Handbook for Guideline Development

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On behalf of the IGHG core group and the PanCare Guidelines Group

This handbook has been developed by a collaborative effort of the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) (www.ighg.org) and the PanCare Guidelines Group) (www.pancare.eu).

This handbook can be used by the chairs and members of the IGHG guideline panels after they have been assigned to develop a special guideline.

This Handbook should be cited as Mulder RL, van Dalen EC, Brown MC, Skinner R, Hudson MM, Kremer LCM. Handbook for guideline development; collaboration between International Guideline Harmonization Group and PanCare Guidelines Group. 2024

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Contents

1 Introduction

1.1 Aim of the handbook

The principle aim of this handbook is to serve as a reference tool and provide guidance to the members of the guideline panels involved in the guideline development work of the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG)[1] (www.ighg.org) and the PanCare Guidelines Group (www.pancare.eu). The systematic approach outlined in this manual aims to improve the methodological quality of the clinical practice guidelines for childhood, adolescent and young adult (CAYA) cancer patients and the follow-up of survivors, and positively impact on the quality of care CAYA cancer patients and survivors receive.

1.2 Clinical practice guidelines

Clinical practice guidelines are defined by the Institute of Medicine as *"statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options*.[1] Guidelines aim to provide appropriate recommendations for practice based on a transparent process and informed by evidence. Guidelines are essential to ensuring that childhood cancer patients and survivors receive optimum health care.[1,2] However, it is essential to ensure optimum quality of guidelines if they are to improve both the process and outcome of care.

It is critical that guidelines are developed based on the methods of evidence-based medicine (EBM). EBM is defined as *"the process of integrating clinical expertise with the best research evidence to make high-quality decisions about the care of individual patients"*.[3,4] A clinical decision based on the EBM principles combines high-quality clinical research with clinical expertise, patient values (such as preferences and expectations) and social considerations (such as cost). [3,5] The introduction of EBM has informed clinical decision-making in health care by clarifying the quality of the evidence available and knowledge gaps related to specific clinical topics.

Within pediatric oncology there are a lot of protocols in which there is no clear distinction between the evidence and recommendations. Moreover, it is often unclear where the recommendations are based on. When evidence-based guidelines are developed, there should be a clear distinction between scientific knowledge and recommendations. When generating recommendations from evidence, several factors are considered, such as the quality of the evidence, clinical expertise and patient values (see Figure 1).

Figure 1. Clinical practice guidelines: from evidence to recommendations

1.3 Guidelines for the long-term follow-up of CAYA cancer survivors

Several guidelines for the long-term follow-up of CAYA cancer survivors have been developed, published and widely disseminated, including those produced by the US Children's Oncology Group (COG), Dutch Childhood Oncology Group (DCOG), United Kingdom Children's Cancer Study Group (UKCCSG) and Scottish Intercollegiate Guidelines Network (SIGN). A recent survey performed by PCSF found that these guidelines were in widespread use across Europe and that some European nations have also developed additional local guidelines.

However, as existing guideline development groups worked independently, inconsistencies exist in the methodology used and also in the final recommendations of these guidelines. A major consequence of this is uncertainty among clinicians regarding which guidelines to implement.

Therefore, the goal of the IGHG and PanCare Guidelines Group is to harmonise efforts and employ a systematic and rigorous methodology to produce clinical consensus in guidelines for long-term follow up of major late adverse effects in CAYA cancer survivors. We aim to promote healthy lifestyles, provide on-going monitoring of health status, facilitate early detection of late effects, and advise about timely intervention strategies to preserve health.

1.4 Structure of this handbook

In this handbook we aim to provide information that may be useful to members of the IGHG/PanCare Guidelines Group guideline panels. Specifically the handbook will:

1. Outline the key steps in the development of clinical practice guidelines.
2. Direct guideline panel members to other important and more detailed sources of information integral to the guideline development.
3. Provide practical information regarding the organisation and management of guideline development.

As opposed to fully reproducing information which is documented elsewhere, this handbook provides an overview and directs members to other documents that explain the relevant issues in more detail. Links to these other documents are embedded in the text, and can be accessed by clicking on the document name. These documents include a published methodology paper, protocols from previous guideline topics that have been completed by IGHG, and also practical examples from the published guidelines to more clearly illustrate the process.

2 Methodology to develop evidence-based guidelines

Developing a guideline is a structured process and consists of three phases:

1. Preparation phase
2. Development phase
3. Finalisation phase

2.1 Preparation phase

The guideline panel

Convening an effective guideline panel is a crucial stage in producing a guideline. Each guideline panel will consist of a working group including:

- Chair(s), leading the guideline panel as leaders in the field.
- Coordinator(s), managing the guideline development process.
- Advisors, providing methodological support and specific expertise.
- In case of different working groups: Working group leaders, leading a specific working group of focused clinical questions.
- Working group members, including the experts in the field.

Diversity is an essential feature of a guideline panel. Its exact composition should be tailored to the guideline topic and reflect the range of stakeholders involved. At a minimum the panel should comprise at least of content experts, non-expert clinicians, health care providers and methodologists. In addition, there is evidence that involving patients or their representatives may positively influence the scope, process and recommendations of a guideline. Therefore it is important to involve patient representatives as well.

Scope of the guideline

It is important to define the scope of the guideline, including the goal, population of interest and definition of outcomes or health problems.

The age range of the population of interest should be determined, e.g. childhood, adolescent and young adult cancer survivors diagnosed with cancer up to age 25 years. Depending on the health problem, adaptation of the age range (i.e., 18, 21, 30 or 35 years) may be appropriate.

In addition, the survival time of the population of interest should be determined, e.g. childhood, adolescent and young adult cancer survivors 2-years after completion of treatment. Depending on the health problem, adaptation of the survival time (i.e., immediately following or 5 years post-treatment) may be appropriate.

For every surveillance guideline topic, the following key issues can be considered which are important for the final recommendations:

- Does early diagnosis result in better outcomes?
- Who needs surveillance?
- At what age or time from exposure should surveillance be initiated?
- At what frequency should surveillance be performed?

- When should surveillance be stopped?
- What surveillance modality should be used?
- What should be done if abnormalities are identified?

2.2 Development phase

In general, the guideline development process consists of five steps:

1. Evaluation of concordant and discordant guideline areas in existing recommendations.
2. Formulation of clinical questions.
3. Identification of available evidence by systematic literature searches.
4. Summarizing and grading the evidence.
5. Formulation and grading the recommendations.

Figure 2 outlines the main steps for the development of guideline recommendations.

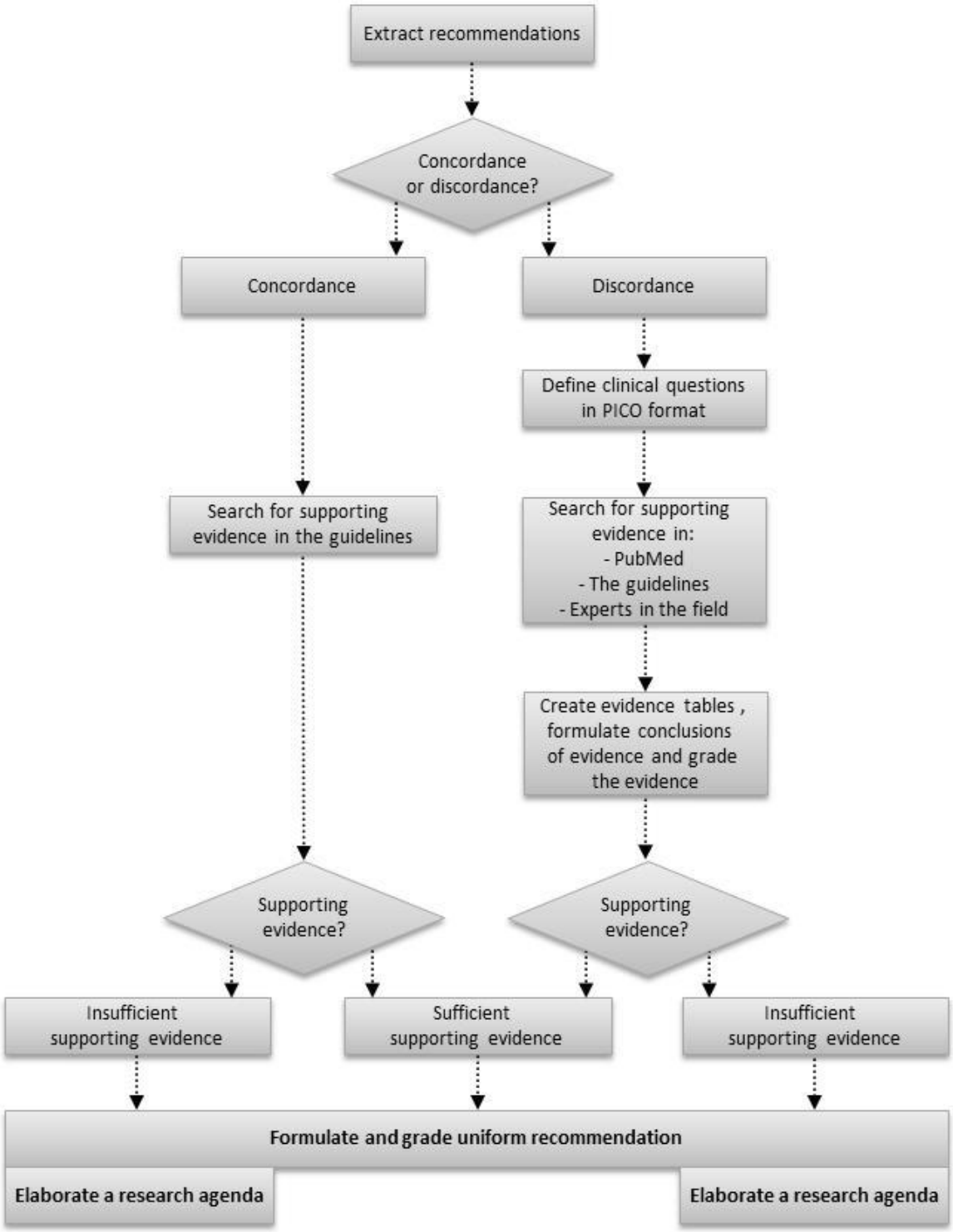

Figure 2. Key stages in the development of recommendations

Step 1: Evaluation of concordant and discordant guideline areas

The first step is to extract the recommendations for the topic from the existing and more widely disseminated guideline groups (e.g., COG, DCOG, UKCCLG and SIGN guidelines). The level of discordance/concordance between these recommendations is then evaluated.

If recommendations are concordant, the quality of the supporting evidence will be reviewed to determine if it is sufficient or insufficient. Extensive evidence summaries will not be developed for concordant recommendations.

Discordant recommendations will form the basis for the formulation of clinical questions. These clinical questions will clearly state what the evidence aims to answer.

Below is an example of the evaluation of the concordance and discordance regarding the surveillance of breast cancer in survivors (Table 1).

Table 1. Concordance and discordance 'Who needs breast cancer surveillance?'

	COG	DCOG	UKCCLG	Concordant/ discordant
Who needs breast cancer surveillance?				
At risk **Chest radiation**	Yes	Yes	Yes	**Concordant**
± Alkylating agents	Not specified	Not specified	Yes	**Discordant**
High risk	Not specified	≥7-20 Gy chest radiation (excl. TBI) ≥14-40 Gy abdominal radiation	Not specified	**Discordant**
Highest risk	≥20 Gy chest radiation	≥20 Gy chest radiation ≥40 Gy abdominal radiation TBI	Not specified	**Discordant**

Step 2: Formulation of clinical questions

Effective and efficient guideline development involves asking and answering clinical questions. These questions should be clear, focused and closely define the boundaries of the topic. The clinical questions may relate to etiology, screening and prevention, diagnosis, therapy and interventions, prognosis and follow-up, and organization of care. They will serve as a starting point for the systematic literature search that aims to identify all the available evidence.

The PICO (Participants, Interventions, Control group & Outcome) framework is helpful to identify the main elements of the clinical question. It breaks the question down into four key elements:

- What are the characteristics of the participants you are interested in? (e.g. type of malignancy, stage of disease, gender, age, minimal survival time)
- What is the intervention you want to evaluate? (e.g. type of treatment)
- What is the comparison you are interested in? (e.g. different type of treatment, no intervention; this is not always relevant)
- What are relevant outcomes? (e.g. survival, adverse effects)

Examples of the PICO method and the formulation of a clinical question are shown in Table 2.

Table 2. Examples of the PICO method and clinical questions

Does early diagnosis result in better outcomes?

P	I	C	O	Clinical question
Childhood, adolescent and young adult cancer survivors with a CNS neoplasm	Tumor size, asymptomatic or symptomatic stage	Not applicable	Mortality, recurrence, survival, adverse events, quality of life	Does the detection of a meningioma in a smaller size or asymptomatic stage contribute to a reduced mortality rate in CAYA cancer survivors?

Who needs surveillance?

