Received: 5 February 2021 | Revised: 15 February 2021 | Accepted: 17 February 2021

DOI: 10.1002/pbc.28993

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

SUPPLEMENT ARTICLE

# Facing the challenges of very rare tumors of pediatric age: The European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) background, goals, and achievements

Andrea Ferrari[1] | Dominik T. Schneider[2] | Gianni Bisogno[3] | Yves Reguerre[4] | Jan Godzinski[5,6] | Ewa Bien[7] | Teresa Stachowicz-Stencel[7] | Giovanni Cecchetto[8] | Bernadette Brennan[9] | Jelena Roganovic[10] | Tal Ben-Ami[11] | Calogero Virgone[8] | Nuno Reis Farinha[12] | Serena Mancini[3] | Daniel Orbach[13] | Ines B. Brecht[14]

[1] Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy

[2] Clinic of Pediatrics, Dortmund Municipal Hospital, Dortmund, Germany

[3] Hematology-Oncology Division, Department of Women's and Children's Health, Padova University Hospital, Padua, Italy

[4] Pediatric Hematology-Oncology Department, Centre Hospitalier Universitaire, Saint Denis de La Réunion, France

[5] Department of Pediatric Surgery, Marciniak Hospital, Wroclaw, Poland

[6] Department of Pediatric Traumatology and Emergency Medicine, Wroclaw Medical University, Wroclaw, Poland

[7] Department of Pediatrics, Hematology and Oncology, Medical University, Gdansk, Poland

[8] Pediatric Surgery, Department of Women's and Children's Health, Padova University Hospital, Padua, Italy

[9] Department of Pediatric Oncology, Royal Manchester Children's Hospital, Manchester, UK

[10] Department of Pediatrics, Clinical Hospital Centre Rijeka, Rijeka, Croatia

[11] Pediatric Hematology Unit, Kaplan Medical Center, Rehovot, Israel

[12] Pediatric Oncology Unit, Hospital S. João, Porto, Portugal

[13] SIREDO Oncology Center (Care, Innovation and Research for Children, Adolescents and Young Adults with Cancer), Institut Curie, PSL University, Paris, France

[14] Pediatric Hematology and Oncology, Children's Hospital, Eberhard-Karls-Universitaet Tuebingen, Tuebingen, Germany

**Correspondence**
Andrea Ferrari, Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Via G. Venezian, 1, 20133 Milano, MI, Italy.
Email: andrea.ferrari@istitutotumori.mi.it

**Funding information**
HP-PJ-06-2016: Rare diseases - support for New Registries, Grant/Award Number: CHAFEA Grant Nr: 777336

## Abstract

It has become increasingly clear in recent years that we need to develop ad hoc strategies to combat very rare tumors (VRT) of pediatric age. In 2008, several schemes being run in different countries were pooled together to create the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) project: a cooperative study group that aimed to promote research in the relatively uncharted territory of rare tumors of pediatric age. EXPeRT members were able to activate different levels of cooperation to achieve their goals, and to obtain dedicated funding by participating in EU-financed projects. Their experiences emphasize the merits of networking, seeking new partnerships, joining forces, and pooling resources to extend the reach of research efforts, and ultimately improve the quality of patient care. Between 2018 and 2021, the EXPeRT has been active in establishing the Pediatric Rare Tumors Network - European

**Abbreviations:** EXPeRT, European Cooperative Study Group for Pediatric Rare Tumors; ExPO-r-Net, European Expert Pediatric Oncology Reference Network for Diagnostics and Treatment; JARC, Joint Action on Rare Cancers; PARTNER, Pediatric Rare Tumors Network - European Registry; VRT, very rare tumor

Registry (PARTNER). This project had the main purposes of building a European common registry of pediatric VRT, but also the major task of developing diagnostic and treatment guidelines for VRT (or at least part of them). These clinical recommendations are the subject of a series of papers on Pediatric Blood and Cancer.

