BACKGROUND NOTE ON PAEDIATRIC AND RARE CANCERS

Though there are many different rare cancers, due to their rarity they share similar problems concerning diagnosis and treatment. On the patients’ side it leads to difficulties in accessing timely and accurate diagnosis, highly specialised care and adequate treatments; and on the side of the healthcare system, it manifests in poor research opportunities, difficulties in clinical trials and lack of therapies. Paediatric cancers are all rare cancers and share the same challenges; but given their age-related, biological, clinical and organisational specificities, they need to be addressed distinctively.

With 5.1 million rare cancer patients in Europe, representing approximately 25% of all cancer cases, rare cancer is a major public health issue.

I. Overview on rare and paediatric cancers

In EU legislation and regulatory decisions, rare diseases are considered as those affecting less than 5 in 10 000 people. The EU-funded Surveillance of Rare Cancers in Europe (RARECARE) project adopted a different approach, and proposed to define rare diseases based on incidence, i.e. on the basis of new cases each year; according to this approach, rare cancers can be defined as those malignancies whose incidence is below 6 out of 100 000 people per year.

As mentioned above, rare cancer is a major public health concern with 5.1 million rare cancer patients in Europe, accounting for almost a quarter of all cancer cases. And though only 1% of all cancer cases fall into the "extremely rare" category (whose incidence is below 0.2 out of 100,000 people), they represent 61% of rare tumorous cancers. Haematological malignancies, female genital cancers and digestive cancers are the most frequent rare cancers, with more than 100,000 annual new cases each, and rare skin cancers represent only approx. 7 000 annual new cases. Estimated 5-year relative survival is significantly lower for rare cancers than for their common counterparts (48.5% and 63.4% respectively); and the overall relative

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1 N. Couspel, R. Price: Strengthening Europe in the fight against cancer - study by the European Cancer Organisation, 2020
2 Prevalence: proportion of persons having a condition at or during a particular time period; incidence: proportion or rate of persons developing a condition during a particular time period.
survival for rare adult cancers has been improving to a lesser extent than that for common adult cancers. Moreover, the geographical divide is also significant, with lower survival values in Eastern European countries (falling all below 45%, down to less than 35% in Bulgaria) than in all others (all above 45%), especially in Northern and Central European countries (up to more than 55% in Iceland).  

**Rare cancer families as presented by RARECARENet, based on robust data set collected from cancer registries**

- head and neck cancers
- digestive cancers*
- thoracic cancers*
- female genital cancers*
- male genital and urogenital cancers*
- neuroendocrine tumours
- cancers of the endocrine organs
- sarcomas
- cancers of the Central Nervous System (CNS)
- skin cancers and non-cutaneous melanoma*
- paediatric cancers
- haematological malignancies*

*Cancer families marked with asterisk include both common and rare cancers

**Cancer remains the principal cause of death by disease in children** beyond the age of one. Pursuant to the most recent estimates from the European Cancer Information System for EU-27, as cited by the Commission in the Europe’s Beating Cancer Plan, in 2020 over 15,500 children and adolescents were diagnosed with cancer, and more than 2,000 young patients died of cancer.

With over 100 types of childhood cancer, each case is considered as a rare cancer. Though high dose ionising radiation and prior chemotherapy are accepted causes of paediatric cancers, apart from those, no further environmental risk factors have been identified for paediatric cancers. What concerns known risk factors, genetic predisposition account for approximately 10% of paediatric cancers. A Cancer Predisposition Syndrome (CPS) diagnosis is important, because it opens the door to prevention, surveillance, counselling and psychological support, though these are currently underdeveloped services in Europe.

Thanks to advancement in research, survival at five years is 80%; however, there has been very little advancement for some types of paediatric cancers. Based on survival and prognosis, paediatric cancers form three main groups:

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- **paediatric cancers with good prognosis**, with a higher than 85% chance of survival after five years under current standard multidisciplinary treatments, using cytotoxic drugs in often an intensive mode: acute lymphoblastic leukaemia, lymphomas, retinoblastoma and renal tumours;

- **paediatric cancers with poor prognosis**, with 50% or less chance to reach the 5-year survival mark: acute myeloid leukaemia, several Central Nervous System tumours, neuroblastoma, bone and soft tissue sarcomas; and

- **the extremely rare tumours**, for which there is insufficient information on their real incidence and survival.

