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Angaben zur Veröffentlichung / Publication details:

Kuhlen, Michaela, Andrea Ferrari, Michael Abele, Yves Reguerre, Ewa Bien, Maja Cesen Mazic, Malgorzata A. Krawczyk, et al. 2025. "The European Cooperative Study Group for Paediatric Rare Tumors (EXPeRT group): a model for collaborative research and clinical care in very rare paediatric tumours." *ESMO Rare Cancers*, 100118. https://doi.org/10.1016/j.esmorc.2025.100118.

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PII: S3050-4619(25)00117-0

DOI: https://doi.org/10.1016/j.esmorc.2025.100118

Reference: ESMORC 100118

To appear in: *ESMO Rare Cancers*

Received Date: 22 July 2025

Revised Date: 11 November 2025

Accepted Date: 17 November 2025

Please cite this article as: Kuhlen M, Ferrari A, Abele M, Reguerre Y, Bien E, Mazic MC, Krawczyk MA, Lopez-Almaraz R, Ben-Ami T, Virgone C, Bisogno G, Schneider DT, Brecht IB, Orbach D, The European Cooperative Study Group for Paediatric Rare Tumors (EXPeRT group): A Model for Collaborative Research and Clinical Care in Very Rare Paediatric Tumours, *ESMO Rare Cancers* (2025), doi: https://doi.org/10.1016/j.esmorc.2025.100118.

Position Paper

The European Cooperative Study Group for Paediatric Rare Tumors (EXPeRT group): A Model for Collaborative Research and Clinical Care in Very Rare Paediatric Tumours

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Keywords
Very rare tumours, paediatric oncology, EXPeRT, virtual tumour board, clinical guidelines, international cooperation.

Brief running title: Very rare paediatric tumours

Word counts

Abstract	142
Main text	2,773
Tables/Figures	3/2
References	45

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Abstract

Paediatric cancers, though all considered rare, have benefited substantially from international collaborative protocols. However, very rare tumours (VRT) in children and adolescents, defined by an annual incidence < 2/1,000,000, pose significant challenges. These malignancies represent more than 50 different histotypes and collectively account for approximately 11% of all paediatric cancers. The European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT) was established in 2008 to address the unique challenges posed by these rare malignancies through collaborative research, multidisciplinary clinical expertise, and international cooperation. Over the past 15 years, EXPeRT has established a comprehensive framework integrating expert clinical consultation, harmonized consensus guideline development, retro- and prospective collaborative research, and strategic international partnerships. This article provides a comprehensive overview of EXPeRT's structure, scientific contributions, and vision for future cross-disciplinary and cross-border initiatives aimed at improving outcomes for children and adolescents with very rare tumours.

Introduction - The Challenge of Very Rare Tumours

Paediatric oncology has achieved remarkable advances over the past decades through international cooperative clinical trials, leading to significant improvements in survival for most childhood malignancies. However, a distinct subset of paediatric cancers, collectively referred to as very rare tumours (VRT), remains particularly challenging to study and manage, mainly due to their low incidence. VRTs are defined as malignancies each with an incidence below 2 cases per million children and adolescents per year and together account for approximately 10 to 11% of all paediatric cancers. [1-4] This group contains a wide variety of tumour types with different biological characteristics, ranging from cancers unique to childhood like pleuropulmonary blastoma and pancreatoblastoma to those typically affecting adults but uncommon in paediatric cases, including carcinomas and melanomas. Overall, 50 different paediatric cancer entities are included in this group of tumours (Table 1).

The intrinsic rarity of these entities results in considerable gaps in knowledge across epidemiology, molecular pathogenesis, diagnostic criteria, and evidence-based management. Mainly due to their rarity, randomized prospective clinical trials are generally infeasible, leading to highly heterogeneous therapeutic approaches and, in some cases, inferior outcomes compared to more common paediatric cancers. Addressing these challenges requires innovative collaborative models that integrate multidisciplinary expertise, facilitate cross-border data aggregation, and enable harmonized research efforts on an international scale. [5,6] Furthermore, studies have highlighted disparities in the registration and management of paediatric VRTs across European countries with differing health expenditure levels, emphasizing the ongoing need for coordinated efforts to reduce inequalities in care. [7,8]

The Burden and Complexity of Paediatric VRTs

Beyond their rarity, paediatric VRTs frequently present complex diagnostic and therapeutic challenges stemming from the unique biological underpinnings. Histopathological classification is often difficult, particularly for tumours exhibiting overlapping features with both paediatric embryonal and adult-type malignancies. Importantly, many paediatric VRTs are biologically distinct from their adult counterparts, often reflecting disruptions of normal developmental pathways rather than accumulation of somatic mutations over time. Several VRTs may arise during defined windows of ontogenesis, with characteristic epigenetic, transcriptomic, and telomeric alterations contributing to their pathogenesis. [2]

Unlike adult tumours, most paediatric VRTs display lower mutational burden, distinct chromosomal instability patterns, and limited immune infiltration, classifying them as "immunologically cold". Molecular diagnostics – while increasingly informative – are not always readily available across centres, potentially contributing to diagnostic uncertainty and treatment delays. In many cases, adult-derived classification systems and treatment protocols are still applied by default, risking both overtreatment and suboptimal care when paediatric-specific evidence is lacking. Treatment frequently requires highly individualized approaches, balancing the need for effective local control against the lifelong risks of late toxicity. Moreover, the absence of harmonized paediatric-specific protocols contributes to substantial variability in clinical practice, even across high-income healthcare systems.

