D35, D9.4 Report summarising proposals to address extremely rare cancers in young patients

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DELIVERABLE DESCRIPTION

Joint Action on Rare Cancers (JARC)

The Joint Action on Rare Cancers (JARC) is aimed to integrate and maximize efforts of the European Union (EU) Commission, EU Member States and all stakeholders to advance quality of care and research on rare cancers.

The public health challenges posed by rare cancers include the limited professional expertise in the community, the difficulties in clinical research, the need of a timely and appropriate diagnosis and optimal treatment from the very beginning of the patient's journey. An accurate clinical, pathologic and biological assessment of the disease of the individual patient is key to survival and cure, as well as an expert clinical decision provided by a multidisciplinary team. To this end, proper referral of patients and effective clinical networking are crucial in rare cancers. This is the main reason why JARC decided to shape its efforts around the new European Reference Networks (ERNs) with the following objectives:

1. Improving epidemiological surveillance of rare cancers in the EU
2. Identifying standards of care for all families of rare cancers to ensure sharing of best practices and equality of care for rare cancers across Europe, particularly through clinical networking
3. Improving the implementation at local level and within ERNs of clinical practice guidelines on rare cancers
4. Promoting integration of translational research innovations into rare cancer care
5. Improving education on rare cancers for medical and non-medical experts to ameliorate management of rare cancers and to improve rare cancer patients' empowerment in the EU
6. Identifying core strategies to incorporate in National cancer plans and Rare disease plans to address the specific needs of rare cancers across EU MSs

The JARC is structured in 10 work packages (WPs). Three cross cutting WPs (WP1 coordination, WP2 dissemination, WP3 evaluation) and 7 specific WPs based on the JARC objectives: WP4 epidemiology, WP5 quality of care, WP6 clinical practice guidelines, WP7 innovation and access to innovation, WP8 medical education, WP9 childhood cancers and, WP10 rare cancers policy. Patients work across all work packages, driving the JARC efforts along the needs of the only end users of all what we can do, in care and research as well.

Description of WP

Work Package 9 – Childhood cancers contains actions to define evidence-informed recommendations for:

- Ensuring access to standard and innovative therapies for children with cancer

- Addressing the research and clinical issues in young people with extremely rare cancers and in survivors of childhood cancers.

The aim and the purpose of the specific deliverable

The aim of this deliverable is to identify solutions for delivering optimal care and research for young people with extremely rare cancers.

The target group of the specific deliverable

The recommendations are targeted to stakeholders involved in decision-making on health research as well as treatment organisation and delivery in the field of paediatric haematology oncology in Europe.

Summary of the main conclusions of the deliverable

Paediatric malignancies are rare according to the definition of rare cancers (Gatta et al., 2017). Each paediatric malignancy is then rare or very rare (Ferrari, Brecht et al. 2019). Paediatric very rare tumours (VRT) have been referred to in the community as 'orphan' diseases. Though all together accounting for 11% of all paediatric cancers, the single VRT entities are exceedingly rare. Often, only single cases are identified in Europe within one year. Therefore, research interest is limited, data and specimen cannot easily be collected, and therefore results are difficult to generate. Consequently, incidence rates are underestimated, funds are limited, the number of experts small, and new medicines are not developed due to the likewise limited economic interest.

Thus, improvement has to be reached in the following fields:

1. Definition, classification and epidemiology
2. Awareness and support
3. Building a common European database
4. Diagnostic and therapeutic guidelines
5. Aetiology and Research
6. Access to modern therapies.

In the last years, members of the European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT) worked within the Joint Action on Rare Cancers (JARC) Work Package 9 led by the European Society for Paediatric Oncology (SIOP Europe) and with the European Reference Networks on solutions to improve the care and research in the field. However, more financial resources, awareness and support by stakeholders are urgently needed.

Introduction

Childhood cancer is rare worldwide, accounting for significantly less than 1% of all cancer diagnoses. Major groups of childhood cancers include: leukaemias, lymphomas, central nervous system tumours, sympathetic nervous system tumours, retinoblastoma, kidney tumours, liver tumours, bone tumours, soft-tissue sarcomas, gonadal and germ-cell tumours, epithelial tumours, and other and unspecified malignant neoplasms. Among these, there is still a difficult-to-define group of patients with very rare cancers that do not fall into the larger, 'classic', categories of paediatric oncology (i.e. malignant melanoma, ENT tumours and colon cancer). These entities are characterized by their very low incidence rates (<2/million/year) and the absence of available clinical and scientific information. From a clinical and scientific perspective, these very rare cancers might be referred to as 'orphan' diseases, indicating that no clinical structures have been developed to aid in their diagnosis and treatment and no scientific research is ongoing.

