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Solutions for optimal care and research for children and adolescents with extremely rare cancers developed within the Joint Action for Rare Cancers (JARC)

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ABSTRACT

Very rare cancers in children and adolescents pose a unique challenge for optimal care and research. Due to their rarity and diversity, there is a lack of standardized treatments and limited data to guide clinical decision-making. This paper aims to provide solutions for addressing these challenges through a multidisciplinary approach involving clinicians, researchers, and patient advocates. In recent years, members of the European Cooperative Study Group for Paediatric Rare Tumors (EXPeRT) and members of the European Society of Pediatric Oncology (SIOPE) clinical council worked within the EU Joint Action on Rare Cancers (JARC) and the Paed Can European Reference Network (ERN) on solutions to improve the care and research in the field. This includes a better classification, more financial resources, higher awareness and support by stakeholders, an international database, as well as harmonized diagnostic and therapeutic guidelines. Further research projects in the field of molecular biology, a better collaboration between medical oncologists and pediatricians, and a general strategy to facilitate access to modern therapies are urgently needed.

1. Introduction

Pediatric very rare tumors (VRTs) in children and adolescents are characterized by low incidence rates defined as those with an incidence of less than two cases per million per year [1]. Among pediatric cancers, some particularly rare tumors (such as pancreatoblastoma, salivary gland carcinomas, NUT carcinoma, colorectal carcinoma) were not included in any clinical registries or national and international treatment protocols. These so-called VRTs have historically attracted little clinical or research interest. Their rarity and heterogeneity have made it nearly impossible to conduct clinical trials to develop effective treatments in a reasonable amount of time. Yet, these entities often have unique clinical and biological features that remain largely misunderstood and complicate their treatment. Thus, due to their rarity, there is a lack of evidence-based guidelines for their management, and clinical decision-making is often based on anecdotal experience rather than large scientific data.

The gap in clinical and scientific knowledge about pediatric VRTs was recognized in Europe in the first decade of the new millennium. National cooperative groups focusing on pediatric VRTs have been established in several European countries, including Italy (2000) [2], Poland (2002) [3], Germany (2006) [4], France (2007) [5], and the United Kingdom (1997) [6]. Although their organizational plans and levels of activity varied widely, their experiences have strengthened collaborative networking and underscored the need to create larger international cooperative group with prospects for further improvement. With this in mind, the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) was established in 2008 with the main goal of developing international clinical and biological research on pediatric VRTs. Early EXPeRT achievements included the introduction of a virtual tumor board composed of experts who provide their expertise to the clinicians in charge, and the publication of several combined registry data for specific very rare entities in children and adolescents followed by recommendations on their diagnosis and treatment (Table 1).

In recent years, as for other pediatric tumors, it became (more and more) evident that not only pediatric oncologists and researchers, but epidemiologists, surgeons, pathologists, adult oncologists, and other specialists in various fields, as well as patient advocates, regulatory authorities, funding councils, patients' advocates, industry and information technology specialists, need to join forces to build stronger structures to improve the management of children and adolescents with VRTs. With the support from the European Society for Pediatric Oncology (SIOPE), EXPeRT has participated in several important collaborative European Union (EU)-funded projects: ExPO-r-Net (European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment; 2014–2017), JARC (Joint Action on Rare Cancers; 2016–2019), and PARTNER (Paediatric Rare Tumors Network European Registry) as a part of ERN PaedCan (European Reference Network on Paediatric Cancer; 2018–2021). These projects brought the work of the EXPeRT Group to a new level.

The purpose of this publication is to highlight the achievements of JARC Work package WP9, Deliverable D9.4, Task 9.3 collaborative group headed by German Society of Paediatric Oncology (GPOH) that focused on proposals to address pediatric VRTs. The Deliverable was part of the joint action "724161/JARC" which had received funding from the European Union's Health Program (2014–2020). The paper shares the report summarizing proposals to address extremely rare cancers in young patients developed by the EXPeRT within the JARC initiative. Possible solutions for optimal care and research for children and adolescents with extremely rare cancers will be presented.

