National Initiatives in Europe

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For children affected by very uncommon malignancies, the very low incidence of their disease has often limited the interest in research capable of collecting significant clinical and biological data: as a consequence, it has always been difficult to produce evidence-based treatment guidelines, and physicians are forced to treat such patients only on an individual basis. Historically, the pediatric oncology community dedicated little resources to pediatric very rare tumors (VRTs), and research focused on them remained a challenge. In the first years of the new millennium, however, the situation changed; pediatric oncologists have increasingly recognized the necessity to develop specifically dedicated projects; and various national groups have launched national initiatives (in Italy first and then in Poland, Germany, and France).

5.1 The Italian TREP Project

The pioneering national-scale cooperative project on VRTs—the TREP project (Tumori Rari in Età Pediatrica [*Rare Tumors in Pediatric Age*])—was launched in Italy in 2000 under the auspices of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) and in cooperation with the Società Italiana Chirurgia Pediatrica (SICP) (Ferrari et al. 2007).

To clearly define its area of interest, the TREP group adopted a pragmatic definition of *rare pediatric tumors*, considering practical and clinical issues rather than epidemiological data and including "any solid malignancy characterized by an annual incidence <2 per million and not considered in other clinical trials." As a consequence of this definition, the TREP project did

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not include tumors with such a low incidence but already "covered" by other national studies, i.e., renal rhabdoid tumors were registered in the AIEOP Wilms Tumor Study, hepatoblastoma and malignant germ cell tumors had their own protocols, rare histotypes of soft part sarcomas (non-rhabdomyosarcoma soft tissue sarcomas) were covered by the cooperative study on soft tissue sarcomas, and so on. The definition adopted was considered suitable for classifying the "orphan" tumors in the Italian pediatric setting, i.e., in the sense that most pediatricians might encounter these tumors only once in their working lives, there were few or no published reports on clinical experiences, it was difficult to establish shared treatment guidelines (and there were no evidence-based therapeutic recommendations available), and few or no cooperative groups dedicated and structured projects or financial support for studies on these tumors.

An assortment of tumors was thus involved in the TREP project, including some neoplasms that are rare at any age, and also (and mainly) tumors that are rare in childhood and adolescence but more common in adulthood, e.g., nasopharyngeal carcinoma, adrenocortical tumors, pleuropulmonary blastoma (and other lung tumors), carcinoid tumors, cutaneous melanoma, renal cell carcinoma, pancreatoblastoma (and other pancreatic exocrine tumors), gonadal non-germ-cell tumors (ovary/testis), pheochromocytoma and paraganglioma, thyroid carcinoma, salivary gland tumors, breast carcinoma, carcinoma of the gastrointestinal tract, and carcinoma of the thymus.

The main aims of the TREP project were:

1. To develop diagnostic and therapeutic recommendations for each rare tumor
2. To collect and centralize clinical data by using specific printed forms for diagnostic workup, treatment, and follow-up
3. To identify one (or more) researcher(s) "dedicated" to each histotype who could act as an expert to consult
4. To create a network for cooperation with other specialists (adult oncologists and surgeons, endocrinologists, dermatologists, gastroenterologists, etc.) involved in managing these tumors
5. To organize pathological and biological studies

From September 2000 to September 2016, 964 patients <18 years of age were registered in the TREP database, which means a rate of more than 50 patients a year. Patients were registered by 39 different Italian centers, confirming the broad adhesion to the project. Patients range in age from 12 days to 18 years, with a median of 12 years (70% of cases were over 10 years old). Thyroid carcinoma proved the most common histotype (166 cases), followed by carcinoid/neuroendocrine tumors (154 cases), skin tumors including melanoma (123 cases), gonadal non-germ-cell tumors (109 cases), and nasopharyngeal carcinoma (63 cases).

Table 5.1 reports a list of the series published by the TREP group.

