PROJECT FINAL REPORT

PanCareLIFE

Grant Agreement number: 602030
Project acronym: PanCareLIFE
Project title: PanCare Studies in Fertility and Ototoxicity to Improve Quality of Life after Cancer during Childhood, Adolescence and Young Adulthood
Funding Scheme: HEALTH.2013.2.4.1-3 Investigator-driven supportive and palliative care clinical trials and observational studies
Project Start Date: 1/11/2013
Project End Date: 31/10/2018

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1 Final publishable summary report

1.1 *Executive summary*

The number of survivors of childhood cancer in Europe has steadily increased as therapies and supportive care have improved. Survival rates after childhood cancer now reach and exceed 80% in developed European countries. However, the treatments that have improved survival are harsh and cause serious late effects that can greatly reduce the long-term quality of life of survivors. It is estimated that **as many as 75% of survivors will have experienced at least one late effect** by middle age.

Learning more about late effects is important so that we can learn how to provide survivors with the best possible long-term follow-up care. It is important for survivors and their families who live the reality of survivorship, as well as for healthcare systems that must deliver follow-up care to an ever-increasing number of survivors. Through research, we can develop clinical guidelines that help healthcare professionals know what care is needed, for which survivors and when so that they can help survivors to manage their own health in the long-term. We can also develop new treatments that cause fewer late effects and learn which survivors are at greatest risk for late effects so they can be carefully followed for early diagnosis and treatment. The goal of PanCareLIFE is to **help survivors of childhood and adolescent cancer to face fewer late effects and enjoy the same quality of life and opportunities as their peers who have not had cancer**.

The rarity of childhood cancer and differences in the way that information about cancer and survivorship is collected across Europe make it hard to study late effects. **The information provided to PanCareLIFE by survivors is a valuable resource for pioneering studies of late effects**. In our secure central data centre in Germany, there are now records from over 14,000 survivors from Germany, Denmark, the Netherlands, France, Switzerland, Italy, the Czech Republic, the United Kingdom, Poland, Austria, Norway and Israel, including information from hospitals, clinics, cancer registries, patient questionnaires, hormone analysis, genetic testing and hearing tests. To make sure that this valuable data can be re-used in future and to help other projects studying late effects, **PanCareLIFE has also focused on developing a consistent approach to collecting and sharing information that other researchers can follow in their own studies**.

In PanCareLIFE, we have focused on three important late effects: fertility impairment, hearing impairment (ototoxicity) and quality of life. Using the large amount of data collected, we have conducted **research to identify ways to improve care for survivors and treatment for future childhood cancer patients**. For example, what we learn will help doctors pick treatments with the lowest risk for fertility problems for girls and young women who are about to start cancer treatment and counsel them about what options are available to them. For survivors who are now adults, our research will help doctors to provide better information on future parenthood and discuss fertility preservation options. We are also developing recommendations for standardised hearing tests for before, during and after treatment in order to support better follow-up care, as well as developing recommendations for how quality of life should be routinely monitored following clinical trials and cancer treatment in hospitals. **Improvements to quality of life will benefit both survivors and society**, as survivors will be better able to remain productive members of society, requiring less support from families and other carers.

Sharing what we have learned is an important part of PanCareLIFE, so we have **actively communicated our work to key stakeholders**, including other European cancer projects and organisations for survivors of childhood cancer and their families. Through the PanCare network, from which the project arose, we

have reached out to a wide network of researchers and survivor advocates, hosting a joint Closing Conference at the end of the project where we shared our results with survivors and their families, policymakers, physicians, nurses and researchers. We will also publish our findings and work to see them improve clinical care, clinical trials and future research.

1.2 *A summary description of project context and objectives summary*

Survival **rates after childhood cancer are nearly 80% in more developed European countries** as a result of more effective therapies and better supportive care. Due to this increase in survival rates and a gradual increase in how many children get cancer, the number of childhood cancer survivors is steadily growing. In Europe, it is estimated that there are between 300,000 and 500,000, so that approximately 1 in every 640 adults is a survivor of childhood cancer.[1]

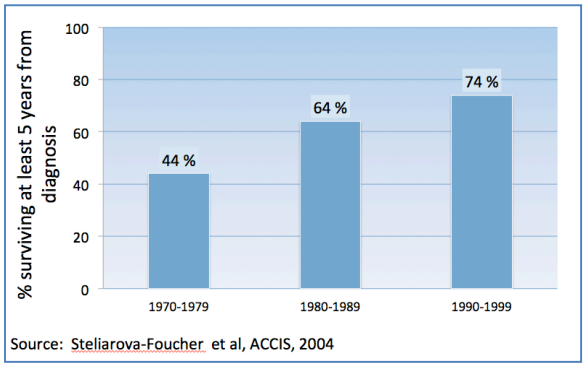

Figure 1 Overall 5-year survival after cancer during childhood and adolescence in Europe

However, the treatments that have led to increased survival rates are harsh, and their long-term complications can be serious. Over 25% of childhood cancer survivors have a severe or life-threatening adverse event,[2] which include another cancer or heart disease. But many more, perhaps **as many as 75%, have at least one late effect**,[3] including fertility or hearing impairment and reduced quality of life. Late effects can seriously impact on survivor's quality of life, and the growing number of survivors with late effects puts a strain on medical and psychosocial health services, which will increase into the future.

Research is urgently needed to better understand late effects, why they occur, and how they can be prevented or treated, as well as to develop recommendations on how to educate, counsel and monitor survivors for late effects during follow-up care. Drug development and clinical trials can also benefit, as it may also be possible to develop cancer treatment protocols with at least similar survival rates but fewer late effects.

PanCareLIFE originated from the PanCare network (www.pancare.eu), a multidisciplinary European network of professionals, survivors and their families that **aims to reduce the frequency, severity and impact of late effects, with the goal that survivors should enjoy the same quality of life and opportunities as their peers who have not had cancer**. The project brought together a team of European experts in the fields of epidemiology, clinical medicine, audiology, and genetics to study three late effects that can seriously affect survivors' quality of life - fertility, hearing impairment (ototoxicity) and health-related quality of life (HRQoL).

In order to learn more about late effects, we first needed to **collect information from a large group of European survivors of childhood, adolescent, and young adult cancer**, called a "cohort". We needed a large cohort because childhood cancer is rare, and while many survivors have a late effect, the number

[1] Childhood Cancer Survivorship: Improving Care and Quality of Life. Institute of Medicine (US) and National Research Council (US) National Cancer Policy Board; Hewitt M, Weiner SL, Simone JV, editors. Washington (DC): National Academies Press (US); 2003.
[2] Oeffinger, K.C. et al. Chronic Health Conditions in Adult Survivors of Childhood Cancer N Engl J Med 2006; 355:1572-1582
[3] Geenen, M.M. et al. **Medical assessment of adverse health outcomes in long-term survivors of childhood cancer.** JAMA. 2007 Jun 27;297(24):2705-15.

of survivors with a specific late effect is small. Information was provided by 25 “data providers” from across Europe and Israel, with information from more than 14,000 survivors. Putting together a cohort of this size is only possible when many countries work together, as we did in PanCareLIFE.

Not only did we collect information about a lot of survivors - **we collected a lot of detailed information about each individual survivor**. This was necessary as many factors influence whether survivors develop late effects or not, and why. For example, the type of cancer and age of diagnosis are important. Surgery, drugs or radiation, or a combination of these treatments, is used to treat cancer and can cause late effects, so detailed information about what type of treatments were received is essential knowledge. The information already available in cancer registries and other databases is often minimal, so it was necessary to look back at medical records and to ask survivors to complete questionnaires to gather all the data needed. Biological samples (DNA, saliva, blood/serum) and hearing tests (“audiograms”) were also needed for genetic testing, hormone testing and to measure hearing loss or impairment.

Since information on cancer and survivorship is collected and recorded in different ways across Europe, part of PanCareLIFE’s work was to create new partnerships between clinical trialists, clinical personnel and late effects researchers to create efficient and effective methods to collect and share information for research. We standardised and harmonised the collected information to be able to make comparisons, and developed procedures for this work to share with other researchers. Following PanCareLIFE, we **leave behind a legacy of structures for data collection and harmonisation that will help carry out future studies** of late effects after cancer.

Fertility impairment – risk factors, guidelines and education

Radiation therapy and certain drugs can damage the reproductive organs and make it more difficult for survivors to have children when they reach adulthood, which can cause distress and reduced quality of life. In women, impaired production of hormones related to fertility can also increase the risk of heart disease and osteoporosis, resulting in the need for long-term medical attention. But, the risk for fertility impairment is not the same for all survivors. In PanCareLIFE, different studies were carried out to learn more about risk factors for fertility impairment in women, learning more about known risk factors and looking for new ones. We also looked to identify new genetic risk factors. Knowing more about risk factors means that, in future, doctors can pick treatments with the lowest risk for fertility problems for girls and young women who are about to start cancer treatment and counsel them about what options are available to them. For survivors who are now adults, our research will help doctors to provide better information on future parenthood and discuss fertility preservation options.

Adequate counselling of childhood and adolescent cancer patients about fertility issues and family planning is important, but must be based on solid evidence. So, we developed clinical guidelines for fertility preservation in girls and boys. Clinical guidelines are developed by international experts to provide doctors and other healthcare professionals with recommendations about what care is needed for their patients. The guidelines are based on the best available evidence, like the evidence from PanCareLIFE studies. We will share these guidelines and recommendations with parents/survivors, healthcare professionals and other stakeholders to make sure they are used in clinics across Europe and around the world.

It can be very difficult for parents and doctors to discuss fertility when children are about to undergo cancer treatment. Having educational materials to help with this discussion can help, but we need to make sure the materials work to share the right message. So, in PanCareLIFE, we tested a set of brochures to educate parents and patients about fertility preservation.

Ototoxicity (hearing impairment)

Platinum-based drugs can damage parts of the ear, resulting in hearing impairment, also called ototoxicity. Hearing impairment can affect a child's speech development, as well as their ability to learn and develop socially. The risk for hearing impairment is not the same for all survivors. Researchers in PanCareLIFE looked for both clinical and genetic risk factors to help them create risk profiles to help doctors decide what cancer treatments to give to which patients and to know when giving additional drugs to protect hearing ("otoprotectants") would be useful. They also looked at over 10,000 hearing tests ("audiograms") to learn more about hearing impairment over time and to identify different types of hearing impairment in different patients. From this work, recommendations for standardised hearing tests for before, during and after treatment are being developed in order to support better follow-up care.

Genetics

Genetics may also play a role, with some survivors being more or less likely to have certain late effects based on their DNA characteristics. Combining the results of cutting-edge genetic testing with extensive clinical and treatment data, PanCareLIFE looked for genetic variants that were linked to a higher risk of fertility impairment and/or hearing loss. The results of our genetic testing are now being compared with those from other research groups in the USA and Canada to confirm our findings.

Health-related Quality of Life

HRQoL does not describe one late effect, but rather many things that can impact on survivors' physical, mental and social states. Decreased HRQoL after successful cancer treatment can have a negative influence on development, education and social functioning. It can make it tougher for survivors to become well-integrated adults compared to their peers, add to the burden of care resting on families and increase the costs of childhood cancer for society. As for fertility and hearing impairment, the risk for all survivors is not equal. PanCareLIFE looked at the HRQoL of survivors according to their stage of disease at diagnosis, cancer treatment, fertility status and degree of hearing impairment to develop risk models and study how HRQoL changes over time. The results of this work will feed into recommendations for how quality of life should be routinely monitored following clinical trials and cancer treatment in hospitals.