1.1. EU joint action on rare cancers (JARC)

JARC was a 3-year initiative (October 2016 – October 2019) that aimed to integrate and maximize the efforts of the EU Commission, EU Member States and all stakeholders to prioritize and advance quality of care and research on rare cancers in adults and children. In adults, rare cancers are categorized in the group of orphan diseases, which are defined in the EU as those affecting fewer than 5 people in 10,000. The project Surveillance of Rare Cancers in Europe (RARECARE) developed a new list of 186 rare cancers and redefined rare cancers as those with an incidence of less than 6/100,000 persons/year. Based on this definition, the estimated annual incidence rate of all rare cancers in adults in Europe was about 108/100,000, corresponding to 541,000 new cases annually or 22% of all cancers. This definition considers all pediatric cancers as "rare" [1].

Rare cancers generally face specific challenges including late and incorrect diagnosis, limited professional expertise, lack of research interest, the shortage of new innovative medicines, poorer survival rates, scanty epidemiological studies, and the lack of interest from the economic and political community. With this in mind, JARC was instrumental in supporting the establishment of the European reference networks for rare cancers and in optimizing the process of their development on the areas of quality of care, epidemiology, research and innovation, innovation and state of the art definition on diagnosis and treatment of rare cancers. JARC included 18 member states and 34 partners including Ministries of Health, public health institutions, oncological institutes, universities, cancer registries, patients' associations and professional societies, coordinated by the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan, Italy.

Six specific objectives of JARC were: improving epidemiological surveillance of rare cancers in the EU; identifying standards of care for all families of rare cancers to ensure sharing of best practices and equality of care for rare cancers across Europe, particularly through clinical networking; improving the implementation at local level and within European Reference Networks (ERNs) of clinical practice guidelines on rare cancers; promoting integration of translational research innovations into rare cancer care; improving education on rare cancers for medical and non-medical experts to ameliorate management of rare cancers and to improve rare cancer patients' empowerment in the

Table 1
Retrospective analyses and recommendations on diagnosis and treatment of the EXPeRT.

Publication and VRT	Series	Main results	Recommendations
Bien et al., 2011[7] **Pancreatoblastoma**	20 patients study period 2000–2009	5-year EFS 58.8%, OS 79.4% rate of response to chemotherapy 73% outcome correlates with complete surgical excision	Bien et al., 2021[8]
Schneider et al., 2015[9] **Sertoli-Leydig Cell Tumors**	44 patients study period 1993–2008 (depending on the country)	5-year EFS 70%, OS 87% stage, histopathological differentiation and intra/preoperative rupture or positive ascites determine prognosis impact of chemotherapy in incompletely resected and advanced stages still to be assessed	Schneider et al., 2021 [10]
Bisogno et al., 2014[11] **Pleuropulmonary blastoma**	65 patients study period 2000–2009	Type I: 5-year EFS 83.3% OS 91.7%. Type II/III: 5-year EFS 42.9% OS 57.5% favourable prognostic factors: complete tumour resection at diagnosis and absence of invasiveness role of doxorubicin-based chemotherapy in type II/III type (5-year EFS 70% vs 31.3% in patients with or without doxorubicin-based regimens)	Bisogno et al., 2021[12]
Stachowicz-Stencel et al., 2014 [13] **Thymoma and thymic carcinoma**	36 patients 16 thymomas and 20 thymic carcinomas study period 2000–2012	16 thymomas: 14 pts are alive with no evidence of disease 20 carcinomas: 5 patients alive, 5-year OS 21% surgical R0 resection: milestone of treatment role of chemotherapy is unclear	Stachowicz-Stencel et al., 2021[14]
Cecchetto et al., 2017[15] **Adrenocortical carcinomas**	82 patients study period 2000–2013	3-year EFS 38.8%, OS 54.7% survival rates influenced by distant metastases, tumour volume, lymph node involvement, age, vascular involvement and incomplete surgery for localized disease alone: EFS 51.1% OS 73% surgery if R0 achievable; if not, neoadjuvant chemotherapy with various regimens and delayed surgery in case of response)	Virgone et al., 2021[16]
Brecht et al., 2018[17] **Melanoma**	219 patients study period 2002–2012	3-year EFS 84.0%, OS 91.4% AJCC staging system: 42.5% stage I, 26.9% stage II, 20.1% stage III, 4.6% stage IV Prognostic factors: site of origin, ulceration status, histology, T-status, N-status, AJCC stage Patients treated by paediatric oncologists (n = 140) were more likely to have advanced disease than those treated by dermatologists (n = 79) (N1 were 31% and 12%, respectively, p = 0.0029).	Ferrari et al., 2021[18]
Abele et al., 2022[19] **Lung carcinoma**	38 patients study period 2000–2021	3-year OS mucoepidermoid carcinoma 95% 3-year OS adenocarcinoma / squamous cell carcinoma 60% Clinical characterisation Identification of possible prognostic factors Identification of common treatment strategy, proposal for multimodal treatment approach	To be followed
Schneider et al., 2023 (published in this series) **Salivary gland tumours**	121 patients study period 2000–2014	14 relapses occurred and 5 patients died Higher histological tumor grade was associated with advanced local tumor stage, incomplete resection and risk of recurrence	Surun et al., 2021[20]
Nasopharyngeal carcinoma			Ben-Ami et al. 2021[21]
NUT Carcinoma			Lemelle et al. 2023[22]