An analysis performed in cooperation with the AIEOP epidemiology group compared the number of cases actually registered (between 2000 and 2006) with the number of cases predicted in the light of incidence data in the Italian population-based cancer registries (AIRTum). The number of rare pediatric tumors predicted to occur in Italy between 2000 and 2006 was 305 among the 0 to 14-year-olds and 400 among the 15 to 17-year-olds (on average, 44 children and 57 adolescents are expected to develop a rare pediatric tumor each year), while the numbers of cases actually identified by the TREP were 261 and 75, respectively. For the 0 to 14-year-olds, the ratio of observed to expected cases was even 1:1 for several tumors (i.e., nasopharyngeal carcinoma, adrenocortical tumors, renal cell carcinoma, and gonadal non-germ-cell tumors), while for the adolescents, underreporting was statistically significant for all tumor types except nasopharyngeal carcinoma (Pastore et al. 2009). These findings were generally regarded as an indication of the TREP project's success (the vast majority of patients with rare pediatric tumors under 15 years of age were registered and treated according to TREP guidelines) and of the feasibility of cooperative protocols even for rare

Table 5.1 Various series published by the Italian TREP project

Series	Main results
Pleuropulmonary blastoma (Indolfi et al. 2007)	22 patients 5 cases on congenital lung cysts; 5-year EFS 44%, OS 49% Better prognosis with total resection, worse prognosis with extrapulmonary involvement
Pancreatic tumors (Dall'Igna et al. 2010)	21 patients 4 pancreatoblastomas, 2 pancreatic carcinomas, 3 neoplasms of the endocrine pancreas, 12 solid pseudopapillary tumors
Sex cord-stromal tumors of the testis (Cecchetto et al. 2010)	11 patients 4 Leydig cell tumors, 4 juvenile granulosa cell tumors, 1 Sertoli cell tumor, 1 incompletely differentiated tumor, 1 tumor with an intermediate pattern Sertoli cell tumor/mixed form All the patients are in first complete remission
Sex cord-stromal tumors of the ovary (Cecchetto et al. 2011)	23 cases, 9/23 cases with signs of hormonal secretion; 12 juvenile granulosa cell tumor, 6 Sertoli-Leydig cell tumor, 3 fibrothecoma, 2 sclerosing stromal tumor 22/23 alive; cisplatin-based chemotherapy seemed to be effective for locally advanced tumors
Epithelial thymic tumors (Carretto et al. 2011)	9 cases, 4 thymoma and 5 carcinoma; all patients with thymic carcinomas died of their disease despite of multidrug chemotherapy and radiotherapy
Nasopharyngeal carcinoma (Casanova et al. 2012)	46 patients (45 N1, 5 M1) 3 courses of cisplatin/5-fluorouracil induction chemotherapy followed by radiotherapy (doses up to 65 Gy) with concomitant cisplatin 90% response rate to primary chemotherapy 5-year PFS 79.3%, OS 80.9% 65% incidence of late sequelae The use of lower radiotherapy doses than those used in adults did not affect locoregional failure rates
Esthesioneuroblastoma (Bisogno et al. 2012a, b)	9 cases 3 Kadish stage B, 6 stage C; chemotherapy response in 5/7; 8/9 alive, 7 in first remission, 1 in second remission; treatment-related sequelae (endocrine dysfunctions, craniofacial growth impairments)
Adrenocortical tumors (Magro et al. 2012)	20 patients Wieneke scoring system: 7 tumors were classified as malignant, 12 tumors as benign, 1 tumor with "unpredictable behavior"; matrix metalloproteinase 2 was expressed in all malignant and in most benign tumors; HLA class II antigen immunoreactivity was absent in all benign tumors and restricted to rare isolated cells in most malignant tumors; unlike in adults, metalloproteinase 2 or loss of HLA class II antigens does not discriminate between benign and malignant tumors in children
Ovarian sex cord-stromal tumors (Virgone et al. 2012)	15 cases GATA-4 and FOG-2 expression: high expression of GATA-4 does not correlate with aggressive behavior as seen in adults
Salivary gland carcinomas (Chiaravalli et al. 2014)	17 patients (in 4/17 cases, it was a second tumor); 14 arising in the parotid gland; 14 low-grade tumors, often low-stage; all patients underwent surgical resection, with free margins in 9/17; adjuvant radiotherapy in 6 cases; 16/17 alive in first continuous remission
Myoepithelial carcinoma (Bisogno et al. 2014)	7 cases chemotherapy with ifosfamide, cisplatin and etoposide, radiotherapy; 6/7 alive in first remission (median follow-up, 2.5 years; range, 0.9–5)

(continued)

Table 5.1 (continued)

