RARE CANCER AGENDA 2030

Ten Recommendations
from the EU Joint Action on Rare Cancers

JARC
JOINT ACTION ON RARE CANCERS
2016-2019

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Introduction

Rare cancers are rare occurrences of a common disease. They affect one in five new patients with cancer.

This enshrines many of the distinct features of rare cancers among rare diseases, with which they share most of the issues that are typical of rarity. This booklet puts forward the main recommendations of the *Joint Action on Rare Cancers*, which in 2016, in parallel to a *Joint Action on Rare Diseases*, the European Commission decided to launch to help tackle such issues. In 2017, the European Commission set up the *European Reference Networks* on rare diseases, including rare cancers.

We hope that these recommendations can be instrumental to the policy agenda on rare cancers in the European Union for the years to come. We do need an agenda on rare cancers, to minimize the risk that rare cancer patients may be discriminated against simply because of the numbers of the disease they suffer from. At least, we need to relieve these patients from what would further be added thereby to all obvious burdens of a serious disease, and could be avoided.
How could it be avoided? We would say that, in essence, healthcare networking and clinical and research methodology are the two areas that could make the difference. These two areas give rise to much of the “rare cancer agenda 2030” of this booklet, which, in the end, was drafted as of 2019 by many disease-based communities. All the more in rare conditions,

disease-based communities are vital to get what a disease is and what it needs across to policymakers and health administrators, to industry, to the public. These communities are made up of patients, obviously first, and all health professionals (in the broadest sense) who decide to dedicate their lives to a disease, or a group of diseases. We simply ask that their voice, their knowledge, is listened to.

Much of what this Joint Action has done was built on the work of the EU-funded project S*urveillance of Rare Cancers in Europe* (RARECARE), the multi-stakeholder effort *Rare Cancers Europe*, founded in 2008 and involving patients, healthcare professionals, industry and others, the *European Society for Paediatric Oncology* (SIOP Europe) for paediatric cancers, and many others. Once the *Joint Action on Rare Cancers* comes to an end, the whole European rare cancer community will take over the task of pursuing the most specific recommendations of this booklet. Obviously in the European Union, and importantly within its single Member States, but then throughout the whole of Europe and globally. Indeed, we might recall that *Rare Cancers Europe* is now launching projects with *Rare Cancers Asia*, and so forth.

This booklet is structured around the ten gross recommendations of the *Joint Action on Rare Cancers*. They correspond to ten chapters, each paragraph of which is a distinct item: often, it is a single, specific recommendation. We hope that all this may be useful. It was the output of the work of so many communities, gathering under a Joint Action of the European Union, in the spirit of service to future rare cancer patients.

Paolo G. Casali
Annalisa Trama

RARE CANCER AGENDA 2030

Ten Recommendations from the EU Joint Action on Rare Cancers

Each Chapter of this booklet builds upon one of the ten gross recommendations of the Joint Action on Rare Cancers (its Rare Cancer Agenda 2030). Chapters are divided into Sections, with numbered Paragraphs, each corresponding to conceptually distinct items, which often serve as single, specific recommendations. These more detailed recommendations reflect the outputs of the Joint Action's Work Packages. However, their associated deliverables have obviously been much more extensive. Sometimes, they are mentioned throughout the text, and the reader is then referred to the Joint Action's website.

Paediatric cancers are rare cancers. However, they often require specific approaches, in line with their distinct age-related biological, clinical and organizational characteristics.
Considerations about paediatric cancers are thus summarized in a dedicated Paediatric cancer Section within each Chapter. With a view to fostering appropriate health polices, specific recommendations on paediatric cancers are included therein.

1. Rare cancers are the rare diseases of oncology…

…needing specific approaches by the cancer community and national health systems

1.1 Rare cancers can be defined as those malignancies whose incidence is <6/100,000/year.

1.1.1 This definition is conventional, since no absolute threshold is able to distinctly separate cancers, or other diseases, because of their frequency. Essentially, the definition was the product of a consensus process within the European oncology community that took into account issues posed by rare cancers in terms of health care organization, clinical research, and clinical decision-making. The European Union (EU) funded this effort (RARECARE project) *(Gatta, 2011)*.

1.1.2 This definition is based on incidence, valuing that: a) unlike prevalence, incidence does not change depending on a factor other than frequency, i.e. expected survival; b) many steps of the diagnostic and therapeutic pathway occur “once” in cancers, so that incidence renders better than prevalence much of the burden of cancer disease (in terms of health resources, costs, etc.) *(Gatta, 2011; Gaddipati, 2012)*.

1.1.3 Thus, a definition based on incidence works better than the definition provided by the EU in regard to orphan drug designation, which defines rare diseases as those having a prevalence lower than 50 in 100,000 *(European Parliament and Council of the European Union, 1999)*. In the US, the Orphan Drug Act defines rare diseases as those affecting <200,000 people in

the country, i.e. around <70/100,000 *(Food and Drug Administration, 1983)*. Of course, these definitions based on prevalence may work even in the field of rare cancers whenever these pose problems close to chronic rare diseases.

1.2 A list of rare cancers is useful for several purposes, from healthcare organization to clinical research and new therapy approval and reimbursement.

1.2.1 Being the result of a process of selection within cancers, any list of rare cancers needs to be based on a list of cancers. The most obvious choice has been the *International Classification of Diseases for Oncology* (ICD-O), which incorporates topographical and histological labels (*Percy, 2000)*. The pathological ("morphological") entities enlisted in the ICD-O need to be grouped into clinically distinct entities, which in turn may be assembled into gross families of neoplastic diseases. This effort gave rise to a consensus process that took place within the RARECARE project, involving a panel of experts set up in 2007, including clinicians, pathologists and epidemiologists. This panel eventually agreed to build the list of clinically relevant entities on the basis of combinations of topographies and morphologies coded in the ICD-O3 (third edition of ICD-O). In 2016, the EU launched this *Joint Action on Rare Cancers* (JARC), within which another consensus effort was set up to re-examine the list of rare cancers as developed by the RARECARE project, also encompassing rare cancer "families". In essence, the rare cancer list comprises three tiers. Tier 3 corresponds to the morphological entities of the ICD-O. Then, the experts were asked to group the ICD-O3 morphological entities, to give rise to a second tier of clinically distinct entities (Tier 2) based on morphologies and topographies (e.g. "squamous cell carcinoma of nasal cavity and sinuses", "soft tissue

sarcoma of limb", etc.). These entities had to be viewed as clinically relevant by clinicians. In general, these diagnoses had to correspond to consistent diagnostic and therapeutic approaches (for example, they could be used as eligibility criteria in a clinical trial). The Tier-2 entities were then assembled into a smaller number of Tier-1 entities. Tier-1 entities were intended to be major cancer entities in a clinical sense (e.g. "epithelial tumours of nasal cavity and sinuses", "soft tissue sarcoma", etc.) and to be of organizational importance: for example, they could underlie patient referral policies. Focusing on referral of patients, Tier-1 entities can be grouped into gross partitions, which give rise to families of rare cancers, dividing them into major groups (e.g. "rare cancers of head & neck", "sarcomas", etc.). By and large, these are managed by the same disease-based communities of physicians and clinical researchers. To define major families of rare cancers, the experts combined the Tier-1 entities with an incidence rate <6/100,000/year (Table 1). There are two exceptions: central nervous system tumours (with an incidence that is only slightly higher than the threshold) and lymphoid malignancies (which have a relatively high incidence). In both cases, however, they also share patient referral patterns that are typical of rare cancers and in any case each Tier-2 entity within them is rare.

1.2.2 With regard to cancers in children and adolescents, all the malignancies in this population are rare, including leukaemias and lymphomas. The RARECARE list includes some of these entities under the "family" of paediatric cancers, but several are included under specific "families", namely haematological tumours, sarcomas, central nervous system tumours, head and neck cancers, digestive cancers, thoracic cancers, endocrine tumours (Table 1). The scope of paediatric cancer entities is well reflected through the *International Childhood Cancer Classification* (ICCC-3) *(Steliarova-Foucher, 2005)*. One should also note that the genetic profile of common cancer entities in

the very young age groups may have a distinct biological make-up and a different clinical behaviour and prognosis.

1.2.3 Some cancers have a hereditary risk component. Some of them are rare cancers as such, while others belong to common entities (e.g. sarcomas and breast cancer, respectively, when occurring in a Li Fraumeni syndrome). Currently, there is no specific code for heredofamilial cancers as such but for familial adenomatous polyposis. Hereditary cancer syndromes may be recorded in rare disease registries. Cross-links between these and cancer registries may then be envisaged.

1.2.4 The decision was made not to single out subgroups of common cancers, such as the molecular ones. This was done because the basis for the list of rare cancers was the ICD-O. Likewise, clinical subgroups were not considered (e.g. inflammatory breast cancer was not singled out as an entity, though it is rare). This means that any rare molecular subgroup will be appropriately incorporated, as soon as it is recognized in the ICD-O as a cancer entity, but not otherwise. Most probably, this may happen when any molecular characteristic is perceived to be relevant to the natural history of a disease, not just to the sensitivity of the disease to a class of anticancer agents, and the like.

1.2.5 The list of rare cancers built on the basis of a threshold at 6/100,000/year refers to the EU. In other words, cancers were selected with an incidence <6/100,000/year in the EU. In other geographical areas, and even within single countries in the EU, cancers may have different incidences. Unless the problem being dealt with involves a specific country, or region, and in any case when decisions are made at the EU level, we encourage using the list based on EU data.

1.2.6 Amongst rare cancers, some are exceedingly rare. They could be labelled as “ultra-rare”, as in the *EU Clinical Trials Regulation (European Parliament and Council of the European Union, 2014)*. This regulation identifies ultra-rare diseases as those with a prevalence lower than 2/100,000. Since the threshold for rare diseases is set at a prevalence of 50/100,000, the ratio in prevalence of ultra-rare diseases to rare diseases is 1:25. By applying the same ratio to the definition adopted for rare cancers, ultra-rare cancers would be those with an incidence lower than 0.2/100,000/year.

1.2.7 Rare cancers make up at least one fifth of all malignancies, corresponding to 650,000 new diagnoses of rare cancers annually in Europe. However, about three quarters of rare cancers have an annual incidence rate of <0.5/100,000 and account for only 70,000 (3%) of the 2.5 million cancers diagnosed each year *(Gatta, 2011)*. Annual age-adjusted incidence rates for all rare cancers range from <100/100,000 (Finland, Portugal, Malta, and Poland) to >140/100,000 (Italy, Scotland, France, Germany, and Switzerland) *(Gatta, 2019)*. In any case, rare cancers contribute to 20-30% of the new cancer cases across EU Member States. Differences across countries do exist also with regard to outcomes: 5-year relative survival for all rare cancers, adjusted by age and case mix, vary from 55% or over (Italy, Germany, Belgium and Iceland) to less than 40% (Bulgaria, Lithuania and Slovakia). For all rare cancers, a large survival gap was reported between Eastern and Nordic and Central European regions. Of note, geographical variations include curable cancers like testicular and non-epithelial ovarian cancers, suggesting that clinical expertise may be substantially relevant to the outcome *(Gatta, 2019)*.

Table 1.

Rare cancers: RARECARE "families" and "Tier-1" entities with an incidence <6/100,000/year

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HEAD & NECK
Epithelial tumours of the larynx
Epithelial tumours of the hypopharynx
Epithelial tumours of the nasal cavity and sinuses
Epithelial tumours of the nasopharynx
Epithelial tumours of major salivary glands and salivary-gland type tumours
Epithelial tumours of the oropharynx
Epithelial tumours of the oral cavity and lip
Epithelial tumours of the eye and adnexa
Epithelial tumours of the middle ear

DIGESTIVE
Epithelial tumours of the small intestine
Epithelial tumours of the anal canal
Epithelial tumours of the gallbladder and extrahepatic biliary duct

THORACIC
Epithelial tumours of the trachea
Thymomas and thymic carcinomas
Malignant mesothelioma

FEMALE GENITAL
Non-epithelial tumours of the ovary
Epithelial tumours of the vulva and vagina
Trophoblastic tumours of the placenta

MALE GENITAL & UROGENITAL
Tumours of the testis and paratestis
Epithelial tumours of penis
Extragonadal germ cell tumours
Epithelial tumours of renal pelvis, ureter and urethra

SKIN CANCERS & NON CUTANEOUS MELANOMA
Mucosal melanoma
Uveal melanoma
Adnexal skin carcinomas
Kaposi sarcoma

SARCOMAS
Soft tissue sarcoma
Bone sarcoma
Gastrointestinal stromal tumours

NEUROENDOCRINE TUMOURS (NET)
NET gastrointestinal pancreatic
NET lung
NET other sites

ENDOCRINE ORGAN
Thyroid cancers
Parathyroid cancer
Adrenal cortex cancer
Pituitary gland cancer

CENTRAL NERVOUS SYSTEM (CNS)
Glial tumours and others**
Malignant meningioma
Embryonal tumours of CNS

PAEDIATRIC*
Hepatoblastoma
Neuroblastoma & ganglioneuroblastoma
Nephroblastoma
Odontogenic malignant tumours
Olfactory neuroblastoma
Pancreatoblastoma
Pleuropulmonary blastoma
Retinoblastoma

HAEMATOLOGICAL
Lymphoid malignancies**
Myelodysplastic syndromes
Myeloproliferative neoplasms (including mastocytosis)
Myelodysplastic/myeloproliferative neoplasms
Myeloid/ lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2
Acute myeloid leukaemia and related neoplasms

** Other neoplasms which mainly, or also, occur in childhood are included under other labels (e.g. Ewing's sarcoma and osteosarcoma under bone sarcomas; rhabdomyosarcoma under soft tissue sarcoma; medulloblastoma under embryonal tumour of CNS)*

*** All subgroups (Tier-2 entities) within are rare*

1.3 Rare cancers are the rare diseases of oncology.

1.3.1 Conceptually, rare cancers pose all the main problems that are typical of rare diseases. These affect: a) clinical decision-making, due to a lack of available medical expertise and high-quality evidence from clinical research; b) healthcare organization, due to difficulties in serving a territory with specialized facilities; c) clinical research, due to the low number of patients and thus the difficulty to generate high-quality evidence from well powered clinical studies.

1.3.2 There are an estimated 6,000 rare diseases, which are highly specific and heterogeneous, and many are genetic and/or chronic. About 75% of rare diseases affect children. On the other side, there are about 200 rare cancers, amounting to roughly 20% of new cancer cases *(Gatta, 2017)*, most of them occurring in adults. About 80% of rare diseases are of genetic origin, in striking contrast with inherited rare cancers, though some genetic rare diseases may give rise to cancers (not necessarily rare cancers). Rare diseases are highly specific, such that the number of centres specializing in their diagnosis and treatment tends to be low. On the contrary, rare cancers are cancers to all effects and purposes, i.e. they belong to one of the most common “non-communicable chronic” diseases. While obviously there are only some cancer centres that specialize in selected rare cancers, it is much easier to cover rare cancers than rare diseases through networking. In fact, health services for rare cancer patients can fall within the scope of any cancer centre: from diagnostic imaging to handling side effects and long-term sequelae of cancer treatment, from palliative oncology to psycho-oncology, and so forth. Paediatric haematology-oncology institutions manage all children and adolescents with cancer across a continuum of care. Finally, population-based rare cancer registration is provided by the fairly widespread cancer registries, while a large number of

the 6,000 rare diseases do not have structured registries.

1.3.3 From a health policy perspective, it follows that rare cancers should be approached within national cancer plans. These may be very useful as a means to help countries shape their policies, to harmonize these across countries, to monitor ongoing progress. Thus, checklists of items to be prioritized in national cancer plans (e.g. network development, etc.) should be worked out and updated by the rare cancer community, in order to constantly assess and monitor how rare cancer policies are shaped across the EU. The rare cancer community can look at synergies with EU rare disease policies and national rare disease plans on matters relevant to tackle rarity.