1.3 *A description of the main S&T results/foregrounds*

1.3.1 Introduction

PanCareLIFE has successfully achieved all of the planned scientific objectives. In order to carry out our research studies in fertility, ototoxicity and quality of life, PanCareLIFE researchers have collected large amounts of different information about survivors, such as what type of cancer they had, what treatments they received and their quality of life after treatment. We exceeded our initial target of 12,000 survivors and have now collected Information from over 14,000 survivors of childhood and adolescent cancer from Germany, the Netherlands, France, Switzerland, the Czech Republic, the United Kingdom, Poland, Austria, Norway and Israel, which is now stored in our secure central data centre in Germany. In addition to information from medical records, cancer registries and patient questionnaires, we also collected and measured 1,647 serum samples and 1,422 DNA samples, as well as over 10,000 hearing tests. None of these studies would have been possible without the participation of many thousands of cancer survivors, to whom we are very grateful.

Using this data, we have conducted:

- two studies of female fertility impairment to identify how many survivors typically experience fertility impairment, and the effect of the type of cancer diagnosis and age at diagnosis on impairment, as well as how different treatments and treatment doses affect risk of impairment,
- four genetic studies to identify genes potentially involved in fertility impairment and hearing impairment (ototoxicity),
- two studies of ototoxicity in patients who received platinum-based treatments looking at risks associated with different drugs, with drug in combination with radiotherapy and age at diagnosis, and
- two studies of HRQoL, one looking at HRQoL across Europe and the other looking at HRQoL over time.

We have also completed a rigorous process in collaboration with international experts to develop two guidelines for fertility preservation, and conducted a study to evaluate existing educational materials for fertility preservation.

1.3.2 WP1 Data Centre and Biostatistical Support

Work package (WP) 1 was responsible for setting up and running the central data centre, which received and checked all information collected by the data providers, laboratories and Audiological Reference Centre. WP1 also provided support for the analysis of the collected data, a process called "biostatistics", through the Biostatistical Support Group.

Central Data Centre

The main job of the data centre was to receive information from all 25 data providers involved in the project and put it together in a way that it could be used for the planned studies of fertility, hearing impairment and HRQoL. Data was also received from laboratories and the Audiological Reference Centre. The main challenge was that data providers provided their information from many different sources, such as previous surveys, clinical records, cancer registries, hospital records and clinical studies, as well as from new surveys or follow-up clinical visits. So, the process for data collection needed to be standardised so that the final information in the data centre was uniform in the end, but also as flexible as possible to allow for differences in data sources.

The first step in the process was to develop lists of what information was needed, called the "variables lists". These lists were included in "Study Protocols", documents that were developed during the first year of the project to describe the planned studies and how they would be conducted. Common variables needed for all survivors ("baseline variables") and variables that were specific to a certain study ("WP-specific" variables), were agreed by WP1, all data providers and leaders of the fertility, hearing impairment, genetics and HRQoL studies (WPs 2 – 6). Briefly, in addition to some technical variables, the baseline variables provided information on the patient's date of birth, sex, date of diagnosis or diagnoses, codes for the diagnosis/diagnoses, starting dates for the main treatments and follow-up status. When different studies needed to collect similar information, WP1 and the study leaders worked together to agree on common variables that would work for both studies. This process of agreeing variables harmonised the data, making it comparable across studies.

The second step was to develop a common database and a secure process for data transfer and handling that would make sure the survivor data was well protected. The data centre created a data

protection plan that made sure that study staff only saw information they absolutely needed, and the keys to link individual survivors (name and other identifying information) with their data were kept securely by each data provider only. This separation of identifying data from medical and other data is called "pseudonymisation". By using pseudonymised data, the data centre acts as a trusted link between the data providers, laboratories, Audiological Reference Centre, and study teams. The data centre was responsible for linking clinical, laboratory and audiogram data but without being able to identify individual survivors. In the same way, combined data from the data centre sent to the laboratories, Audiological Reference Centre or study teams contained all the required clinical, laboratory and audiogram data, but with no way to link to individual survivors. Audiograms were sent directly to the audiogram centre, which analysed them and sent the resulting data to the data centre. Data providers sent their biosamples directly to the laboratories, which sent the analyses results to the data centre for linkage with other survivor data.

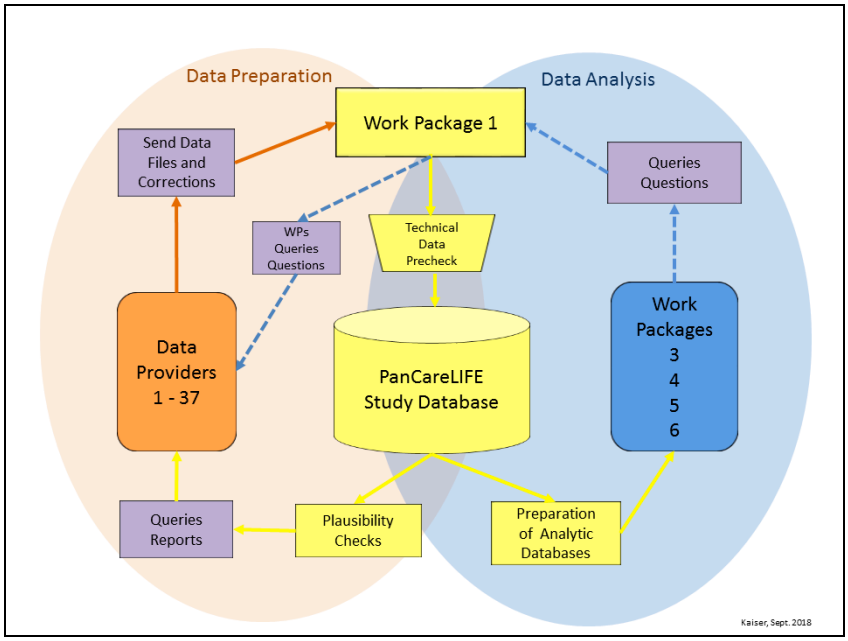

Figure 2 Schematic presentation of the data collection and quality control process of PanCareLIFE

Other measures were also taken to maximise data protection. For example, all dates, especially date of birth, were collected at the month level only, to make re-identification less likely. All data was encrypted to make sure it was safe during transfer from the data providers to the data centre and from the data centre to the study teams. Large amounts of data from the genetic analyses required additional safety measures that were developed by WP1 and the genetics study team.

Having decided what information to collect and technically implemented how to securely manage it, the third step was to issue the "Call for Data" to start the data collection process. All data providers needed to provide the baseline variables for all survivors. As not all data providers were providing information for all studies, they did not all need to collect and send the same information to the data centre. To make the data collection process as simple as possible, WP1 issued a Call for Data, tailored to each data provider, telling them exactly what variables needed to be collected and summarizing the study groups' criteria for including and excluding survivors. The call also included deadlines, file format instructions, data encryption instructions, and a manual/video for the file share server.

Once they received the Call for Data, data providers began to extract data from existing databases and adapt them to the study requirements and to newly extract data from hospital or clinical study records, where needed. To support the collection of new data related to treatment, the data centre wrote a

data entry tool, the “therapy database”, and provided training and support for this to data providers. To make it user-friendly, the tool had separate sections for the fertility and hearing impairment, and genetic studies.

Wherever needed, the data centre was flexible in acting as a channel between data providers and study teams. For example, an extra loop of exchange for a subset of more detailed data was needed for the fertility case-control studies. The data centre provided the fertility study team with preliminary data so that they could identify the survivors for whom detailed treatment data was needed. The data centre then issued a “Second Call for Data” for those specific survivors only to those data providers who had not already provided detailed treatment data. This process saved data providers a lot of unnecessary work, removing the need for them to collect detailed treatment data for all survivors.

In addition to collecting information from survivors eligible for the study (“responders”), some very basic data (for example, year, sex, age and diagnosis) was collected from another 18,000 survivors, who could not be included in the studies (“non-responders”) and sent to the data centre. Non-responder data was collected to see how representative the responders were of the survivor population in general for the study questions.

The fourth step of the data collection process was data validation, where the plausibility of data and coding rules were checked by the data centre. As the data was received, it was checked very thoroughly for technical mistakes, clearly wrong data, and unlikely combinations. The data centre also classified all cancer diagnoses centrally into the International Classification of Childhood Cancer (ICCC), applying the official “child check” procedures provided by the International Agency for Research on Cancer (IARC) in the process. The data was also checked for duplicates, as the structure of the data providers (hospitals, registries and central clinical work groups) naturally led to some patients being included in more than one dataset. Together with the data providers, the data centre determined which survivor information was duplicated and informed the study teams.

Once all the data had been transferred to the data centre and checked, the fifth step was started with transfer of harmonised datasets to the study teams for further, study-specific checks and analyses. Through this process, the data centre continued to act as the trusted link between the study teams, data providers, laboratories and Audiological Reference Centre, maintaining pseudonymisation of survivor data to ensure high standards of data protection were maintained.

Once the final checks were completed by the study teams, the data was ready for careful archiving and preparing the data for possible future re-use. Overall, 25 data providers provided data from more than 14,000 survivors, as well as 1,647 serum samples for hormone analysis, 1,422 DNA samples and hearing test data from more than 2,000 survivors.

Biostatistical Support Group

A group of biostatistical experts was formed to provide support for the analysis of the collected data. This group gave advice to the study teams on the Study Protocols and helped to develop “Statistical Analysis Plans” for each study. The Statistical Analysis Plans included detailed plans on how the data would be analysed, as well as power calculations, which told the study teams how many survivors they needed to collect information from in order to have valid results. The group played an important role in creating a process that made sure that the genetic data transferred from the laboratories to the data centre and then to the study teams was secure and stable. Experts from the group also developed a harmonised approach for dealing with non-responder data, essential for publication in many areas.

Lessons Learned and Future Plans

In a large collaborative project like PanCareLIFE, clear communication and a commitment to working together are essential. The data centre made sure to regularly update data providers and study teams about data collection and management at face-to-face meetings, teleconferences and newsletters, and offered one-to-one support wherever needed. Showing the strong partnership across the project, a number of data providers volunteered to act as beta-testers for data centre processes. Hands-on training sessions and Q&A sessions were offered at face-to-face meetings, in particular for file formats, data encryption, file share server operation, and the tool developed for treatment data entry.

In addition to the large dataset collected during the project, PanCareLIFE has developed structures for data collection and harmonisation that will help carry out future studies of late effects after cancer. The structures build on those developed in our predecessor sister project PanCareSurFup (http://www.pancaresurfup.eu) and represent the extension of a virtual pan-European structure for studies of long-term survival after cancer. The harmonisation process and structure will be useful for future PanCare projects, and to future wider collaborations with other European and international researchers.

1.3.3 WP2 Fertility Preservation Guidelines

1.3.3.1 Guidelines

Survivors' ability to have their own children, called fertility, may be affected by the cancer treatment they received during childhood or young adulthood as it may damage the reproductive organs (ovaries and testes). This is of great concern to both survivors and to their families. There are procedures, called fertility preservation, which can be given to patients before cancer treatment that may help them to have children, offsetting the impact of cancer treatment on fertility. However, what fertility preservation options are being offered by healthcare professionals and to which patients varies a lot across Europe and many parts of the world. These differences exist because healthcare systems are not all the same, and because it can be difficult for healthcare professionals to keep up to date with all the latest research evidence when many new scientific articles are published all the time, and many health care personnel do not consider themselves expert in fertility preservation.

Guidelines can help healthcare professionals and healthcare systems to provide the best care for patients and survivors. To develop guidelines, international experts review the latest evidence and then provide recommendations to help healthcare professionals make the best choices for helping patients and their families. Decisions about fertility preservation are made during difficult and stressful times for patients and their families (i.e. after receiving a cancer diagnosis), so guidelines in fertility preservation can also help healthcare professionals communicate with patients and their families in the best way possible. In PanCareLIFE, we have developed two guidelines on fertility preservation, one for girls and young females and one for boys and young males diagnosed with cancer before 25 years.

