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JARC
JOINT ACTION ON RARE CANCERS

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Rare cancers policy: recommendations for health policy from the Joint Action on Rare Cancers (JARC)

TASKS 3.2, WP10

Joint Action on Rare Cancers (JARC)

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Joint Action on Rare Cancers (JARC)

Description:

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

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

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

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

This deliverable was included in the WP10 Health Policy and the objective was to. The leader of this task was the Catalan Institute of Oncology (ICO).

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Work Package 10. Health policy

Description of work:

Governments use National Cancer Plans (NCPs) to articulate their goals and implementation strategies on cancer control. A review of their main objectives was carried out in the EPAAC Joint Action, and we plan to build on that work in order to understand the specific proposals and strategies made at the national level regarding the formulation and implementation of rare cancer/diseases policies, including the commonalities and divergences between such policies. Two approaches are included in its development. On one side, WP10 is intended to assess the potential to develop criteria to harmonize rare cancer planning and coordination, with a view to streamlining strategies and measures to be proposed to Member States at the national level for rare cancers. On the other, WP10 will highlight the main open political issues on the EU agenda of relevance to rare cancers and, specifically, those policy recommendations aimed at raising awareness about the issues surrounding rare cancer care, thereby suggesting stakeholder action and public policies both at the EU and national levels.

The development of ERNs makes this exercise relevant, as it will shed light on the potential for positive synergies between measures targeting rare diseases at national and EU levels. WP10 will build on and integrate the outcomes from all WPs related to policy recommendations in order to compile them through a common framework this is corresponding to this task 3.2.

Aim and purpose of this deliverable (task 3.2)

The Joint Action on Rare Cancers (JARC) is a partnership among EU countries, the European Commission, scientific societies, patients, industry and other stakeholders with the aim of contributing to improve health outcomes for patients with rare cancers in the EU and to decrease health inequalities across EU countries. Strategically, maximizing chances of European Reference networks (ERNs) for rare cancers to be successful is seen as a key factor.

This deliverable will integrate policy recommendations from all WPs in order to coordinate all the health policy relevant aspects in a common framework. This deliverable will describe the methodology followed to achieve the consensus among all partners and will present the recommendations in straightforward way.

The target group of the specific deliverable

Policy makers, cancer plans, and rare diseases' plans.

Introduction:

One of the critical components of JARC has been to discuss and review the current situation for rare tumours in Europe, from a perspective that combines research, training, service organisation and health policy, and within the context of development and implementation of European Reference Networks (ERN).

Since the launch of JARC, participants have understood the importance of synthesizing all of these perspectives in a way that is usable in communications with the administrators of cancer plans, rare disease plans and health policies. The ultimate aim has been to present clear and concise recommendations that transmit the contributions from different WPs and partners, reflecting the discussions that have taken place throughout the process.

Over the course of JARC's work, different WPs have produced deliverables that constitute the main input for the development of the proposed recommendations. The participation of all the WP leaders, along with patient associations, has been a crucial aspect in shaping the recommendations during this process.

This document presents a synthesis of the consensus recommendations by all partners and WP leaders. In the final months of JARC, the rationale for these proposals, as well as the evidence that supports them (in many cases stemming from JARC itself), will be described, and the full set of recommendations, plus the supporting rationale, will be presented in the final General Assembly for their definitive review and approval, in September 2019.

Methodology:

The work performed for this task has been based on the various deliverables of each WP and the evidence review. The different organisational models for rare cancer care within national networks and the ongoing developments with the ERN framework have also been taken into account.

All the WP leaders have participated in the process, as have the representatives of patient associations. Moreover, the partners directly involved in the development of JARC have also had the opportunity to review the work.

The process began in October 2018 in the JARC General Assembly in Milan, where a preliminary, synthesised list of recommendations – limited to 10 areas – were presented and discussed. Attendees agreed that once the final recommendations were approved in the WP10 meeting, to be held in June 2019, the development of the supporting rationale would be drafted collaboratively among the different WP leaders.

The preliminary list of recommendations was sent to all participants of the General Assembly, and following its review, it served as a key input for the discussions held in the WP 10 meeting in Barcelona on 19–20 June 2019. Representatives from the leadership of all WPs (see Annex 1) participated in the meeting, whose agenda provided the opportunity to discuss each recommendation in detail (Annex 2).

