European Journal of Cancer 103 (2018) 227–237

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

# PanCareLIFE: The scientific basis for a European project to improve long-term care regarding fertility, ototoxicity and health-related quality of life after cancer occurring among children and adolescents

Julianne Byrne [a,*], Desiree Grabow [b], Helen Campbell [a], Kylie O'Brien [c], Stefan Bielack [d], Antoinette am Zehnhoff-Dinnesen [e], Gabriele Calaminus [f], Leontien Kremer [g,h], Thorsten Langer [i], Marry M. van den Heuvel-Eibrink [h,j], Eline van Dulmen-den Broeder [k], Katja Baust [f], Andrea Bautz [l], Jörn D. Beck [m], Claire Berger [n,o], Harald Binder [p], Anja Borgmann-Staudt [q], Linda Broer [j], Holger Cario [r], Leonie Casagranda [n], Eva Clemens [h,j], Dirk Deuster [e], Andrica de Vries [j], Uta Dirksen [s], Jeanette Falck Winther [l,t], Sophie Fosså [u], Anna Font-Gonzalez [g], Victoria Grandage [v], Riccardo Haupt [w], Stefanie Hecker-Nolting [d], Lars Hjorth [x], Melanie Kaiser [b], Line Kenborg [l], Tomas Kepak [y,z], Kateřina Kepáková [y], Lisbeth E. Knudsen [aa], Maryna Krawczuk-Rybak [ab], Jarmila Kruseova [ac], Claudia E. Kuehni [ad], Marina Kunstreich [ae], Rahel Kuonen [ad], Herwig Lackner [af], Alison Leiper [ag], Erik A.H. Loeffen [ah], Ales Luks [ac], Dalit Modan-Moses [ai,aj], Renee Mulder [g], Ross Parfitt [e], Norbert W. Paul [ak], Andreas Ranft [s], Ellen Ruud [u], Ralph Schilling [q], Claudia Spix [b], Joanna Stefanowicz [al], Gabriele Strauß [am], Andre G. Uitterlinden [j], Marleen van den Berg [k], Anne-Lotte van der Kooi [h,j], Marloes van Dijk [k], Flora van Leeuwen [an], Oliver Zolk [ao], Daniela Zöller [p], Peter Kaatsch [b] on behalf of the PanCareLIFE consortium[1]

[a] *Boyne Research Institute, 5 Bolton Square, East, Drogheda, Co. Louth A92 RY6K, Ireland*

* *Corresponding author*: Boyne Research Institute, 5 Bolton Square, East, Drogheda A92 RY6K, Ireland. Tel./fax: +353 (0)41 9836041.
*E-mail address:* jbyrne@boyneresearch.ie (J. Byrne).

[1] Members of the PanCareLIFE consortium is listed in the Acknowledgements section.

https://doi.org/10.1016/j.ejca.2018.08.007

[b] German Childhood Cancer Registry (GCCR), Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Center, Mainz, Germany
[c] Pintail Ltd, Dublin, Ireland
[d] Department of Paediatrics &- Oncology, Hematology and Immunology, Centre for Paediatric, Adolescent and Women's Medicine, Klinikum Stuttgart – Olgahospital, Stuttgart, Germany
[e] Department for Phoniatrics and Pedaudiology, Universitätsklinikum, Münster, Germany
[f] Department of Paediatric Haematology and Oncology Universitätsklinikum, Bonn, Germany
[g] Department Pediatric Oncology, Emma Children's Hospital/Academic Medical Center (AMC), Amsterdam, The Netherlands
[h] Prinses Máxima Center for Paediatric Oncology, Utrecht, The Netherlands
[i] Paediatric Oncology and Hematology, University Hospital for Children and Adolescents, University zu Lübeck, Lübeck, Germany
[j] Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands
[k] Amsterdam UMC, Vrije Universiteit Amsterdam, Pediatrics, Cancer Centre Amsterdam, Amsterdam, The Netherlands
[l] Danish Cancer Society Research Center, Copenhagen, Denmark
[m] Klinik für Kinder und Jugendliche, Friedrich-Alexander- Universität, Erlangen, Nürnberg, Germany
[n] Department of Paediatric Hematology and Oncology Unit, University Hospital of Saint-Étienne, Saint-Étienne, France
[o] Epidemiology of Childhood and Adolescent Cancers, CRESS, INSERM, UMR 1153, Paris Descartes University, Villejuif, France
[p] Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany
[q] Charité - Universitätsmedizin, Berlin, Germany
[r] Department of Paediatrics and Adolescent Medicine, University Medical Center Ulm, Ulm, Germany
[s] Pediatrics III, Pediatric Hematology and Oncology, West German Cancer Centre, University Hospital, Essen, Germany
[t] Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark
[u] Institutt for Klinisk Medisin, Universitetet I Oslo, Oslo, Norway
[v] University College London Hospital, London, UK
[w] Epidemiology and Biostatistics Unit and Italian Off-Therapy Registry (OTR), Istituto Giannina Gaslini, Via Gerolamo Gaslini, 5, 16148, Genova, Italy
[x] Department of Paediatrics, Lund University, Skåne University Hospital, Lund, Sweden
[y] University Hospital Brno, Brno, Czech Republic
[z] International Clinical Research Center (FNUSA-ICRC), Brno, Czech Republic
[aa] Institute of Public Health, University of Copenhagen, Copenhagen, Denmark
[ab] Medical University of Bialystok, Bialystok, Poland
[ac] Motol Teaching Hospital, Prague, Czech Republic
[ad] Swiss Childhood Cancer Registry, Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[ae] Department of Paediatric Oncology, Haematology and Immunology, Medical Faculty, Heinrich-Heine-University of Düsseldorf, Düsseldorf, Germany
[af] Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria
[ag] Great Ormond Street Children's Hospital, London, UK
[ah] Department of Pediatric Oncology/Hematology, University of Groningen, Beatrix Children's Hospital, University Medical Center Groningen, Groningen, the Netherlands
[ai] Edmond and Lily Safra Children's Hospital, Chaim Sheba Medical Center, Tel Hashomer, Israel
[aj] The Sakler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[ak] Institute for the History, Philosophy, and Ethics of Medicine, Johannes Gutenberg University Center Mainz, Mainz, Germany
[al] Klinika Pediatrii, Hematologii I Onkologii, Medical University, Gdansk, Poland
[am] Helios Kliniken Berlin-Buch, Klinik Für Kinder-und Jungendmedizin, Berlin, Germany
[an] Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
[ao] Institute of Pharmacology of Natural Products and Clinical Pharmacology, University Hospital Ulm, Ulm, Germany