These considerations are especially relevant for paediatric presentations of adult-type cancers, where age-related biology can be demonstrably different (e.g., *KIT*/*PDGFRA* wild-type paediatric GIST; higher frequency of oncogenic fusions in paediatric thyroid carcinoma; enrichment of *ALK* fusions and *TP53* alterations in paediatric primary lung carcinoma). [2,10-12] Accordingly, we advocate joint paediatric–adult multidisciplinary review for every such case, comprehensive molecular profiling to inform age-calibrated risk stratification, and access to molecularly matched therapies or trials when appropriate. For AYA patients, shared-care pathways between paediatric and adult centres, with tumour-board consensus on whether paediatric-adapted or adult protocols are most appropriate, can reduce fragmentation of care and align treatment intensity with disease biology.

The Establishment of EXPeRT - A European Collaborative Model

In response to the unmet needs, several national initiatives were established in Europe in the early 2000s. These included the German Malignant Endocrine Tumours Registry (GPOH-MET, 1997), the Tumori Rari in Età Pediatrica (TREP, Italy, 2000), the Polish Paediatric Rare Tumour Study Group (PPRTSG, 2002), the German Rare Tumour Committee (STEP, 2006), and the Groupe FRAnCais des TUmeurs Rares de l'Enfant (FRaCTurE, France, 2007). Recognizing

shared challenges and synergistic goals, these national groups joined forces in 2008 to create the European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT), formally endorsed by the European Society for Paediatric Oncology (SIOPE). [13,14] The EXPeRT consortium was established with two principal objectives: (1) to provide expert multidisciplinary clinical consultations for challenging individual VRT cases across national borders; and (2) to foster collaborative research through the integration of retrospective case series, development of prospective studies, and generation of harmonized clinical guidelines. This dual structure has enabled EXPeRT to function both as a clinical advisory board and as a scientific research platform.

Organizational Structure and Governance

EXPeRT is structured around a central board that oversees its strategic direction and activities. The organization includes an advisory system composed of panels of experts dedicated to specific tumour types (e.g., pancreatoblastoma, pleuropulmonary blastoma, rare gonadal tumours, thymic tumours). An international consultation desk provides centralized support for clinical consultations and case discussions. EXPeRT members represent over 15 European countries and various disciplines, including paediatric oncology, surgery, pathology, radiology, endocrinology, genetics, and supportive care. The group maintains close collaborations with major European rare cancer platforms such as SIOPe, ERN PaedCan (European Reference Network for Paediatric Cancer), EURACAN (European Reference Network for adult rare cancers), and the Joint Action on Rare Cancers (JARC). Its work is supported by regular meetings, the development of guidelines, and its presence on the ERN website (www.raretumors-children.eu). Figure 1 provides an overview of the EXPeRT organizational structure and governance.

Young EXPeRT - Building the Next Generation of VRT Expert

To promote the integration of early-career professionals into the field of paediatric VRT, EXPeRT established Young EXPeRT as a dedicated forum for members under 40 years of age. The group provides young clinicians and researchers from all member countries with structured access to EXPeRT activities, fostering a pan-European network focused on collaboration, education, and scientific engagement.

Young EXPeRT coordinates educational initiatives, including dedicated sessions at major conferences (e.g., SIOPE Congress) and participation in international webinars on VRTs. A quarterly newsletter summarizing recent key publications and updates is distributed, alongside the regular maintenance of public educational resources. Importantly, a Young EXPeRT representative is appointed to the EXPeRT board, ensuring that early-career perspectives are integrated into organizational planning and strategic priorities.

Expansion of Thematic Working Groups - Endocrine Tumours

Recognizing the distinct clinical, biological, and genetic complexity of endocrine tumours, EXPeRT has established a dedicated Endocrine Tumours Working Group. This multidisciplinary platform focuses on the full spectrum of adrenal, thyroid, and neuroendocrine tumours arising in children and adolescents. Given the high prevalence of cancer predisposition syndromes (e.g., Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, multiple endocrine neoplasia syndromes, and DICER1 syndrome) in these entities, the group integrates expertise from oncology, endocrinology, surgery, pathology, radiology, and genetics. Beyond addressing clinical diagnostic challenges and management complexities, the working group is actively developing new consensus-based diagnostic and therapeutic guidelines for rare endocrine malignancies. Importantly, the group also serves as a scientific platform for planning collaborative biological studies, particularly in adrenocortical carcinoma (ACC), where molecular and translational research opportunities remain substantial. A major strategic objective of the group is the preparation of a pan-European prospective clinical trial for paediatric ACC, which will address longstanding gaps in evidence and treatment standardization for this highly challenging tumour entity.

