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JARC
JOINT ACTION ON RARE CANCERS

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RARE CANCER AGENDA 2030

Despite the rarity of each of the 198 identified rare cancers, collectively they represent 24% of all new cancer cases diagnosed in the EU28 each year. Five-year relative survival is worse for rare cancers (47%) than for common cancers (65%), and differences in survival exist across European countries, therefore suggesting the existence of inequalities in healthcare.

The "information network on rare cancers" RARECAREnet project (www.rarecarenet.eu) on quality of care regarding three families of rare cancers (soft tissue sarcomas of limbs, head and neck cancers, testicular cancers) showed that diagnosis and treatment may lie below optimal standards in some EU countries. This is more likely when healthcare is delivered by institutions with limited expertise and/or low case volumes. There is a wide consensus that especially diagnostic pathologic confirmation and primary treatment of rare cancers should be centralized to reference centres and/or to collaborative health networks with multidisciplinary, highly specific expertise.

Also clinical and translational research would need a high level of centralization and international collaboration. In fact, the problem of rare cancers is by definition the low number of cases.

In the last few years, initiatives prompted by the rare cancer community have been ongoing on rare cancers, like the *European Action Against Rare Cancers* (www.rarecancers.org), launched in 2008 by the ESMO in partnership with the many stakeholders who must have a say to advance our knowledge and practices in this challenging, "orphan" area of human diseases. Patient advocacy groups have continuously raised the issue of rare cancers as a challenge to take on, given the risks of discriminations against rare cancers patients just due to the rarity of their diseases. The EU recognised the results of RARECARE and supported a second project (RARECAREnet), which updated and enriched the information on rare cancers in Europe. Importantly, the EU created the European Reference Networks (ERNs) in 2017 on several rare diseases, including four related to rare cancers: ERN on rare adult cancers (ERN EURACAN), ERN on haematological diseases (EuroBloodNet), ERN on paediatric cancer (ERN PaedCan), ERN on genetic tumour risk syndromes (ERN GENTURIS). Also following this evolution in the perception of rare cancers as a distinct issue in the world of oncology, the EU prompted JARC (Joint Action on Rare Cancers).

JARC gathered around the same table all stakeholders in the field of rare cancers and rare diseases. The goal of JARC was to contribute to improve health outcomes for patients with rare cancers in the EU maximizing chances of ERNs on rare cancers to be successful.

JARC was a joint action between the European Commission and 18 Member States lasting 3 years (September 2016-2019). JARC had 34 associated partners including representatives from Ministry of Health, public health institutions, comprehensive cancer centres, universities, scientific societies (e.g. SIOPE, OECI) and patients associations namely European Cancer Patient Coalition (ECPC), EURORDIS-Europe and Childhood Cancer International-Europe (CCI-Europe).

JARC intentionally chose to be strategically concerned with the new ERNs, viewed as a great opportunity for rare cancer patients in the EU. Thus, JARC aimed at optimizing the process of creation of the ERNs, by providing them with operational solutions and professional guidance in the areas of quality of care, research and innovation, education, clinical practice guidelines development and epidemiology.

After 3 years of work, JARC produced 10 recommendations instrumental to the policy agenda on rare cancers in the European Union for the years to come. An agenda on rare cancers was perceived as instrumental to prioritise rare cancers in the agenda of the EU and Member States to minimise the risk that rare cancer patients may be discriminated against simply because of the numbers of the disease they suffer from.

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

1. Rare cancers are the rare diseases of oncology

Rare cancers are malignancies whose incidence (number of new cases in a year) is <6/100,000/year. This 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 E) funded the RARECARE project that proposed the rare cancer definition and the list of rare cancers. A consensus effort to re-examine the list of rare cancers as developed within RARECARE took place within JARC, with a view also to the rare cancer families (Table 1).

Rare cancers share all the main problems that are typical of rare diseases and that are due to the low number of cases:

1. clinical decision-making, due to a lack of available medical expertise and high-quality evidence from clinical research;
2. healthcare organization, due to difficulties in serving a territory with specialized facilities;
3. clinical research, due to the low number of patients and thus the difficulty to undertake clinical studies.