Received 23 May 2018; received in revised form 2 August 2018; accepted 2 August 2018

**KEYWORDS**
Childhood cancer survivors;
Late effects;
Gonadal impairment;
Ototoxicity;
Quality of life;
Guidelines

**Abstract** ***Aims:*** Survival after cancer diagnosed during childhood or adolescence continues to improve with new treatments and supportive therapies. Optimal long-term care requires that risks to vulnerable organs are clearly defined and translated into guidelines that are implemented into practice. PanCareLIFE is a pan-European consortium that addresses survivorship issues comprising fertility, hearing impairment and quality of life. This article describes the scientific basis of PanCareLIFE's studies.
***Methods:*** PanCareLIFE involves 17 partner institutions from eight European countries, with additional 11 data providers from five other countries. Study designs and methods include molecular genetic, cohort and case-control studies, a longitudinal study and an intervention

study. Ethics and data protection issues have been taken into account from the beginning.
***Results:*** PanCareLIFE will investigate the way that treatment impairs female fertility, by evaluating anti-Müllerian hormone levels and the underlying genetic susceptibility to loss of fertility. For our fertility studies, more than 6000 survivors have completed questionnaires, more than 1500 provided serum samples and more than 400 case-control triads have been identified. Fertility preservation guidelines for boys and girls will be developed. More than 2000 survivors have contributed audiograms for the ototoxicity study. Almost 1000 samples were sent for genetic analysis related to ototoxicity and gonadal reserve. The SF-36 questionnaire will measure quality of life in more than 10,000 survivors.
***Conclusions:*** The large number of subjects enrolled in PanCareLIFE and the detailed information accumulated will allow in-depth evaluation of important outcomes. Fertility preservation guidelines will help patients and their families make informed decisions and contribute to their long-term well-being.


## 1. Introduction

Most children who are diagnosed with cancer during childhood or adolescence (hereinafter called 'childhood') now survive. Consequently, the percentage of survivors in the population is increasing steadily. In Europe, nearly 80% of children survive at least 5 years on average, with survival after some types of cancer reaching even higher levels [1]. However, the price for this impressive achievement is the persistence and gravity of late complications of treatment, which are frequent and can be life threatening. As an example, medical assessment of survivors in the Netherlands showed that almost 75% had one or more adverse event at a median attained age of 24.4 years by the end of follow-up [2].

Despite decades of investigation, many late complications remain poorly defined. For instance, children receiving platinum-based agents acquire hearing loss, but we know little of the magnitude of the risk, or of the risk factors; we have little information on the pathways by which quality of life can be negatively impacted by cancer treatments; effects of treatments on fertility in adult female survivors are poorly described, and we have only just begun to evaluate the effectiveness of fertility preservation strategies.

While the late effects of treatment can impact many survivors, not all survivors actually experience serious late effects. This has two consequences: one is an increased emphasis on understanding the genetic constitution of survivors and combining this information with other risk factors to determine who is more at risk; the second is the need for risk-stratified counselling and guidelines to assist groups of survivors and their caregivers make the best choices to safeguard their health, both immediately and in the long term.

Large numbers of research subjects are needed to carry out these investigations. But cancer in childhood is rare: between 130 and 160 of every million children will develop cancer each year [3]. Hence, assembling a cohort to adequately study even one late effect is difficult. Achieving reliable scientific results that can be translated into care, therefore, requires collaboration among many institutions and many countries. The large number of European experts assembled into the PanCareLIFE consortium will pool data from their patients to achieve significant impact, not only on the lives of survivors and their families but also on the scientific arena.

PanCareLIFE (www.pancarelife.eu) was established as the second consortium emerging from PanCare (www.pancare.eu), the pan-European network for survivors of childhood cancer; the first was PanCareSurFup (www.pancaresurfup.eu) [4]. The PanCareLIFE consortium includes eight work packages (WPs; Table 1). Its scientific projects deal with estimation of risk factors for female fertility issues, the efficacy of educational brochures to reduce anxiety and to improve rates of sperm cryopreservation; other projects involve hearing impairment (ototoxicity) and assessments of quality of life of survivors. In addition, two genetic laboratories seek evidence for an underlying genetic susceptibility to both gonadal impairment and ototoxicity. Guidelines that are intended to increase fertility preservation are incorporated. Dissemination of the results to the general public and to survivors and parents will directly impact their lives with new and useful information. This report provides an overview of the scientific basis for the PanCareLIFE project, its objectives, methods and anticipated results.

## 2. Methods

### 2.1. Introduction

The five scientific WPs (Table 1) of PanCareLIFE, covering guidelines, fertility, ototoxicity, molecular genetics investigations and quality of life, are the focus of this article. The fertility studies encompass investigations

Table 1
List of work packages in PanCareLIFE.

| Work package number | Title |
|---|---|
| 1 | Data centre and biostatistical support |
| 2 | Fertility preservation guidelines |
| 3 | Female fertility impairment |
| 4 | Genetics of gonadal impairment and hearing |
| 5 | Ototoxicity |
| 6 | Health-related Quality of Life |
| 7 | Dissemination and exploitation |
| 8 | Project management |

into the clinical and molecular genetic aspects of loss of gonadal function in women (WPs 3 and 4a), as well as an intervention study to increase knowledge and use of fertility preservation methods (WP2b). The ototoxicity studies aim to describe the occurrence of damage to the inner ear and investigate the molecular susceptibility to hearing loss (WPs 5 and 4b, respectively). The health-related quality of life (HRQoL; WP6) studies investigate the impact of cancer on the quality of life in children and adults who survived cancer during childhood and the further impact of hearing loss and fertility impairment on HRQoL. WP2a prepares guidelines for fertility preservation of both boys and girls, including ethical aspects. The structure of PanCareLIFE includes a central data centre and biostatistical support unit (WP1), and other WPs that provide for dissemination of project methods and results (WP7), and management, including ethics (WP8). This article describes the scientific questions of PanCareLIFE.