Paediatric Cancer Section

Although all paediatric malignancies are rare according to the definition of rare cancers *(Gatta, 2011)*, they represent a major public health issue in Europe. Each year, there are over 35,000 new cases, and more than 6,000 young patients lose their lives to the disease *(International Agency for Research on Cancer, 2018)*. Despite research progress that has enabled to achieve 80% survival at 5 years, there has been very little advancement for some types of paediatric cancers *(Vassal, 2016)*. Today, paediatric cancers are still the leading cause of deaths in children above one year of age in Europe. Inequalities in access to essential therapies and care account for differences in survival rates of up to 20% across Europe *(Gatta, 2014; Kowalczyk, 2014)*. The number of survivors in Europe is estimated to reach 500,000 by 2020, the majority of whom are affected by long-term morbidity due to their disease and treatment side effects *(Hjorth, 2015)*.

Each type of paediatric malignancy is rare or ultra-rare. Within paediatric cancers, as reflected in the ICCC-3, a distinction can be made between haematological malignancies, brain tumours and solid cancers. Some cancers occurring in the paediatric population with an incidence of less than 0.2 cases/100,000/year are classified as extremely rare. Here, two subgroups can be identified: tumour types typical of childhood (i.e. hepatoblastoma, pleuropulmonary blastoma, pancreatoblastoma) and those typical of adult age occurring extremely rarely in the young population (i.e. carcinomas, melanoma) *(Ferrari, 2019)*.

Whereas cancers in adults typically result from long-term processes often influenced by carcinogen exposures, paediatric cancers develop early in life and over a much shorter time period, suggesting that fewer and stronger events are required for them to arise.

For up to 90% of newly diagnosed paediatric cancer patients in Europe there are standard protocols established

through prospective clinical research, and up to 40% of all patients are treated within clinical studies.

Treatment and care for children and adolescents with cancer in Europe are delivered in about 330 paediatric haemato-oncology centres. The vast majority are public hospitals. Over the last 50 years, they have given rise to collaborative networks and steadily improved diagnosis and treatments. At present, the *European Reference Network (ERN) for Paediatric Oncology* (PaedCan) is coordinating activities on childhood cancers in the EU, as part of the *European Society for Paediatric Oncology* (SIOP Europe) community.

Recommendations

- National cancer control plans should include a clearly designated section on paediatric cancers and integrate specific provisions concerning at least the following areas: epidemiology; healthcare organisation and quality; access to the best possible multimodal standard treatment; clinical research and access to innovative therapies; access to social needs of patients and families; survivorship.
- Coordinated research and health policies and programmes are ideally placed at the European level, given the rarity of individual paediatric cancers and their huge burden across countries.
- The multistakeholder-endorsed *SIOP Europe Strategic Plan – A European Cancer Plan for Children and Adolescents* can serve as guidance for childhood cancer strategies at the national and European levels *(Vassal, 2016)*.

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2. Rare cancers should be monitored…

...epidemiologically and clinically, properly valuing population-based cancer registry data and real-world clinical data, encouraging all efforts to make all available databases interoperable

2.1 Rare cancers are covered by widespread cancer registration in the EU.

2.1.1 At the moment, nearly 200 population-based cancer registries (CRs) are active in Europe. Together, they cover about 60% of the European population, with an upward trend *(Forsea, 2016)*. Thus, over the last three decades, cancer registration has become an important component of the EU's strategy against cancer, implemented within the framework of the *European Action Against Cancer Programme* (1985–2008), the *European Partnership for Action Against Cancer* (EPAAC) (2009–2014), the *EU Cancer Control Joint Action* (CANCON) (2014-2017), as well as the currently ongoing *Innovative Partnership for Action Against Cancer* (iPAAC) (2018-2021). CRs are a crucial source of data on the number of new cancer cases ("incidence"), cancer-related deaths ("mortality"), individuals living with cancer ("prevalence"), as well as cancer "survival" rates. CRs register all cancers, therefore also the rare ones. The *International Agency for Research on Cancer* (IARC), the *International Association of Cancer Registries* (IACR) and, in Europe, the *European Network of Cancer Registries* (ENCR) promote collaboration among CRs, define data collection standards and provide training for CR personnel. As a result, from the end of the '60s, CRs have contributed data to *Cancer Incidence in Five Continents* and to other collaborative

European projects such as EUROCARE (*European Cancer Registry Based Study on Survival and Care of Cancer Patients* http://www.eurocare.it/), EUROPREVAL *(Cancer Prevalence in Europe)* and EUROCOURSE (*EUROpe against Cancer: Optimisation of the Use of Registries for Scientific Excellence in research*). These collaborations have contributed to set common criteria and rules to improve the quality and comparability of data among CRs. Based on data from EUROCARE, the project RARECARE (www.rarecare.eu) proposed a list and a definition of rare cancers and estimated the burden of rare cancers in Europe. The project RARECAREnet provided the burden of rare cancers across EU Member States (MSs) and monitored rare cancer incidence and survival over time (www.rarecarenet.eu).

2.1.2 The quality of a CR inevitably depends on the local healthcare environment and the available sources of information. For a CR to function, it needs to define a catchment area and to have access to reliable population statistical data, medical data from hospitals, death certificates, etc. *(Forsea, 2016)*. Quality of care is relevant to quality of CRs. For example, inappropriate pathological diagnoses will result in misclassification in CRs. Rare adult solid cancers are particularly exposed to discrepancies in quality of care, with some of them (e.g. sarcomas) being especially affected in comparison to others (e.g. squamous cell head and neck carcinomas). Thus, as a by-product of their impact on quality of care, healthcare networks can be expected to also improve quality of registration. Misclassification at registration may also happen when: a) source information is correct and complete, but registration is wrong; b) classifications are ambiguous, obsolete terms are used, entities lack proper codes. The former case can be addressed by sound registration rules and recommendations, training of registrars and quality check softwares. JARC started a collaboration with

European CRs to develop recommendations about rare cancer registration and specific quality checks. The ENCR should take over this task, in collaboration with the ERN on rare adult solid cancers (EURACAN). Collaboration with expert clinicians (e.g. on training, etc.) is important to let registrars appreciate the complexity of some cancers, properly interpret the information sources and code correctly. Problems in classification may be caused by delays between description of new entities and updates of the *WHO Classification of Tumours* series, the so-called "blue books" (https://whobluebooks.iarc.fr/), and between changes thereof and updates of ICD-O. Involvement of registrars in discussions leading to updates of "blue books" may be useful.

2.1.3 Data collected by CRs provide reliable estimates about rare cancers. However, rare cancer burden indicators are exposed to high sampling variability due to their low numbers. Thus, CRs should be encouraged to provide them with variability measures, such as confidence intervals. Occurrence indicators (i.e. incidence, mortality, and prevalence rates) and outcome indicators (net or relative survival) are the most used population-based indicators, but their statistical properties and performances in the rare cancer setting have not been sufficiently studied to date. For example, many systematic studies on properties of survival estimates have been carried out in common cancers, none specifically in rare cancers. Little evidence is available from the analysis of cohorts of, say, less than 200 patients. Going beyond such a sample size is unfeasible for most rare cancers, particularly in medium/low population countries. One priority is therefore to evaluate the performance of standard statistical methods when applied to small numbers. When they do not perform appropriately, new methods should be worked out for rare cancers. Possible solutions include the following.

- A consensus should be developed about how many cases allow safe implementation of

standard methods. This would be invaluable in determining how many years of observation are needed to make reliable estimates, or how many registries should be gathered.

- Bayesian methods can be conveniently used when prior probabilities can be estimated. Geographical analysis of incidence and survival rates of common cancers in small areas is efficiently carried out by random effect modelling and is increasingly approached by means of Bayesian methods.
- Modelling approaches allow to efficiently draw inference from sparse data, but model components (hazard functional form, covariates definition, link between hazard and covariate functions, distributional assumption, etc.) need to be made explicit.

2.1.4 On each cancer case, CRs collect information on date of incidence, basis of diagnosis, topography (site), morphology (histology) and behaviour. However, routine cancer statistics are provided mainly by site, except for haematological malignancies. This undermines the availability of epidemiological data for those rare cancers defined on the basis of the combination of their morphology and topography. The use of morphology is essential to identify neuroendocrine tumours, sarcomas of both soft tissue and viscera, germ cell tumours, central nervous system cancers and all childhood cancers. For the latter, ICCC-3 was implemented to better reflect the diagnostic spectrum of childhood cancers *(Steliarova-Foucher, 2005)*. The use of topography alone may be acceptable mainly for rare cancers of epithelial origin, such as those of head and neck, digestive or respiratory origin. However, even for these site-specific cancers, the use of morphology could be extremely useful to distinguish cancers with a completely different natural history from each other, e.g. thymoma and thymic carcinoma, squamous cell and salivary-gland type cancers of the head and neck,

etc. Double data reporting would be feasible and more informative.

2.1.5 Additional clinically relevant data, e.g. on detection, staging, treatment and treatment effects tend to lack, or to be provided diversely, across CRs *(Siesling, 2014)*. Furthermore, no clear recommendations on the registration of relevant clinical data have been issued by the European and/or international authorities, e.g. the *ENCR-Joint Research Centre* (JRC). For each of the 198 rare cancers, the RARECAREnet project collected clinical information from several CRs, i.e. pathological and clinical stage, simplified stage (localized, regional extension, metastatic), simplified treatment (surgery, radiotherapy, systemic, other, or none), hospitals where diagnoses were made, hospitals where treatment was carried out. These data were of good quality and complete, and were used to study centralization of treatments in rare cancers *(Gatta, 2017)* and childhood cancers (*Gatta, 2019)*. Based on these experiences, discussions within JARC and a pilot study on the ability of CRs to collect childhood cancer stage based on the *Toronto Staging Guidelines*, it was suggested that CRs should collect additional clinical information, including at least: simplified stage, treatment modality (surgery, radiotherapy, systemic, other, or none), hospital where diagnosis was made and hospital where treatment was made *(Gupta, 2016)*. This is in line with the position of the ENCR-JRC and IACR that formally endorsed the Toronto staging guidelines, which will be integrated in the dataset of the 2020 ENCR-JRC call for data. Further discussions with, and validation by, the SIOP Europe *European Clinical Trial Groups* (ECTG) will contribute to successful implementation.

2.1.6 Widespread, effective interoperability of CRs with electronic patient records is obviously desirable. That said, integration of CRs with administrative databases is an opportunity which can also be exploited, to collect additional, though essential, clinical information. Administrative databases include hospital

discharge data, healthcare datasets with socioeconomic and sociodemographic information, health insurance data, etc. As the administrative databases are not designed to provide clinically relevant data, quality systems should be in place.

2.1.7 On the other hand, administrative databases cannot replace clinical data. Efforts are thus needed to strengthen links between CRs and clinical registries. On rare cancers, an opportunity is provided by the development of ERNs' *Rare Disease Registries*, i.e. clinical registries with detailed clinical information set up within ERNs. A strong collaboration needs to be established between epidemiologists and the clinicians of healthcare providers (HCP) of ERNs. Strategic interoperability between CRs and ERNs' Registries would be crucial. MSs should provide clear mandates thereon. For example, tracking cases managed within ERNs' HCPs, or, possibly, within national networks, would be instrumental. At the same time, data would be collected about the proportion of rare cancer patients actually accessing ERNs or the national networks linked thereto. The European population-based CR database managed by ENCR (thus by JRC) could be a formidable tool to collect all this information at the EU level.

2.1.8 The ERNs' IT tool, the *Clinical Patient Management System* (CPMS), should be shaped in such a way as to feed a prospective clinical database and should be interoperable with the ERNs' Registries. Proper tagging of these cases should be designed to allow interoperability with European as well as national healthcare repositories.

2.2 Clinical registration should be implemented.

2.2.1 The Council of the EU recommended that, in the field of rare diseases, MSs consider supporting registries and databases at all appropriate levels, including the

EU level *(Council of the European Union, 2009)*. To support this process and the interoperability of data in rare disease registries, the Commission decided to set up a *European Platform on Rare Disease Registration* and to develop specific standards for the interoperability of such rare disease registries. Furthermore, as laid down in Article 12 of Directive 2011/24/EU, clinical registries will be one item of ERNs' activities *(European Parliament and Council of the European Union, 2011)*. They will be a major instrument to monitor ERNs' impact and to steer ERNs towards achieving their objectives. These clinical registries will prospectively collect clinical information on the entire patient journey, in order to increase knowledge on rare cancers, to support clinical research, to improve clinical practices within the ERNs. It is hoped that ERN's Registries will be automatically populated from the electronic health records, or local datawarehouse, of each contributing HCP and/or from the IT tool of the national networks on rare cancers. Of course, the databases pertaining to such clinical registries should be based on semantics specifically tailored to cancers (i.e. to rare cancers rather than to rare non-neoplastic diseases).

2.2.2 Additional data sources need to be linked to ERNs Registries, such as:

- population data, usually owned by government or health authorities, such as national population and death registries, cancer (or disease-specific) registries, census data;
- administrative and health insurance data;
- research data, which is owned by academia, collaborative research groups;
- patient monitoring data with wearable devices;
- omic science data.

The integration of these data is challenging. Big data approaches, exploiting artificial intelligence, including machine learning, are needed. Proper funding for research projects focusing on technological and methodological solutions thereon should be provided.

2.3 Legal and regulatory issues should be addressed.

2.3.1 Being an EU Regulation, the new EU *General Data Protection Regulation* (GDPR) (https://eugdpr.org/), should lead to harmonization of data protection rules across the EU. However, considerable efforts are still required in terms of interpretation of GDPR's provisions. The first issue is the degree to which all CRs will be granted waivers from patient consent requirements evenly throughout the EU. Clearly, without such waivers, the activity of CRs would by definition be made impossible for all cancers. Recital 52 of the GDPR states that "derogating from the prohibition on processing special categories of personal data should be allowed when provided for in Union or Member States law and subject to suitable safeguards, so as to protect personal data and other fundamental rights, where it is in the public interest to do so". This should allow CRs to fulfil their public interest mission without the need for individual patient consent.

2.3.2 With regard to any kind of clinical database (ERNs Registries, etc.) and biorepository, it is important to emphasize that any "re-consent" requirements for any new retrospective analyses on stored data or biological samples pose an overwhelming burden on academic institutions, to such an extent that efforts may become impossible. Recital 33 of the GDPR acknowledges that "it is often not possible to fully identify the purpose of personal data processing for scientific research purposes at the time of data collection. Therefore, data subjects should be allowed to give their consent to certain areas of scientific research when in keeping with recognized ethical standard for scientific research". This should result in the recognition of the right of EU citizens to give "one-time consent" to use their health data and/or biological samples for future research purposes, provided the consent is withdrawable, proper data protection safeguards are implemented, scientific and ethical

review is foreseen, the scope of research can be modulated by the patient.

2.3.3 Harmonized interpretation of the GDPR should also affect rules about data transfers across institutions and national countries within the EU. Procedures should clearly be as simple as possible. Research on rare cancers desperately needs data, even more than research on common cancers, and international distant collaboration is all the more crucial. This means that any additional burden on data transfer across institutions would affect rare even more than common cancers.

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Population-based registration of childhood cancer cases is crucial to evaluate improvements in access to high quality care and innovation. The long-term follow-up dimension is key, as health sequelae and long-term complications of treatment are of major concern in childhood cancers. Approaches thereto are multidisciplinary and involve several health professionals and survivor group representatives. A high degree of patient migration across cities and countries is apparent in young adulthood and may cause problems in long-term registration in the absence of secure cross-border health data transfer modalities.

Recommendations

- Data collection should be enhanced, incorporating more tumour details, patient demographics and reporting of outcomes most relevant to patients. Proper feedback should be provided to regions, countries, healthcare professionals, and the public.
- The roll-out of a *European Unique Patient Identifier* should be encouraged, to ensure monitoring of long-term outcomes in childhood cancer survivors in a cross-border setting.
- Systematic registration and cross-linkage of databases should be fostered with regard to moderate to severe long-term side effects of paediatric cancer treatments.