However, rare cancers differ from rare diseases.

Rare diseases	**Rare cancers**
There are 6000 rare diseases, which are highly heterogeneous and mainly chronic.	There are 200 rare cancers, which are sub-acute disease and rarely become chronic because of available treatment.
About 75% of rare diseases affect children.	Most of rare cancers occur in adults.
About 80% of rare diseases are of genetic origin.	Inherited rare cancers are rare. Most of rare cancers as all cancers have a multifactorial aetiology (i.e. are due to the interaction of different factors such as risky life style, environmental exposure to cancerogenic substance, genetic predisposition etc.).
Rare diseases definition, being mainly chronic diseases, is prevalence-based (number of patients alive with a rare disease) < 50/100,000.	Rare cancers definition, being mainly sub-acute diseases, is incidence-based (number of new cases of rare cancers) < 6/100,000.
A large number of the 6,000 rare diseases do not have structured registries.	Rare cancers registration is provided by the widespread population-based cancer registries.
The number of centres specializing in rare diseases diagnosis and treatment tends to be low because these diseases are heterogeneous and very specific.	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.

For the above reasons:

- Rare cancers should be approached within national cancer plans which should include provisions concerning at least the following areas: epidemiology; healthcare organisation and networking; access to the best possible standard treatment; clinical research and access to innovative therapies; medical and non-medical education, clinical practice guidelines, access to social needs of patients and families; survivorship.
- Coordinated health policies and programmes should be placed at the European level, given the rarity of individual rare cancers.
- The rare cancer community can look at synergies with EU rare disease policies and national rare disease plans on matters relevant to tackle rarity.

Table 1. Rare cancer families

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

Families of rare adult solid cancers

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)*

2. Rare cancers should be monitored

Rare cancers are covered by widespread cancer registration in the EU. As of 2019, nearly 200 population-based cancer registries are active in Europe. For a cancer registry 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. Thus, the quality of a CR inevitably depends on the local healthcare environment and the available sources of information. Quality of care is relevant to quality of cancer registries. For example, inappropriate pathological diagnoses will result in misclassification (i.e. a wrong registration of a diagnosis) in cancer registries. Rare 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). Clinically relevant data, e.g. on detection, staging, treatment and treatment effects tend to lack across cancer registries. A way to obtain clinically relevant information is to perform ad hoc high-resolution studies but, these studies performed by the RARECAREnet project resulted to be costly, time consuming, lacking detailed information and not able to provide information in real-time. Integration of cancer registry with administrative databases is another 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. On the other hand, administrative databases cannot replace clinical data.

ERNs' *Rare Disease Registries*, i.e. clinical registries with detailed clinical information set up within ERNs are an opportunity for rare cancers. 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.

ERN's registries:

- Should be automatically populated from the electronic health records, or local database, of each contributing hospitals and/or from the IT tool of the national networks on rare cancers.
- Should be interoperable (i.e. able to integrate data) with the *Clinical Patient Management System* (the IT platform currently used by the ERNs to provide second-opinion) and with population-based cancer registries.
- Should be linked to additional information source such as administrative and health insurance data; research data; patient monitoring data with wearable devices; omic science data.
- Should be able to take advantage of a harmonised interpretation of the data protection rules across the EU. To this extent it will be important:
    - to recognise the right of EU citizens to give "one-time consent" to use their health data and/or biological samples for future research purposes;
    - to ensure simple procedures for data transfers across institutions and national countries within the EU. Research on rare cancers desperately needs data thus, any additional burden on data transfer across institutions would affect rare even more than common cancers;
    - to adopt a *European Unique Patient Identifier*, to ensure monitoring of long-term outcomes in childhood cancer survivors in a cross-border setting.

3. Health systems should exploit networking

Centralized referral has always been a recommendation in the rare cancer field. Referring rare cancer patients to centres of reference (expert centres) 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. However, some limiting factors need to be considered.