Delayed diagnoses resulting into advanced stages and a lack of effective treatment strategies are the consequences.

This problem was addressed recently as several very rare paediatric study groups have been founded to improve the situation of children and adolescents with VRT. In 2008, a paediatric very rare tumour consortium was established throughout Europe: European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT). Within this cooperative group, several multinational disease specific projects have been initiated and EU-funded projects such as the ExPO-r-Net (European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment: European Union Health Programme 2008-2013, grant agreement nr. 2013 12 07, https://www.expornet.eu/) followed by the ERN PaedCan (European Reference Network for Paediatric Oncology: European Union's Health Programme 2014-2020, http://paedcan.ern-net.eu) and more recently the ERN-PARTNER project (Paediatric Rare Tumours Network European Registry: (European Union Health Programme 2014-2020, project 777336/PARTNER, https://www.raretumors-children.eu/about-us/partner-project/) were launched. These experiences underscore the importance of networking, seeking new partnerships and pooling forces and resources to extend research and improve the quality of patient care.

However, several questions remained unanswered. Do we estimate the incidence numbers correctly, as extremely rare cancers are known to be underestimated? How can we reach evidence for the treatment strategies applied in children and adolescents with extremely rare cancers considering the lack of clinical trials? Do adult-type cancers found in children have the same biological characteristics and behaviour as the same cancer occurring in an adult patient? Why and how do children and adolescents develop adult-type tumours in a very short time period compared to a prolonged development in adults? Can we use the same treatment standards as in adults or do we need specific treatment concepts for adult-type cancers occurring in children?

Addressing very rare cancers is an integral part of the Strategic Plan of SIOP Europe – the European Society for Paediatric Oncology (Vassal et al 2016). Solutions have to be found in order not to leave young patients with very rare cancers behind but let them benefit from the rapid advances in clinical paediatric oncology.

Very rare tumours (VRTs) in children and adolescents are considered those with an incidence of less than 2 cases/million/year and that are not included in already defined international or national protocols. Examples are colorectal carcinoma or pancreatoblastoma. Univocal diagnostic/therapeutic criteria for these neoplasms do not exist; moreover, because of their extreme rarity, physicians often have less resources and, in some cases, less interest in understanding their natural history and developing clinical studies and biological research. Additionally, the small number of cases cannot amortize the costs of specific pharmacologic research, which leads to scarce information- and knowledge-sharing. For all these reasons, very rare tumours in paediatric age represent an area or high unmet need and might be referred to as 'orphan' diseases to indicate the lack of relevant clinical structures and ongoing scientific research. The aim of this deliverable is to identify solutions for delivering optimal care and research for young people with extremely rare cancers.

Material and methods

The work was performed in collaboration with SIOP Europe, Childhood Cancer International – Europe (CCI-Europe), EXPeRT group, and RARECAREnet as part of the JARC Work Package (WP) 9, Task 9.3. The expertise of EXPeRT underpinned all activities, with member GPOH leading the Task and other members involved actively including as Collaborating Partners. These EXPeRT members were also involved in the EXPO-r-Net and are members of the ERN PaedCan.
CCI-Europe was involved throughout as Collaborating Partner representing the patient perspective, as was SIOP Europe as Work Package leader representing the pan-European professional community in paediatric cancers.

Box 1. Overview of key contributors to JARC WP9, Task 9.3

Partner	Contact	Area of contribution
GPOH - German Society of Paediatric Oncology - University of Tuebingen	Ines Brecht ines.brecht@med.uni-tuebingen.de Dominik T. Schneider dominik.schneider@klinikumdo.de	Task 9.3 Lead
INT - Fondazione IRCCD Istituto Nazionale dei Tumori	Gemma Gatta gemma.gatta@istitutotumori.mi.it Annalisa Trama annalisa.trama@istitutotumori.mi.it	Epidemiology
CCI Europe - Childhood Cancer International - Europe	Anita Kienesberger a.kienesberger@kinderkrebshilfe.at oesterreichische@kinderkrebshilfe.at	European questionnaire to parents
EXPeRT - European Cooperative Study Group for Paediatric Rare Tumours	Andrea Ferrari Andrea.Ferrari@istitutotumori.mi.it Daniel Orbach daniel.orbach@curie.fr	Expertise and support in all areas
Clinical Hospital Centre Rijeka, Croatia	Jelena Roganovic roganovic.kbcri@gmail. com	LHEAR countries
SIOPE Europe – the European Society for Paediatric Oncology	Olga Kozhaeva Samira Essiaf Elena Botanina office@siope.eu	Overall coordination and support