P	I	C	O	Clinical question
Female childhood, adolescent and young adult cancer survivors	Low dose chest radiation	Childhood cancer survivors treated without chest radiation	Breast cancer risk	What is the risk of breast cancer in female CAYA cancer survivors treated with 1-9 Gy chest radiation compared to survivors treated without chest radiation?

At what age or time from exposure should surveillance be initiated?

P	I	C	O	Clinical question
Female childhood, adolescent and young adult cancer survivors	Chest radiation	N/A	Latency time breast cancer	What is the latency time (time of onset) to develop breast cancer in CAYA cancer survivors treated with chest radiation?

At what frequency should surveillance be performed?

P	I	C	O	Clinical question
Female childhood, adolescent and young adult cancer survivors	Chest radiation	N/A	Breast cancer risk over time	Does the breast cancer risk change over time (improve, deteriorate, plateau) in female CAYA cancer survivors treated with chest radiation? What is the timing of such change?

When should surveillance be stopped?

P	I	C	O	Clinical question
Female childhood, adolescent and young adult cancer survivors	Chest radiation	N/A	Breast cancer risk in CAYA cancer survivors aged >60 years	What is the risk of breast cancer in CAYA cancer survivors treated with chest radiation aged >60 years?

What surveillance modality should be used?

P	I	C	O	Clinical question
Female childhood, adolescent and young adult cancer survivors	MRI	Mammography	Diagnostic value to detect breast cancer	What is the diagnostic value (sensitivity, specificity, predictive value) of a MRI compared to a mammography to detect breast cancer in female CAYA cancer survivors?

What should be done if abnormalities are identified?

P	I	C	O	Clinical question
Childhood, adolescent and young adult cancer survivors	Physical activity training	No physical activity training	Pulmonary outcomes	What are the positive and adverse effects of physical activity on pulmonary outcomes in CAYA cancer survivors?

Step 3: Identification of available evidence by systematic literature searches

It is important that the literature search is thorough, objective and rigorous. An inefficient or biased literature search can compromise the validity of the recommendations and the guidelines. The aim is to identify as many relevant studies as possible (within the limits of resources and time). It is also essential that the literature search is transparent, well documented and reproducible.

Where adequate published systematic reviews exist, additional literature searches may be limited to updating, covering the time period since the review was conducted.

Carrying out a literature search to identify and select relevant studies will involve:

A. Developing search strategies.
B. Defining in- and exclusion criteria.
C. Selecting relevant studies.

A. Developing search strategies

Where to search? Searches are carried out in bibliographic databases. There are several that can be searched but PubMed/MEDLINE and Embase are two of the key international health databases. Although there is significant overlap in these databases, differences do exist. The Cochrane Central Library of Controlled Trials is also a database for systematic reviews that can be searched.

In addition to searching bibliographical databases, papers should also be identified through references in the existing guidelines, as well as important reviews and key papers known to the group members.

What to search? The clinical questions serve as the starting point for the development of a sensitive search strategy. The search strategy is based on the PICO model and should use controlled vocabulary (which is specific for each database, like MeSH in PubMed/MEDLINE and EMTREE in Embase) and free-text words. It is important to consider all of the related terms, variations in spellings and synonyms for each PICO item included in the search. It is strongly advised that this is done in collaboration with a trained information specialist.

Different search terms can be combined using Boolean operators like “OR” (retrieves articles labelled by at least one of the search terms), “AND” (retrieves only articles labelled by all search terms), and “NOT” (excludes search terms from the search) (see Figure 3). “NOT” must be used very carefully as important publications may be missed when it is included in the search strategy. An example of a full search can be found in Appendix 1.

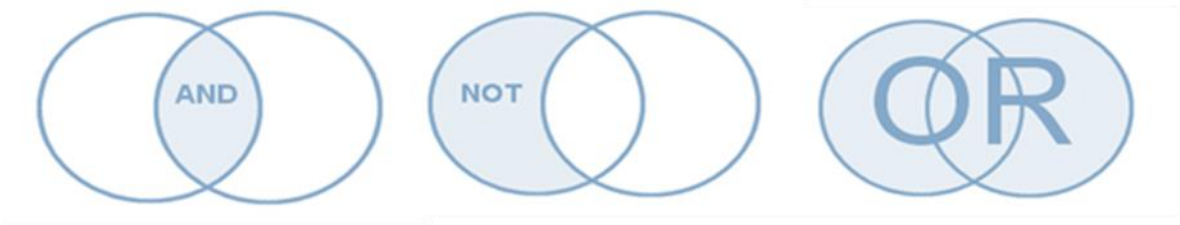

Figure 3. Use of Boolean operators

In order to be transparent and reproducible it is important to report your search strategy in detail: which database, what interface, complete and detailed search terms, the date the search was run in each source, the years covered by the search and, if applicable, use of any limits.

Standard search strategies developed by the Systematic Review & Guideline Unit are presented in Appendix 2.

More information on developing a search strategy:

- ✓ *Lundh A, Kremer LCM, Leclercq E. Development of a search strategy. Evid.-Based Child Health 2007; 2(2): 937-939*
- ✓ *Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from https://handbook-5-1.cochrane.org/*
- ✓ *Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook*
- ✓ *Van Dalen EC, Kremer LC. Inclusion of studies into a Cochrane review. Evid.-Based Child Health 2006; 1(4): 1349-1351*

B. Defining in- and exclusion criteria

The selection of studies for inclusion in the guideline should be based on clearly defined in- and exclusion criteria based on the PICO model. The following points should be considered, but for each specific clinical question additional issues can apply:

- **Participants:**
  - Childhood, adolescent and young adult cancer survivors
  - At least 75% diagnosed with cancer prior to the defined age range (i.e.,18 / 21 / 25 / 30 / 35 years)
  - At least 50% survived the defined survival time (i.e., immediate end of treatment / ≥ 2 years post-treatment / ≥ 5 years post-treatment)
- **Intervention and comparison treatments:** be very specific (for example, should only one chemotherapeutic agent be different between the treatment groups, dosage, timing).
- **Outcomes:**
  - Outcome definition of specific late effect
  - Studies investigating one of the following outcomes depending on the clinical question:
    - For 'Who needs surveillance?': risks and risk factors.
    - For 'At what age or time from exposure should surveillance be initiated?: latency time / time of onset after exposure.
    - For 'At what frequency should surveillance be performed?': risks over time.
    - For 'What surveillance modality should be used?': diagnostic value / sensitivity, specificity, positive predictive value, negative predictive value of diagnostic tests.
    - For 'What should be done if abnormalities are identified?': effectiveness of interventions that may result in better outcomes.
  - For each outcome decide if you are:
    - Only interested in a specific definition or in all definitions used by the included studies.

        - Only interested in multivariable risk factor analyses or also univariable ones (when you are looking at risk factors in your review).
- **Types of studies:**
    - Study design: choose the most optimal study design to answer the specific clinical question. For example randomized controlled trials for intervention questions, diagnostic test accuracy studies for diagnostic questions, or observational studies for etiological questions. Case reports and case series will be excluded.
        - Regarding reviews: During screening of abstracts include all reviews (both systematic and narrative reviews). In cases of systematic reviews, include and use data / conclusions for generating evidence tables. In cases of narrative reviews, exclude, but screen reference lists in order to check for missing relevant papers.
    - Define minimum sample size, for example at least N=20 depending on the clinical problem and availability of evidence.
    - Language: for pragmatic reasons, studies published in English will be included only.
    - Define dates of search parameters, e.g., published from a specific date onwards (i.e. 1990).

C. Selecting relevant studies

When the searches have been run and the results are de-duplicated (for example in endnote software: https://endnote.com) two independent reviewers should assess if publications meet the inclusion criteria.

There are different phases in the study selection process:

1. Title and/or abstract phase:
   In the title/abstract phase you can choose: eligible, not eligible, or unclear if eligible. In case of doubt always select the article for full text assessment. The results of the reviewers' assessments should be compared and discrepancies discussed and resolved. If that is not possible, a so-called third party arbitration by another reviewer can help.
2. Obtain full text publications for articles labelled as eligible or unclear if eligible for inclusion. Some will be publicly available and others will be available at your local library (or can be requested there).
3. Full text phase:
   In the full text phase you can choose: eligible or not eligible. Again, the results of the reviewers' assessments should be compared and discrepancies discussed and resolved. If that is not possible, a so-called third party arbitration by another reviewer can help. Reasons for study exclusion should be noted.

There is software available that can help you with this step of the review process, for example Rayyan (https://rayyan.ai) or Covidence (https://get.covidence.org/systematic-review-software).

Systematic reviews are eligible for inclusion, but narrative reviews are not. In this case, reviewers should screen reference lists of important narrative reviews to obtain relevant papers not included in other search sources. Reviewers can for example make a list of possible relevant reviews during the title and/or abstract phase and obtain the full text publications to look at the reference lists.

In addition to the PubMed search, additional studies will be identified by:

- References in reviews
- References supporting the existing long-term follow-up guidelines
- Experts in the field

When evidence is lacking for childhood and young adult cancer survivors, you can decide to carefully extrapolate evidence from other populations.

Step 4: Summarizing and grading the evidence

A. Extracting data into evidence tables

The identified studies should be summarized in evidence tables (see Appendix 3). The evidence tables provide information about study and patient characteristics, primary study outcomes, risk of bias, and additional remarks, such as other factors that may bias results. Different checklists are available to assess the risk of bias in included studies and largely depend on the type of clinical question. In Appendix 4 the different risk of bias criteria are listed.

The data-extraction of the studies should be performed by one author and checked by another independent author. It is useful to prepare instructions on how to fill out the evidence tables for authors performing or checking the data extraction.

B. Preparing summary of findings tables and grading the quality of evidence

The next step is the preparation of summary of findings tables. They provide an overview of the body of evidence for a specific clinical question and include information on study and patient characteristics, outcomes and associated effect estimates per study (see Appendix 5).

For every clinical question, an assessment of and rationale for the quality of the evidence using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodology (https://www.gradeworkinggroup.org/) should be included. The GRADE Working Group has developed a system for grading the quality of a body of evidence.[6-9] The quality of a body of evidence is defined as the extent to which one can be confident that an identified effect or association is true.

The evidence is graded according to four levels:

- ⨁⨁⨁⨁ High: further research is unlikely to change the confidence in the estimate of effect.
- ⨁⨁⨁⊖ Moderate: further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.
- ⨁⨁⊖⊖ Low: further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.
- ⨁⊖⊖⊖ Very low: any estimate of effect is very uncertain.

The initial score (start point) is based on study type and clinical question. For example for intervention questions, randomized studies start at high level of evidence, while controlled clinical trials and observational studies start at a low level of evidence. In addition, for etiologic questions, observational studies start at high level of evidence.

Assessing the quality of a body of evidence involves several considerations. There are five reasons for downgrading the quality of a body of evidence:

- Study limitations (risk of bias, see Appendix 4): the confidence in the body of evidence decreases when studies have major limitations that may bias the risk estimates. Every study addressing a particular outcome will differ, to some degree, in the risk of bias. The reviewers must make an overall judgement on whether the quality of evidence for an outcome warrants downgrading on the basis of study limitations.

- Inconsistency of the results (heterogeneity): the confidence in the body of evidence decreases when there is a degree of inconsistency of effect between or within studies (when studies yield widely differing estimates of effect). When heterogeneity exists and affects the interpretation of results, but reviewers fail to identify a plausible explanation, the quality of the evidence decreases.
- Indirectness of the study population and outcomes: the confidence in the body of evidence decreases when the study population and outcomes from the studies are not generalizable to the population and outcome of interest. Reviewers should make judgements transparent when they believe downgrading is justified, based on differences in anticipated effects in the group of primary interest.
- Imprecision of the effect estimates: the confidence in the body of evidence decreases when the effect estimates are imprecise. This is the case if studies include relatively few patients and few events and thus have wide confidence intervals.
- Risk of publications bias: the confidence in the body of evidence decreases when investigators fail to report studies or outcomes on the basis of results, typically those studies that show no effect.

There are also circumstances in which the quality of the body of evidence can be upgraded:

1. Large magnitude of effect: the confidence in the body of evidence increases when methodologically well-performed observational studies yield large, consistent and precise estimates of the magnitude of effect.
2. Dose response gradient: the confidence in the body of evidence increases when there is evidence for a dose response across or within studies, or when inconsistency across studies is explained by a dose response.
3. Plausible confounding: the confidence in the body of evidence increases when adjustment for confounding factors would have increased the effect size.

In Appendix 6 the criteria for grading the quality of the body of evidence is described.

The GRADE-CERQual approach is used to assess the confidence of evidence from qualitative research (see Appendix 7).[10]

The rational for grading the quality of the body of evidence should be described in the summary of findings table (see Appendix 5).

C. Formulating conclusions of evidence

Based on the quality of the body of evidence an overall conclusion will be formulated for that specific clinical question (see Appendix 5). All conclusions of evidence and their levels of evidence should be summarized in a conclusion of evidence table (see Appendix 8).

