

# Family hopes set on the oncopediatric research

Synthesis of the day of exchanges between  
Families and Searchers on Oncopediatry  
organized by UNAPECLE 13th February 2016 at the  
French Ministry of Social Affairs and Health





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[www.rencontres2016.unapecle.net](http://www.rencontres2016.unapecle.net)

## Recommendations and expectations to better anticipate the future

**UNAPECLE**

Union Nationale des Associations  
de Parents d'Enfants atteints  
de Cancer ou LEucémie

[www.unapecle.net](http://www.unapecle.net)



## acknowledgments

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## Introduction

This synthesis is the result of an important work which lasted for months; First of all, I'd like to thank, from the deepest of my heart, all those who contributed.

Firstly, families who answered all our questions, and those who came to get information and share their experience on that day of exchanges.

Many thanks to all those who contributed to the organization of that day, Le Ministère des Affaires Sociales et de la Santé (The Ministry of Social Affairs and Health), who put at our disposal their site and all the speakers of the day.

Thanks to all those who participated beforehand and overall afterwards, mainly Scien'Ass association which helped us all the way through.

Last but not least, thanks to Catherine Vergely who was the mainspring of all the different steps of the day , from preparation, through realization, to the analysis of all the information collected and to the writing of this synthesis in French.

In order to organize our day of exchanges around Research, we had decided to hold a survey on families and former patients, to find out what they had understood and what they expected from Research on children and teenagers 'cancers. We got over 200 answers.

The analysis of these results which will be found in this booklet allowed us to emphasize on four major themes on which people want to get information on and identify the best experts capable of presenting them:

- **The causes of cancers on children and teenagers**
- **Information on Research**
- **Ethics of Research on pediatric oncology**
- **And after ...**

This analysis gave us a first idea of questions people were asking to themselves, and it was enriched by the questions asked all through the day of exchanges. You will find them as well in the verbatims.

The objective of that day of exchanges was to highlight and draw the lines in which ill people and their families wish Research to be made and also to express their expectations and their suggestions in terms of simple objectives.

You will find all that in that booklet and I invite you to share them largely.

Frédéric Arnold, UNAPECLE President 2016

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## Chapter One

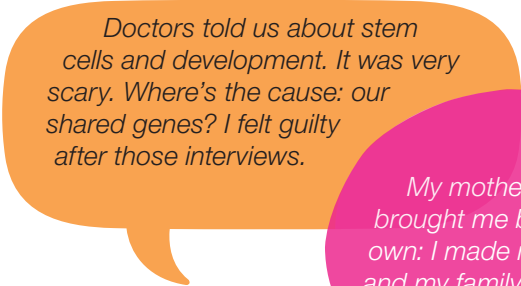
# Causes of Pediatric Cancer

« Your child has a cancer », the medical diagnostic is there. Leukemia, central system tumor, lymphoma, neuroblastoma, retinoblastoma, nephroblastoma, hepatoblastoma, etc, strange words with confusing sounds to name a life-threatening disease.


A disease that is inherently unjustifiable. From there, in what to hang on? All the testimonies express the chaos of the thoughts which insecure, anxiety and too often the feeling of guilt. Sooner or later, parents look for explanations that would allow them to put their child's illness into a story. Then, they wonder why.

## « Why is my child sick? What I have done wrong? »

The feeling of guilt is stronger because, in some cases, cancer can be hereditary. Then, the parents feel like that they are “bad” and accuse themselves of having given life to the disease:

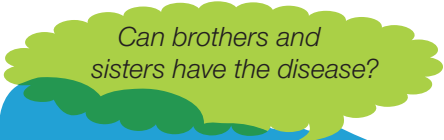


*Doctors told us about stem cells and development. It was very scary. Where's the cause: our shared genes? I felt guilty after those interviews.*

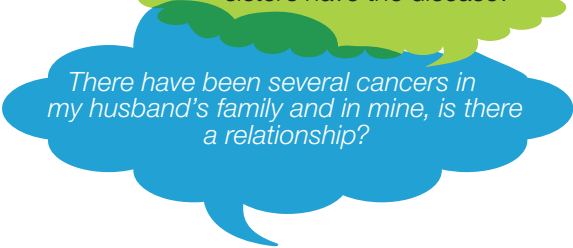


*My mother's guilt brought me back to my own: I made my parents and my family suffer with this disease*

To the guilt is added the anxiety of seeing the disease hit another member of the family:



*Can brothers and sisters have the disease?*



*There have been several cancers in my husband's family and in mine, is there a relationship?*

Sometimes, parents blame themselves in an unjustifiable way for not being protectors enough, for not being able to anticipate the disease, for not seeing on time their child's distress. They take on some responsibility for tumor process:

*If we had been able to identify the sign of the disease earlier, we might have been capable to prevent or reduce the severity of the cancer.*

*Can some cancers be related to stress and depression from the teenagers?*

To the guilt is added the anxiety of seeing the disease hit another member of the family:

*As for Epigenetic<sup>1</sup>, factors and environmental elements, can they influence on the development of the disease?*

*Can drugs taken before, during pregnancy and before conception for men, promote childhood cancer? The same question applies for tobacco and alcohol.*

*Why cancer with a good lifestyle?*

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<sup>1</sup> As opposed to genetics, epigenetics studies encoded inheritance in DNA. The challenge: understanding the transition from genotype (the set of genes) to phenotype (the set of traits of an individual).

The only certainty is that paediatric cancer is one of the so-called 'rare' diseases. A qualifier that, in parents' minds, involves a sort of shift from a feeling of guilt to a feeling of exclusion. Then, children are seen as different or even exceptional human beings since «rare» or isolated from the others. This term risks to limit the feeling of abandonment if research does not take hold of the fundamental questions asked by parents, their children and former patients.

## What we do know today about pediatric cancer causes?

Too little. And this worries parents and former patients. Concern is all the more legitimate since in many industrialized countries, the annual rate of new cases of pediatric cancers increased by 13% in the 2000s compared to the 1980s. This is shown in a study on *Incidence<sup>1</sup> International Infant Cancer (IIIC)*<sup>2</sup> published in April 2017 by the *International Agency for Research on Cancer (IARC - CIRC)*<sup>3</sup>.

After analyzing 153 cancer registries in 62 countries, departments and territories (about 300,000 cases of pediatric cancers recorded between 2001 and 2010), *IARC*'s discoveries are alarming. With children under 15, the annual incidence of cancer is 140 cases per million. Leukemia alone accounts for almost one-third of cases, followed by central nervous system tumours (20%) and lymphomas (12%). For children under five, one third of the cases are embryonic tumours (neuroblastoma, retinoblastoma, nephroblastoma or hepatoblastoma).

For teenagers from 15 to 19, based on records of approximately 100,000 cases of cancer, *IARC* reports an annual incidence rate of 185 cases per 1 million. Lymphomas are the most common (23%) ahead of carcinomas and melanomas (skin and mucous membranes cancers 21%).

Among the reasons given for the increase in the incidence of paediatric cancers over more than two decades, *IARC* suggests "Improving diagnostic techniques and early detection". In what proportion? *IARC* doesn't give an answer, nor does it provide answers on the links between pediatric cancers and the environment. This is not the objective of this study. Its objective is to provide the first pieces of information needed to promote research into the causes and implementation of pediatric cancer control.

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2 disease onset frequency index

3 « International Incidence of Childhood Cancer (IIIC), 2001-10 : a population-based registry study, and the IIIC-3 », Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, Hesselting P, Shin HY, Stiller CA, Published online 11 April 2017. <http://iicc.iarc.fr/results/>

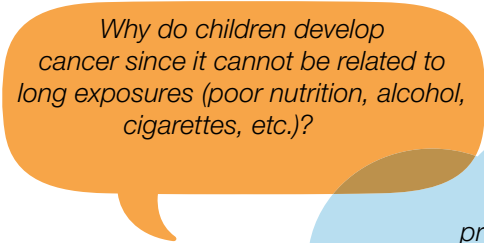
4 The International Agency for Research on Cancer (IARC) is an agency of the World Health Organization (WHO) based in Lyon. The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. IARC, involved in epidemiological and laboratory research, distributes scientific information through publications, meetings, courses and grants..

First, of all *IARC* wants “This unique global source of pediatric cancer incidence is being used for etiological research and to inform public health policy, helping to support one of WHO’s 17 Sustainable Development Goals: to enable everyone to live healthy lives and to promote the well-being of all people at all ages...”.

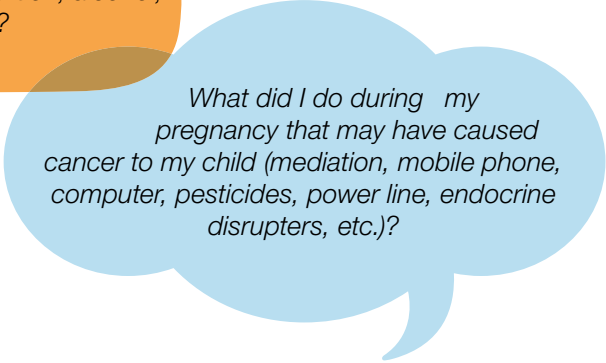
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## When the “why” question the answers given in the data

Epidemiological studies are increasingly providing information on risk factors and the likelihood of developing cancer on adults, but they are lacking in pediatrics.



*Why do children develop cancer since it cannot be related to long exposures (poor nutrition, alcohol, cigarettes, etc.)?*



*What did I do during my pregnancy that may have caused cancer to my child (mediation, mobile phone, computer, pesticides, power line, endocrine disrupters, etc.)?*

During discussions with families, the searchers were cautious in pointing out that cancer is a multifactorial disease of extreme complexity. Although the understanding of the role of environment and its potential interactions with genetic factors is currently the subject of strong international research, for the moment, the causes of children tumors remain mysterious.

Sometimes the signature of certain trends is quite obvious. For example, thyroid cancer is higher following the Tchernobyl nuclear accident in the region of Ukraine and neighboring countries. However, the role of ionizing

radiation, well established at high doses, is controversial at low doses. The risks of leukemia for children living within 600 meters of a high-voltage line are discussed according to the intensity of the magnetic field.