**KEYWORDS**
adolescents, children, EXPeRT, ExPO-r-Net, international case registry, JARC, PARTNER, treatment recommendations, very rare tumors, virtual consultation system

## 1 | INTRODUCTION

Pediatric cancers are always rare, in as much as they meet the criterion of an incidence of <6/100,000 population a year.[1,2] That explains why pediatric oncologists have always taken effort and joined resources to develop national and international research and cooperative treatment protocols. This approach has enabled us to advance our knowledge and improve patient survival rates for many tumors affecting children and adolescents.[3] That said, among pediatric cancers, there is a set of diseases that are encountered so rarely that the patients affected have yet to benefit from the fruits of large-scale pediatric oncology networking. They are the so-called very rare tumors (VRT) of pediatric age, and their common denominator lies in the lack of knowlegde typical of orphan diseases.[4]

Pediatric VRT include a very diverse assortment of neoplasms. Some of them only ever occur in children (such as pleuropulmonary blastoma or pancreatoblastoma). Others (such as carcinomas) are relatively common in adults, but extremely unusual in pediatric age. Years ago, VRT generally attracted little interest: very few specific projects were developed, and little or no effort was made to establish any shared treatment guidelines. The young patients involved were consequently treated in various different ways and on an individual approach. In short, the combined rarity of their tumors and shortage of dedicated research negatively affected their chances of cure.[5]

This situation changed after the turn of the century. As the pediatric oncology community became increasingly aware of the problem, VRT began to attract the attention of cooperative groups of researchers in the early 2000s.[6] The strategies developed to focus on VRT followed two different models. One approach (adopted mainly in the United States) involved setting up dedicated tumor registries for each type of disease, such as the International Pediatric Adrenocortical Tumor Registry (IPACTR),[7] or the International Pleuropulmonary Blastoma Registry (IPPBR).[8] The alternative approach (preferred in Europe) was based on developing large cooperative projects/networks with a view to enrolling all rare tumors (or at least a lengthy list of them), adopting a common framework, and a centralized coordination and data registration.

The establishment of Europe's various national cooperative programs began with the Italian Tumori Rari in Età Pediatrica (TREP), which was launched in 2000.[4] It was followed by the Polish Pediatric Rare Tumor Study Group (PPRTSG) in 2002.[9] The German Rare Tumor Committee, Seltene Tumor-Erkrankungen in der Paediatrie (STEP), was established in 2006.[10] The French Group on Rare Tumors in Children, called FRaCTurE (Groupe FRAnCais des TUmeurs Rares de l'Enfant), was created in 2007.[11] Each of these national programs had its own policies and approach—to patient registration/classification, for example—but they also had much in common. They considered pediatric VRT as orphan diseases. The strategy of their cooperative networks focused on involving pediatric oncologists and surgeons, together with experts on adult cancers, and specialists in various other branches of medicine, such as endocrinologists or dermatologists. They were aiming for a centralized coordination and a common framework for the management of all VRTs. Their goals were two-fold: to promote research, and to provide an advisory service for physicians encountering single clinical cases.[5]

The experiences of these networks showed that it was feasible to conduct research and undertake prospective studies even on such rare tumors. It also became clear that they needed to go a step further, and pool their efforts in larger scale, international projects. Thus, in 2008, the groups working on pediatric VRT in Italy, France, Germany, and Poland, together with researchers from the United Kingdom joined forces to create the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT).[12,13]

## 2 | EXPeRT: A EUROPEAN PROJECT FOR PEDIATRIC VRT

The goals of EXPeRT were to empower research on pediatric VRT by promoting cooperation between the national groups behind its foundation; supporting the creation of other such groups elsewhere in Europe; and fostering international collaboration schemes with other networks further afield. The newly founded EXPeRT received the formal acknowledgment of the European Society for Paediatric Oncology (SIOPE), officially becoming the European cooperative group dedicated to pediatric VRT.

The EXPeRT's founding members had several specific objectives to work on over the years. They aimed first to pool their national retrospective series of specific types of VRT to obtain series large enough to allow for them to examine risk-stratified treatment strategies. This would subsequently provide a frame for arriving at a consensus on treatment recommendations. Then, promoting research on

pediatric VRT required the establishment of a structured organization. Moreover, EXPeRT wanted to bundle expertise and to provide advice to physicians confronted with children with VRTs. For this purpose, an online consultation system was established to help physicians cope with difficult decisions regarding single clinical cases. In addition, EXPeRT planned to establish an international prospective case registry. This was a critical step, as it allowed for pooling together enough expertise, resources, and cases to be able to conduct prospective (and possibly even randomized) clinical trials on at least some types of pediatric VRT, as well as organizing biological studies and creating a bio-bank for these diseases.