### 2.2. PanCareLIFE studies concerned with fertility

Fertility is one of the most important concerns of long-term survivors of childhood cancer. PanCareLIFE conducts the following investigations: guideline development for both male and female fertility preservation (WP2a); an intervention study to increase knowledge and use of fertility preservation methods in boys and girls before treatment begins (WP2b); a comprehensive evaluation of female fertility by questionnaire and clinical tests (WP3) and candidate as well as genome-wide association studies (GWAS) approaches to detect polymorphisms associated with female gonadal impairment due to cancer treatment (WP4). The expected numbers of subjects are set out in Table 2. They were recruited from a number of sources, including both retrospective and prospective hospital series, clinical trials, newly diagnosed patients and cancer registries. In addition, data for some PCL studies were gathered from questionnaires administered to survivors.

#### 2.2.1. Guidelines

Across Europe, there is little uniformity of approach or uptake to fertility preservation [5], and few European guidelines of sufficient quality to help healthcare providers and their patients make the best choices to preserve their fertility. Even sperm banking, a simple and tested procedure, is not widely used [6]. PanCareLIFE will develop guidelines for male and female fertility preservation for children and young adults treated for cancer, including related ethical issues, and will harmonise these efforts among Europe, Canada, Australia, New Zealand and the USA in collaboration with the International Guideline Harmonisation Group. An article describing the identification of existing guidelines and evaluation of their quality and differences in recommendations has been published [7]. The outcome is expected to be two guidelines, one each for men and women.

#### 2.2.2. Intervention study

Although fertility impairment after cancer therapy is frequent, many families are surprised when, later in the treatment course, they learn that fertility may be impaired [8]. Their lack of understanding may be due to their shocked state at the time of diagnosis and/or the lack of discussion by the treating physicians. Timely education about possible fertility impairment and prevention options is important because there are viable options for fertility preservation [9]. Development of a sensitively worded brochure has shown to be effective in discussing cancer issues [10]. The planned intervention study will test the efficacy of flyers and brochures on patient education about risks for fertility and fertility-preserving measures. The primary outcome will be an increased awareness about risk factors for fertility impairment in male and female survivors.

#### 2.2.3. Cohort, case-control and genetic studies on female fertility

PanCareLIFE will investigate the way that treatment impairs female fertility by evaluating anti-Müllerian hormone (AMH) levels and the underlying genetic susceptibility to loss of gonadal function. More than 6000 survivors have completed questionnaires, more than 1500 provided serum samples and more than 1200 case-control triads (400 cases and 800 controls) have been identified.

The occurrence of fertility impairment—reduced pregnancy rates and increased risk of early menopause—after radiation and alkylating agent treatment for cancer during childhood has been known for at least 25 years [11–13]. But because the degree of fertility impairment differs significantly in similarly treated patients, a role is postulated for genetic variation in susceptibility to gonadal damage [14].

Treatment may deplete or accelerate the decline of the non-renewable pool of primordial follicles in the ovary leading to primary ovarian insufficiency with subsequent infertility [15,16]. This results not only in a reduced fertile lifespan and associated risk for involuntary childlessness which can, in turn, negatively impact

Table 2
Name of the scientific work package, objectives and numbers expected to be enrolled into each project of PanCareLIFE.

| Work package and project number | Title | Numbers of research subjects expected |
|---|---|---|
| WP2a | **Fertility preservation guidelines**<br>Specific objectives:<br>1. To develop guidelines for fertility preservation for girls and young females treated for cancer including ethical issues<br>2. To develop guidelines for fertility preservation for boys and young males treated for cancer including ethical issues<br>3. To develop guidelines for interventions intended to preserve fertility that have been shown to be effective in informing children and parents | NA |
| WP2b | **Intervention study to preserve fertility**<br>Specific objectives:<br>1. The primary hypothesis is that an intervention consisting of a flyer and a brochure embedded in counselling about fertility can significantly increase knowledge of fertility among cancer patients (patient empowerment).<br>2. The secondary hypothesis is that the intervention will significantly increase the use of fertility-preserving measures (e.g. cryopreservation) among the study subjects.<br>3. The third hypothesis is that there will be a significant decrease in dysfunctional cognition and fertility-related fears (e.g. I will not be able to have children) and other worries | 128 cases<br>128 controls |
| WP3a | **Female fertility impairment cohort study**<br>Specific objectives:<br>1. To assess the overall absolute risk of fertility impairment in a pan-European cohort of 5-year female survivors of childhood, adolescent and young adult cancer based on clinical and self-reported data.<br>2. To assess the absolute risk and risk factors of fertility impairment for subgroups of female survivors based on the type of cancer, type of treatment (CT yes/no, RT yes/no, surgery yes/no), age group at time of treatment, calendar period at time of treatment | 6339 questionnaires;<br>1916 serum samples |
| WP3b | **Nested case-control study to evaluate effects of treatment on fertility impairment**<br>Specific objectives:<br>1. To identify specific treatment-related and other risk factors most strongly associated with an increased risk of fertility impairment;<br>2. To investigate the nature of the dose-response relationship among the cumulative dose of radiation from radiotherapy, cumulative dose of specific anticancer drugs and the risk of fertility impairment. | 400 cases<br>800 controls |
| WP4a | **Genetics of female gonadal impairment**<br>Specific objectives:<br>1. To validate previously identified genetic polymorphisms associated with gonadal impairment in female childhood cancer survivors, using a candidate gene approach.<br>2. To identify novel SNPs that are independently associated with gonadal impairment in female childhood cancer survivors, using GWAS. | 1450 |
| WP4b | **Genetic risk factors for platinum-related ototoxicity**<br>Specific objectives:<br>1. To confirm previously reported candidate genes to be associated with an increased risk of cisplatin-related hearing impairment in children with cancer<br>2. To identify new susceptibility loci for cisplatin-related hearing impairment through a genome-wide screening approach (GWAS) in an international cohort of children with cancer | 1100 |
| WP5 | **Ototoxicity**<br>Specific objectives:<br>1. Study on phenotypes of platinum-based ototoxicity and non-genetic risk factors (WP5)<br>a) To identify discrete phenotypes of hearing deterioration with respect to severity and time course (early versus late onset) and to describe the frequency of occurrence of different phenotypes.<br>b) To compare the frequencies of hearing loss in platinum-treated patients with the frequencies of hearing loss in a general age-matched population. | 1600 |

(*continued on next page*)