The result of this discussion is presented in the form of 10 recommendations, which will be subjected to final review in the last General Assembly of JARC. Moreover, the rationale for each recommendation (in development) will be presented for review by the participants in the discussion process within the WP10 framework.

In the following section we will offer both the recommendations and rationalse for rare cancers in adults while recognizing the singularity of paediatric cancer patients.

Health policy recommendations and rationale and from the EU Joint Action on Rare Cancers (JARC)

RECOMMENDATION 1

RARE CANCERS ARE THE RARE DISEASES OF ONCOLOGY NEEDING SPECIFIC APPROACHES BY THE CANCER COMMUNITY AND BY NATIONAL HEALTH SYSTEMS

Rationale:

Rare cancers can be defined as those malignancies whose incidence is <6/100,000/year. This definition is conventional, since there is no absolute threshold separating cancers, and diseases, based on their frequency. Essentially, it was the product of a consensus process within the European oncology community, taking into account problems posed by rare cancers in terms of health care organization, clinical research, clinical decision-making (Gatta et al., EJC 2011). This effort was funded by the European Union (EU) (RARECARE project).

Given a threshold, one can draw up a list of rare cancers that is useful for several purposes, from healthcare organization to clinical research and new therapy approval and reimbursement (see table 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 corresponds to the International Classification of Diseases for Oncology (ICD-O), which incorporates topographical and histological labels. The morphologic entities enlisted in the ICD-O need to be grouped into clinically distinct entities, which in turn may be gathered into families of neoplastic diseases. With regard to cancers in children and adolescents, the RARECARE list includes some of them under the family of “paediatric cancers”, but several were included under specific families, namely, haematological tumours, sarcomas, Central Nervous System tumours, head and neck cancers, digestive cancers, thoracic cancers, endocrine tumours. As said, however, all childhood cancers are rare. Furthermore, some cancers have a hereditary risk component. Some of them are rare cancers as such (e.g., sarcomas in a Li Fraumeni syndrome), others belong to common entities (e.g., colon adenocarcinoma in a familial adenomatous polyposis). Currently, there is no specific code for registration of heredofamilial cancers as such. On the other side, hereditary cancer syndromes may be incorporated into rare diseases.

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) health care organization, due to difficulties in covering a territory with specialized resources; c) clinical research, due to the low number of patients and thus the difficulty to generate high-quality evidence from clinical studies.

Recommendations for paediatric cancer:

- ✓ 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 multi-modal 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 multi-stakeholder endorsed SIOP Europe Strategic Plan – A European Cancer Plan for Children and Adolescents (Vassal, 2016) can serve as guidance for childhood cancer strategies at the national and European levels.

Rationale for childhood cancers

All paediatric malignancies are rare according to the definition of rare cancers (Gatta et al., EJC 2011). Each paediatric malignancy is then rare or extremely rare (Ferrari et al., 2019). At the same time, paediatric cancers overall 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 an overall 80% cancer-free rate at 5 years, there has been very little advancement for some types of paediatric cancers (Vassal et al., 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 account for differences in survival rates of up to 20% across the EU (Gatta et al., Lancet Oncol 2014) (Kowalczyk et al., 2014). The number of survivors is estimated to reach 500,000 by 2020, the majority of whom, however, are affected by long-term morbidity due to their disease and treatment side-effects (Hjorth et al. 2015).

Whereas cancers in adults typically result from long-term processes often influenced by external 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. Up to 90% of newly diagnosed patients in Europe are treated according to standard protocols established through prospective clinical research, and up to 40% of all patients are treated within clinical trials. 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 gave rise to networks to collaborate and steadily improve diagnosis and treatment.

Table 1. Rare cancers: RARECARE "families" and "tier-1" entities with an incidence <6/100,000

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

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

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

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

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

SARCOMAS
Soft tissue sarcoma
Bone sarcoma
Gastrointestinal stromal tumours

NEUROENDOCRINE
NET GEP
NET lung
NET other sites

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

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

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

HEMATOLOGICAL
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 under Sarcomas)

RECOMMENDATION 2

RARE CANCERS SHOULD BE STRICTLY MONITORED EPIDEMIOLOGICALLY AND CLINICALLY, PROPERLY VALUING POPULATION-BASED CANCER REGISTRY DATA AND REAL-WORLD CLINICAL DATA, FAVOURING ALL EFFORTS TO MERGE DATA FROM ALL AVAILABLE DATA BASES