The first phase of the JARC coincided with the consolidation of the synergic ExPO-r-Net project and its WP8: Integrating children with very rare tumours in a European Reference Network. Here, activities were undertaken to identify centres of reference and formulate standard of care guidelines.

A face-to-face meeting of ExPO-r-Net WP8 with the participation of JARC Coordinator and WP4 – Epidemiology Lead INT took place on 29-30 March 2017 in Padova, Italy, to streamline the approach and transition between the project activities. Participants worked on a detailed plan of the JARC Task 9.3 methodology and planning and discussed an analysis on incidence of very rare paediatric cancers in Europe. RARECAREnet was identified as a basis for better understanding the epidemiology of the concerned entities.

A second face-to-face meeting on VRT in children and young people took place in Frankfurt, Germany on 17 November 2017. The meeting discussed the core areas of the work with the EXPeRT group, CCI Europe and INT and identified future orientations for the outcome recommendations report on extremely rare tumours in children and adolescents:

1. Definition, classification and epidemiology
2. Awareness and support
3. Building a common European database
4. Diagnostic and therapeutic guidelines
5. Aetiology and Research
6. Access to modern therapies.

1. *Definition, classification, and epidemiology of very rare cancers in children*

The annual incidence of cancer in individuals under 15 years of age is 14-16/100,000 (Steliarova-Foucher 2017). Therefore, all types of cancer occurring in childhood are rare. How do we define 'very rare' tumours?' Until recently, very rare paediatric tumours were not defined by incidence but also by their status as 'orphan disease' in line with the following characteristics:

- often under-registered in registries → incidence difficult to define
- a paediatrician might see them only once in the professional life
- little clinical experiences and no evidence-based guidelines for diagnosis and treatment
- few or no cooperative groups dedicated to these entities
- scarce financial support for studies on these tumours

The EXPeRT Group defined 'very rare tumours' (VRT) of paediatric age as 'any malignancies characterized by an annual incidence of <2 per million in the population up to 18 years old and not considered in other trials'.

2. *Awareness and support*

Patient advocacy groups are key partners in all paediatric cancers. They can help to disseminate information, promote the structures for patient care and play a role in the regulatory process. They can also support the recruitment of patients into clinical trials or registries.

In JARC Task 9.3, a questionnaire was designed in collaboration with CCI-Europe to collect experiences and perceptions of parents of children with VRT across Europe in relation to the relevant structures and needs at the national level. The survey was launched on 22 March 2018 with deadline in April 2018.

3. *Building a common European database*

PARTNER is a 3-year long project operated by the EXPeRT group. It aims to create a Paediatric Rare Tumour European Registry dedicated to children and adolescents with VRT linking existing national registries and to provide a registry for those countries without a registry for VRT in place. PARTNER gets separate funding from the EU and is linked to the ERN PaedCan. There is a close connection with the JARC project.

4. Diagnostic and therapeutic guidelines

Most very rare tumours in children and adolescents are so-called “adult-type” tumours. However, first clinical studies indicate that they show a different biological behaviour.
Therefore, treatment concepts from adult medicine cannot be directly applied to children due to the lack of evidence. Besides, diagnosis of these tumours might be difficult in children. Furthermore, medicines or medicine combinations applied in adult patients may not be familiar to paediatric oncologists, and toxicity in children has not yet been studied (few phase I/II studies). Due to the rarity, randomized clinical studies are impossible or difficult to perform. The strategic value of PARTNER in the field of public health is based on the European-wide gathering of information on the treatment of VRT and the provision of this information to experts generating new guidance recommendations for clinical practice for use by ERN and non-ERN institutions. The data collection will contribute to optimised consultation of patients with VRTs. Within the PARTNER project, recommendations for diagnosis and treatment are being developed and will be published.