- Appropriate referral of a suspect rare cancer patient implies a degree of collaboration with/among clinicians/institutions, starting from the general practitioner.
- In rare cancers, even centres of excellence need to collaborate with each other on clinical practice guidelines definition, clinical research, medical education, highly challenging clinical cases, etc.
- 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 clinical history.
- 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.

In order to maximize the exploitation of their clinical expertise, centres of excellence should be able to focus on strategic clinical decision-making, pathological diagnosis and complex treatments, with special regard to local treatment. 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. Thus, networking is important to optimize patient referral to centres of expertise and maximize the use of their expertise in the community.

In the EU, ERNs were launched in 2017, as networks of healthcare providers selected by Member States 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. ERNs are "peer-to-peer" networks, since they are made up of expert centres.

ERNs to be effective should liaise nationally, or regionally, with "hub-and-spoke" networks, thus becoming **networks of networks**. 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. However, networking is always challenging and needs:

1) proper funding for infrastructures (from IT network systems to service centres, and the like);
2) 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;
3) explicit rules on governance (including responsibilities of members, network management, leadership, etc.);
4) well developed quality systems at the healthcare provider level, the overall network level and the network patient level (i.e. the patient accessing to the network*.

   **According to the network's managed care pathways, the network patient may: a) be taken care of within a hub; 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.*

4. Medical education should exploit and serve healthcare networking

The main difficulty with medical education in rare diseases, including rare cancers, is 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, in ways that do not differ substantially from what may happen with medical education on common cancers.

Additional and challenging targets for medical education include:

- Medical personnel belonging to spokes of hub-and-spoke networks. 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.
- Undergraduates and general practitioners. 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.
- Case managers, clinical patient navigators, nurses and other health professionals or social workers specializing in supporting network functioning and the rare cancer patient's journey.
- Patients and their carers. The involvement of European patient advocacy group (ePAG) representatives in the rare cancer ERNs' work on education and training is crucial. They help provide necessary information tools and specific training resources to the patients and their carers.

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. To this extent:

- Medical oncology units allocated to rare adult solid cancers should be created within spokes of hub-and-spoke networks on rare cancers.
- Educational pathways for clinical oncologists willing to specialize in rare adult solid cancers should be provided and should cover all or some of the 10 "families" or rare adult solid cancers (see Table 1 in Chapter 1).
- These educational pathways should include: a) courses on each of the rare adult solid cancers, based on a syllabus (every other year); b) clinical updates on adult solid rare cancers (yearly) b) clinical fellowships (of 2-6 months) on selected rare adult solid cancers; c) an examination, with a certification of competence.
- The professional figure of the paediatric oncologist should be recognized in all Member States, and mutual recognition of qualifications across the EU should be considered.
- Non-competitive EU funding should be allocated to support twinning and clinical fellow-ship within the ERN.
- 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.

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

The difficulties of rare cancers in terms of clinical research are by definition related to the low number of patients. Other specific problems affecting research include:

- Lack of clinical expertise. In fact, suboptimal quality of care in a disease impairs results of any treatment, including research treatments.
- Shortage of biological samples.
- Scarcity of funding dedicated to rare cancers.

There are organizational and methodological solutions to address this inherent difficulty of rare cancers.

Organizational solutions.

- Public funding for investigator-driven clinical studies should increase for rare cancers. Partnerships with reimbursement bodies and national health systems could be foreseen to fund these studies.
- Networks (first of all through ERNs, but also through the national networks linked thereto) should be exploited to decrease costs of clinical trials in rare cancers by: sharing standard operating procedures; using clinical databases also for research purposes, developing biobanking, etc. 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.
- Administrative requirements should be limited as much as possible.
- 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.
- Initiatives on health data standardization and system interoperability to facilitate cross-border health research should be supported.
- Reimbursement of cross-border participation in clinical trials for children with non-curable malignancies should be envisioned.