Grading the evidence gives an impression of the quality of the included studies. It is not related to the importance of the recommendation but to the strength of the supporting evidence.

More information on summary of findings tables and GRADE assessment:

- ✓ *Langendam MW, Kuijpers T, de Beer H, Kremer LCM. An introduction to the GRADE approach; rating the quality of evidence for an intervention Evid.-Based Child Health 2010; 5(2):537-540*
- ✓ *Schünemann H, Brożek J, Guyatt G, Oxman A (editors). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. Available from https://gdt.gradepro.org/app/handbook/handbook.html*
- ✓ *Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook*
- ✓ *Other articles from the GRADE working group in the Journal of Clinical Oncology: https://www.gradeworkinggroup.org/*

D. What to do when evidence is lacking

When evidence is lacking or of low quality, and more evidence is needed to formulate recommendations, you can carefully extrapolate evidence from other populations, e.g. other pediatric diseases or adult oncology. First, evidence-based guidelines should be identified for this population of interest. The recommendations from these guidelines can be extracted to refine the considerations and inform the recommendations (see step 5). Moreover, the conclusions of evidence included in the identified guidelines can be extracted if there is a need to identify the evidence base for these recommendations.

Other potential sources of additional literature are systematic reviews from other populations. However, it is not advisable to perform additional systematic literature searches since the time investment is in most cases not worth the yield.

Step 5: Formulation and grading of the recommendations

Once the selection and summary of the evidence is complete, the available evidence must be combined and translated into recommendations. For this purpose we will use the GRADE Evidence to Decision (EtD) framework (see Appendix 9).[11] The EtD framework ensures that all important criteria for making a decision is considered and informs the guideline panel about the relative pros and cons of the interventions or options being considered. It makes the decision making process structured and transparent.

The following criteria should be considered when formulating clinical recommendations:

1. Problem: Is the problem a priority?
2. Desirable effects: Are the desirable anticipated effects large?
3. Undesirable effects: Are the undesirable anticipated effects small?
4. Certainty of the evidence: What is the overall certainty of the evidence of effects?
5. Values: Is there important uncertainty about or variability in how much people value the main outcomes?
6. Balance of effects: Are the desirable effects large relative to the undesirable effects?
7. Resources required: Are the resource required small?
8. Certainty of evidence of required resources: What is the overall certainty of the evidence of the resources require?
9. Cost effectiveness: Is the incremental cost small relative to the net benefits?
10. Equity: What would be the impact on health equity?
11. Acceptability: Is the intervention/option acceptable to key stakeholders?
12. Feasibility: Is the intervention feasible to implement?

Based on these considerations a balance of consequences will be made for all different interventions/options:

- Undesirable consequences *clearly outweigh* desirable consequences in most settings
- Undesirable consequences *probably outweigh* desirable consequences in most settings
- The balance between desirable and undesirable consequences *is closely balanced or uncertain*
- Desirable consequences *probably outweigh* undesirable consequences in most settings
- Desirable consequences *clearly outweigh* undesirable consequences in most settings

How important each of the considerations are for a recommendation can vary. To make a recommendation, the guideline panel must consider the implication and importance of each of the above judgments. In many cases, this will be straightforward and not require detailed consideration. However, when there is uncertainty or disagreement, it can help to explicitly consider this for each criterion. Based on the overall assessment across criteria the guideline panel must reach a conclusion about the direction and the strength of the recommendations.

Recommendations will be classified into three categories: strong recommendation to do (green); moderate recommendation to do (yellow); and recommendation not to do (red) (see Appendix 10).[12] The guideline panel should provide a justification for the recommendations, based on the criteria used in their assessment.

The recommendations should be a stand-alone text written in a complete sentence. The wording should be unambiguous, clearly defined, easy to translate into clinical practice, and agreed by the complete guideline panel.

A first draft of the recommendations will be prepared by a smaller guideline group (i.e. chairs, coordinator, advisors and working group leaders). Next, the recommendations will be discussed and further formulated by the total guideline panel. Additional experts and patient representatives in the field can be invited to participate in this final discussion.

Examples of recommendations are shown in Table 3.

Table 3. Example recommendations

Who needs breast cancer surveillance?
Breast cancer surveillance is recommended for female childhood, adolescent and young adult cancer survivors treated with ≥10 Gy chest radiation (level A evidence, strong recommendation).
Breast cancer surveillance is reasonable for female childhood, adolescent and young adult cancer survivors treated with upper abdominal radiation exposing breast tissue at a young age. The surveillance decision should be an individual one, taking into account additional risk factors[2] and personal values regarding the harms and benefits of surveillance (see Survivor Information Form) (level B evidence, moderate recommendation).

Who should be treated with dexrazoxane?
Administration of dexrazoxane is reasonable in children who are expected to receive a cumulative doxorubicin or equivalent dose of at least 250 mg/m² (very low to low-quality evidence, moderate recommendation). The health-care provider should discuss the balance between harms and benefits of dexrazoxane with the patients and families, and the final decision should be guided by the medical knowledge of the health-care provider.

Who should be counselled about fertility preservation?
We strongly recommend that healthcare providers[1] discuss fertility preservation options and alternative family planning with CAYA cancer patients and their parents/caregivers/partners if planned treatment will include alkylating agents[2] (high-quality evidence), radiotherapy to volumes exposing the ovaries (high-quality evidence), HSCT (very low-quality evidence), unilateral oophorectomy (very low-quality evidence), and/or cranial radiotherapy (very low-quality evidence).

2.3 Finalisation phase

External review

After the recommendations have been formulated, there will be a commentary phase where external experts review the guideline for content and implementability. Feedback is sought preferably among the scientific, professional and patient organisations involved. Feedback can also be invited from methodological experts who review the guideline for methodological validity.

Writing the guideline

All guideline topics will be summarized in a manuscript appropriate for publication in a peer-reviewed journal. The guideline should include the following items:

- Introduction
- Methods, including:
    - Guideline panel
    - Scope
    - Systematic literature review
    - Translating evidence into recommendations
- Results, including:
    - Description of evidence
    - Conclusions and quality of the evidence
    - Considerations when translation evidence into recommendations, according to the GRADE Evidence to Decision framework
    - Recommendations
- Discussion including the research agenda based on the identified knowledge gaps
- Reference list

Updating the guideline

Guidelines should be kept up to date. All guidelines should include a statement indicating that they will be considered for revision five years after publication. Searches for new evidence should be performed and updating of the recommendations might be considered.

3 Practical information regarding the organisation of guideline development

3.1 Roles

The IGHG core leadership group

- Melissa Hudson; co-chair, advisor, COG representative
- Leontien Kremer; co-chair, advisor, PanCare and DCOG representative
- Renée Mulder; coordinator, advisor, DCOG representative
- Elvira van Dalen; coordinator, advisor, DCOG representative
- Rod Skinner; advisor, PanCare and UKCCLG representative
- Sandy Constine; advisor and radiation expert, COG representative
- Hamish Wallace, advisor; SIGN representative
- Saro Armenian; COG representative
- Smita Bhatia; COG representative
- Wendy Landier; COG representative
- Gill Levitt; UKCCLG representative
- Kevin Oeffinger; COG representative
- Lars Hjorth; PanCare representative

Roles of the IGHG core leadership group

- The core leadership group members will set up the methodology.
- The core leadership group members will develop future plans.
- The core leadership group members will organize meetings for the guideline panels.
- The core leadership group members will guide the work of guideline panels.

Roles of the guideline panel

- The guideline panel consists of: chairs (representing different continents), a coordinator, advisors, working group leaders and working group members.
- The chairs and advisors will appoint the guideline panel.
- The guideline panel coordinator will facilitate the group's work and online meetings.
- The chairs, coordinator and working group leaders will formulate clinical questions with help of the advisors.
- The final clinical questions will be reviewed by the advisors before discussion with the guideline group members.
- The chairs, coordinator and working group leaders will formulate inclusion criteria for evidence selection with help of the advisors.
- The final inclusion criteria will be reviewed/approved by the advisors before discussion with the guideline panel members.
- The advisors from the Princess Máxima Center will develop the search strategy with input from the chairs, coordinator, working group leaders.

- The chairs, coordinator, working group leaders and members will select studies meeting the criteria established for evidence selection.
- The coordinator will produce evidence tables, which will be checked by the chairs, leaders and members.
- The final evidence tables will be reviewed by the advisors.
- The coordinator will produce the summary of findings tables and performs the GRADE assessment, which will be checked by the advisors.
- The chairs, coordinator and working group leaders will formulate conclusions of evidence with help of the advisors.
- The final conclusions of evidence will be reviewed by and discussed with the guideline panel members.
- The chairs, coordinator, working group leaders and advisors will prepare a first draft of the recommendations that will be subsequently discussed with the guideline panel members.

3.2 Authorship and manuscript writing

Authorship

- Authorship criteria and author order should be communicated at the start of the guideline process.
- The decision regarding authorship will be made by the chairs of the guideline group in consultation with the advisors.
- The guideline panel members will be co-authors of the manuscript if they are substantially involved in the guideline process (i.e. both the guideline and the manuscript development) (see the authorship guidelines of the International Committee of Medical Editors: http://www.icmje.org/). If not, their contribution can be included in the acknowledgements section of the manuscript.
- In general, the first author coordinates the guideline development. He or she is one of the authors performing study selection, data extraction, risk of bias assessment and GRADE assessment of all included studies. He or she drafts the first version of the protocol and the manuscript of the guideline.
- The chairs will be shared last authors.
- Other people, e.g., working group members, IGHG core leadership group members, experts in the filed who have not been substantially involved in the guideline or manuscript development will be acknowledged in the manuscript if their contribution is limited to review and approval of the final manuscript draft.
- If financially supported by PanCare, the collaboration between IGHG and PanCare or other funding sources should be acknowledged in the titles of the published manuscripts.

Manuscript writing process

- A primary manuscript of the whole guideline will be drafted that will include a description of the evidence and recommendations.
- The chairs and coordinator of the guideline group will write the first draft of the manuscript.
- The advisors and working group leaders will review/revise the first draft.

- The revised manuscript will be distributed to the guideline panel members.
- The final manuscript will be approved by the IGHG core leadership group.
- The development of additional manuscripts describing special aspects of the guideline topic should be discussed with and approved by the advisors.

External review

- At least two expert reviewers and two patient representatives will be asked to review the final manuscript of the guideline.
- These reviewers will be acknowledged in the manuscript.

Presentations

- The advisors should be informed if the methods and results of IGHG endeavors are to be submitted for presentation at national and international conferences.
- All presentations in which the results of the guideline harmonization endeavor are highlighted should acknowledge the names of the IGHG core group and the specific guideline group.
- All publications and presentations should acknowledge funding sources.

3.3 Timeline for guideline development

It is difficult to provide a strict timeline for guideline development as it depends on many factors, like number of possible studies identified while running the search, number of eventually included studies and the time the guideline panel can dedicate to the guideline.

A timeline is shown in Appendix 11**.** This provides an illustration of the stages of the work scope that are expected to occur in development work and approximate timelines. However, these timelines will be modified according to the work of each guideline panel and most likely revised as the groups progress through their work.

Be aware that journals sometimes require the search not be older than a specific time period. This means that it might be necessary to perform a search update before submitting a guideline manuscript.