Table 2 (*continued*)

| Work package and project number | Title | Numbers of research subjects expected |
|---|---|---|
| | c) To identify non-genetic risk factors for ototoxicity in cancer survivors and to estimate their predictive value.<br>2. Study on health-related quality of life (in collaboration with WP6)<br>a) To collect data on health-related quality of life (HRQoL) from childhood cancer survivors with hearing impairment<br>b) To compare HRQoL in survivors with population norms.<br>c) To determine the main predictors of HRQoL, particularly the association with sociodemographic, cancer and treatment-related factors and late morbidity, with a focus on hearing impairment.<br>d) To assess intraindividual changes in HRQoL over time and to determine factors associated with change.<br>e) To develop a model for the implementation of regular HRQoL assessment during treatment and in long-term follow-up. | |
| WP6 | **Health-related quality of life**<br>Specific objectives:<br>1. To compare HRQoL among participating countries compared with relevant population norms.<br>a. To compare HRQoL between the pooled European data and already published North American data on HRQoL<br>b. To determine the main predictors of HRQoL, including particularly the association with sociodemographic, cancer and treatment-related factors and late morbidity. A specific focus will be on effects of fertility and hearing impairment on HRQoL and on differences between countries.<br>2. To develop a model for the implementation of regular HRQoL assessment during treatment and in long-term follow-up, linking knowledge on risk groups, clinical trial expertise and follow-up care.<br>3. To assess changes in HRQoL over time within long-term survivors of osteosarcoma and Ewing sarcoma in Europe and to determine factors associated with change, focussing on effects of fertility and hearing impairment and include particularly the association with sociodemographic, cancer and treatment-related factors and late morbidity. | 10,000 |

SNP, single nucleotide polymorphism; GWAS, genome-wide association studies; CT, computed tomography; RT, radiotherapy.

the quality of life [17,18] but also accelerates the risk of developing menopause-associated conditions, such as osteoporosis and ischaemic heart disease [19].

Despite growing knowledge, studies establishing precise estimates of the treatment-related risk, contribution of genetic factors and effects of recently introduced therapeutic agents are still lacking. Nowadays, women often postpone childbearing, so survivors need more precise fertility risk assessments. Therefore, large cohort studies with extended follow-up including relatively new markers of risk, such as AMH, should provide more precise estimates of the risk of future (premature) loss of gonadal reserve [20–22]. PanCareLIFE uses both cohort and case-control methods to investigate risk factors for fertility loss, using clinical outcomes and genetic predictors in female survivors. In addition to validating previously determined relevant single nucleotide polymorphisms, PanCareLIFE uses advanced state-of-the-art studies by using GWAS and meta-analyses in large numbers of samples. PanCareLIFE's genetic studies aim to identify new susceptibility loci for treatment-related gonadal toxicity in female childhood cancer survivors.

### *2.3. PanCareLIFE's studies into ototoxicity*

Platinum derivatives are the basis of a family of chemotherapeutic agents successfully used to treat a variety of malignancies in adulthood and childhood; however, their antitumour efficacy brings potentially severe side-effects. One of the commonest, particularly of cisplatin, is ototoxicity, which can include permanent hearing loss and tinnitus secondary to sensorineural degradation [23]. Recently, sodium thiosulfate has been shown to protect against hearing loss in some children being treated with cisplatin [24].

The degree of hearing loss is highly variable among children treated for cancer with cisplatin [25]. The currently known non-genetic risk factors, such as platinum dose and compound, short-time infusion, renal dysfunction, age, concomitant use of other ototoxic drugs, cranial irradiation and pretherapeutic hearing loss, only partially explain the interindividual variability [26,27]. This led to the hypothesis that genetic factors may render certain individuals more susceptible to the adverse effects of platinum compounds. Accordingly, in recent years, much effort has been spent on identification of

genetic factors predisposing to cisplatin-related ototoxicity [23].

Children, especially, suffer from severe and irreversible ototoxicity after cisplatin administration, in a dose-dependent manner [28,29]. High frequency hearing loss can lead to disturbed speech discrimination in background noise and neurocognitive development, including social and educational development that can impair the quality of life [30,31].

Based on data from pan-European participants, PanCareLIFE will carry out a cohort study, with two sub studies—a pharmacogenetics study and a quality of life study. The genetics study obtained data from cohorts of patients who have been treated in the past for cancer; these patients/survivors were recontacted to update their information and to obtain biospecimens. To obtain standardised and high-quality results, the audiological tests (audiograms) were reviewed and scored by the PanCareLIFE partners at the Audiological Reference Centre in Münster, Germany. Audiograms for more than 2000 survivors were analysed, and almost 1000 samples were sent for genetic analysis related to ototoxicity and fertility.

The objectives are to identify non-genetic, therapy-related risk factors for ototoxicity in cancer survivors, to identify different kinetic phenotypes of hearing deterioration by expert evaluation and to set up the first international GWAS of cisplatin-induced direct ototoxicity in childhood cancer patients to identify novel allelic variants. Finally, these approaches will be combined into an overall assessment of risks relating to ototoxicity in childhood cancer survivors.

### *2.4. PanCareLIFE studies concerned with HRQoL*

As the number of childhood cancer survivors in the European population increases, their HRQoL has become more important [32]. While overall survivors' HRQOL may be little different from siblings/norms [33], differences emerged within tumour entities, when comorbidities are present [34] and when different control groups were used. Furthermore, women seemed more likely to report reduced HRQoL compared with men [35], and HRQoL may decrease with increasing time from diagnosis [36]. Also, there may be differences among European countries [33]. PanCareLIFE will combine a number of different European cohorts for a total of more than 10,000 survivors, some of whom have already had HRQoL assessments using the SF-36 questionnaire.

PanCareLIFE capitalises on the opportunity to conduct a repeated HRQoL assessment in sarcoma survivors [37], who are expected to be at high risk of both fertility impairment and of hearing loss after cancer therapy [38] Levels of HRQoL may deteriorate over time after the end of therapy [39]. Because there is no corresponding information for European childhood cancer survivors, PanCareLIFE includes a longitudinal study of HRQoL, using data from European trials that already have serial HRQoL measures and adding a final measurement.

PanCareLIFE will determine the main predictors of HRQoL, including the loss of fertility and hearing impairment, will assess changes in HRQoL over time within survivors, will determine factors associated with change and will develop a model for the implementation of regular HRQoL assessment during treatment and in long-term follow-up, linking knowledge on risk groups, clinical trial expertise and follow-up care.