Table 1 summarizes the main findings emerging from retrospective series of pediatric patients with pancreatoblastoma,[14] pleuropulmonary blastoma,[15] thymic tumors,[16] ovarian Sertoli–Leydig cell tumors,[17] adrenocortical carcinoma,[18] cutaneous melanoma,[19] and mesothelioma.[20]

It proved relatively straightforward for the group to develop joint retrospective studies on a given VRT, even without financial support. It soon became clear, however, that two fundamental needs had to be met in order to achieve its other goals. First, the group needed to obtain dedicated funds. Second, it had to strive for further cooperation on multiple levels, engaging with all actors with a potential interest in pediatric VRT. This meant looking beyond the sphere of pediatric oncology and contacting specialists in various fields of medicine, not only in adult oncology. But it also demanded interaction with care providers, patients, and their families, regulators, and potential providers of financial resources.[21]

## 3 | EU-FUNDED PROJECTS

The EXPeRT network was able to pursue its goals thanks to three EU-funded collaborative efforts. From 2014 to 2017, it was part of the 3-year ExPO-r-Net (European Expert Pediatric Oncology Reference Network for Diagnostics and Treatment) project. This was a wide-ranging scheme developed under an EU directive.

This was a wide-ranging scheme developed under the EU directive 2011/24/EU (a pilot network of cooperation between pediatric oncology centers). The main goal was to reduce inequalities in health care across EU Member States, particularly for patients with rare diseases who require special expertise.[5]

As part of the ExPO-r-Net project (and thanks to the financial support it provided), the EXPeRT had the chance to conduct its activities, strengthen cooperation inside and outside the network. It was also able to adopt e-Health solutions to make it easier to exchange information and knowledge, and thereby usually avoid moving patients. A dedicated website (https://www.raretumors-children.eu/) was developed for the purpose of informing scientific and other communities.

An online tumor board and advisory desk (http://vrt.cineca.it/) was also set up to serve professionals working in the area of pediatric VRT. The virtual consultation system was considered of great importance due to the absence of clinical protocols or standardized therapeutic guidelines for VRT. For young patients with such rare entities, any clinical decisions regarding young patients with VRTs could rarely be supported by validated experiences or data from clinical studies. Their physicians were often seeing their first ever case, and this is where the EXPeRT virtual tumor board platform has come in useful. Professionals can seek advice by submitting anonymized documents (clinical reports and images too). The virtual consultation system is open to any diagnosis of a VRT. However, the panel of experts responding to the specific request varies with diagnosis. These tumor-specific panels were selected by the EXPeRT team, including not only pediatric oncologists and surgeons but also specialists from other disciplines and experts in the specific adult cancers. When a case is submitted, the dedicated panel discusses it, answers specific questions, and offers recommendations reached by consensus. The virtual consultation system was formally opened in mid-2017. In 3 years of activity, 101 patients from 21 countries have been discussed until January 2021, including eight patients from non-European countries. In a survey, 92.3% of requesting physicians considered the advice given by the consultation system helpful (19.2%) or very helpful (73.1%). Moreover, 92.3% reported that the recommendations were likely to have an impact on the treatment of the patient with VRT.

Another noteworthy EXPeRT undertaking as part of the ExPO-r-Net project has been to identify other structured, national cooperative groups focusing on VRT in other European countries. A survey conducted by contacting the Chairs of all the national pediatric oncology societies and associations in Europe revealed that there were initiatives established in less than a third of their countries. This survey had the important effect of prompting other countries to follow the EXPeRT model, and various VRT programs have since been set up.

From 2016 to 2019, the EXPeRT was also involved in another project promoted by the European Commission, which was called the Joint Action on Rare Cancers (JARC) (https://www.jointactionrarecancers.eu/). There were 12 different working groups, each of which focused on a family of rare cancers: 11 groups were concerned with adult diseases and one with rare pediatric cancers. The groups' work revolved around the definition, prevention, diagnosis, and treatment of these diseases, related research, and education.[22] Working with the JARC gave the EXPeRT team more opportunities to broaden its cooperation with the adult oncology community, and to establish links with the world of epidemiology and big numbers, an aspect fundamental to research on extremely rare tumors.

As part of its cooperation with the JARC, the EXPeRT promoted efforts to find ways to provide young people with VRT with the best available care, and to promote clinical and basic research in the field of pediatric VRT.