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Appendices

Appendix 1. Example of a search strategy for the surveillance of premature ovarian insufficiency for childhood, adolescent and young adult cancer survivors

Search 1: Childhood cancer	leukemia OR leukemi* OR leukaemi* OR "childhood ALL" OR AML OR (leukemia, lymphocytic, acute[mh]) OR (leukemia, lymphocytic, acute*) OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR non-hodgkin* OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR brain tumor OR brain tumor* OR brain tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system neoplasm* OR central nervous system tumor OR central nervous system tumour OR central nervous system tumor* OR central nervous system tumour* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR childhood tumour OR childhood tumours OR childhood tumor* OR childhood tumour
Search 2: Female	female[tiab] OR females OR girl OR girls OR girlfriend OR girlhood OR girl* OR femal*
Search 3: Chemotherapy	Antineoplastic agents, alkylating OR antineoplastic alkylating agents OR alkylating antineoplastic drugs OR antineoplastic alkylating drugs OR alkylating antineoplastic agents OR alkylating antineoplastics OR Alkylating Agents OR alkylating* OR busulphan OR busulphan* OR busulfan OR busulfan* OR carmustine OR carmustin* OR bcnu OR ifosfamide OR ifosfa* OR iphosphamide OR iphospha* OR cyclophosphamide OR cyclophospha* OR lomustine OR lomustin* OR CCNU OR mechlorethamine OR mechlorethamin* OR nitrogen mustard OR melphalan OR melphalan* OR procarbazine OR procarbazin* OR thiotepa OR thiophosphamide OR thiothep* OR oxaliplatin OR oxaliplatin* OR carboplatin OR carboplatin* OR platinum compounds OR cisplatin OR cisplatin* OR cytosine OR cytosin* OR cytarabine OR cytarabin* OR ara-c OR arac OR temozolomide OR temozolomid* OR dacarbazine OR dacarbazin* OR methotrexate OR methotrexat* OR MTX OR Fludarabine OR fludarabin* OR etoposide OR etoposid* OR anthracyclines OR anthracyclin* idarubicin OR idarubic* OR epirubicin OR epirubic* OR adriamycin OR adriamyc* OR doxorubicin OR doxorubic* OR daunorubicin OR daunorubic* OR daunoxome OR daunoxom* OR daunosom* OR doxil OR caelyx OR myocet
Search 4: Radiotherapy	Radiotherapy OR radiotherap* OR radiation OR radiation therapy OR irradiation OR irradiat* OR radiation* OR radiations OR photon radiotherapy OR “photons/therapeutic use”[mh] OR proton radiotherapy OR “protons/therapeutic use”[mh] OR proton therapy OR proton radiation OR proton beam OR photon therapy OR photon radiation OR photon beam
Search 5: Radiation field	Ovary OR ovar* OR Pelvis OR pelv* OR Lesser Pelvis OR Abdomen OR abdom* OR Spine OR spin* OR Lumbosacral Region OR lumbosacral* OR Urinary Bladder OR Vagina OR vagin* OR Ilium OR illi* OR total body OR whole body OR total body* OR body whol* OR TBI OR craniospinal OR craniospin*
Search 6: Ovariectomy	Ovariectomy OR ovariectomy[mh] OR ovariectom* OR oophorectomy OR oophorectom* OR unilateral ovariectomy OR partial ovariectomy OR unilateral oophorectomy OR partial oophorectomy
Search 7:	Stem cell transplant[mh] OR stem-cell transplant OR stem cell transplant* OR

Stem cell transplant	stem-cell transplant* OR stem cell transplantation OR bone marrow transplantation[mh] OR bone marrow transplant* OR transplantation, conditioning[mh] OR hematopoietic stem cell transplantation[mh] OR hematopoietic OR haematopoietic OR reduced-intensity conditioning regimen OR myeloablative agonists[mh] OR myeloablativ*
Search 8: novel agents	antibodies, monoclonal OR Monoclonal antibodies OR monoclonal antibod* OR monoclonal antibody OR Tyrosine kinase inhibitors OR tyrosine kinase inhibitor OR tyrosine kinase inhibitor* OR Tyrosine Protein Kinase Inhibitors OR tyrosine protein kinase inhibitor* OR CAR-T OR bevacizumab OR (Poly(ADP-ribose) Polymerase Inhibitors OR Poly(ADP-ribose) Polymerase Inhibitor OR Poly(ADP-ribose) Polymerase Inhibitor* OR PARP inhibitor* OR Demethylating agent* OR M-TOR inhibitor* OR Akt Inhibitor* OR PDK-1 inhibitor* OR RAF inhibitor* OR MEK inhibitor* OR FTS inhibitor* OR Drugs targeting HER Receptors OR Drugs Targeting c-MET Receptor OR Drugs targeting IGF-IR receptor OR SRC-targeting Small Molecule Inhibitor* OR Anti VEGF/VEGFR agent* OR Vascular disrupting agent* OR Heat shock protein inhibitor* OR HSP-90 inhibitor* OR Inhibitors Ubiquitin Proteosome System OR Histone Deacetylases Inhibitor*)
Search 9: POI/DOR/delayed puberty	premature menopaus* OR early menopaus* OR menopausal status* OR ovarian fail* OR premature ovarian fail* OR acute ovarian fail* OR imminent ovarian fail* OR ovarian insufficienc* OR ovarian function* OR ovarian damag* OR Gonadotropin-Resistant Ovary Syndrom* OR gonadotropin resistant ovary syndrom* OR Female Genital Diseas* OR Female infertilit* OR primary ovarian insufficienc* OR gonadotoxicity OR gonado toxic* OR gonadotoxic* OR gonado toxicity OR gonadal damag* OR hypergonadotropic amenorrhea* OR gonad dysfunction* OR gonadal function* OR gonadal effect* OR ovarian reserv* OR gonadal hormone deficienc* OR amenorrhea* OR oligomenorrhea* OR ovarian reserv* OR ovarian reserve OR menopause, premature OR primary ovarian insufficiency OR diminished ovarian reserv* OR DOR OR POI OR amenorrhea OR oligomenorrhea OR Puberty, Delayed OR delayed puberty* OR “tanner stage” OR “tanner staging”
Combined	**#1 AND #2 AND (#3 OR (#4 AND #5) OR #6 OR #7 OR #8) AND #9** Filter humans Filter English

Appendix 2. Standard search strategies

Childhood cancer

leukemia OR leukemi* OR leukaemi* OR "childhood ALL" OR AML OR (leukemia, lymphocytic, acute[mh]) OR (leukemia, lymphocytic, acute*) OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR non-hodgkin* OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR brain tumor OR brain tumor* OR brain tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system neoplasm* OR central nervous system tumor OR central nervous system tumour OR central nervous system tumor* OR central nervous system tumour* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR childhood tumour OR childhood tumours OR childhood tumor* OR childhood tumour*

Childhood cancer, testis cancer and breast cancer

leukemia OR leukemi* OR leukaemi* OR “childhood ALL” OR AML OR (leukemia, lymphocytic, acute[mh]) OR (leukemia, lymphocytic, acute*) OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR non-hodgkin* OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR brain tumor OR brain tumor* OR brain tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system neoplasms* OR central nervous system tumor OR central nervous system tumour OR central nervous system tumor* OR central nervous system tumour* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR breast cancer OR breast cancers OR breast neoplasm OR breast neoplasms OR breast neoplasm* OR testis neoplasm OR neoplasm, testicular OR testicular neoplasm OR testicular neoplasms OR testis cancer OR testicular cancer OR testis tumor OR cancer of testis OR testis tumour OR testis neoplasm* OR testis tumour* OR testis tumor*

Childhood brain tumors

PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR astrocytoma OR astrocytom* OR chondrosarcoma OR chondrosarcoma* OR ependymoma OR ependymom* OR germ cell tumor OR germ cell tumor* OR glioblastoma OR glioblastoma* OR glioma OR gliom* OR hemangioma OR hemangioma* OR lipoma OR lipom* OR meningioma OR meningioma* OR schwannoma OR pineal tumor OR pineal tumor* OR chordoma OR chordom* OR oligodendroglioma OR oligodendrogliom* OR rhabdoid tumor OR rhabdoid tumor* OR craniopharyngioma OR craniopharyngiom* OR pituitary tumor OR pituitary tumor* OR CNS embryonal tumor OR CNS embryonal tumor* OR pineoblastoma OR pineoblastom* OR medulloepithelioma OR medulloepitheliom* OR ependymoblastoma OR ependymoblastom*

Posterior fossa tumor
(Posterior fossa OR cranial fossa OR "cranial fossa, posterior"[MeSH Terms] OR clivus) AND (Tumor OR cancer OR neoplasm OR neoplasms) OR (infratentorial AND (cancer OR tumor))

Cancer
Cancer OR cancers OR cancer* OR oncology OR oncolog* OR neoplasm OR neoplasms OR neoplasm* OR carcinoma OR carcinom* OR tumor OR tumour OR tumor* OR tumour* OR tumors OR tumours OR malignan* OR malignant OR hematooncological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo*

Children
infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school [tiab] OR school*[tiab] OR prematur* OR preterm*

Children and young adults
infan*OR newborn*OR new-born*OR perinat*OR neonat*OR babyOR baby*OR babiesOR toddler*OR minorsOR minors*OR boyOR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm* OR young adult[mh] OR young adult

Survivors
Survivor OR survivors OR long term survivor OR long term survivors OR long term survivo* OR survivo* OR surviving OR long term survival OR survival[mh] OR long-term survivor OR long-term survivors OR long-term survivo* OR childhood cancer survivor OR childhood cancer survivors OR childhood cancer survivo* OR cancer survivors[mh]

Late effects
"late effect" OR "late effects" OR "late effect*" OR "late side effect" OR "late side effects" OR "late side effect*" OR "late adverse effect" OR "late adverse effects" OR "late adverse effect*" OR long term effect[tiab] OR long term effect* OR long term adverse effects[mh] OR “follow up study” OR follow-up studies[mh] OR aftercare[mh] OR aftercare* OR after treatment[tiab]

Male
male[tiab] OR males OR boy OR boys OR boyfriend OR boyhood

Female
female[tiab] OR females OR girl OR girls OR girlfriend OR girlhood OR girl* OR femal*

Offspring
Offspring OR Descendant OR Generation OR Heir OR Progeny OR Heredity OR Lineage OR Offshoot OR Posterity OR Succession successor OR Progeniture OR Spawn OR Brood OR breed OR baby

Radiotherapy extensive
Radiotherapy OR radiation OR radiation therapy OR irradiation OR irradiat* OR radiation injuries OR injuries, radiation OR injury, radiation OR radiation injury OR radiation syndrome OR radiation syndromes OR syndrome

radiation OR radiation sickness OR radiation sicknesses OR sickness radiation OR radiation* OR irradiation OR radiations OR stereotactic RT OR stereotactic radiotherapy[tiab] OR gamma knife OR intensity modulated radiotherapy OR IMRT OR radiotherapy, intensity-modulated[mh] OR (three dimenstional OR 3D OR 3d CRT) OR image guided radiotherapy OR IGRT OR radiotherapy, image-guided[mh] OR photon radiotherapy OR XRT OR "photons/therapeutic use"[Mesh] OR proton radiotherapy OR PRT OR proton therapy OR proton radiation OR proton beam OR carbon ion radiotherapy

Radiotherapy general
Radiotherapy OR radiotherap* OR radiation OR radiation therapy OR irradiation OR irradiat* OR radiation* OR radiations OR photon radiotherapy OR "photons/therapeutic use"[mh] OR proton radiotherapy OR "protons/therapeutic use"[mh] OR proton therapy OR proton radiation OR proton beam OR photon therapy OR photon radiation OR photon beam

Dose-response relationship – combine with radiotherapy search
radiometry OR radiation dosage OR radiation dose OR radiation doses OR radiation dosis OR radiation dosage* OR radiation dosimetry OR radiation dosimetr* OR dose-response relationship, radiation OR radiometr* OR radiotherapy dosage OR radiotherapy[sh] OR radiotherapy/adverse effects OR irradiation dose OR radiotherapy dose OR dose calculation OR near beam dose OR in beam dose OR outside beam dose OR out of beam dose OR radiation/epidemiology OR Radiation monitoring OR Organs at risk OR radiation effects[sh] OR radiation injury OR radiation injuries OR radiation OR Radiotherapy/complications[Mesh]

Radiotherapy fields – combine with radiotherapy search
<u>Cranial, head and neck</u>
Cranial OR craniospinal OR OR head[tiab] OR neck[tiab] OR skull

<u>Hypothalamic-pituitary</u>
Hypothalamus OR Hypothalamus, Middle OR Hypothalamus, Anterior, OR Hypothalamus Posterior OR Pituitary Gland, Posterior OR Skull OR Orbit OR Orbits OR Eye OR Ear OR Nasopharynx

<u>TBI</u>
TBI OR Total body OR whole body OR total body* OR body whole*

<u>Testes</u>
Testicles OR testicle OR testes OR testis OR testis* OR testicle* OR testes* OR pelvic region OR region, pelvic OR pelvis region OR region pelvis OR pelvis* OR pelvic*

<u>Ovaries</u>
Ovary OR ovar* OR Pelvis OR pelv* OR Lesser Pelvis OR Abdomen OR abdom* OR Spine OR spin* OR Lumbosacral Region OR lumbosacral* OR Urinary Bladder OR Vagina OR vagin* OR Ilium OR illi*

<u>Thorax</u>
Chest OR lung OR axilla OR mediastinal OR mantle OR supraclavicular OR susclavicular OR cranial axis OR total axis OR supra diaphragm[tiab] OR abdominal OR Inverted Y[tiab] OR Left Flank OR Hemiabdomen OR Left upper quadrant OR Paraaortic OR Spleen OR craniospinal

Cranial and craniospinal radiation
cranial irradiation [mh] OR craniospinal irradiation [mh])

Chemotherapy
Antineoplastic Protocols OR Antineoplastic Combined Chemotherapy Protocols OR Chemoradiotherapy OR Chemoradiotherapy, Adjuvant OR Chemotherapy, Adjuvant OR Consolidation Chemotherapy OR Induction chemotherapy OR Maintenance chemotherapy OR Chemotherapy, Cancer, Regional Perfusion OR Antineoplastic agents OR chemotherap*

Alkylating agents
Antineoplastic agents, alkylating OR antineoplastic alkylating agents OR alkylating antineoplastic drugs OR antineoplastic alkylating drugs OR alkylating antineoplastic agents OR alkylating antineoplastics OR Alkylating Agents OR alkylating* OR busulphan OR busulphan* OR busulfan OR busulfan* OR carmustine OR carmustin* OR bcnu OR ifosfamide OR ifosfa* OR iphosphamide OR iphospha* OR cyclophosphamide OR cyclophospha* OR lomustine OR lomustin* OR CCNU OR mechlorethamine OR mechlorethamin* OR nitrogen mustard OR melphalan OR melphalan* OR procarbazine OR procarbazin* OR thiotepa OR thiophosphamide OR thiothep* OR temozolomide OR temozolomid* OR dacarbazine OR dacarbazin*

