pathway genes as well as mutations in the DNA repair genes *MUTYH*, *CHEK2*, and *BRCA2*, which were found in 17 % of patients [99]. These discoveries may help predict the clinical behaviour of sporadic pNET and hopefully develop new biomarkers predicting response to everolimus or other targeted agents, including peptide receptor radionuclide therapy. Although it was previously thought that driver mutations were exclusively found in high-grade neuroendocrine carcinoma, a recent study identified driver mutations in about 50 % of SI-NET, of which the majority affected tumour suppressor genes such as *TP53*, *RB1*, and *CDKN1B*; however, potentially targetable alterations were detected in 21 % of patients with metastatic SI-NET [100]. In general, NET have a low mutational burden, which may render these tumours less sensitive to immune checkpoint inhibition. Additionally, features of the NET microenvironment, such as low expression of PD1 and its ligand PDL1 and a modest T-cell infiltrate, further temper expectations regarding response to currently used immune checkpoint inhibitors, although this remains to be investigated [101].

Unfortunately, our current understanding of the molecular pathology of NET is still insufficient to provide information on tumour behaviour, predict its clinical course, and personalise the treatment of NET patients. This is partly due to the rarity of the disease, which makes clinical trials involving integrated genomic analyses scarce. In the coming years, hopefully, international collaborations will enable larger studies to correlate (epi)genetic alterations with clinical outcomes and identify targetable (epi)genetic alterations. Larger studies combined with evolving molecular technologies might lead to more effective treatment strategies in which patients with specific molecular profiles will be selected for targeted interventions.

3. Role of clinical genetics in the diagnostics, prevention, and treatment of rare cancers

Most cancers associated with heritable cancer predisposition syndromes are managed in the same way as sporadic cancers of the same histopathologic subtype, with some notable exceptions. Certain heritable cancer predisposition syndromes may confer differential response rates or risk of excessive toxicity to radiotherapy or chemotherapeutic agents. Affected individuals may also be at risk of second primary cancers and require a tailored surgical approach, follow-up, and onward surveillance. Furthermore, identification of a heritable disorder in the affected patient has significant implications on the cancer risk, surveillance, and management of their blood relatives and may impact family planning to minimise the risk of transmission to future progeny.

Many cancer predisposition syndromes are associated with dysmorphic features or other characteristic stigmata of disease and are usually obvious early in childhood (Table 2). Such syndromes include rare recessive disorders of DNA repair caused by alterations in genes encoding DNA helicases, such as Bloom (*BLM*), Werner (*WRN*), Rothmund Thomson (*RECQL4*), or Nijmegen Breakage (*NBN*) syndromes, or mismatch repair genes (congenital mismatch repair deficiency [*MLH1, MSH2, MSH6, PMS2*]) [102]. A number of dominant syndromic disorders also increase cancer risk and may present with dysmorphic features and/or congenital anomalies, including Rubenstein-Taybi syndrome (*CREBBP*, *EP300*), Diamond-Blackfan anaemia (>16 ribosomal genes), and Rasopathies (multiple genes in the RAS-MAPK pathway) [103]. Many germline variants are associated with variable expressivity, such that syndromic features, even when present, may be subtle and easily overlooked. Furthermore, several cancer predisposition syndromes have no syndromic features other than a significantly increased lifetime risk of cancer and are therefore unlikely to be evident prior to a cancer diagnosis. Familial cancer history, or lack thereof, may not be informative, as a significant proportion of pathogenic germline variants may arise de novo [102,104], be mosaic, or associated with recessive or other inheritance patterns. Moreover, a number of cancer-predisposing germline variants are associated with incomplete penetrance [105].

3.1. *Genetic predisposition to sarcomas*

Most sarcomas occur as apparently sporadic events. For example, certain subtypes typically occur consequent to recurrent somatic translocation events (see above). However, a significant proportion of affected individuals harbour an underlying pathogenic germline variant in a cancer predisposition gene [106], and several heritable syndromes have well-established associations with specific sarcoma subtypes (Table 2).