Methodological solutions.

- 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.
- Bayesian appraisal of all available evidence should be encouraged in rare cancers, because it may be expected to maximize the amount of information exploited.
- Adaptive mechanisms in clinical trials are aimed at modulating a study throughout its implementation. In rare cancers, may be particularly useful given the paucity of cases and the long study timelines.
- The technologies of big data are exceedingly promising in rare cancers and 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.

Major research topics in rare cancers

- re-purposing of an available drug in a rare cancer
- natural history of rare cancers
- off-label or compassionate use
- healthcare service research investigator-driven clinical trials on surgical and radiation treatment modalities to define multimodal treatment strategies
- surrogate end-points and tumour response.

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

In rare cancers, uncertainty is higher than average by definition. This is due to the difficulties of clinical research to generate high quality evidence. 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.

As patient-physician shared decision-making is key to appropriate decision-making in rare cancers, it is vital that:

- It is widely taught as part of medical education. During their medical training, medical students and rare cancer clinicians should also receive proper training in terms of psychological abilities to manage the challenges of the process of patient information and awareness.
- Patient information tools are produced. Shared decision-making poses several burdens on patients, too. An "expert" patient is better involved in medical decisions.
- Methodological and psychological research on shared decision-making in conditions of high uncertainty are undertaken and financially supported, viewing this as an area of potential methodological innovation.
- Clinical decision support systems are developed factoring in the methodological requirements of shared decision-making in conditions of high uncertainty.
- The regulatory framework, e.g. regulatory mechanisms and practices about new drug approval, allows 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.

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

The high degree of uncertainty that characterizes rare cancers should not be viewed as an obstacle to building clinical practice guidelines. A clinical decision needs to be made at the patient's bedside, whether the patient has a rare or a common cancer. 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.

Within JARC, an effort was made to evaluate the quality of existing clinical practice guidelines on rare cancers. In total, 537 guidelines were collected. 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. 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. In essence, these "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.

Furthermore, patient representatives should always be involved in the processes leading to the production of clinical practice guidelines since they may bring important inputs to the assessment of evidence.

Regarding childhood cancers, about 90% of newly diagnosed paediatric cancer patients have treatment options either within prospective clinical studies or according to European recommendations established through clinical research. However, ERN PaedCan, started a collaborative work with *European Clinical Trial Groups* 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.

To ensure clinical practice guidelines development and use, some recommendations follows.

- Clinical practice guidelines on rare cancers are exposed to all limitations affecting the generation of evidence when a disease is rare. Thus, levels of evidence may more often be suboptimal in rare as compared to common cancers. It follows that the "strength of recommendations" should be higher in rare than in common cancers in the presence of lower levels of evidence. 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.
- Clinical practice guidelines should be conceived in such a way as to allow patient/physician shared decisions in conditions of uncertainty. 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.
- 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. Thus, spokes of hub-and-spoke networks, not only centres of reference, should be engaged as much as possible.
- 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.
- Mechanisms to monitor compliance of clinical practice with clinical practice guidelines should be encouraged within the ERNs and the national networks.
- Official recognition of clinical guidelines, developed within the ERNs, by national health authorities should become the backbone of decision-making agreed upon in the setting of cross-border healthcare and of reimbursement decision at national level.

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

The higher degree of uncertainty in rare cancers should be factored in also from the regulatory point of view. In other words, 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 and organisational solutions for clinical trials taking advantage of the ERN. Thus, for example:

- Adaptive licensing (i.e. mechanisms to provide availability of new agents throughout their development) 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.
- The off-label use of drugs in rare cancers is relatively widespread. ERNs should help generate new prospective evidence. Data generated thereby should be liable to complement data used for new drug registration.
- 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 and reimbursement in these clinical subsets of rare cancers may be foreseen within the ERNs and networks linked thereto.

Detailed regulatory solutions proposed by JARC follow.