Exposures to pesticides (production, agricultural application or feeding) and benzene from high-traffic roads are also discussed without sufficient evidence to give rise to specific prevention measures. « *Nowadays, there is no solid, well-argued scientific evidence that would allow one or more environmental factors to be implicated in childhood cancer,*», explains Jacqueline Clavel, epidemiologist, searcher at the *National Institute of Health and Medical Research (NIHMR)*. And specifies: « *Even when a risk factor is identified, a constellation of other factors can increase this risk (exposure to asbestos, lead, chromium, etc.). This sometimes makes it possible to raise certain hypotheses. For example, long exposure of children to benign infections in industrialized societies could play a role in abnormal immune system reactions and cause allergies such as asthma or cancers such as Leukemia Aigue lymphoblastic (LAL)*».

There is also question about the effects of breastfeeding, parents' habits and consuming habits during preconception and early pregnancy (drugs, alcohol, tobacco, meat, grilling, etc.), on the impact of ovarian stimulation, anxiety, depression, stress. But here again, the answers are lacking. « *Numerous studies are being launched all over the world, but it is long, very complex. Research into the causes of paediatric cancer is like the work of an ant,*», notes Jacqueline Clavel.

## Answers from oncogenetic epidemiology

**What can be said?** A cancer is a genetic alteration (mutation, modification) of the cell with two consequences: promote tumour growth (oncogenesis) or, conversely, and oppose tumour transformation (tumour suppressor genes). During this process, most of the changes are referred to as « acquired » or « somatic » (non-communicable). However, some are present from conception. Consequently the term « constitutional » or « germinal » (transmissible) mutation is used. For example, a genetic disease such as trisomy 21 increases the risk of leukemia.

**What is new?** The involvement of acquired or constitutional mutations in the tumour process is the cornerstone of oncogenetic research. « *The development of high-speed analysis technologies already allows the study of a multitude of genetic variations. And with the new generation of DNA sequencers, thousands of tumours will be sifted through molecular biology and this knowledge will enrich international databases,* » explains Isabelle Janoueix, geneticist at the Curie Institute. One of the difficulties with these data masses, however, is to identify mutations that have an impact on the tumour process.

Created in 2008, the mission of the *International Cancer Genome Consortium (ICGC)* is to carry out the complete sequencing of the tumour genome of 50 types of cancers considered to be of greatest clinical and societal concern, and to allow availability to the scientific community to a database of characteristic somatic mutations. This inventory includes teams from a dozen countries. The French teams coordinated by the *INCa* are in charge of breaking through the secret of Ewing's sarcoma and retinoblastoma.

**What can be seen.** Prospects are gradually opening up for new cancer treatment strategies and the possibility of preventing them. « *Through studies of predisposition to adult cancer, the identification of known genetic abnormalities has in some cases led to research in the area of predisposition to childhood tumours.* », says Laurence Brugières, Onco-pediatrician at *Gustave Roussy Institute (IGR)*

The *Anaplastic Lymphoma kinase (ALK) gene* is a perfect illustration of this phenomenon. It is a tyrosine kinase<sup>4</sup> receptor present on the surface of cells that functions as a switch. Identified in large-cell anaplastic lympho-

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<sup>4</sup> Tyrosine's kinases are naturally occurring enzymes in cells. They are compared to switches activating or deactivating cellular functions, and are therefore the target of many drugs blocking this functions..

mas in 1994, the expression of ALK is now reported in a growing number of tumours, including the development of the most common extra-cerebral solid tumour in children, the neuroblastoma. « *Genetic analysis of more than 500 samples of neuroblastoma revealed that the alteration of the ALK gene was closely associated with the development of this pediatric cancer. The ALK receptor, which is constantly turned on, allows tumour cells to multiply continuously. Based on this finding, we have launched clinical trials with inhibitors to block this gene and thus reduce tumour proliferation (targeted therapies)*», explained Isabelle Janoueix, geneticist at the Curie Institute. On top of that, by studying the family forms of this tumour, the searchers also found that mutations in the ALK gene were transmissible. ALK is therefore a neuroblastoma predisposition gene.

« *The interest of working on genetic predispositions is to identify in families at risk, the children carrying this mutation and to offer them appropriate surveillance. This should allow for early diagnosis of the disease or, eventually, for patients to undergo treatment that limits the risk of a second tumour,*», says Laurence Brugières.

**What we hope for is** uncover the causes of the child's tumors. The validated catalogue of genomic alterations<sup>5</sup> specific to each type and/or subtype of cancer should open up a wide field of functional investigations. This would not only help to understand the role of alterations in tumour development, but also to develop new strategies for prevention, diagnosis and treatment.

As promising as it is, sequencing a gene that shows genetic variation between individuals is not all. If certain variations are associated with susceptibility, it will then be a matter of understanding how several variations can interact with each other. It is still too early to answer because, according to the searchers, some variations are difficult to interpret and their complexity increases with knowledge. « *Broadband approaches are fabulous, says Isabelle Jouaneix, they add another dimension, but the multifactorial nature of cancers and the combination of so many parameters are still very difficult to integrate.*».

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<sup>5</sup> genomics is a discipline of modern biology. It studies the functioning of an organism, organ, cancer, etc. at the genome level, rather than the scale of a single gene. The two branches of genomics: structural genomics (whole genome sequencing) and functional genomics (sequenced gene function and expression)..



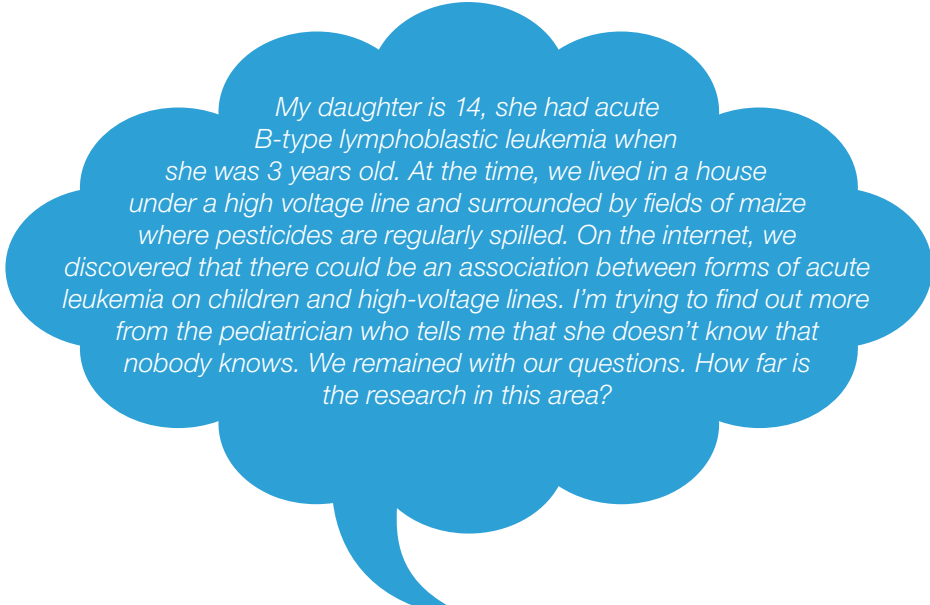
## Research into the causes of pediatric cancer remains the poor parent of cancer epidemiology.

Research into the causes of pediatric cancer remains a neglected area. However, it is essential for the prevention and detection of tumours that, diagnosed early, allow patients to live.

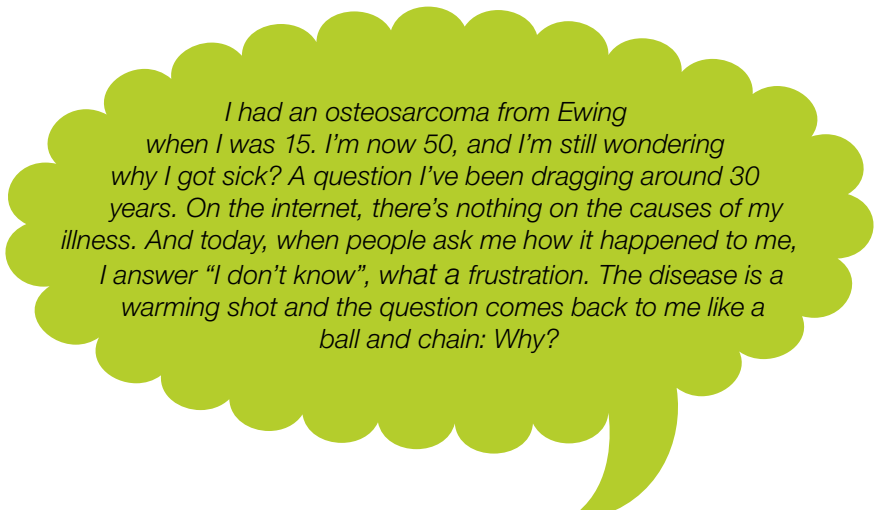
The implementation of the *Integrated Research Action Program (IRAP)* in pediatric cancer has raised a lot of expectations among parent's associations. As part of this scheme, a call for projects was launched in October 2016. Objective: to improve the management of children with cancer and, in doing so, to better identifies the causes of tumours. The announced ambition is to increase the state of knowledge at the interface of all disciplines: biology, clinic, epidemiology, humanities and social sciences (sociology, psychology, law, etc.), the economy and public health. So far, no study has been launched.

Overall, searchers regret the lack of funding, but also the lack of time. Compared to other countries, the organization of pediatric oncology in France doesn't allow doctors involved in day-to-day care, to have protected research times during which they could generate important biological or clinical studies. « *The INCa will probably help us a lot in terms of funding, but in terms of time, structural issues complicate everything. The project leader must devote 70% of his or her time to the clinical research project and this is only possible when a searcher initiates the research, but not when it is a doctor-Clinician,*», says Laurence Brugières.