Abbreviations: EFS - event-free survival; OS - overall survival

EU; and identifying core strategies to incorporate in National cancer plans and Rare disease plans to address the specific needs of rare cancers across EU Member States (Table 2) [23].

1.2. Joint actions on childhood cancers

The JARC Work Package on Childhood Cancers (WP9) contained actions to define collaborative measures for ensuring access to standard and innovative therapies for children with cancer, and to address the research and clinical issues of young people with VRTs and of survivors of childhood cancers. It was coordinated by SIOPE with the participation of 24 partners. SIOPE closely worked with the European Committee of Childhood Cancer International (CCI) Europe, the biggest pan-European organization representing childhood cancer parents, patients and survivors in a continuation of a long-term and instrumental partnership. JARC has been the opportunity to advance key objectives of the SIOPE Strategic Plan, developed in cooperation with parents, patients and survivors, and to build on achievements of some previous EU projects where SIOPE played a key role: the European Network for Cancer Research in Children and Adolescents (ENCCA), ExPO-r-Net, PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup), and the European Partnership for Action Against Cancer (EPAAC). It was also set to further strengthen the existing cooperation between pediatric and adult oncology (strategic plan of SIOPE https://siope.eu/news/siop-europe-strategic-plan-update-2021–2026/).

1.3. Proposals to address extremely rare cancers in young patients

The aim of the task 9.3 was to "Identify solutions for optimal care and research for young people with extremely rare cancers". Several important aspects requiring improvement were identified: definition, classification and epidemiology; awareness and support; building a common European database; diagnostic and therapeutic guidelines; etiology and research; and access to modern therapies.

The target group was stakeholders involved in decision-making on health research, healthcare organization and delivery in the field of pediatric oncology both at the national and at the EU level. The task leader was the German Society of Paediatric Oncology – represented by the University of Tuebingen, and the work was performed in collaboration with SIOPE (representing the pan-European professional community working in the field of childhood cancers), CCI Europe (representing the pan-European childhood cancer parents' and survivors' organization), EXPeRT (representing the only dedicated international VRT network) and RARECAREnet (representing the largest information network on rare cancers database).

The first phase of the JARC coincided with the consolidation of the synergic ExPO-r-NeT project and its WP8 led by Azienda Ospedaliera di Padova, Italy: Integrating children with VRTs in a European Reference Network. The activities were undertaken to identify centers of reference, formulate and implement standard of care guidelines, offer consultancy services to European centers of pediatric oncology, allow the exchange

Table 2
The JARC book "Rare Cancer Agenda 2030": Citation of "Ten Recommendations from the EU Joint Action on Rare Cancers"[23].

Ten Recommendations from the JARC:
1. Rare cancers are the rare diseases of oncology
2. Rare cancers should be monitored
3. Health systems should exploit networking
4. Medical education should exploit and serve healthcare networking
5. Research should be fostered by networking and should take into account an expected higher degree of uncertainty
6. Patient-physician shared clinical decision-making should be especially valued
7. Appropriate state-of-the-art instruments should be developed in rare cancer
8. Regulation on rare cancers should tolerate a higher degree of uncertainty
9. Policy strategies on rare cancers and sustainability of interventions should be based on networking
Rare cancer patients should be engaged

of data between centers, and planning of clinical and biological studies. A face-to-face meeting of ExPO-r-NeT WP8 with the participation of JARC WP4 (Epidemiology) coordinator took place in March 2017 in Padua to streamline the approach and transition between project activities. Second face-to-face meeting on pediatric VRTs took place in November, 2017 in Frankfurt, Germany. Core areas of the work with the EXPeRT group, CCI Europe, and the National Tumor Institute of Milan were debated and future orientations for the outcome recommendations report on extremely rare tumors in children and adolescents were identified. The main activities were carried out in the following areas, which reflect the most important aspects that can improve the care of rare childhood tumors:

1.3.1. Definition, classification and epidemiology

VRTs are defined by their status as orphan diseases. The EXPeRT defined VRTs of pediatric age as "any malignancy characterized by an annual incidence of < 2 per million in the population up to 18-years old and not considered in other trials". In order to confirm this definition and better understand the spectrum of entities and epidemiology of pediatric VRTs, a list of all rare entities and a report on incidences in Europe was prepared and published by Ferrari et al. [1]. The data was received through the database of the RARECAREnet project (83 European databases, 2000–2007). The results show that 11% of all cancers in patients aged 0–14 years represent a group of VRTs. Two subgroups were identified: tumor types typical for childhood (i.e. hepatoblastoma, pleuropulmonary blastoma, pancreatoblastoma) and those typical for adult age (i.e. carcinomas, melanoma). Using a lower threshold (< 1 per million) excluded extragonadal germ cell tumors, skin melanoma, hepatoblastoma, thyroid carcinoma and non-epithelial ovarian tumors from VRT list. Using higher cut-off led to the inclusion of tumors typical for pediatric age in the VRT group (i.e. rhabdomyosarcoma, Ewing sarcoma and osteosarcoma have an incidence rate of 4.4, 2.8 and 3/1.000.000, respectively, in the 0–14 years group). The threshold of 2/1.000.000 could also be adopted in the population aged 0–19 years: in this case, three tumor types had an incidence rate which was $> 2/1.000.000$ (i.e. thyroid cancer, testicular cancer and skin melanoma), but the consensus experts considered them as 'very rare' according to their clinical needs (e.g. shortage of knowledge and clinical expertise as the other rare pediatric cancers) (Table 3).

1.3.2. Awareness and support

Key partners in the field of rare cancers are patient advocacy groups. They can help to disseminate information, support recruitment of patients, promote the structures for patient care, and play a role in the regulatory process. In collaboration with CCI Europe, a questionnaire was designed to collect experiences and perception of parents across Europe on VRT structures and needs at the national level. The survey was launched in March, 2018. It was sent to all European members of CCI (60 member organizations in 33 countries). A total of 35 individuals from 15 countries (Austria, Belgium, Bulgaria, Croatia, United Kingdom, France, Germany, Greece, Ireland, Italy, Romania, Serbia, Slovakia, Spain, and Sweden) took part in the survey. Overall, 63% of all participating individuals did not know of any patient groups for VRTs in children. However, only one of these groups fell precisely within the scope of VRTs in children (Grace Kelly Ladybird Trust, www.gkcct.org). In addition, 29 respondents (59%) did not know of any professional networks, registries or working groups for very rare childhood cancers; 31% knew of specific working groups in their country; 24% knew of professional networks for rare childhood cancers in primary care; 17% knew of registries in their country. Specific professional networks/registries/working groups for very rare childhood cancers mentioned were the EXPeRT, the German Rare Pediatric Tumor Group (STEP), the French Very Rare Cancer Registry Working Group (FRACTURE), and the Italian Rare Pediatric Tumor Group (TREP). Most participants (81%) felt

Table 3
Number of observed cases in the RARECAREnet database in the period 2000–2007, incidence rate $< 2{,}000{,}000$, in children (0–14 years at diagnosis), modified according to Ferrari et al. [1].