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3. Health systems should exploit networking…

…around multidisciplinary centres of reference, to improve quality of care in rare cancers by rationalizing patient access to available best expertise and lowering/rationalizing health migration

3.1 Networking is the best option in rare cancers.

3.1.1 Centralized referral has always been a recommendation in the rare cancer field *(Institut National du Cancer, 2012; National Health Service Commissioning Board, 2012; Stordeur, 2016)*. Referring rare cancer patients to centres of reference means that their cases are dealt with by institutions with a high degree of multidisciplinary clinical expertise, high-tech facilities and open clinical studies. It is intuitive that this maximizes quality of care. There is evidence supporting the notion in oncology that volume of cases correlates with outcomes *(Gatta, 2019; Hillner, 2000)*. This is all the more the case with rare cancers. However, there are some limiting factors that need to be considered. 1. Appropriate referral of a suspect rare cancer patient implies a degree of collaboration with/among clinicians/institutions, starting from the general practitioner. 2. In rare cancers, even centres of excellence need to collaborate with each other on state-of-the-art definition, clinical research, medical education, highly challenging clinical cases, etc. 3. The whole variegated clinical expertise required today in oncology often goes beyond the boundaries of a single centre, comprehensive and multidisciplinary though the centre may be. Regular collaborations among

close facilities may solve the problem, but in rare cancers it is possible that some items of expertise can only be found more or less far away. 4. Continuity of care is crucial for quality of care in oncology. The rare cancer patient's outcome may be impacted at any step of his/her clinical journey, so that proper referral is needed throughout the (often long) clinical history. 5. Since the number of centres owning expertise on rare cancers is inevitably limited, at least in some countries depending on their geography, a significant degree of health migration would be generated by simply centralizing referral. Health migration implies an adverse impact on quality of life of patients, as well as costs, including non-health related direct costs for patients and their families and indirect costs for patients and their families and society. 6. In order to maximize the exploitation of their clinical expertise, centres of excellence should be able to focus on multidisciplinary strategic clinical decision-making, pathological diagnosis and complex treatments, with special regard to local treatment. Otherwise, their expert resources may be overwhelmed, determining waiting lists and the like, i.e. some degree of implicit rationing of resources *(Frezza, 2019; Honoré, 2015; Ray-Coquard, 2017)*. One should always be aware that in the rare cancer field, professional expertise is inevitably a scarce resource, given the low number of cases, and the creation of professional skills always requires a long time, i.e. several years, or even decades. In other words, the number of centres of expertise on rare cancers will always be limited. All this highlights the importance of both centres of expertise and networking in rare cancers. Networking will be important to optimize patient referral to centres of expertise and maximize the use of their expertise in the community. At the same time, any networking will require the presence of strong centres of expertise *(Goodwin, 2004)*. Many patients will be entirely taken care of by centres of expertise, others will benefit from networking throughout their clinical history or for limited time spans. Ultimately, networking may mean

collaborations for rationalizing patient referral and sharing high-tech health facilities, producing state-of-the-art instruments (e.g. clinical practice guidelines, etc.), doing collaborative research, carrying out medical and patient education, sharing individual clinical cases. Some networks will cover one or some of these items, others will cover them all *(Popp, 2013)*.

3.1.2 Health networks are collaborations in the health field among healthcare providers sharing explicit goals and rules *(Provan, 2007)*. This definition is very broad and can cover very diverse kinds of networks. Historically, especially in the oncology area, many clinical research networks have been developed. By and large, these are the research cooperative groups focusing on collaborative clinical trials. Thus, they have a research mission. However, it may be assumed that they also have a role in improving quality of care, since collaboration on clinical trials allows a number of centres to share research discussions, clinical expertise and clinical practices with centres of reference, while clinical trials require a high degree of compliance with quality criteria. In some cases, these efforts have given rise to clinical, non-managed networks of professionals, sharing a common interest in a specific item, such as a group of rare cancers. Other networks have been deployed by health systems, giving rise to managed, formalized efforts, aimed at sharing resources and expertise within a given health system *(Brown, 2016)*. In the EU, ERNs were launched in 2017, as networks of healthcare providers selected by MSs across the EU, with the goals of: sharing clinical cases; making sure that all rare cancer patients have access to a multidisciplinary expert assessment at any strategic clinical decision; endorsing reference centres and rationalizing patient referral; integrating existing resources; developing clinical practice guidelines; fostering education; promoting collaborative research on translational, clinical and outcome research *(Héon-Klin, 2017)*. Health networks on rare cancers do in fact exist only

in some countries in Europe. A report by JARC, available on JARC's website, provides details thereof as of 2019.

3.1.3 Networking is always challenging. First, it needs proper funding for infrastructures (from IT network systems to service centres, and the like). Second, it needs the resulting additional professional workload to be properly valued, which may be addressed by proper reimbursements for teleconsultations or by extra staffing of centres providing network clinical services. Third, it needs explicit rules on governance (including responsibilities of members, network management, leadership, etc.) (*Tremblay, 2016)*.

3.2 Networking may follow different designs.

3.2.1 Healthcare systems may operate according to different models. Some healthcare models are "market-oriented", lacking any formal endorsement of centres for specific diseases, and thus do not have a policy of centralized referral. Trust and perceived quality then become critical in determining referral. Other healthcare models are more centrally governed, so that some centres are endorsed by the system to treat specific patients, etc. Hybrid solutions may be in place, for example combining patient's choice with some kind of managed referral *(Prades, 2019)*. These models reflect the variegated organization of healthcare systems and pose constraints over the functioning of networks.

3.2.2 Aside from the healthcare model, network design may depend on whether the centres involved have similar or different scopes, namely whether they are all centres of expertise or some are centres of expertise and others are more generalist. The former networks have a "peer-to-peer", the latter a "hub-and-spoke" design. Peer-to-peer networks may well produce clinical practice guidelines, drive medical and patient

education, conduct clinical and translational research. Currently, ERNs are “peer-to-peer” networks, since they are made up of centres endorsed by their governments for their specific expertise on rare cancers. It is assumed that for this reason ERNs should liaise nationally, or regionally, with “hub-and-spoke” networks, thus becoming networks of networks. Hub-and-spoke networks are more suitable for providing healthcare services to patients, maximizing their chances to access high-quality clinical expertise and minimizing health migration or implicit rationing of resources *(Calman, 2016; Elrod, 2017)*. In a hub-and-spoke logic, one centre behaves as a “provider” of clinical expertise or expert services and another as a “user”. For example, pathological diagnosis may be provided by one expert centre to several others. Likewise, local treatments may be provided by a few expert centres. On the other hand, several medical treatments may be provided by several spokes, permanently belonging to a network within which they exploit the multidisciplinary expertise of hubs. In general, as long as a spoke permanently belongs to a network, it will develop a degree of expertise on the disease, allowing it to continuously improve its quality of care on the disease and optimally collaborate with hubs within the network. Of course, a centre may serve as a hub for some areas of expertise or services and as a spoke for others; moreover a centre may be a hub on one rare cancer and a spoke on another.

3.2.3 Some clinical networks are “managed”, in the sense that centres are bound to deliver some services within the network and there is clear hierarchical governance and a kind of top-down endorsement of centres by the health system. Others are “professional” networks, since they arise from a voluntary choice of professionals, thus following a bottom-up attitude, often with light governance *(Brown, 2016)*. Managed networks are important because they are built into a health system. One major consequence is that centres

are endorsed by the health system, and clearly this is crucial in rare cancers *(Ferlie, 2013)*. The main added values of non-managed networks, being largely voluntary, are the motivation of participants and their flexible functioning. Collaborative research groups are good examples of the successes of such networks. In the end, both kinds of networks have pros and cons and different purposes. Possibly, the two models may be merged into networks made up of publicly endorsed centres, with a clear definition of their responsibilities, but governed and enlivened by professionals.

3.2.4 In small countries, the problem of rare cancers is even more critical. No institution, by definition, will see enough patients with certain rare cancers to meet the case volumes generally selected as thresholds for good quality. Obviously, it is possible to lower thresholds according to country populations. However, this is questionable, as long as one assumes that these thresholds have a rationale in terms of minimum amount of expertise required to achieve good-quality care. An interesting option is then to collaborate on a cross-border basis with other nations. In the EU, one of the aims of ERNs is in fact to identify “affiliated centres” in some small countries, which then will liaise with the “full members”.

3.3 Cancer-related ERNs will play a major role in the EU.

3.3.1 The ERN on rare adult solid cancer, EURACAN, is sharing best practice tools and connecting reference centres for rare adult solid cancers. It is also establishing regularly updated diagnostic and therapeutic clinical practice guidelines. The network aims to reach all EU countries in 5 years and to foster a referral system exploiting national and regional networks. It seeks to produce communication tools in all languages for patients and physicians and develop

multinational databases and tumour tissue biorepositories. EURACAN builds on pre-existing clinical and research networks that have successfully carried out clinical trials through the *European Organisation for Research and Treatment of Cancer* (EORTC), and on established clinical practice guidelines through the *European Society for Medical Oncology* (ESMO) (http://euracan.ern-net.eu).

3.3.2 The ERN on Rare Haematological Diseases, EuroBloodNet, builds on the experience gained thanks to the EU-funded *European Network for Rare and Congenital Anaemias* (ENERCA) and the *European Haematology Association* (EHA). This ERN is seeking to: improve access to healthcare for rare haematological disease patients; promote clinical practice guidelines and best practices; improve training and knowledge-sharing; offer clinical advice where national expertise is scarce; increase the number of clinical trials open in Europe (www.eurobloodnet.eu).

3.3.3 The ERN on paediatric cancers, ERN PaedCan, involves healthcare providers across Europe in an effort to deliver high quality, accessible and cost-effective cross-border healthcare to children and adolescents with cancer, regardless of where they live in the EU. Given the burden of health-related travels on families, ERN PaedCan prioritises movement of information, clinical practice guidelines and knowledge, rather than patients, whenever possible. The aim is to extend local and national multidisciplinary 'tumour-board' culture to the cross-border level. One of the means by which ERN PaedCan fulfils its mission is linking pre-existing reference centres inherent to the established ECTGs. ERN PaedCan is implementing Objective 4 of the *SIOP Europe Strategic Plan*, i.e. equal access to standard care (in both diagnosis and treatment), medical expertise and clinical research across Europe. ERN PaedCan governance involves SIOP

Europe and *Childhood Cancer International – Europe* (CCI-Europe) (http://paedcan.ern-net.eu/).

3.3.4 The ERN on genetic tumour risk syndromes, ERN GENTURIS, is working to improve identification of genetic tumour risk syndromes, minimize variation in clinical outcomes, design and implement clinical practice guidelines, develop registries and biorepositories, support research and empower patients *(Vos, 2019)*. The network will carry out medical and patient education and foster sharing of best practices across Europe. Access to multidisciplinary care will be improved, with new models and standards for sharing and discussing complex cases. The network is enhancing the quality and interpretation of genetic testing and is stimulating patient participation in clinical research programmes. GENTURIS will cooperate with other ERNs to improve care of patients with genetic tumour risk syndromes who develop conditions that fall within the expertise of other networks (www.genturis.eu).

3.4 Healthcare networks in rare cancers should have quality systems.

3.4.1 Clinical networking should improve effectiveness in rare cancer care, i.e. the efficacy in the “real world” of a health system. By definition, this means improving survival and quality of life, as the natural goals of any medical intervention. In fact, networking should allow the best implementation of available technologies and the best transfer of innovation into clinical practice. Quality of life is also improved per se by lowered health migration. In theory, clinical networking should also improve efficiency, i.e. cost-effectiveness, at the very least because it is expected to decrease direct health costs from inappropriate care. There has been a consensus in the JARC community that the benefits of clinical networking in terms of cost-effectiveness do not need to be demonstrated in comparison to other

organizational strategies for rare cancer patient healthcare. Today, it would be hard to find a comparator other than some form of networking (aspects of networking are increasingly spreading through everyday clinical practice). Efforts should instead be made to implement formalized quality systems at both network and healthcare provider levels. The following points apply to the functioning of all networks, from ERNs to national, or regional cancer networks. Following the established Donabedian model, there should be structure, process and outcome quality criteria. Compliance with the quality standards should be monitored regularly. There should be instruments such as e-tools for self-assessment. External evaluations by an independent evaluation provider should be implemented, using experts in the field as auditors. Final reports with recommendations should be sent to the networks and to national health authorities, and the accreditation certificate should be recognized by the health system. Patient involvement in these strategic processes is recommended. At the present time, the European Commission is setting up a continuous monitoring system for ERNs (the *Assessment, Monitoring and Evaluation of Quality Improvement System* – AMEQUIS).

3.4.2 All MSs with established networks for "families" of rare cancers should agree on quality standards and indicators for such networks, to sustain improvements of patient care. Quality standards and indicators agreed upon by expert consensus are listed on the JARC website.

3.4.3 In a peer-to-peer or in a hub-and-spoke network, structure standards for hubs should include:

a) oncology general accreditation criteria;
b) case volumes of rare cancer patients;
c) availability of a multidisciplinary tumour board, with a core group of experts and an expanded group with additional experts;

d) availability of, or access to, a set of facilities known to be essential in the disease.

Process criteria for hubs should include:

a) compliance with network rules as far as network patients (see 3.5.5) are concerned (e.g. compliance with timelines on teleconsultations, etc.);
b) active involvement in clinical, epidemiological and translational research;
c) active involvement in the production of clinical practice guidelines;
d) active involvement in, and promotion of, educational initiatives for all types of professionals in rare cancers, as well as involvement in patient education in conjunction with relevant patient organizations.

3.4.4 In a hub-and-spoke network, the quality criteria for spokes should factor in that they are not reference centres by definition and thus cannot meet the same rare-cancer related requirements for hubs. Structure standards for spokes should include oncology general accreditation criteria. Process standards for spokes should include: a) compliance with network rules as far as network patients are concerned; b) participation in clinical education initiatives; c) participation in clinical research.

3.4.5 For both ERNs and national networks, quality criteria should focus on the way the network operates, so as to optimize the patient's pathway and maximize access to multidisciplinary knowledge and high quality care, supported by excellence in education and training. There should also be a major focus on the holistic patient-centeredness of care. Critical items are IT connectivity and the gathering of data for research purposes. All rare cancer networks have a major role to play in clinical research and in professional education. The quality criteria for all these networks should have as their main domains: a) governance

and co-ordination; b) patient-centeredness (e.g. governance mechanisms should include patients, etc.); c) multi-disciplinarity; d) delivery of care; e) research; f) medical education; g) patient information and communication; i) data handling; and l) quality systems (exploiting IT tools and electronic health records). A detailed list of quality standards for ERNs and national networks was worked out within the framework of JARC and is available on its website.

3.4.6 The way patients enter networks (e.g. the services they receive) may differ substantially, depending on the network, and also on the clinical support from the network that the institutions taking care of them require. In a sense, the number of patients entering a network will be a measure of its success. However, some networks may deliberately target only a limited population of patients, depending on the network's aim. How many patients out of the total are shared over the network by any single centre will also be a quality indicator for that centre. However, the denominator of all patients who in theory could enter a network will often be hard to measure. On the other hand, it is easier to define who is a "network patient". Conceptually, a network patient will be a patient who: a) is treated according to the network's clinical practice guidelines; b) exploits the clinical expertise available on the network; c) is registered in the network database. According to the network's managed care pathways, the network patient may: a) be taken care of within a hub following the network's clinical practice guidelines and exploiting the hub's expertise; or b) have his/her case virtually shared over the network, either between a hub and a spoke, or even between a hub and a high-technology facility (e.g. a hadron therapy centre); or c) in addition to his/her case being virtually shared, physically move to another network centre, generally for a limited portion of the diagnostic and treatment pathway. Thus, all patients will be "logically" network patients (even if diagnosed and treated in a single hub); some will be "virtually shared"

network patients; some will be “physically shared” network patients. One should be aware that some patients will enter the network as from the very beginning of their clinical history, while others will be included only at a given stage of their pathway, while some patients may leave the network sometimes. In any case, the quality system of the network will apply to the entire journey spent over the network, and this will be recorded in the network database. The network patient should enjoy the highest standards of care made possible by the network, whichever the point of access to the network.