There are nearly half a million childhood cancer survivors in Europe, and the positive trend is that survival rates are expected to further increase in the future. By 2030, there will be an anticipated 750 000 paediatric cancer survivors in Europe. But the majority of survivors experience **adverse long-term effects, and even beyond five years from diagnosis, disease-free survivors have higher mortality rates**. Seventeen years after diagnosis, 27% of survivors report severe or life-threatening chronic condition related to prior therapy. Moreover, the geographical divide is present here as well, resulting in up to 20% of difference in children's survival rates among European countries.

The **social consequences of childhood cancer and its effects later in life** are long-lasting, and affect education, employment, work ability, and income. Though the majority of survivors of childhood cancer can return to their studies and enter employment (with the exception of brain tumour survivors, who are more often unemployed or economically inactive), access to insurance for loans and mortgages is difficult. In most countries, they face additional challenges as they have to disclose that they had a cancer diagnosis in the past, and they are denied insurance or have to pay a premium that is significantly higher than for a person with other chronic conditions.\(^5\)

In the EU, as there is no uniformly applied specific criteria in the **Mortgage Credit Directive** concerning cancer survivorship, the practice of creditworthiness assessment is fragmented. Recognising the problem, France, Belgium, Luxembourg and the Netherlands have passed legislation about **the right to be forgotten for cancer survivors**. The provisions of the legislation in these Members States are very similar. They stipulate that the longest period for which medical information relating to cancer can be collected is ten years after the end of

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\(^5\) A.Dumas & others: The right to be forgotten: a change in access to insurance and loans after childhood cancer? *Journal of Cancer Survivorship* [https://link.springer.com/article/10.1007/s11764-017-0600-9](https://link.springer.com/article/10.1007/s11764-017-0600-9)
treatment if there is no relapse, and, for cancers occurring before the age of 18 (age of 21 in the Netherlands), five years after the end of treatment. A list of exceptions for cancers with an excellent prognosis complement the provisions, where a shorter timeline is applicable to exercise the right to be forgotten. The provisions are subject to regular review, in order to adjust them to scientific data and advancement in treatments.  

Another important topic for many young cancer survivors is fertility. The impact of cancer therapy on fertility is related to the age of the patient and to the duration, dose/intensity, and type of treatment. It does not only affect the crucial issue of being able to have a child and raise a family, but influences a broad range of matters from body image to sexuality, dating relationships, marriage patterns and sense of wellbeing.

Different methods to preserve fertility exist. In girls before puberty, ovarian tissue freezing, in vitro maturation, and surgical movement of ovaries outside the field of irradiation are still experimental. In pubescent and postpubescent girls and young women, oocyte-embryo freezing is an established option. In men, the options are sperm cryopreservation, gonadal transposition, and testicular tissue or spermatogonial cryopreservation and re-implantation. Despite these advancements, cancer patients in the EU are still not receiving appropriate counselling and do not have adequate access to fertility preservation solutions. Apart from the emotional burden, it is also a financial matter, namely to what extent health insurance covers the preservation of patient sperm and eggs, fertility treatment and psychological support.  

II. Diagnostic and treatment challenges

Diagnosis for rare and paediatric cancers can be delayed due to (i) the presence of perhaps only negligible symptoms, (ii) the lack of associated risk factors, and (iii) the fact that patients developing rare cancers are not from the usual population groups considered as “at risk of cancer”. An additional difficulty with the accurate and timely diagnosis of paediatric cancers is that in early stages symptoms can be mistaken for symptoms of childhood diseases; by the time of diagnosis, 80% of paediatric cancers have already spread to other parts of the body, compared to about 20% of adult cancers.