Scientific Achievements - Guideline Development

Among EXPeRT's most impactful contributions is the development of comprehensive, evidence-informed diagnostic and therapeutic guidelines for several paediatric VRT entities. Published as part of the EXPeRT/PARTNER collaborative output, these recommendations currently include consensus protocols for adrenocortical tumours, pancreatoblastoma, pleuropulmonary blastoma, thymic tumours, salivary gland carcinomas, cutaneous melanoma, nasopharyngeal carcinoma, NUT carcinoma, sex cord stromal tumours, olfactory neuroblastoma, and appendiceal neuroendocrine tumours. [15-26] Several additional guidelines are currently under development to further expand coverage across the diverse spectrum of VRT entities (e.g., pheochromocytoma/paraganglioma, lung carcinomas, pseudopapillary pancreatic tumour, myoepithelial carcinoma). These guidelines serve as critical resources for clinicians worldwide (European Cooperative Study Group for Paediatric Rare Tumours). Importantly, they have been widely incorporated into the European Standard Clinical Practice (ESCP) project coordinated by ERN PaedCan, thus contributing directly to the harmonization of VRT management across Europe.

Cancer Predisposition Syndromes - A Crossroads in VRT Care

Cancer predisposition syndromes (CPS) play a critical role in the aetiology of very rare paediatric tumours (VRTs). Germline pathogenic variants are identified in approximately 8–

10% of paediatric cancer patients overall, with notably higher prevalence in certain VRT subtypes. Specific tumour types and histologies are highly suggestive of an underlying CPS and should prompt systematic evaluation. [27,28] According to EXPeRT guidelines, CPS assessment integrates personal and family history, tumour histology, and increasingly, tumour genomic profiling to identify germline-suspect alterations. [29] The identification of a CPS has significant clinical implications, mandating adapted surveillance, tailored therapies, and genetic counselling for affected families. [30-33]

Table 2 summarises key VRT types, their most frequently associated CPSs, and estimated CPS prevalence where available.

Multidisciplinary Clinical Consultation - The Virtual Tumour Board

EXPeRT established a virtual tumour board to address the limited local expertise many centres face with individual VRT types. In fact, for most paediatric oncologists facing a patient with a VRT, this patient may be his or her first-in-a-lifetime with this specific diagnosis. Between its inception in May 2017 and 2024, the EXPeRT virtual tumour board has reviewed over 170 complex VRT cases submitted from 27 countries, including both European and non-European countries. [34] This system facilitates expert multidisciplinary guidance for diagnostic clarification, molecular testing strategies, surgical planning, and therapeutic sequencing. In many cases, expert consultation resulted in changes in diagnosis or therapeutic strategy based on collective expert input. Importantly, feedback surveys indicated that in more than 90% of cases, the advice provided was considered helpful and had a significant impact on patient management. The virtual tumour board provides an open, scalable mechanism to broaden access to specialised expertise across Europe and beyond; nevertheless, current utilisation captures only a fraction of incident cases and likely reflects referral bias toward larger centres, which we are actively addressing through tailored recommendations and structured follow-up. [34] The system has recently been integrated into the Clinical Patient Management System (CPMS) of ERN PaedCan to ensure its long-term sustainability and technical development (European Reference Networks - Clinical Patient Management System - CPMS), and with the most recent update, the usability has significantly been improved. [35] Case presentations to the CPMS are welcome at: https://cpms2.ern-net.eu/.

Retrospective Collaborative Studies - Foundational Knowledge Generation

One of EXPeRT's earliest scientific priorities was to overcome fragmented case reporting by integrating national retrospective datasets. Several landmark studies have since generated the largest existing clinical cohorts for multiple VRT entities. Key examples include: A multi-country study of adrenocortical tumours identifying clinical prognostic factors; a European pancreatoblastoma series defining staging and treatment outcome correlations; collaborative

studies on thymic tumours, primary lung carcinoma, NUT carcinoma, mesothelioma, cutaneous melanoma, pleuropulmonary blastomas, high-risk adrenocortical carcinomas, salivary gland carcinomas, melanotic neuroectodermal tumour of infancy, and ovarian Sertoli Leydig cell tumour, which established management frameworks where none previously existed. [9,26,36-46] These studies have not only elucidated disease-specific clinical characteristics but also directly informed guidelines development.