## 3. Results

At the time of writing, PanCareLIFE partners are preparing the overall results from the assembled PCL data set for publication. Some articles have been published that are part funded by PanCareLIFE. They concern methods, literature review and results from national or hospital-based data providers and are described briefly here. Thus, for the guidelines WP, Font-Gonzalez [7] noted that only about one-third of existing clinical practice guidelines were of sufficient quality, and these varied substantially. A single-centre longitudinal study [40] showed that the median decline in AMH levels in long-term female survivors is not accelerated and is similar to that observed in controls. A systematic review of the literature on the influence of genetic variation on late toxicity [41] identified 27 articles including 26 candidate gene studies and one GWAS. From Switzerland [42], a report on audiological monitoring showed that monitoring is inadequate, especially before treatment. Another Swiss study [43] of the validity of questionnaire-reported hearing loss showed good agreement with medical records when hearing loss was defined as $>$ grade 1 on the SIOP Boston Ototoxicity Scale. A study of survivors treated with platinum-based chemotherapy evaluated the Distress Thermometer [44] and the Hospital Anxiety and Depression Scale to determine if the challenges facing survivors resulted in more distress and/or anxiety; no differences were found among survivors who were hearing impaired and those who had normal hearing, possibly due to small numbers of subjects. However, a longitudinal study in a small number of survivors from the Netherlands found that hearing loss after cisplatin is irreversible [45]. From the Swiss Childhood Cancer Survivor Study came a report of a significantly decreased prevalence of hearing loss after cisplatin for children treated more recently, suggesting that new treatment regimens with lower doses are benefitting survivors [46]. Seven paediatric oncology centres in the Netherlands reported that higher cumulative doses of cisplatin, young age and furosemide chemotherapy are independently associated with

hearing loss [27]. These results will all be taken into account in analyses of the pan-European PanCareLIFE data set.

## 4. Discussion

PanCareLIFE offers a comprehensive and integrated approach to improve the quality of life for childhood cancer survivors because the new scientific information on risk factors will be translated into guidelines to be disseminated to survivors and healthcare professionals.

Guidelines can bridge the gap between research and clinical practice, improve the quality of care, reduce variability in daily practice and reduce costs, especially as cancer treatments continue to develop and become more complex. The guidelines will be promoted globally to the cancer treatment community and will provide caregivers with specific information to use when discussing fertility preservation with their patients. Survivors will also benefit as the guidelines are intended for their use, enabling them to work cooperatively with their caregivers to achieve fertility preservation, whenever possible.

PanCareLIFE will advance the state of the art in our understanding of fertility impairment resulting from childhood, adolescent and young adult cancer treatment by developing risk assessment models. The overall objectives are to change the clinical practice to reduce the risk of impaired fertility in female survivors and to provide reliable and unbiased evidence for early referral for testing of ovarian reserve in high-risk patients and for counselling, educating and empowering survivors. Our intervention study to determine if written material can increase uptake of fertility preservation measures will help understand how to reach and motivate young patients and their families at diagnosis.

Given the complexity and debilitating short- and long-term side-effects associated with platinum-based therapies, a sustained ototoxicity evaluation must be an essential component of care. Based on the results from PanCareLIFE's association studies, a scoring scheme for risk assessment and guidance of preventive strategies will be developed. Recommendations for standardised hearing tests before, during and after therapy will be compiled. In the future, risk stratification based on epidemiological factors and molecular genetic-based data together with an improved understanding of the pathogenesis of platinum ototoxicity will inform appropriate treatment modifications.

PanCareLIFE's results will help the treatment community, survivors and their families to make informed choices based on their individual risk profile. Thus, our results will form part of the growing impetus towards personalised medicine. For example, children who are genetically predisposed to platinum-related hearing impairment could be treated with regimens that reduce cisplatin or replace it with carboplatin and may benefit from newly developed and validated otoprotection.

The ultimate objective of the HRQoL studies is to develop evidence-based interventions to improve quality of life after cancer and to inform caregivers about patients at risk for decreased HRQoL and lower psychosocial adjustment.

Access to long-term follow-up expertise is essential to ensure that survivors receive appropriate care. Health system barriers may hinder the access to long-term follow-up care, such as minimal resourcing of long-term survivorship programmes and a lack of continuity of care, as survivors transition from paediatric to adult health systems [38]. Care for survivors of childhood cancer involves a range of healthcare providers, who may be unaware of the long-term side-effects of cancer therapies [39]. Government policies directly determine the level of treatment provided by public health systems and can influence the level of treatment covered by health insurance companies. PanCareLIFE will enable the prediction of long-term side-effects so that policy makers can ensure the provision of and access to appropriate long-term follow-up care.

PanCareLIFE's ultimate goal is to improve the health and quality of life of survivors. Because there are few late effects clinics across Europe, we will work with PanCare and the umbrella organisation of survivors and parents, Childhood Cancer International (www.childhoodcancerinternational.org), to reach national organisations of survivors and professionals. The results from PanCareLIFE will be disseminated to numerous audiences across Europe and the United States, including survivors, parents, healthcare providers, researchers and policy makers. Results from our fertility studies will help survivors make informed decisions about their fertility and will assist families and newly diagnosed patients decide about fertility preservation. Guidelines for fertility preservation will be widely available through various media. PanCareLIFE's studies of hearing impairment will provide recommendations for standardised hearing tests, before, during and after treatment. Overall results from the PanCareLIFE consortium will be part of an effort to persuade national and regional governments to put long-term clinics in place.

In describing the PanCareLIFE project, this article has laid out the scientific questions and hypotheses, as well as the specific objectives, design and methodological approaches that the consortium has developed to meet its ambitious goals. It is clear that cure of their original cancer is not the end of the story for many, if not most, survivors. These projects will produce a rich and varied body of knowledge intended to improve the lives of childhood cancer survivors.

## Conflict of interest statement

The authors declare that they have no conflict of interest.

## Role of the funding source

The material presented and views expressed here are the responsibility of the authors only. The EU Commission takes no responsibility for any use made of the information set out.

## Acknowledgements

The authors gratefully acknowledge the participation of survivors of childhood and adolescent cancer and their families in this research. This project has received funding from the European Union Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602030.