Anthracyclines extensive
anthracyclines OR anthracyclin* OR anthracycline OR 4-demethoxydaunorubicin OR 4-desmethoxydaunorubicin OR idarubicin OR idarubic* OR 4'-epiadriamycin OR 4' epiadriamycin OR 4'-epidoxorubicin OR 4'-epi-doxorubicin OR 4'-epi-adriamycin OR 4'-epi-DXR OR farmorubicin OR farmorubic* OR epirubicin OR epirubic* OR adriablastine OR adriblastin* OR adriablastin OR adriamycin OR doxorubic* OR adriamyc* OR dauno-rubidomycin* OR rubidomycin OR rubomycin* OR daunomycin* OR cerubidine OR daunoblastin* OR daunorubicin OR daunorubic* OR rubidomyc* OR rubomycin* OR daunoxome OR daunoxom* OR daunosom* OR doxil OR caelyx OR (liposomal AND (doxorubicin OR adriamycin OR daunorubicin OR epirubicin OR idarubicin)) OR myocet OR doxorubicin OR daunorubicin

Anthracyclines general
anthracyclines OR anthracyclin* idarubicin OR idarubic* OR epirubicin OR epirubic* OR adriamycin OR adriamyc* OR doxorubicin OR doxorubic* OR daunorubicin OR daunorubic* OR daunoxome OR daunoxom* OR daunosom* OR doxil OR caelyx OR myocet

Mitoxantrone
mitoxantrone OR novantrone OR dihydroxyanthracenedione OR mitoxantr*

Platinum agents extensive
Cisplatin OR Platinum Diamminodichloride OR cis-Platinum OR cis Platinum OR Dichlorodiammineplatinum OR cis-Diamminedichloroplatinum OR cis Diamminedichloroplatinum OR Platinol OR Platidiam OR Platino OR Biocisplatinum OR CDDP OR CACP OR cisplatin* OR abiplatin OR neoplatin OR cis-DDP OR Carboplatin OR CBDCA OR Carbosin OR Carbotec OR Ercar OR Neocarbo OR Paraplatin OR Carboplat OR Paraplatine OR Platinwas OR Ribocarbo OR Blastocarb OR Nealorin OR carboplatin* OR Oxaliplatin OR oxaliplatin* OR oxaliplatine OR Eloxatine OR Eloxatin OR eloxatin* OR dacotin OR dacplat OR OR l-ohp OR oxalatoplatinum OR Platinum OR Platinum Compounds OR platinum* OR organoplatinum compounds [mh]

Platinum agents general
Oxaliplatin OR oxaliplatin* OR carboplatin OR carboplatin* OR platinum compounds OR cisplatin OR cisplatin*

Cytarabine
Cytosine OR cytosin* OR cytarabine OR cytarabin* OR ara-c OR arac

Fludarabine
Fludarabine OR fludarabin*

Etoposide
Etoposide OR etoposid*

Methotrexate
Methotrexate OR methotrexat* OR MTX OR amethopterin OR methotrexate hydrate OR dicesium salt methotrexate OR me xate OR sodium salt methotrexate OR disodium salt methotrexate OR amethopter* OR mexat*

Nitrosoureas
Nitrosourea OR Nitrosourea* OR Nitrosourea compounds OR Arabinopyranosyl-N-methyl-N-nitrosourea OR Aranose OR Carmustine OR BCNU OR BiCNU OR Chlorozotocin OR Ethylnitrosourea OR Fotemustine OR Lomustine OR CCNU OR Nimustine OR N-Nitroso-N-methylurea OR NMU OR Ranimustine OR MCNU OR semustine OR streptozocin OR I-nitrosourea

Novel agents
Antibodies, monoclonal OR Monoclonal antibodies OR monoclonal antibod* OR monoclonal antibody OR Tyrosine kinase inhibitors OR tyrosine kinase inhibitor OR tyrosine kinase inhibitor* OR Tyrosine Protein Kinase Inhibitors OR tyrosine protein kinase inhibitor* OR CAR-T OR bevacizumab OR (Poly(ADP-ribose) Polymerase Inhibitors OR Poly(ADP-ribose) Polymerase Inhibitor OR Poly(ADP-ribose) Polymerase Inhibitor* OR PARP inhibitor* OR Demethylating agent* OR M-TOR inhibitor* OR Akt Inhibitor* OR PDK-1 inhibitor* OR RAF inhibitor* OR MEK inhibitor* OR FTS inhibitor* OR Drugs targeting HER Receptors OR Drugs Targeting c-MET Receptor OR Drugs targeting IGF-IR receptor OR SRC-targeting Small Molecule Inhibitor* OR Anti VEGF/VEGFR agent* OR Vascular disrupting agent* OR Heat shock protein inhibitor* OR HSP-90 inhibitor* OR Inhibitors Ubiquitin Proteosome System OR Histone Deacetylases Inhibitor*)

MIBG
131I-Meta-iodobenzylguanidine OR 131I-MIBG OR 131I-metaiodobenzylguanidine OR Iodine-131 Metaiodobenzylguanidine OR Iobenguane (131I) OR (3-Iodo-(131I)benzyl)guanidine OR Iodine Radioisotopes/therapeutic use OR 3-Iodobenzylguanidine/therapeutic use) OR (iodine-131-metaiodobenzylguanidine OR 131I-MIBG therapy OR I-metaiodobenzylguanidine OR I-131-MIBG OR I-131-Metaiodobenzylguanidine OR (131) I-MIBG OR 3-Iodobenzylguanidine[mh] OR (131) I-metaiodobenzylguanidine OR (MIBG AND (treatment OR therapy))

Steroids
dexamethasone OR dexamethasone* OR prednisone OR prednisone* OR prednisolone OR prednisolone* OR glucocorticoids OR glucocorticoid* OR "Steroids"[Mesh:NoExp] OR steroids*

HSCT
Stem cell transplant[mh] OR stem-cell transplant OR stem cell transplant* OR stem-cell transplant* OR stem cell transplantation OR bone marrow transplantation[mh] OR bone marrow transplant* OR transplantation, conditioning[mh] OR hematopoietic stem cell transplantation[mh] OR hematopoietic OR haematopoietic OR reduced-intensity conditioning regimen OR myeloablative agonists[mh] OR myeloablativ*

Surgery
Surgery OR injury OR injuries OR surgery* OR injury* OR injuries*

Surgery extensive
surgery[tiab] OR surgical procedures, operative[mh] OR general surgery[mh] OR surgery[sh] OR operation OR ((operative OR peroperative OR perioperative OR preoperative OR intraoperative) AND procedure)

Neurosurgery
Neurosurgery OR neurosurger* OR neurosurgical procedure OR neurosurgical procedure* OR (brain[tiab] AND surgery) OR (cranial* AND surger*)

Ovariectomy
Ovariectomy OR ovariectomy[mh] OR ovariectom* OR oophorectomy OR oophorectom* OR unilateral ovariectomy OR partial ovariectomy OR unilateral oophorectomy OR partial oophorectomy

Oophoropexy
Oophoropexy OR Oophoropex* OR ovarium transposition OR ovarian transposition

Orchidectomy
Orchidectomy unilateral OR orchiectomy unilateral OR unilateral orchidectomy OR unilateral orchiectomy OR unilateral orchiectomy* OR unilateral orchidectomy*

Rretroperitoneal lymph node dissection and genitourinary surgery
Lymph Node Excision[mh] OR Lymph Node Excision OR (Lymph Node AND excision) OR Lymph Node Excis* OR Pelvic exenteration[mh] OR ((prostate OR bladder OR bladder neck OR rectum) AND surgery) OR pelvic exenteration

Nephrectomy
Nephrectomy[mh] OR nephrectom* OR postnephrectomy OR partial nephrectomy OR subtotal nephrectomy OR radical nephrectomy OR unilateral nephrectomy OR renal surgery

Pulmonary surgery
pulmonary metastasectomy OR pulmonary lobectomy OR thoracotomy OR sternotomy OR thoracoscopy OR rib resection[tiab] OR spinal surgery OR spinal fusion OR (resection AND (pulmonary wedge OR lung OR claviculae OR scapulae OR muscle tissue on thorax))

Hypdrocephalus VP/CSF shunts
Hydrocephalus OR hydrocephaly OR ventriculomegaly OR ventriculomegal* OR Ventriculoperitoneal Shunt OR Ventriculo peritoneal Shunt OR Cerebrospinal Fluid Shunt OR Cerebro Spinal Fluid Shunt OR ((VP OR CSF) AND shunt*) OR intracranial pressure

Ear or cranial nerve VIII
vestibulocochlear OR cochleovestibular OR statoacoustic OR cranial nerves[mh] OR cranial nerve[tiab]

Brain injury
intracranial pressure[mh] OR intracranial pressur* OR meningitis OR intracranial thrombosis[mh] OR cerebral thrombosis OR cerebral bleeding OR cerebral hemorrhage OR (cerebral[tiab] AND leukemi*[tiab]) OR brain abscess OR brain abscess* OR encephalopathy OR cerebral inflammation OR brain inflammation OR encephalitis OR (brain AND fungal infection*) OR (vasculitis AND (brain OR central nervous system)) OR (graft versus host disease AND brain) OR hydrocephalus

Hormonal therapy

hormonal therap* OR hormone therap* OR Hormone Replacement Therapy[mh] OR Estrogen Replacement Therapy[mh] OR tamoxifen OR goserelin OR aromatase inhibitors[mh] OR aromatase inhibitor* OR anastrozole OR exemestane OR fadrozole OR formestane OR letrozole OR vorozole OR plomestane OR androgen deprivation therap* OR antiandrogen* OR antiestrogen* OR hormone receptor positive[tiab] OR estrogen receptor positive[tiab] OR fulvestrant OR flutamide OR faslodex

Subsequent neoplasm

Neoplasms, Radiation-Induced [Mesh] OR "Neoplasms, Radiation-Induced" OR "Radiation-Induced Neoplasms" OR "Neoplasm, Radiation-Induced" OR "Radiation Induced Neoplasms" OR "Radiation-Induced Neoplasm" OR "Radiation Induced Cancer" OR "Cancers, Radiation-Induced" OR "Radiation-Induced Cancers" OR "Cancer, Radiation-Induced" OR "Cancer, Radiation Induced" OR Neoplasm, Second Primary [Mesh] OR "Neoplasms, Second Primary" OR "Neoplasm, Second Primary" OR "Second Primary Neoplasm" OR "Metachronous Second Primary Neoplasms" OR "Neoplasms, Metachronous" OR "Second Malignancy" OR "Malignancies, Second" OR "Malignancy, Second" OR "Second Malignancies" OR "Second Neoplasm" OR "Neoplasm, Second" OR "Neoplasms, Second" OR "Second Neoplasms" OR "Second Primary Neoplasms" OR "Metachronous Neoplasms" OR "Metachronous Neoplasm" OR "Therapy Associated Neoplasm" OR "Neoplasms, Treatment-Related" OR "Neoplasms, Treatment Related" OR "Treatment-Related Neoplasm" OR "Therapy-Related Neoplasms" OR "Therapy Related Neoplasms" OR "Treatment-Associated Neoplasms" OR "Treatment Associated Neoplasms" OR "Treatment-Related Neoplasms" OR "Treatment Related Neoplasms" OR "Neoplasms, Therapy-Related" OR "Neoplasm, Therapy-Related" OR "Neoplasms, Therapy Related" OR "Therapy Related Neoplasm" OR "Therapy Associated Cancer" OR "Cancer, Therapy-Associated" OR "Therapy Associated Cancer" OR "Therapy-Related Cancer" OR "Cancer, Therapy-Related" OR "Cancers, Therapy-Related" OR "Therapy Related Cancer" OR "Therapy-Related Cancers" OR "Treatment-Related Cancer" OR "Cancer, Treatment-Related" OR "Cancers, Treatment-Related" OR "Treatment Related Cancer" OR "Treatment Related Cancers" OR "Treatment-Associated Cancer" OR "Cancer, Treatment-Associated" OR "Treatment Associated Cancer" OR "Treatment-Associated Cancers" OR "Cancer, Second Primary" OR "Cancers, Second Primary" OR "Second Primary Cancer" OR "Second Primary Cancers" OR "Second Cancer" OR "Cancer, Second" OR "Cancers, Second" OR "Second Cancers" OR "Neoplasms, Radiation effects" OR "second primary malignancy" OR "second primary malignancies" OR "second malignant neoplasm" OR "second malignant neoplasms" OR SMN OR "subsequent malignant neoplasm" OR "subsequent malignant neoplasms" OR "subsequent neoplasm" OR "subsequent neoplasms" OR "new malignancy" OR "new malignancies" OR "subsequent primary malignancy" OR "subsequent primary malignancies" OR "subsequent primary neoplasm" OR "subsequent primary neoplasms" OR "subsequent primary tumor" OR "subsequent primary tumors" OR "subsequent malignancy" OR "subsequent malignancies" OR "subsequent tumor" OR "subsequent tumors" OR "secondary cancer" OR "secondary neoplasm" OR "secondary malignancy" OR "secondary tumor" OR "secondary cancers" OR "secondary neoplasms" OR "secondary malignancies" OR "secondary tumors" OR "secondary primary malignancy" OR "second tumor" OR "second tumors" OR "second primary tumor" OR "second primary tumors" OR "second malignant tumor" OR "second malignant tumors" OR "subsequent malignant tumor" OR "subsequent malignant tumors" OR "secondary breast cancer"