At present, however, we cannot robustly estimate what proportion of all EU VRT cases are captured across EXPeRT's integrated national datasets. Available country-level snapshots suggest partial and heterogeneous capture: for example, in a nationwide French series of paediatric bronchial carcinoid, only 12/48 patients (25%) were directly recorded in the FRACTURE database, with additional cases identified via the National Registry of Childhood Cancers. [47] This underscores likely selection and tertiary-centre referral biases in retrospective datasets and motivates systematic linkage with population-based paediatric cancer registries and pathology networks.

Table 3 summarises number of cases and survival rates of different VRTs in children and adolescents published by the EXPeRT group.

Prospective Research - The PARTNER Project

EXPeRT´s prospective research capabilities were solidified through coordination of the Paediatric Rare Tumours Network - European Registry (PARTNER), funded by the European Union (EU) and initiated in 2018. The PARTNER study provides a pan-European data platform linking existing national rare tumour registries and offering registry access for countries without established VRT databases. Since the start of patient enrolment in June 2023, this study has accumulated over 100 prospective cases, capturing harmonized data on histology, diagnostic work-up, treatment modalities, and outcome across multiple European centres. [48]

A major objective of PARTNER has been the harmonization of data collection standards, supported by centralized metadata repositories within the European Rare Disease Registry Infrastructure (ERDRI). Thereby, it can support future denominator-based completeness assessments (e.g., capture–recapture analyses against population cancer registries). [48]

While biobanking has not been integrated into PARTNER, this component will be incorporated in the upcoming PARTNER4VRT project (see below) scheduled to launch in 2026, which will also initiate first biological studies, and serve as a pilot framework for prospective clinical studies in very rare tumour entities.

Integration into the European Rare Cancer Ecosystem

EXPeRT's achievements have positioned the consortium as a key stakeholder within the broader European rare cancer community. The group maintains active collaborations with:

- SIOPE, serving as the central European platform for paediatric oncology.
- SIOPE Host Genome Working Group, the European working group for cancer predisposition in children, providing expertise on cancer predisposition syndromes.
- ERN PaedCan, contributing expertise to cross-border healthcare delivery and virtual consultations.
- EURACAN, fostering synergies at the paediatric-adult interface for rare tumours across the age spectrum.
- JARC, supporting European policy development and advocacy for rare cancers.
- ESMO Rare Cancers, facilitating scientific dialogue with adult oncology communities.

In addition, EXPeRT actively collaborates and synergizes with other rare tumour initiatives such as the MELCAYA project (see below).

Addressing Low-Expenditure Health Systems

Despite progress in EXPeRT's coverage, significant inequalities persist in European countries with lower healthcare expenditure. A 2025 survey within LHEAR countries revealed that most lack organized registration systems, multidisciplinary VRT expertise, and access to advanced diagnostics or treatment modalities. [7] In Eastern Europe, rare tumours like pleuropulmonary blastoma are under-recognized, with observed-to-expected registration rates as low as 0.65, compared to >1.2 elsewhere. [8] These disparities underscore the need for targeted strategies—such as extending registry infrastructure, bolstering pathology review networks, and incorporating the low healthcare-expenditure regions into virtual consultation platforms—to ensure EXPeRT's model is truly inclusive and equitable across Europe.

MELCAYA - Advancing Melanoma Care in Children, Adolescents, and Young Adults

The MELCAYA project (Novel Health Care Strategies for Melanoma in Children, Adolescents, and Young Adults, CAYA), a pan-European interdisciplinary initiative funded under the Horizon Europe framework (2022–2026), aims to understand risk factors and determinants of melanoma in children, adolescents, and young adults, and to improve prevention, diagnosis, and prognosis through integrated research, and the development of tailored public health strategies. Bringing together a multidisciplinary consortium of 25 partners across 10 countries, MELCAYA integrates clinical cohorts, registry data, and advanced omics technologies to develop improved classification systems and risk stratification tools for melanoma in young patients. Novel diagnostic approaches, including artificial intelligence-supported image analysis and non-invasive detection methods, are being explored. Within this consortium, EXPeRT contributes its expertise on paediatric melanoma and very rare tumour management, complementing its existing guideline development and collaborative activities in this field. [49]

Toward Global Collaboration - PARTNER4VRT and Transatlantic Synergies

Building upon its European leadership, EXPeRT is now extending its global collaborative scope through the EU-funded PARTNER4VRT project, awarded in 2025 under the EU4Health framework and scheduled to run from January 2026 to December 2027. This unique initiative represents a formal transatlantic partnership between EXPeRT, ERN PaedCan, the US National Cancer Institute (NCI), and EUROCAN, initially focusing on two ultra-rare paediatric tumour entities: pancreatoblastoma and adrenocortical carcinoma.