Guideline development process

The process to develop the guidelines involved the following steps: 1) Setting up working groups of international experts; 2) Identifying existing guidelines on fertility preservation; 3) Evaluating variations between recommendations in existing guidelines; 4) Formulating questions relevant to fertility preservation; 5) Identifying available evidence; 6) Summarising and appraising the evidence; 7) Formulating recommendations; and 8) Sharing recommendations to put them into practice.

Setting up working groups

International working groups with experts from many different areas related to cancer treatment and fertility preservations were set up, including pediatric oncology/hematology, gynecology, endocrinology, radiation oncology, reproductive medicine, embryology, psychology, nursing, urology, epidemiology and ethics. Experts represented many parts of the world, and came from Australia, Belgium, Canada, Czech Republic, France, Germany, Italy, the Netherlands, New Zealand, Sweden, Switzerland, Turkey, the United Kingdom and the United States. A total of 8 working groups (4 for male and 4 for female) and 59 experts contributed, led by a core leadership group of 10 experts consisting of guideline development experts and pediatric oncologists.

Identification of existing guidelines on fertility preservation

As a first step, we looked for guidelines about fertility preservation in cancer patients in the scientific literature (via PubMed searches), guideline databases and websites of oncology, as well as pediatric and fertility organisations. A total of 25 existing guidelines were identified.

Evaluation of variations among recommendations in existing guidelines

Next, a standard methodology called AGREE was used to assess the quality of the 25 guidelines. Only approximately one third of the identified guidelines were considered to be of high enough quality, and the guidelines sometimes contradicted each other. The results from this study of available guidelines were published in a peer-reviewed journal in an article called "Fertility preservation in children, adolescents and young adults with cancer: Quality of clinical practice guidelines and variations in recommendations" (Font-Gonzalez et al, Cancer 122(14) 2016). This article was important as it showed the urgent need for new, clear guidelines that could be used across Europe and around the world, which was the next part of our planned work.

Formulation of questions regarding clinical issues in fertility preservation

Based on the areas of disagreement in the existing guidelines and areas where there was debate in the literature, the experts formulated questions about fertility preservation in terms of clinical knowledge, as well as ethics. We used an established methodology, called PICO, to formulate the questions in a well-structured way.

The questions covered the following topics:

- With which patients should healthcare professionals discuss the potential risk for infertility?
- With which patients should healthcare professionals discuss fertility preservation?
- Which fertility preservations methods can be offered to girls/boys with cancer diagnosed before 25 years?
- What are the issues (including ethical issues) related to discussing infertility risks and fertility preservation?

Identification of available evidence

The scientific literature was searched to find articles that would help the expert working groups to answer these questions. A systematic literature search using the search engine PubMed was performed. To ensure a comprehensive search, additional evidence was obtained by consulting the experts and cross-checking the bibliographic references of relevant articles. Overall, we screened 7,920

abstracts and 1,064 full-text articles, with 167 studies meeting our criteria. As this took a lot of time and effort, we shared the work across the working groups. Two experts reviewed each article separately and any disagreements were resolved by consensus.

Summary and appraisal of the evidence

To summarise the information from each article, the work was again shared among the working groups. Two experts summarised the information from each article in a table and a third expert checked the tables. Then, we grouped together all the tables that addressed the same questions. The evidence from the articles was assessed using an established methodology in guideline development called GRADE (Grading of Recommendations Assessment, Development and Evaluation) and a final score was given to the quality of the evidence, either high, moderate, low or very low. For the evidence relating to the ethical issues in fertility preservation, GRADE was used to show that the evidence was relevant but the experts did not formally assess the quality of the evidence as the articles were opinion papers or narrative papers.

Formulation of the recommendations

The evidence was translated into recommendations following the standard methodology from GRADE. During several meetings and telephone conference calls, the experts discussed the evidence in detail. They also discussed the potential advantages/disadvantages of fertility preservation, the costs of the fertility preservation procedures, and how to apply them in different healthcare systems. To make it as easy as possible to put our recommendations into clinical practice in the real world, we made every effort to use unambiguous, clear language. We also colour-coded the recommendations to make them easier to understand: green and orange for strong and moderate recommendations for an intervention, and red for a strong recommendation against an intervention (Figure 3).

Strong recommendation to do

Moderate recommendation to do

Strong recommendation not to do

Figure 3 Colour coding of the recommendations

Sharing recommendations to put them into practice

The recommendations are now being prepared as two papers (one for girls/young females and one for boys/young males) to be published in peer-reviewed scientific journals, which will be ready by the end of 2018. As a final step, patient representatives and external reviewers will review the papers before they are promoted globally to the cancer community. The guidelines will also be summarised in lay language (PLAIN English) and disseminated widely, via CCI (Childhood Cancer International), the IGHG (International Guideline Harmonization Group) website, meetings of oncologists and other clinicians, and newspaper articles, where possible.

In summary, PanCareLIFE has worked with experts around the world to create new guidelines for fertility preservation based on the latest evidence available to address shortcomings and even contradictions in existing guidelines. These guidelines have been developed using transparent methods, well accepted by the guidelines community to ensure high-quality recommendations. The process relied on collaboration of experts around the world who are working to improve the quality of life of patients with cancer, survivors and their families. Putting these guidelines into practice will mean that there is less variation in how fertility preservation is offered across countries. PanCareLIFE's guidelines use the latest evidence to help healthcare professionals communicate with patients and their families in the best way possible, and make sure that children and young adults with cancer have the greatest chance of having their own children in future.

1.3.3.2 Patient education

Discussing possible fertility impairment and fertility preservation options with patients and their families before cancer treatment is challenging as patients may be quite young at the time of cancer diagnosis and there are a lot of decisions to be made about other treatments at a very stressful time. Healthcare professionals may also lack knowledge about possible fertility impairment and fertility protection options, or be unsure how to best discuss the topic. However, education about possible fertility impairment and prevention options is important. Informed patients may be able to improve their chances of having children of their own with the help of fertility-preserving measures.

In PanCareLIFE, we carried out a study in 11 clinical centres in Germany, Poland, Austria and the Czech Republic. The aim was to see how well educational materials helped patients, families and healthcare professionals discuss fertility impairment. The educational materials included a short flyer and a brochure that was tailored to boys or girls of specific ages. The materials explained fertility risks and fertility preservation options. Two groups were established: patients and families in one group received the flyer at diagnosis and before cancer treatment and the brochure three months after diagnosis, while the other group received usual care. Everyone was asked to complete questionnaires three months and 6 months after diagnosis. These questionnaires were designed to see if the flyer and brochure improved knowledge about fertility risks and fertility preservation options in both patients and parents. The study also looked at whether receiving the educational materials increased the number of patients using fertility preservation or had any impact on fears or worries related to fertility. Overall, 214 patients joined the study.

The study found that patient information through age-appropriate and gender-specific flyers and brochures can improve patient and parent knowledge about fertility. No difference in the use of fertility preservation methods was seen between the two groups. There was no evidence that the educational materials reduced fertility-related concerns, but importantly, education did not increase concerns either. In the future, the educational materials can be further improved on the basis of health literacy to provide every adolescent cancer patient in Europe the same chance for the best possible family planning.

1.3.4 WP3 Female Fertility Impairment

One of the adverse effects of treatment of cancer during childhood, adolescence, and young adulthood studied by PanCareLIFE is reduced fertility, or fertility impairment, in females. The brain and reproductive organs (ovaries and uterus) play an important role in becoming pregnant and having a child. These organs can be affected by cancer treatments, causing irregularities in menstrual cycles, a reduced chance of becoming pregnant, and a higher chance of adverse pregnancy outcomes, such as miscarriage or premature delivery. Treatment can also result in menopause occurring at a much earlier

age in survivors than most women, because cancer treatments may destroy all, or some of, the eggs in a woman's ovary, which cannot be replaced. Not being able to become pregnant or experiencing early menopause causes substantial psychological distress among survivors, and so reduces their quality of life.

Previous studies that looked at the impact of cancer treatment on female fertility have shown that whether or not treatment damages the brain or one of the reproductive organs depends on the type of treatment, as well as how much of a certain treatment they received (dose). Most of these studies looked at only small numbers of patients making it hard to draw conclusions that apply to all childhood cancer survivors. In addition, these studies did not have detailed treatment information available or were based only on self-reported data without any clinical measurements. There is still a lot to learn about how specific cancer treatments affect fertility in female survivors. It is important to know who is at risk for reduced fertility so that we can counsel patients who are about to start cancer treatment as well as survivors regarding future family planning and options for fertility preservation.

In order to learn more about specific treatment-related fertility risks, studies with large groups of well-defined survivors are needed. Studies need to have information from patients who have been followed up over a long time, including questionnaires and clinical measurements of fertility impairment (e.g. evaluation of menstrual cycle patterns, levels of follicle stimulating hormone (FSH) and/or anti-Müllerian hormone (AMH)). PanCareLIFE carried out two such studies: a cohort study and a case-control study. The aim of the cohort study was to see how many female survivors had reduced fertility, while the case-control study looked at which specific treatments give a higher risk of reduced fertility and what relationships there might be between the total dose of treatment and reduced fertility.

Study Protocol and Data Collection

At the start of the PanCareLIFE project, we wrote an extensive 'plan of action', called the Study Protocol. This protocol described the reason for doing the cohort and case-control studies and described the study designs. It also listed the institutions that would provide data to each of the studies, described what type of survivors could participate, how data would be collected and the number of survivors needed for the studies. As described earlier (WP1), the protocol included an extensive list of WP-specific variables that would be collected during the project.

Together with data providers, the study team assembled the numbers needed for the cohort study. Overall, 14,377 women from 13 data providers representing 16 institutions in 9 different countries (Germany, Czech Republic, the Netherlands, Italy, Switzerland, France, the United Kingdom, Norway, and Israel) were identified as adult 5-year survivors of CAYA cancer (= base cohort). Some of our data providers used information they had already collected in the past, as part of a local study on fertility, while others collected information specifically during PanCareLIFE. To tell other researchers about our cohort and planned studies, we published a protocol paper called "Fertility Among Female Survivors of Childhood, Adolescent, and Young Adult Cancer: Protocol for Two Pan-European Studies (PanCareLIFE)" (Van den Berg et al. JMIR Res Protoc. 2018 Sep 14;7(9):e10824).

As a first step, we agreed how to say whether a survivor was fertility impaired or not. We consulted experts and agreed on eight criteria, or rules, that defined fertility impairment. A survivor was classified as being fertility impaired if at least one of the following eight criteria was met:

1. She never had a natural menstrual cycle (primary amenorrhea) in combination with abnormal hormone levels (high FSH and/or a low AMH level),

2. At the time of study, she had had no menstrual cycles for more than 12 months before the age of 40 years old (secondary amenorrhea) in combination with abnormal hormone levels (high FSH and/or a low AMH level),
3. She had abnormal hormone levels (high FSH level in combination with a low AMH level), and was less than 40 years old at time of study,
4. She never had a natural menstrual cycle (primary amenorrhea), even if there was no information on hormone levels (AMH or FSH),
5. At the time of study, she had had no menstrual cycles for more than 12 months before the age of 40 years old (secondary amenorrhea), even if there was no information on hormone levels (AMH or FSH)
6. She had an abnormal hormone level (AMH only), was less than 30 years old at the time of study, and was not having hormone therapy at the time her blood sample was taken,
7. She had used artificial reproductive techniques (unless in cases where her partner was known to be the cause of infertility) and was less than 40 years old at time of study,
8. She had tried to conceive for at least 12 consecutive months without success and was less than 40 years old at the time of study.

In order to assess fertility impairment according to the eight criteria above, information was collected about age, fertility (menstrual cycle characteristics, menopausal status, use of oral contraceptives and hormones, reproductive history). Blood samples were also analysed for AMH, a hormone that gives insight into the remaining number of eggs. Levels of another hormone, FSH, were also collected, if they had been measured as a part of regular patient care in the two years before questionnaire completion.