Li-Fraumeni syndrome (LFS) is a rare autosomal dominant cancer predisposition syndrome caused by germline variants in *TP53*. It is highly penetrant, with a lifetime risk of cancer approaching 70 % for males and 90 % for affected females [107,108]. Cancers commonly occurring in patients with LFS include sarcomas, particularly rhabdomyosarcoma and osteosarcoma, breast cancer, brain tumours, haematologic malignancies, and adrenocortical cancers. Sarcomas account for a quarter of the cancers in LFS, most of which occur before the age of 50 years [109]. Variants within *TP53* exons 5–8, encoding the DNA-binding domain, are associated with a higher risk of cancer and earlier age of onset [109]. Approximately 82–95 % of patients with pathogenic germline *TP53* variants will meet the revised Chompret clinical criteria for LFS, which are based on the proband's personal and family history of cancer [110,111]. However, in light of the relatively high de novo mutation rate [102], germline *TP53* testing should be considered in patients affected with certain types of sarcoma, particularly those affected at unexpectedly young ages, even in the absence of a family history of cancer. As genetic testing for cancer predisposition continues

Table 2
Heritable causes of sarcomas and/or NET.

Tumour type	Associated cancer predisposition syndrome (gene)
Sarcoma	
Osteosarcoma	Hereditary retinoblastoma (*RB1*)†
	Hereditary *TP53*-related cancer (Li-Fraumeni syndrome; *TP53*)†
	Hereditary non-polyposis colorectal cancer (Lynch syndrome; *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*)†
	Rothmund-Thomson syndrome II (*REQL4*)*
	Werner syndrome (*WRN*)*
	Bloom syndrome (*BLM*)*
	Diamond-Blackfan anaemia (*RPS5*†, *RPL11*†, *RPL35A*†, *RPS10*†, *RPS17*†, *RPS19*†, *RPS24*†, *RPS26*†, *GATA1*‡, *RPL15*†, *RPL18*†, *RPL26*†, *RPL27*†, *RPL31*†, *RPL35*†, *RPS7*†, *RPS15A*†, *RPS27*†, *RPS28*†, *RPS29*†, *TSR2*‡)
Desmoid fibromatosis	Familial adenomatous polyposis (*APC*)†
Leiomyosarcoma	Hereditary retinoblastoma (*RB1*)†
	FH tumour predisposition syndrome (hereditary leiomyomatosis and renal cell cancer syndrome, Reed syndrome; *FH*)†
Chondrosarcoma	Hereditary multiple osteochondromas (*EXT1*, *EXT2*)†
Malignant peripheral nerve sheath tumour	Neurofibromatosis type 1 (*NF1*)†
Rhabdomyosarcoma	Hereditary *TP53*-related cancer (Li-Fraumeni syndrome; *TP53*)†
	Neurofibromatosis type 1 (*NF1*)†
	Beckwith-Wiedemann syndrome (*CDKN1C*)†§
	Nijmegen breakage syndrome (*NBN*)*
	Werner syndrome (*WRN*)*
	Congenital mismatch repair deficiency (*MLH1*, *MSH2*, *MSH6*, *PMS2*)*
	DICER1 syndrome (*DICER1*)†
	Gorlin syndrome (*PTCH*, *SUFU*)†
	Mosaic-variegated aneuploidy (*BUB1B*)*
	Rasopathies (*PTPN11, SOS1, BRAF*)†
	Rubenstein-Taybi syndrome (*CREBBP, EP300*)†
GIST	Carney-Stratakis syndrome (*SDHx*)†
	Neurofibromatosis type 1 (*NF1*)†
	PDGFRA-associated familial GIST (*PDGFRA*)†
	KIT-associated familial GIST (*KIT*)†
Malignant rhabdoid tumour	Atypical teratoid rhabdoid tumour syndrome (*SMARCA4*, *SMARCB1*)†
Perivascular epithelioid cell tumour	Tuberous sclerosis (*TSC1*, *TSC2*)†
Liposarcoma	Hereditary *TP53*-related cancer (Li-Fraumeni syndrome; *TP53*)†
NET	
Gastroenteropancreatic NET	Neurofibromatosis type 1 (*NF1*)†
	von Hippel-Lindau syndrome (*VHL*)†
	MEN type 1 (*MEN1*)†
	MEN type 4 (*CDKN1B*)†
	Tuberous sclerosis (*TSC1*, *TSC2*)†
	Glucagon cell hyperplasia and neoplasia (Mahvash disease, *GCGR*)*
Paraganglioma/ phaeochromocytoma	Neurofibromatosis type 1 (*NF1*)†
	von Hippel-Lindau syndrome (*VHL*)†
	MEN type 2A/2B (*RET*)†
	Familial paraganglioma/phaeochromocytoma syndromes (*SDHA*, *SDHB*, *SDHC*, *SDHD**, *SDHAF2**, *TMEM127*, *MAX, MDH2*)†
	Polycythaemia-paraganglioma syndrome (*EPAS1*)†
Medullary thyroid cancer	MEN type 2A/2B (*RET*)†
	Familial medullary thyroid cancer (*RET*)†
Pituitary adenoma	MEN type 1 (*MEN1*)†
	AIP-related familial pituitary adenoma (*AIP*)
Parathyroid cancer	MEN type 2A/2B (*RET*)†
	CDC73-related disease (*CDC73*)†