5. Aetiology and Research

Etiopathogenesis of very rare tumours in children and adolescents is widely unclear due to several barriers for biological studies resulting from the rarity. Differences in tumorigenesis in VRT compared to classical tumours of childhood or adulthood are very likely, there are several hints, but detailed studies are rare. Also, for several very rare adult-type tumours occurring in childhood (e.g. carcinomas), a genetic susceptibility has been identified in sporadic cases, but this was also not systematically studied. Several very rare tumour working groups seek to further advance the research in the field and projects have been launched. However, there are several barriers for biological studies resulting from the rarity, e.g. missing biological material and funding.

In the future, it will be necessary to join forces on a European level in order to reach sufficient patient numbers. Significant financial support is needed.

6. Access to modern therapies

For many advanced-stage very rare tumours in children and adolescents, no evidence-based treatment concepts are available. Therefore, alternatives have to be developed. In particular, the advent of cancer immunotherapy has revolutionized the therapeutic landscape for a broad variety of cancer entities. In contrast to conventional cancer therapeutics (chemotherapy and radiotherapy), primarily aiming on the proliferating cancer cell, immunotherapies focus on the idea to utilize the patient’s own immune system to fight against the cancer. Several strategies to achieve this goal have entered the clinic or are close to clinical translation.
However, few phase I / II trials are available for very rare cancers due to the small size of the patient populations and therefore lack strength of evidence. On the other hand, for very rare tumours there is a long-standing and urgent need for innovative treatment. It is important not to exclude young patients with very rare cancers from these scientific achievements and treatment advances.

The German Rare Tumour Group plans to prospectively characterize very rare paediatric tumours molecularly - especially those in advanced tumour stages – in order to evaluate all possible treatment strategies at the beginning of the therapy. This work will be performed in cooperation with the German INFORM registry. For the future, cooperation not only interdisciplinary, but also internationally is planned.

Results

In order to understand the spectrum of entities and epidemiology of very rare paediatric cancers, a list of all rare entities and a report on incidences in Europe was prepared and published (Ferrari, Brecht et al. 2019). The information was received through the database of the RARECAREnet project (94 European databases, 27 countries, 2000-2007). The RARECAREnet list of cancers was developed by combining the International Classification of Diseases for Oncology, third edition, morphology and topography codes.

Table 1 shows the incidence rate of the rare cancers in the subpopulations of 0- to 14-year-olds and of 0- to 19-year-olds ranked by the declining incidence rate in 0- to 14-year-olds. These results show that 11% of all childhood cancers represent the group of 'very rare paediatric cancers', which is extremely heterogeneous in terms of tumour types and incidence. All other childhood cancers listed are considered as relatively more 'common' in children (lymphomas, acute leukaemias, central nervous system tumours, sarcomas, nephroblastoma, neuroblastoma and retinoblastoma), with an annual incidence >2/1.000.000 (incidence rate bolded in Table 1) and account for the majority (89%) of all childhood cancers.

According to the consensus, paediatric VRTs were identified as those with an annual incidence <2/1000000 and corresponded to 11% of all cancers in patients aged 0-14 years. Two subgroups were identified: tumour types typical of childhood (i.e. hepatoblastoma, pleuropulmonary blastoma, pancreatoblastoma) and those typical of adult age (i.e. carcinomas, melanoma). Using a lower threshold (<1 per million) excluded extragonadal germ cell tumours, cutaneous melanoma, hepatoblastoma, thyroid carcinoma and non-epithelial tumours of ovary from the very rare tumours list (Ferrari, Brecht et al. 2019).

In the future (outside the tasks within JARC), new epidemiological data is expected to be available in 2019 (registry data 2000-2013), based on which an analysis can be done to understand if the reported incidence rates could be increased by further developing structures in Europe.

Table 1: Number of observed cases and crude incidence rates (Ferrari, Brecht et al. 2019)

Table 1
The number of observed cases and crude incidence rate of RARECAREnet 'tier 1' cancers diagnosed in children (aged 0–14 and 0–19 years at diagnosis) in 83 European cancer registries in the years 2000–2007.