We also collected other information from survivors, including general socio-demographic (education, income, etc.), and health (smoking, alcohol consumption) data. Some data providers already had this information available, while others collected it during the project using a specific PanCareLIFE fertility questionnaire, available in English, German, Czech, Italian, and Hebrew. Where the information had already been collected as part of a local fertility study, there were some differences between the data collected and the PanCareLIFE fertility questionnaire. So, the data providers and study team worked together to translate, or recode, the information into the WP-specific variables, making it as similar as possible. In addition, data on cancer diagnosis and treatment were retrieved from medical records.

Following the secure data management process established by the data centre, the data providers collected their data locally, assigned each survivor a unique number, and then sent the data to the data centre for checking. Once checked, the data centre merged information from all data providers together and sent a single database to the study team for further checking and final analysis.

Cohort Study

From the study population of 14,377 female survivors (Table 1), 10,969 survivors had either been invited to a local fertility study in the past (n=8,463) or were invited to join the PanCareLIFE female fertility study (n=2,506). In total, 6,618 (60%) survivors participated in the cohort study (n=6,546 questionnaire ± blood sample; n=72 blood sample only).

Data analyses regarding the percentage of survivors with a reduced fertility, overall, and according to each of the 8 criteria of fertility impairment, as well as the effect of specific diagnoses and age at diagnosis are underway and results will be published in peer-reviewed scientific journals. This new information will help doctors, researchers and other health care professionals to better understand which and why some survivors suffer from fertility impairment.

Case-Control Study

The case-control study was performed on only some of the survivors from the cohort study. Cases were defined as women who were fertility impaired, as assessed by the 8 criteria described above, whereas controls were defined as survivors without fertility impairment. Both cases and controls were selected from survivors who participated in the cohort study. For the case-control study, we needed detailed treatment data, which was available from only some data providers (11 out of the 16 participating institutions) (Table 1). Controls were matched to cases based on certain characteristics. For our study, we matched cases and controls by country, age at study, cancer treatment year, and age at cancer treatment.

Table 1 Characteristics of study populations included in the cohort and case-control studies

Name of study cohort	Data provider/ Institute	Cancer diagnosis	Type of data[a]	Total base cohort size[b]	# women invited	No. of questionnaires provided (n)	# serum samples	case-control study[c]
DCOG LATER cohort	DCOG LATER (Amsterdam UMC, Erasmus Medical Center Rotterdam), NL	Various diagnoses	PR	2,190	1,684	1,109	619	Yes
Hodgkin Lymphoma cohort	Netherlands Cancer Institute Amsterdam, NL	Hodgkin Lymphoma	PR	450	291	203	0	No
VIVE cohort	Universitätsklinikum Bonn, DE	Various diagnoses	PR	5,909	4,467	2,482	0	No
Ewing 2008 Clinical Trials cohort	Westfaelische Wilhelms-Universitaet Muenster, DE	Ewing's sarcoma	DU	161	140	46	24	Yes
Berlin Hormone Analyses cohort	Charité - Universitätsmedizin Berlin, DE	Various diagnoses	PR	402	344	83	69	No
Cohort female 5-yr cancer survivors Brno	Fakultni nemocnice Brno, CZ	Various diagnoses	DU	283	203	182	180	Yes
Cohort female 5-yr cancer survivors Motol	Fakultni nemocnice v Motol, CZ	Various diagnoses	DU	1,397	1,062	573	300	Yes
Gaslini female survivors cohort	Istituto Giannina Gaslini, IT	Various diagnoses	DU	1,111	814	563	122	Yes
Swiss Childhood Cancer Survivor Study cohort 1	University of Bern, CH	Various diagnoses	PR	1,135	977	685	0	No
Swiss Childhood Cancer Survivor Study cohort 2		Various diagnoses	PR	335	228	113	0	No
Hematopoietic stem cell transplantation cohort	Great Ormond Street Children's Hospital/ University College London Hospital, UK	Various diagnoses	DU	95	93	50	44	Yes
Lymphoma survivor cohort	Oslo University Hospital, NO	Lymphoma	PR	unknown	72	51	46	Yes
Acute lymphoblastic leukaemia survivor cohort		Acute lymphoblastic leukaemia	PR	175	103	82	65	Yes
Rhone Alpe cohort 1	University hospital Saint-Étienne, FR	Various diagnoses	PR	212	120	120	35	Yes
Rhone Alpe cohort 2		Various diagnoses	PR	284	220	102	62	Yes
The Edmond and Lily Safra Children's Hospital Late Effects cohort	Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Israel	Various diagnoses	DU	238	151	102	73	Yes
Total number				**14,377**	**10,969**	**6,546**	**1,639**	

[a] PR = data collected prior to PanCareLIFE project; DU = data collected during PanCareLIFE project

[b] Base cohort = those subjects fulfilling inclusion criteria of study

[c] Yes = cohort participating in the case-control study; No = cohort not participating in the case-control study

In total, 450 cases and 882 matched controls were included in the case-control study. Preliminary results have shown that certain groups of survivors are at a high risk for fertility impairment. More and extensive detailed analyses are underway to identify which specific cancer drugs and at what doses lead to high risk of fertility impairment. Results of these analyses will be published in peer-reviewed journals.

Overall, the information generated by the PanCareLIFE fertility studies will advance our understanding of fertility impairment resulting from cancer treatment during childhood, adolescence and young adulthood by discovering new knowledge about risk factors linked to cancer treatment. This evidence, together with genetic evidence from PanCareLIFE, will improve how fertility is managed in clinics. It will help healthcare professionals to put survivors and patients they treat into risk groups so that they can better inform them about their risks for fertility impairment and what options are available to them. Our results can also be used in evidence-based clinical guidelines for counselling, educating and empowering female patients and survivors to manage their fertility issues and family planning to improve or maintain their quality of life.

1.3.5 WP4 Genetics of Fertility (Female Gonadal) Impairment and Hearing Loss

Not all patients receiving the same treatment have the same late effects. For example, there is a large variation in whether similarly treated patients will have fertility (gonadal) impairment or hearing loss, and in the severity of the late effects. Why do some patients develop late effects after similar treatment while others do not? At the level of our genetic material, our DNA, we are all 99.9% identical, with only 0.1% difference between us. For example, we may have different eye colour, blood group, or responses to drugs. These small differences are due to single nucleotide variants in our DNA that are present at particular locations in the DNA, called *single nucleotide polymorphisms (SNPs),* and that are associated with a specific phenotype. In PanCareLIFE, we looked at the role of genetic vulnerability in fertility (gonadal) impairment or hearing loss after treatment of cancer during childhood and adolescence to see if we could identify specific SNPs that are associated with the late effects. Knowing these associations will allow healthcare professionals to identify patients and survivors at the greatest risk for fertility (gonadal) impairment or hearing loss, so that they can receive appropriate treatment, prevention and follow-up care.

Figure 4 Genetic code (DNA)

Genetic testing and analysis

To carry out our genetic work, we collected DNA from survivors, either from a blood or saliva sample. The samples were collected by data providers across Europe and sent to a central laboratory for analysis. The DNA was extracted and placed on a tiny chip, called an array (Figure 5). Each spot on the array represents a SNP. The array was scanned using a special instrument that can read the genetic code of each survivor. We compared the DNA of the survivors with and without impaired gonadal reserve and hearing loss, to look for differences in presence of particular SNPs. Each dot on the array represents a *single nucleotide polymorphism.* If certain SNPs were found more often in survivors with a late effect compared to survivors without, then the SNP was "associated" with the late effect. Once single nucleotide polymorphisms (genetic associations) are identified, researchers can use the information to

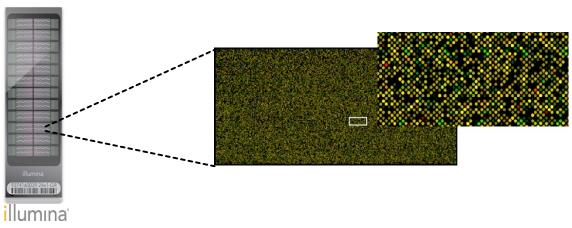

Figure 5 Illumina genetic array analysis

inform clinicians to develop better strategies to prevent gonadal impairment or hearing loss, or to reduce these late effects.

We used two statistic approaches to analyse the genetic data in our studies. First, we used a *candidate gene approach*, where we looked at SNPs that were already known from other research to be associated with gonadal impairment or hearing loss in the general population but not as yet confirmed in survivors. Secondly, we used *genome-wide association screening*, where we searched for new SNPs associated with gonadal impairment or hearing loss. These studies used the results of the genetic testing, in combination with all the general, clinical and questionnaire data collected by data providers for the fertility and ototoxicity studies (WP3, WP5) and sent to the data centre. In order to keep the data pseudonymised, which was part of our data protection process, the genetic data was also sent to the data centre. The study team then received back a compiled database with all the needed information for their analyses.

Female fertility (gonadal impairment)

In our genetic study of female fertility, we focused on damage to the ovaries (gonads), which are important in reproduction as they produce eggs and hormones. We concentrated on survivors who had received chemotherapy, but not radiotherapy of the ovaries or pituitary, an important organ in reproduction. Many cancer drugs, in particular ones called alkylating agents (e.g. cyclophosphamide), damage the ovaries, shortening the time window for female survivors to have children or making it impossible altogether. In addition, gonadal impairment or early menopause carries adverse health risks for women, such as an increased risk for cardiovascular disease and osteoporosis, which require intensive and long-term medical attention.

Our study included female adult survivors (18 years and older) who had received chemotherapy, with a follow-up time of at least 5 years after diagnosis. We excluded survivors treated with radiotherapy of the whole body, both ovaries or the pituitary, as well as those who had received stem cell transplants or had their ovaries removed. In order to join the study, survivors had to give a DNA sample and a blood sample for analysis of AMH (the same hormone analysed in WP3), which was used as a marker of gonadal impairment. Overall, 10 institutions from seven countries provided data (Italy, Czech Republic, France, Norway, Germany, the Netherlands and Israel).

DNA from 749 survivors was analysed for the fertility genetic study. For the candidate gene approach, we looked at 14 SNPs in genes that have been associated with gonadal impairment in the general population. For example, we chose SNPs associated with a higher chance of premature menopause in otherwise healthy women. We looked to see if these SNPs were also associated with an increased risk of gonadal impairment in survivors, and whether the amount of alkylating agents they had been given affected the association. Using the genetic results and all the other information provided by the data providers, we made statistical models to look at the association between the SNPs and gonadal impairment. We identified one SNP with an effect on its own on gonadal impairment. We identified one SNP with an effect on its own on gonadal impairment, and another SNP that increased gonadal sensitivity for chemotherapy-induced damage. We also found a combination of a few specific and related SNPs, called a haplotype, that may be associated with an effect of chemotherapy on AMH levels, as well as another haplotype that may be associated with an effect of chemotherapy on gonadal impairment. In any genetic study, it is necessary to replicate results in another, independent group, called a replication cohort. The need for replication cohorts in all genetic studies highlights the importance of strong, international collaborations. Currently, we are waiting for results from the St. Jude's Lifetime Cohort (Memphis, USA) before we can draw strong conclusions.

For the genome-wide association screening, we looked to see if any new SNPs associated with gonadal impairment could be identified and found 14 SNPs (Figure 6, Manhattan plot) that are worth further exploring and validating, based on the biological characteristics of the involved genes. As with the candidate gene approach, the results are currently being replicated in the St. Jude's Lifetime Cohort. Once the analysis is complete, together we can perform a joint analysis of both our discovery and the St Jude's replication cohorts and publish the results of our genetic studies on female gonadal impairment in survivors of childhood and adolescent cancer.