3.4.7 Therefore, there should be outcome and process quality criteria pertaining to the single network patient. Outcome criteria will be based on the recording of the patient’s outcomes in the network database. Process criteria will have to do with the operating procedures with which he/she will be managed (e.g. timelines, etc.) and with compliance with clinical practice guidelines. IT solutions should be implemented to assess compliance with clinical practice guidelines.

3.4.8 In summary, healthcare networks in rare cancers should have well developed quality systems at the healthcare provider level, the overall network level and the network patient level. These systems should be capable of being self-assessed and then externally assessed against specific quality standards and indicators, which have been developed by expert consensus. This quality assurance will protect and enhance the quality of diagnosis and care for network patients, improve their survival and quality of life, educate all professionals in the network and provide a secure basis of clinical research in rare cancers.

Paediatric Cancer Section

It is acknowledged that optimal care for paediatric cancer is delivered in specialized multidisciplinary care units, also known as reference or principal treatment centres, which provide the full range of diagnostic, therapeutic and supportive care options to optimize survival and minimize toxicity *(SIOP Europe, 2009)*. Multidisciplinarity is the hallmark of paediatric haematology and oncology. In addition to clinical specialists and nurses, other professionals such as, say, psycho-oncologists, play therapists and educators, are required *(SIOP Europe, 2009)*. Specialized paediatric haemato-oncology professionals provide their services across the entire continuum of care. Innovative therapies, including new drugs in early phase clinical trials, represent another chance for the treatment of children and adolescents with relapsed or refractory malignancies, but access is still very limited.

The following organizations and network structures in paediatric haematology and oncology are deployed at the European level. They share an overarching strategy embedded in the *SIOP Europe Strategic Plan (Vassal, 2016)* and are interconnected through mutual membership affiliations, official partnerships, and joint projects.

- SIOP Europe (*European Society for Paediatric Oncology*) represents national societies of paediatric haemato-oncology professionals (NaPHOS) and all disease-specific ECTGs. The ECTGs address each group of paediatric malignancies (leukaemias, lymphomas, brain tumours, neuroblastoma, soft tissue sarcomas, bone sarcomas, etc.) and are assembled in the *SIOP Europe Clinical Research Council* (CRC).
- CCI Europe (*Childhood Cancer International – Europe*) represents parents, patients and survivors.
- ITCC (*European Academic Consortium for Innovative Therapies for Children Cancer*) represents a network of research excellence and hubs of expertise on innovative therapies delivered in early clinical trial settings.

- PanCare (*Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer)* represents professionals, survivors and their families.
- EXPeRT (The *European Cooperative Study Group for Paediatric Rare Tumours*) represents the community specializing in very rare paediatric tumours.
- ERN PaedCan is an integral part of an established pan-European community linking researchers, physicians, as well as parents, patients and survivors.

Diagnosis, treatment and research of paediatric cancers pose special requirements for networking, including specific quality standards and indicators (see the JARC website).

To ensure that children and adolescents can benefit from networking, appropriate reimbursement should be foreseen for cross-border care (for example, when patients travel to another country to access complex or poorly available interventions, including potentially life-saving treatment in early clinical trials). The S2 programme, formerly E112, under Regulation EC No 883/2004 on the coordination of social security systems, is in place for EU citizens seeking healthcare abroad. However, access to innovative therapies in clinical trials is not currently considered as part of the S2 programme. At a time when numerous examples show that access to innovative medicines under development can provide significant benefit for individual patients, it is of concern that they cannot go across borders to have access to novel therapies and be reimbursed.

Given the mission of ERN PaedCan to foster cross-border collaborations by providing virtual advice to correctly deliver standard of care treatments in widening countries whenever possible, better integration of these efforts into national healthcare systems is required and needs the attention of MSs. This could be achieved by modifying the current S2 programme, to compensate also for virtual care time provided by experts through teleconsultations.

There are important links between the area of rare adult cancers and paediatric haematology oncology. One important example is in the field of childhood cancer

survivorship (CCS), when former patients become adults and necessitate appropriate care transition and surveillance of late effects. The PanCare network has been working with SIOP Europe and ERN PaedCan on the *Survivorship Passport (Haupt, 2018)* to empower survivors and guide healthcare workers by providing personalized information on the type of long-term follow-up required. A strong global collaboration on producing guidelines has been facilitated by the *International Guideline Harmonization Group* (IGHG) *(Kremer, 2013)*. It is crucial for the success and further development of CCS care that ERN PaedCan be able to keep spreading accumulated knowledge and facilitate the implementation of survivorship facilities and programmes throughout Europe. Other areas common to paediatric and adult oncology include the teenager and young adult population (TYA), where SIOP Europe has a Memorandum of understanding and is engaging in a common working group with ESMO *(Stark, 2016)*. Children and adolescents affected by cancers typically occurring in adults are a distinct population where there is a need for collaboration with the adult clinical oncology (e.g. adult cancers such as thyroid cancer, breast cancer and melanoma) *(Vassal, 2016)*. Continuous cross-talk and knowledge sharing with EURACAN is an important priority for ERN PaedCan. Already existing synergies include the collaboration with EURACAN on clinical practice guidelines and cross-cutting projects on common diagnostic entities *(Casali, 2018)*.

<u>Recommendations</u>

- To secure the benefits of networking for patients, appropriate compensation for cross-border teleconsultations by individual healthcare providers within ERNs is required.
- Solutions are urgently needed to ensure seamless access to, and reimbursement of, cross-border care, including innovative therapies under development, for paediatric cancer patients.
- EU and national support is required to enable secure life-long relevant treatment information

(*Survivorship Passport*) about treatment burden and late effects, capitalizing on European eHealth developments. As an example of integration into national strategies, the Survivorship Passport is now included in the National Cancer Plan of Austria.

- High quality guideline development underpins European long-term quality care models for childhood cancer survivors across the EU and calls for MSs' support and non-competitive European funding.
- The current S2 programme should be adapted to the needs of an eHealth based virtual cross-border care.

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4. Medical education should exploit and serve healthcare networking…

...by proper integration of the university system and all educational players, being instrumental to dedicated career mechanisms and opportunities

4.1 **Medical education is different in rare vs. common cancers**.

4.1.1 It is important to be aware of the main difficulty with medical education in rare diseases, including rare cancers, which makes it essentially different from common diseases, including cancers: the lack of reinforcement of information conveyed to receivers. For example, when a physician attends an educational event on a common cancer, he/she will be likely to encounter patients with that cancer very soon and very often throughout his/her practice. The same does not apply when the cancer is rare. Thus, the educational frame of any educational initiative in rare cancers must take into account this challenge. For example, one should accurately select the receivers, for example those working within rare cancer networks, and in any case accurately tailor the educational contents to their actual clinical needs. As to the current state of affairs, a survey was made on training programmes available for under- and post-graduates related to adult rare and paediatric cancers, as of 2019. Its results are available on the website of JARC.

4.1.2 Clearly, this does not apply to the medical personnel of reference centres, who therefore are a natural target of medical education on rare cancers, in ways that do not differ substantially from what may happen with medical education on common cancers.

However, by definition, this target is scarce and there may be less opportunities for private sponsorships. This means that this kind of educational events would need to be properly supported.

4.1.3 The medical personnel belonging to spokes of hub-and-spoke networks should be privileged by medical education on rare cancers, since they represent an important target. In fact, it is vital that clinicians within the spokes are able to collaborate effectively with hubs, in such a way as to virtually create the same kind of environment that exists within centres of reference. In other words, clinicians working in spokes should be well aware of the diseases they deal with, although their institutions do not get to a number of cases comparable to hubs. For example, a medical oncologist in a spoke must be able to interact effectively with an experienced surgeon of a reference centre, in order to make medical therapy optimally match a planned highly specialized surgical procedure. Of course, spoke clinicians are hardly likely to specialize only in one rare adult solid cancer. Thus, it is always logical to conceive educational events grouping several rare adult solid cancers, considering similarities (e.g. sarcomas and mesothelioma, etc.). On the other hand, one difficulty is that rare adult solid cancers do not constitute a distinct set of cancers, as different from paediatric cancers, which are grouped together in the paediatric oncology area, and haematological cancers, which are grouped within the domain of haemato-oncology.

4.1.4 Undergraduates and general practitioners make up a particularly challenging educational target, since lack of reinforcement is a major problem, while the first clinical diagnosis of any new suspect case as well as proper new case referral rely on general practitioners. In general, it is important that non-oncologists perceive the size and importance of rare cancers and are aware of the main organizational challenges, the importance of proper referral, the meaning and

organization of clinical networking, the difficulties of clinical research, the methodology of shared decision-making in conditions of uncertainty *(Dittrich, 2016)*.

4.1.5 Given the crucial importance of these professional figures for networks, training opportunities should be arranged for case managers, clinical patient navigators and other health professionals or social workers specializing in supporting network functioning and the rare cancer patient's journey. The professional background of these professionals may vary substantially, but educational facilities focusing on rare cancers would be worthwhile *(Wells, 2018)*.

4.1.6 Nurses specializing in single rare cancers, within centres of reference, or in some rare cancers, within rare cancer networks, should increase in number. Training facilities should be properly provided by centres of reference and universities.

4.2 **Medical education should be shaped around networking.**

4.2.1 Networking may help provide the contents of the educational offer on rare cancers. It may also help shape training modalities, including distance learning, distance mentorships and the like. While a drawback of distance learning may be a lack of interaction between the mentor and the learner, this may be overcome within a network *(Mausz, 2017)*. The basic tool of teleconsultations within clinical networks is also a powerful educational tool. After being teleconsulted, several clinical cases can then be grouped and offered as background educational material to the other members of the network, with a special view to young oncologists and other specialists.

4.2.2 Fellowships within networks may be especially important and specifically shaped. In fact, a clinical network is also based on personal relationships

among professionals across centres. In this sense, even a relatively short fellowship at a centre of reference may not only mean a big opportunity for a young oncologist, but also a way to make sure that in the future two institutions may continue to work together. This is the reason why funding fellowships, even short fellowships, can be especially important. Proper funding should therefore be guaranteed. It is important to realize that these fellowships may primarily have an educational aim, even before a research one. EU funding should be arranged accordingly.

4.3 **Medical careers in rare adult solid cancers should be implemented and should have corresponding training pathways.**

4.3.1 Training on rare cancers should always be viewed as connected with available medical careers. Efforts should be made to implement new medical careers focusing on rare cancers. Otherwise, rare cancer patients will inevitably be discriminated against. In fact, on one side, young clinicians will not be attracted by these diseases. On the other side, in the rare cancer area there is always the risk that professionals specializing in specific rare cancers may leave their centres of reference along their career. In order to avoid this, it is vital that medical careers are fully developed on rare cancers, to encourage professionals to dedicate themselves to rare cancers throughout their professional life. Clearly, reference centres have always developed careers on rare cancers. Centres belonging to ERNs should be proactive in guaranteeing medical careers on rare cancers. Now, it would be important to also develop careers within the spokes of the hub-and-spoke networks on rare cancers.

4.3.2 There is a lack of institutions and units allocated to all rare adult solid cancers, while some institutions or

units may be allocated to one or a few rare adult solid cancers. Medical oncology units allocated to rare adult solid cancers should be created within spokes of hub-and-spoke networks on rare cancers, with full careers. Any specific training is lacking. One may assume that a clinical oncologist specializing in rare adult solid cancers (or some of them) has already completed his/her training as a medical oncologist, a radiation oncologist or a surgical oncologist. Thus, there is the need to provide educational pathways for clinical oncologists willing to specialize in rare adult solid cancers. These educational pathways should provide education on such diseases under a multidisciplinary perspective. They should be flexible enough to accommodate educational needs that may cover all or only some of the 10 “families” or rare adult solid cancers. These educational pathways could be provided in collaboration with EURACAN by the European university system, i.e. by the universities linked to EURACAN, as well as by comprehensive cancer centres, during or after the conventional board certification pathway (i.e. in medical oncology, radiation oncology, surgical oncology). These pathways should include: a) courses on each of the rare adult solid cancers, based on a syllabus; b) clinical fellowships on selected rare adult solid cancers. There should be an examination, with a certification of competence. All this could give rise to an integrated system leading to the creation of experts on rare adult solid cancers, hopefully finding dedicated careers for them at the centres of hub-and-spoke networks. The *European Union of Medical Specialists* (UEMS) (https://www.uems.eu/) may serve as the provider of the certification and the European training requirements. The UEMS can also be involved in continuing medical education and continuing professional development processes.

4.4 Patient engagement in dissemination of information and training.

4.4.1 The rarity and severity of rare cancers lead patients and their carers to search for the most up-to-date information on the best available treatment options, but also on centres of reference. This underscores the importance of processes resulting in the endorsement of centres of reference on rare cancers. Internet has been a major game changer in terms of access to such information. However, finding reliable and consumer-friendly information may be challenging. Patient advocacy groups are often able to convey to patients relevant and accurate information through their websites. In Europe, there is an additional problem of language barriers, that needs to be addressed.

4.4.2 The involvement of European patient advocacy group (ePAG) representatives, the “ePAG advocates”, in the rare cancer ERNs’ work on education and training is recognized as crucial, given their expertise. They help provide necessary information tools for the patients and their carers. The involvement of expert patients in hub-and-spoke networks on rare cancers is thus to be encouraged. Patient advocacy groups have also been key in providing specific training resources to patients and carers. This takes the form of onsite training, conferences, online webinars, video-recorded tutorials. Training resources for patients and their carers include two equally important subsets.
General training tools. Educational items include orphan medicinal products, innovative therapies, clinical trial designs for small populations, health technology assessment on treatments targeting rare conditions and access to these treatments. The *EURORDIS – Rare Diseases Europe* Open Academy, *European Cancer Patient Coalition* (ECPC) and CCI-Europe provide such forms of training and teaching materials. They are also involved, together with other

patient organisations, in the design of courses intended for patients and provided by EUPATI (*European Patients' Academy*), the *European School of Oncology* (ESO), EORTC, as well as in the development of Patient Advocacy Track in annual congresses of major European professional societies such as ESMO and EHA.

Specialized training tools. This category includes training sessions on specific rare cancers made by patient organizations as well as by learned societies and other organizations. For instance, the ESO-ESMO-RCE (*Rare Cancers Europe*) training course for patient advocates is an opportunity for patients and their representatives to learn from their peers and interact with medical experts in rare cancers.

4.4.3 The partnership between patient organizations and healthcare professionals, including case managers, is a key success factor in improving the training of both patients and their carers and professionals, who can learn from the experience of patients living with a rare cancer.

Paediatric Cancer Section

A *European Paediatric Haematology and Oncology Syllabus (Riccardi, 2013)* and dedicated educational programmes and events are in place, including the SIOP Europe Annual Meeting and the SIOP Europe-ESO Masterclass.

While there are well established, full medical careers in paediatric oncology, a comprehensive training pathway is lacking in many MSs. Paediatric oncologists are overall either paediatricians or medical oncologists. Some radiation oncologists and surgeons may specialize in treating some or all childhood cancers, in both cases without dedicated training pathways. Thus, a comprehensive educational strategy is being developed under the leadership of SIOP Europe.

From ERN PaedCan's perspective, twinning programmes between institutions are a very useful resource. They allow healthcare personnel exchanges across centres in Europe, to share knowledge on a day-to-day basis using the CPMS platform, thereby serving as a source of continuing medical education.

