

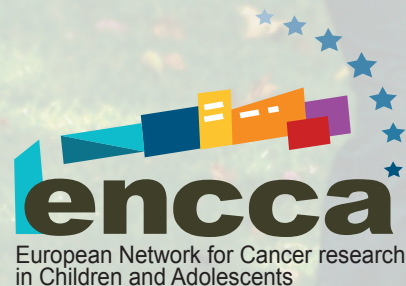
# Paediatric Haematology Oncology: the European Roadmap to Horizon 2020



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SIOP Europe  
the European Society for Paediatric Oncology



European Network for Cancer research  
in Children and Adolescents

# Introduction



We would like to present a summary of the 'European Roadmap to Horizon 2020' for paediatric haematology and oncology, a first outline which has been shared and discussed with all the participants of the SIOPE-ENCCA Conference 2014 'Joining Efforts for a Brighter Future for Children and Adolescents with Cancer - The European Roadmap to Horizon 2020'.

The full strategy will take into account the discussions held during the event and will be published extensively in the next months, further defining how to run and implement the future 'European Paediatric Cancer Plan'.

SIOPE and ENCCA are strongly determined to overcome the public health challenge of childhood cancer: notwithstanding the important progresses made in the last decades, more than 6,000 young people die each year of cancer, which remains the first cause of death by disease beyond one year of age. Moreover, the quality and availability of paediatric cancer care widely varies across Europe, with survival generally 10 to 20% lower in Eastern Europe, a disparity that becomes even larger for cancers with poor outcomes.

We believe it is important to find a way to solve these unacceptable inequalities, as there is an urgent need to increase the cure rate and to enhance the quality of cure for all patients and survivors, addressing the divide between low/medium and high income European countries in terms of research and care.

This is why we have set up a dedicated Working Group that - together with the parents from the ENCCA PPAC (Parent Patient Advocacy Committee) and the European branch of ICCCP (International Confederation of Childhood Cancer Parent Organizations) - developed a first outline of this Roadmap to address these needs over the next 15 years. Created within ENCCA to ensure the long-term sustainability of the project's results, the Working Group analysed the several challenges encountered by all actors involved in paediatric oncology, including patients, parents and survivors.

We are extremely glad of the broad consensus this Roadmap summary received during the SIOPE-ENCCA Conference. Today, we are ready to work together to ensure that this shared strategy will effectively achieve the key objectives for paediatric oncology research and care, allowing us to jointly trace the road ahead for paediatric oncology in Europe.

Gilles Vassal,  
SIOPE President

Ruth Ladenstein,  
ENCCA Coordinator





# Paediatric Haematology Oncology: the European Roadmap to Horizon 2020

## CANCER IN YOUNG PEOPLE IN EUROPE

### 1. Still a public health issue, despite high survival rate as compared to adult cancers

- Each year there are 35,000 new cases of cancer in young people in Europe (15,000 <15 years and 20,000 15-24 years).
- 80% can be cured with multidisciplinary treatments:
  - ▶ 300,000 - 500,000 EU citizens are paediatric cancer survivors;
  - ▶ 20 to 40% have treatment related side-effects.
- 6,000 young people die each year of cancer.
- Cancer is still the first cause of death by disease beyond one year of age in the EU.
- Cancers in children differ from cancers in adults, the most frequent being leukaemia, CNS tumours, lymphomas and neuroblastoma, with various age-dependent incidences. They occur from birth to adolescence.
- There are three groups of malignancies:
  - ▶ Those with a good prognosis (>85% 5-year survival) under current standard multidisciplinary treatments, using cytotoxic drugs in often an intensive mode (acute lymphoblastic leukaemia, lymphomas, retinoblastoma and renal tumours);
  - ▶ Those with a poor prognosis, around 60% as a whole (acute myeloid leukaemia, CNS tumours, neuroblastoma, bone and soft tissue sarcomas). Among those diseases, some have a very poor prognosis such as diffuse intrinsic pontine glioma, high-risk neuroblastoma and metastatic sarcomas;
  - ▶ The extremely rare tumours, for which there is a lack of information on their real incidence and survival.
- CNS tumours (33%), leukaemia (29%) and neuroblastoma (8%) are responsible for 60% of deaths by cancer from 0 to 14 years.