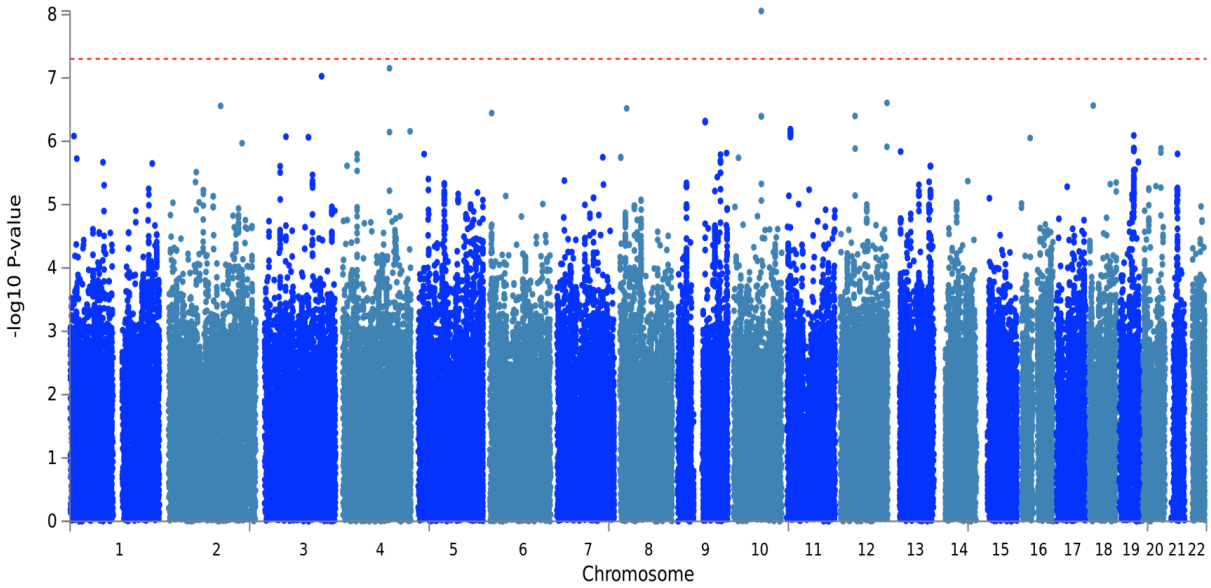

Figure 6 Manhattan plot of association with low AMH in survivors. Preliminary data, results currently under replication.

Hearing impairment

About 50% of all childhood cancer patients who received chemotherapy with cisplatinum-based drugs develop hearing loss, and 40% of these survivors require a hearing aid. Hearing loss is often accompanied by tinnitus (buzzing or ringing of the ears). Such loss of hearing starts often at high frequencies, which makes it hard to hear conversations in noisy places or larger groups, or to hear birds or other high-pitched sounds. For younger children, high-frequency hearing loss can make learning and speech tough, and can also cause social problems. Hearing loss can also impact on quality of life, as it can result in distress, anxiety or even depression. There are several known risk factors for hearing impairment, including treatment with cisplatin (a platinum-based drug) or other ototoxic drugs (such as diuretics and antibiotics, often used for supportive care), younger age at diagnosis and radiotherapy of the head, but little is known about the role of genetic vulnerability in developing these side-effects. There is variability in the occurrence of these toxicities in similarly treated patients of the same age, so genetics may play a role.

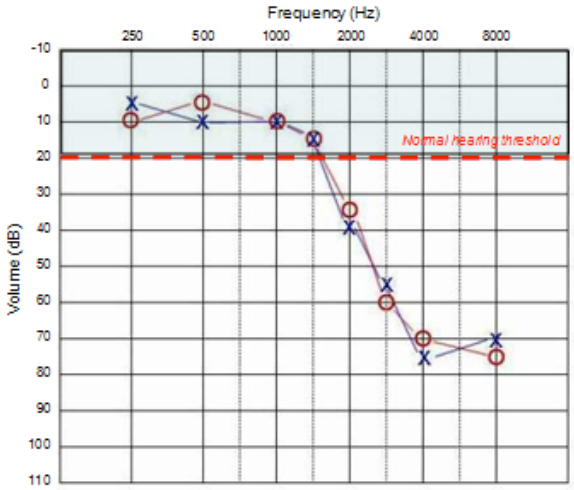

Figure 7 Example of a tone audiogram

The hearing impairment genetic study included survivors who were younger than 18 years old when diagnosed with cancer, and who were treated with cisplatin but not radiotherapy of the head. Survivors had to provide a blood or saliva sample (for extraction of DNA) and a hearing test had to be available from the end of treatment (either from their medical records or collected during the project). The hearing test gives a result called an tone-audiogram (Figure 7). Audiograms were scored according to the Münster criteria, which grades the level of hearing impairment. Significant hearing impairment is greater than or equal to Münster grade 2b. Fourteen data providers from seven countries were involved (Switzerland, Italy, Czech Republic, Denmark, Germany, Austria and the Netherlands) in the study.

For the candidate gene approach, we chose ten SNPs in genes that were likely to be involved in hearing impairment as they are found in genes involved in hearing or are affected by cisplatin in previous publications in small groups of survivors or in the normal population. For example, the genes have a role in the development of hair cells in the ear involved in hearing or are involved in breaking down drugs like cisplatin. DNA from a total of 598 patients/survivors was obtained, but some were not included in the analysis for a number of reasons, like missing audiograms or treatment data or poor quality DNA samples. In total, 344 patients were included in the candidate gene study of hearing loss. None of the 14 SNPs we looked at in our study were associated with hearing loss in our study samples. We then looked to see if we could find any associations if we combined our study with previous studies, a process called a meta-analysis. The meta-analysis revealed a possible association between one particular SNP and hearing loss. This finding might help in counselling and in developing prediction models and treatment strategies so that hearing loss occurs less often after childhood cancer treatment.

For the genome-wide association screening, we looked for new SNPs associated with hearing impairment. We identified eight SNPs potentially associated with hearing impairment (Figure 8, Manhattan plot). As with the fertility study, we are currently awaiting the results of a replication study with the Canadian Pharmacogenomics Network for Drug Safety. For the purpose of this study, we reviewed and reclassified > 2000 tone audiograms of children in Canada, with the same classification used in PanCareLIFE (from the CTCAE scheme to Münster 2b), in order to be able to compare the two groups. Once the analysis is complete, together we can perform a joint meta-analysis of both our discovery and the Canadian Pharmacogenomics Network for Drug Safety replication cohorts and publish the results of our genetic studies on hearing impairment in survivors of childhood and adolescent cancer.

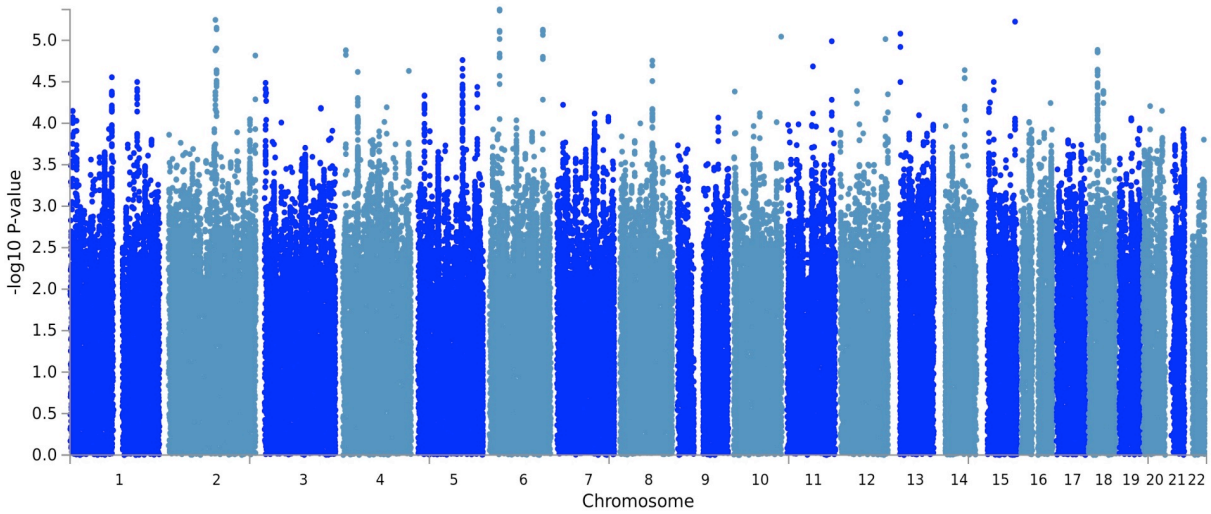

Figure 8 Manhattan plot of association with ototoxicity after cisplatin treatment. Preliminary data, results currently under replication.

In addition to completing the replication studies, we will also do further work to understand what cellular, (epi-)genetic and molecular processes are involved in the association of specific genes with the clinical outcomes for both gonadal damage and hearing loss.

1.3.6 WP5 Ototoxicity

Platinum-based drugs are used to treat cancer, but are also ototoxic, meaning they damage the ear. One of the symptoms of ototoxicity is hearing loss. Between 25 and 90% of survivors experience ototoxicity, with a considerable impact on their quality of life. We already know that ototoxicity can be caused by platinum-based drugs, other ototoxic drugs given at the same time or radiotherapy of the head. New knowledge is needed in order to make sure that patients are treated in a way that reduces their risk of ototoxicity. For example, steps can be taken during treatment to protect hearing, called otoprotective measures, such as treatment with otoprotective drugs. We also need to learn more about how to best monitor patients during treatment to detect ototoxicity and monitor it over the long-term in survivors. PanCareLIFE has conducted studies into ototoxicity, or hearing impairment, to achieve these aims.

13 data providers from Switzerland, Italy, the Czech Republic, Denmark, Austria, Germany and the Netherlands were involved in the ototoxicity studies. As for other studies, the data was collected by the data providers locally and sent to the data centre for checking and merging into one dataset for the study team to analyse. Baseline variables for 2,696 patients were sent to the data centre, exceeding our initial target of 1,860.

In addition to the information sent to the data centre, data providers also sent over 10,000 audiograms to the central Audiological Reference Centre for analysis and classification using the Münster classification, which grades hearing loss by severity (Figure 9). As the audiograms were most often filed in medical records, this took a lot of time and effort. 9,427 audiograms were of a high enough quality to be classified. 1,946 patients had at

Figure 9 Münster classification

least one classifiable audiogram, with an average of 4.8 audiograms per patient. Classifying this large number of audiograms was also a significant activity.

667 patients (48.2% of patients with at least one post-treatment audiogram) demonstrated clinically-significant hearing loss following treatment with platinum-based compounds. This finding shows how common ototoxicity is in these patients and highlights the need to improve treatment and provide adequate follow-up care for hearing impairment.

The timing of an audiogram is very important for our ototoxicity studies. In order to be able to look at the relationship between factors like age, sex, dose of platinum-based drug and hearing impairment, at least one classifiable audiogram is needed after the last platinum-based drug cycle. In our study, we had 1,385 patients that had a post-treatment audiogram.

Our initial analyses show that children younger than five years old are more likely to develop a hearing loss at the end of treatment than older children. Our analyses also supported the theories that an increased risk of post-treatment hearing loss would be found following treatment with higher doses of cisplatin and following radiotherapy of the head.

Hearing phenotypes

Sufficient data was obtained for 736 patients to be grouped according to different pre-defined "phenotypes" characterising the time course and degree of hearing loss. This helped us to identify individuals who may be particularly susceptible to ototoxicity. This means we expected these individuals to develop hearing loss at an early time point during treatment and have more severe hearing loss at the end of treatment. Membership in the different phenotype groups will also be used for more detailed analyses concerning genetics and clinical aspects during the course of treatment, such as the effect of multiple drug treatments being given at the same time.

Overall, the primary aims of the ototoxicity study have been met, with 2,696 patients included in the study and over 10,000 audiograms classified. We found that 48.2% of patients have hearing loss following platinum treatment and that there is a difference in the risk for hearing loss depending on which platinum-based drug is used, with cisplatin alone causing greater hearing loss than carboplatin alone, especially at high doses. We also found that there is a greater risk for ototoxicity when platinum-based chemotherapy is combined with radiotherapy of the head, and when children younger than 5 years old are treated for cancer. Lastly, how hearing is impaired over time seems to predict hearing loss at the end of treatment.