Specifically:

- ✓ The collaboration with expert clinicians is important to let registrars understand the complexity of some cancers, properly interpret the information source and correctly code.
- ✓ A priority is therefore to evaluate the performance of standard statistical methods when applied to small numbers and, when they do not perform appropriately, new methods should be specifically worked out for rare cancers (e.g. Bayesian methods).
- ✓ Routine cancer statistics are provided mainly by site but for haematological diseases. The use of morphology (histology) could be extremely useful to distinguish cancers with a completely different natural history, e.g., thymoma and thymic carcinoma.
- ✓ Cancer Registries (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.
- ✓ A strong collaboration needs to be established between epidemiologists and clinicians of health care providers (HCP) of ERNs, as the expertise and knowledge of clinicians is crucial for the correct interpretation of administrative data.

Rationale:

The quality of a Cancer Registry (CR) inevitably depends on the local setting 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 AM et al., Ecancermedicalscience 2016). Quality of care is important as well, since, say, inappropriate pathologic diagnoses will result in biased registration. Rare cancers are more 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). However, misclassification may also happen when: a) source information is correct and complete, but the registration is wrong; b) classifications are ambiguous, obsolete terms are used, some entities lack proper codes. The former case can be addressed by proper registration rules and recommendations, training of registration staff and quality check softwares.

Data collected by CRs provide reliable estimates about rare cancers. However, rare cancer burden indicators are exposed to a high sampling variability due to their low number. Thus, it should be encouraged to provide them along with a variability measure, such as confidence intervals. Occurrence (i.e., incidence, mortality, and prevalence rates) and outcome (net or relative survival) are the most used population-based indicators, but their statistical properties and performances in the rare cancer settings have not been sufficiently studied so far.

On each cancer 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 but for haematological diseases. This undermines the availability of epidemiological data for rare cancers that are defined on the basis of their morphology and topography. The use of morphology is essential to identify neuroendocrine tumours, sarcomas of both soft tissue and viscera, all childhood cancers, germ cell tumours and central nervous system cancers. The use of topography only may be acceptable for rare cancers which are mainly of epithelial origin, such as those of head and neck, digestive or uro-genital origin.

Integration with administrative databases and clinical registries is an opportunity which should be exploited because, although rare, collectively rare cancers represent one fourth of all new cancer diagnoses. Administrative databases, like hospital discharge data, healthcare data bases with socio-economic and socio-demographic information, health insurance data are repositories of potentially relevant information. As the administrative databases are not

designed to provide health data, quality systems should be in place. Likewise, administrative databases cannot replace clinical data, so that efforts are needed to strengthen links between CRs and clinical registries, electronic health records and pathology reports.

Recommendations for paediatric cancer:

- ✓ 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 cancer treatments.

Rationale for childhood cancers:

Long-term health sequelae and side effects of treatments are of major concern in childhood cancers. Besides, approaches to such sequelae are multidisciplinary and involve several health figures. A high degree of patient migration across cities and countries is apparent in the young adulthood. This emphasizes the need for a European unique patient identifier to monitor long-term outcomes in rare cancers. It is worth noting that it would be crucial to foster a systematic registration of moderate to severe long-term side effects of cancer treatments as well as to cross-link databases.

RECOMMENDATION 3

HEALTH SYSTEMS SHOULD EXPLOIT NETWORKING AROUND MULTIDISCIPLINARY CENTRES OF REFERENCE, TO IMPROVE QUALITY OF CARE IN RARE CANCERS WHILE DIMINISHING/RATIONALIZING HEALTH MIGRATION

Specifically:

- ✓ Networking may contribute to optimize patient referral to centres of expertise and maximize the use of their expertise in the community. At the same time, any networking requires the presence of strong centres of expertise.
- ✓ 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.
- ✓ For both ERNs and national networks, quality criteria should focus on the way the network operates, so as to optimise the patient's pathway and maximize access to multi-disciplinary 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 (not simply focussing on clinical outcomes).
- ✓ For small countries, an option is to collaborate on a cross-border basis with other national countries.

Rationale

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 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). All the more, this is the case with rare cancers. However, there are some limiting factors that need to be considered. These are as follows: 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-off. 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 long-time interval of the clinical history. 5. Since the number of centres owning an 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 centralized 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 the multidisciplinary strategic clinical decision-making, pathologic diagnosis, complex treatments, with special regard to local treatment.