PARTNER4VRT aims to overcome several key challenges inherent to research in very rare paediatric cancers, including extreme data scarcity, heterogeneity in diagnostic and treatment approaches, and substantial regulatory barriers to international data sharing. The project will establish a coordinated EU-US observational platform that builds upon the existing PARTNER registry while developing shared definitions, harmonized eligibility criteria, and common data elements (CDEs) to standardize data collection across continents. Specific emphasis is placed on capturing both clinical and molecular data, integrating genomic, transcriptomic, and epigenetic information relevant to these rare tumour types.

In addition, PARTNER4VRT will systematically address the legal and ethical complexities of cross-border data exchange by aligning European (GDPR) and US (HIPAA) regulatory frameworks through dedicated legal and privacy expertise. Patient-reported outcomes (PROs), long-term follow-up strategies, and direct involvement of patient advocacy organizations will be incorporated to ensure patient-centeredness throughout the program.

Importantly, PARTNER4VRT also prepares the foundation for future large interventional studies, with the long-term goal of launching a pan-European prospective clinical trial in paediatric adrenocortical tumours. The pilot observational platform is designed to be scalable, serving as a proof-of-concept for expanding this transatlantic collaborative model to additional paediatric VRT entities in future phases.

Future Perspectives and Strategic Priorities

Despite major advances, multiple critical gaps remain for paediatric VRT research:

- Harmonized tumour classification, staging, and risk stratification systems tailored to paediatric populations.
- Expanded translational research platforms incorporating genomics, transcriptomics, proteomics, epigenetics, metabolomics, and imaging, supported by prospective biobanking efforts.
- Development of adaptive, international trial designs enabling prospective interventional studies for ultra-rare entities.
- Comprehensive legal and regulatory frameworks to enable secure, ethical, and efficient cross-border data exchange both within Europe and transatlantically.

- Closer integration of paediatric and adult rare tumour networks to ensure seamless lifelong care across age transitions.
- Sustainable long-term funding models to support the maintenance and growth of international registries, data infrastructures, and research networks in paediatric VRTs.

Conclusions and Outlook

EXPeRT represents a successful, sustainable, and internationally recognized model for collaborative care, research, and policy leadership in paediatric VRTs. Through its integrated clinical consultations, harmonized guidelines, collaborative registries, translational studies, and expanding international partnerships, EXPeRT has significantly advanced the clinical and scientific landscape for these highly challenging malignancies. The ongoing development of transatlantic collaborations such as PARTNER4VRT, the launch of thematic working groups, and the establishment of pan-European prospective trials reflect the next stage of growth for the consortium.

Moving forward, sustained investment in international cooperation, large-scale data integration, cutting-edge biological research, and harmonized regulatory frameworks will be critical. These efforts will enable the creation of a unified global ecosystem for paediatric VRTs, driving innovation in precision diagnostics, biomarker development, therapeutic discovery, and individualized patient care. Ultimately, EXPeRT is poised to serve as both a scientific and organizational template for advancing care for children and adolescents with rare cancers worldwide.

DECLARATION OF INTERESTS

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.

ACKNOWLEDGMENT AND FUNDING

CRediT author statement: Conceptualization, Mi.Ku., A.F., D.O.; Formal analysis, Mi.Ku.; Methodology, Mi.Ku., A.F., D.O.; Resources, Mi.Ku.; Supervision, Mi.Ku.; Writing - original draft, Mi.Ku.; Writing - review & editing, all authors. All authors have read and agreed to the published version of the manuscript.

Data availability statement: Not applicable.

Ethics approval: Not applicable.

Funding: The French Fracture database is supported by a grant from SFCE-Imagine For Margo. The Italian TREP Registry has been partially supported by Fondazione Giovanni Celeghin, ONLUS. The German MET and STEP Registries are being funded by the German Childhood Cancer Foundation (Deutsche Kinderkrebsstiftung). The MELCAYA project is

funded by an EU Horizon Grant (HORIZON-MISS-2021-CANCER-02, ref. 101096667). The funders had no role in the design, data collection, data analysis, and reporting of this study.

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Figure Legends

Figure 1. Overview of the EXPeRT Organizational Structure and Governance

Figure 2. Overview of key collaborative initiatives and research activities involving EXPeRT, including clinical recommendations, virtual tumour boards, retrospective analyses, and partnerships across endocrine and paediatric oncology groups.

Table Legends

Table 1. Main very rare tumours occurring during childhood and adolescents

Table 2. Key very rare tumour types, their most frequently associated cancer predisposition syndromes (CPSs), and estimated CPS prevalence

Table 3. Number of cases and survival rates (retrospective studies) of different very rare tumours in children and adolescents published by the EXPeRT group