### 2. Unequal access to standard care and research across Europe

- 5-years survival is generally 10 to 20% lower in Eastern Europe, a disparity that becomes even larger for cancers with poor outcomes.
- Standards of care for paediatric oncology are established, but unequally applied across Europe.
- Teenagers and Young Adults (TYA) have a poorer survival rate than younger patients, and they also have very specific needs.

### 3. Little progress in difficult-to-treat diseases during the last 5 years

- Major progresses have been made over the last 50 years by using intensive cytotoxic chemotherapy regimens, including improved outcome in the poor prognosis malignancies, such as high-risk neuroblastoma (40% survival with highly intensive chemotherapy regimens including immunotherapy) and acute myeloid leukaemia (60% survival with intensive chemotherapy and allogeneic hematopoietic stem cell transplantation).
- Survival curves plateaued over the last 5 years for difficult-to-treat diseases, calling for innovative treatments with new mechanisms of action to control refractory and resistant diseases.







## PAEDIATRIC HAEMATOLOGY ONCOLOGY IN EUROPE

Paediatric haematology-oncology presents an extreme complexity in a rare population, with more than 60 different diseases from new-borns to teenagers (even more when biomarkers are considered).

### Strengths

- Private practice is not common (approximately 350 European public specialised centres in paediatric university hospitals and comprehensive cancer centres).
- Centres are coordinated at the European and international level for clinical research since 1968:
  - ▶ 40% of patients are treated within trials (Phase I to III);
  - ▶ 40% of patients are treated according to standard within prospective studies;
  - ▶ Mainly academia-led research, with less than 5% of pharma-sponsored trials.
- Paediatric oncology care and research are well integrated.
- Most clinical trials are run at the European level for each malignancy by the well-organized European Clinical Trial Groups (ECTGs).
- Strong awareness of the needs and challenges for survivors, with dedicated groups (PanCare) regrouping both healthcare professionals and survivors.
- Many high-level basic and translational research teams dedicated to paediatric malignancies.
- A community used to work together for more than 50 years, with a strong track record of publications.

### Weaknesses

- Fragmentation, in spite of a long history of networking.
- Struggling to run investigator-driven clinical trials since the 2001 EU Clinical Trial Directive. The new EU Clinical Trial Regulation is expected to facilitate academic research when it will be implemented (not before 2016).
- Still poor access to new drugs, despite the 2007 EU Paediatric Medicine Regulation (5-year survey on its outcome in 2013), which nevertheless changed the landscape of paediatric drug development in Europe.
- Insufficient integration between biology and clinical research, although there have been several successful FP5 and FP6 EU projects (KidsCancerKinome, EET-pipeline, etc.)

- Lack of sustained and sufficient funding, with competition for funding and need for prioritization.
- Disparity in Europe in regards to the implementation of research (clinical, translational and basic) and access to standard care, in particular for teenager and young adults.
- Paediatric haematology-oncology not recognised as a sub-specialty in most countries.
- Parents/patients organizations and survivors need to better join forces.
- Paediatric oncology grew and achieved successes so far in a relative isolation (as compared to adult oncology and paediatrics).

### Opportunities

- Major (current and upcoming) progresses in understanding paediatric tumour biology, through high-throughput technologies now widely available.
- Effective innovative therapies (targeted agents, immunotherapy) in refractory adult cancers.
- Paediatric haematology-oncology is part of the EU agenda, as illustrated by ENCCA – FP7 network of excellence structuring paediatric cancer research in Europe – and ExPO-r-NET, a DG Sanco project piloting the concept of ‘European networks of reference centres’ within the scope of the EU Cross-Border Healthcare Directive.
- Strong commitment of the Members of the European Parliament to support the paediatric haematology oncology agenda (the SIOPE-ENCCA-ICCCPO Manifesto for Paediatric Oncology).
- Parents and patients advocacy currently well organized in Europe (ICCCPO Europe), with parents, patients and survivors strongly committed and equal partners in the European care and research agenda.
- Charities in several countries committed to support and finance research programmes on cancer in children and teenagers.