The PanCareLIFE Consortium

PanCareLIFE (Grant Agreement no. 602030) is a collaborative project in the 7th Framework Programme of the European Union. Project partners are: Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Germany (PD Dr. P Kaatsch, Dr. D Grabow), Boyne Research Institute, Drogheda, Ireland (Dr. J Byrne, Ms. H. Campbell), Pintail Ltd., Dublin, Ireland (Mr. C Clissmann, Dr. K O'Brien), Academisch Medisch Centrum bij de Universiteitvan Amsterdam, Netherlands (Dr. LCM Kremer), Universität zu Lübeck, Germany (Professor T Langer), Stichting VU-VUMC, Amsterdam, Netherlands (Dr. E van Dulmen-den Broeder, Dr. MH van den Berg), Erasmus Universitair Medisch Centrum Rotterdam, Netherlands (Professor dr. MM van den Heuvel-Eibrink), Charité −Universitätsmedizin Berlin, Germany (Professor A Borgmann-Staudt), Westfälische Wilhelms-Universität Münster, Germany (Professor A am Zehnhoff-Dinnesen), Universität Bern, Switzerland (Professor CE Kuehni), Istituto Giannina Gaslini, Genoa, Italy (Dr. R Haupt), Fakultni Nemocnice Brno, Czech Republic (Dr. T Kepak), Centre Hospitalier Universitaire Saint Etienne − CHU, St. Etienne, France (Dr. C Berger), Kraeftens Bekaempelse, Copenhagen, Denmark (Professor J Falck Winther), Fakultni Nemocnice v Motole, Prague, Czech Republic (Dr. J Kruseova), Universitaetsklinikum Bonn, Bonn, Germany (Dr. G Calaminus, Dr K. Baust) and University Hospital Essen (Professor U. Dirksen).

Data is provided by: Academisch Medisch Centrum bij de Universiteit van Amsterdam, on behalf of the DCOG LATER Study centres, Netherlands (Dr. LCM Kremer), Stichting VU-VUMC, Amsterdam, Netherlands (Dr. E van Dulmen-den Broeder, Dr. MH van den Berg), Erasmus Medisch Centrum Rotterdam, Netherlands (Dr. MM van den Heuvel-Eibrink), Prinses Maxima Centrum, Netherlands (Professor dr. MM van den Heuvel-Eibrink), Netherlands Cancer Institute (Professor F van Leeuwen), Charité −Universitätsmedizin Berlin, Germany (Professor A Borgmann-Staudt, Mr. R. Schilling), Helios Kliniken Berlin Buch, Germany (Dr. G. Strauss), Westfälische Wilhelms-Universität Münster, Germany (Professor A am Zehnhoff-Dinnesen, Professor U Dirksen), University Hospital Essen (Professor U. Dirksen, Dr. A. Ranft), Universität Bern, Switzerland (Professor CE Kuehni), Istituto Giannina Gaslini, Genoa, Italy (Dr. R Haupt, Dr. M-L Garré), Fakultni Nemocnice Brno, Czech Republic (Dr. T Kepak), Centre Hospitalier Universitaire Saint Etienne, France (Dr. C Berger), Kraeftens Bekaempelse, Copenhagen, Denmark (Professor J Falck Winther), Fakultni Nemocnice v Motole, Prague, Czech Republic (Dr. J Kruseova), Universitetet i Oslo, Norway (Professor S Fosså ), Great Ormond Street Hospital (Dr. A Leiper), Medizinische Universität Graz, Austria (Professor H Lackner), Uniwersytet Medyczny w Białymstoku, Bialystok, Poland (Dr. A Panasiuk, Dr. M Krawczuk-Rybak), Heinrich Heine Universität Düsseldorf, Germany (Dr. M Kunstreich), Universität Ulm, Germany (Professor H. Cario, Professor O Zolk), Universität zu Lübeck, Germany (Professor T Langer), Klinikum Stuttgart, Olgahospital, Stuttgart, Germany (Professor S Bielack), Uniwersytet Gdánski, Poland (Professor J Stefanowicz), University College London Hospital, UK (Dr. V Grandage), Sheba Academic Medical Center Hospital, Tel Aviv, Israel (Dr. D. Modan-Moses) and Universitaetsklinikum Bonn, Bonn, Germany (Dr. G Calaminus).

Independent ethics advice was provided by professors Norbert W Paul at the University of Mainz and Lisbeth E. Knudsen from University of Copenhagen.

## References

[1] Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5 − a population-based study. Lancet Oncol 2014;15(1):35−47. https://doi.org/10.1016/S1470-2045(13)70548-5. PMID:24314616.

[2] Geenen MM, Cardous-Ubbink MC, Kremer LC, van den Bos C, van der Pal HJ, Heinen RC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 2007;297(24):2705−15. https://doi.org/10.1001/jama.297.24.2705. PMID:17595271.

[3] Kaatsch P. Epidemiology of childhood cancer. Cancer Treat Rev 2010;36(4):277−85. https://doi.org/10.1016/j.ctrv.2010.02.003. PMID: 20231056.

[4] Hjorth L, Haupt R, Skinner R, Grabow D, Byrne J, Karner S, et al., On behalf of the PanCare Network. Survivorship after childhood cancer: PanCare: a European Network to promote optimal long-term care. Eur J Cancer 2015;51(10):1203−11. https://doi.org/10.1016/j.ejca.2015.04.002. PMID:25958037.

[5] Wallace WH, Critchley HO, Anderson RA. Optimizing reproductive outcome in children and young people with cancer. J Clin

Oncol 2012;30(1):3–5. https://doi.org/10.1200/JCO.2011.38.3877. PMID: 22124090.

[6] Terenziani M, Spinelli M, Jankovic M, Bardi E, Hjorth L, Haupt R, et al. On behalf of the PanCare Network. Practices of pediatric oncology and hematology providers regarding fertility issues: a European survey. Pediatr Blood Cancer 2014;61(11): 2054–8. https://doi.org/10.1002/pbc.25163. PMID: 25065353.

[7] Font-Gonzalez A, Mulder RL, Loeffen EA, Byrne J, van Dulmen-den Broeder E, van den Heuvel-Eibrink MM, et al. Fertility preservation in children, adolescents, and young adults with cancer: quality of clinical practice guidelines and variations in recommendations. Cancer 2016;122(14):2216–23. https://doi.org/10.1002/cncr.30047. PMID: 27175973.