RARECAREnet tier 1 cancer entities	0–14 years			0–19-years		
	Observed cases	Incidence rate	SE	Observed cases	Incidence rate	SE
Lymphoid diseases	12,571	**47.9**	0.4	18,970	**52.5**	0.4
Tumours of central nervous system	3,815	**14.5**	0.2	5,089	**14.1**	0.2
Soft tissue sarcoma	2,248	**8.6**	0.2	3,453	**9.6**	0.2
Acute myeloid leukaemia and related precursor neoplasms	1,842	**7.0**	0.2	2,571	**7.1**	0.1
Nephroblastoma	1,829	**7.0**	0.2	1,953	**5.1**	0.1
Embryonal tumours of central nervous system	1,775	**6.8**	0.2	2,026	**5.6**	0.1
Bone sarcoma	1,731	**6.6**	0.2	3,199	**8.9**	0.2
Neuroblastoma and ganglioneuroblastoma	1,499	**5.7**	0.1	1,513	**4.2**	0.1
Retinoblastoma	856	**3.3**	0.1	856	**2.4**	0.1
Extragonadal germ cell tumours	489	1.9	0.1	702	1.9	0.1
Skin melanoma	348	1.3	0.1	1,619	**4.5**	0.1
Hepatoblastoma	329	1.3	0.1	335	0.9	0.1
Carcinomas of thyroid gland	315	1.2	0.1	1,367	**3.8**	0.1
Non-epithelial tumours of ovary	303	1.2	0.1	666	1.8	0.1
Myeloproliferative neoplasms	268	1.0	0.1	543	1.5	0.1
Neuroendocrine tumours	255	1.0	0.1	707	2.0	0.1
Myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases	228	0.9	0.1	297	0.8	<0.1
Histiocytic and dendritic cell neoplasms	217	0.8	0.1	258	0.7	<0.1
Testicular and paratesticular cancers	210	0.8	0.1	2,016	**5.6**	0.1
Epithelial tumours of skin	146	0.6	<0.1	446	1.2	0.1
Epithelial tumours of major salivary glands and salivary gland–type tumours	114	0.4	<0.1	274	0.8	<0.1
Epithelial tumours of liver and intrahepatic bile tract	91	0.3	<0.1	187	0.5	<0.1
Epithelial tumours of kidney	82	0.3	<0.1	189	0.5	<0.1
Carcinoma of adrenal gland	82	0.3	<0.1	112	0.3	<0.1
Epithelial tumour of lung	28	0.1	<0.1	56	0.2	<0.1
Epithelial tumours of oral cavity and lip	21	0.1	<0.1	54	0.1	<0.1
Epithelial tumours of nasopharynx	17	0.1	<0.1	47	0.1	<0.1
Malignant melanoma of uvea	14	0.1	<0.1	44	0.1	<0.1
Epithelial tumour of colon	13	<0.1	<0.1	92	0.3	<0.1
Olfactory neuroblastoma	13	<0.1	<0.1	20	0.1	<0.1
Epithelial tumours of hypopharynx and larynx	12	<0.1	<0.1	27	0.1	<0.1
Carcinomas of pituitary gland	11	<0.1	<0.1	14	<0.1	<0.1
Epithelial tumours of stomach	10	<0.1	<0.1	58	0.2	<0.1
Adnexal carcinoma of skin	10	<0.1	<0.1	20	0.1	<0.1
Epithelial tumour of ovary and fallopian tube	9	<0.1	<0.1	169	0.5	<0.1
Epithelial tumours of bladder	9	<0.1	<0.1	63	0.2	<0.1
Epithelial tumours of nasal cavity and sinuses	8	<0.1	<0.1	20	0.1	<0.1
Pleuropulmonary blastoma	8	<0.1	<0.1	8	<0.1	<0.1
Epithelial tumours of pancreas	7	<0.1	<0.1	22	0.1	<0.1
Kaposi sarcoma	7	<0.1	<0.1	19	0.1	<0.1
Pancreatoblastoma	6	<0.1	<0.1	10	<0.1	<0.1
Epithelial tumours of thymus	5	<0.1	<0.1	24	0.1	<0.1
Malignant melanoma of mucosa	5	<0.1	<0.1	6	<0.1	<0.1
Epithelial tumours of oropharynx	4	<0.1	<0.1	11	<0.1	<0.1
Epithelial tumours of rectum	4	<0.1	<0.1	28	0.1	<0.1
Epithelial tumours of pelvis and ureter	4	<0.1	<0.1	8	<0.1	<0.1
Epithelial tumours of eye and adnexa	3	<0.1	<0.1	8	<0.1	<0.1
Epithelial tumours of small intestine	2	<0.1	<0.1	12	<0.1	<0.1
Epithelial tumour of trachea	2	<0.1	<0.1	5	<0.1	<0.1
Epithelial tumours of vulva and vagina	2	<0.1	<0.1	5	<0.1	<0.1
Epithelial tumours of prostate	2	<0.1	<0.1	6	<0.1	<0.1
Gastrointestinal stromal sarcoma	2	<0.1	<0.1	8	<0.1	<0.1
Epithelial tumours of oesophagus	1	<0.1	<0.1	8	<0.1	<0.1
Epithelial tumours of anal canal	1	<0.1	<0.1	3	<0.1	<0.1
Epithelial tumours of gallbladder and extrahepatic biliary tract	1	<0.1	<0.1	2	<0.1	<0.1
Epithelial tumours of corpus uteri	1	<0.1	<0.1	1	<0.1	<0.1
Epithelial tumours of cervix uteri	1	<0.1	<0.1	40	0.1	<0.1
Trophoblastic tumour of placenta	1	<0.1	<0.1	13	<0.1	<0.1
Malignant mesothelioma	1	<0.1	<0.1	14	<0.1	<0.1
Odontogenic malignant tumours	1	<0.1	<0.1	4	<0.1	<0.1