### Threats

- Decision-making leaders at the European and national levels may consider that paediatric cancer is not a major issue (80% cure rate) and that all efforts should



be concentrated only on cancer prevention in adults and on transforming cancer in a controlled chronic disease in the ageing population.

- Current competition for funding projects and initiatives.
- The global economic crisis, impacting the capacity of several EU Member States to improve their healthcare system to deliver standard treatments for young people with cancer.

- Difficult access to essential medicines, due to drug shortages and to the high price of new medicines.
- EU regulatory initiatives which may negatively impact the implementation of the European agenda, e.g. the EU Data Protection Regulation currently under discussion.

## OVERALL GOALS AND OBJECTIVES

### The overall goals, until Horizon 2020 and beyond:

- To increase the cure rate in poor prognosis malignancies;
- To increase the quality of life in survivors.

### The 7 objectives:

- 1 Introducing safe and effective innovative treatments (new drugs, new technologies) in multidisciplinary standard care;
- 2 Driving therapeutic decision by improved risk classification and use of molecular characteristics (tumour, patient) – precision medicine;
- 3 Increasing knowledge on tumour biology and speeding up translation to the patients;
- 4 Increasing equal access across Europe to standard care, expertise and clinical research;
- 5 Addressing the specific needs of teenagers and young adults, in cooperation with adult oncology;
- 6 Addressing the long-term toxicity and cancer treatment consequences including the genetic background/risk – quality of survivorship;
- 7 Understanding the causes of paediatric cancers and setting prevention where possible.

### Key elements to achieve these objectives:

- Better integration, coordination and improved long-term sustainability of research at the European level, especially at a time access to EU funding is more fragmented;
- Commitment of all funding bodies to fund projects and structures (European Commission, national funding bodies, charities, industry);
- Strengthening the presence of paediatric haematology oncology in the European cancer agenda;
- A strong partnership with parents, patients and survivors, including better information;
- Better collaboration with adult oncology;
- Being part of the global paediatric oncology agenda and developing further collaborations with other continents;
- Intelligent partnerships with industry;
- Facilitating EU Regulations;
- Increased visibility through a more efficient and active communication strategy.

## OBJECTIVE 1: PRECISION MEDICINE IN HEALTHCARE

*Introducing safe and effective innovative treatments (new drugs, new technologies) in multidisciplinary standard care*

Innovative oncology drugs with new mechanisms of action are already available for adult cancers, and are often more effective in several refractory diseases than cytotoxic drugs.

The field of drug development is currently being enlarged, beyond signal transduction, to target host immune system, epigenetics and metabolism. Despite recent EU regulatory initiatives, access of children and adolescents to innovative therapies remains insufficient (ref. G. Vassal et al, *Lancet Oncology*, February 2013).



## Strategy

To run a new biology-driven drug development strategy by disease and across diseases, integrated into current therapeutic strategies and ongoing/planned clinical trials. Through inter-group coordination and using the principle of precision medicine, this strategy will provide a frame for efficient public-private partnerships with the pharmaceutical industry and for better Paediatric

Investigation Plan (PIP) evaluation under the EU Paediatric Medicine Regulation.

As an ENCCA deliverable, the CDDF (Cancer Drug Development Forum) paediatric platform was created in 2013 with the main stakeholders (academia, industry, parents, regulatory bodies) in order to make proposals for improving new oncology drugs development for children and adolescents.

## OBJECTIVE 2: PRECISION MEDICINE IN HEALTHCARE

*Driving therapeutic decision by improved risk classification and use of molecular characteristics (tumour, patient)*

Risk stratification is a hallmark of paediatric haematology oncology to adapt the intensity of treatment to individual risk of failure. It is part of standard of care, always based on disease extension and increasingly on tumour biology. Recent progress in the molecular classification of paediatric malignancies such as medulloblastoma, high grade glioma, ependymoma and rhabdomyosarcoma, will provide new biomarkers to be used in clinical practice in order to improve risk stratification and better adapt treatment to each patient.