After diagnosis, rare and paediatric cancer patients have the best chance if they receive treatment in centres of expertise. Well trained, specialised oncology workforce; multidisciplinary approach to care; adequate equipment and medicines; the possibility for the patients and their family or guardians to travel in order to receive treatment and receiving reimbursement are among the key conditions for the success of treatment.

The centres of expertise follow a multidisciplinary approach to care, in order to address the complex and diverse conditions. The Council, in its recommendation of 2009, encouraged Member States to identify or create such centres for rare diseases. In 2016 the European Parliament, in its resolution on Paediatric Medicines Regulation pointed out unmet paediatric

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medical needs, and called for appropriate incentives and funding in research and drug development and an overview of the regulatory framework. Ten years later the Parliament, in its resolution of 2019, underlined the importance of EU-wide cooperation to tackle rare and chronic diseases, including rare cancers; and encouraged the Commission to support the setting up of specialised centres for rare diseases in the EU, which should be fully integrated into the European Reference Networks. **Comprehensive training for rare cancer specialists and paediatric oncologists** is lacking in many Member States; such those training programmes should be worked out and the qualifications should be recognised via mutual recognition schemes.

The **availability of medicines and other treatments** also poses a problem. The difficulty to organise clinical trials due to small patient populations, lack of available quality epidemiological and clinical data, shortages of dedicated public funding, and low attractiveness of private research and investment hinder the development of, and through that the access to, rare cancer medicines and other treatments.

### III. European policy and legislation on rare and paediatric cancers

#### III.1. Regulatory framework

Satisfactory treatments for patients with rare diseases and for children were lacking for a long time, and given the small patient population, the pharmaceutical industry did not invest sufficiently into research and the development of these medicines. To bridge that gap, the EU put in place a regulatory framework to foster the development of medicines in the early 2000’s.

The **Regulation on medicinal products for paediatric use** ("Paediatric Regulation", Regulation (EC) No 1901/2006) aims to ensure that paediatric medicines have been researched and tested specially for children in an ethical way, that they meet the needs of children and that they have age-appropriate doses and formulations. Pharmaceutical companies carry out studies on children to obtain evidence about the safety and efficacy of new medicines before requesting marketing authorisation. The EMA’s Paediatric Committee assesses those studies and the data generated by them.

Orphan medicinal drugs are specifically designed to treat rare diseases. The **Regulation on orphan medicinal products** ("Orphan Regulation", Regulation (EC) No 141/2000) lays down the centralised procedure for the designation of orphan drugs. The regulation foresees giving orphan designation for substances that could be used for treating, preventing or diagnosing a rare and serious condition. Orphan designation can help the medicine’s developer to advance the medicine to the stage where it can be authorised for being put on the market. Applications for orphan designation are examined by the EMA’s Committee for Orphan Medicinal Products (COMP), using the network of experts that the Committee has built up. Formal approval (marketing authorisation) is needed before a medicine can legally be marketed.

To date, the EU has authorised just a few orphan medicines and paediatric cancer drugs, as, owing to the low number of people who are affected by rare diseases, research in this field has been neglected.

In its **2016 resolution**, the Parliament pointed out the shortcomings of the Paediatric Regulation. The resolution notes that, according to the current situation, pharmaceutical companies can ask
to waive the obligation to investigate the potential benefit of a drug in children if the adult cancer for which the medicine was originally developed does not exist in children. However, what matters for cancer drugs is the mechanism of action rather than the specific cancer type targeted, and such medicines could still be used to treat other childhood cancer types. One of the key calls of the resolution was to limit room for pharmaceutical companies to avoid the obligation to investigate and develop drugs for children, and the Parliament proposed to revise the regulation in this regard.

In 2020, the Commission published a comprehensive evaluation of the two regulations, looking into the period from the date of application until 2017. The two regulations were evaluated together, given that the majority of rare diseases may appear already in children and many children’s diseases are also rare.