Breast cancer

breast cancer OR breast cancers OR breast neoplasm OR breast neoplasms OR breast neoplasm* OR mamma carcinoma OR mamma carcinomas OR mammary gland carcinoma or mammary gland carcinomas OR Neoplasm, Breast OR Neoplasms, Breast OR Tumors, Breast OR Breast Tumors OR Breast Tumor OR Tumor, Breast OR Mammary Carcinoma, Human OR Carcinoma, Human Mammary OR Carcinomas, Human Mammary OR Human Mammary Carcinomas OR Mammary Carcinomas, Human OR Human Mammary Carcinoma OR Mammary Neoplasms, Human OR Human Mammary Neoplasm OR Human Mammary Neoplasms OR

Neoplasm, Human Mammary OR Neoplasms, Human Mammary OR Mammary Neoplasm, Human OR Cancer, Breast OR Cancer of the Breast OR Cancer of Breast OR Breast Malignant Neoplasm OR Breast Malignant Neoplasms OR Malignant Tumor of Breast OR malignant tumors of breast OR Breast Malignant Tumor OR Breast Malignant Tumors OR Breast Carcinoma OR Breast Carcinomas OR Malignant Neoplasm of Breast OR malignant neoplasms of breast OR Mammary Cancer OR Mammary Cancers OR breast cancer* OR mamma carcinom* OR mammary gland carcinom* OR breast tumor* OR mammary carcinom* OR mammary neoplasm* OR breast tumours OR breast tumour OR breast tumour* OR breast carcinom* OR mammary cancer*

Glioma
Glioma OR gliom*

Meningioma
meningioma OR meningiom*

Other CNS neoplasms
Pituitary neoplasm OR pituitary neoplasm* OR pituitary tumor OR pituitary tumour OR pituitary tumor* OR pituitary tumour* OR neurilemmoma OR neurilemmom* OR neurilemoma OR neurilemom* OR schwannoma OR schwannom* OR craniopharyngioma OR craniopharyngiom* OR pinealoma OR pinealom* OR pineal tumor OR pineal tumour OR pineal tumor* OR pineal tumour* OR pineal neoplasm OR pineal neoplasm* OR pineoblastoma OR pineoblastom* OR pineocytoma OR pineocytom* OR choroid plexus neoplasm OR choroid plexus neoplasm* OR choroid plexus tumor OR choroid plexus tumour OR choroid plexus tumor* OR choroid plexus tumour* OR supratentorial neoplasm OR supratentorial neoplasm* OR supratentorial tumor OR supratentorial tumour OR supratentorial tumor* OR supratentorial tumour* OR opticus glioma OR opticus gliom* OR optic nerve glioma OR optic nerve gliom* OR optic glioma OR optic gliom* OR medulloblastoma OR medulloblastom* OR pilocytic astrocytoma OR pilocytic astrocytom* OR oligodendroglioma OR oligodendrogliom* OR oligodendroblastoma OR oligodendroblastom* OR ganglioglioma OR gangliogliom* OR ependymoma OR ependymom*

Colorectal cancer
colonic neoplasms[MeSH Terms] OR cecal neoplasms[MeSH Terms] OR colorectal neoplasms[MeSH Terms] OR rectal neoplasms[MeSH Terms] OR ((colonic[tiab] OR colon[tiab] OR large intestine[tiab] OR intestinal[tiab] OR intestines[tiab] OR intestinal[tiab] OR cecal[tiab] OR caecal[tiab] OR cecum[tiab] OR caecum[tiab] OR colorectal[tiab] OR rectum[tiab] OR rectal[tiab] OR digestive[tiab] OR bowel[tiab] OR gut[tiab]) AND (cancer[tiab] OR cancers[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab] OR neoplasm[tiab] OR neoplasms[tiab] OR carcinoma[tiab] OR carcinomas[tiab]))

Cardiomyopathy, heart failure
(Heart/adverse effects[Mesh] OR Heart/toxicity[Mesh] OR Ventricular Dysfunction[Mesh] OR Cardiotoxicity[mesh] OR cardiotoxicit* OR ejection fraction OR LVEF OR “shortening fraction” OR “fractional shortening” OR contractilit* OR cardiomyopathies[Mesh] OR cardiomyopath* OR ((cardiac OR myocard* OR heart OR ventricular OR systolic) AND (damage OR injur* OR toxicit* OR disease* OR dysfunct* OR function OR strain)) OR Echocardiography OR echocardiogram OR (Magnetic Resonance Imaging[Mesh] AND (heart OR cardiac)) OR Congestive heart failure OR CHF OR heart failure OR clinical heart failure OR clinical cardiotoxicity OR clinical cardiotoxicities OR clinical cardiotoxicit* OR Cardiac Failure OR Myocardial Failure OR Heart Failure, Left-Sided OR Heart Failure, Left Sided OR Left-Sided Heart Failure OR Left Sided Heart Failure OR Heart Failure, Right-Sided OR Heart Failure, Right Sided OR Right-Sided Heart Failure OR Right Sided Heart Failure OR Heart Failure, Congestive OR Heart Decompensation OR Decompensation, Heart OR cardiomyopathy OR cardiomyopathies OR cardiomyopath* OR cardiac damage OR cardiac toxicity OR cardiac toxicities OR cardiac dysfunction OR cardiac dysfunctions OR cardiac failure OR cardiac failures OR heart pathology OR

heart/radiation effects OR heart ventricles/radiation effects OR heart disease OR heart diseases) OR myocardial dysfunction

Echocardiography
(Echocardiography OR echocardiogram OR Ventricular Dysfunction[Mesh] OR ejection fraction OR LVEF OR "shortening fraction" OR "fractional shortening" OR contractilit* OR ((cardiac OR myocard* OR heart OR ventricular OR systolic) AND (damage OR injur* OR toxicit* OR disease* OR dysfunct* OR function OR strain))

Stress echocardiography
(Echocardiography, Stress[mesh] OR stress echocardiogram OR stress echocardiography) AND (Echocardiography OR echocardiogram OR Ventricular Dysfunction[mesh]) AND (diastol* AND (dysfunct* OR function OR heart OR cardiac))

Cardiac MRI
Magnetic Resonance Imaging[mesh] AND (heart OR cardiac)

MUGA
radionuclide angiography OR radionuclide ventriculography OR gated blood-pool imaging OR blood pool scintigraphy OR gated radionuclide ventriculography OR ventriculogr* OR scintigr* OR MUGA OR angiocardiography

Cardiac blood biomarkers
Natriuretic Peptides[mesh] OR Atrial natriuretic factor OR ANP OR ANF OR atrial natriuretic peptide OR Brain natriuretic peptide OR BNP OR Pro-brain natriuretic peptide OR N-terminal pro-BNP OR NTproBNP OR NT-proBNP OR proBNP OR troponin T OR troponin I OR ctnt OR ctni OR troponin*

Coronary artery disease
angina OR angina pectoris[mh] OR coronary artery disease OR coronary artery disease[mh] OR myocardial infarction OR myocardial infarction[mh] OR heart attack[tiab] OR heart arrest[mh] OR cardiac arrest OR ischemic heart disease OR ischaemic heart disease OR myocardial ischemia [mh] OR ischemic cardiomyopath* OR ischaemic cardiomyopath* OR coronary ischemia [tiab] OR coronary ischaemia [tiab] OR atherosclerotic heart disease[tiab] OR (coronary AND (vasculopathy OR thrombosis OR occlusion[tiab] OR plaque[tiab] OR occlusive disease* OR atherosclerosis OR artery disease* OR atherosclerotic disease* OR artery calcification* OR angiogram OR angioplasty OR artery bypass OR arteriosclerosis OR aneurysm)) OR coronary angiography[mh] OR angioplasty, balloon, coronary [mh] OR coronary balloon angioplasty OR coronary artery bypass[mh] OR coronary aneurysm[mh] OR (cardiac AND (atherosclerosis OR atherosclerotic*))

Thyroid cancer
(Thyroid carcinoma OR thyroid cancer OR papillary thyroid carcinoma OR follicular thyroid carcinoma OR papillary thyroid cancer OR follicular thyroid cancer OR thyroid neoplasm OR thyroid neoplasms OR non-medullary thyroid carcinoma OR non-medullary thyroid cancer OR thyroid gland OR thyroid adenoma OR thyroid nodule) NOT graves[tiab]

Thyroid ultrasound
Ultrasonography OR ultrasound OR thyroid ultrasound OR thyroid ultrasonography OR thyroid gland/ultrasonography OR thyroid neoplasms/ultrasonography OR thyroid neoplasms/ultrasonography OR neck palpation OR clinical examination OR imaging[tiab] OR diagnosis[sh] OR ultrasonography[sh]

Thyroid cancer diagnostic test
((Mibi OR pertechnate OR pertechnetate OR methoxyisobutylisonitrile) AND (scan OR scintigraphy OR scintigraphic OR scintigraph* OR imaging OR SPECT OR SPECT/CT OR protocol*)) OR FNAC OR fine needle aspiration cytology OR biopsy OR diagnostic test OR elastography OR tg OR thyroglobulin

Thyroid cancer diagnostic test complications
Complications OR complication rate OR bleeding OR haemorrhage OR hemorrhage OR haematomas OR haematoma OR hematoma OR hematomas OR swelling OR infection OR recurrent nerve injury OR tracheal puncture OR vasovagal reaction OR dysphagia

Impaired spermatogenesis
spermatogenesis OR gonadal disorder OR spermiogenesis OR spermatocytogenesis OR spermatogenic failure OR azoospermia OR oligospermia OR asthenozoospermia OR teratozoospermia OR oligoasthenoteratozoospermia OR dysspermia OR normozoospermic OR semen OR semen analysis[text] OR semen quality[text] OR sperm OR sperm count OR sperm motility OR spermatozoa OR progeny OR offspring OR posterity OR fertility OR infertility OR subfertility OR reproduction OR fertilization OR conception OR paternity OR fatherhood OR parenthood OR pregnancy outcome OR fertile OR infertile OR subfertile OR sperm maturation OR aspermia OR spermatozoon abnormality

Testosterone deficiency
Androgen hormone insufficiency OR leydig cell OR cells, leydig failure OR testicular interstitium cell failure OR testicular failure OR gonadal failure OR hypogonadism OR low testosterone OR testosterone deficiency OR androgen deficiency OR low testosterone* OR hypogonadism* OR leydig cell*

Sexual dysfunction
erectile dysfunction OR dysfunction, erectile OR impotence OR male sexual impotence OR impotence, male sexual OR sexual impotence, male OR male impotence OR impotence, male OR impotence male* OR male sexual impotence* OR erectile dysfunction* OR premature ejaculation OR ejaculation, premature OR ejaculations, premature OR premature ejaculations OR ejaculatio praecox OR praecox, ejaculation OR ejaculation* OR delayed ejaculation OR retarded ejaculation OR ejaculation dysfunction OR ejaculation dysfunction* OR sexual dysfunctions OR sexual dysfunction OR sexual disorder OR sex disorders OR sexual disorder* OR sexual dysfunction* OR male sexual dysfunction*

Obstructive azoospermia
spermatogenesis OR gonadal disorder OR spermiogenesis OR spermatocytogenesis OR spermatogenic failure OR azoospermia OR oligospermia OR asthenozoospermia OR teratozoospermia OR oligoasthenoteratozoospermia OR dysspermia OR normozoospermic OR semen OR semen analysis[text] OR semen quality[text] OR sperm OR sperm count OR sperm motility OR spermatozoa OR progeny OR offspring OR posterity OR fertility OR infertility OR subfertility OR reproduction OR fertilization OR conception OR paternity OR fatherhood OR parenthood OR pregnancy outcome OR fertile OR infertile OR subfertile OR sperm maturation OR aspermia OR spermatozoon abnormalit

Quality and yield of sperm
Semen analysis OR semen analysis[mh] OR DNA fragmentation[mh] OR (DNA fragmentation AND sperm) OR sperm count[mh] OR sperm count OR (sperm AND yield)

FSH
Follicle stimulating hormone OR FSH OR follicle-stimulating hormone OR follitropin OR gonadotrope OR luteinizing hormone OR follicle stimulating hormon*