## Strategy

To use tumour and host molecular profiling at diagnosis in order to improve risk stratification for adapted treatment by identifying:

- Patients with a high probability of cure with standard treatment who may be proposed new interventions to decrease the risk of late effects;
- Patients with a poor prognosis malignancy who may be proposed innovative therapeutic interventions to increase their probability of cure.

This strategy will be implemented by the European Clinical Trial Groups developing research in each paediatric malignancy, and it will be facilitated by the cross-tumour European platforms and programs set up within SIOPE.

## OBJECTIVE 3: INCREASE BIOLOGY KNOWLEDGE ON PAEDIATRIC TUMOURS

*Increasing knowledge on paediatric tumour biology and speed up translation to patients*

Cancers in adults result from a multi-step process, mainly under-exposure to external carcinogens (tobacco, alcohol, UV, diet, etc.) and often progress over many years. Paediatric malignancies however develop early in life and over a much shorter time period, suggesting that fewer and stronger events are required for progression. They are rare and they show fewer genetic defects and a lower genetic complexity as compared to adult cancers. Major progresses have been made in understanding paediatric tumour biology leading to the discovery of unique cancer hallmarks (Rb gene in retinoblastoma and, more recently, Histones H3 mutations in diffuse intrinsic pontine gliomas) that are involved as well in oncogenesis in adults. These progresses have already been turned into new classification of several diseases.

The challenge is to translate this new biology knowledge into innovative therapies.

## Strategy

- To use modern and innovative technologies to further decipher the mechanisms of paediatric tumour development and progression, exploring epigenetic regulation, interactions with microenvironment and immune system and role of metabolism.
- To speed up translation to the patients for improved tumour classification and specific, eventually efficient, innovative therapeutic interventions.

Within ENCCA (WP5), several tumour research networks are developed connecting basic and translational research teams with a common interest in each paediatric malignancy.



## OBJECTIVE 4: INCREASE EQUAL ACCESS TO STANDARD CARE, EXPERTISE AND RESEARCH

*Increasing equal access to standard care, expertise and research for all patients across Europe*

Treating children with cancer is a complex matter, and needs the expertise of a multidisciplinary specialized team. The European Standards of Care in Europe have been defined and a SIOPE survey within the EPAAC European project showed there is a wide disparity in implementing those standards of care in European countries (ref. J. Kowalczyk et al., European Journal of Cancer, December 2013).

### Strategy

To implement the European 'hub-and-spoke model' and to adapt it to each national context:

- A limited number of specialist centres (the hubs) are responsible for accurate diagnosis, risk-stratified treatment decision and complex treatments. They deliver standard care and treatment and run late Phase II and III European clinical trials.

- They liaise with local centres (the spokes) to share the patient care, providing less complex treatments such as simple chemotherapy and components of supportive care, along with careful monitoring closer to patient's home.
- An even more limited number of hub centres (expert centres) are also resourced to deliver even more specialized treatments requiring expert teams in, for example: complex surgery, high-precision radiation therapy in vulnerable locations, high-dose chemotherapy with hematopoietic stem cell support, access to innovative drugs in early phase trials, MIBG therapy for high-risk neuroblastoma and treatment for extremely rare cancers.

The ExPO-r-NET project, funded by DG Health and Consumers, is currently piloting the concept of a European Reference Network (ERN) in paediatric haematology-oncology, and it also specifically addresses the topic of extremely rare cancers and long-term follow-up.

## OBJECTIVE 5: ADDRESS THE NEEDS OF TEENAGERS AND YOUNG

*Addressing the specific needs of teenagers and young adults in cooperation with adult oncology*

Although cancer in teenagers and young adults (TYA) is rare, it is a substantial cause of death in this population. Outcome is poorer than in younger patients and several factors have been identified: the type of malignancies, their biology and sensitivity to current therapies, as well as the low participation of TYA in clinical trials. TYAs have specific and unmet needs, including complex psychological and social supportive care. Their 'interface' position between adults and children's services in the healthcare systems does not provide the context to optimally deliver multidisciplinary care and dedicated

research in order to improve their survival and quality of survival.