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*My daughter is 14, she had acute B-type lymphoblastic leukemia when she was 3 years old. At the time, we lived in a house under a high voltage line and surrounded by fields of maize where pesticides are regularly spilled. On the internet, we discovered that there could be an association between forms of acute leukemia on children and high-voltage lines. I'm trying to find out more from the pediatrician who tells me that she doesn't know that nobody knows. We remained with our questions. How far is the research in this area?*



*I had an osteosarcoma from Ewing when I was 15. I'm now 50, and I'm still wondering why I got sick? A question I've been dragging around 30 years. On the internet, there's nothing on the causes of my illness. And today, when people ask me how it happened to me, I answer "I don't know", what a frustration. The disease is a warming shot and the question comes back to me like a ball and chain: Why?*

## A focus on ...

### Epidemiological research: how does it work?

#### **The first step is enumeration.**

All cases of pediatric cancers in a country are registered, characterized, and classified by pathology.

#### **Step two is about studies and surveys..**

They make a connection between a disease and an exposure factor. When the factor is determined, we talk about experimentation; For example, the link between cardiovascular disease and diet. Since, the difference observed is due to the exposure factor, the conclusions seem obvious. However, most of the time the exposure factor is random, so causality is difficult to determine. For example, an association between an exposure factor (tobacco with pregnant women) and a disease (fetal intrauterine growth retardation), does not mean that tobacco is the cause. Other (so-called confounding) factors differentiating between smokers and non-smokers should be identified and then eliminated.

#### **The third step is about descriptive studies.**

They indicate the frequency and variation of diseases per person (age, sex, etc.), duration, location (regional and international cross-sectional surveys). Results are given in incidence (number of new cases observed during a given period, (often the year), prevalence (number of cases at a given time), morbidity (number of deaths for a given period and population, sex, age, cause, lethality, deaths related to a given disease). Descriptive studies make assumptions, but do not allow for interpretation.

## Step four is about analytical or etiological studies.

They cover two methods:

1. **Case-control surveys:** selected population on disease (cases) and disease-free (control). Their aim is retrospective (from known disease to exposure). Objective: to collect exposure information and compare the frequency of exposure between patients and non-patients.

*Example. In the case of blood samples showing constitutional genetic factors, if 40% of the population carries a variant increasing the risk of cancer (almost one in two people) the question then is whether the environment has an impact or not.*

**Benefits:** cost, number of people (often used for rare diseases) and duration (no follow-up).

**Disadvantages:** minimum of two methodological bias.

- An observation bias. People may recall some exposures (corn field, power lines, etc.) and forget others, which is confusing to the extent that another unknown factor may still be involved (occupational exposure, home smoking, etc.).
- Bias in selection of cases and controls. How to select the sick person? Able/very ill, sex, etc. Where to find the right witnesses? Hospital, outpatient or general population. So many criteria will prevent the extension to the general population at the time of conclusion.

2. Longitudinal or exposed/unexposed cohort surveys. Their purpose is prospective (from known exposure to disease). The follow-up of a group of people, some of whom are exposed to a factor and some of whom are not, allows us to look at several diseases for which the factor studied could be a risk factor.

*Example: tobacco, ionizing radiation, magnetic fields, pesticides (exposures) associated with several diseases in the same cohort (coronary artery disease, lung cancer, bladder cancer, etc.).*

The results are most often presented in terms of relative risk, ratio.

**Benefits:** No bias as exposure is known at baseline and disease is analyzed upon arrival.

**Disadvantages:** the cost, the large number of people (not really suitable for the study of rare diseases) and the duration involving risks of «losing sight» before the end of the survey. This phenomenon is all the more frequent as the subjects included sometimes have to be monitored over several years before the disease occurs).

## Investigation of causes: time, complementarity and replication

To make the distinction between an epidemiological observation result and a result on a cause against which it is possible to place oneself, there must be replication between different populations, multi-year follow-up and complementary approaches with many disciplines including clinical medicine, genetic research and bio-statistics.

In France, the Hope-Epi program, financed by the Grand Borron, has set up a systematic collection of all cases and an epidemiological watch. Thus, each time a large number of patients appear in a region, a study is conducted to understand whether it is a random effect or whether there are possible causes. For example, work has been done to find a possible link between leukemia and high-voltage power lines or nuclear power plants.

There is no evidence at this point. It is true for endocrine disrupters, as well.



# Recommendations / Expectations: The cause for Pediatric Cancer

Pediatric cancers are rare and they have their own characteristics.

- • Consider childhood cancer as a specific research voice.
- • Establish and fund cross-cutting research programs combining different specialties as has already been done for rare, genetic or pediatric diseases.
- • Develop basic research combining genetics, epigenetics, epidemiology and clinical.
- • Conduct environmental studies that integrate illness aspects of children and share the results.
- • Better understand the origin of pediatric cancers to reduce parents and children's guilt
- • Associate parents, pediatricians, searchers, associations, etc. to carry out research projects to obtain faster results on complex subjects.



- • Create links between distant but complementary fields to understand the complexity of the problems posed : for example, between basic genetics and the humanities and social sciences or embryonic development and the occurrence of cancerous diseases on children.
- • Implement early screening, where possible, based on a better understanding of the mechanisms that can lead to the development of paediatric cancers.
- • Identify genetic abnormalities related to childhood cancers, measure their impact and develop new therapeutic approaches in pediatrics.
- • Ensure accurate studies to identify possible genetic predispositions to childhood cancer.



## Chapter two

# The right to information: the moment, the art and the way to say things

Since the Kouchner law of 4 March 2002<sup>6</sup>, information is a right in itself and searchers as well as clinicians are fully aware of it. And measure 7.13 of the Cancer Plan 2014-2019, says nothing else but that: “Making appropriate information available to patient and loved ones”. But medical information is a complex matter. It is plethora, uncertain, controversial and sometimes gives parents the impression of a “big mess” in which they get lost in a desperate quest for answers to their questions.

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<sup>6</sup> The law of 4 March 2002 enshrines in Chapter 1, under the title « Information for users of the health system and expression of their will.»

## Time for diagnosis: too much information at once

Because information is a right, the announcement consultation (flagship measure of the *1st cancer plan 2003-2007*) was put in place at the request of the patient associations and was deeply redefined by the last two plans (2009-2013 and 2014-2019). In pediatric oncology, this device has several objectives: to give a diagnosis, explain the management and present the *Personalized Care Program (PPS)*. The fact that the legal obligation to provide information is one thing, finding the words, the time and the way to make it accessible is another. Despite the progress made, progress still remains in that sense

Today, the announcement consultation condenses in a relatively short time a flow of information that parents are rarely able to receive, left alone assimilate the violence of the diagnosis itself-even plunges them into an emotional chaos. Whatever the intellectual level of the parents, the vital threat that suddenly falls upon their child, obfuscates their mental faculties:

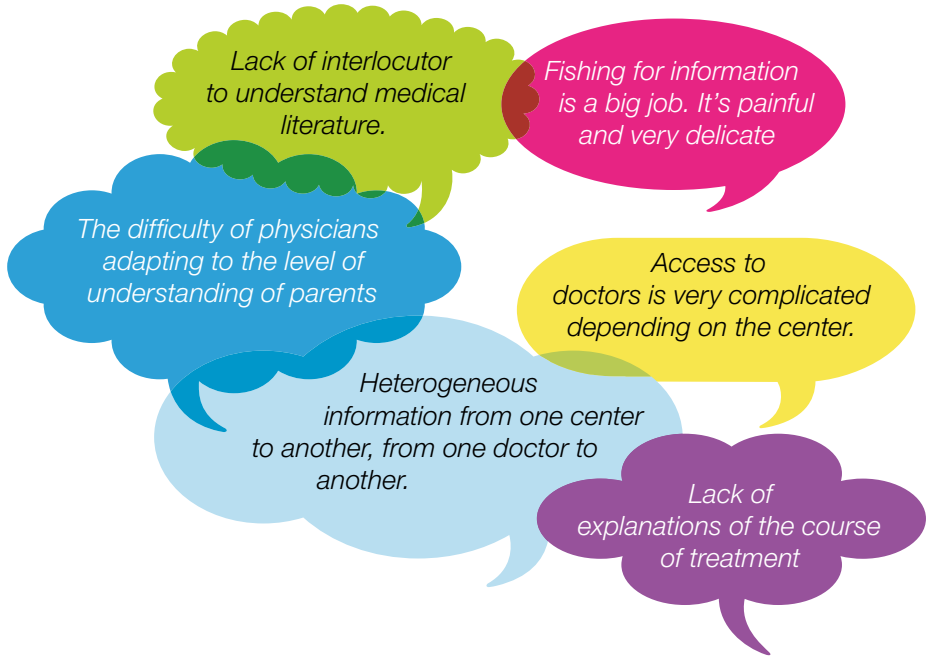
*For my daughter, I was told « biliary atresia ». I am a pharmacist, but it was extremely difficult remembering that barbaric name and memorizing the problem because I was shocked by the announcement. The doctor could have repeated ten times, twenty times, I couldn't hear anything and I was traumatized*

Most often, the desire to understand will appear later. The reflex of most parents is to consult internet:

*After the consultation, I wanted to know what this disease was; I searched in vain on the web.*

*I got some answers online, but they weren't all the same, so I got scared.*

Finding the right interlocutor to get reliable information is not that easy. Many families complain:



As a result, it is impossible to fully understand the situation. Faced with a lack of understanding of the issues to enable them to take informed decisions about what is good for their child, parents feel that they, on their own, stand with the crushing responsibility for possible bad choices: ***“We feel dispossessed of our role as parents”***.

It is also impossible for many parents to talk to their children about the disease as doctors recommend during the consultation. A recommendation that is all the more justified since the journey of treatment is often long and difficult with repeated hospitalizations, treatments or potentially painful gestures that require children to adapt constantly. But how can parents handle the questions that their child will not fail to ask? How can they find the words that will allow the child to assimilate the situation when they themselves are struggling in the jungle with meaningless terms which they don't understand? How can they tell the reality of the disease and its physical and psychological consequences, diagnostic procedures and therapeutics? How can they say aplasia, chemotherapy, side effects, pain, tiredness, cognitive impairment, care protocol, etc.?