1.3.7 WP6 Health-related Quality of Life

WP6 addresses HRQoL in European childhood cancer survivors. In addition to physical effects, the concept of HRQoL focuses also on emotional and social dimensions of health. In this way, it reflects the different aspects of cancer survival better than outcomes based on physical effects alone. Not all survivors have HRQoL impairments and those that do have different levels of impairments. Research is needed to identify groups of survivors at risk for a decreased HRQoL, so that they can receive appropriate follow-up care.

PanCareLIFE has increased our knowledge about risk factors for impaired HRQoL based on harmonised data from a multi-national cohort. National differences can also play an important role in HRQoL evaluation, for example, due to differences in healthcare systems, so PanCareLIFE also looked to see if there were differences in HRQOL between several European countries. Linked to other PanCareLIFE studies, we examined if survivors with treatment-related impairment of hearing and/or fertility increased the risk of HRQoL impairment and reduced psychosocial adjustment. Lastly, to understand

how HRQoL and related risks change over time, we collected longitudinal HRQoL data from two clinical trials of sarcoma patients, with HRQoL assessment during, two years after and at least five years after treatment.

Two different studies were performed to answer our different research questions:

A *retrospective study*, including HRQoL data and further relevant information from large national or regional childhood cancer survivor cohorts, was carried out using the *SF-36* questionnaire. The SF-36 is the most commonly used questionnaire to measure HRQoL. The questionnaire measures quality of life in eight areas, and also gives two summary scores that measure overall physical quality of life and mental quality of life.

The retrospective study of HRQoL brought together scientists from Germany, Switzerland, the UK, Czech Republic, the Netherlands and France. Swiss data were provided by the University of Bern, originating from the Swiss Childhood Cancer Survivor Study. Czech data were provided from two Czech hospitals engaged in long-term follow-up care (University Hospital Brno and the Fakultni Nemocnice V Motole in Prague). French data were provided by the Rhone-Alpe cohort study through the CHU Saint-Étienne hospital. Dutch data was provided by the DCOG LATER consortium. German data was provided from the University of Bonn, including data from the VIVE study.

A *longitudinal study*, including HRQoL data and further relevant information from the clinical trials EURAMOS-1 and EWING 2008, was carried out using different, age-appropriate questionnaires over a long assessment period. For older survivors, the SF-36 questionnaire was used, while a different pediatric questionnaire was used for children. We also used the EORTC-QLQ-C30 questionnaire, which has been developed specifically for cancer patients.

Experiences and results from both studies have been included in a model for the implementation of HRQoL assessments in follow-up care.

Retrospective study

9,872 fully evaluable SF-36 questionnaires from all countries combined were available for the analysis in the *retrospective study*. German survivors made up the largest proportion of questionnaires, while French survivors contributed the smallest proportion. In addition, 15,186 data-sets from non-responders were available and included basic information, such as sex, specific cancer diagnosis and age at cancer diagnosis. These non-responder data-sets provide valuable information for the data interpretation, where we need to know any differences between those who responded and did not respond.

As for many other self-report surveys, more women than men completed an SF-36 questionnaire, even though the percentage of men in the cohort invited for participation was higher. Leukemia and lymphoma survivors represent the largest proportion both in the responder and in the non-responder cohort. This reflects the typically higher frequencies for this diagnosis.

The responders in the retrospective study covered a wide range of years since cancer diagnosis. As shown in Figure 10, nearly 40 % of the cohort were survivors of more than 25 years. More than 20% of the cohort were diagnosed before 1985 and nearly 50% were younger than 10 years at diagnosis, while the other half of the cohort was diagnosed before age of 18. This wide range in years since cancer diagnosis, treatment era and age at diagnosis provides a good basis for risk stratification.

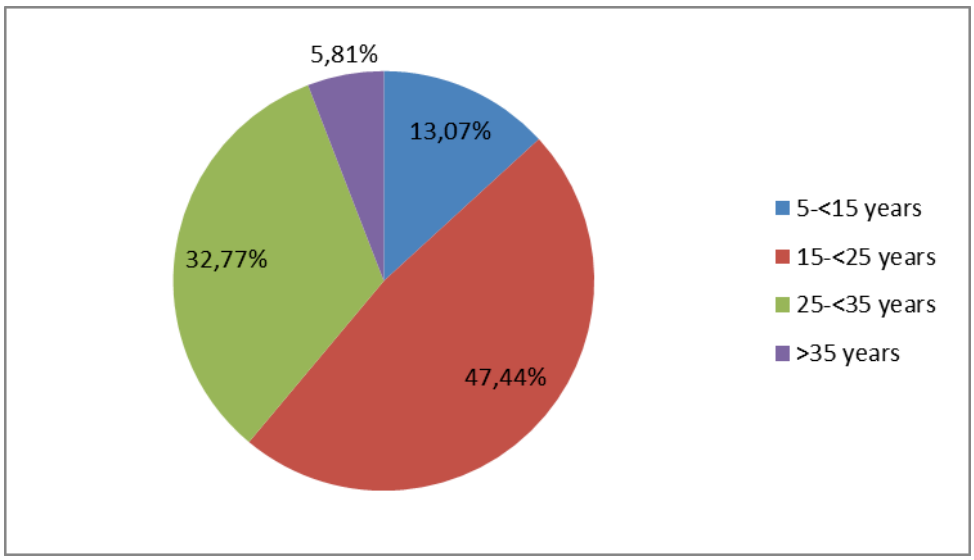

Figure 10 Years since cancer diagnosis (percent) in the SF-36 responder cohort.

Comparison of the HRQoL data assembled in PanCareLIFE with data from the normal population showed that the SF-36 scores of European survivors were lower than the normal population in four out of the eight areas measured, higher in three areas and the same in one area. The overall physical and mental health summary scores also showed no difference to the normal population.

In terms of differences between countries, differences were seen for both physical and mental health scores between the included European countries. Swiss survivors had the most favourable HRQoL outcomes, while and French survivors had the most unfavourable outcomes.

Our results showed that there are important risk factors related to disease and treatment. For example, sarcoma patients have a higher risk of HRQoL impairment. Other factors, such as education level, living situation and occupational status, were also found to impact on HRQoL in childhood cancer survivors. Further analyses for risk stratification are on-going, as are detailed analyses of the influence of fertility and hearing impairment on HRQoL.

Longitudinal study

In the *longitudinal study*, data-sets from 124 participants were available for the analysis (25% response rate). We combined HRQoL information gained during the EURAMOS-1 and EWING 2008 clinical trials with a further HRQoL assessment during long-term-follow-up, collected for PanCareLIFE. This last assessment was crucial for analysing changes in HRQoL to gain valuable insight into the dynamic nature of HRQoL.

An innovative method was used to analyse the HRQoL data in the longitudinal study. We mapped the physical functioning scores of all the questionnaires used on a common scale, where lower scores represent lower physical HRQoL. Figure 11 shows the individual absolute scores per participant (n = 124) during time course of assessment. Clearly, there is an overall improvement of physical functioning scores from time-point one to time-point five, with some individual exceptions. More detailed analyses are on-going.

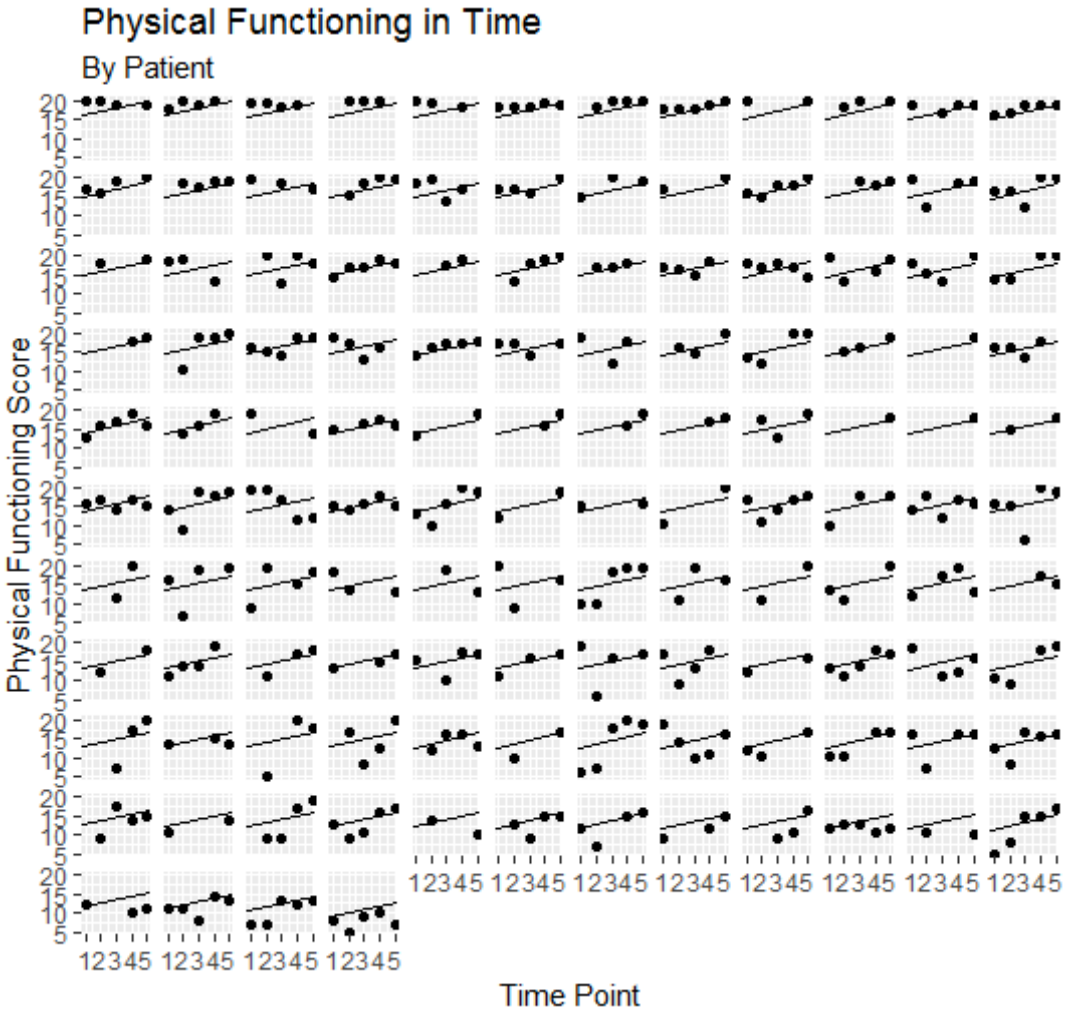

Figure 11 Individual absolute scores per participant for physical function during time course of assessment

Results from the longitudinal study were valuable for proposing strategies to enhance response-rates and continuous data collection on HRQoL between clinical trials and long-term follow-up. These results informed our *model for implementation of HRQoL assessments in follow-up care*. For example, the model recommends that patients completing questionnaire surveys also receive additional on-line information.

Clear conclusions concerning HRQoL in survivors of childhood cancer are often limited by a lack of international collaboration, small sample sizes and heterogeneous methodologies. With the cooperation described above, PanCareLIFE was able to overcome these limitations and harmonised a large amount of HRQoL information. The database assembled during the retrospective study consists of nearly 10,000 data-sets and is a unique source of information on HRQoL after childhood cancer in Europe. It will be used for many further analyses to refine risk-stratification and sub-group analyses. Longitudinal data collected are valuable to learn more about how HRQoL changes over time in sarcoma patients, a group at high risk for impaired HRQoL.