Series	Main results
Cutaneous melanoma (Ferrari et al. 2014)	54 patients 5-year EFS 75.2%, OS 84.6%; the variables influencing survival in children are the same as for adults
Adrenocortical tumors (Dall'Igna et al. 2014)	58 patients, stage II treated with mitotane, stage III–IV with mitotane + chemotherapy; 45 alive, 12 died of disease, 1 died because of cardiomyopathy; p53 mutation found in 7 cases
Appendiceal neuroendocrine tumors (carcinoid of the appendix) (Virgone et al. 2014)	113 patients 108/113 size <2 cm; 111/113 free excision margins; primary reexcision in 3 cases only; all 113 of 113 patients are alive in complete remission appendectomy alone should be considered curative for most patients, and a more aggressive surgical approach is warranted only in the cases with incompletely excised tumors
Epithelial tumors of the ovary (Virgone et al. 2015a, b)	16 patients 8 benign tumors (7 mucinous cystadenomas and 1 serous cystadenoma) and 8 borderline tumors (2 serous and 6 mucinous); 15/16 patients maintained the complete remission after surgical treatment alone; 1 died due to synchronous Wilms tumor (Proteus syndrome)
Atypical Spitz tumors (Massi et al. 2015)	50 cases Analysis of histological parameters associated with a diagnosis of atypical Spitz tumors over Spitz nevus; *minimal lethal potential; no data to support any clinical benefit for the sentinel lymph node biopsy procedure and completion lymphadenectomy*
Neuroendocrine tumors of the appendix (Virgone et al. 2015a, b)	5 cases with neuroendocrine tumor of the appendix associated with a parasitic bowel infection Possibility of inflammation-triggered carcinogenesis
Urothelial neoplasms of the bladder (Di Carlo et al. 2015)	12 patients Low-grade (11/12 G1), scarcely aggressive disease with an excellent prognosis; the role of intravesical chemotherapy is debatable
Papillary thyroid carcinoma (Spinelli et al. 2016)	250 patients 46% N1, 4% M1 90% total thyroidectomy, 10% lobectomy; 21% surgical complications (hypoparathyroidism, vocal fold palsy), all in case of total thyroidectomy group; 12% recurrent disease, 100% overall survival; pediatric patients are likely to benefit from a tailored surgical strategy; uniformly offering patients total thyroidectomy seems to be an overly radical approach
Gastrointestinal tract carcinoma (Indini et al. 2017)	15 cases, 12 colorectal carcinomas; all but one patient had advanced-stage disease and the majority had aggressive histological subtypes; 9 alive (but 3 with very few follow-up), 6 died due to disease
Solid pseudopapillary tumors (Crocoli et al. 2019)	43 patients One recurrence in a patient with intraoperative rupture; all alive

EFS event-free survival, *OS* overall survival, *PFS* progression-free survival, *N1* nodal metastases, *M1* distant metastases

diseases. The underreporting of adolescents was similar to what was seen also for the more common pediatric malignancies.

The key elements of the TREP project—and the lessons learned from it—were more than one. First is the dual need of the project, i.e., to prompt research and to provide all centers with practical patient management schemes. In Italy, there was a shortage of information on these rare pediatric tumors, and doctors were calling for treatment guidelines; the various experts involved in the project have been able to offer a real advisory

service. Second—and consequently—is the importance of developing a network involving several centers and specialists from different branches of medicine and science. Third is the adoption of a common framework: the different working groups (one for each tumor type) developed their "protocols" in the context of the same structured manner, and this ensured homogeneous methods and guaranteed the discipline essential to the efficacy of cooperative clinical trials.

5.2 The Polish Paediatric Rare Tumours Study Group

The Polish Paediatric Solid Tumours Study Group (in Polish: Polska Pediatryczna Grupa Guzów Litych, PPGGL) was created in 1992 in Poznań. During the first 10 years of activity, the PPGGL developed, adapted, or joined international therapeutic programs for the majority of the common pediatric malignancies. In 2002, a specific initiative dedicated to pediatric VRTs was launched, named Polish Paediatric Rare Tumours Study Group. The interest of the group focused on those malignancies which had extremely low incidence and were not included in other already existing therapeutic protocols. Study started its activity with the call for retrospective data on VRTs from preceding decades in order to build a core database. This database served for a number of retrospective reviews on particular diseases presented and published widely (Bien et al. 2004; Bien et al. 2009a, b; Godzinski et al. 2004; Stachowicz-Stencel et al. 2010). Second objectives were the prospective registration of new cases and the building of an expert advice platform based on the experience gained thus far, on literature, and, to some extent, on the contacts with other experts identified for particular malignancies (e.g., International experts, experts in adult oncologists). The consultation platform and data bank organized by the Rare Tumours Study Committee served not only to the pediatric oncology centers cooperating within PPGGL but also to general pediatricians and other specialists, if requested.