## Access to treatment information: a journey for the fighter

In the medical decision-making process as it is currently recommended, the opinion of the experts is gathered during the *Multidisciplinary Concertation Meeting (RCP)*. In principle, this advice must be communicated and explained to the parents with the different treatment options considered and then discussed for a choice as far as possible. But in practice, unfortunately, this is rarely the case:

*I had to take notes, decrypt the information.*

*Some hospitals report on RCP, others don't. Why?*

*I had to cross-reference oncologists in four cancer centers to try to get a more or less global view of the treatment, its benefits, and its side effects.*

*Communication about what has been decided is done without any written support; it is oral and not complete.*

*The treatments and their progress are not very formalized.*

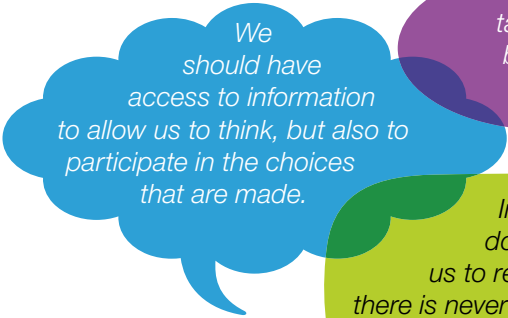
The problem is the same for *Personalized Care Program (PPS)*. For most parents who have had a *PPS* in their hands, the written document produced with specialized terms is incomprehensible. Franck Bourdeaut, Pediatrician oncologist at *the Curie Institute* notes: « *We might think to have passed on information that, in our opinion, corresponds to what we intend to do, but it is illegible to non-specialists. Therefore, even a written document should be translated with comprehensible words*».

In addition, many parents do not dare to ask questions for fear that their questions will be taken as an assault that could have an impact on their child's care.

## Parents and health professionals: two logics whose balance remains to be found.

Translating the lexical fields of pediatric oncology is essential, but it cannot be done without the contribution of parents, because sharing a common lexicon is not enough, doctors and parents need to agree on the ideas that each of them has in mind.

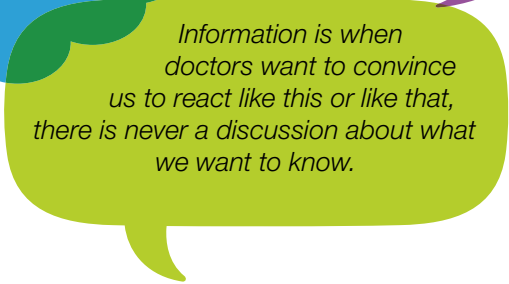
Parents expect a genuine health democracy that will allow a process of adjustment of the therapeutic issues:



*We should have access to information to allow us to think, but also to participate in the choices that are made.*




*The media keeps talking about health democracy, but when our children are sick, I don't know where it stands*



*Information is when doctors want to convince us to react like this or like that, there is never a discussion about what we want to know.*

Many parents are shocked to find out after the decision taken that other care protocols exist.

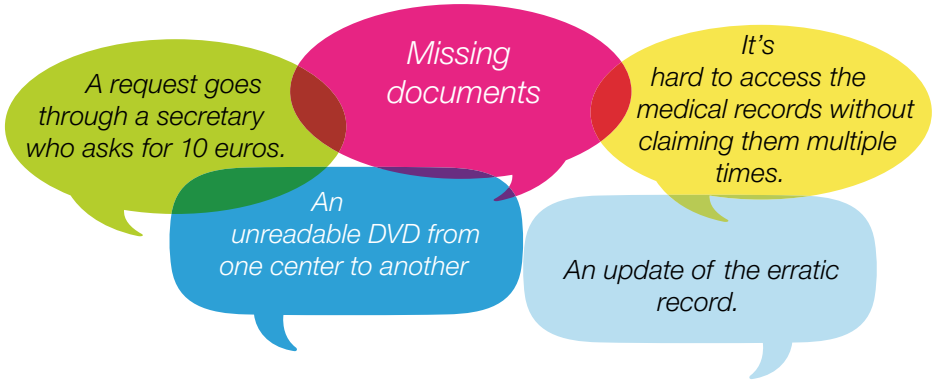


*After starting the first therapeutic protocol, we are told another one is applied in other centers. I would have liked to know beforehand*



*At the time of treatment, we discover divergent opinions. At some point, we wonder if truth isn't elsewhere*

Look for another truth, a double opinion, requires having the complete medical record of the child. But again it is not easy task:



High-speed information techniques and the right to information could disrupt the situation between doctors and parents. But even nowadays, nothing has changed or so little. To change the tendency, it is urgent to change the reflex, to change the scale in the way of understanding and managing information sharing.

Among the questions that parents legitimately ask themselves:



All these questions are recurring, Volona Rabeharisoa, sociologist at the School of Mines in Paris, believes there should be an answer to what parents want to understand through a thematic directory compiled collectively (patients, families, searchers, clinicians, psychologists, sociologists, etc.) « *Parents are competent enough to ask the right questions, find the*



*right answers and evaluate them. This work consisting in formalizing information can only be the result of collective work ».*

In all cases, mediation by parent associations would facilitate exchanges between physicians and families. A way to avoid discomforts, misunderstandings, latent conflicts, worries and risks of not negligible loss of confidence.

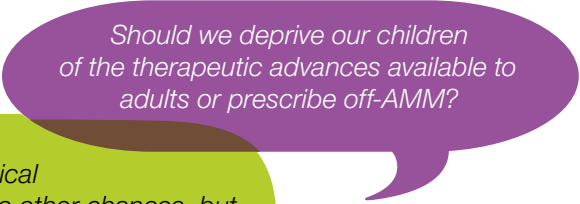
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## Lack of accessible information on research progress

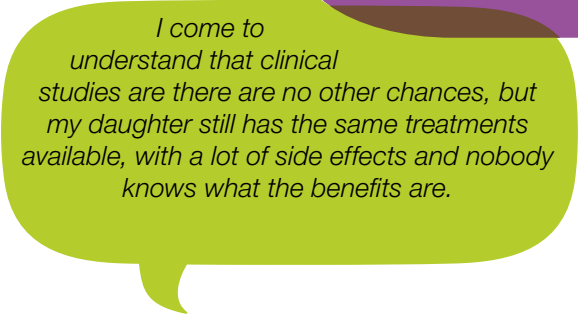
The combination of increasingly effective chemotherapy, the collaborations between the different fields of pediatric oncology and the emergence of innovative therapies have allowed an undeniable advance in the overall survival rate of children.

However, pediatric treatments are still carried out today with molecules developed for adults. Doctors have, of course, learned to adjust dosages through a lot of research. But, from birth to adolescence, children differ from adults, their physiology and tumors are different and most adult cancers do not exist in children.

This situation too often refers to an alternative which, in its presentation, seems disarming, even despairing:



*Should we deprive our children of the therapeutic advances available to adults or prescribe off-AMM?*



*I come to understand that clinical studies are there are no other chances, but my daughter still has the same treatments available, with a lot of side effects and nobody knows what the benefits are.*

To get out of this unbearable alternative, parents appreciate the invention of therapeutics adapted to children and want to be part of the research to accelerate their progress:

*Can we imagine a large national or even European body managing all child cancer research projects in which patients and healed adults could participate?*

However, being truly involved in research and having a chance to be heard, parents need information. **That's where the shoe pinches. And pinches three times:**

**The first one** is on the nature of the therapeutics administered:

*Had I been told clearly how clinical study works and had I been told a site listing the ones that are in progress, I would not have wasted time and energy?*

*We need to know exactly what treatment our children are taking.*



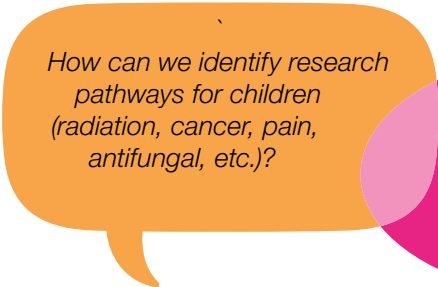
**The second one** is on the lack of feedback on the results of clinical trials in which the child was involved:

*Research with a positive or promising result is done in France, but the feedback remains confidential. Why?*


*How is feedback made on experience after a research protocol?*



**And last but not least** the lack of visibility of research taking place in France or elsewhere:




*How can we identify research pathways for children (radiation, cancer, pain, antifungal, etc.)?*

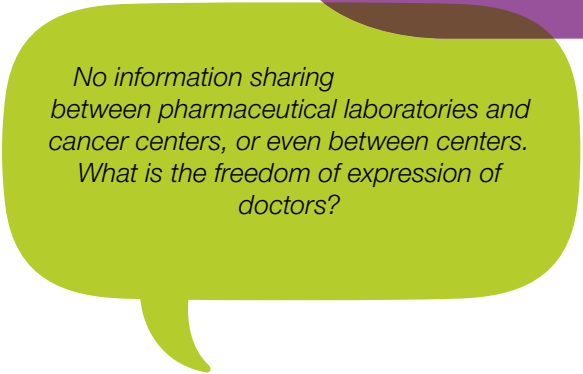


*Where and how can we find reliable information about ongoing research and advances in treatment?*

This lack of information has the perverse effect of doubt in people's minds:



*Arent's research projects only intended to allow publications highlighting their authors?*



*No information sharing between pharmaceutical laboratories and cancer centers, or even between centers. What is the freedom of expression of doctors?*

## How could parents express themselves as counterparts with searchers?

To move forward pragmatically on both sides, the challenge would be to have the right tools to understand how basic research, applied research and clinical research currently work.

Parents don't ask for greater protection for the weak people they represent, but how to make the weak people become stronger. This creed alone sums up the "*States General of children, teen agers, young adult and their families*" which took place throughout France in 2010 and whose White Paper enabled the public authorities to become aware of the urgent need to take better account of the demands of parents of children suffering from cancer.

Since then, there have been initiatives to increase the capacity of pediatric cancer to provide children with a better chance of recovery. Just let them bear fruit.