1.3.8 Ethics in PanCareLIFE

Making sure we carried out our research in an ethical way was important for the PanCareLIFE team. Our research involved many topics that raise potential ethics issues. For example, our research used data collected from children, so it was important to make sure the proper informed consent was in place

from parents for previously collected data and from adult survivors for data collected during the project. We also collected data at many locations and transferred it to a central data centre, so we needed to make sure data transfer processes were secure and respected data privacy. Local ethics boards at each data provider were responsible for reviewing our planned research and giving us approval before we started. We also had the help of two dedicated ethics experts from outside the team on our Ethics Advisory Board, who provided us with independent advice. They helped us to solve any issues that arose and made sure we knew about new requirements as they arose over the lifetime of the project.

1.3.9 Conclusion

PanCareLIFE has successfully achieved all it's aims, generating high-quality research results on fertility impairment, hearing impairment (ototoxicity) and quality of life that will reduce the frequency, severity and impact of late effects to improve the lives of survivors of childhood and adolescent cancer. The project saw an impressive collaboration between 25 data providers from Germany, Denmark, the Netherlands, France, Switzerland, Italy, the Czech Republic, the United Kingdom, Poland, Austria, Norway and Israel, with information collected from over 14,000 survivors. Assembling, harmonising and securely sharing such a large amount of data was challenging and we learned many lessons along the way. Building on the foundation of our predecessor sister project PanCareSurFup, we have extended a virtual pan-European structure for studies of long-term survival after cancer and developed structures for data collection and harmonisation that will be useful for future PanCare projects, and to future wider collaborations with other European and international researchers.

For fertility impairment, we have developed two clinical guidelines on fertility preservation in collaboration with experts from around the world. Once published, these guidelines can be put into practice to help healthcare professionals discuss fertility preservation with patients and their families in the best way possible, and make sure that children and young adults with cancer have the greatest chance of having their own children in future. An intervention study on patient education for fertility preservation has also been carried out to see if available materials are effective. We have also generated new evidence about female fertility, learning more about what factors increase the risk of fertility impairment, including genetic risk factors currently being validated. This evidence will help healthcare professionals to put survivors and patients they treat into risk groups so that they can better inform them about their risks for fertility impairment and what options are available to them in a timely manner. Our results can also be used in future clinical guidelines for counselling, educating and empowering female patients and survivors to manage their fertility issues and family planning to improve or maintain their quality of life.

For ototoxicity, our findings confirmed that hearing loss is found in almost half of all patients after treatment with platinum-based drugs, but that there are differences in the risk based on which drug is used and at which dose, if radiotherapy of the head is also used and the age of the child. The role of genetics has also been examined, with candidate markers currently being validated in a replication cohort. These findings will have important impacts in clinics, helping healthcare professionals decide which treatments are best for their patients. Our studies have also shown the importance of monitoring hearing before, after and during treatment to ensure the best treatment and follow-up care for patients and survivors.

For HRQoL, our international studies harmonised a large amount of HRQoL information. The database assembled during the retrospective study consists of nearly 10,000 data-sets and is a unique source of information on HRQoL after childhood cancer in Europe that will be used for risk-stratification and improvement of HRQoL assessment in follow-up care.

1.4 *Impact, dissemination and exploitation*

1.4.1 Impact and exploitation

PanCareLIFE set out to learn more about fertility, ototoxicity and HRQoL late effects in order to reduce the number of survivors experiencing these effects and to provide survivors with the best possible long-term follow-up care. This type of research is important for survivors and their families, as well as for healthcare systems that must deliver follow-up care to an ever-increasing number of survivors. Our results can be used to develop clinical guidelines that help healthcare professionals know what care is needed, for which survivors and when so that they can help survivors manage their own health in the long-term. They can also be used to develop new treatments that cause fewer late effects and learn which survivors are at greatest risk for late effects so they can be carefully followed for early diagnosis and treatment.

Improving how we study late effects

Studying late effects is challenging as childhood cancer is rare and the number of survivors with a given late effect is small. In order to have enough survivors to carry out high-quality studies, international collaboration is necessary. Different countries and even different clinics or hospitals in the same country, all collect information in different ways, so it can be difficult to make comparisons. Standardised and harmonised approaches are needed to maximise the value of research projects like PanCareLIFE. In addition, a lot of information is needed about each survivor, which can be a time-consuming process, so the data should be collected and stored in a well-structured way so that it can be used again in future studies, removing the need to re-collect data.

In order to improve how we study late effects, PanCareLIFE has developed structures for data collection and harmonisation that will help carry out future studies of late effects after cancer. The structures build on those developed in our predecessor sister project PanCareSurFup (http://www.pancaresurfup.eu) and represent the extension of a virtual pan-European structure for studies of long-term survival after cancer. The harmonisation process and structure will be useful for future PanCare projects, and to future wider collaborations with other European and international researchers. The project website directs any researcher interested in collaborating with PanCareLIFE data providers or adopting our approach to the PanCareLIFE Legacy Committee to learn more. We also anticipate that our data providers and others will learn from PanCareLIFE as we work towards the collection of long-term follow-up data in a consistent way across Europe.

Helping healthcare professionals, patients, families and survivors with fertility preservation decisions

Existing guidelines for fertility preservation were surveyed during the project, revealing gaps and even contradictions, making it difficult for healthcare professionals to provide the best advice to childhood cancer patients and their parents, and survivors. We have developed two guidelines, based on international agreement and the latest research to overcome the shortcomings of current guidelines, which will be promoted globally so that there will be less variation in how fertility preservation is offered across countries. PanCareLIFE's guidelines will also help healthcare professionals communicate with patients and their families in the best way possible, and make sure that children and young adults with cancer have the greatest chance of having their own children in future.

Defining risk groups to reduce the occurrence or impact of late effects

Applying the results of our studies in clinical practice can reduce the occurrence of late effects. Our improved understanding of risk factors resulting from PanCareLIFE can be used to reduce the

occurrence of late effects with current treatment approaches. Less toxic treatments with the same effectiveness can be chosen, or lower doses can be chosen if the toxic effect is dose dependent.

For example, alternative drugs could be considered for patients at high risk for ototoxicity or otoprotectants could be used. Hearing could be monitored more closely to detect early hearing loss during treatment, shown in PanCareLIFE to be associated with a greater risk of permanent hearing loss after treatment, so that doctors could decide whether to continue with treatment or modify the treatment to minimise the risk of hearing loss. Similarly, the detailed examination of a wide range of chemotherapy drugs and at many doses in our fertility studies could identify treatments that have a lower risk for fertility impairment in general or in certain groups of patients, but have the same survival rates. Or high-risk patients could be counselled to pursue fertility preservation before the start of treatment. Our genetic studies also open the door for treatment choices or fertility preservation to be informed by genetic testing, before treatment is given.

Providing evidence for new treatment development

PanCareLIFE's results will be useful for those developing new treatments for cancer. Patient groups at greatest risk for late effects with current treatments can become target groups for new drugs or new treatment protocols with different drug combinations or doses. As we raise awareness about late effects, clinical trial researchers can begin to consider balancing treatment effectiveness with the risk for late effects, and incorporate late effects into personalised medicine approaches where therapies are tailored to the risk profile of individual survivors. Researchers conducting clinical trials will also benefit from our recommendations for hearing impairment and HRQoL monitoring during treatment and short- and long-term follow-up, which can be applied during trials. We will communicate our findings to the European Cancer Research Council (ECRC), which is increasingly looking at how to integrate the results from long-term follow-up studies, like PanCareLIFE, into clinical care and clinical trials.

Providing better follow-up care – monitoring and treatment

Our results can also be used to improve the quality of life for patients who have already been treated for cancer and are in long-term follow-up care. As part of their care, healthcare professionals can use what we have learned in PanCareLIFE to identify survivors at the greatest risk for fertility impairment, ototoxicity or HRQoL impairments and ensure that they are routinely monitored for these effects so that if they occur, they get treatment as soon as possible. They can also learn what advice to give to survivors to help them to manage their own health and quality of life. For example, female survivors at high risk for fertility impairment could be advised about their current fertility status during follow-up and informed of their shortened window for childbearing. Particularly important for follow-up care are our recommendations for systematic monitoring of HRQoL over time so that psychological and social supports can be provided as the need arises.

Building a sustainable, multidisciplinary community of experts

Studying late effects requires the involvement of experts from a broad range of disciplines from doctors specialising in childhood cancer to healthcare professionals involved in follow-up care of survivors to researchers, geneticists, and more. As a whole, the PanCareLIFE team represents a truly multi-disciplinary team of researchers and clinicians, with strong links to networks of key stakeholders in childhood cancer survivorship. Many team members have links to other important initiatives in cancer and late effects research, such as our sister project PanCareSurFup and the ENCCA project, which developed the Survivorship Passport. The team is committed to maintaining the collaborative research relationships developed during PanCareLIFE and to working together to identify and pursue new challenges where research can be used to advance clinical practice for the benefit of survivors of

childhood cancer. The consortium is also committed to building on the knowledge, expertise and impact generated by the project through the PanCareLIFE Virtual Research Community. In the last year of the project, the community developed a Joint Action Plan for Research, which included studies planned for the future. Further EU funding has already been secured for one of the planned studies, PanCareFollowUp, which will look at how to best deliver survivorship care in adult survivors starting in 2019.

Societal benefits

Cure of their original cancer is not the end of the story for many survivors and families. As treatment regimes have improved and survival rates have increased, the impact of late effects on survivors' quality of life has come more into focus. PanCareLIFE has improved our understanding of fertility impairment, ototoxicity and HRQoL in ways that can improve quality of life. As described above, benefits include better, more uniform guidance about fertility preservation, greater knowledge about risk that can reduce the occurrence of late effects, improve follow-up care and inform clinical trials for new and better cancer treatments, and recommendations for more rigorous monitoring of hearing loss and HRQoL during and after cancer treatment.

Our results will also help healthcare professionals, healthcare decision makers and policymakers to deliver better evidence-based cancer treatment and follow-up care. The ability to stratify cancer survivors into risk categories after treatment will allow healthcare decision makers to support treatments that reduce the occurrence of late effects and their impact on quality of life, such as funding fertility preservation measures for survivors. Our evidence base will also support the need for follow-up care and identify what care is needed and for which survivors. The long-term nature of late effects means that the cost to health insurers and public health systems extends far beyond the initial cost of cancer treatment and in some cases may be life-long. Risk assessments based on PanCareLIFE research can reduce the cost of cancer survivorship for health insurers and public health systems by using risk grouping of patients and survivors to both prevent and reduce the incidence of late effects.

Exploitation – benefit to partners

PanCareLIFE results will not be commercially exploited, but the project partners have exploited the project results to advance their strategic agendas and the careers of their researchers. Many staff were directly employed by partners as a result of involvement in the project, including data managers, audiologists, nurses, biostatistician, research assistants. Impacts in the area of exploitation included:

- strengthening of new collaboration partnerships amongst researchers in many different disciplines across Europe - as evidenced in this report, partners are already planning future work together to improve the long-term well-being of survivors of childhood and adolescent cancer,
- establishment of a database of survivors at their institute which they can use long into the future for the benefit of survivors and researchers, with the help of the PanCareLIFE data centre,
- improvement of long-term follow-up of survivors, previously lost to follow-up, who were asked to attend follow-up clinics as part of the data and sample collection for PanCareLIFE, and
- increased profile of many of the project partners, allowing for additional national funding for new research relating to survivors of childhood and adolescent cancer.

There were also benefits at national level resulting from the EU funding from the project. For example, PanCareLIFE encouraged greater national cooperation between hospitals within the Czech Republic,

Germany and Denmark. Clinicians and researchers from a wide range of disciplines had the opportunity to share ideas which could be used at a local level, and the EU funding helped to attract other funds for research/clinical care in the Czech Republic, France, Italy, Germany and Israel.