From the patient perspective, dedicated training resources on paediatric cancer have been developed, including a guide to clinical trials for young people with cancer and their parents *(CCI, SIOPE & ENCCA, 2014)*. In relation to educational events, the annual conference of CCI-Europe is an integral part of the SIOP Europe Annual Meeting. Timely access to an overview of available early clinical trials across Europe is an important patient need.

<u>Recommendations</u>

- The professional figure of the paediatric oncologist should be recognized in all MSs, and mutual recognition of qualifications across the EU should be considered.

- Non-competitive EU funding should be allocated to support twinning of paediatric haematology and oncology healthcare providers within the ERN PaedCan, to foster mutual learning and improve standards of care.
- Appropriate training of specialized professionals who regularly work with children with cancer should be foreseen, based on existing European guidelines *(Janssens, 2019; SIOP Europe, 2009)* and the SIOP Europe educational strategy under development as of 2019.

  Information on early-phase clinical trials across Europe should be publicly available, easily accessible and understandable to parents and patients.

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5. Research should be fostered by networking and should take into account an expected higher degree of uncertainty...

...exploiting clinically annotated biobanking, clinical registering, patient referral to ongoing clinical studies, as well as innovative methodologies for clinical research

5.1 Research on rare cancers faces specific, additional challenges.

5.1.1 In principle, the difficulties of rare cancers in terms of clinical research are by definition related to the low number of patients *(Casali, 2015)*. This limits "statistical precision" in clinical, translational and outcome research. There are organizational and methodological solutions that can be deployed to address this inherent difficulty of rare cancers. In principle, no solution should entail diluting a distinct patient population of rare cancer patients into a larger one with wider entry criteria. This tends to dilute efficacy as assessed in clinical studies, thus jeopardizing innovative treatments for rare cancer patients. All the more, the use of biomarkers should never be discouraged in rare cancers, even if creating subgroups may seem even more problematic. However, an effective biomarker also tends to amplify the effect, thus increasing statistical precision *(Buyse, 2010)*.

5.1.2 Lack of clinical expertise is another specific problem affecting research, besides healthcare organization. In fact, suboptimal quality of care in a disease impairs results of any treatment, including research treatments. For example, even a randomized trial will

be biased by lower quality of care, since the experimental arm may be comparably more affected than the control arm (any improvement deriving from a possibly more effective experimental treatment will be less exploited during, after or before the trial, if quality of care is suboptimal, and thus less able to result in, say, survival improvement over the control arm).

5.1.3 Shortage of dedicated funding is an obvious difficulty. Rare cancers, if eligible, should be clearly identified as such in public calls for research projects. At the EU level, mechanisms should be in place in order to make sure that a reasonable total amount of funds allocated to cancer is granted to rare cancers, taking into account that they amount to about 20% of all cancer cases.

5.1.4 Limited marketing opportunities affect the motivation of pharmaceutical and other companies to develop technologies, such as new drugs, in rare cancer oncology. The mechanisms foreseen by the *EU Orphan Drug Regulation* have been instrumental in determining the development of many orphan drugs in recent years in oncology, though not in paediatric oncology *(European Parliament and Council of the European Union, 2000)*. However, one should be aware that one factor potentially discouraging companies from developing health technologies in rare cancers could be the risk of discrepancies in reimbursement by national/regional authorities across the EU, after regulatory approval. The higher degree of uncertainty makes rare cancers particularly exposed to this risk. This difficulty can only be addressed by harmonizing health technology assessments across the EU as far as efficacy is concerned, though leaving the possibility to national countries or regions to further assess local sustainability on the basis of cost-effectiveness considerations. Innovative methodological solutions

for clinical research should be accepted as evenly as possible throughout MSs.

5.1.5 Low numbers also imply shortage of biological samples, thus affecting basic and translational research, but also clinical research, since it should increasingly be driven by biomolecular rationales. Thus, organizational solutions to facilitate biobanking should be arranged in rare cancers. All the more, hurdles due to legal constraints should be removed as much as possible, with special reference to data protection rules. It is exceedingly important in rare cancers to miss as few cases as possible.

5.2 **Organizational solutions.**

5.2.1 Appropriate public funding for investigator-driven clinical studies is essential in rare cancers. Academia may be especially instrumental in some studies, that can be of specific value in rare cancers, as follows. a) Signal-seeking studies about new agents may be particularly useful to the repurposing of agents already marketed, or under clinical development in other cancers. One may assume that pharmaceutical companies may then be willing to further develop a drug in the presence of positive findings, while investments in signal-seeking trials might be less attractive. b) Should pharmaceutical companies decide not to develop the re-purposing of an available drug in a rare cancer, e.g. an ultra-rare cancer, the clinical development should also be funded. Partnerships with the disease-based communities could be exploited to this end. c) Prospective observational studies, up to clinical registries, should be funded, as a means to generate knowledge on the natural history of rare cancers, with special reference to ultra-rare cancers, but also potential external controls for uncontrolled studies on new agents. d) The off-label or compassionate use of drugs should be assessed prospectively as much as possible,

especially within networks, to be potentially used to generate new hypotheses and/or confirm claims of efficacy. In general, these clinical databases generate real-world evidence, liable to be used for outcome research, cost-effectiveness research and the like. Opportunities for partnerships with population-based CRs can be exploited, for example to assess the representativeness of a clinical registry in a population. e) Healthcare service research should be funded to give rise to evidence about optimization of organizational solutions for rare cancers to increase cost-effectiveness and reduce disparities. f) Appropriate funding is vital for investigator-driven clinical trials on surgical and radiation treatment modalities, as well as their clinical combinations within distinct treatment strategies, and in general multimodal treatment strategies. With a lack of economic motivation from the private sector, only academia is able to promote this kind of clinical research. Some strategies may also entail limiting toxicities and/or costs (e.g. by minimizing duration of treatments, etc.). Partnerships with reimbursement bodies and national health systems could be foreseen to fund these trials. In general, health systems should be proactive in funding and stimulating investigator-driven clinical studies on rare cancers, thus helping to fill gaps that in principle can penalize rare cancer patients.

5.2.2 Networking (first of all through ERNs, but also through the national networks linked thereto) is naturally instrumental to clinical research. A very simple mechanism for this is patient referral towards open clinical trials (which may well be open only in selected centres). Networks should be exploited to decrease costs of clinical trials in rare cancers, by means of economies of scale (e.g. by sharing standard operating procedures [SOP], etc.), use of clinical databases also for research purposes, maximization of quality of care within trials, etc. To this end, it would be important to design clinical databases of networks,

and network institutions, to be as interoperable as possible and to facilitate data exportation to trial databases. Agreements with contract-research organizations, managing the organization of clinical trials, to standardize and optimize the participation of network centres in trials, may be instrumental in decreasing costs of both investigator-driven and industry-sponsored studies. This could make it possible for academia to run more clinical trials and encourage pharmaceutical companies to undertake studies also in orphan indications.

5.2.3 Networking is advantageous for prospective biobanking, whether physically centralized or virtual ("federated"). The first added value of networking to biobanking is the clinical annotation of biosamples by linking them to a network clinical database. The next added value is the opportunity to set common practices on storage of specimens in terms of standard SOPs. Virtual biorepositories are easier and cheaper, but have the disadvantage that sample collection is managed according to local SOPs, which may be different from one another. Even if shared SOPs are in place, monitoring will be difficult, especially as far as long-term storage is concerned. On the other hand, centralized biorepositories can be successful only if proper funding is available for each institution, to reimburse the extra-burden entailed by procedures related to collection, annotation and shipment. Clearly, centralized biobanking may be particularly appropriate for highly selected subsets of specimens (e.g. ultra-rare cancers, etc.) and clinical trials. Patient representatives should be involved in the governance of biorepositories. Examples of biorepositories active in Europe in the field of cancer include *Screening Patients for Efficient Clinical Trial Access* (SPECTARare) and *Biobanking and Biomolecular Resources Research Infrastructure* (BBMRI).

5.2.4 The administrative requirements implied by clinical trials as well as by sharing data and biological samples are substantial and are indeed a limiting factor to the feasibility of collaborative research amongst academic institutions. With regard to clinical trials, an agreement among participating institutions is needed for each of them to be set up. However, templates can be worked out in such a way that any new agreement may become much easier to finalize. ERNs, and networks linked thereto, should develop such templates, in order to speed up as much as possible the administrative component of the process leading to any new trial. Likewise, ERNs are not legal entities and cannot fulfil the study sponsor's role. Thus, in a clinical trial joined by ERNs' institutions, the sponsor's tasks may be allocated to one of them, or split among some of them. Split sponsorship in clinical trials is an opportunity made possible by the new *EU Clinical Trials Regulation*. Otherwise, ERNs should partner with collaborative research groups, as long as these can fulfil sponsorship tasks. With regard to observational research on clinical data and/or biological samples through clinical registries or biorepositories within ERNs, and networks linked thereto, efforts should be made to ensure that administrative agreements amongst institutions can be arranged once and for all, so as to minimize the burden for researchers and their institutions.

5.2.5 Patient organisations should be viewed as invaluable stakeholders to orient priorities and designs of clinical trials, as well as to promote and possibly fund them. Optimization of patient accrual can be determined by involvement of patient communities across countries.

5.2.6 In the rare cancer area, new drugs or technologies may be available within clinical trials only in selected EU countries. Thus, all the more in rare cancers, it would be vital to make it as easy as possible for EU citizens to be enrolled even outside their countries. Regulatory constraints should be minimized and

information about clinical trials in the EU should be disseminated.

5.2.7 Likewise, efforts should be fostered to open clinical trials on highly promising treatments as widely as possible in the EU. Cross-age enrolment in clinical trials should be definitely encouraged.

5.3 **Methodological solutions.**

5.3.1 The principle that a higher degree of uncertainty needs to be tolerated in rare cancers should be acknowledged in selecting the methodology of new clinical studies. In general, clinical studies should also be done when a lower statistical precision is likely, given available numbers, and their patient populations should be selected exclusively to maximize the chances of any new treatment to display its maximum efficacy, without widening eligibility criteria inappropriately. Even the study duration should be reasonable, given available numbers.

5.3.2 The choice about whether a clinical trial will be randomized or not should be viewed as independent of its feasible numerical power. In any case, proper methodologies for non-randomized clinical studies should be worked out, to make them as rigorous as possible, and as convincing as possible from the regulatory point of view. This entails identifying a priori external (historical) controls to be explicitly used as comparisons. To this end, clinical registries should be encouraged, namely within networks. This would imply conceiving non-randomized clinical trials in the Phase III setting, with overall survival and quality of life as end-points (or others as surrogates) *(Bogaerts, 2015)*. In practice, this would mean refraining from resorting to the methodology of Phase II studies just because of the lack of an internal control.

5.3.3 Bayesian appraisal of all available evidence is appealing in rare cancers, because it may be expected to maximize the amount of information exploited *(Adamina, 2009)*. Generally, one major weakness of Bayesian approaches lies in the subjectivity entailed by the concept of prior probabilities. One way forward could be to deploy consensus mechanisms within the medical community, e.g. within a disease-based rare cancer community, giving rise to explicit, transparent and fair priors, with the option of neutral/pessimistic/optimistic sensitivity analyses on posterior probabilities. Rare cancer communities could be proactive in setting up such consensus-building efforts.

5.3.4 Adaptive mechanisms in clinical trials are aimed at modulating a study throughout its implementation, depending on data from, or outside, it. This includes interim analyses and stopping rules, changes in eligibility criteria, changes in end-points, changes to the statistical plan (including seamless Phase II/III designs), etc. *(Mistry, 2017)*. In rare cancers, adaptive mechanisms may be particularly useful given the paucity of cases and the long study timelines, by improving effectiveness and cost-effectiveness of trials, as well as their ethical acceptability.

5.3.5 The technologies of big data are exceedingly promising in rare cancers, given their ability to speedily combine large and diverse databases, such as biological (omic-based), clinical (electronic health record-based), administrative datasets *(Baro, 2015)*. All the more in rare cancers, it would be crucial to define how the logic of artificial intelligence through machine learning on big data can complement the logic of clinical trials. Methodological debate is ongoing as to whether and how machine learning can generate new knowledge and change clinical practice outside the framework of clinical trials. On the other side, it is clear how clinical decision support systems can particularly aid clinical decision-making in rare

cancers, where the clinical expertise is by definition an issue.

5.3.6 Surrogate clinical end-points should be valued in clinical trials on rare cancers, since they tend to give rise to larger differences (thereby allowing lower sample sizes) and/or to be assessable earlier (thereby allowing shorter trial duration) *(Casali, 2015)*. Indeed, surrogate end-points need to be validated, with the difficulty that the validation process requires large numbers, that by definition are problematic in rare cancers. Sometimes, personalized clinical decision-making in conditions of uncertainty may exploit surrogate end-points, aside from their validation in research (for example, a tumour response may be expected to give rise to some clinical benefit in single patients, e.g. when a surgically unresectable lesion may become operable, a shrinking lesion may become less painful, etc.). Research into surrogate end-points should be encouraged. In particular, methodological research into tumour response might be rewarding, as long as it could refine the concept and help improve its surrogacy. Patient involvement in the methodological research into surrogate end-points should be encouraged, bringing patients' perspective therein.

Paediatric Cancer Section

Most standard therapies in paediatric oncology have been established through European and international cross-border academic-driven clinical research. The concept of national and international networks has been fundamental to make this progress possible and provided a basis for current best practices in paediatric haematology and oncology, allowing substantial improvements in survival rates over the past 50 years. A defined research agenda for paediatric cancer in Europe for the next ten to twenty years, developed jointly by academia and patient groups, is currently in place *(Kearns, 2019)*.

Innovative therapies delivered in early clinical trials can be life-saving for children with relapsed or refractory non-curable malignancies. The ITCC network of excellence unites centres running such trials across Europe. As of 2019, 25 ITCC centres were also members of ERN PaedCan, maximizing synergies between the two initiatives.

From a regulatory perspective, the *EU Orphan Regulation* has been ineffective for paediatric cancer medicine development *(Vassal, 2017)*. The *Paediatric Regulation (EC) N° 1901/2006* has been a potentially more relevant instrument, but also faced challenges in addressing the needs of paediatric cancer patients (*Vassal, 2016)*. Global regulatory developments to boost therapeutic innovation in childhood cancers, such as the *Race for Children Act* in the US, are of high relevance (see Chapter 8).

Further optimization of therapy is increasingly difficult through randomized clinical trials. The paradigm of paralleling prospective clinical research with assessments of whole-population outcomes has been particularly interesting in rare cancers *(Mathoulin-Pélissier, 2019)*. This can be accomplished by use of “real-world” data on diagnosis and treatment, enriched with more relevant clinical data, linkage to long-term health outcomes, including patient-reported data, and increasingly large

amounts of data automatically generated by electronic health records and other administrative and research databases. Such linkages are essential to measure very long-term health outcomes of patients enrolled in previous clinical trials and studies, and to monitor side effects and possible late complications of newer agents, in an efficient way beyond the usual 5-to-10-year follow-up of clinical trials.

Recommendations

- Sustained public investment in childhood cancer research at the EU level holds the potential for transformational change. The allocation of resources should allow to further integrate care and research, and support permanent and sustainable clinical trial platforms within international collaborations.
- In relation to research studies, the following points should be implemented:
    - age-inclusive participation to potentially life-saving clinical trials;
    - innovation in trial design, including methodologies of data extraction from matching populations, while getting maximum information from any recruited patient;
    - centres' participation in available therapy-optimizing trials and studies;
    - recruitment of all patients in prospective observational studies, registries, and/or audits about adherence to (inter)national guidelines;
    - initiatives on health data standardization and system interoperability to facilitate cross-border health research;
    - appropriate reimbursement of cross-border participation in early phase clinical trials for children with relapsed or refractory non-curable malignancies.

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6. Patient-physician shared clinical decision-making should be especially valued...