[8] Hohmann C, Borgmann-Staudt A, Rendtorff R, Reinmuth S, Holzhausen S, Willich SN, et al. Patient counselling on the risk of infertility and its impact on childhood cancer survivors: results from a national survey. J Psychosoc Oncol 2011;29(3):274–85. https://doi.org/10.1080/07347332.2011.563344. PMID: 21590573.

[9] Quinn GP, Vadaparampil ST, Gwede CK, Miree C, King LM, Clayton HB, et al. Discussion of fertility preservation with newly diagnosed patients: oncologists' views. J Cancer Surviv 2007;1(2): 146–55. https://doi.org/10.1007/s11764-007-0019-9. PMID: 18648955.

[10] Vadaparampil ST, Quinn GP, Giyshi A, Pal T. Development of a brochure for increasing awareness of inherited breast cancer in black women. Genet Test Mol Biomarkers 2011;15(1–2):59–67. https://doi.org/10.1089/gtmb.2010.0102. PMID: 21275654.

[11] Byrne J, Mulvihill JJ, Myers MH, Connelly RR, Naughton MD, Krauss MR, et al. Effects of treatment on fertility in long-term survivors of childhood or adolescent cancer. N Engl J Med 1987;317(21):1315–21. https://doi.org/10.1056/-NEJM198711193172104. PMID: 3683460.

[12] Byrne J, Fears TR, Gail MH, Pee D, Connelly RR, Austin DF, et al. Early menopause in long-term survivors of cancer during adolescence. Am J Obstet Gynecol 1992;166(3):788–93. PMID: 1550144.

[13] Reulen RC, Zeegers MP, Wallace WH, Frobisher C, Taylor AJ, Lancashire ER, et al. Pregnancy outcomes among adult survivors of childhood cancer in the British Childhood Cancer Survivor Study. Cancer Epidemiol Biomark Prev 2009;18(8):2239–47. https://doi.org/10.1158/1055-9965.EPI-09-0287. PMID: 19661083.

[14] van Dorp W, van den Heuvel-Eibrink MM, Stolk L, Pieters R, Uitterlinden AG, Visser JA, et al. Genetic variation may modify ovarian reserve in female childhood cancer survivors. Hum Reprod 2013;28(4):1069–76. https://doi.org/10.1093/humrep/des472. PMID: 23360674.

[15] Larsen EC, Müller J, Schmiegelow K, Rechnitzer C, Andersen AN. Reduced ovarian function in long-term survivors of radiation- and chemotherapy-treated childhood cancer. J Clin Endocrinol Metab 2003;88(11):5307–14. https://doi.org/10.1210/jc.2003-030352. PMID: 14602766.

[16] van den Berg MH, Overbeek A, Lambalk CB, Kaspers GJL, Bresters D, van den Heuvel-Eibrink MM, et al. Long-term effects of childhood cancer treatment on hormonal and ultrasound markers of ovarian reserve. Hum Reprod 2018 Jul 6. https://doi.org/10.1093/humrep/dey229. Epub ahead of print.

[17] Gorman JR, Su HI, Roberts SC, Dominick SA, Malcarne VL. Experiencing reproductive concerns as a female cancer survivor is associated with depression. Cancer 2015;121(6):935–42. https://doi.org/10.1002/cncr.29133. PMID: 25377593.

[18] Benedict C, Shuk E, Ford JS. Fertility issues in adolescent and young adult cancer survivors. J Adolesc Young Adult Oncol 2016; 5(1):48–57. https://doi.org/10.1089/jayao.2015.0024. PMID: 26812452.

[19] Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: long-term health consequences. Maturitas 2010;65(2):161–6. https://doi.org/10.1016/j.maturitas.2009.08.003. PMID:19733988.

[20] Van Dorp W, van Beek RD, Laven JS, Pieters R, de Muink Keizer-Schrama SM, van den Heuvel-Eibrink MM. Long-term endocrine side effects of childhood Hodgkin's lymphoma treatment: a review. Hum Reprod Update 2012;18(1):12–28. https://doi.org/10.1093/humupd/dmr038. PMID: 21896559.

[21] Hamre H, Kiserud CE, Ruud E, Thorsby PM, Fosså SD. Gonadal function and parenthood 20 years after treatment for childhood lymphoma: a cross-sectional study. Pediatr Blood Cancer 2012;59(2):271–7. https://doi.org/10.1002/pbc.23363. PMID: 22021108.

[22] Lie Fong S, Lugtenburg PJ, Schipper I, Themmen AP, de Jong FH, Sonneveld P, et al. Anti-müllerian hormone as a marker of ovarian function in women after chemotherapy and radiotherapy for haematological malignancies. Hum Reprod 2008;23(3):674–8. https://doi.org/10.1093/humrep/dem392. PMID: 18216040.

[23] Langer T, am Zehnhoff-Dinnesen A, Radtke S, Meitert J, Zolk O. Understanding platinum-induced ototoxicity. Trends Pharmacol Sci 2013;34(8):458–69. https://doi.org/10.1016/j.tips.2013.05.006. PMID:23769626.

[24] Brock PR, Maibach R, Childs M, Rajput K, Roebuck D, Sullivan MJ, et al. Sodium thiosulfate for protection from cisplatin-induced hearing loss. N Engl J Med 2018;378:2376–85. https://doi.org/10.1056/NEJMoa1801109. PMID: 29924955.

[25] Al-Khatib T, Cohen N, Carret AS, Daniel S. Cisplatinum ototoxicity in children, long-term follow up. Int J Pediatr Otorhinolaryngol 2010;74(8):913–9. https://doi.org/10.1016/j.ijporl.2010.05.011. PMID: 20846503.

[26] Weissenstein A, Deuster D, Knief A, Zehnhoff-Dinnesen AA, Schmidt CM. Progressive hearing loss after completion of cisplatin chemotherapy is common and more pronounced in children without spontaneous otoacoustic emissions before chemotherapy. Int J Pediatr Otorhinolaryngol 2012;76(1):131–6. https://doi.org/10.1016/j.ijporl.2011.10.020. PMID: 22104469.

[27] Clemens E, de Vries AC, Pluijm SF, am Zehnhoff-Dinnesen A, Tissing WJ, Loonen JJ, et al. Determinants of ototoxicity in 451 platinum-treated Dutch survivors of childhood cancer: A DCOG late-effects study. Eur J Cancer 2016;69:77–85. https://doi.org/10.1016/j.ejca.2016.09.023. PMID:27821322.