In particular, in cooperation with the JARC, the EXPeRT aimed to arrive at a consensus on the definition of pediatric VRT, and therefore produced a list of VRT entities. A list was drawn up of all the rare tumors, with a report on their incidence in Europe in order to shed more light on the epidemiology of pediatric VRT. The information required to do so was obtained through the database of the RARECAREnet project (which pooled details from 83 European databases for the years 2000–2007).[1] This RARECAREnet database is the offspring of EUROCARE-5, a European cancer registry-based

**TABLE 1** Main findings from the retrospective series of studies by the EXPeRT on specific types of tumors

| Publication | Main results | Comments |
|---|---|---|
| Pancreatoblastoma<br>Bien et al., 2011[14] | 20 Patients <18 years (study period 2000–2009)<br>5-year EFS 58.8%, 5-year OS 79.4%<br>Rate of response to chemotherapy: 73%<br>Outcome correlates with complete surgical excision | Proposal of a standardized approach to the diagnosis (e.g., staging system) and treatment (conservative surgery followed by cisplatin-doxorubicin chemotherapy, then postponed aggressive surgery on primary tumor and metastases) |
| Pleuropulmonary blastoma<br>Bisogno et al., 2013[15] | 65 Patients <18 years (study period 2000–2009)<br>Type I: 5-year EFS 83.3, OS 91.7%<br>Type II/III: 5-year EFS 42.9%, OS 57.5%<br>Role of doxorubicin in type II/III type (5-year EFS 70% vs. 31.3% in patients with vs. without doxorubicin-based regimens) | Identification of a common therapeutic approach<br>Identification of prognostic factors (i.e., complete tumor resection at diagnosis and absence of invasiveness) |
| Thymoma and thymic carcinoma<br>Stachowicz-Stencel et al., 2015[16] | 36 Patients <18 years (study period 2000–2012)<br>16 Thymomas: 14 patients are alive with no evidence of disease<br>20 Carcinomas: 5 patients are alive, 5-year OS 21% | Common therapeutic guidelines in pediatric population have yet to be established. Surgical excision remains the mainstay of treatment. The role of chemotherapy is unclear |
| Sertoli–Leydig cell tumors<br>Schneider et al., 2015[17] | 44 Patients <18 years (study period 1993–2008, depending on the country)<br>5-year EFS 70%, 5-year OS 87%<br>Stage, histopathological differentiation, and intra-/preoperative rupture or positive ascites determine prognosis | Identification of possible prognostic factors<br>Impact of chemotherapy in incompletely resected and advanced stage cases still to be assessed |
| Adrenocortical carcinomas<br>Cecchetto et al., 2017[18] | 82 Patients <18 years (study period 2000–2013)<br>3-year EFS 38.8%, OS 54.7%<br>Survival rates influenced by distant metastases, tumor volume, lymph node involvement, age, vascular involvement, and incomplete surgery<br>For localized disease alone: EFS 51.1%, OS 73% | Identification of a common treatment strategy (surgery alone if R0 achievable; if not, neoadjuvant chemotherapy)<br>Prognostic factors in adult population lack sensitivity and specificity<br>Complete surgical resection is fundamental, whenever possible. The impact of chemotherapy could not be ascertained |
| Cutaneous melanoma<br>Brecht et al., 2018[19] | 219 Patients <18 years (study period 2002–2012)<br>3-year EFS 84%, OS 91.4%<br>Sentinel lymph node biopsy was performed in 112 patients and positive in 37.5%<br>Stage III cases: similar survival whether patients received adjuvant therapy (23 cases) or not (21 cases)<br>Tumor site, tumor stage, and ulceration influenced survival rates | Patients treated by pediatric oncologists ($n = 140$) were more likely to have advanced disease than those treated by dermatologists ($n = 79$)<br>The clinical history of melanoma in children and adolescents might resemble that of the adult counterparts |
| Mesothelioma<br>Orbach et al., 2020[20] | 33 Patients <21 years (study period 1987–2018, depending on country)<br>6 Multicystic mesothelioma of the peritoneum; 5 surgery, and 1 surgery plus hyperthermic intraperitoneal chemotherapy; 6/6 alive;<br>27 malignant mesothelioma - multimodal therapy with chemotherapy, surgery, hyperthermic intraperitoneal chemotherapy;<br>Response to cisplatin-pemetrexed chemotherapy = 6/12<br>5-year EFS 45.1%, 5-year OS 82.3% | Extremely rare in pediatric age<br>It seems different from the adult counterpart: fewer asbestos exposures (1 case), more peritoneal primary sites, better outcome<br>The cisplatin-pemetrexed regimen showed promising efficacy. Relapses could be salvaged with active therapy, including hyperthermic intraperitoneal chemotherapy |