- In ultra-rare cancers, there may be a lack of knowledge about the disease, which can hamper the development of new technologies. 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.
- 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.
- Mechanisms should be available allowing drug registration initiatives promoted by academia and/or disease-based communities (involving patients) especially where pharma's motivation may be low.
- 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.
- Consistency in efficacy assessment should be encouraged between the decisions of the European Medicines Agency (EMA) and the health technology assessments of Member States. 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.
- The regulatory environment for therapeutic innovation in childhood cancer, also in relation to the *EU Paediatric Regulation* and its implementation, should be significantly improved.
- 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.

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

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. Thus:

- Each MS should establish and maintain networks for all "families" of rare cancers.
- Networks need 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). To this extent, networks should always provide evidence that their effectiveness is as high as possible. Thus, they should monitor their performance, in terms of outcomes and costs, and provide data thereof.
- Further integration of care and research should be enabled by supporting stable and sustainable clinical trial platforms and international collaborations.
- 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.
- 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.

Finally, at a time when JARC has come to an end, a priority will be to create mechanisms to 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. To this extent, it is important to:

1) look at rare cancers as a specific area within cancer and within rare diseases
2) establish frameworks dedicated to rare cancers, such as joint programmes, annual conferences, etc.
3) identify specific advisory mechanisms to the EU Commission on rare cancers and a forum of the four ERNs focusing on rare cancers.

The objective should be to contribute to building and updating policy strategies on rare cancers at the EU level.

10. Rare cancer patients should be engaged

JARC had four Pan-European umbrella patient organisations as partners:

- ***Childhood Cancer International Europe*** **(CCI Europe)** is the European arm of *Childhood Cancer International*. It is the biggest pan-European childhood cancer parent and survivor organization. CCI Europe is represented in the Oversight Committee of ERN PaedCan and has 4 members elected to the ERN PaedCan ePAG.
- The ***European Cancer Patient Coalition*** **(ECPC)** is Europe's largest cancer patient umbrella organization. As of 2019 ECPC represented over 450 cancer patient organizations in 46 countries. ECPC has set up a *Working Group on Rare Cancers* (WGRC). 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 to voice the needs and expectations of people living with a rare disease in Europe, also including rare cancer patients. As of 2019, it involves over 860 rare disease patient organizations from 70 countries. Along with the development of 24 ERNs, EURORDIS has established 24 ePAGs. In the field of rare cancers, EURORDIS teams up with the ePAG Advocates in EURACAN, ERN PaedCan, EuroBloodNet and GENTURIS.

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 by providing secured long-term funding and facilitating public-private partnerships.
- Support the inclusion of new members in the ERNs, especially from countries not yet represented.
- Integrate ERNs into national healthcare systems by developing national healthcare networks for rare cancers. National rare cancer patient organizations should be involved in the implementation of national networks.
- Facilitate cross-border healthcare from one country to another exploiting national contact point established in each EU MS to provide citizens with information related to their rights to access care in a EU country other than their own and to recommend a specialized centre.
- Facilitate virtual consultations developing national referral policies and making ERNs tool (CPMS) and the electronic health records kept by healthcare providers that are members of the ERNs interoperable.
- Foster patient registries and clinical research through ERNs ensuring patients meaningfully involvement.
- Support the harmonization of clinical guidelines and their approval in all EU MSs including the integration of psycho-oncology as part of patient treatment.
- 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.

The situation in paediatric cancers and patient engagement differs from adult rare cancers because 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. 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 and defined the following recommendations to reflect the specifics of the childhood cancer.

- Support the eradication of inequalities in paediatric cancer outcomes establishing full or affiliated ERN PaedCan centre in each EU country and supporting twinning activities with centres in low health expenditure rate (LHEAR) countries.
- Support patient organizations and European level facilitators. National patient organisation 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. Mapping, training and coordination of patient organizations at the local levels are critical to ensure patients access to ERNs.
- Ensure reimbursement of cross-border healthcare including early clinical trials and related travel and accommodation for children and their families.
- Develop and implement long-term follow-up facilities for survivors of childhood cancers.