One should always be aware that in the rare cancer field, the professional expertise is inevitably a scarce resource, given the low number of cases, and the creation of professional skills always requires long time intervals, 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 underscores the importance of both centres of expertise and networking in rare cancers.

In small countries, the problem of rare cancers is even more critical. No institution, by definition, will see a number of patients with certain rare cancers as large as 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 requested to fulfil good-quality care.

Structure and process standards for hubs

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 volume 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's rules as far as network patients 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 organisations.

Quality criteria for spokes

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 of the 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's rules as far as network patients are concerned; b) participation in clinical education initiatives; c) participation in clinical research.

Recommendations for paediatric cancer:

- ✓ 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.
- ✓ Enabling secure life-long relevant treatment information (Survivorship Passport) about treatment burden and late effects, capitalizing on European eHealth developments, requires EU and national support. 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.

Rationale for childhood cancers:

It is acknowledged that optimal care for paediatric cancer is delivered in specialised multidisciplinary care units, also known as reference or principal treatment centres, that 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-oncology. In addition to clinical specialists and nurses, other figures such as, say, psycho-oncologists, play therapists and educators are required (SIOP Europe, 2009). Specialised 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.

RECOMMENDATION 4

MEDICAL EDUCATION SHOULD EXPLOIT AND SERVE HEALTHCARE NETWORKING BY PROPER INTEGRATION OF THE UNIVERSITY SYSTEM, CONTINUOUS MEDICAL EDUCATION PROVIDERS AND ALL EDUCATIONAL PLAYERS, SERVING DEDICATED CAREER MECHANISMS AND OPPORTUNITIES FOR RARE CANCERS

Specifically:

- ✓ There is the need to provide educational pathways for clinical oncologists willing to specialize on rare adult solid cancers. These educational pathways should provide education on such diseases under a multidisciplinary perspective.
- ✓ 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.
- ✓ 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 does exist within centres of reference. 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.
- ✓ Proper funding should 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.

Rationale:

It is important to be aware of the main difficulty with medical education in rare diseases, including rare cancers, that makes it essentially different from common diseases: 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. Clearly, this does not apply to the medical personnel of reference centres, who therefore are a natural target of medical education on rare cancers.

However, 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.

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, as long as hub-and-spoke networks spread. 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 surgery. Of course, spokes' clinicians will hardly specialize only in one cancer amongst rare adult solid cancers. Thus, it is always logical to conceive educational events grouping several rare adult solid cancers, considering similarities (e.g., sarcomas and mesothelioma, etc.). 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). Fellowships within networks may be especially important and peculiarly shaped.

Given the crucial importance of case managers for networks, training opportunities should be arranged for them, clinical patient navigators and other health professionals or social workers specializing in supporting network functioning and the rare cancer patient's journey. The partnership between patient organisations and healthcare professionals, as well as other professionals such as case managers, is a key success factor to improve the trainings of both the patients and their carers and the professionals, who can learn from the experience of patients living with a rare cancer.

Training on rare cancers should always be viewed as connected with available medical careers. An effort should be made to implement new medical careers focusing on rare cancers. Otherwise, rare cancer patients will be inevitably discriminated against. In fact, on one side, young clinicians will not be attracted by these diseases. Centres belonging to ERNs should be proactive in guaranteeing medical careers on rare cancers.

The rarity and the 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 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. Patient advocacy groups have also been key in

providing specific training resources to patients and carers. This may take place through onsite trainings, conferences, online webinars, video recorded tutorials.

Recommendations for paediatric cancer:

- ✓ 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 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 and the SIOP Europe educational strategy under development as of 2019.

Rationale for childhood cancers

While there are well established full medical careers in paediatric oncology, a comprehensive training pathway is generally lacking. 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 under development under the leadership of SIOP Europe.

RECOMMENDATION 5

RESEARCH SHOULD BE FOSTERED BY NETWORKING EXPLOITING CLINICALLY ANNOTATED BIO BANKING, CLINICAL REGISTERING, PATIENT REFERRAL TO ONGOING CLINICAL STUDIES

Specifically:

- ✓ 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.
- ✓ 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. Missing as few cases as possible is exceedingly important in rare cancers.
- ✓ It would be important that clinical databases of networks, and network institutions, are designed to be as much interoperable as possible and to allow easy data exporting 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 the academia to run more clinical trials and encourage pharmaceutical companies to undertake studies also in orphan indications.
- ✓ 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.
- ✓ In the rare cancer area, new drugs or technologies may be available within clinical trials only in selected EU countries. 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 spread.