5.3 The German STEP Project

In Germany, approximately 2200 children and adolescents are diagnosed with cancer each year (Kaatsch 2016). The 55 pediatric oncological centers cooperate within the clinical and scientific network of the German Society for Pediatric Oncology and Hematology (GPOH), which coordinates national and international clinical studies and registries. Compared to other countries, the infrastructure for pediatric rare tumors has a distinct history in Germany. Thus, some rare cancers have long been integrated into cooperative therapy optimization studies. Among others, these include endocrine cancers (e.g., thyroid cancers, adrenocortical carcinoma, carcinoids), nasopharyngeal carcinoma, and rare soft tissue sarcomas. With the advent of the EU regulation on clinical trials, these initiatives have developed into clinical registries that provide a therapeutic guidance based on consensus recommendations, central clinical data collection, and support of coordinated molecular genetic studies.

Apart from these, there remains a group of patients with VRTs that have not yet been cared for within the clinical network of GPOH until the foundation of the German Working Group in Pediatric Rare Tumors (Seltene Tumorerkrankungen in der Pädiatrie (STEP) in 2006 (Brecht et al. 2009). The work of this multidisciplinary working group focuses on all VRTs not registered to other studies or registries within the GPOH. Thus, some rare tumor entities such as rhabdoid tumors, nasopharyngeal carcinoma, endocrine cancers, or rare soft tissue sarcomas are explicitly excluded but reported to the respective diagnosis-specific registry. In 2012, the prospective registration of patients with VRTs into the STEP Registry started and will be continued in the STEP 2.0 registry in 2019 (www.seltene-tumoren.de). The annual accrual rate approaches 100 patients, i.e., 4% of all childhood cancer patients in Germany.

The patient registration is accompanied by a close consultation service for pediatric oncological centers (contact: step@klinikumdo.de). The working group also provides information on VRTs for physicians and affected families (www.

kinderkrebsinfo.de). In addition, the STEP working group studies potential associations of very rare cancers with hereditary cancer predisposition (Weber et al. 2016; Ripperger et al. 2017; Bauer et al. 2019). Lastly, the STEP registry provides access to tumor banking and molecular profiling platforms for the analysis of potential therapeutic targets in prognostically unfavorable situations (Ernestus et al. 2006; Worst et al. 2016).

By promoting these activities, STEP aims to providing children and adolescents with VRT access to optimal care within the clinical and scientific infrastructure of GPOH.

5.4 The French FRaCTurE

The French Group on Rare Tumors in Children (FRaCTurE; Groupe FRAnCais Des TUmeurs Rares de l'Enfant) was formally launched in 2007. It was developed in a context where the incidence of pediatric rare, malignant, or borderline tumors in France was difficult to evaluate, also due to the fact that only patients with severe, recurrent, or complicated forms were referred to oncology departments. In fact, also nowadays the incidence of a large number of rare diseases is severely underestimated, giving a false impression of the true incidence of the disease. The French Registry of Solid Tumours in Children—*Registre National des Tumeurs Solides de l'Enfant* (RNTSE)—provides epidemiological data on childhood cancers in France. However, certain rare tumors are not included in this registry, either because their malignant nature remains uncertain or because they are managed by adult oncology teams or pediatric specialities other than oncology, less accustomed to systematic patient registration. The RNTSE initially only recorded tumors occurring in children under the age of 15 years in metropolitan France and since 2011 extended to all patients less than 18 years old and living in overseas departments. Concomitant registration of borderline tumors is performed but is not comprehensive. The exceptional nature of these diseases and their heterogeneous management in terms of both the medical specialty involved (surgery, dermatology, ophthalmology, etc.) and the site of treatment (private clinic or public hospital, pediatric or adult medicine department) account for these difficulties (Réguerre et al. 2010).