- The evaluation concludes that both regulations promoted the development and availability of orphan drugs and paediatric medicines, owing to redirecting private and public investment through incentives, obligations and rewards. EU and national research programmes in the field of rare diseases complemented the regulatory framework. The number of medicines increased, became available faster and reached a higher number of patients in the Member States, and the number of clinical trials in children increased.
- The evaluation also shows, however, that the medicines developed thanks to the two regulations are not accessible by patients equally in all Member States. This is mainly due to factors outside the scope of the regulations, such as strategic launch decisions by pharmaceutical companies and national pricing policies and reimbursement systems.
- The evaluation points out that the two regulations have not succeeded to support adequately drug development in those areas where the need for medicines is greatest, as products tend to be developed in certain more profitable therapeutic areas for which the number of available treatments is increasing.
- The Paediatric Regulation obliges companies to test new medicines in children, but it has no dedicated instrument to direct development in areas relevant for children. The development of new medicines for children therefore remains mainly driven by adults’ needs. As a result, it does not necessarily address the greatest therapeutic needs of children such as treatments for children’s cancers and for newborns.
- The evaluation points out that while both regulations have increased costs for healthcare systems, thanks to the treatment with medicines for rare diseases, patients benefited from an improvement in their quality of life, and the benefits the legislation brought for children appear to outweigh the costs imposed on both industry and society.
- In conclusion, the Commission notes that any future solution to the and ineffecticiencies should strike a balance between the needs of fostering innovation and ensuring the availability of and access to medicines.

**III.2. Research incentives**

EU-supported work on innovative medicines started already under the Sixth Framework Programme for Research (FP6). The European Technology Platform on Innovative Medicines (INNOMED) brought together a range of stakeholders and was led by the pharmaceutical industry. IMI1, the Innovative Medicine Initiative was created as a joint undertaking, in the form of a public-private partnership, for the period of 2008-2013. Its overall goal was to significantly improve the efficiency and effectiveness of the drug development
process with the long-term aim that the pharmaceutical sector produce more effective and safer innovative medicines. It had a budget of 2 bn EUR, of which 1 bn EUR came from the Seventh Framework Programme (FP7), and the rest as in-kind contributions from European Federation of Pharmaceutical Industries and Associations (EFPIA) and its member companies. Building on the successes of the IMI, IMI2 was set up for 2014 to 2020 as a joint undertaking, with the total budget of up to 3.276 bn EUR. Similarly to IMI, for IMI2 had half of the budget from Horizon 2020, and the remaining half from EFPIA and its member companies. IMI2 carried out its research pursuant to the Strategic Research Agenda. They concentrated their efforts on delivering ‘the right prevention and treatment for the right patient at the right time’; cancer and rare diseases are amongst their focus areas.

Through the **Seventh Framework Programme (FP7) and Horizon 2020**, more than 200 research and innovation projects into **rare diseases** received over 1.4 bn EUR of EU financial support. Major lines of research in rare diseases include basic research to understand rare diseases; pre-clinical research to develop diagnostics and new therapies; proof-of-concept (pre-clinical and exploratory clinical validation studies of new therapies); clinical research (clinical trials and prospective cohort studies). In addition, several EU projects enabled the creation of infrastructures, in particular linking research and clinical data repositories, databases, biobanks, registries and other valuable resources in support of research into rare diseases. Via the research programmes the EU have been facilitating the formation of multidisciplinary consortiums with participants from universities, research organisations, healthcare providers, SMEs, industry and patient organisations.9

In the new programming period of 2021-2027, cancer research will be conducted under **Horizon Europe’s Cancer Mission**, with the budget of 2 bn EUR. The **Mission Board** of the Cancer Mission presented their report in September 2020, outlining ambitious research targets by 2030. Pursuant their agenda, research efforts in this decade should focus on, among others, increasing understanding the molecular processes at the cancer cell level and the interactions of the tumour and its host. It requires a new level of investment in innovative research, including high-potential/high-risk projects. The Mission Board proposes a Europe-wide platform, UNCAN.eu, making use of relevant research infrastructure and investing in the development of new models and technologies; UNCAN.eu has now been integrated into the Europe’s Beating Cancer Plan (EBCP). The Mission Board also proposed to focus efforts on cancers in children, adolescents and young adults. These recommendations have also been taken up in the EBCP.