Rationale:

Difficulties of rare cancers as to clinical research are by definition related to the low number of patients (Casali, 2015). This limits the "statistical precision" in clinical, translational and outcome research. There are organizational and methodological solutions that can be deployed to cope with this inherent difficulty of rare cancers. In principle, no solution should entail diluting a distinct patient population of rare cancer patients into a larger 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 look all the more problematic. However, an effective biomarker also tends to amplify the effect, thus increasing statistical precision (Buyse, 2010).

Lack of clinical expertise is another specific problem affecting research, in addition to healthcare organization. In fact, suboptimal quality of care on 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.

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 over the last years in oncology, though not in paediatric oncology (European Parliament and Council of the European Union, 2000). However, one should be aware that a factor potentially discouraging companies from developing health technologies in rare cancers can be the risk of discrepancies in reimbursement by national/regional authorities across the EU, after regulatory approval in the EU.

Low numbers also imply shortage of biological samples, thus affecting basic and translational research, therefore clinical research as well, assuming that more and more clinical research should be rationally driven by biomolecular insights.

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 (that 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.

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 be done also when a likely lower statistical precision is foreseen, given available numbers, and their patient populations should be selected exclusively to maximize the chances of any new treatment to display its highest efficacy, without widening inappropriately eligibility criteria. Even the study duration should be reasonable, given available numbers.

The choice about whether a clinical trial will be randomized or not should be viewed as distinct from 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.

Recommendations for paediatric cancer:

- ✓ Sustained public investment in childhood cancer research at the EU level holds the potential for transformational change. The allocation of resources should allow further integrating care and research and supporting permanent and sustainable clinical trial platforms within international collaborations.

Rationale for childhood cancers:

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 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.

RECOMMENDATION 6

PATIENT-PHYSICIAN SHARED CLINICAL DECISION-MAKING SHOULD BE ESPECIALLY VALUED BEING CRUCIAL TO THE APPROPRIATE APPROACH TO THE POSSIBLY HIGH DEGREE OF UNCERTAINTY POSED BY RARE CANCERS

Specifically:

- ✓ Within the framework of a patient-physician shared clinical decision-making, a clinical decision will be feasible even if uncertainty is high. The higher degree of uncertainty may not be an obstacle to exploit innovation in rare cancers.
- ✓ Patient advocacy groups can give assistance to patients challenged with shared clinical decisions and help develop such information tools.
- ✓ The methodology of collaborative, multidisciplinary, remote 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.
- ✓ The 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.

Rationale:

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. Namely, randomized clinical trials are difficult to set up. In addition, the clinical expertise tends to be lower, though proper referral of patients may limit this kind of difficulty (Casali, 2015). Aside from all attempts towards shrinking uncertainty as much as possible, ultimately uncertainty can be appropriately managed by sharing it with the single patient.

If patient-physician shared decision-making is key to an appropriate decision-making in rare cancers, it is vital to make sure that its practice is widely taught as an item of medical education (Thornton, 1992).

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.

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

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.

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, to integrate results of clinical trials at the patient’s bedside and to generate evidence on rare and ultra-rare cancers (Shortliffe, 2018).

Rationale for childhood cancers:

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

RECOMMENDATION 7

APPROPRIATE STATE-OF-THE-ART INSTRUMENTS SHOULD BE DEVELOPED IN RARE CANCERS FIT TO SERVE CLINICAL DECISION-MAKING IN CONDITIONS OF UNCERTAINTY

Specifically:

- ✓ Clinical practice guidelines are expected to improve quality of care not only by what they say, but also through the processes of their own construction. This is why a reasonably high number of cancer centres should be involved, as possible, in the consensus development processes leading to clinical practice guidelines.
- ✓ Clinical practice guidelines on rare cancers should leave room for treatments of uncertain efficacy that, though not standard, may be viewed as "options" amenable to a shared patient/physician decision in conditions of uncertainty.
- ✓ Mechanisms to monitor compliance of clinical practice with clinical practice guidelines should be encouraged. Healthcare networks' IT tools, including those adopted by ERNs, should be shaped also to support such monitoring.
- ✓ Collaborations between rare cancer communities and agencies in charge of state-of-the-art instruments, as well as with agencies producing evidence-based medicine tools should be encouraged (Brouwers, 2016).
- ✓ 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.