The creation of a rare childhood tumor group by the *Société Française des Cancer de l'Enfant et de l'Adolescent* (SFCE) in November 2006 (and then launched few months later) was the first step designed to address these issues. This group, mainly composed of pediatricians, surgeons, radiotherapists, and pathologists, meets at least twice a year to discuss a specific theme, e.g., aggressive vascular tumors (Boccara et al. 2016), neuroendocrine tumors (de Lambert et al. 2015), mucoepidermoid carcinoma (Rebours et al. 2017), etc. Since the creation of the FRaCTurE group, diagnostic and treatment guidelines have been proposed for certain tumors such as adrenal cortical tumors (Picard et al. 2018, 2019), pleuropulmonary blastomas, pancreatic tumors (Irtan et al. 2016), melanomas (Reguerre et al. 2016), and nasopharyngeal carcinoma (Jouin et al. 2019), based on retrospective analyses of patients previously treated in France, data of the literature, and proposals from other European or international rare tumor groups. These clinical practice guidelines are then made available to clinicians via the SFCE website.

A local representative responsible for VRTs has been designated in each of the 30 SFCE centers throughout France to ensure diffusion of these guidelines. The presence of surgeons in the group also ensures close collaboration with the other members of the *Société Française de Chirurgie Pédiatrique* (SFCP). Another objective of this group is to improve the knowledge and treatment of pediatric VRTs by creating, in collaboration with the SFCE and the RNTSE, a national database for collection of medical information. Clinical, laboratory and radiological characteristics, the treatments administered, and outcome of the disease are recorded. Current treatment guidelines, initiated in the context of the FRaCTurE group, constitute the basis for setting up this database. This database therefore concerns diseases corresponding to various histologies, sharing in common their very low

incidence (less than 2 cases per million children under the age of 18) and the absence of formal treatment guidelines. For practical purposes, tumors with an exceptionally low incidence, but for which treatment guidelines or data collection are already available in the context of the SFCE, will not be included in this group. It was also arbitrarily decided not to include in this rare childhood tumor group those rare hematological malignancies included in the "leukemia group." Consequently, the main diseases concerned by this group are undifferentiated nasopharyngeal carcinoma; pancreatoblastoma and Frantz's tumor (pseudopapillary tumor of the pancreas); pleuropulmonary blastoma; pseudo-inflammatory tumor; mesothelioma; thymoma (Rod et al. 2014); gastrointestinal stromal tumors; adrenal cortical tumor; malignant pheochromocytoma; carcinoid of the appendix; melanotic neuroectodermal tumor of infancy (Moreau et al. 2017); carcinoid of the small intestine; carcinoid tumor of the bronchus; midline carcinoma (Lemelle et al. 2017); aggressive giant-cell bone tumors; chondroblastoma; chondrosarcoma; malignant head and neck tumors, sialoblastoma, mucoepidermoid carcinoma, aggressive benign vascular tumor; lung carcinomas; urothelial carcinomas (Grapin-Dagorno et al. 2017); and chordomas.

From 2007 to 2018, overall 675 patients were registered from 34 centers and concerned 130 different histotypes. The most frequent tumors were neuroendocrine tumors of the appendix (55 cases, 8% of all), undifferentiated nasopharyngeal carcinoma (43 cases), pheochromocytoma/paraganglioma (34 cases), solid pseudo-papillary tumor of the pancreas (32 cases), salivary gland tumors (30 cases), pleuropulmonary blastoma (24 cases), and cutaneous melanoma (23 cases). National and international retrospective analyses on VRTs have been presented in 35 scientific congresses and published in 14 peer-reviewed journals.

5.5 The UK

In the UK, VRTs have been historically defined as those with an age-standardized annual incidence of less than 1 per million children, based on the categories of the International Classification of Childhood Cancer (Steliarova-Foucher et al. 2005) and the incidence rates from the UK National Registry of Childhood Tumours (NRCT). Overall, these tumors were considered to have an annual incidence rate of 6.8 per million, accounted for 16% of non-CNS malignant solid tumors, and accounted 5% of all childhood cancers. In both relative and absolute terms, they were most frequent in the age group 10–14 years, where their incidence was 12.4 per million and where they accounted for 35% of non-CNS solid tumors and 11% of all cancers. Carcinomas of all sites counted as rare tumors and collectively formed 50% of the total. Soft tissue sarcomas were the next most frequent histological group, representing 36% (Stiller 2007). It is important to note that the same diagnostic groups are not necessarily rare in all populations. Most strikingly, Kaposi sarcoma is one of the most frequent childhood cancers in parts of central and east Africa most severely affected by the AIDS epidemic, whereas malignant melanoma is rare throughout most of Africa and Asia.