Table 1. Main very rare tumours occurring during childhood and adolescents

Histotype	Incidence	Overall outcome	EXPeRT experience
Adrenocortical tumours (ACTs)	0.2 cases / 1 m children / year	– survival depends on stage and histology – OS >80% for patients with small localized resected ACT – OS <20% for patients with metastatic adrenocortical carcinoma (10-33% of all cases)	Virgone C. et al. 2021 (ESCP) Cecchetto G. et al. 2017 [33] PARTNER4VRT project
Carcinomas and carcinoid tumours of the lung/bronchi		– 10-year OS 90-100% in mucoepidermoid carcinomas of the lung and bronchial carcinoids; atypical bronchial carcinoid – lower survival rate – 5-year OS ~25% in lung adenocarcinoma, squamous cell carcinoma, and rare cases of small cell lung cancer	Abele M. et al. 2022 ESCP finalized
Colorectal cancer	1-2 cases / 1 m children / year	– 5-year OS ~50% – better outcome in children with cancer predisposition syndromes	ESCP in preparation
Gastric cancer	< 1 case / 1 m children / year	– durable remissions after complete resection at localized stage – poor prognosis at stage IV	-
Melanoma	4.5 cases / 1 m children / year; 0.7–0.8 cases / 1 m children / year in the first decade of life; >10 cases / 1 m children / year in the second decade of life	– 5-year OS 90% for localized disease, <20% for unresectable and metastatic melanomas	Forchhammer S. et al. 2024 Mandala M. et al. 2024 Liebmann A. et al. 2023 Ferrari A. et al. 2021 (ESCP) Brecht I. et al. 2018 MELCAYA project
Melanotic neuroectodermal tumour of infancy	< 0.05 cases / 1 m children / year ; >90% of cases in	– OS ~97.5% in tumours located in maxilla/ mandible – worse OS in children aged >12 months	Krawczyk M. et al. 2023 ESCP – in preparation

	children <6 months of age	– 20-30% local recurrences particularly in young children (<2 months)	
Malignant mesothelioma	0.05-0.1 cases / 1 m children / year	– 4-year OS ~80%, EFS ~45% – better outcomes in patients with an isolated peritoneal primary site than those with thoracic/multiple sites	Orbach D. et al. 2020
Nasopharyngeal carcinoma	0.4 cases / 1 m children / year; in endemic countries 2 cases / 1 m children / year	– 5-year OS and PFS >90%	Ben-Ami T. et al. 2021 (ESCP)
Neuroendocrine tumours of the appendix	1-10 cases / 1 m children / year	– OS and EFS 100%	Virgone C. et al. 2025 (ESCP)
NUT carcinoma	unknown – frequently undiagnosed or misdiagnosed cases	– 2-year OS and EFS ~15-20% – long-term survival or cure rare	Flaadt T. et al. 2025 Lemelle L. et al. 2023 (ESCP)
Olfactory neuroblastoma	1 case / 1 m children / year	– 5-year OS and EFS 70-90%	Di Carlo D. et al. 2023 (ESCP)
Pancreatoblastoma	< 0.5 cases / 1 m children / year	– 5-year OS 79%, EFS 60% – congenital and infantile PBL associated with particularly good prognosis	Bien E. et al. 2021 (ESCP) Bien E. et al. 2011
Pseudopapillary pancreatic tumour	0.1-0.2 cases / 1 m children / year	– OS 100% after complete tumour resection	ESCP – in preparation
Pheochromocytoma/ Paraganglioma	0.5-2 cases / 1 m children / year	– high prevalence of hereditary disease – higher risks of bilateral, multifocal, recurrent, and metastatic tumours	ESCP finalized
Pleuropulmonary blastoma	0.5-1 cases / 1 m children / year	– type I: OS 98% – type II: OS 80% – type III: OS 60%	Bisogno G. et al. 2021 (ESCP) Bisogno G. et al. 2014

Salivary gland carcinoma	0.8-1.4 cases / 1 m children / year	– 5-year OS 95% – 10-year OS >90%	Schneider DT. et al. 2023 Surun A. et al. 2021 (ESCP)
Sex cord stromal tumours	0.1-0.7 cases / 1 m children / year; incidence depends on the histotype of the tumour)	– ovarian SCST: 5-year OS 87%, EFS 70% – testicular SCST: 5-year OS 100%	Schneider DT. et al. 2021 (ESCP) Schneider DT. et al. 2015
Thymoma and thymic carcinoma	≤0.1 cases / 1 m children / year	– thymoma: 5-year OS 100% – thymic carcinoma: 5-year OS 20%	Stachowicz-Stencel T. et al. 2021 (ESCP) Stachowicz-Stencel T. et al. 2015

Abbreviations: EFS (Event-free survival). ESCP (European Standard Clinical Practice document - EXPeRT/PARTNER recommendation). M (Million). OS (Overall survival). PFS (Progression-free survival):