Inhibin B
Inhibin OR inhibins, testicular OR testicular inhibins OR inhibin, testicular OR testicular inhibin OR inhibin* OR inhibin B OR inhb

LH
Luteinizing hormone OR LH OR hormone, luteinizing OR interstitial cell-stimulating hormone OR interstitial cell stimulating hormone OR ICSH OR luteinizing hormon* OR LH*

Testosterone
Testosterone OR testosterone OR 17-beta-Hydroxy-4-Androsten-3-one OR testosterone*

Premature ovarian insufficiency - diminished ovarian reserve - delayed puberty
Premature menopaus* OR early menopaus* OR menopausal status* OR ovarian fail* OR premature ovarian fail* OR acute ovarian fail* OR imminent ovarian fail* OR ovarian insufficienc* OR ovarian function* OR ovarian damag* OR Gonadotropin-Resistant Ovary Syndrom* OR gonadotropin resistant ovary syndrom* OR Female Genital Diseas* OR Female infertilit* OR primary ovarian insufficienc* OR gonadotoxicity OR gonado toxic* OR gonadotoxic* OR gonado toxicity OR gonadal damag* OR hypergonadotropic amenorrhea* OR gonad dysfunction* OR gonadal function* OR gonadal effect* OR ovarian reserv* OR gonadal hormone deficienc* OR amenorrhea* OR oligomenorrhea* OR ovarian reserv* OR ovarian reserve OR menopause, premature OR primary ovarian insufficiency OR diminished ovarian reserv* OR DOR OR POI OR amenorrhea OR oligomenorrhea OR Puberty, Delayed OR delayed puberty* OR “tanner stage” OR “tanner staging”

Ovarian function tests
Follicle Stimulating Hormone OR Follicle Stimulating Hormon* OR follicle-stimulating hormon* OR Estradiol OR Estrogens OR oestradiol* OR estradiol* OR estrogen* OR Anti-Mullerian Hormon* OR anti-mullerian hormone OR Anti Mullerian Hormon* OR Antimullerian Hormon* OR Ovarian Follicl* OR ovarian follicle OR Antral Follicle Count* OR AFC OR FSH OR ovarian function tests OR ovarian function test*

Hormone replacement therapy
Hormone replacement therapy OR hormone replacement therap* OR HRT OR estrogen replacement therapy OR estrogen replacement therap* OR Estrogen Progestin Replacement Therap* OR estrogen Progestin Combination Therap*

Live birth
Live birth [mh] OR live birth OR live birth* OR live-birth* OR progeny OR offspring OR posterity OR ovarian reserve OR fertile OR fertilization OR fertility OR birth OR parturition OR childbirth OR live birth[mh] OR reproduction[tiab] OR reproduction* OR reproduction[mh:noexp] OR ovulation[mh] OR gravidity OR term birth[mh] OR term birth [tiab] OR ((full term[tiab] OR term) AND (birth[tiab] OR births[tiab]))

Ototoxicity
deafness OR hearing loss OR Loss, Hearing OR hearing disorder OR hearing disorders OR auditory OR hearing impairment OR hearing impairments OR hearing impairment* OR audiology OR audiologic OR audiometry OR audiometr* OR audiogram OR audiography OR ototoxicology OR ototoxic* OR hypoacusis OR hypoacuses OR

hypoacus* OR ototoxicity OR deaf* OR cochleotoxicity OR tinnitus[mh] OR tinnitus[tiab] OR tinnitus* OR unable to hear

Ototoxicity diagnostic test

pure tone audiometry OR audiometry, pure-tone[mh] OR extended high frequency audiometry[tiab] OR speech audiometry OR audiometry,speech[mh] OR otoscopy OR otoscopic* OR otologic* OR diagnostic techniques, otological[mh] OR ear microscopy OR speech discrimination test OR speech discrimination tests[mh] OR speech reception threshold test[mh] OR speech reception threshold test OR evoked potentials, auditory, brain stem[mh] OR acoustic evoked brain stem potential* OR auditory brain stem evoked response OR auditory brain stem evoked respons* OR auditory brain stem respons* OR brain stem auditory evoked potential OR brainstem auditory evoked potential OR brain stem auditory evoked potential* OR auditory brainstem response OR auditory brainstem respons* OR otoacoustic emissions, spontaneous[mh] OR otoacoustic emission OR otoacoustic emissions OR tinnitus evaluation OR acoustic impedance test OR Audiometry[mh] OR tympanometry

Ototoxicity interventions

hearing aid OR hearing aids OR hearing aids[mh] OR ear mold OR earmold OR ear mould OR earmould OR (cochlear AND (implant OR implantation OR implants OR prosthes*)) OR auditory prosthes* OR (tinnitus AND (mask OR masking OR mask*)) OR acoustic stimulation[mh] OR acoustic stimulation OR (acoustic AND (stimulation* OR implant OR implants)) OR (mainstreaming OR “mainstreaming (education)”[Mesh] OR persons with hearing impairments OR (acoustics AND classroom) OR speech therapy[mh] OR language therapy[mh] OR ((speech OR remedial) AND therapy[tiab]) OR sign language OR aural rehabilitation OR ((aural OR auditory) AND rehabilitation[tiab]) OR vocational guidance OR special education[tiab] OR education, special[mh] OR acoustic stimulation OR tinnitus retraining therapy OR (tinnitus AND (training [tiab] OR management[tiab])) OR ((counseling[tiab] OR counselling[tiab]) AND (structured[tiab] OR education[tiab])) OR speech perception OR speech acoustics OR auditory threshold OR linguistics) OR ((vocational AND (rehabilitation OR accommodations OR modifications)) OR noise management OR noise protection OR ear protective device OR ear protective devices[mh] OR (hearing AND (protection OR protector OR conservation OR impairment OR preservation)) OR hearing loss prevention OR amplification system OR hearing assistive technology)

Hepatic toxicity

liver fibrosis OR liver cirrhosis OR liver disease OR liver diseases OR liver diseas* OR liver dysfunction OR liver dysfunctions OR liver damage OR liver failure OR liver enzyme[all fields] OR liver enzymes[all fields] OR liver enzym* OR liver toxicity OR liver disfunction OR radiation-induced liver disease OR radiation induced liver disease OR RILD OR liver function test OR liver function tests OR liver insufficiency OR Hepatic Cirrhosis OR Cirrhoses, Hepatic OR Cirrhosis, Hepatic OR Hepatic Cirrhoses OR Cirrhosis, Liver OR Cirrhoses, Liver OR Liver Cirrhoses OR Fibrosis, Liver OR Fibroses, Liver OR Liver Fibroses OR Disease, Liver OR Diseases, Liver OR Dysfunction, Liver OR Dysfunctions, Liver OR Liver Dysfunctions OR Function Test, Liver OR Function Tests, Liver OR Liver Function Test OR Test, Liver Function OR Tests, Liver Function OR Insufficiency, Hepatic OR Liver Insufficiency OR Insufficiency, Liver OR hepatic dysfunction OR hepatic dysfunctions OR hepatic cirrhosis OR hepatic failure OR hepatic function[all fields] OR liver function[all fields] OR radiation hepatitis OR hepatitis irradiation OR impaired liver function OR hepatic fibrosis OR hepatic fibroses OR drug induced hepatitis OR toxic hepatitis OR hepatitides OR ASAT OR ALAT OR SGPT OR SGOT OR GGT OR alanine transaminase OR Transaminase, Alanine OR Glutamic-Alanine Transaminase OR Glutamic Alanine Transaminase OR Transaminase, Glutamic-Alanine OR Alanine-2-Oxoglutarate OR Aminotransferase OR Alanine 2 Oxoglutarate Aminotransferase OR Aminotransferase, Alanine-2-Oxoglutarate OR Alanine Aminotransferase OR Aminotransferase, Alanine OR Glutamic-Pyruvic Transaminase OR Glutamic Pyruvic Transaminase OR Transaminase, Glutamic-Pyruvic OR gamma Glutamyltransferase OR Glutamyl Transpeptidase OR

Transpeptidase, Glutamyl OR GGTP OR gamma-Glutamyl Transpeptidase OR Transpeptidase, gamma-Glutamyl OR gamma Glutamyl Transpeptidase OR gammaglutamyltransferase OR Aspartate Aminotransferases OR Aminotransferases, Aspartate OR Aspartate Apoaminotransferase OR Apoaminotransferase, Aspartate OR Aspartate Transaminase OR Transaminase, Aspartate OR Glutamic-Oxaloacetic Transaminase OR Glutamic Oxaloacetic Transaminase OR Transaminase, Glutamic-Oxaloacetic OR L-Aspartate-2-Oxoglutarate Aminotransferase OR Aminotransferase, L-Aspartate-2-Oxoglutarate OR L Aspartate 2 Oxoglutarate Aminotransferase OR Aspartate Aminotransferase OR Aminotransferase, Aspartate OR Glutamate-Aspartate Transaminase OR Glutamate Aspartate Transaminase OR Transaminase, Glutamate-Aspartate OR Serum Glutamic-Oxaloacetic Transaminase OR Glutamic-Oxaloacetic Transaminase, Serum OR Serum Glutamic Oxaloacetic Transaminase OR Transaminase, Serum Glutamic-Oxaloacetic OR hepatotoxicity OR hepatotoxic OR hepatotoxic* OR Veno-occlusive disease OR VOD OR Veno occlusive disease OR hepatic veno-occlusive disease OR Disease, Hepatic Veno-Occlusive OR Hepatic Veno-Occlusive Diseases OR Sinusoidal Obstruction Syndrome OR Syndrome, Sinusoidal Obstruction OR Hepatic Veno Occlusive Disease OR Veno-Occlusive Disease, Hepatic OR Veno Occlusive Disease, Hepatic OR bilirubin OR bilirubins OR bilirubin* OR Bilirubin IX alpha OR Bilirubin, (4E)-Isomer OR Bilirubin, (4E,15E)-Isomer OR Hematoidin OR Bilirubin, Disodium Salt OR Disodium Salt Bilirubin OR Bilirubin, Monosodium Salt OR Monosodium Salt Bilirubin OR delta-Bilirubin OR delta Bilirubin OR Bilirubin, (15E)-Isomer OR Bilirubin, Calcium Salt OR Calcium Salt Bilirubin OR Salt Bilirubin, Calcium OR Calcium Bilirubinate OR Bilirubinate, Calcium OR albumin OR albumins OR albumin* OR prothrombin OR prothrombins OR prothrombin* OR Factor II OR Blood Coagulation Factor II OR Differentiation Reversal Factor OR Factor, Differentiation Reversal OR Coagulation Factor II OR Factor II, Coagulation OR II, Coagulation Factor OR Alkaline phosphatase

Iron overload

iron overload OR hemosiderosis OR siderosis OR heamosiderosis OR haemosiderosis OR Hemosideroses OR Overload, Iron

Hypothalamic-pituitary dysfunction general

hypothalamic diseases OR pituitary diseases OR hypopituitarism OR pituitary hormones, anterior[mh] OR anterior pituitary hormone deficiency OR endocrine system diseases[mh] OR endocrine disorder OR hypophyseal deficiency OR (pituitary AND (dysfunction* OR hypofunction)) OR panhypopituitarism OR combined pituitary hormone deficiency OR multiple pituitary hormone deficiency OR (("endocrine system"[MeSH Terms] OR (endocrine AND system) OR endocrine system OR endocrine) AND ("complications"[Subheading] OR complications OR sequelae))

Growth hormone deficiency

(growth hormone OR GHD OR GH) AND (deficien* OR disorder OR impairment OR deviation)

Growth hormone deficiency diagnostic tests

insulin-like growth factor I OR insulin-like growth factor 1 OR IGF-1 OR IGF-I OR insulin like growth factor I OR insulin like growth factor 1 OR somatomedin C OR insulin-like somatomedin peptide I OR insulin like somatomedin peptide I OR insulin-like somatomedin peptide 1 OR insulin like somatomedin peptide 1 OR insulin-like growth factor binding protein 3 OR insulin like growth factor binding protein 3 OR IGF-binding protein 3 OR IGF binding protein 3 OR IGFBP-3 OR ((growth hormone stimulation OR GH stimulation) AND (test[tiab] OR testing)) OR glucagon stimulation test[tiab] OR arginine test[tiab] OR clonidine test [tiab] OR ((GHRH OR growth hormone releasing hormone) AND (test[tiab] OR assay)) OR insulin tolerance test[tiab] OR ITT OR (propranolol AND (l dopa OR levodopa)) OR human growth hormone/blood[mh] OR growth hormone overnight

Central hypothyroidism
((Thyroid stimulation hormone OR TSH OR Thyrotropin releasing hormone OR TRH OR thyroxine OR tri iodothyronine OR triiodothyronine) AND (deficiency OR disease)) OR (thyroid hormones[mh] AND (deficiency OR disease)) OR thyroid diseas* OR hypothyroidism[mh] OR hypothyroidism* OR thyroxine OR levo-thyroxine OR tri-iodothyronine