The Rare Tumour Working Group of the Children's Cancer and Leukaemia Group (CCLG) initially focused on those pediatric VRTs that occurred only in childhood and had a poor prognosis. From about 1997, various members of the CCLG Rare Tumour Working Group took charge pulling together guidance for several rare tumors. The format consisted of the known data from the UK NRCT and an up to date review of the literature using this to conclude guidance around management, diagnosis, and treatment. Where possible, information regarding open International registries/protocols was also made available. The list of the Rare Tumour Guidelines was available to members on the CCLG website or incorporated into study protocols or published. In 2005, a multidisciplinary consensus statement of best practice for the management and treatment for pediatric endocrine tumors from a working group convened under the auspices of the BSPED (British Society of Paediatric Endocrinology and Diabetes) and CCLG was published as a booklet available to all members. The working group was multidisciplinary, consisting of pediatric endocrinologists, oncologists,

and surgeons together with adult surgeons, oncologists, and clinical geneticists with pediatric expertise. The following endocrine tumors were covered in the booklet: craniopharyngioma, adrenocortical neoplasms, pheochromocytoma, thyroid carcinoma (differentiated), medullary thyroid carcinoma and multiple endocrine neoplasia type 2 (MEN 2) syndromes, parathyroid and pituitary tumors (including primary hyperparathyroidism), and multiple endocrine neoplasia type 1 (MEN1) syndromes.

Although the registration of these rare tumors continues in the UK in the NRCT for patients 15 years and under, it is less complete for older teenagers and contains limited details on treatment received and factors which may be important for prognosis such as tumor dimensions, sites of metastases, etc.

For over the last 5 years, the information on incidence, survival, prevalence, and mortality for cancer diagnosed among children under the age of 15 resident in England only has been published with data from the National Cancer Registration and Analysis Service (NCRAS) from the department of Public Health England, as advised by the Children, Teenagers and Young Adults Expert Advisory Group, NCRAS. This of course limits the completeness of the data by excluding the other countries in the UK. While the report has extensive details on the common cancers in childhood, the small numbers limit the analysis of the rare tumors, and hence they are grouped together. An example would be "other malignant epithelial neoplasms and malignant melanomas" from the ICCC-3 coding with a mean number in this category per year up to 2015 of 66 cases versus specific data for thyroid cancer of on average 12 cases per year. Malignant melanoma is also coded separately on average 10 cases per year. It is important to note that the cut-off is 15 years old. This of course limits the survival analysis, but we can say that 5-year survival from thyroid carcinoma was well over 90% throughout the study period 2001–2015. Survival from malignant melanoma was 78% for children diagnosed during 2001 to 2005 and around 90% for those diagnosed during 2006 to 2015. Whether the later improvement is due to better reporting or potentially over diagnosis of atypical spitzoid nevi, one cannot comment (Irvine and Stiller 2019).

5.6 From National Initiatives to a Comprehensive European Project

When dedicated schemes for pediatric VRTs began to appear on the scene, two different models emerged: the first focused on large cooperative projects that enrolled all rare tumors (or at least a lengthy list of them) within the same framework; the second (adopted for some tumor types in the USA) was based on the creation of ad hoc tumor registries for specific entities, like the International Pediatric Adrenocortical Tumor Registry (IPACTR) (Ribeiro et al. 2012) or the International Pleuropulmonary Blastoma Registry (IPPBR) (Messinger et al. 2015).

These pioneering European national projects were based on the first model. Though they had many similarities, each organization had its own characteristics, different registration/classification policies, different processes for central pathology review and data verification, and different forms of cooperation with other national disease-specific groups (Bisogno et al. 2012a, b). However, the rarity of the tumor entities always remained a key limitation, even on a national level: the small number of cases hinders the feasibility of randomized study that could test the treatment considered standard against an alternate arm of therapy. All the European groups dedicated to pediatric VRT, therefore, agreed that the low incidence, the heterogeneity, and the complexity of these tumors called for a broader, international cooperation. In 2008, the national VRT groups in Italy, France, the UK, Poland, and Germany thus joined forces to form the EXPeRT (European Cooperative Study Group for Pediatric Rare Tumors), the primary aim of which was to promote international clinical and biological research on these diseases (Bisogno et al. 2012a, b; Ferrari et al. 2013, 2021).

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