...being crucial to the appropriate approach to the high degree of uncertainty posed by rare cancers

6.1 **The extra degree of uncertainty of rare cancers should be ultimately managed by sharing it with the patient.**

6.1.1 In rare cancers, uncertainty is higher than average by definition. This is due to the difficulties of clinical research to generate high quality evidence, as long as the statistical precision of clinical studies is limited by the number of cases. Specifically, randomized clinical trials are difficult to set up. In addition, clinical expertise tends to be lower, though proper referral of patients may limit this kind of difficulty *(Casali, 2015)*. Aside from all attempts towards reducing uncertainty as much as possible, ultimately uncertainty can be appropriately managed by sharing it with the individual patient. Within the framework of patient-physician shared clinical decision-making, a clinical decision will be feasible even if uncertainty is high. In the end, this is one of the ways in which a higher degree of uncertainty may cease to be an obstacle to exploit innovation in rare cancers.

6.1.2 If patient-physician shared decision-making is key to appropriate decision-making in rare cancers, it is vital to make sure that it is widely taught as part of medical education *(Thornton, 1992)*. During their medical training, medical students and rare cancer clinicians should be exposed to its theoretical implications, in terms of prescriptive decision theory in conditions of risk and uncertainty. They should also receive proper

training in terms of psychological abilities to manage the challenges of the process of patient information and awareness.

6.1.3 Shared decision-making poses several burdens on patients, too. An “expert” patient is better involved in medical decisions *(Brody, 1980)*. Thus, patient information tools should be produced. This should be an item for health networks, which should devise patient information tools to be used for clinical decisions in the networking setting. Patient advocacy groups can give assistance to patients challenged with shared clinical decisions and help develop such information tools.

6.1.4 Methodological and psychological research on shared decision-making in conditions of high uncertainty should be encouraged, viewing this as an area of potential methodological innovation.

6.2 **Shared decision-making in conditions of uncertainty implies organizational requirements.**

6.2.1 Clinical decisions for rare cancer patients in conditions of high uncertainty should all the more involve expert centres, since shared decision-making requires a high degree of clinical culture on the medical side. In a hub-and-spoke network, the main challenge is to make sure that all the necessary clinical information is conveyed to the patient and that the decision is properly shared at the level of spokes. Actually, a hub-and-spoke network in itself is shaped so as to determine a continuous virtuous circle of improvement of spokes. In other words, the continuous exposure of spokes to clinical cases of rare cancers allows them to improve their expertise on the disease, though not on the technological aspects of diagnostic and therapeutic options that belong to the expertise of hubs. The methodology of collaborative, multidisciplinary, remotely shared decision-making

should be an item of methodological research and medical education. Appropriate health personnel should be trained and deployed to facilitate all this, both in hubs and spokes, such as case managers, patient navigators, psycho-oncologists and the like.

6.2.3 Clinical decision support systems are expected to spread in oncology. In the rare cancer area, they should function in such a way as to allow decision processes leading to personalized shared decisions in conditions of uncertainty. On the other side, their added value may be even higher in rare as compared to common cancers, given the lack of expertise and knowledge in the community. Intense research should be promoted on the improvement of current prototypes, factoring in the methodological requirements of shared decision-making in conditions of high uncertainty.

6.3 **Shared decision-making in conditions of uncertainty implies consequences in shaping and interpreting clinical research, from clinical to regulatory decisions.**

6.3.1 How evidence is shaped is crucial in terms of the feasibility of probabilistic shared decision-making at the patient's bedside. Methodological research should be encouraged on medical statistics, including Bayesian solutions, on analysis of clinical trials and translation of their results into adequate patient information instruments.

6.3.2 Artificial intelligence tools, including machine learning on big data (from clinical data from electronic health records to genomics and the like) should be viewed as an opportunity, as a means to integrate results of clinical trials at the patient's bedside and to generate evidence on rare and ultra-rare cancers *(Shortliffe, 2018)*.

6.3.3 The regulatory framework, e.g. regulatory mechanisms and practices about new drug approval, should allow degrees of flexibility enabling personalized decision-making at the patient's bedside, acknowledging that the same uncertainty may be valued differently across patients. Innovative regulatory mechanisms should be worked out to try and accommodate this variegated perception of uncertainty.

Paediatric Cancer Section

Shared decision-making with parents is a standard of care in paediatric haematology and oncology *(SIOP Europe, 2009)* and the empowerment of survivors is at the heart of the *Survivorship Passport (Haupt, 2018)*. ERN PaedCan has a long-standing cooperation with parents, patients, and survivors with CCI-Europe through SIOP Europe and PanCare.

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7. Appropriate state-of-the-art instruments should be developed in rare cancers...

...fit to serve clinical decision-making in conditions of uncertainty

7.1 Proper state-of-the-art definition is required in rare cancers, including ultra-rare cancers.

7.1.1 The high degree of uncertainty that characterizes rare cancers should not imply that they lack “state of the art”. In other words, uncertainty should not be viewed as an obstacle to building state-of-the-art instruments, such as clinical practice guidelines, and the like. A clinical decision needs to be made at the patient’s bedside, whether the patient has a rare or a common cancer. Thus, in principle, the same instruments that usually support clinical decision-making should be available in both common and rare cancers. This applies also to ultra-rare cancers, even if the lack of evidence therein may be substantial. The rare, and ultra-rare, cancer patient has the same rights as any other patient to be approached along diagnostic/therapeutic lines agreed upon by the international medical community.

7.1.2 Within JARC, an effort was made to evaluate the quality of existing clinical practice guidelines on rare cancers. In total, 537 guidelines were collected. The results are available on the JARC website. In a subset of clinical practice guidelines on rare adult solid cancers, 40% proved to be of good quality and the others of moderate quality, if assessed according to dedicated tools *(Cluzeau,1999; Grimmer, 2014)*. Thus, it would be important to develop high quality clinical practice guidelines on all rare cancers. Each of

them should cover the entire spectrum of a disease, as a set of recommendations on all clinical presentations. These disease-based clinical practice guidelines should be clearly distinguished from guidelines focusing on a single question within a disease (e.g. on a treatment option in a clinical presentation, etc.). The latter are the product of ad hoc initiatives to settle specific open questions perceived as highly controversial by the community. More formalized methodologies for systematic review of the literature and consensus measurement and consensus development are generally exploited. On the other side, disease-based clinical practice guidelines are meant to convey recommendations on all disease presentations, setting a number of standards for typical patients. Inevitably, the methodological requirements need to be flexible enough to cover an entire disease and then to provide fast updates over time. In particular, the requirement to conduct systematic, formalized reviews of literature may be problematic (and possibly of low added value when a wide, representative community of knowledgeable experts is involved in developing the guidelines), as well as over formal mechanisms of consensus measurement. Thus, the distinction between disease-based and single-question clinical practice guidelines should be taken into account by efforts to review the quality of guidelines. In essence, disease-based clinical practice guidelines should:

- reflect a multidisciplinary consensus of representative experts;
- be based on the whole available evidence of efficacy, explicitly providing levels of evidence and taking into account the magnitude of absolute clinical benefits;
- be updated on a regular basis.

On ranking evidence, difficulties in generating evidence in rare cancers should be taken into account. Conflicts of interests of all experts should be declared and made transparent to the end-users. Possible ways to manage conflicts proactively, for example

through mechanisms to balance different “interests” amongst panelists, should be in place. Especially in rare cancers, where there is often a paucity of experts, the risks of “silencing the expertise” due to over stringent policies on conflicts of experts need to be avoided. Transparency, wide consensus and possible management strategies should be viewed as appropriate remedies to conflicts of interests.

7.1.3 In the European healthcare environment, the “willingness to pay” determines the extent to which those clinical practice guidelines may be implemented across health systems. Decisions on reimbursement are generally made at the national level. Conceptually, they reflect cost-effectiveness assessments. State-of-the-art instruments such as *managed care pathways* and the like may then convey reimbursement decisions, in addition to actual availability of resources in real-world conditions.

7.1.4 Ideally, clinical practice guidelines and above all managed care pathways on rare cancers should be modelled as to serve healthcare networks. Appropriate patient referral to networks should be provided for. Mechanisms leaving higher degrees of flexibility, for example in drug reimbursement, may be accommodated within healthcare networks for rare cancers (in this way, third payers may be confident that, if expert centres are involved, medical decisions potentially resulting in high health expenditures will be reasonably limited).

7.2 Clinical practice guidelines have peculiarities in rare cancers.

7.2.1 Clinical practice guidelines on rare cancers are exposed to all limitations affecting the generation of evidence when a disease is rare, namely to all the difficulties inherent in carrying out large clinical trials in rare cancers. Thus, levels of evidence may more

often be suboptimal in rare as compared to common cancers. This could give rise to discrimination against rare cancer patients. It follows that the “strength of recommendations” should be higher in rare than in common cancers in the presence of lower levels of evidence *(Mercuri, 2018)*. Nevertheless, the quality of evidence implied by studies exploiting new methodologies should be properly ranked, factoring in the need for innovative methodologies in rare cancers. Collaborations between rare cancer communities and agencies responsible for state-of-the-art instruments, as well as with agencies producing evidence-based medicine tools, should be encouraged *(Brouwers, 2016)*.

7.2.2 Patient representatives should always be involved in the processes leading to the production of clinical practice guidelines. Though consensus measurement may well be based only on the medical component, patient communities may bring important inputs to the assessment of evidence.

7.2.3 Clinical practice guidelines should be conceived in such a way as to allow patient/physician shared decisions in conditions of uncertainty. This is even more necessary in rare cancers, since, in the end, the higher degree of uncertainty can only be managed by sharing it with patients. However, this becomes impossible if enough flexibility is not guaranteed in the clinical decision-making process at the patient’s bedside. This means that, as well as accepting possibly lower levels of evidence to recommend some treatments as “standards”, clinical practice guidelines on rare cancers should also leave room for treatments of uncertain efficacy which, though not standard, may be viewed as “options” amenable to a shared patient/physician decision in conditions of uncertainty.

7.2.4 Clinical practice guidelines are expected to improve quality of care not only in terms of what they say, but also of the processes of their own construction. This is

why a reasonably high number of cancer centres should be involved in the consensus development processes leading to clinical practice guidelines. Spokes of hub-and-spoke networks, not only centres of reference, should be engaged as much as possible.

7.2.5 Clinical practice guidelines should be first used by clinicians, but their use is improved as long as they are also conveyed to patients. Thus, it is useful to produce them in different formats, including those fit for use by patients, patient advocates and patient communities. In Europe, this also means that translations into national languages should be planned.

7.2.6 Clinical decision support systems are expected to spread in today's clinical medicine. Proper incorporation of clinical practice guidelines therein will be crucial to improve clinical decision-making. However, one should be aware that incorporating clinical practice guidelines will probably be a complex task, likely to change their format and scope. It is crucial for this process of adaptation to take place as comprehensively in rare cancers as in common cancers.

7.2.7 In all cases, mechanisms to monitor compliance of clinical practice with clinical practice guidelines should be encouraged. IT tools used in healthcare networks, including those adopted by ERNs, should be shaped also to support such monitoring.

Paediatric Cancer Section

For as high as 90% of newly diagnosed paediatric cancer patients there are treatment options either within prospective clinical studies or according to European recommendations established through clinical research. European standards concerning the organization of care in paediatric haematology and oncology are being developed and updated in the SIOP Europe community and include the overarching *European Standards of Care for Children with Cancer (SIOP, 2009)*, the *Recommendations on the Organisation of Care in Paediatric Radiation Oncology across Europe (Janssens, 2019)*, the PanCare/IGHG guidelines on childhood cancer survivorship and the EXPeRT guidelines on very rare tumours in the paediatric population.

There are substantial inequalities in access to the best standard treatment, care, and research, particularly in central and Eastern Europe but also in other European countries, as highlighted most recently by the JARC findings. Reducing these inequalities is a primary aim of ERN PaedCan and ITCC, in line with the SIOP Europe Strategic Plan.

<u>Recommendations</u>

- ERN Paedcan, along with SIOPE CRC, started a collaborative work with ECTG to produce up-to-date clinical practice guidelines across paediatric cancer entities for countries unable to participate in prospective clinical trials or without open trials, to make sure that feasible and harmonized recommendations are available. Official recognition of these guidelines by national health authorities should become the backbone of decision-making agreed upon in the setting of cross-border healthcare, and support MSs' decisions on S2 referrals if patient requirements go beyond such

standard clinical practice guidelines and are validated by multidisciplinary tumour boards.

- Regional, national or European virtual tumour boards should be set up and promoted to ensure that all patients with a new diagnosis or in relapse are discussed and have access to recommended standard treatment options and, when relevant, are offered access to innovative therapies in clinical trials through appropriate referral pathways.
- Each country in Europe should have at least one full or affiliated partner in ERN PaedCan, while twinning initiatives between ITCC investigating centres and ERN PaedCan partners should be encouraged especially in low health expenditure rate (LHEAR) countries.
- Further cooperation should be supported among centres in countries covered by the ITCC Consortium, by enabling the creation of regional or national networks, to ensure continuity of care when patients are referred to an investigating centre to participate in an innovative therapy trial.

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8. Regulation on rare cancers should tolerate a higher degree of uncertainty…

...being disease-adapted and providing developers of innovation with certainty of rules across the EU

8.1 Regulatory principles.

8.1.1 The higher degree of uncertainty in rare cancers should be factored in also from the regulatory point of view, when assessing meaningful magnitudes of clinical benefit. In other words, while the rarity of a tumour does not imply that the thresholds of meaningful magnitude of benefit could be lower, it should be recognized that the amount and statistical quality of evidence can be lower than in common cancers. This suggests a degree of openness to innovative methodological solutions for clinical trials. Indeed, these should be encouraged, in an effort to achieve the highest quality of evidence possible. Thus, there may be room for methodological research in the rare cancer area, also with a view to generating new solutions (which could potentially be useful also for common cancers, if validated). Non-randomized study designs and clinical registries, Bayesian statistics, surrogate end-points are amongst the areas of major interest for methodological research in the field of rare cancers. It is important for regulators to encourage all this, from the stage of scientific advice on new drug development to the final regulatory decisions.

8.1.2 In the regulatory setting, rare cancers may be less known with respect to their natural history, standard

treatments, relevant clinical end-points, etc. Optimal regulatory criteria may thus be highly specific. This calls upon regulatory bodies to tap all the necessary clinical expertise, as available within the rare cancer disease-based communities, including clinical experts and patient advocates.

8.1.3 When the lack of evidence in rare cancers determines a paucity of available therapeutic options, regulators should factor in that risk aversion is poorly tenable from the patient's perspective *(Eichler, 2013)*. At least, reasonably risk-prone personalized decisions should be made possible at the patient's bedside. Proper involvement of disease-based patient communities may help identify such scenarios.

8.1.4 Along regulatory pathways, effective management of conflicts of interests should be encouraged, obviously prior to the regulatory decision stage, in order to avoid the risk of "silencing the expertise". Such risk is particularly worrisome in rare cancers due the shortage of available expertise. This means that experts in rare cancers should be allowed to provide their opinions to regulators, as envisaged by several guidelines, even in the presence of significant conflicts of interests.

8.1.5 Consistency in efficacy assessment should be encouraged between the decisions of the European Medicines Agency (EMA) and the health technology assessments of MSs. The concept of a "joint clinical assessment" may be particularly interesting in the rare cancer field, due to the high degree of uncertainty, which might be used as a reason for implicit denials of resources at the national level.

8.1.6 In principle, mechanisms to make promising agents temporarily available within ERNs, and networks linked thereto, should be encouraged, as long as this allows to generate new evidence. This may then

confirm or not early data and further drive the regulatory process *(EURORDIS, 2018)*.