During the project, a number of senior researchers received awards. For example, Coordinator, Dr. Peter Kaatsch received the "Dietrich-Niethammer-Preis" of the German Society for Pediatric Oncology and Hematology (GPOH) in September 2014, recognizing his contribution to the field of pediatric oncology. In 2015, Dr. Anja Borgmann-Staudt (Charité-Universitätsmedizin Berlin) and her team from the Working Group for Fertility after Chemotherapy and Radiotherapy in Childhood and Adolescence (FeCt) were awarded the German Aftercare Prize 2015. Three investigators advanced in their careers to Professor (Marry van den Heuvel-Eibrink, Leontien Kremer and Jeanette Falck Winther). Those working within the Management Team, WP study teams and some DPs also gained valuable project management skills essential for future European project success, for example in the next EU-funded PanCare project PanCareFollowUp.

Participation in the project also advanced the careers of promising, early stage researchers. The research undertaken in the PanCareLIFE project contributed to seven PhD theses and three Masters theses in three countries. Many young investigators were given the opportunity to present their PanCareLIFE work at national and international scientific meetings, as well as in publications. These dedicated researchers also received awards for their work. In 2014, Anna Font-Gonzalez (Amsterdam Medical University Centre) was awarded a Young Investigator Award by the International Society of Paediatric Oncology (SIOP) and her abstract "Fertility preservation in children with cancer: quality of clinical practice guidelines and variations in recommendations" was selected as one of the eight best abstracts submitted to the Amsterdam Kindersymposium in Feb 2016. Eva Clemens (Erasmus Medical Centre) was also granted a Young Investigator Award by SIOP and won the Giulio d'Angio prize in at the 2016 European Symposium on Late Complications after Childhood Cancer.

A number of PanCareLIFE partners have been invited to join policy groups. For instance, Tomáš Kepák from University Hospital, Brno, the Czech Republic, was invited to join a national group on the EU health research program and policy making group. Jarmila Kruséova from Motol Hospital Prague is on the national group for children with genetic syndromes. Claire Berger from St. Étienne, France has been invited to join the fertility preservation group in France, Groupe de Recherche et d'Etude sur la Cryoconservation de l'ovaire et du testicules (GRECOT). Antoinette am Zehnhoff-Dinnesen of Universtitatsklinkum Münster, Germany, has joined the IGHG. Thorsten Langer of Lübeck, Germany and Peter Kaatsch of Mainz, Germany are involved with the German National Cancer Control Plan working group partly because of PanCareLIFE involvement. Anne Lotte van der Kooi and Eva Clemens of the Erasmus Medical Centre, Rotterdam are now involved in the IGHG on obstetric care for female childhood cancer survivors and ototoxicity surveillance, respectively. Julianne Byrne of the Boyne Research Institute provided input into the new Irish National Cancer Control Plan, as a result of which the issues of survivorship and children's cancer were included for the first time.

In participating institutes, there is now an increased awareness of late effects. In Brno, which represents about 40% of all survivors in the Czech Republic, patients will now undergo more frequent audiological testing before, during and after treatment and there is now a grant to pay for early intervention with hearing aids for children to improve speech and school performance. Patient AMH values were also made available to clinicians as a result of PanCareLIFE.

Lastly, PanCareLIFE boosted the economies of the towns or cities that hosted consortium meetings, namely Mainz, Germany, Amsterdam, the Netherlands, Drogheda, Ireland, Prague, the Czech Republic

and Paris, France. Smaller work package meetings were also held in Rotterdam, the Netherlands, Münster, Germany, Genoa, Italy and Oslo, Norway.

1.4.2 Dissemination and communication

Key to achieving our intended impacts is effective engagement with key stakeholders, including other researchers, clinicians, nurses, survivors and their families, and health policymakers. Dissemination and communication activities to reach these audiences have been an important and on-going activity since the project start. We recognise that our different target audiences have different levels of scientific literacy, so our dissemination and communications activities have been carried out with this in mind.

Website, social media, mass media and promotional materials

The project website (www.pancarelife.eu) and social media channels (Twitter: @pancarelife; facebook: @pancarelife) have been an important window into the project. Through them, visitors can learn more about the project, keep up to date with all our latest news and join our conversation about research and survivorship.

We also developed promotional flyers and brochures that explain the project in English, French and Czech. These materials are available on the project website and were distributed at events and conferences. For example, PanCareLIFE brochures were distributed to Professor Cieza and Professor Chadha, organizers of the seminar 'Childhood hearing loss: act now; here is how!', at World Hearing Day 2016 at the WHO headquarters in Geneva, attended by Prof. Antoinette am Zehnhoff-Dinnesen (UKM). We also shared the materials with Childhood Cancer International (CCI), an international patient and survivor organization with close links to the PanCare network and the PanCareLIFE project.

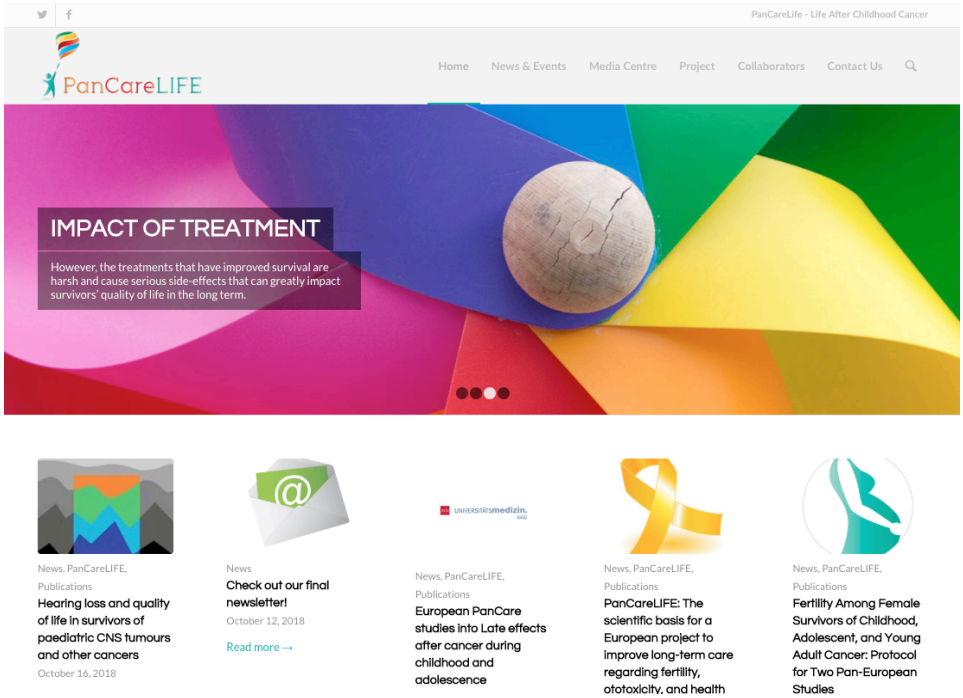

Figure 12 Project website, http://www.pancarelife.eu

Mass media has been used as an amplifier of our message, making sure our research reaches the wider general public. For example, we had excellent media coverage in the Czech Republic on television, radio and print media following press briefings held by our partners in Brno (http://www.pancarelife.eu/media-centre/press-coverage/).

Newsletters

Five newsletters were issued during the project, sharing all our latest activities (http://www.pancarelife.eu/media-centre/). A broad range of topics were covered, from updates on our data collection and laboratory analyses to scientific publications to national survivorship initiatives and more!

Figure 13 Press briefing at University Hospital Brno: Dr. Tomáš Kepák of PanCareLIFE and survivor Zuzana Wimmerova

'Explainer video'

Seeing something makes it easier to understand, so we developed an 'explainer video' to share what PanCareLIFE is all about (http://www.pancarelife.eu/pancarelife-video-available/). The engaging animated video explains what late effects are, and how the project collected massive amounts of data for research into fertility impairment, ototoxicity and HRQoL.

Figure 14 'Explainer Video'

Publications, presentations and engagement with other projects

Peer-reviewed publications in academic journals are an important dissemination channel, reaching researchers and health care professionals. PanCareLIFE has already published 16 publications and more are on the way as we finalise our results. We have also presented our results at important academic conferences, such as the annual conferences of the International Society of Pediatric Oncology, the

European Symposium on Late Complications after Childhood Cancer and the International Conference on Long-Term Complications of Treatment of Children & Adolescents for Cancer. The team has given over 20 oral presentations and presented over 20 posters.

PanCareLIFE builds on the work of national registries and oncology societies across many European countries, so the team presented the project relevant national and European society meetings, as well as the pan-European PanCare meetings that are held twice-yearly. The project has also been featured in a number of university magazines and institutional newsletters.

Engagement in national initiatives for survivorship

PanCareLIFE researchers are also active in national initiatives to advance long-term care after childhood cancer. For example, the first Workshop on Long-Term Care after Childhood Cancer in Germany was held in Bonn, Germany (27 – 28 Sept 2017), hosted by the German Childhood Cancer Foundation and PanCareLIFE researchers Dr. Gabriele Calaminus (UKB) and Prof. Dr. Thorsten Langer (UzL), representing the German Pediatric Oncology and Hematology Society (GPOH) working group on long-term surveillance. Researchers (e.g. PanCareLIFE Coordinator, Dr. Peter Kaatsch) gave presentations on high priority late effect issues. Survivors' experiences and day-to-day difficulties were also discussed at the workshop. Six dedicated focus groups were established to continue discussions on future medical and psychosocial long-term care, education and occupational issues, health behaviour and secondary prevention, as well as future research infrastructures.

Figure 15 Attendees of the first Workshop on Long-Term Care after Childhood Cancer in Germany

Closing Conference

On 26 Oct 2018, the PanCareLIFE Closing Conference was held in Paris, immediately following the twice-yearly PanCare network meeting. The meeting included a joint symposium with PanCare and presentations of PanCareLIFE results. Over 120 participants attended the conference, representing researchers, clinicians, nurses, survivors and their families, and policymakers.

Key stakeholders participated with presentations and participation in lively round table discussions (Figure 16), including:

- Heleen van der Pal, Chair, PanCare Network,
- Samira Essiaf, Chief Executive Officer, European Society for Pediatric Oncology (SIOP-Europe),
- François Doz, Board Member, SIOP-Europe,

- Jaap den Hartogh, Survivor, Childhood Cancer International Europe,
- Eline van der Meulen, Survivor, Childhood Cancer International Europe,
- Roderick Skinner, Founding Member, PanCare Network,
- Ruth Landenstein, Coordinator, European Reference Network for Paediatric Cancers (ERN Paedcan),
- Aimilia Tsirou, Survivor, Childhood Cancer International Europe,
- Ioannis Vouldis, Policy and Programme Officer, European Commission, and
- Françoise Meunier, Director General of the European Organization for Research and Treatment of Cancer (EORTC).

Figure 16 Roundtable discussion, hearing the survivor viewpoint: from left, Samira Essiaf, François Doz, Jaap den Hartogh, Eline van Dulmen den Broeder, Leontien Kremer, Roderick Skinner

Throughout the day, we posted live from the event to twitter, asking participants to do the same #PanCareLIFEConference. Videos of the sessions were also recorded and will be posted to our website so that we can more widely share our results with those unable to join us in person.

Overall, the PanCareLIFE consortium has worked together to effectively disseminate and communicate the project to a wide range of key stakeholders, helping us to reach our aim of improving the evidence base for better survivorship care. To reach professional audiences, we have published 16 peer-reviewed publications, with many more planned as we complete our final analyses, and given over 20 oral presentations at academic conferences. We have also developed guidelines for fertility preservation and the findings of our research will inform the development of future guidelines, as well as further clinical research in the areas of fertility impairment, ototoxicity and HRQoL. Importantly, we have engaged with survivors and their families, as well as the general public, developing and distributing engaging lay materials (e.g. 'explainer' video) to explain the aim of our project. Our Closing Conference was a resounding success, bringing together a wide audience to share our findings and to learn more from our stakeholders about the current state of and future needs for survivorship care.