Among these initiatives, the *INCa Early Stage Centers (CLIPP)*: « *The recent introduction of CLIPP in pediatrics should allow children to integrate studies of innovative molecules and fill the gap in feedback to children themselves and their families.*», says Fabien Calvo, cancer specialist, Scientific Director of Cancer Core Europe.

And he adds, « *Information is at the heart of our research project*».

## Medical information between uncertainty and controversy

Here again, the problem stands for clinicians this time, since the information from the doctor to the biologist and the feedback from the biologist to the doctor is sometimes very complex to apprehend: « *There is a data interpretation problem that concerns information on basic research, so-called applied research and clinical research*», says Fabien Calvo.

In the case of advanced treatments, the information remains complex and delicate to handle for healthcare professionals, given the areas of uncertainty in therapeutic responses and their evolution. It is the learning by doing for patients, parents and caregivers. « *Research is going in all directions and on a wide variety of pathologies. It is clear that we are not always the most knowledgeable interlocutor in laboratory research*» says Franck Bourdeaut, Oncopédiatre at the Institut Curie.

The level of uncertainty and the quality of the relationship between families, patients, physicians and searchers is at stake. How to share and to what extent uncertainty should be shared? When a decision has to be made, should it be mentioned? Should other options be offered to parents when the decision has been taken? Franck Bourdeaut said: « *Not all physicians react the same way and this adaptation to parental expectations is something that needs to be worked on with associations*».



## A focus on ...

### What is the status of pediatric cancer research?

The development of medical products in pediatric cancer shows a certain delay compared to adult cancer, since pediatric indications are not considered a priority by pharmaceutical laboratories. *The Pediatric Cancer Research Strategy*, led by the *National Cancer Institute (INCa)* as part of the *2014-2019 Cancer Plan*, is based on three complementary pillars:

- complete genome sequencing of child tumors by the end of the Plan and seek new therapeutic targets;
- promote innovative clinical trials on children, based on a national collaborative group of pediatric hematologists and oncologists, researchers and parent's associations as well as a territorial structuring of Early Phase *Clinical Trial Centers in Pediatrics (CLIP)*<sup>7</sup>. L'INCa is negotiating with the drug industries to encourage them to systematically offer their molecules to children as part of the CLIP program.
- Support the revision of the European Regulation on pediatric medicinal products to make the regulation more incentive for clinical trials of new molecules. The development of pediatric cancer drugs has been announced by international public and charitable organizations, funding cancer research from 23 countries, as one of the five research priorities for the coming years.



[www.unapecle.net/actions-unapecle/plan-cancer/](http://www.unapecle.net/actions-unapecle/plan-cancer/)



[www.e-cancer.fr/Plan-cancer/Plan-cancer-2014-2019-priorites-et-objectifs](http://www.e-cancer.fr/Plan-cancer/Plan-cancer-2014-2019-priorites-et-objectifs)

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<sup>7</sup> The CLIP was the subject of a call for applications for labelling in 2014 in order to extend their skills to childhood cancers. Six CLIP are open to early-stage clinical research in cancer-ropedia since 2015..

## INTERVIEW

Daniel Oziel from Eurodis

*Eurodis is a non-governmental alliance representing 792 rare disease patient associations in 69 countries, representing the 30 million people affected by rare diseases in Europe.*

### **The Internet has revolutionized everyone's approach to information: how to make it out?**

**D.O :** Information sources are varied and widely spread. Even on the most reliable sites, the information is not exhaustive. One clinical trial for example, appears in four major sources around the world. The largest and most comprehensive one is the Clinical Trials (200,000 clinical trials in more than 200 countries). Then come France, the *CNIB Online Registry* and the *ANSM Directory*<sup>8</sup>, and last the European Register of Clinical Trials.

Concerning the clinical trials currently underway on neuroblastoma, Clinical Trials lists 14 clinical trials, compared to 10 for the European registry, six for the *INCa* and zero for the *ANSM*. It is difficult to say to a parent: " here is the right source"

Another problem is updating information as it takes time and money. This is the reason why for several years training courses have been launched on all aspects of information retrieval. When the sick person, the parents, the relatives acquire this competence, they can find their way more easily in the care system, have better exchanges with the health professionals. It is about sustaining health democracy in which searchers, doctors, the sick people and their families are seen as counterparts.



*Clinical Trials* ..... [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

*European Register of Clinical Trials* : ..... [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu)

*INCa - RECF* : ..... [www.e-cancer.fr](http://www.e-cancer.fr)  
Register of clinical trials in cancer in France

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<sup>8</sup> ANSM : National Agency for the Safety of Medicines and Health Products



## A focus on ...

### Online discussion platforms

A discussion platform enables the development of community spaces. In most cases, it is supplemented by information modules: testimonials, expert opinions, topical texts, etc. Platforms where patients and those who help them can share experiences and information include:



**RareConnect** ([www.rareconnect.org](http://www.rareconnect.org)). Dedicated to rare diseases, the platform is led by patients and patient associations collaborating with EURORDIS (European patient association) to create patient communities and provide moderators from their network.



**Cancer Contribution** ([www.cancercontribution.fr](http://www.cancercontribution.fr)) its mission is to bring together patients, doctors and political leaders to change laws and attitudes.



**Médicaliste** ([www.medicalistes.fr](http://www.medicalistes.fr)) proposes to facilitate communication between people affected by a rare, serious or chronic disease, through; in particular, discussion lists in order to participate in the development of a collective knowledge associating patients, family members and doctors. Pediatric cancers are among the discussion lists.

*Access to information on ongoing research today doesn't really exist and when it exists, it is incomprehensible. I even looked for contacts in pharmaceutical laboratories to find out if there were any new existing treatments. Of course, I used Internet and found everything and nothing. When I came across the Curie site, I found a list of studies in progress, it was unreadable.*



# Recommendations / Expectations

The right to  
information: The time,  
the art and the way of  
doing it

- • Facilitate the visibility of associations in the hospitals. Encourage the teams to talk about the associations and to transmit their names and telephone numbers and the information materials they publish.
- • Allow the sick people and their families to have access to reference information popularising the technical and medical environment in the form of glossaries and written materials accessible to families, but also to children (comic books such as « Gaspard chemo » or « Roby Radioqui »).
- • Identify and set up people to refer to for families in services and associations for consistent and shared information. An essential function to guide families and answer their questions ; it saves parents a lot of time and energy.
- • Involve parent's associations in a partnership with health care teams to ensure that patients and their families receive appropriate information, particularly on the key stages of illness.
- • Model and share the associative experiences that work in the field of disseminating information on ongoing research and its results.

- • Encourage and facilitate the involvement of associations in scientific meetings and decision-making bodies of research programs. The involvement of families and patients is essential both in terms of discussions and of decisions. It helps research, government funding, the dissemination of medicines and so on to make considerable progress
- • Take the opportunity of the research already undertaken to extend it to the field of pediatric oncology : for example, model the associative experiments that have allowed to move forward with the research workers on transversal subjects : genetics, pain, etc.
- • Identify reliable information and create a database collected by associations via through laboratories and research institutes: a kind of big data per cancer accessible to the public.



## Chapter three

# Pediatric Oncology Research, Ethic

*« We didn't know that samples could be retained and used for research.»*

*« Are all the steps of our child's samples recorded somewhere? ».*

**Having little or no knowledge of the history and fate of the biological samples taken from their child and the accompanying date, parents sometimes face painful situations that they deal with difficulty:**

*« Several months after my daughter died, the department where she was treated asked if we would agree to give her samples. We were shocked».*

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9 Research ethics are about clinical trials and biobanks.

## From sampling to biobanks

For diagnosis purposes or in the course of care, the taking of blood, DNA and any element or product of the human body, as well as the associated personal data (clinical, genealogical, biological, lifestyle, etc.), are collected and stored in biobanks. *«The samples are kept after diagnosis for forensic reasons, but also for research purposes»*, explains Marie-France Mamzer searcher in medical ethics at the Paris Descartes laboratory. She added: *«All the samples, some of which were once considered as waste (urine, stool, for example), are now preserved and are likely to be of interest to non-interventional research<sup>10</sup>. Biomarkers can be defined from samples, which can be used to identify, track or evaluate the response to a treatment»*.

Biobanks are the keystone of translational research<sup>11</sup>, and offer hope that will enrich the state of knowledge in the field of biological and medical sciences. Already, this link between basic research and clinical applications has paved the way for diagnostic methods, novel prognostications or predictions and innovative therapeutics such as targeted therapies or immunotherapy.



<sup>10</sup> Retrospective non-interventional research doesn't focus on individuals, but on existing data and/or biological elements.

<sup>11</sup> In medicine, translational research allows either to develop clinical applications based on a discovery in fundamental research, or to promote the exploration of new theories or concepts from a clinical observation.



## Free and informed consent: a pillar of the ethics of research involving the human body<sup>12</sup>

All research involving the human body is subject to the national and international ethical and legal rules in force<sup>13</sup>. The free and informed consent of the individual or their legal representatives is one of the pillars.

In accordance with the principles of personal autonomy, inviolability and integrity of the human body, the collection of consent by the searcher<sup>14</sup> or by a physician representing him or her is mandatory. To do this, the research framework, the purpose of the method, the degree of uncertainty in the outcome, the fate of the samples and the data acquired must be clearly explained. In most cases, written permission is requested. *«Research from biological samples and testing from any sample can only be done with the explicit consent of the patient or the parents when it comes to children»*, says Marie-France Mamzer.



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12 Research involving the human person\* replaces the notion of "biomedical research" and refers to any trial or experimentation organized and practiced on the human being, for the development of biological or medical knowledge, Law no. 2012-300 of 5 March 2019, known as the "Jardé Law".

13 At the international level: Article 25 to 32, amendment October 2013 of the Helsinki Declaration of the World Medical Association adopted in June 1964. In Europe: Chapter II, Oviedo Convention for the Protection of Human Rights and the Dignity of the Human Being with regard to the Applications of Biology and Medicine. In France, principle of the Bioethics Act of 29 July 1994 laid down in Article 16-1 and 16-3 of the Civil Code.