Cancer entities with incidence rate $< 2000{,}000$, In children (0–14 years at diagnosis)	Incidence rate
Extragonadal germ cell tumours	1.864
Malignant skin melanoma	1.327
Hepatoblastoma	1.254
Carcinomas of thyroid gland	1.201
Non-epithelial tumours of ovary	1.155
Myeloproliferative neoplasms	1.022
Neuroendocrine tumours	0.972
Myelodysplastic syndrome and Myelodysplastic / Myeloproliferative diseases	0.869
Histiocytic and dendritic cell neoplasms	0.827
Testicular and paratesticular cancers	0.801
Epithelial tumours of skin	0.557
Epithelial tumours of major salivary glands and salivary-gland type tumours	0.435
Epithelial tumours of liver and intrahepatic bile tract	0.347
Epithelial tumours of kidney	0.313
Carcinoma of adrenal gland	0.313
Epithelial tumours of lung	0.107
Epithelial tumours of oral cavity and lip	0.080
Epithelial tumours of nasopharynx	0.065
Malignant melanoma of uvea	0.053
Epithelial tumours of colon	0.050
Olfactory neuroblastoma	0.050
Epithelial tumours of hypopharynx and larynx	0.046
Carcinomas of pituitary gland	0.042
Epithelial tumours of stomach	0.038
Adnexal carcinoma of skin	0.038
Epithelial tumour of ovary and fallopian tube	0.034
Epithelial tumours of bladder	0.034
Epithelial tumours of nasal cavity and sinuses	0.031
Pleuropulmonary blastoma	0.031
Epithelial tumours of pancreas	0.027
Kaposis sarcoma	0.027
Pancreatoblastoma	0.023
Epithelial tumours of thymus	0.019
Malignant melanoma of mucosa	0.019
Epithelial tumours of oropharynx	0.015
Epithelial tumours of rectum	0.015
Epithelial tumours of pelvis and ureter	0.015
Epithelial tumours of eye and adnexa	0.011
Epithelial tumours of small intestine	0.008
Epithelial tumours of trachea	0.008
Epithelial tumours of vulva and vagina	0.008
Epithelial tumours of prostate	0.008
Gastrointestinal stromal sarcoma (GIST)	0.008
Epithelial tumours of oesophagus	0.004
Epithelial tumours of anal canal	0.004
Epithelial tumours of gallbladder and extrahepatic biliary tract	0.004
Epithelial tumours of corpus uteri	0.004
Epithelial tumours of cervix uteri	0.004
Trophoblastic tumours of placenta	0.004
Malignant mesothelioma	0.004
Odontogenic malignant tumours	0.004

that specific actions for pediatric VRTs were still needed in their country. Reasons cited included: the lack of a community truly knowledgeable about rare childhood cancers with skills to advocate with policymakers for awareness, funding, close collaboration with physicians, registries, participation in early clinical trials, research, education of families and healthcare providers, clinical guidelines, establishment of centers specialized in the treatment of rare childhood tumors, support for survivors, psychological support, and international networking. The EXPeRT has set itself the task of improving these aspects and strengthening the participation of patient groups. First steps have been taken in this regard in cooperation with CCI.

1.3.3. Building a common European database

Rarity can be overcome by joining forces. The PARTNER (Paediatric Rare Tumours Network – European Registry) was a 4-year EU-funded project running from January 2018 to December 2021 [24]. It aimed to create a Paediatric Rare Tumour European Registry dedicated to children and adolescents with VRTs linking existing national registries, and to provide a registry for countries that do not yet have VRT registries. The registry started to recruit first patients in 2022.

1.3.4. Diagnostic and therapeutic guidelines

Most VRTs in children and adolescents, although so-called "adult-type" tumors, show a different biological behavior. Therefore, treatment concepts from adult medicine cannot simply be applied to pediatric population [17,25]. Besides, diagnosis of VRTs might be difficult in children. Furthermore, drugs or drug combinations applied in adults may not be familiar to pediatric oncologists, and toxicity in children has been studied extremely rarely (few phase I/II studies). Due to the rarity, prospective randomized comparative clinical studies are extremely difficult to perform. The strategic value of PARTNER in the field of public health is based on the European wide gathering of information on the treatment of VRTs and the provision of this information to experts generating new guidance recommendations, considering also adults' experience in the same disease if it exists, for daily practice use by ERN and non-ERN institutions. The data collection contributes to optimized consultation of patients with VRTs. Within the PARTNER project recommendations for diagnosis and treatment were worked out and published (Table 1).