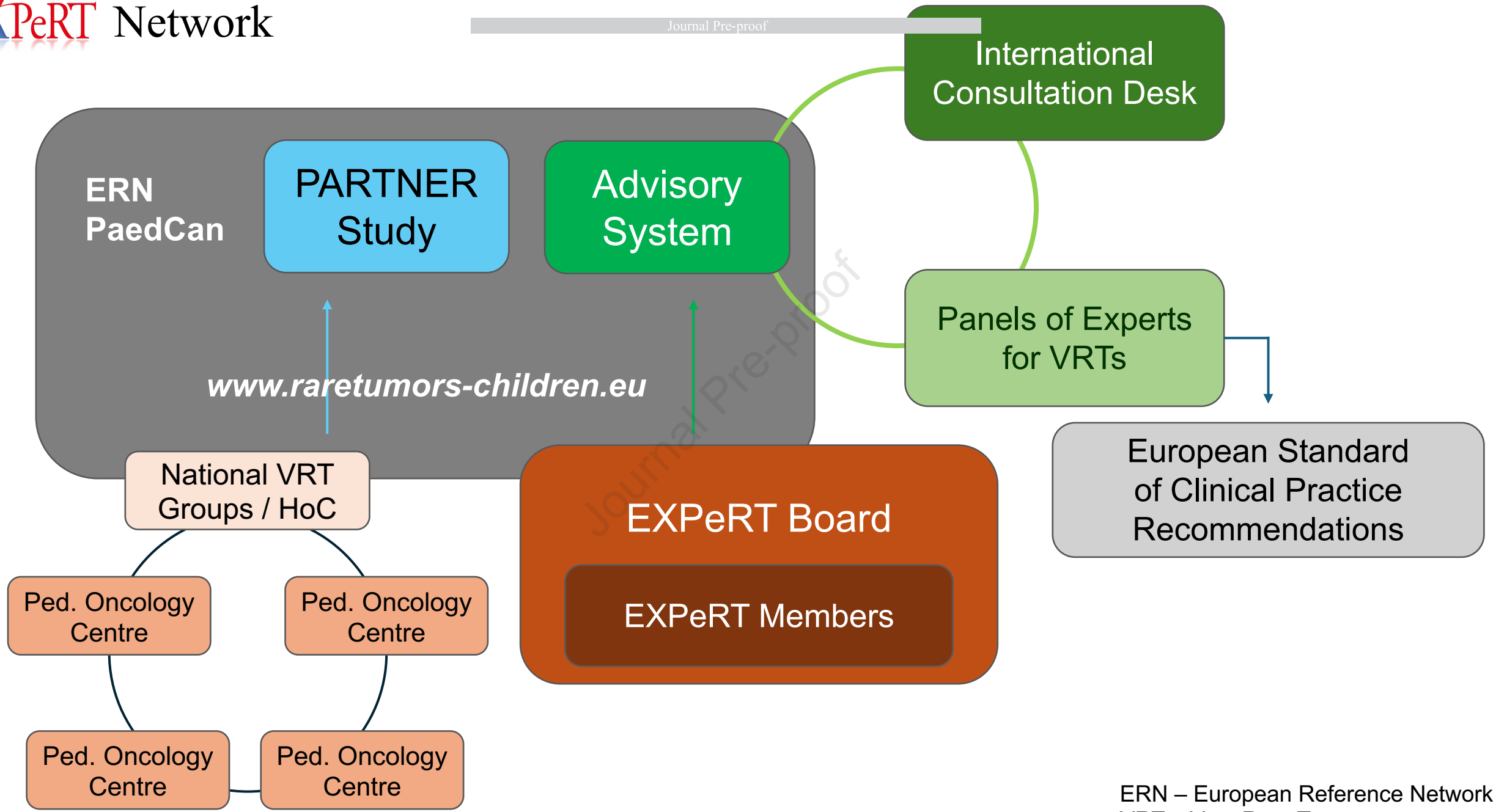
Table 2. Key very rare tumour types, their most frequently associated cancer predisposition syndromes (CPSs), and estimated CPS prevalence

Tumour type	Most frequent associated CPS(s)	Estimated CPS prevalence in tumour type
Adrenocortical carcinoma (ACC)	Li-Fraumeni syndrome (TP53), Beckwith-Wiedemann syndrome (11p15 imprinting defects)	45–50% (Europe); up to 80% (Brazil)
Choroid plexus carcinoma (CPC)	Li-Fraumeni syndrome (TP53)	45–50% (Europe)
Pleuropulmonary blastoma (PPB)	DICER1 syndrome	>65%
Sertoli-Leydig cell tumour (SLCT)	DICER1 syndrome	>60%
Differentiated thyroid carcinoma	DICER1 syndrome, PTEN hamartoma tumour syndrome	Variable; ~15% in some series
Colorectal carcinoma	Lynch syndrome (MMR genes), familial adenomatous polyposis (APC)	Rare in paediatric cases, but high if present
Melanoma (paediatric)	Xeroderma pigmentosum, Li-Fraumeni syndrome, familial melanoma (CDKN2A)	Rare overall; high in XP
Pancreatoblastoma	Beckwith-Wiedemann syndrome	~10%
Hepatoblastoma	Beckwith-Wiedemann syndrome, familial adenomatous polyposis	~10% (BWS); <1% (FAP)