14 Investigator: Medically qualified person responsible for conducting the research

## Protection of personal data: warning points

Under medical secrecy, the protection of individuals and their privacy, the processing of personal data associated with the samples is also subject to consent. *«It is forbidden to use this data for any other research purpose without a new consent from CNIL<sup>15</sup>»,* says Eric Charikane, an expert in personal data management.

Moreover, anonymization of personal data is a mandatory principle to avoid any misuse (exploitation for commercial purposes, discrimination from employers or insurers, etc.).

*But in practice this is not always the case. Many infrastructures continue to work according to a still very artisanal mode. Witness, Stéphanie Doniau, Study Engineer at INSERM<sup>16</sup>: «The anonymization of the samples is not always done. I get angry when I see a label with the name of the patient. I cannot understand how the anonymization of samples is still not permanent».*

However, anonymization cannot be everything. According to Eric Charikane, *«The effectiveness of protection systems cannot be totally guaranteed and this calls into question the principle of justice and non-discrimination which refers to the use of data and their control. Today, some companies have tools to analyze and understand the content and keywords of a message. One must therefore be vigilant about the transmission of data that impact privacy, because data are not forgotten, they can be processed and re-worked».*

In addition, all users of connected objects give information about themselves worldly accessible to both private companies and public authorities. *«If physicians have a duty of confidentiality and want to use secure messengers»,* says Charikane, *«All the data we produce ourselves can tell a lot about our health. For example, when someone uses his /her mobile phone or a free service provider, the destination of the messages and their content are all accessible data. And this data is collected, monitored and controlled. One must remain vigilant because anonymity is less and less available».*

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<sup>15</sup> Commission national de l'informatique et des libertés (CNIL) from France. This independent administrative authority ensures that information technology does not undermine human identity, human rights, and privacy, individual or public freedoms. It shall carry out its tasks in accordance with Law No 78-17 of 6 January 1978 as amended on 6 August 2004 and shall incorporate in May 2018 the new European Directive adopted in April 2016.

<sup>16</sup> INSERM, National Institute of Health and Medical Research

How can the exchange of information be organized and a high level of personal data protection ensured?

*This issue is part of the new provisions of the General Data Protection Regulation (RGPD)<sup>17</sup> repealing Directive 95/46/EC which provides for a portal for submitting projects at European level.*

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From the samples taken from research results, what is the feedback for patients?



For parents and former patients, the feedback of their contribution to research is a matter of trust, transparency, sharing, dialogue, reciprocity, communication and respect. There are fundamental values that, according to them, involve all those involved in research. **« We are people, not research objects and this raises the question of the place of patients, families in research protocols.»**

In order to be truly enlightened and to put themselves in the position of actors, parents and former patients feel that feedback of information implies two lines in the protocols of consent. First, add: **«agree to be taken, yes/no»**, then they consider it appropriate to add **« I would like to have general information on the follow up that this research may have given , yes/no»**.

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<sup>17</sup> The General Data Protection Regulation (GDPR) No 2016/679 repeals Directive 95/46/EC on the protection of natural persons with regard to the processing of personal data and on freedom of movement. Its provisions will be directly applicable without transposition in the 28 Member States of the European Union from 25 May 2018. [www.cnil.fr/fr/reglement-europeen-protection-donnees](http://www.cnil.fr/fr/reglement-europeen-protection-donnees).

## The rise of biobanks

Over the past 20 years, the rise of new technologies has led to a massive development of biobanks, accumulating an ever-increasing number of collections of samples and associated data. These infrastructures have acquired an unbelievable scientific potential.

Collections can be mutualized in the context of national or international research, supporting ever more efficient analytical techniques. *«Under biobanks, nothing is lost, everything is digitized, computerized and kept », Eric Charikane says. «Consent is an ongoing issue for clinical trials and biological specimens. It is also a question of data collection and use: what is impossible today might become possible tomorrow.»*

Can the relationship with the body, unavailable and not seen as a commercial object be rethought in terms of solidarity through the sharing of biological collections and the personal data that accompany them? Can these collections be considered as common heritage?

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## The notion of consent challenged

*Thirty years ago, my parents signed a document that allowed bone removal to participate in research. Could a new search be requested? How long is the permission to keep part of me?*

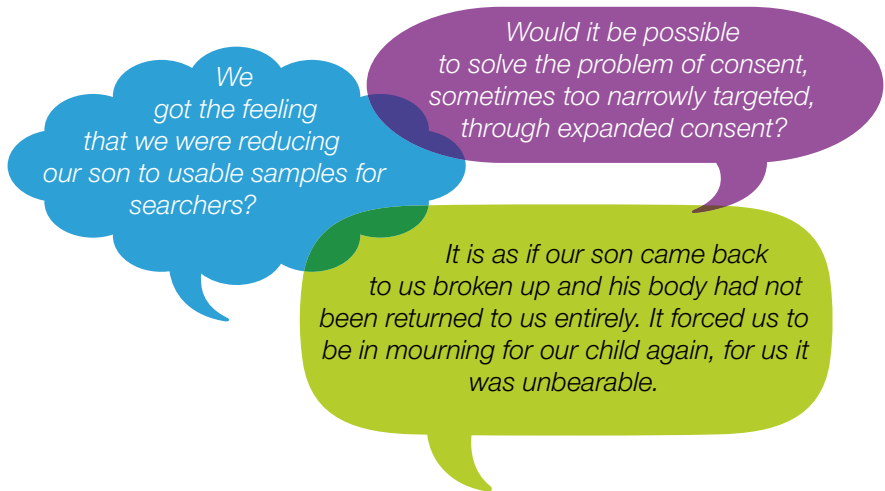
*Three years after my son's death, we received a handwritten letter from the oncologist asking for permission to use samples from our son stored when they were taken for medical research.*

Taking into account the possibilities for the shelf-life of samples for multiple use, evolving or even unknown uses at the time of consent, the application of the ethical principles underlying consent (freedom of choice, autonomy, protection of privacy and personal data) is being breached. *«The law requires that the individual has access to explicit consent for what he or she proposes to be involved in. But the spirit of the law is not at all adapted to current research practices and this is a blocking factor»*, egreets Marie-France Mamzer.

So how can anticipation be seen as a dimension of ethics applied to biobanks? Could participation in a biobank be subject to consent, rather than the intended use of the samples? Which ethical body independent of the biobank could then be responsible for decision-making?

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## Towards an Extension of the Scope of Consent



Physicians and searchers are currently faced with an important dilemma: samples exist and their origin is known, but they cannot be used without the consent of the patient or his family. This means reconnecting with the people concerned without knowing their psycho-social situation. The interest of informing the course of a sample before consent. The importance of building trust between donors and biobanks in general, and searchers and physicians in particular.

Today, research is based on a double level of regulation. An individual level, in the name of respect for the principle of autonomy, with a graduation adapted to the degree of competence of under 18 and the commitment of the responsibility of the parent. A collective level assumed by the research regulatory bodies in the first place, *the Committees for the Protection of Persons (CPP)*<sup>18</sup> responsible for issuing an opinion on the conditions of validity if any research involving the human person (prior explanation, collection of consent, exclusion period, reflection period, relevance of the research and admissibility of the benefit/risk assessment).

As part of an extended consent. *«Not only searchers fully required to explain to the patient and/or their family that the studies will be conducted in relation to the pathology, but at each new research, they also commit themselves to asking for the advice of a CPP. The preparation of the initial document is then elaborated according to the nature of the research envisaged, and the searcher MUST inform the patient and/or his family»*, Marie-France Mamzer summarizes before urging parents and former patients to take part in the CPP: *«it would be appropriate for the construction of the criteria to be established with the representatives of the associations. Their presence is important in the CRUCQ (User Relations and Support Quality Committee), but also in the CPP. Those are essential places to invest in research fields, but also to organize and contribute to reflection on the ethics of research. We clearly need you»*. And Francois Doz, a pediatrician at the Curie Institute, insists: *«it is essential that representatives or parents have a leading place in the design of pediatric oncology research such as the Retinostop association<sup>19</sup> that is involved in the design of the protocols we propose at the Curie Institute.»*

If this is also the wish of the associations, One must note the difficulty they sometimes have in being admitted in certain instances: *«Our participation is not accepted everywhere. But our experience and the information we bring back from the field are of value»*.

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18 The Committees for the Protection of Persons (CPP) are covered by articles L 1121-1 to L 1126-11 of the Public Health Code..

19 Retinostop: French association on retinoblastoma, retinal cancer, disease affecting children

## Literati: Explain the incomprehensible

*Since it was to treat him, we signed it. I don't even know what it was used for, I have the impression that it was mostly for them.*

*I lost two children with lysosomal disease, I learned to understand the content of a protocol, but it's not obvious, it has to be made comprehensible.*

*We signed a lot of papers when our child was involved in a therapeutic trial. We didn't understand anything.*

*There is a lack of communication about research and child management. But above all, there is a lack of ability to communicate, which is tragic.*

Any research involving a human sample requires parents to be sufficiently informed about the entire research procedure, its purposes, benefits and risks. Consent is conditioned by the clarity of the explanation that will be given. However, it is difficult to explain the complexity of the tools and techniques used and the value of obtaining results that will be expressed as risk factors.

However, written consent alone is not sufficient, to a consent as clearly written as it is and cannot be spared a process of oral exchange and validation of the understanding of what has been expressed.

It takes time to do research, but it also takes time to really get informed consent. *«A whole field of research must be developed today in partnership (searchers, doctors, patients, associations), which is that of health literacy and digital literacy<sup>20</sup>»,* says Marie-France Mamzer.

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<sup>20</sup> Health literacy: motivation and skills of individuals to access, understand, evaluate and use information to make decisions about their health.

Digital literacy: the ability to participate in a society that uses digital communications technology in professional, educational, cultural, leisure, civic spaces and homes. Using, understanding and creating are the three key digital literacy skills..

Behind these communicative issues foreshadows research ethics, justice and equity. The majority of parents and former patients agree that *«physicians and searchers need to improve their ability to communicate»*. An ability to develop not to speak to their peers but to speak to people who don't have the level of health literacy that allows them to exercise their independence, access the services they need and to which they are entitled.