Rationale:

Uncertainty should not be viewed as an obstacle to building state-of-the-art instruments, such as clinical practice guidelines, and the like. As a matter of fact, 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 usually supporting clinical decision-making should be available in 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 according to diagnostic/therapeutic patterns agreed upon by the international medical community.

In a subset of clinical practice guidelines on rare adult solid cancers, 40% proved to be of good quality, the others being 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.

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.

Clinical practice guidelines on rare cancers are exposed to all limitations affecting generation of evidence when a disease is rare, namely to all difficulties to carry out large clinical trials in rare cancers. Thus, levels of evidence may be more often suboptimal in rare as compared to common cancers. This might give rise to discriminations against rare cancer patients. It follows that the "strength of recommendations" should be higher in rare as compared to common cancers in the presence of lower levels of evidence (Mercuri, 2018). Nevertheless, quality of evidence implied by studies exploiting new methodologies should be properly ranked, factoring in the need for innovative methodologies in rare cancers.

Clinical practice guidelines should be conceived in such ways 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.

Recommendations for paediatric cancer:

- ✓ Regional, national or European virtual tumour boards should be set up and promoted to ensure that all patients with a new diagnosis or relapsing are discussed and, when relevant, 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 the ERN PaedCan, while twinning initiatives between ITCC investigating centres and ERN PaedCan partners should be encouraged especially in low health expenditure rate (LHEAR) countries.
- ✓ Cooperation should be supported between 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.

Rationale for childhood cancers:

A proportion as high as 90% of newly diagnosed paediatric cancer patients are treated within prospective clinical studies or according to European recommendations established through clinical research. European standards concerning the organization of care in paediatric haematology 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 the access to the best standard treatment, care, and research, particularly in central and eastern Europe but also in other European countries (JARC Deliverable 9.1). Reducing these inequalities is a principal aim of the ERN PaedCan and ITCC in line with the SIOP Europe Strategic Plan.

RECOMMENDATION 8

REGULATORY MECHANISMS ON RARE CANCERS SHOULD PROPERLY FACE THE CHALLENGE OF A POSSIBLY HIGHER DEGREE OF UNCERTAINTY BEING DISEASE-ADAPTED, OPENING UP TO INNOVATIVE RESEARCH METHODOLOGIES, ASSURING CERTAINTY OF RULES TO DEVELOPERS OF INNOVATION, RECOGNIZING ENOUGH FLEXIBILITY AS TO ALLOW A PERSONALIZED CLINICAL DECISION-MAKING IN CONDITIONS OF UNCERTAINTY

Rationale:

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 the statistical quality of evidence can be lower compared to 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 generate new solutions (that possibly can well be useful also for common cancers, if validated). Non-randomized study designs and clinical registries, Bayesian statistics, surrogate end-points are amongst areas of major interest for methodological research in the field of rare cancers. It is important that regulators do encourage all this, from the stage of scientific advice on new drug development to the final regulatory decisions.

In the regulatory setting, rare cancers may be less known with regard 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 access all the necessary clinical expertise, as available within the rare cancer disease-based communities, including clinical experts and patient advocates.

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 might be allowed at the patient's bedside. Proper involvement of disease-based patient communities may help identify such situations.

In ultra-rare cancers, there may be a lack of knowledge about the disease, that 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 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.

Regulatory choices, reimbursement decisions and managed care pathways should be based on assessments of efficacy 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 a rare cancer, in spite of a potentially low level of evidence. Within each ERN, a task force should be deployed as to monitor the consistency of ERN's clinical practice guidelines with local guidelines, if any, and managed care pathways, with regular reports thereon.

Involvement of pharmas in risk-sharing mechanisms for drug reimbursement should be exploited, as a way not to discourage investments in areas where uncertainty may be higher and the market is narrower (ERN Board of Member States, 2019).

Recommendations for paediatric cancer care:

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

Rationale for childhood cancers:

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) N° 1901/2006 has been a potentially more relevant instrument, but also fell short of success (Vassal, 2016): only very few innovative anti-cancer medicines were 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 pediatric malignancies (SIOP Europe, Unite2Cure, 2016).