†Autosomal dominant, *autosomal recessive, ‡X-linked, §imprinted, *parent-of-origin effect.

to evolve from single-gene testing to a broader approach involving multigene panel or whole-exome/genome sequencing, pathogenic germline *TP53* variants are increasingly being detected in patients that do not meet traditional diagnostic criteria for LFS. This has prompted the implementation of the term heritable *TP53*-related cancer to encompass LFS and more atypical phenotypes in carriers of such variants [112].

Patients affected by hereditary cancer predisposition are at high risk of metachronous multiple primary cancers [113]. Identification of an underlying germline variant in *TP53* can influence treatment planning as well as surveillance for subsequent new primary cancers. Treatment with radio- and/or chemotherapy may add to the excess risk of second and subsequent primary malignancies [114–116]. Therefore, surgery with curative intent is favoured, as long as such an approach is not inferior to standard treatment options [117]. Similarly, patients with pathogenic germline variants in *RB1* are at high risk of second primary cancers, most commonly osteo- or leiomyosarcoma, after diagnosis of retinoblastoma, particularly those treated with external beam radiotherapy [118]. Second primary cancers in such individuals have been reported to occur both within and outside the radiotherapy field [119,120]. Individuals with cancers due to DNA repair defects are particularly susceptible to radiotherapy-related second primary malignancies, as well as to excess toxicity to treatment [121,122].

Screening for individuals at high risk of sarcoma is challenging given the potentially diverse cancer phenotype. A number of studies have demonstrated the utility of whole-body magnetic resonance imaging in the early detection of potentially curable cancers in patients with LFS [123,124], leading to improved survival [125]. Patients should be educated with respect to symptomatic awareness, and health care providers should provide an "open door" policy for at-risk patients with early investigation of any new symptoms.

More recently, a number of studies have identified an excess of pathogenic variants in DNA repair genes in individuals affected with sarcoma, including genes more typically associated with predisposition to other solid organ cancers, such as *PALB2*, *BRCA2*, and *ATM* [106,126,127]. Further research is warranted to explore the aetiologic significance and therapeutic implications of such variants. Osteosarcoma has also recently been recognised as a Lynch syndrome-associated cancer [128]. A proportion of the heritable risk of sarcoma may be accounted for by common low-penetrance polymorphisms. Several sarcoma predisposition loci have been identified by genome-wide association studies [129–133]. Further research is required before polygenic risk scores using information from low-risk loci can be translated to clinical risk estimation.

3.2. Genetic predisposition to NET

NET are among the most heritable malignancies. The contribution of germline predisposition varies between tumours of different types and locations. Approximately 35 % of paragangliomas/phaeochromocytomas are due to an underlying cancer predisposition syndrome, compared to 20 % of gastroenteropancreatic NET and 5 % of pulmonary/thymic NET [134]. Several NET-predisposing syndromes have been defined, which are associated with a high lifetime risk of benign and malignant neuroendocrine disease, and some of which are associated with increased risk of other solid organ cancers or other non-neoplastic features. Gain-of-function germline variants in *RET* are associated with MEN types 2A and 2B and confer high lifetime risks of medullary thyroid tumours, phaeochromocytoma, and parathyroid disease. Compared to MEN2A, MEN2B is more likely to arise de novo [104]. MEN2B is also less likely to be associated with parathyroid disease and more likely aggressive medullary thyroid cancer. MEN2B also has additional features, including mucosal neuromas, marfanoid habitus, and hypermobility. In certain families, the phenotype associated with a germline *RET* variant is restricted to medullary thyroid cancer (familial medullary thyroid cancer). A number of genotype-phenotype correlations have been established, with certain genotypes predisposing to a high risk of

very early-onset medullary thyroid cancer [135]. Presymptomatic carriers of germline *RET* variants are advised to have early prophylactic thyroidectomy. The age at which this is recommended should be guided by the genotype, the family history, and baseline calcitonin levels [136]. The age at which biochemical and radiologic surveillance for parathyroid and adrenal disease should commence is also guided by age and should be introduced from as young as eight years of age for those at highest risk.