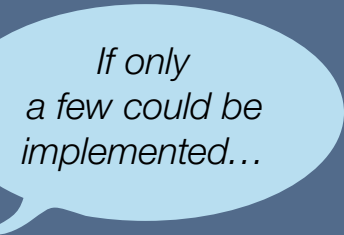
However, it is not easy to communicate the ethical implications of the conservation and use of biological samples, the risks, benefits and social consequences, cultural and economic that it represents. What has to be done now is to find tools, relays, support and language elements that will make explanations accessible to all. Once again, mediation with parent associations could be a relevant relay.





# Recommendations / Expectations

## Pediatric Oncology Research Ethic



*If only  
a few could be  
implemented...*

- • Establish disease partnerships, families' searchers on upstream ethics, during and after the research to regularly question the dangers and potential risks of scientific advances applied in Oncopediatrics without blocking them by inappropriate regulation.
- • Organize thematic working groups on the ethics of Oncopediatrics research bringing together parents, caregivers, philosophers, psychologists, searchers, doctors, etc.
- • Revisit bioethics legislation to regulate new practices in the areas of biomedical research (interventional and non-interventional). Within the framework of the States General of Bioethics that are currently taking place, the debates focus on clinical trials, PMA and organ donation and do not deal with this problem.
- • Define a regulation of practices for the conservation and use of human biological samples and to ensure that they are communicated to sick people.

we  
*believe...*

- • Measure the governance of bios banks to ensure their quality and ensure that they participate in a real breakthrough for people (physical integrity, freedom in choices and decisions).
- • Go beyond legal consent so that patients and their families receive clear and transparent information to help them understand the issues of the research they consent to (the research framework, the purpose of the method, the degree of uncertainty in the outcome and the data acquired). Mutualize resources and expertise in favor of Oncopediatrics research: Developing databases to facilitate their analysis and encourage the exchange of information between searchers and institutions.
- • Improve communication between health professionals and searchers: training and transmitting good practice: training through companionship and integration of health literacy.
- • Mutualize resources and expertise in favor of research in Oncopediatrics: developing databases to facilitate their analysis, promote the exchange of information between searchers and institutions.





## Chapter four

# And after...

*Because it is not enough to care for children, It is also important to ensure a good quality of life for the adults they will become, supporting them after the disease is one of the priorities of the Cancer Plan 2014-2019<sup>21</sup>. From the identification of long-term complications, emerged the need to organize follow-up procedures: “various devices are in place or are gradually being organized under the influence of the French society for the fight against childhood and teenagers cancers and leukemia’s and the *Institute National of Cancer (INCa)*”, says Natalie Hoog-Labouret, head of pediatric research at the l’*INCa*.*

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21 Action 8.2 of the 2014-2019 Cancer Plan: “Structuring long-term monitoring of children and adolescents”

## «If we are here, it means there's an afterlife»

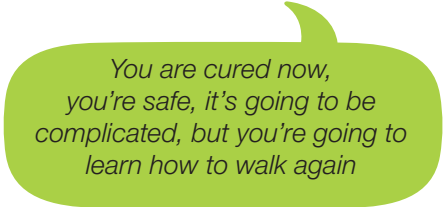
With the revolution of chemotherapy, the greater effectiveness of radiotation therapy, the advances of surgical techniques, living long after pediatric cancer is no longer exceptional. For all tumours and at all ages, the five year survival rate has improved significantly in recent decades and now exceeds 80%. 83% for children under 15 81.8% for teenagers 15-19<sup>22</sup>.

Globally , a child or a teenager is considered as “cured” when his /her life expectancy is similar to that of a population who, at the same age, did not develop a cancer (on average, five years after diagnosis or three years after the end of treatment ).

It is a fact that over the years, the rate of cure increases. However, this word would really take on its full dimension without the physical and psychosocial complications, responsible for more or less severe handicaps weighing on the quality of life.

The price for cure remains high for many of the former patients.

*30 years ago, I was diagnosed with Ewing's sarcoma on the right iliac wing. I had the part of my hip that was affected by cancer removed, I had chemotherapy, I had a transplant and then I was told :*



*You are cured now, you're safe, it's going to be complicated, but you're going to learn how to walk again*

*At the end of my cancer, I was not told that while growing up I would have pain because of these operations and problems with chemotherapy.*

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22 Cancer in France, 2016 report, CNIB, Institute national of cancer



## The legacy of Treatment

*My son was nine years old when he had cancer. His growth was stopped by radiation therapy. And now he is completely deaf from the right ear, and partially deaf from the left one.*

Treatment in pediatric oncology may include chemotherapy or/and radiation therapy or/and surgery. And depending on their specificity and dosage, all these treatments have long-term effects. According to Odile Oberlin and Brice Fresneau, pediatric oncologists in charge of the long-term follow-up clinic at the *Gustave Roussy institute (IGR)*: « *Some complications can be asymptomatic for decades. Sometimes, the effects occur at the end of growth, or only in adulthood*».

Thanks to the epidemiological studies carried out in France and abroad, many of these complications are now known from Oncopediatrics.

Radiation therapy can lead to risks of hormonal disorders (growth retardation delayed or advanced puberty) and hearing loss. But also risk of Cardiovascular Stroke or thyroid dysfunction when the rays were aimed at the head and/or neck; diabetes in the abdomen, and so on...

Studies also show the deleterious effects of some chemotherapy. Depending on the type of tumour and stage of disease, cancer patients including platinum salt, for example, may be toxic to the kidneys and/or hearing function. At high doses, other chemotherapy treatments have the potential to destroy or alter the quality of the reproductive cells.

Odile Oberlin and Brice Fresneau agree that: « *The risk of developing a second cancer favoured by treatment is rare, but possible. However, the children of many former patients are doing well and have no more malformation or cancer than the general population*».

## Genesis of follow-up consultations in Île-de-France

In the 1990s, INSERM established a cohort<sup>23</sup> including former patients treated at the IGR and the Institute Curie. Early research focused on the carcinogenic effects of radiation therapy. The following were used to establish a list of indicators of epidemiological risk: risk of developing heart disease, cerebrovascular disease, second tumour, and so on... As a result of this research, implementation of long-term follow-up consultations was required.

It then became necessary to contact all former pediatric cancer patients in childhood, some of them were difficult to find for a long time, others had moved,. But finding them is sometimes complicated; young women had married and changed names, etc. *« In 2000, the Health Insurance Fund, which considered long-term follow-up of patients to be important enough, obtained by ministerial order the authorization to communicate new addresses of former patients. 84% of them were found»,* reminds Odile Oberlin *« We sent them a first letter to find out if they agreed to the process, followed by a 50-pages survey with informed consent. 88% responded, representing three-quarters of all treated patients».*

In 2010, a 18 month experimental phase was launched in the pediatrics department of the IGR. *« During this phase, 330 former patients came to see me. Their average age was 38 years, almost 32 years after their cancer»,* explain Odile Oberlin and Brice Fresneau, both involved in the implementation of the device. They added: *« Sometimes patients didn't know their history and some didn't even know they'd had a cancer. In that case, it really was a dramatic announcement"».*

At the end of this experimental phase, follow-up consultations were held in various dedicated centers in Île-de-France.

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<sup>23</sup> Cohort: group of people considered together and participating in a statistical study of disease onset circumstances

## The three stages of a follow-up consultation in Île-de-France

**First stage of the consultation, a psychological interview** allowing to listen to the feelings and, if necessary, to detect a psychic suffering and to support a work of reorientation towards a proximity professional: « *Problems with disability, fertility, working life and the psychological consequences of treatment often lead to long discussions*», says Oberlin.

**Second stage: jointly led by an oncopediatrics and general practitioner** involved as a local reference: The detail of the nature and consequences of the treatments. « *A number of patients feel lost and want to make contact with their pediatric oncologist*», notes Odile Oberlin. This is an opportunity to review their case in depth, to learn more about the treatment received and to ask questions.

**The third stage is personalized follow-up recommendations..** « *Depending on the treatment received during childhood or adolescence and the current state of health of the former patient, his medical, personal, family history, and so on..., personalized recommendations are detailed in a follow-up file*, says Brice Fresneau, «*At the end of the consultation, this file is given to the patient and, with his agreement, sent to the attending physician in network with various health professionals who will have to intervene within the framework of these recommendations*».

Odile Oberlin and Brice Fresneau insist on the importance of the involvement of the general practitioner in the follow-up of people who are receiving specific treatment for sometimes severe sequelae. He often has a good knowledge of the socio-family context; best ensures the overall management of these people at risk and the coordination of the different actors of the management. It therefore seems essential to provide him with information on the specific effects of treatment received in childhood, knowledge that is often lacking given the rarity of this situation in his list of patients. « *The role of the attending physician general practitioners is therefore important even if they themselves most often admit to need help in organizing the follow-up*»

## Consultations widely approved by former patients

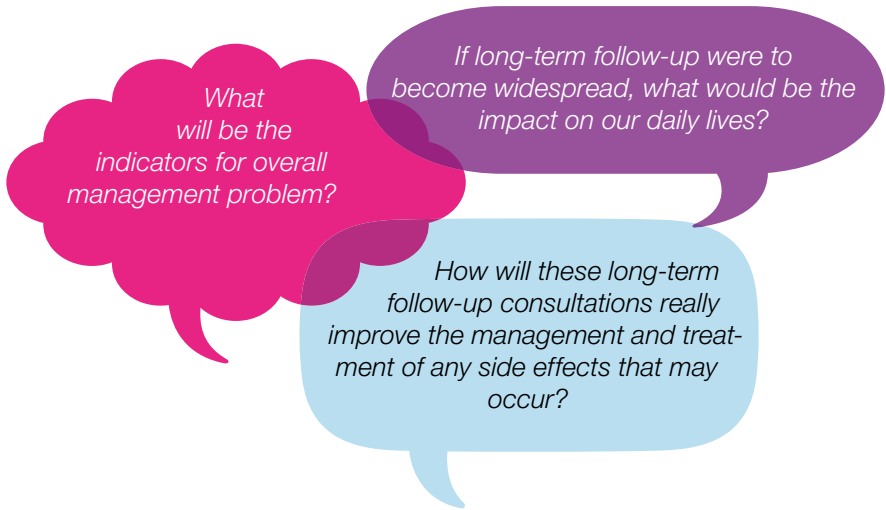
On the whole, the former patients who benefited from a follow-up consultation appreciated it:

*The recommendations are made with a follow-up that encourages us to be pro-active in our own health.*

*Three years ago, IGE called me for a long-term follow-up consultation. At that time, they warned me of the secondary risks associated to treatments: problems with heart thyroid, hearing, and so on... 20 years later, I know where my pain comes from. This consultation is a very good thing but it makes me furious. If someone had explained things to me earlier, it might have saved me some stress and some anxiety, as associating a new pain with the symptom of a new tumour waking up.*

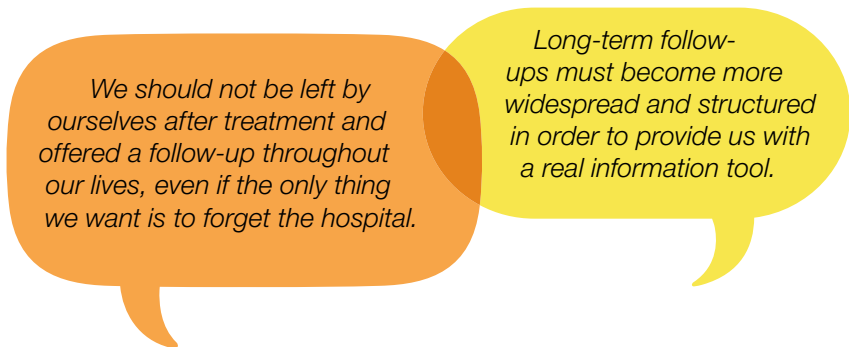
These anxieties, which arise as soon as a pain occurs, undeniably change the way of thinking one's daily life. And to a certain extent, follow-up consultations can also relieve the elderly from often unfounded worries, perceptions exposed to dramatizing amplification, to anguish. Then there is the question of access for everyone to these consultations.

Some former patients legitimately wonder about the impact of these arrangements:



These issues raise the issue of people's commitment to long-term follow-up, but also the limitations of long-term follow-ups. It is a question of discerning legitimate and effective incitement from unreasonable harassment.

Everybody agrees on the need for long-term support, right from the end of treatment, when leaving the hospital:



Another argument in favor of long-term follow-up is the progress of knowledge:

*Without long-term follow-up, how could oncologists cross-reference pediatric cancer data and establish a state of knowledge about the side effects of long-term treatment?*

*How could general practitioners better take into account the symptoms that develop over the years?*

*How could pharmacovigilance be operational?*

*How can psychologists, sociologists and health economists understand the impact of cancer on our lives?*

Long-term follow-up: a process that is slow to become operational

*How to meet the people to offer them consultations?*

*Will this follow-up be globalized nationally for all former patients?*

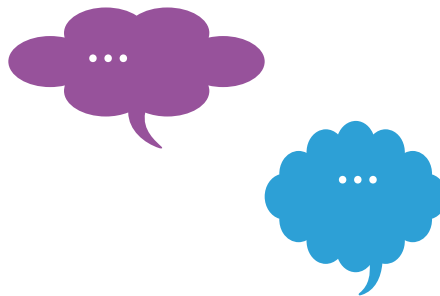
*How is it going to be for patients who've been followed in other hospitals, will they be contacted again?*

*Which centers have a long-term follow-up consultation?*

*In Paris, the IGR and the Curie Institute are referenced centers for long-term follow-up, that's great, but how does this follow up become a generality in all small provincial towns?*

When the follow-up consultation was set up in Île-de-France, the first invitations were addressed to patients with a high risk, mainly those who had received brain, mediastinal, or anthracycline radiotherapy. « *Today, important work needs to be done to make the long-term follow-up consultation obvious for everyone. This is far from the case. Currently, people who have been treated outside the pediatric oncology unit are not called in*, Brice Fresneau points out. Moreover, he adds: « *the very sustainability of these arrangements is not clear yet. Associations and institutes have a role to play in reversing the trend*».

Natalie Hoog-Labouret focuses on the time and diversity of initiatives: « *The Third Cancer Plan focuses on the Personalized after Cancer Program (PPAC) and intends to integrate pediatric specificity. In fact, it is expected that the long-term follow-up consultation will be included in a specification, in a routine and will be valid for all; but it will take time for its implementation. In addition, consultation is not necessarily the only model to follow. Other projects are also supported by the INCa. At least five other experimentation programs are in sight. In northern France, a program focused on social reintegration, for example*».



## The impact of pediatric cancer on life trajectories

Former patients have a lot to say about how cancer is present in their every day life.

Especially when, because of the consequences of the treatment received twenty or thirty years earlier, it forces the person to become handicapped:

*I always worked full-time. Despite the pain and the exhaustion, I used to rush. Today, I only work 24 hours a week, but I work and that's the main thing. I had to do a recognition of disabled workers, an application for a disability card, so the MPDH, I had to go through all the paperwork. Unfortunately, you have to go through this honestly to know what it is like.*

*When it impedes procreation and then adoption:*

*Twenty-four years ago, chemotherapy was done in an emergency, not enough time to take an egg sample, so i'm sterile. Nine years ago, we wanted to adopt a child. The adoption process is already very complicated, but with cancer, it's very hard. Luckily, we finally managed to adopt a boy who's six now. And then, two years ago, we wanted to start the procedure again, but again, cancer is still a problem, we'll have to go back to a child psychiatrist again, and so on...*

Former patients would also have much to say about how the experience of pediatric cancer has shaped their social and professional activity. On how it influenced their perception of health, their relationship to relatives, to parents. On the future of their emotional life.



One of the big problems right now is the lack of psychological follow-up for family and siblings.

Today, cancer is part of my life, it comes back to me all the time. Treatments have cured me but they have also hurt me. The consequences of ablation of the right iliac and chemotherapy make me limp and I have orthopedic problems. I live with a cane and the pain center.

Living after cancer and living with treatment-related complications are complex concepts for which research in the *Humanities and Social Sciences (SHS)* could provide knowledge to document the life trajectories of people with pediatric cancer. Lessons could be drawn to improve the long-term follow-up of psychosocial risks, to better understand and prevent them. But this research is still too rare, notes Martine Brungener, Sociologist and economist at the *CNRS (National center for Scientific Research)*, she says: « *Research in the humanities and social sciences must be firmly rooted in participatory reflection and debate, collaboration with patients and patient associations who have their word to say on the very purpose of the research, on the problematics to be built and on the methods to be developed*».

For information, Martine Brungener indicates that “quality of life” is a new field of research that opens in the sociology of chronic disease or disability: « *it could also open up in the psychosociology of post-cancer. The question would then be what is a “good life” despite pediatric cancer, despite the sequelae of treatment. It would also be a question of understanding better the value of the notion of quality and of knowing who decides for this value, former patient or/and institutions?*».

*In 1992, I had Ewing's sarcoma to the right iliac bone, I was 16.*

*I had chemotherapy, an autologous and a right iliac ablation that was extremely painful.*

*For 9 months, I had to learn how to sit, how to stand, how to walk. Because I was a happy character, they didn't think I had a psychological need. That was a big mistake, but it was like that.*

*After the cancer, I was left alone; I was never told I was cured but it doesn't matter. I still believe.*

*My daughter is 16, she has finished treatments for lymphoblastic leukemia a year ago. The oncologist gave us a prescription for a cardiac ultrasound and it was marked in brackets anthracycline. On the internet, we saw that there were a long-term risks. To think that maybe in 20 years she will develop something else again, it was a big shock.*





# Recommendations / Expectations

And after...

- • Generalize long-term follow-up consultations and ensure the sustainability of existing arrangements.
- • Facilitate the involvement of general practitioners in the organization of side-effect follow-up consultations.
- • Build with the public authorities the indicators of long-term follow-up consultations to think of the content of these consultations, on the creation of a medical diary and on a professional network with treating physicians trained to improve the follow-up of everybody.
- • Set up a platform on the net with permanent exchanges with oncopediatric, general practitioners, psychologists, so as to answer questions from former patients.
- • Inform former patients of the benefits of entering the world of disability, which opens up rights and opportunities for work and social inclusion despite red tape and stigma. Advocate that the “right to be forgotten” of former patients applies to those who wish to adopt a child.

- • Organize a network of « worried watchmen » in France and Europe so that powerful cohorts can be funded with a view to launching qualitative work and associated trauma. On the impact for a sibling to have a brother or sister sick especially when a person doesn't mention the diagnosis. The impact of a child's illness on the lives of parents, the couple, etc.
- • Translate the studies on the effects of long-term cancer treatments written in English and entrust the dissemination of them to the associations of former patients to make the results of the research accessible to all.
- • Make a comprehensive synthesis of social science research on life with chronic diseases and use the results as a basis for study for this multi-faceted pathology, then identify the most specific questions to open up new fields of investigation and new methodologies. Cancer could then appear as an archetype of chronic disease that serves as an example for many of these works. Adults who have been treated for pediatric cancer have for some years had their own demands developed by the experience of daily living to organize , sometimes according to the sequelae of treatments or disease. Their intimate and legitimate wording completes that of the parents and creates a prospective for actions to be built once again in common.

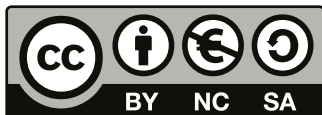
- • Develop a network of former adult patients through the association “Les Aguerris” to find peers to help create a community of experts.
- • Share a common experience with similar feelings not to stay with unanswered questions : Forum des Aguerris, afterworks (informal monthly meetings between aguerris), scientific network with oncopediatric, doctors, parents, etc.
- • Inform former patients of long-term consequences of treatments received through national conferences that answer shared questions (social-professional problems, disabilities, medical follow-up, fertility, insurance, and so on...)
- • Have access to one’s medical records and require reliable information for each patient about the treatments received and their long-term effects in order to adopt an appropriate and preventive lifestyle and prevention.







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thanks