**III.3. RARECAREnet**

The Information Network on Rare Cancers project (RARECAREnet, 2012-2016) was a Europe-wide epidemiological study. It producing updated data about rare cancers in the EU and studied the degree of centralisation of treatment of rare cancers.

9 Collaboration: A key to unlock the challenges of rare diseases research; European Commission, 20202 https://ec.europa.eu/info/sites/info/files/research_and_innovation/research_by_area/documents/ee_rtd_eu-rare-diseases-research_factsheet.pdf
III.4. EU Joint Action on Rare Cancers and the Rare Cancer Agenda 2030

EU Joint Action on Rare Cancers (JARC) was a multi-stakeholders collaboration between 18 Member States and the European Commission, coordinated by the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan. 34 partners involved in the JARC included ministries of health and representatives of national cancer control programmes, universities, public health institutions, population-based cancer registries, oncological institutes, patients associations (ECPC, EURORDIS, CCI-Europe) and other societies and organisations (including the Organisation of European Cancer Institutes, OECI and European Society for Paediatric Oncology, SIOPE). The JARC produced the Rare Cancer Agenda 2030, including ten key policy recommendations on rare cancers, which are to be implemented at national and EU level.

**Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers**

1. Rare cancers are the rare diseases of oncology, needing specific approaches by the cancer community and national health systems

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

3. Health systems should exploit networking around multidisciplinary centres of reference, to improve quality of care in rare cancers by rationalizing patient access to available best expertise and lowering/rationalizing health migration

4. Medical education should exploit and serve healthcare networking by proper integration of the university system and all educational players, being instrumental to dedicated career mechanisms and opportunities

5. Research should be fostered by networking and should take into account an expected higher degree of uncertainty exploiting clinically annotated biobanking, clinical registering, patient referral to ongoing clinical studies, as well as innovative methodologies for clinical research

6. Patient-physician shared clinical decision-making should be especially valued, being crucial to the appropriate approach to the high degree of uncertainty posed by rare cancers

7. Appropriate state-of-the-art instruments *(such as clinical practice guidelines)* should be developed in rare cancer, fit to serve clinical decision-making in conditions of uncertainty

8. Regulation on rare cancers should tolerate a higher degree of uncertainty, being disease-adapted and providing developers of innovation with certainty of rules across the EU

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

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

*Source: JARC*
III.5. European Reference Networks\(^{10}\)

The EU plays a central role in improving collaboration across countries in respect to rare and paediatric cancers. **Launched in 2017 in connection to the EU’s Cross-Border Healthcare Directive** ([Directive 2011/24/EU](https://eur-lex.europa.eu/eli/dir/2011/24/en)), several **European Reference Networks** (ERNs) were constructed and have been operational since then. ERNs are virtual networks that bring together healthcare providers and centres of expertise, in particular in the area of complex and rare diseases and conditions that require highly specialised treatment and a concentration of knowledge and resource. These networks are based on voluntary participation by their members; to ensure excellence, the directive sets the criteria for healthcare providers to join the network.

ERNs are "peer-to-peer" networks, comprising centres of expertise endorsed by their national healthcare authorities, and European Patient Advocacy Groups established by EURORDIS - Rare Diseases Europe. ERNs on rare cancers liaise with national or regional "hub-and-spoke" networks, and link centres of expertise to more generalist centres taking charge in part or in whole the management of some rare cancer cases. Connecting expert clinicians via a secure web-based platform, ERNs enable patients to get access, without travelling, to multidisciplinary expert assessment and faster diagnosis and treatment.

In small countries, where no institution will see enough patients with certain rare cancers to meet the case volumes thresholds generally used to define highly specialised centres of expertise, ERNs identify “affiliated centres” which then will liaise with their “full members”. This way, rare cancer patients of small countries can also benefit from the specialised expertise of the network.