Table 3. Number of cases and survival rates (retrospective studies) of different very rare tumours in children and adolescents published by the EXPeRT group

Very rare tumour type; year of publication (reference)	EXPeRT Group				
	n	Ages (years old)	Study period	OS	
				EFS	
Pancreatoblastoma; 2011 (36)	20	0-17	2000-2009	79,4% +/- 9,2% (5-year OS)	
				58,8% +/- 12,5% (5-year EFS)	
Pleuropulmonary blastoma; 2014 (37)	65	0-17	2000-2009	Type I	91,7% (5-year OS)
					83,3 % (5-year OS)
				Type II/III	57,5% (5-year EFS)
					42,9% (5-year EFS)
Thymic tumors; 2015 (29)	36	0-17	2000-2012	Thymomas: 14/16 DFA Carcinomas: 21% +/-10% (5-year OS)	
Ovarian TCSL; 2015 (35)	44	0-17	1993-2008	87% +/- 5% (5-year OS)	
				70% +/- 7% (5-year EFS)	
Adrenocortical carcinoma; 2015 (33)	82	0-17	2000-2013	55% [95% CI: 42-66] (3-year OS)	
				39% [95% CI: 27-50] (3-year EFS)	
Cutaneous melanoma; 2018 (32)	219	0-18	2002-2012	91,4% [95% CI: 85,8-94,9] (3-year OS)	
				84% [95% CI: 77,3-88,9] (3-year EFS)	
Mesothelioma; 2020 (34)	33	≤ 21	1987-2018	82,3% [95% CI: 67,8-99,9] (5-year OS)	
				45,1% [95% CI: 28,4-77,1] (5-year EFS)	
Progressive and Relapsed PPB type II/III; 2021 (38)	35 (9 PD) (26 RD)	0-17	2000-2018	PD	0% (5-year OS and EFS)
				RD	37% +/- 19% (5-year OS and EFS)
Primary lung carcinoma; 2022 (30)	38	0-18	2000-2018	52% +/-13% (3-year OS)	
Salivary gland carcinoma; 2023 (39)	121	0-17	2000-2014	96% +/-22% (10-year OS)	
NUT carcinoma; 2025 (31)	27	0-18	2011-2023	Median OS 6,5 months	
				Median EFS 1,5 months	

Abbreviations: n (Total number of patients). OS (Overall survival). EFS (Event-free survival). DFA (Disease-free alive). PPB (Pleuropulmonary blastoma SLT (Sertoli-Leydig cell tumour). 95% CI (95% confidence interval). Progressive (PD) or relapsed disease (RD)

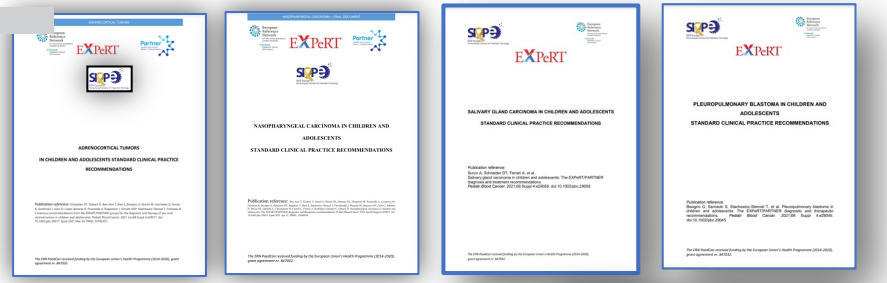


ERN – European Reference Network
VRT – Very Rare Tumour
HoC – Head of Centre

Retrospective studies

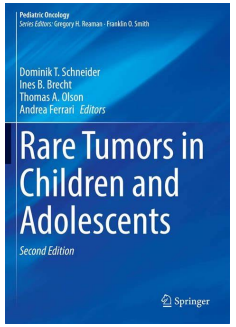
MELCAYA

Clinical-biological study



European Standard Clinical Practice Recommendations

EXPeRT



Collaborative book

VCS

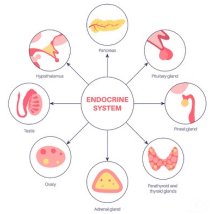
CPMS Care 2.0

Virtual tumor board CPMS

Young EXPeRT

Partner
Paediatric Rare Tumours Network - European Registry

Partner study



Endocrine group

Partner4VRT

Highlights

- EXPeRT provides expert multidisciplinary consultation for very rare paediatric tumours across Europe.
- Harmonized European guidelines for diagnosis and treatment of paediatric VRTs have been developed by EXPeRT.
- The PARTNER registry enables prospective data collection for paediatric VRTs across European centres.
- A virtual tumour board facilitates equitable access to VRT expertise, impacting management in >90% of cases.
- PARTNER4VRT establishes a transatlantic platform to standardize data and foster future interventional studies.