Other heritable causes of phaeochromocytoma include germline variants in *VHL* (von Hippel- Lindau syndrome), *NF1* (neurofibromatosis type 1 [NF1]), *MAX*, *TMEM127*, or rarely *MDH2* or *FH* (FH tumour predisposition syndrome, hereditary leiomyomatosis and renal cell cancer [137]). Variants in other genes, including those encoding subunits of the succinate dehydrogenase (SDH) complex, are more likely to be associated with paraganglioma than phaeochromocytoma. Surveillance protocols and age at which they should commence are gene-specific [138,139]. Some variants, including those in *SDHD,* and possibly those in *SDHAF2*, and *MAX*, are associated with a parent-of-origin effect, and surveillance in presymptomatic carriers will depend on whether the variant allele is maternally or paternally derived. Carriers of pathogenic variants in one of the *SDH* genes may also be at risk of GIST as part of Carney-Stratakis syndrome.

The most common heritable cause of gastroenteropancreatic NET is MEN type 1, caused by germline variants in the *MEN1* gene [134]. This condition is clinically indistinguishable from MEN type 4, caused by germline variants in *CDKN1B* [140]. Most MEN1-associated NET are non-functional, but gastrinomas and consequent Zollinger-Ellison syndrome are commonly reported, as are insulinomas and less frequently glucagonomas or VIPomas [141]. Other MEN1-associated tumours include neoplasms of the anterior pituitary and parathyroid glands, bronchopulmonary carcinoids, and, less commonly, gastric or thymic carcinoids or adrenal disease. Because of the variability in presentation of such tumours, the reported family history may often be vague or non-specific, e.g., gastric ulcers, kidney stones, etc.

NET, particularly in the duodenum, has also been reported in patients with NF1, as have phaeochromocytomas, GIST, malignant peripheral nerve sheath tumours, and other solid organ cancers. NF1 is a relatively common cancer predisposition syndrome, occurring with an estimated population frequency of 1/3000 [142]. Cutaneous features are ubiquitous, with affected individuals demonstrating café au lait spots, axillary and inguinal freckling, and neurofibromas. De novo cases are common, as is mosaicism, which may present with segmental manifestation of disease. Careful genetic counselling is required in such families, as the progeny of individuals with segmental NF1 may still have up to 50 % risk of inheriting the condition, depending on the level of gonadal mosaicism in the affected parent [143].

Identifying a cancer predisposition syndrome in a family facilitates personalised treatment and surveillance of the proband and their at-risk relatives, minimising the morbidity and mortality associated with these rare tumours. Furthermore, the risk of transmission to progeny can be mitigated by providing access to pre-implantation or prenatal testing.

4. Conclusions

The large and heterogeneous group of rare cancers has long received too little attention. This is also reflected by the fact that precision oncology approaches in these diseases – with notable exceptions such as GIST – are less mature than in common entities. This gap is being closed in recent years as the molecular pathogenesis of many rare cancers is increasingly explored, and, as described in this article using sarcomas and NET as examples, the findings are being exploited to enable more precise diagnosis and develop novel molecular mechanism-aware treatment strategies. Progress in the complex clinical management of rare cancers also illustrates the tremendous importance of multidisciplinary collaboration within dedicated centres of expertise, which are increasingly organising themselves into European reference networks [144]. To date, molecularly informed precision oncology approaches in rare cancers have been mostly reserved for patients with advanced disease stages and after standard therapy has been exhausted, leading to missing important clinical signals and thus compromising the added value of advanced profiling technologies. As costs decrease and understanding of its clinical importance grows, comprehensive molecular profiling can hopefully be integrated earlier into the diagnosis, risk stratification, and treatment planning of patients with rare cancers. In this way, early genetic counselling of families with pathogenic germline alterations can also be organised, and patients who are still able to optimally benefit from precision medicine can be enrolled in clinical trials. Finally, precision medicine in rare cancers requires a willingness to collaborate nationally and internationally to provide the best possible individualised diagnostics, treatment, and, if applicable, prevention strategies for familial cancer syndromes to all those affected by a disease that most people have never heard of. In addition, by collecting data from these patients, insights can be gained into biology and the prognosis and optimal treatment of even very rare subtypes of rare cancers – the centrepiece of knowledge-generating care, which is particularly relevant in these diseases.

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