SE, standard error.
Incidence rates x 1,000,000 with SE. In bold, the incidence rates >2 in a million.

In collaboration with CCI-Europe, parents' experiences and perceptions on VRT on VRT structures and needs at the national level across Europe were collected through a questionnaire. 35 individuals answered the questionnaire: Austria (n=3), Belgium (n=1), Bulgaria (n=3), Croatia (n=1), England and UK (n=1), France (n=1), Germany (n=2), Greece (n=1), Ireland (n=1), Italy (n=1), Romania (n=2), Serbia (n=1), Slovakia (n=1), Spain (n=1), Sweden (n=1).

62,9% of all participating individuals did not know of any patient group(s) for VRT in children in their country, while 37,1% were aware of such groups. 58,62% were not aware of any professional networks/registries for VRT in children in their country, while 31,0%, 24,1% and 17,4 respectively were aware of dedicated working groups, professional networks, and registries. 80,8% of participants believed that there was a need for action on very rare cancers in children in their country.

The collaborative effort on VRT in children in the JARC provided an important platform for joint initiatives and involvement of key academic experts and clinicians, including those from LHEAR countries, parents and patients, and the adult rare cancer community. Further collaborative projects are foreseen on this basis in the future.

Discussion

In the last 10 years, care for very rare paediatric cancers improved significantly; however, there is still a remaining conflict between the evidence-based treatment approach in relatively more common cancers and the requirements of patients with very rare cancers.

Gozato (2017) describes the "intrinsic lack of or defect in evidence" and the arising uncertainty to be faced by each stakeholder. His idea is to overcome this dilemma by a new risk-sharing paradigm in very rare cancers due to the urgency for quality treatment. For ethical reasons, patients should not have a disadvantage due to the rarity of the cancer.

In relatively more common cancers, evidence can be generated by patient numbers, such as in randomized cross-border trials. For very rare cancers, there is a need to work on different methodologies. One example would be the so-called basket and umbrella trials. The idea is that tumours respond to treatment due to specific mutations, which is targeted. These studies do not focus on tumour types. Additionally, randomized studies with small patient numbers may lead to differences in treatment outcome due to lager differences treatment effects. It was calculated that only 10-20 patients are required for a 40% improvement in a two-arm study for a 5% statistical significance level with a power of 80-90% if the control arm tumour control rate is 35% (Bentzen et al 1998).

Additionally, expertise has to be organized in a different way for very rare cancers. Journals should publish case reports and small series, reviews and meta-analyses. Experts in the field need to be identified and consulted.

The European working groups joined their forces in 2008 within the EXPeRT group. The first goals were:

(i) to pool national retrospective series of specific tumour types to obtain large series enough to enable treatment-related risk stratification and generate homogeneous therapeutic recommendations, using a shared research methodology and a common framework;

(ii) to develop an organization with the double purpose of promoting research and serving as an advisory network to help with difficult decisions regarding single clinical cases;
(iii) to set up an international prospective case registry.