8.2 **Regulatory solutions.**

8.2.1 In ultra-rare cancers, there may be a lack of knowledge about the disease, which can hamper the development of new technologies. Clarity about regulatory requirements may encourage companies to develop them all the same. In particular, the perceived regulatory risk may be diminished. An innovative tool could be represented by disease-based "scientific advice" on principles to follow when developing a new agent in the specific disease, i.e. prior to any scientific advice provided on specific drugs. Issues such as the best study designs, end-point selection, control groups, and the like, may be dealt with. Relevant disease-based communities, from researchers to patient advocates, may well be involved.

8.2.2 The process of orphan drug designation requires an epidemiological demonstration of the rarity of a given cancer. Following the efforts made within the RARECARE/RARECAREnet projects, the list of all rare cancers, accompanied by incidence, prevalence and survival data, is available. They may well be exploited directly *(Gatta, 2011; Gatta, 2017; www.rarecarenet.eu)*.

8.2.3 In the presence of rigorously assessed benefits in surrogate end-points, even when these are non validated as such, highly selected patient clinical subgroups may, on clinical grounds, be assumed to take benefit from them. Thus, some kind of regulatory approval in these clinical subsets of rare cancers may be foreseen. Possibly, the use of such regulatory approvals and reimbursements could take place within ERNs, and networks linked thereto.

8.2.4 Mechanisms to provide availability of new agents throughout their development include adaptive licensing, by which a drug is temporarily available, thereby allowing to generate evidence, which in turn may continuously modulate availability (widening or narrowing eligible subsets, etc.) *(European Medicines Agency, 2016; Vella Bonanno, 2017)*. This mechanism can be ideally implemented within ERNs and networks linked thereto. These networks guarantee a high level of quality of care and appropriate patient selection processes. On the other side, they are the ideal setting to feed prospectively clinical databases, to be used from the regulatory point of view. Clearly, this is an additional reason why network IT tools should incorporate, or be open to, study databases. Consistency with regulatory requirements for clinical registries should be guaranteed. Patient communities should be involved.

8.2.5 Mechanisms should be available allowing drug registration initiatives promoted by academia and/or disease-based communities (involving patients) on the repurposing (label extension) of available drugs to some rare cancers where pharma's motivation may be low.

8.2.6 Solutions to the off-label use of drugs of proven efficacy in rare cancers should be worked out by MSs through proper lists of reimbursed agents, and attempts to harmonize them across the EU should be made. Indeed, the off-label use of drugs in rare cancers is relatively widespread. Likewise, compassionate use of drugs may be in place in some circumstances. These settings should help generate new prospective evidence. ERNs and networks linked thereto could possibly be a privileged setting within which this takes place. Data generated thereby should be liable to complement data used for new drug registration.

8.2.7 Solutions to the shortage of inexpensive drugs indicated in rare cancers across the EU should be implemented, by establishing: a) national rules foreseeing early notifications of shortages; b) national plans to address shortages; c) catalogues of essential rare cancer drugs amenable to shortages; d) incentives for suppliers; e) procurement models to avoid shortages *(Economist Intelligence Unit, 2017)*.

8.2.8 Real-world data are a resource to refine and confirm evidence about new agents. Data on rare toxicities and efficacy in less selected patient populations may be generated thereby. These data can also be used to review approval or reimbursement of new agents *(Dreyer, 2018)*. However, this should factor in possible difficulties in transferring innovation, all the more in rare cancers, and possible deterioration in outcomes compared to the clinical trial setting. De-licensing or de-reimbursement based on real-world evidence should then be viewed with caution, to avoid discrimination of patient populations that are most sensitive.

8.3 Value-based medicine tools should factor in the extra-degree of uncertainty in rare cancers.

8.3.1 In principle, regulatory choices, reimbursement decisions and managed care pathways should be based on efficacy assessments ideally consistent with rigorous clinical practice guidelines. It may be expected that local cost-effectiveness decisions can differ across countries, because of cost considerations, while efficacy should in principle be assessed consistently across European countries and regions. Differences in assessing evidence may be higher in rare cancers, given the need to accommodate a higher degree of uncertainty. Such differences should not become reasons for denying resources in the presence of a wide expert consensus on the existence of a meaningful clinical benefit, in

spite of a potentially low level of evidence. Within each ERN, a task force should be deployed to monitor the consistency of the ERN's clinical practice guidelines with local guidelines, if any, and managed care pathways, and regular reports thereon should be provided.

8.3.2 Involvement of pharmaceutical companies in risk-sharing mechanisms for drug reimbursement should be encouraged, as a way to avoid discouraging investments in areas where uncertainty may be higher and the market is narrower *(ERN Board of Member States, 2019)*.

Paediatric Cancer Section

The influence of regulatory instruments on the development of therapeutic innovation for children with cancer in Europe has been limited. The *Orphan Regulation (EC) No. 141/2000 EU* has not been effective in the paediatric cancer field, due to the prioritisation of adult indications to trigger incentive mechanisms *(Vassal, 2017)*. The *Paediatric Regulation (EC) No. 1901/2006* is a potentially more relevant instrument, but has also fallen short of success *(Vassal, 2016)*: only very few innovative anticancer medicines have been authorized for paediatric malignancies since its entry into force. The latter is in overt contrast with the number of new anticancer medicines approved for adult cancers. The obligation to undertake a paediatric investigation plan under the *Paediatric Regulation* is currently driven by the medicine's indication in adults, rather than by biological reasons, although there is large evidence that drug targets in adult cancers can be relevant also in paediatric malignancies *(SIOP Europe, Unite2Cure, 2016)*. For example, the *RACE for Children Act*, recently passed in the United States, will require that new cancer medicines be studied in any paediatric cancer for which the molecular target of the medicine is substantially relevant *(Bennet, 2017)*. Another consideration is that the repurposing of molecules originally meant for development in adults may provide opportunities for further studies and potential therapeutic benefit in paediatric cancers.

The ACCELERATE platform gathers all stakeholders, including academia, industry, parents, and regulators, to develop solutions. Initiatives include running the *Paediatric Strategy Forums* jointly coordinated by ACCELERATE and EMA, more recently also involving the US Food and Drug Administration (FDA), to share information and advance learning in a pre-competitive setting and contrasting the "18-years dogma" for participation in clinical trials *(Vassal, 2015)*.

Over the last 50 years, the international paediatric haematology and oncology community has established the efficacy, toxicity, dosage, and pharmacokinetics of essential medicines through academic prospective clinical trials that validated standard treatments to achieve high disease-free survival rates. However, information on paediatric dosages has not been included in the "summary of product characteristics" of medicines. Thus, most medicines used in treating paediatric malignancies are administered off-label.

Due to the challenges in innovative medicine development for children in the pre-marketing authorization phase, the paediatric cancer sector has so far been less active in the pricing debate. This topic is due to become more relevant with the advent of newly authorized immunotherapy medicines for children with cancer. Here, it is argued that value-based medicine pricing models for children should take into account the length of their expected life span.

A JARC survey undertaken by SIOP Europe, in collaboration with CCI-Europe, ESMO and *European Society of Oncology Pharmacy* (ESOP), has shown that children and adolescents with cancer in Europe still experience issues of access to medicines that the scientific and patient community defines as essential. Shortages are the main cause of non-availability. Of particular concern is that pain control during procedures is not consistently provided to young patients across Europe. The lack of child-friendly formulations for all oral medicines is another important concern for both parents and health professionals.

Recommendations

- The regulatory environment for therapeutic innovation in childhood cancer, also in relation to the *EU Paediatric Regulation* and its implementation, should be significantly improved, even in the light of the global regulatory developments in this area.

- Access to essential anticancer and supportive care medicines used in the treatment of childhood cancer across Europe should be ensured, with specific consideration to avoiding shortages, availability of child-friendly doses and formulations, appropriate pricing and reimbursement strategies for the paediatric population and the provision of appropriate pain control to all children.

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9. Policy strategies on rare cancers and sustainability of interventions should be based on networking...

...exploiting national cancer plans, listening to networks and disease-based communities, integrating the EU and the national levels, funding networking

9.1 Policy strategy building on rare cancers in the EU.

9.1.1 When ERNs were created in the EU, the choice was made to tackle the problem of rare cancers through networking, as a key factor addressing the many challenges they pose. Each MS should establish and maintain networks for all “families” of rare cancers, ensuring access to the expertise available throughout its territory and integration with cancer-related ERNs. Networking needs to be properly funded, both at the EU level (with regard to ERNs) and at the national level (with regard to networks linked to ERNs).

9.1.2 Proper awareness about rare cancers among health professionals and healthcare institutions as well as in the public opinion should always be a priority, to make sure that the many issues pertaining to rare cancers are tackled thoroughly and timely.

9.1.3 It is vital to always keep rare cancers high in the EU agenda and to make sure that the rare cancer community is properly listened to by the EU bodies. At a time when JARC has come to an end, a priority will be to create mechanisms by which this can happen. It is important to look at rare cancers as a specific area within cancer and within rare diseases. Thus, frameworks selectively dedicated to rare cancers should be established, such as joint programmes,

annual conferences, etc. Specific advisory mechanisms to the EU Commission on rare cancers and a forum of the four ERNs focusing on rare cancers would be instrumental. The objective should be to contribute to building and updating policy strategies on rare cancers at the EU level.

9.1.4 Given the importance of national networking, in connection with ERNs, all efforts at the EU level should always be made to involve MSs and national networks when shaping strategy policies on rare cancers. National cancer planning should be viewed as an important tool to link the national with the EU level. National cancer control plans should always involve a dedicated section on rare cancers in adults, as well as a dedicated section on childhood cancers, and develop synergies with national plans for rare diseases. Innovative instruments should be devised to improve consistency across national cancer plans.

9.2 **Sustainability of networking.**

9.2.1 In rare cancers, European and national healthcare networks are expected to improve the quality of care and effectiveness and possibly to decrease costs. Effectiveness is expected to improve by making the best available expertise widely accessible. Costs are expected to decrease, in terms of direct health costs from inappropriate care, as well as indirect social costs from less health migration (i.e. costs for patients and families, as well as costs for employers, etc.), although on the other side the costs of networking per se may become additional direct health costs for health systems (see Paragraph 9.2.4). Thus, while one should expect that cost-effectiveness will improve, one should also be aware that, to some extent, some decrease in social costs might come at the expense of higher direct health costs. In this sense, decisions to establish networks should always be viewed as clear-cut policy decisions.

9.2.2 In the rare cancer field, it is not felt that the incremental cost-effectiveness of networks needs to be formally assessed. Apart from being burdensome, today it would be difficult even to find controls totally devoid of any networking component in healthcare. On the other hand, networks should always provide evidence that their effectiveness is as high as possible. To this end, they should always monitor their performance, in terms of outcomes (from overall survival to patient-reported outcomes) and costs (from direct health costs to social costs), and provide data thereof. This should help health systems to allocate resources to networking. Data on the impact of networking within a healthcare system, in terms of the number of patients benefiting within a population, should also be provided, relying on cancer registries and administrative databases. A difficulty may be that it is always hard to identify network patients, as long as degrees of networking are often in place within the management of several rare cancer patients.

9.2.3 That said, the performance of networks should be assured through quality systems, in terms of strict process criteria (see Section 3.5).

9.2.4 Given the above, permanent funding should always be allocated to networks for their functioning. In fact, networking always implies costs. Each network should rely on a service centre able to manage networking routines. Networks must then rely on appropriate IT systems, which in turn must be funded and managed. The medical workload entailed by teleconsultations provided by expert centres within a network (i.e. hubs within hub-and-spoke networks) should also be covered. Reimbursement of teleconsultations should be foreseen, and in any case they should be formally acknowledged by the healthcare system. Unless the amount of such reimbursements matches the additional professional workload, expert centres must be provided with some kind of extra staffing. Solutions matching yearly volumes of teleconsultations with

proportional extra staffing may be worked out. Managed care pathways should help drive patient referral within a community towards centres of reference and/or hub-and-spoke networks. It can be assumed that healthcare routines at the spoke level are covered by normal reimbursements for patients they directly take care of. On the other side, some additional costs for sharing clinical cases and the burden in terms of data upload onto the network IT system should be acknowledged and properly reimbursed to spokes.

9.2.5 As long as national networks are implemented and linked to ERNs, the former will benefit from collaborations with the latter. On the other side, fully supported national networks may have an added value for ERNs, as long as European clinical expertise is made available. A virtuous circle may thus be established between the EU level and MSs, if both ERNs and national networks are properly funded. Proper competitive funding for research projects, preferentially or exclusively carried out by ERNs, should be in place at the EU level, to make sure that healthcare and research may optimally merge with each other and also result in economies of scale.

9.2.6 Mechanisms should be arranged to involve the industry in the ERNs and national networks linked thereto. Potential conflicts of interests resulting therefrom should be managed, but should not constitute a barrier to exploiting the added value that a healthy partnership between the rare cancer communities and the industry may provide.

Paediatric Cancer Section

The rarity of individual paediatric cancer types and their high collective burden across Europe have fostered cross-border academic cooperation, which has led to important scientific and clinical achievements over the last 50 years. The *EU Health Programme* and the *EU Framework Programme for Research and Innovation* have provided instrumental support in this journey. Yet the paediatric cancer sector in Europe still faces several challenges: a pronounced lack of therapeutic innovation; unequal access to high quality standard treatment, care and research; lack of adequate provisions for care and empowerment of childhood cancer survivors. The *SIOP Europe Strategic Plan (Vassal et al, 2016)* defines the objectives and actions needed to make further progress in the next ten to twenty years. The activities of ERN PaedCan are central to the achievement of this shared vision of a Europe where no child dies of cancer and survivors live their lives to the fullest.

Recommendations

- Sustained public investments should be foreseen to address the unmet needs in the paediatric cancer sector, with reference to the objectives and implementation models defined by the scientific, clinical and patient community in the *SIOP Europe Strategic Plan*.
- Non-competitive funding, but also reimbursement of teleconsultations along with formal acknowledgement by relevant healthcare systems, should be foreseen for ERN PaedCan, to enable delivery of the best possible care to children and adolescents with cancer across Europe.
- Further integration of care and research should be enabled by supporting stable and sustainable

	clinical trial platforms and international collaborations.

10 Rare cancer patients should be engaged...

...in all crucial areas, such as disease awareness and education, healthcare organization, state-of-the-art instruments, regulatory mechanisms, clinical and translational research

10.1 Pan-European umbrella patient organisations partners to JARC.

- ***Childhood Cancer International Europe*** **(CCI Europe)** is the European arm of *Childhood Cancer International* and was established in 2012. It is the biggest pan-European childhood cancer parent and survivor organization. As of 2019, CCI Europe comprised 69 member organizations from 30 different European countries, with the aim to share knowledge and expertise, offer and disseminate information, advocate for the rights of childhood cancer patients, survivors, and their families, raise awareness, and actively engage in research and development. CCI Europe is working in partnership with SIOP Europe across all policy areas and with PanCare on survivorship issues. CCI Europe was instrumental in developing the *SIOP Europe Strategic Plan – A European Cancer Plan for Children and Adolescents (Vassal, 2016)*. Based on this framework, CCI Europe is making collaborative steps to pursue the mission of achieving “zero deaths” and “zero late effects” from childhood cancer in Europe, with clear milestones to mark progress over time. CCI Europe’s involvement in ERN PaedCan is three-fold. First, it had a prior long-standing relationship with the coordinating institute and other centres of the network

through the SIOP Europe community and EU projects. Second, the head of the CCI Europe Committee is directly represented in the Oversight Committee of ERN PaedCan and thus is integrated in the decision-making structure of the network. Third, CCI Europe has four committee members elected to the ERN PaedCan ePAG, a participative patient structure affiliated with the ERNs created by EURORDIS.