24 **ERNs** were launched in 2017, involving more than 900 highly specialised healthcare units from over 300 hospitals in 26 Member States. **EURACAN**: European Reference Networks on rare adult solid cancer; **EuroBloodNet**: European Reference Networks on Rare Haematological Diseases; **ERN PaedCan**: European Reference Networks on paediatric cancers; and **ERN GENTURIS**: European Reference Networks on genetic tumour risk syndromes are specifically devoted to rare cancers.

### III.6. Europe’s Beating Cancer Plan initiatives on rare cancers

Published by the Commission on 3 February 2021, **Europe’s Beating Cancer Plan** ([COM(2021)44](https://eur-lex.europa.eu/eli/oc/2021/44/en)) addresses rare cancers in its Flagship 5.

\(^{10}\) See footnote 1
The Cancer Mission Board of Horizon Europe and the EU Joint Action CanCon recommended the establishment of National Comprehensive Cancer Centres and their networking at EU level. Building on this recommendation, in Flagship 5 of the EBPC the Commission undertakes to establish by 2025 an EU Network that links recognised National Comprehensive Cancer Centres in every Member State.

This cross-border collaboration will improve patients’ mobility and patients’ access to high-quality diagnostics and care and the latest innovative treatments. It will be supported by a new “EU Cancer Treatment Capacity and Capability Mapping” project, helping to map and share the different capabilities and expertise available across the EU. With the target to ensure that 90% of eligible patients have access to such centres by 2030, this action aims at delivering higher-quality care and reducing inequalities across the EU.

The EU Network will be supported by the existing four rare-cancer focused ERNs and a group of newly-created ERNs. These new ERNs will look at specific, challenging cancer conditions, including metastatic diseases, co-morbidities in cancer care, complex cancers with poor prognosis, paediatric cancers and specific conditions related to genomics in cancer care, palliative care and survivorship.

Building on experiences with repurposing of medicines to treat COVID-19, in 2021 the Commission will launch an EU platform to improve access to cancer medicines to support the repurposing of existing medicines. Using High-Performance Computing will allow to rapidly test existing molecules and new drug combinations. The work will start with cancers with poor prognosis and rare cancers.

III.7. Europe’s Beating Cancer Plan initiatives on paediatric cancers

A chapter is dedicated to paediatric cancers in the EBPC, underlying the political commitment of the EU, and highlighting the complexity of the issue.

- Flagship 10 of the EBPC is to launch, in 2021, the Helping Children with Cancer Initiative. Funded under the EU4Health programme, the initiative will use the new Network of Comprehensive Cancer Centres as infrastructure, and will complement the actions implemented by the new European Reference Networks, with the aim to ensure that children have access to rapid and optimal detection, diagnosis, treatment and care.

- A new EU Network of Youth Cancer Survivors will be set up in 2022 to (i) complement the actions under the “Helping Children with Cancer Initiative”, (ii) connect young cancer survivors, their families, and informal and formal carers, and (iii) contribute to strengthen long-term follow-up in cancer care plans at national and regional level.

- A new Cancer Survivor Smart-Card will be introduced by 2023 to address the specific needs of childhood cancer survivors, such as long-term monitoring of outcomes and potential toxicity of treatments, tailor follow-up care, rehabilitation, psychological support, educational modules, connectivity with healthcare staff, and information about past clinical history.
A new section, dedicated to childhood cancers, will be introduced into the European Cancer Information System to facilitate monitoring and research.

Horizon Europe Cancer Mission, via the planned “Childhood cancers and cancers in adolescents and young adults: cure more and cure better” initiative would increase understanding of cancer initiation and progression, and provide evidence-based information to advance diagnostics, treatment and survivorship support.

On the regulatory side, the review of the Regulation on orphan medicinal products (Regulation (EC) No 141/2000) and the Regulation on medicinal products for paediatric use (Regulation (EC) No 1901/2006) have the objective of improving the conditions for studying and authorising new cancer medicines for use in children.