Abbreviations: EFS, event-free survival; EXPeRT, European Cooperative Study Group for Pediatric Rare Tumors; OS, overall survival.

study on the survival and care of cancer patients spanning the years 1999–2007. The study considered data on more than 21 million cancer diagnoses provided by 116 cancer registries in 30 European countries. It was agreed at a consensus conference that pediatric cases were to be identified as VRT if their annual incidence was <2/1,000,000, and 11% of all cancers in patients aged 0–14 years fitted the bill. The cut-off adopted for the definition of a pediatric VRT was judged appropriate by the clinicians involved because (i) if lower thresholds (e.g., less than one per million) were adopted, then some diseases considered particularly challenging, such as extragonadal germ cell tumor, cutaneous melanoma, hepatoblastoma, thyroid carcinoma, and nonepithelial ovarian tumor, would be excluded from the list; and (ii) using a higher threshold would lead to the inclusion of classical pediatric tumors (e.g., rhabdomyosarcoma, bone sarcoma, medulloblastoma) in the group of VRT. The cut-off of two per million could also be suitable for populations aged 0–19 years, but making an exception for three particular types of tumor (i.e., thyroid and testicular cancers, and skin melanoma). This is because, although they have an incidence rate higher than two per million, they are generally considered very rare and challenging because of the paucity of knowledge available on them. In short, they pose much the same clinical issues as the other pediatric VRTs.[23] In fact, it is the combination of a low incidence and particular clinical needs that really distinguishes pediatric VRTs from the other pediatric malignancies for the purposes of prioritizing more specific research on these tumors.

The third major European initiative in which the EXPeRT was involved is the Pediatric Rare Tumors Network - European Registry (PARTNER) project, which has been active between 2018 and 2021. Promoted by the European Reference Network for Pediatric Cancer (ERN PaedCan), the main goal of the PARTNER project has been to set up a shared European registry of pediatric VRT by harmonizing all the existing national registries and providing one for the countries that did not already have one. The PARTNER scheme thus aimed to broaden the pediatric VRT network by including Europe's so-called low health expenditure average rate countries.

Another major task envisaged in the PARTNER project was to continue the work started with the ExPO-r-Net project and develop diagnostic and treatment guidelines for at least some VRTs.

Such clinical recommendations form the subject of the present series of papers in this Journal concerning pleuropulmonary blastoma, pancreatoblastoma, sex cord stromal tumors, thymic tumors, nasopharyngeal carcinoma, adrenocortical carcinoma, salivary gland carcinoma, and cutaneous melanoma.

Another goal of the PARTNER project has been to promote a greater awareness regarding pediatric VRT by means of a website and by establishing closer forms of cooperation with Childhood Cancer International (CCI) Europe, which represents the interests of pediatric cancer patients. Patient advocacy groups can help in many ways, by disseminating information, supporting the recruitment of patients in clinical trials, promoting the most appropriate centers for patient care, and taking part in regulatory processes.

## 4 | WORK TO BE DONE

Many goals of EXPeRT have been achieved in recent years, but much remains to be done. We are still far from being able to say that we have sufficient evidence to support the accurate diagnosis and successful treatment of pediatric VRT and the knowledge we need to care for this neglected patient group. Although we have gained in experience of diagnosing and treating VRT in recent years, the scientific evidence behind our clinical approach is still limited.

The etiology and pathogenesis of VRT in children and adolescents are largely unclear as biological studies are hindered by their rarity (which means a shortage of tumor samples, for instance). Differences in tumorigenesis between VRT and the more classical tumors of childhood or adulthood are very likely, but detailed studies are rare.[24] For various adult-type tumors occurring in pediatric age, a genetic susceptibility has been identified, at least in sporadic cases. However, this issue has to be addressed systematically, in more detail and larger studies. There have been suggestions that adult-type tumors have different biological features when they occur in children, meaning that the strategies for treating them should differ too.[25–28] Moreover, some of the VRTs arise in the context of genetic predisposition; for example, as part of the DICER-1 tumor spectrum: in these tumors, the genetic workup provides important information that may guide the further follow-up of these patients.[29] New rare tumors are also coming to light as a result of the molecular characterization of many types of cancer. Several groups working on rare tumors are seeking to further advance research in this field, and some international cooperative projects have been launched.