RECOMMENDATION 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.

Rationale:

When ERNs were created in the EU, the choice was made to tackle the problem of rare cancers through networking, as a key factor to address the many challenges they pose. In order for it to function, 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).

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 the 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.

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 and children and develop synergies with national plans for rare diseases. Innovative instruments should be devised to improve consistency across national cancer plans.

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. Then, networks must rely on appropriate IT systems, which thus must be funded and managed as well. Then, the medical workload entailed by teleconsultations

provided by expert centres within a network (i.e., hubs within hub-and-spoke networks) should be covered. Reimbursement of teleconsultations should be foreseen, and in any case they should be formally acknowledged by the healthcare system.

Recommendations for paediatric cancer care:

- ✓ Sustained public investments should be foreseen to address the unmet need 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 (including compensation schemes) should be allocated to the ERN PaedCan to enable delivery of the best possible care to children and adolescents with cancer across Europe
- ✓ Further integration should be enabled of care and research by supporting stable and sustainable clinical trial platforms and international collaborations.

Rationale for childhood cancers

The rarity of individual paediatric cancer types and their high collective burden across Europe have fostered cross-border academic cooperation, that 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 the 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.

RECOMMENDATION 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

Specifically:

- ✓ 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.

Rationale:

The Pan-European umbrella patient organisations partners to JARC are: Childhood Cancer International Europe (CCI Europe), European Cancer Patient Coalition (ECPC) and EURORDIS - Rare Diseases Europe. 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. These are as follows: ensure the financial sustainability of ERNs; foster the expansion of ERNs; integrate ERNs into national healthcare systems; facilitate cross-border healthcare from one country to another; facilitate virtual consultations and the use of electronic tools; foster patient registries and clinical research through ERNs; support the harmonization of clinical guidelines and their approval in all EU MSs; integrate psycho-oncology as part of patient treatment; implement specific reimbursement mechanisms; and, allocate resources to training.

Recommendations for paediatric cancer care:

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
- ✓ Support patient organizations acting as PASOs and European level facilitators.
- ✓ Reimbursement of cross-border healthcare including early clinical trials and related travel and accommodation for children and their families.
- ✓ Development and implementation of long-term follow-up facilities for survivors of childhood cancers.

Rationale for childhood cancers:

The situation in paediatric cancers and patient engagement differs from adult rare cancers due to the following: (1) 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. And, (2) 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.

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Annex 1: List of participants

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Annex 2: Agenda of the Meeting

JARC WP10 Meeting

Barcelona, 20-21 June 2019

MEETING VENUE:

BSM, Barcelona School of Management

Address: Calle Balmes, 134

https://espais.bsm.upf.edu/en/

DAY 1: *20 JUNE*

13.00-13.45	*Welcome lunch*
13.45-14.00	Introduction & Tour the Table *JM Borras / P Casali*
Book Chapter's Discussion & Review	
14.00-14.45	**CHAPTER 1** *Rare cancers are the rare diseases of oncology*
14.45-15.30	**CHAPTER 2** *Rare cancers should be strictly monitored*
15.30-16.15	**CHAPTER 3** *Health systems should exploit networking*
16.15-16.30	*Coffee break*
16.30-17.15	**CHAPTER 4** *Medical education should exploit and serve healthcare networking*
17.15-18.00	**CHAPTER 5** *Research should be fostered by networking*
18.00-18.15	**Wrap up**

Tour visit

JARC WP10 Meeting

Barcelona, 20-21 June 2019

DAY 2: *21 JUNE*

8.30-9.15	**CHAPTER 6** *Patient-physician shared clinical decision-making should be especially valued*
9.15-10.00	**CHAPTER 7** *Appropriate state-of-the-art instruments should be developed in rare cancers*
10.00-10.45	**CHAPTER 8** *Regulatory mechanisms on rare cancers should properly face the challenge of a possibly higher degree of uncertainty*
10.45-11.00	*Coffee break*
11.00-11.45	**CHAPTER 9** *Sustainability should be addressed by exploiting networking*
11.45-12.30	**CHAPTER 10** *Rare cancer patient advocates should be always involved*
12.30-13.00	**Next steps**
13.00	**LUNCH**