1.3.5. Etiology and research

Etiopathogenesis of VRTs in children and adolescents is widely unclear due to barriers for dedicated biological studies resulting from their rarity (e.g. missing tumor samples). Differences in tumorigenesis in VRTs compared to classical (embryonal) tumors of childhood or adulthood are very likely [26], but detailed studies are rare. VRTs include a large variety of so-called adult-type tumors that occur frequently in adults but very rare in children (e.g. epithelial cancer like salivary gland tumors, colorectal carcinoma). Only limited clinical and biological information is available for VRTs [1,27]. For several rare tumors/adult-type tumors occurring in childhood (e.g. carcinomas), a germline genetic susceptibility has been identified in sporadic cases. Therefore, it is estimated that the frequency of cancer predisposition is higher in pediatric VRTs compared to adults and it is likely that undiscovered pathogenic germline variants and background genetic factors contribute to the development of rare childhood cancers in conjunction with non-genetic risk factors [28]. However, it is not yet clear, why tumorigenesis in adults usually takes several decades and the majority are epithelial tumors (carcinomas) while pediatric malignancies usually develop within months or a few years and the majority are primitive (blastic) or mesenchymal (sarcomas) in origin. VRTs in young patients have not been included in large cancer genome projects, even though there is growing evidence that VRTs are not biologically comparable to histologically identical tumors in adults, which in turn poses major challenges for definition of prognostic factors and therapy. Thus, the molecular pathogenesis of carcinomas as rare pediatric malignancies remains obscure and several rare tumor working groups seek to further advance the research in the field and projects have been launched. In the future, we need to join forces on a European level, probably in collaboration with adults' biologic programs, in order to reach sufficient number of patients. Significant dedicated financial support is therefore needed.

1.3.6. Access to modern therapies

There is a long-standing and urgent need for new drugs for pediatric rare tumors. As for many advanced-stage rare tumors in children and adolescents, few evidence-based treatment concepts are available. There is a special need for new therapy options, as there are very limited options for innovative treatment. Due to their rarity, very few phase I / II trials are offered for VRTs, and therefore lacking strength of evidence. In addition, therapies for pediatric rare cancers do not easily fit into the regulatory system. However, targeted therapies addressing cancer specific genetic alterations, and immunotherapies have demonstrated enormous potential for clinical translation. Especially in very rare cancers, targeted approaches might offer an overarching strategy to group phenotypically and genetically diverse diseases based on shared targets.

Knowledge of the mutational and transcriptomic landscape of tumors as well as the expression of antigenic patterns is a prerequisite for the development of effective biological therapies as immunotherapeutic approaches and other targeted therapies. Research in this area will therefore provide a basis for further exploration of advanced therapeutic approaches. In this context, it is important to form an alliance with adult medicine and, for example, to participate jointly in European calls to form a patient population that includes both adults and pediatric tumors. In this setting, adult oncologists and researchers can benefit from the close network in pediatric oncology and the strong will of scientists, parents, and patients to advance research. This leads to a high rate of approval among those affected and makes research feasible despite its rarity in pediatrics.

Furthermore, in the future, pediatric rare tumors should be consistently analyzed not only by histology, but rather by pathological molecular pathways, as is case in MAPPYACTS Study [29], INFORM registry [30] and other European molecular testing programs. These analyses could facilitate the inclusion of patients with very rare pediatric cancers in specific phase I-II trials or in multi-arms trials as AcSè -ESMART (NCT0281315) or INFORM2 (NCT03838042). In addition, by identifying common therapeutic targets, further "tumor-agnostic" basket trials could be set up and approvals granted across entities, as has already been done for the NTRK inhibitor larotrectinib [31]. In this way, more tumors can be considered together and the problem of rarity can be overcome. It is important not to exclude young patients with rare cancers from scientific achievements and treatment advances.

2. Conclusions

Pediatric VRTs had long attracted little interest because their rarity made it nearly impossible for researchers to produce results of value within a reasonable period. Working with VRTs has meant facing many drawbacks: the lack of interest from the scientific, business, and political communities, the lack of funding, and the lack of colleagues with whom to share ideas and projects. In the last years, members of the EXPeRT worked within the JARC and the ERNs on solutions to improve care and research in the field. However, a better classification, more financial resources, awareness and support by stakeholders, an international database, diagnostic and therapeutic guidelines, further research projects in the field of molecular biology, and a strategy how to access to modern therapies are urgently needed. There is a need to reinforce the collaboration between pediatric oncologists and experienced adult oncologists for adult-type pediatric VRTs. Joint forces at the European level, including intensive collaboration among medical, scientific, technological, pharmaceutical and patient communities, have been and remain a high priority in the field of VRTs. Financial support for rare

cancer research, encompassing basic, pre-clinical, clinical and 'back-to-the-bench' studies, is indispensable.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent statement

Not applicable.

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