[28] Stöhr W, Langer T, Kremers A, Bielack S, Lamprecht-Dinnesen A, Frey E, et al. Cisplatin-induced ototoxicity in osteosarcoma patients: a report from the late effects surveillance system. Cancer Invest 2005;23(3):201–7. PMID: 15945505.

[29] Scobioala S, Parfitt R, Matulat P, Kittel C, Ebrahimi F, Wolters H, et al. Impact of radiation technique, radiation fraction dose, and total cisplatin dose on hearing : Retrospective analysis of 29 medulloblastoma patients. Strahlenther Onkol 2017;193(11): 910–20. https://doi.org/10.1007/s00066-017-1205-y. PMID: 28887665.

[30] Bess FH, Dodd-Murphy J, Parker RA. Children with minimal sensorineural hearing loss: prevalence, educational performance, and functional status. Ear Hear 1998;19:339–54. PMID:9796643.

[31] Tharpe AM. Unilateral and mild bilateral hearing loss in children: past and current perspectives. Trends Amplif 2008;12(1):7–15. https://doi.org/10.1177/1084713807304668. PMID:18270174.

[32] Essig S, Skinner R, von der Weid NX, Kuehni CE, Michel G. Follow-up programs for childhood cancer survivors in Europe: a questionnaire survey. PLoS One 2012;7(12):e53201. https://doi.org/10.1371/journal.pone.0053201. PMID: 23300889.

[33] Lund LW, Schmiegelow K, Rechnitzer C, Johansen C. A systematic review of studies on psychosocial late effects of childhood cancer: structures of society and methodological pitfalls may challenge the conclusions. Pediatr Blood Cancer 2011;56(4): 532–43. https://doi.org/10.1002/pbc.22883. PMID:21298737.

[34] Rueegg CS, Gianinazzi ME, Rischewski J, Beck Popovic M, von der Weid NX, Michel G, et al. Health-related quality of life in survivors of childhood cancer: the role of chronic health problems. J Cancer Surviv 2013;7(4):511–22. https://doi.org/10.1007/s11764-013-0288-4. PMID:23784593.

[35] Alessi D, Dama E, Barr R, Mosso ML, Maule M, Magnani C, et al. Health-related quality of life of long-term childhood cancer survivors: a population-based study from the Childhood Cancer Registry of Piedmont, Italy. Eur J Cancer 2007;43(17):2545–52. PMID: 17869094.

[36] Michel G, Greenfield DM, Absolom K, Ross RJ, Davies H, Eiser C, et al. Follow-up care after childhood cancer: survivors' expectations and preferences for care. Eur J Cancer 2009;45(9): 1616–23. https://doi.org/10.1016/j.ejca.2009.02.026. PMID: 19238676.

[37] Marina N, Bielack S, Whelan J, Smeland S, Krailo M, Sydes MR, et al. International collaboration is feasible in trials for rare conditions: the EURAMOS experience. Cancer Treat Res 2009;152: 339–53. https://doi.org/10.1007/978-1-4419-0284-9_18. PMID: 20213400.

[38] Thouvenin-Doulet S, Berger C, Casagranda L, Oberlin O, Marec-Berard P, Pacquement H, et al. Fecundity and quality of life of women treated for solid childhood tumors between 1948 and 1992 in France. J Adolesc Young Adult Oncol 2018;7(4):415–23. https://doi.org/10.1089/jayao.2017.0126. PMID: 29851372.

[39] Heutte N, Flechtner HH, Mounier N, Mellink WA, Meerwaldt JH, Eghbali H, et al. Quality of life after successful treatment of early-stage Hodgkin's lymphoma: 10-year follow-up of the EORTC-GELA H8 randomised controlled trial. Lancet Oncol 2009;10(12):1160–70. https://doi.org/10.1016/S1470-2045(09)70258-X. PMID: 19828373.

[40] van der Kooi ALF, van den Heuvel-Eibrink MM, van Noortwijk A, Neggers SJCMM, Pluijm SMF, van Dulmen-den Broeder E, et al. Longitudinal follow-up in female Childhood Cancer Survivors: no signs of accelerated ovarian function loss Human Reprod 2017;32(1):193–200. https://doi.org/10.1093/humrep/dew278. PMID: 27821706.

[41] Clemens E, van der Kooi ALF, Broer L, Van Dulmen-den Broeder E, Visscher H, Kremer L, et al. The influence of genetic variation on late toxicities in childhood cancer survivors: a review. Crit Rev Oncol-Hematol 2018;126:154–67. https://doi.org/10.1016/j.critrevonc.2018.04.001. PMID: 29759558.

[42] Weiss A, Kuonen R, Brockmeier H, Grotzer M, Candreia C, Maire R, et al. Audiological monitoring in Swiss childhood cancer patients. Pediatr Blood Cancer 2017;65(3):e26877. https://doi.org/10.1002/pbc.26877. PMID: 29230928.

[43] Weiss A, Sommer G, Kuonen R, Scheinemann K, Grotzer M, Kompis M, et al. Validation of questionnaire-reported hearing with medical records: A report from the Swiss Childhood Cancer Survivor Study. PLoS One 2017;12(3), e0174479. https://doi.org/10.1371/journal.pone.0174479. PMID: 28333999.

[44] Clemens E, van Doorn M, Neggers SJCMM, de Vries ACH, van den Heuvel-Eibrink MM. Socio-demographic impact of platinum-induced ototoxicity in long-term survivors of childhood cancer. Curr Pediatr Res 2017;21(3):470–9.

[45] Clemens E, de Vries ACH, am Zehnhoff-Dinnesen A, Tissing WJE, Loonen JJ, Pluijm SFM, et al. Hearing loss after platinum treatment is irreversible in noncranial irradiated childhood cancer survivors. Pediatric Hematol Oncol 2017;34(2):120–9. https://doi.org/10.1080/08880018.2017.1323985. PMID:28590156.

[46] Weiss A, Sommer G, Kasteler R, Scheinemann K, Grotzer M, Kompis M, et al. Long-term auditory complications after childhood cancer: a report from the Swiss childhood cancer survivor study. Pediatr Blood Cancer 2017;64(2):364–73. https://doi.org/10.1002/pbc.26212. PMID: 27650356.