### Strategy

To develop a comprehensive multidisciplinary European programme, tackling all issues and specific needs of the TYA population as a joint integrated programme between paediatric and adult oncology, in strong partnership with patients.

Within ENCCA (WP17), a pilot project has been initiated in order to build the European Network for Teenagers and Young Adults Cancer (ENTYAC).

## OBJECTIVE 6: IMPROVE THE QUALITY OF SURVIVORSHIP

*Addressing long-term toxicity and cancer treatment consequences including the genetic background/ risk in order to quality of survivorship*

With an 80% cure rate, the number of childhood cancer survivors - presently estimated to be 300,000 to 500,000

in Europe - is likely to continue to increase and improving their quality-of-life is a major goal. It is anticipated in 2030 there will be around 750,000 European paediatric cancer survivors.

The PanCare network was created in 2008 to address this issue. PanCare is a pan-European multidisciplinary



network of health professionals, survivors of a paediatric malignancy and their families, who collaborate to reduce the frequency, severity and impact of late side-effects of treatment, with the aim to ensure that every survivor of childhood cancer receives an optimal long-term care.

### Strategy

- Increase awareness and facilitate research on childhood cancer survivors;
- Empower survivors to take the responsibility for their own follow-up, ensuring that they are well-informed on what to be aware of, how and when to access care and follow-up and who to turn to when and if they need and desire.

- Promote health organizations to address the issues of long-term follow-up and facilitate transition.
- Run prospective clinical research to reduce the likelihood of long-term toxicities in patients with a good prognosis malignancy.

Two ongoing FP7 European projects, PanCareSurFup and PanCareLIFE, carry out research on late effects. The pilot initiative of the 'Survivorship Passport' is being run thanks to the support of ENCCA (WP13) and PanCareSurFup, and the organization of care will be also addressed within the ExPO-r-NET project.

## OBJECTIVE 7: UNDERSTANDING THE CAUSES OF PAEDIATRIC CANCERS AND SETTING PREVENTION WHERE POSSIBLE

*Understanding causes of paediatric cancers and setting up prevention where possible*

'Why my child has cancer?' is a crucial question for parents, which most of the time receives no answer. Relatively few causative factors have been identified so far for childhood cancers. It is estimated that 4 to 8% of paediatric malignancies occur within a known genetic predisposition, and more that 20 genetic syndromes with a risk of cancer in childhood are known. The identification of the genetic basis of rare inherited cancers in children has revealed key pathways that are shared with sporadic tumours, even in adults. The whole genome sequencing will generate new knowledge to improve care and to

identify new genetic hallmarks of cancer to be turned into actionable targets for innovative therapies.

### Strategy

- To use the whole genome sequencing to further decipher genetic predisposition to paediatric cancers.
- To carefully address the pragmatic and ethical issues of genetic testing and counselling at a time DNA testing becomes widely available.
- To address questions on the environmental causes of paediatric cancer through scientifically-led and evidenced based studies.

## CONCLUSION

SIOPE and the European paediatric haematology community have defined within ENCCA the 7 scientific and medical objectives to increase the cure rate and to enhance the quality of cure for all patients and survivors over the next 15 years. The plan to implement this strategy (including tools, platforms, cross-tumour programs and funding strategy) is currently being finalized to warrant integration, facilitation, efficiency and quality, as well as to reduce fragmentation.

The commitment of all stakeholders (parents, patients, survivors, charities, national and European public bodies, policy makers, industry) will be essential and is a key success factor for the sake of children and young people with cancer in Europe.

The goal of the SIOPE-ENCCA Conference on 18th and 19th September 2014 is therefore to share and discuss this strategy with all stakeholders.



## Contact

SIOPE (SIOPE Europe)  
The European Society for Paediatric Oncology  
Web: [www.siope.eu](http://www.siope.eu)  
Email: [office@siope.eu](mailto:office@siope.eu)



ENCCA  
European Network for Cancer research in  
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Web: [www.encca.eu](http://www.encca.eu)  
Email: [encca@ccri.at](mailto:encca@ccri.at)