The development of joint retrospective studies on specific VRTs was the first activity (also relatively easy to realize in the absence of financial support). For this purpose, harmonized core data sheet for uniform documentation of clinical data was developed. The group published joint series on pancreatoblastoma (Bien et al 2011), Sertol-Leydig tumors (Schneider et al 2015), pleuropulmonary blastoma (Bisogno et al 2013), thymic tumors (Stachowicz-Stencel et al 2014), adrenocortical tumors (Cecchetto et al 2017) and melanoma (Brecht et al 2018). Overall, these publications firstly confirmed that cooperation on such topics on a European scale was not only feasible, but also fruitful.

At the same time, treatment guidelines for some specific tumour types were developed as well as a website and a consultation platform were built. The virtual online tumour board and advisory desk was developed with the aim to offer a tool dedicated to professionals who need expert medical advice (vrt.cineca.it). Now it became possible to seek advice on the diagnosis and treatment of very rare paediatric cancers in a timely manner.

The EXPeRT network played a large part in obtaining EU-funded projects, with the involvement in three consecutive important collaborative efforts, i.e. the ExPO-r-Net, the JARC, and the PARTNER. From 2014 to 2017, the EXPeRT was part of the 3-year ExPO-r-Net project, developed under an EU directive aiming to reduce inequalities across EU Member States. Lately, as a major result of this project, EXPO-r-Net and the EXPeRT's activities (the tumour board, for example, which opened the way to the development of further consultation desks involving other paediatric tumours) became a model for a subsequent, broader project to create the ERN PaedCan. Currently, a European database for VRT is built within the ERN PaedCan PARTNER-project.

According to the data obtained in 2015 within the EXPO-r-Net project, structured activities dedicated to children and adolescents with VRT exist in about 30% of the European countries. This translates into the "coverage" of approximately 60% of the European population. The VRT cooperative groups were found to exist and work actively in Italy, Germany, Austria, Poland, France, Spain and the Netherlands. Tumor registries, including data on pediatric VRT, were also active in some other countries, like United Kingdom and Ireland. After the EXPO-r-Net project (and the invitation to cooperate), other VRT groups were set up (the first in Croatia and Israel). It was realized that specific national groups for VRT in children are actively working in only three LHEAR (low health expenditure average rate) countries: Lithuania, Greece and Poland. Therefore, the PARTNER project has aimed to involve more EU countries into creating the active cooperation in the field of VRT in children, including international VRT registries, diagnostic and therapeutic recommendations for certain types of VRT, and consultation system. In this way, the PARTNER project will help pediatric patients with VRT to obtain expert support for diagnosis and treatment despite their geographical location.

From 2016 to 2019, the EXPeRT was involved in the JARC project, which is a cooperation between paediatric oncologists and oncologists dealing with rare tumours in adults as well as patient groups, including to establish links with the world of epidemiology, essential to research on extremely rare tumours. By using the data of the RARECAREnet database, incidence rates for VRT in children in Europe were calculated and a definition of paediatric VRT was obtained.

The JARC consensus produced a definition and a list of paediatric VRTs which may represent a starting point for prioritising research on these tumours, based on data and patients' clinical needs (Table 1). However, this list needs to be considered as "work in progress" as new VRT entities are detected each year, especially due to recent advances in the understanding of cancer biology and consequent reclassification of rare tumours.

In fact, given that all childhood cancers are rare, it is important to differentiate very rare cancers from the other paediatric malignancies, in order to suggest dedicated methodological approaches and reduce the regulatory hurdles for research and availability of innovative treatments also for extremely rare tumours in children.

Despite all above highlighted advances in the care of very rare paediatric cancers, one should clearly keep in mind that the etiopathogenesis of very rare tumours in children and adolescents is widely unclear due to several barriers for biological studies resulting from the rarity. While new insight into the biology of tumours are reached the gap between research results and bedside application seems to widen.

In the future, it will be necessary to further join forces on a European level in order to reach sufficient patient numbers, awareness and financial support. Ferrari, Schneider et al. nicely summarize in their publication "Joining forces for paediatric very rare tumours" (2019):

"The only solution is to join forces, pool our resources, boost our collaborative efforts, involve everyone working on paediatric VRTs, be they international experts, specialists in various fields, care providers, families and patients, regulators, or providers of funding; as well as work in synergy with the adult oncology community, for which our paediatric collaborative experience may serve as a helpful organizational model (Ferrari, Schneider et al 2019)."

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