The limited innovative treatment options for pediatric VRT are one of the biggest concerns and new strategies are needed to facilitate the transfer of potentially effective new agents from adults to pediatric setting. Pediatric oncologists have to face various challenging situations. First, the fact that randomized trials seem simply not feasible because of the low case numbers. Regarding new agents developed in adult setting, pediatric oncologists may be often unfamiliar with treatment tailored for adults; in addition, little is known as yet about toxicity of such treatments in children. As a matter of fact, finally, there are still no evidence-based treatments available for the advanced stages of many of these tumors. New ways of working are required to improve the access to clinical trials and new drugs for pediatric patients with VRT. Just to give an example, a potentially effective strategy to overcome these difficulties may be the inclusion of adolescents in adult phase I/II trials for adult-type cancer,[30] for example, in advanced melanoma.[31] New strategies imply new partnerships: we need to implement a broad international cooperative network with all the possible stakeholders; we need to pursue a better synergy with the adult oncology community; we need to develop better collaborative solutions with new partners, such as regulatory authorities, public health bodies, and also pharmaceutical industries. Finally, we need to find long-term solutions to ensure the sustainability of such programs. The participation of EXPeRT in EU-funded projects has demonstrated how important it is to have the necessary economic support to

achieve these goals. Financial support for research into rare cancers—encompassing basic, preclinical, clinical, and "back-to-the-bench" studies—is indispensable.

In conclusion, promoting research on pediatric VRTs with the ultimate aim of improving the prognosis for the young patients involved remains a challenge. Nevertheless, the EXPeRT project has successfully shown how important it is to join forces, pool resources, and boost collaborative efforts. The slogan adopted by EXPeRT members was "If you work on more common cancers, do randomized trials. If you work on rare cancers, find friends!"[32] This underscores the constant focus on establishing closer international ties to overcome the disadvantage historically borne by children with VRT due to the rarity of their disease and the consequent shortage of clinical and biological information.

## ACKNOWLEDGMENTS

The authors wish to thank all the families and cooperating centers, as well as those who supported national activities on very rare tumors in pediatric age (in particular, Fondazione Città della Speranza and Fondazione Celeghin for the Italian Tumori Rari in Età Pediatrica [TREP] project, Enfants, cancer et santé - SFCE for the French Groupe FRAnCais des TUmeurs Rares de l'Enfant [FRaCTurE], the German Childhood Cancer Foundation for the German Seltene Tumor-Erkrankungen in der Paediatrie [STEP]). In addition, the authors thank the European Union's Health Programme, 2008–2013 (Grant Number: 20131207) and 2014–2020 (Grant Number: 724161) for previous support to the ExPO-r-Net and JARC project, respectively. This publication is part of the PARTNER project (ERN PaedCan Partner Pediatric Rare Tumors Network - European Registry), which received funding from the European Union's Health Programme (2014–2020) (3rd Health Programme Call: HP-PJ-06-2016: Rare diseases - support for new registries; CHAFEA Grant Number: 777336).

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

### Funding information

European Union's Health Programme (2014–2020) (3rd Health Programme Call: HP-PJ-06-2016), CHAFEA Grant Number: 777336; European Union's Health Programme, Grant Numbers: (2008–2013) 20131207 and (2014–2020) 724161

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## ORCID

*Andrea Ferrari* https://orcid.org/0000-0002-4724-0517
*Dominik T. Schneider* https://orcid.org/0000-0001-8153-1601
*Gianni Bisogno* https://orcid.org/0000-0003-4462-5523
*Teresa Stachowicz-Stencel* https://orcid.org/0000-0002-4453-4157
*Bernadette Brennan* https://orcid.org/0000-0003-1614-0289
*Tal Ben-Ami* https://orcid.org/0000-0003-0017-6332
*Calogero Virgone* https://orcid.org/0000-0002-3651-9416
*Daniel Orbach* https://orcid.org/0000-0002-2520-139X

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**How to cite this article:** Ferrari A, Schneider DT, Bisogno G, et al. Facing the challenges of very rare tumors of pediatric age: The European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) background, goals, and achievements. *Pediatr Blood Cancer*. 2021;68:e28993.
https://doi.org/10.1002/pbc.28993