- The ***European Cancer Patient Coalition*** **(ECPC)** is Europe's largest cancer patient umbrella organization. Established in 2003, as of 2019 ECPC represented over 450 cancer patient organizations in 46 countries, effectively acting as a united voice of cancer patients in Europe. ECPC has been a strong partner in European Joint Actions on cancer, bringing fundamental knowledge and understanding of patient conditions through its membership: in the Joint Action CanCon, ECPC co-authored important recommendations on survivorship care and health inequalities, and currently continues to reinforce patient perspectives in the ongoing Joint Action iPAAC work on genomics, cancer information and neglected cancers. ECPC has set up a *Working Group on Rare Cancers* (WGRC), with the mission to support the work of JARC (www.ecpc.org/activities/working-groups/177-wgrc). ECPC's WGRC has grown to include over 60 rare cancer patient organizations as active members. ECPC counts on the expertise and collaboration of rare cancer patient organizations all over Europe to continuously represent the rare cancer patient community. ECPC previously contributed to the RARECAREnet project by collecting patient information materials on rare cancers (http://www.ecpc.org/activities/projects/rarecarenet). An online library of new and existing

patient education materials was then developed as an essential resource for the rare cancer patient community. As part of its ongoing work to support patients with rare cancers, ECPC is currently working to further identify, produce and disseminate patient information on rare cancers, providing essential information for patients to access ERNs across Europe. In collaboration with ESMO, ECPC is developing Patient Guides designed to support patients, their families and caregivers (https://www.esmo.org/Patients/Patient-Guides). Furthermore, ECPC is the elected ePAG representative across all cancer domains for EURACAN and the EURACAN Transversal Task Force (TTF) co-chair on Communication and Dissemination.

- **EURORDIS - Rare Diseases Europe** was established in 1997 to voice the needs and expectations of the 30 million people living with a rare disease in Europe, also including rare cancer patients, with a view to foster research for these rare conditions, and contribute to shaping policies and services that will ultimately improve the lives of patients. As of 2019, it involves over 860 rare disease patient organizations from 70 countries. Since 2006, EURORDIS advocated for the establishment of ERNs for rare diseases. Along with the development of 24 ERNs, EURORDIS has established 24 ePAGs, bringing together patient organizations whose diseases are covered by an ERN. Each ePAG has representatives named “ePAG Advocates”. They are selected based on their knowledge, advocacy track record and willingness to represent patients of their own disease but also the whole patient community covered by one specific ERN. ePAG Advocates are involved in the decision-making committees of an ERN, its clinical domains and TTFs. EURORDIS

supports the ePAG Advocates and works closely with them. In the field of rare cancers, EURORDIS teams up with the ePAG Advocates in EURACAN, ERN PaedCan, EuroBloodNet and GENTURIS.

10.2 Recommendations to the EU institutions and EU Member States on rare adult cancers.

10.2.1 The European Parliament Report on the implementation of the *Cross-Border Healthcare Directive* highlighted shortcomings of the implementation of the Directive, providing a range of recommendations for the European Commission (EC) and the MSs relevant for the ERNs *(European Parliament, 2019)*.

- The MSs and ERNs should prioritize establishment of clear and transparent rules for patient referral and reach an agreement on the support to be provided by the MSs to ERNs.
- The EC, national competent authorities, national contact points (NCPs), ERNs and all relevant stakeholders should collaborate on comprehensive public information campaigns with an aim to foster structural awareness of patients' rights and obligations under the Directive.
- The EC and MSs should work together to support the uptake of the reimbursement rules and their application to telemedicine and harmonize their reimbursement policies.
- The EC should take steps to ensure that the prescriptions used by ERN-linked centres of expertise are accepted for reimbursement in all MSs.
- The MSs and their health authorities should also address the legal and practical issues that are hindering the mutual recognition of medical prescriptions across the EU, and the EC should provide further support to facilitate this.

- The MSs should also support healthcare providers within the ERNs and integrate ERNs into their healthcare systems, adapting their legal and regulatory frameworks and referring to ERNs in their national plans on rare diseases and cancer.
- The EC must further guarantee access to information, medicine and medical treatment for patients with rare cancers throughout the EU, improving access to early and accurate diagnosis.

10.2.2 ePAG Advocates for rare cancers in adults (EURACAN, EuroBloodNet and GENTURIS) and members of the *ECPC WGRC* defined the following recommendations to convey the patient community's key future action points for the long-term development of cancer-related ERNs.

- *Ensure the financial sustainability of ERNs.*
  EU institutions and national institutions (e.g. ministries, departments of state, regulatory agencies, and regional and local authorities) should ensure the financial sustainability and development of ERNs by providing secured long-term funding and facilitating public-private partnerships.
- *Foster the expansion of ERNs.*
  EU and national institutions must continue providing support for the inclusion of new members (centres of expertise) in the ERNs, especially from countries not yet represented. This includes a number of Eastern European countries. Each EU country should have at least one full or affiliated member in the ERNs for rare cancers and member representation for each of the specific clinical domains of the ERNs.
- *Integrate ERNs into national healthcare systems.*
  i. EU MSs, in conjunction with relevant stakeholders, including rare cancer patient organisations, need to raise awareness of

the added value of ERNs, in terms of patient care and outcomes, and support their national centres which are members of ERNs.

ii. The EC should support a plan for the interaction between the MSs and the ERNs, particularly in regard to the deployment of national healthcare networks for rare cancers to be linked with ERNs. The creation of national networks would optimize the referral of rare cancer patients to specialized centres in a timely fashion.

iii. EU MSs' national cancer control plans should include provisions for optimizing care management of rare cancer patients and the integration of ERNs within their national healthcare systems.

iv. National rare cancer patient organizations should be involved in the design and implementation of national healthcare networks for rare cancers and the integration of ERNs into national healthcare systems.

- *Facilitate cross-border healthcare from one country to another.*
  For some patients living with a rare cancer, treatment may be best provided in another MS. NCPs have been established in each EU MS following the adoption of the *EU Cross-Border Healthcare Directive*. The mission of NCPs is to provide citizens with information and help related to their rights to access care in a EU country other than their own and recommend a specialized centre in this case. As rare cancers are difficult to treat, the NCPs should follow the advice of the competent ERN for the transfer of a rare cancer patient to another EU country and facilitate this transfer.
- *Facilitate virtual consultations and the use of electronic tools.*

EU and national institutions in conjunction with ERNs should:

i. develop a clear and shared understanding about how national referral policies for rare cancer patients will be integrated for the purpose of teleconsultations and how these will be delivered in the real world;
ii. develop plans for the interoperability between the informatics tool of ERNs (CPMS) and the electronic health records kept by healthcare providers that are members of the ERNs for rare cancers;
iii. ensure that the CPMS is also fully utilized for research purposes including clinical trials, observational research and virtual biobanking.

- *Foster patient registries and clinical research through ERNs.*
  i. the development and maintenance of patient registries for rare cancers should be promoted: it should be ensured that patients and healthcare experts for each specific rare cancer are meaningfully involved in the establishment of a patient registry;
  ii. the development of clinical trials for each type of rare cancer; should be facilitated;
  iii. it should be ensured that rare cancer patient advocates are involved in the development of clinical trials at all stages, from inception to implementation.
- *Support the harmonization of clinical guidelines and their approval in all EU MSs.*
  i. due to the rarity and complexity of each rare cancer, clinical guidelines should be reviewed or developed by the relevant experts in ERNs, in collaboration with the appropriate patient advocates and medical societies;
  ii. ERN-and-medical-society-approved clinical guidelines should be implemented

by each EU MS with a view to harmonizing care protocols across the EU, hence maximizing equitable patient access to quality care.

- *Integrate psycho-oncology as part of patient treatment.*
  There is a great demand for psychological support as patients and their families often feel very isolated. Care should not be restricted to medical and paramedical aspects: it should also consider psychological support.
- *Implement specific reimbursement mechanisms.*
  The EC needs to provide further guidance to EU MSs to facilitate the development of reimbursement procedures for rare cancer patients in order to fully implement the *EU Cross-Border Healthcare Directive*, while making the most of the now deployed ERN.
- *Allocate resources to training.*
  Training is key for patients and healthcare professionals. Additional public funding should be allocated to help support a range of relevant initiatives. These include, for example, existing training programmes and development of additional programmes organized by rare cancer patient advocacy groups for patients and their families. Additionally, there should be specialized ERN training programmes on rare cancers for oncologists, including young oncologists. Moreover, the exchange of healthcare professionals from one ERN centre to another for the purpose of sharing skills and expertise should be facilitated.

10.3 Recommendations to the EU institutions and EU Member States on paediatric cancers.

10.3.1 The situation in paediatric cancers and patient engagement differs from adult rare cancers due to the following.

- *Particularly heterogeneous patient populations with different needs.*
  Patient involvement in paediatric cancer concerns both patients and their parents and caregivers. Additional complexity is conveyed by the distinct needs of adolescents as well as adult survivors of childhood malignancies.
- *Long-term organized cooperation between patient representatives and professionals.*
  A network of patient representatives and healthcare professionals working in paediatric haematology and oncology has been built over several decades in Europe. A memorandum of understanding is in place between SIOP Europe, representing childhood cancer professionals including national societies and ECTG, and PanCare, representing survivorship care (follow-up), in addition to CCI Europe, representing parents, patients and survivors. The ERN PaedCan's roadmap connects ECTG and national healthcare providers acting also as hubs of coordination.

On behalf of the patient paediatric haemato-oncology community, CCI Europe shares the recommendation on ensuring the sustainability of the ERN model as a clear priority. Another overarching aspect of treatment and care delivery in a cross-border setting is the availability of information on the protocol, surrounding environment and follow-up in a language that the parent/patient can understand. This is an underserved area that demands considerable attention.

10.3.2 CCI Europe defined the following recommendations to reflect the specifics of the childhood cancer sector and the long-term pan-European collaboration.

- *Support the eradication of inequalities in paediatric cancer outcomes.*
  At present, childhood cancer survival is estimated to be approximately 20% lower in countries with LHEAR than elsewhere in Europe *(Kowalczyk, 2014)*. To close this gap,

ERN PaedCan emphasizes the movement of expertise, as well as patients when needed, based on disease-specific European roadmaps.

    - Full or affiliated ERN PaedCan membership of at least one centre in each EU country and twinning activities with centres in LHEAR countries should be encouraged and appropriately supported by EU and MSs.

- *Support patient organizations acting as PASOs and European level facilitators.*
  Within the ERN PaedCan, a roadmap of parent and survivor organisations (PaSOs) sub-network is currently being built by CCI Europe. National contact points support local families and provide information about the existence and value of the ERN PaedCan. They facilitate patient referrals to the network and support families in case treatment abroad is needed. These organizations are linked with CCI Europe and from there on to the ERN PaedCan coordinating centre. Mapping, training and coordination of patient and survivor organizations at the local and national levels are critical to ensure that patients can effectively access the European network. Building cooperation with parent organizations in LHEAR countries will be an important future orientation. These activities are performed by CCI Europe and its members and partner organizations and require appropriate time and human investment.

    - Parent organizations at all levels would thus benefit from dedicated resource allocation to be able to satisfy the information- and referral-related needs for patients to be able to fully benefit from the ERN model.

- *Reimbursement of cross-border healthcare including early clinical trials and related travel and accommodation for children and their families.*
  In the light of the potential burden on families with seriously ill children seeking cross-border health care, ERN PaedCan prioritizes mechanisms to move information and knowledge rather than patients. Nevertheless, as cross-border travel might be required to receive highly specialized care and, for patients in treatment failure or relapse, to participate in early clinical trials, appropriate reimbursement of the interventions, travel and accommodation is needed for parents and their child.
    - Exchanges between MSs are needed to streamline the current rules for cross-border healthcare reimbursement and their implementation, to foster reimbursement predictability, avoid unnecessary burden on families at an already challenging time, and ensure access to potentially life-saving clinical trials.
- *Development and implementation of long-term follow-up facilities for survivors of childhood cancers.*
  The cross-border nature of ERN PaedCan calls for European long-term quality of care models for cancer survivors across MSs including the following items: coordinated transition from paediatric to adult care settings, appropriate surveillance of late effects, and empowering childhood cancer survivors with information about future risks and available care settings and guidelines.
    - The development of further surveillance and care organisation guidelines for childhood cancer survivors requires sustained funding

and the *Survivorship Passport* model deserves inclusion in national and cross-border programmes.

10.4 PAGs' commitments towards the Rare Cancer Agenda 2030.

10.4.1 ERNs are seen as game changers to improve access to diagnosis and care in a timely and fair manner wherever patients live in the EU. Health is a national competence, and ERNs must tackle all difficulties associated with the dichotomy of power between EU institutions and the MSs, in order to successfully treat rare cancers, bring together expertise across the EU and collaborate beyond borders.

- **CCI Europe** will continue its work and partnership with the SIOP Europe community, including ERN PaedCan, ECTGs and PanCare. Furthermore, CCI Europe will continue to collaborate with the broader oncology and rare disease stakeholders, to ensure that paediatric cancer patients and their families across Europe are able to access the best possible treatment and expertise at the right time, and survivors of childhood cancers are empowered and able to receive patient-tailored follow-up advice and care.
- **ECPC** emphasizes the need to look to the future and the need for political willpower to drive change for rare cancer patients in Europe. The European Parliament Report on the implementation of the *EU Cross-Border Healthcare Directive* adopted in 2019 provides a range of recommendations for the EC and the MSs to implement. Alongside the expert and patient recommendations recalled herein, ECPC's WGRC will work with patient organizations representing rare cancer patients at the national level, to ensure their

timely and appropriate implementation and that the *EU Cross-Border Healthcare Directive* is functional and its provisions accessible. In addition, ECPC will endorse the ERN Board of MSs' recommendations to further enhance the integration process of ERNs into national healthcare systems. JARC mapped existing networks of care for all "families" of adult rare cancers across all MSs. It also identified gaps in current care provision and inequalities of patient access, proposed consistent and Europe-wide system-based standards for all "families" of rare cancers and the networks serving them, including provision for holistic care of patients and their care providers from the beginning of the diagnostic process through to survivorship, rehabilitation and end-of-life care. ECPC will guide WGRC towards adequate uptake of recommendations to achieve improvements of health outcomes for patients with rare cancers and to decrease health inequalities for rare cancer patients across Europe. ECPC will also advocate and raise awareness through its members to ensure that the adoption of the Commission *Implementing Decision 2019/1269* of 26 July 2019, amending *Decision 2014/287/EU*, launching the first call for new members to join the existing 24 ERNs, is well conveyed locally, to make sure that centres of excellence apply for membership in due time as needed.

- **EURORDIS – Rare Diseases Europe** will continue its advocacy actions towards the sustainability and development of ERNs, most notably by promoting the launch of the European Commission call for new members, following the adoption of the *Commission Implementing Decision 2019/1269*, and will foster the involvement of more patient advocates in ERN's endeavours to strengthen

the patients' voice. It will also continue to promote the benefits of ERNs for patients and their carers at EU and national level. EURORDIS will further support the establishment of formalized links between ERN and national healthcare specialists and general practitioners (the primary contact point of patients with rare disease or cancer). It will advocate for the formal integration of ERNs into MSs' national healthcare systems, as outlined in its *Recommendations on the Integration of European Reference Networks into National Health Systems* and those stemming from the *Statement of the ERN Board of Member States on Integration of the European Reference Networks to the healthcare systems of Member States (EURORDIS, 2018; ERN Board of Member States, 2019)*. Based on the work carried out within JARC, EURORDIS will pursue its activities towards relevant synergies between national rare disease plans and national cancer control plans.

10.4.2 After the end of JARC, the three partner patient organizations, CCI-Europe, ECPC and EURORDIS-Rare Diseases Europe will continue their collaboration to implement JARC recommendations, including the ones related to patient engagement, and the relevant European policies for rare cancers. Special attention will be devoted to those recommendations requiring joint work at European level, notably in the field of ERNs. They shall also ensure that the voice of rare cancer patients is always heard in EU and national institutions and that patient advocates are always involved in projects and endeavours as active and acknowledged partners.

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RARE CANCER AGENDA 2030

Ten Recommendations from the EU Joint Action on Rare Cancers

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