Central hypothyroidism diagnostic tests
FT4 OR TSH OR FT3 OR FT3 FT4 ratio* OR (TRH AND (test[tiab] OR surge OR value* OR peak OR nadir OR measurement OR assay OR concentration*)) OR Thyroxine/blood[mh] OR thyrotropin/blood[mh] OR thyroid hormones/blood[mh]

Central hypocortisolism
((adrenocorticotropic hormone[mh] OR adrenocorticotropic hormone* OR ACTH OR hydrocortisone) AND (insufficiency OR deficiency)) OR ((adrenal OR hydrocortisone) AND (insufficiency OR deficiency OR crisis)) OR hypocortisolism OR hypocortisolism* OR Addison disease[mh]

Central hypocortisolism diagnostic tests
Cortisol OR hydrocortisone OR ACTH OR adrenocorticotropic hormone OR morning glucose OR ITT OR insulin tolerance test[tiab] OR synacthen test[tiab] OR synacthen tests OR metyrapone

Hypogonadotropic hypogonadism
hypogonadotropic hypogonadism OR hypogonadism[mh] OR (infertility AND pituitary) OR ((follicle stimulating hormone OR FSH OR gonadotropin* OR luteinizing hormone OR LH OR estrogen OR testosterone) AND deficiency) OR ((puberty OR menarche OR sexual development) AND delay*) OR ((gonadotropin OR estrogen OR testosterone) AND (deficiency OR insufficiency))

Central Precocious puberty
(precocious AND (sexual OR puberty pubarche OR menarche)) OR CPP OR puberty, precocious[mh] OR premature puberty OR breast development puberty OR skeletal maturation OR epiphyseal plate closure OR bone age* OR skeletal age*) OR thelarche

Hypogonadotropic hypogonadism and central Precocious puberty diagnostic tests
(tanner[tiab] AND (scale* OR stage* OR staging)) OR bone age* OR skeletal age* OR ((follicle stimulating hormone OR FSH OR gonadotropin* OR luteinizing hormone OR LH OR estrogen OR testosterone OR LHRH OR gonadotropin-releasing hormone OR GnRH OR triptorelin OR GnRHa OR Gonadotropin-Releasing Hormone Agonist) AND (assay OR level OR test[tiab])) OR pelvic ultrasound OR gonadotropin-releasing hormone/blood[mh] OR (growth velocity AND puberty)

Hypertension
Hypertension[mh] OR hypertension[tiab] OR blood pressure[mh] OR blood pressure[tiab] OR arterial pressure[mh]

Hyperlipidemia
hyperlipidemias[mh] OR hyperlipidemia* OR "triglycerides"[MeSH Terms] OR tryglyceride* OR cholesterol OR Cholesterol, HDL[mh] OR Cholesterol, LDL[mh] OR hypertriglyceridemia[mh] OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hypercholesterolemia[mh] OR hypercholesterolemia* OR hypercholesterolaemia* OR statin* OR hydroxymethylglutaryl-coa reductase inhibitors[mh] OR lipoproteins[mh] OR lipoprotein*

Impaired glucose metabolism

diabetes mellitus[tiab] OR diabetes mellitus[mh] OR prediabetic state[mh] OR prediabetes[tiab] OR fasting glucose OR glucose tolerance[tiab] OR glucose intolerance[mh] OR glucose intolerance[tiab] OR insulin resistance[mh] OR insulin resistance[tiab] OR hyperinsulinaemia OR insulin sensitivit* OR homeostasis model assessment[tiab] OR HOMA OR hemoglobin a, glycosylated[mh] OR HbA1c OR glycosylated hemoglobin a OR glycated haemoglobin[tiab] OR hypoinsulinaemia

Obesity

Obesity[mh] OR obesity[tiab] OR obese[tiab] OR overweight[mh] OR overweight[tiab] OR body mass index[mh] OR body mass index OR BMI OR waist circumference OR waist hip ratio OR waist height ratio OR fat body[mh] OR fat body OR body fat[tiab] OR adipose tissue[mh] OR adipose

Metabolic syndrome

metabolic syndrome OR metabolic syndrome X[mh] OR insulin resistance[mh] OR insulin resistance[tiab]

Nephrotoxicity

glomerular filtration rate OR GFR OR Filtration Rate, Glomerular OR Filtration Rates, Glomerular OR Glomerular Filtration Rates OR Rate, Glomerular Filtration OR Rates, Glomerular Filtration OR glomerular OR glomerul* OR tubular OR tubula* OR renal tubular acidosis OR RTA OR Acidosis, Renal Tubular OR Renal Tubular Acidosis, Type I OR Type I Renal Tubular Acidosis OR Distal Renal Tubular Acidosis OR Acidosis, Renal Tubular, Type I OR Classic Distal Renal Tubular Acidosis OR Renal Tubular Acidosis, Distal, Autosomal Dominant OR Renal Tubular Acidosis, Type II Acidosis, Renal Tubular, Type II OR Renal Tubular Acidosis, Proximal, with Ocular Abnormalities OR Proximal Renal Tubular Acidosis OR Type II Renal Tubular Acidosis OR renal acidosis OR renal insufficiency OR Renal Insufficiencies OR Kidney Insufficiency OR Insufficiency, Kidney OR Kidney Insufficiencies OR microalbuminuria OR microalbumin* OR hypophosphatemia OR hypophosphataemia OR hypophospha* OR hypomagnes* OR hypomagnesemia OR hypomagnesaemia OR magnesium OR phosphorus OR Hyponatremia OR Hyponatremias OR hyponatraemia OR hyponatraemias OR hyponatrem* OR hyponatraem* OR Potassium OR Potassium Ion Level OR Ion Level, Potassium OR Level, Potassium Ion OR Hypokalemia OR Hypokalemias OR Hypopotassemia OR Hypopotassemias OR hypokalemic OR hypokalem* OR hypokalaemic OR hypokalaem* OR Hypocalcemia OR hypocalcemias OR hypocalciuria OR hypocalciuri* OR hypocalcem* OR hypocalc* OR “hypocarbia” OR Proteinuria OR proteinurias OR proteinuri* OR albuminuria OR albuminurias OR albuminuri* OR Aminoaciduria OR Renal Aminoaciduria OR Renal Aminoacidurias OR Aminoacidurias, Renal OR Aminoaciduria, Renal OR aminoacidur* OR Glucosuria OR glucosurias OR glucosur* OR glycosuria OR glycosurias OR glycosuria, renal OR low molecular weight OR LMW OR alpha 1 microglobulin OR a1 microglobulin OR beta 2 microglobulin OR b2 microglobulin OR 2-Microglobulin, beta OR creatinine OR Creatinine Sulfate Salt OR Salt, Creatinine Sulfate OR Sulfate Salt, Creatinine OR 60-27-5[rn] OR inulin OR 9005-80-5[rn] OR "(51) Cr EDTA" OR 51chromium edetic acid OR “(99) Tc DTPA” OR Tc DTPA OR 65454-61-7[rn] OR Technetium Tc 99m Pentetate OR (99m)Tc-DMSA OR 99mTc(V)DMSA OR DMSA OR dimercaptosuccinic acid OR Technetium Tc 99m Dimercaptosuccinic Acid OR 65438-08-6[rn] OR 99Tc-Succimer OR 99Tc Succimer OR 99mTc-Dimercaptosuccinate OR 99mTc Dimercaptosuccinate OR renal scan OR “kidney size” OR cystatin c OR gamma-Trace OR gamma Trace OR Cystatin 3 OR cystatins OR cystatin* OR renal failure OR kidney failure OR Failure, Kidney OR Failures, Kidney OR Kidney Failures OR Failure, Renal OR Failures, Renal OR Renal Failures OR renal plasma flow OR Plasma Flow, Renal OR Flow, Renal Plasma OR RPF OR ERPF OR Renal clearance OR reabsorption OR re-absorption OR nephrotoxicity OR nephrotox* OR rickets OR rickets*

Osteoporosis

"Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR "Bone Density"[Mesh] OR "Bone Remodeling"[Mesh] OR "Bone Demineralization, Pathologic"[Mesh] OR osteoporos*[tiab] OR osteopenia*[tiab] OR bone mineral

densit*[tiab] OR bone densit*[tiab] OR bone loss*[tiab] OR bone health[tiab] OR bone turnover[tiab] OR bone morbidit*[tiab] OR bone fragil*[tiab] OR bone content[tiab] OR bone mass*[tiab] OR bone deformit*[tiab] OR fracture*[tiab] OR broken bone*[tiab]

Osteonecrosis

"Osteonecrosis"[Mesh] OR osteonecros*[tiab] OR avascular necros*[tiab] OR bone necros*[tiab] OR bone aseptic necros*[tiab]

DXA

DXA OR DEXA OR absorptiometry, photon[mh] OR photon absorptiometry OR dual energy x ray absorptiometry OR bone density[mh] OR bone densitometry

Obstetric problems

hypertension, pregnancy-induced[mh] OR pregnancy induced hypertension OR PIH OR pre-eclampsia[mh] OR pre eclampsia OR hellp syndrome[mh] OR HELLP OR placentation[mh] OR placental development OR ((placenta AND (accreta OR increta OR percreta OR previa)) OR placenta accreta[mh] OR placenta previa[mh] OR vasa previa OR fetal malpresentation OR fetal malposition OR pregnancy outcome[mh] OR pregnancy complications[mh] OR breech presentation[mh] OR breech OR obstetrics labor complication[mh] OR obstetric complication* OR transverse lie[tiab] OR shoulder presentation[tiab] OR cord presentation[tiab] OR birth weight[mh] premature birth[mh] OR fetal growth retardation[mh] OR obstetric labor, premature[mh] OR fetal development[mh] OR ((fetal OR intrauterine) AND (growth OR development OR restriction)) OR small for gestational age[tiab] OR SGA OR birth weight[mh] OR low birth weight OR premature birth OR infant, premature[mh] OR premature delivery[tiab] OR immature delivery OR dysmature OR miscarriage OR spontaneous abortion OR abortion OR abortion, spontaneous[mh] OR postpartum hemorrhage[mh] OR post partum hemorrhage OR hemorrhage post-partum OR (manual removal[tiab] AND placenta) OR placenta, retained[mh] OR lactation OR lactat* OR breast feeding[mh] OR breast feeding[tiab] OR breastfeeding* OR ((vaginal ultrasonography OR pulsatility index[tiab]) AND (gestation OR pregnancy)) OR stillbirth

Pulmonary disease

Pulmonary Fibrosis OR lung fibrosis OR (scarring AND (lung OR lungs*)) OR interstitial lung disease OR acute respiratory distress syndrome[tiab] OR ARDS OR respiratory distress syndrome OR shock lung[tiab] OR pneumonia OR COP[tiab] OR pneumonitis[tiab] OR pulmonitis[tiab] OR (lung AND (cancer OR carcinoma OR tumor)) OR lung neoplasms[mh] OR (lung AND (infection OR disease)) OR lung diseases[mh] OR (chest wall AND (abnormalit* OR disease)) OR kyphoscoliosis OR fibrothorax OR bronchitis OR bronchiectasis OR emphysema OR fibroelastosis OR Bronchiolitis OR BOS[tiab] OR BOOP OR cryptogenic organizing pneumonia[mh] OR cryptogenic organizing pneumonia[tiab] OR pulmonary disease OR pulmonary disease, chronic obstructive[mh] OR COPD OR pulmonary complications OR OSA OR respiratory tract diseases[mh] OR respiratory disease* OR low infectious respiratory disease OR respiratory defect OR apnea OR asthma

Pulmonary symptoms

dyspnea OR cough OR mucus OR sputum OR hypoxia OR oygen requirement[tiab] OR exercise intolerance[tiab] OR respiratory sounds[mh] OR wheeze OR wheeze* OR breathlessness[tiab] OR shortness of breath OR chest pain OR chest discomfort[tiab] OR snore OR snoring OR hemoptysis OR oxygen requirement

Pulmonary diagnostic tests

respiratory function tests[mh] OR (function test AND (lung OR pulmonary OR respiratory)) OR spirometry OR bronchospasmolysis OR plethysmography OR DLCO OR diffusion capacity OR breath washout OR pulsoxymetry OR therapeutic irrigation[mh] OR broncho alveolar lavage[tiab] OR bronchoscopy OR blood gas analysis OR

FEV1 OR forced expiratory volume OR LCI OR lung clearance index OR TLC OR total lung capacity OR FVC OR forced vital capacity OR PEF OR peak expiratory flow OR forced expiratory flow OR FEF OR maximum expiratory flow OR MEF OR KCO OR diffusion capacity OR maximal inspiratory pressure OR maximal expiratory pressure OR respiratory muscle pressure OR ((HR-CT OR MRI OR X-ray OR Biopsy OR lavage) AND (lung OR pulmonary OR chest OR thorax)) OR (transfer factor AND lung)

Fatigue

fatigue[mh] OR fatigue OR fatigu* OR tired[tiab] OR tiredness[tiab] OR tired* OR asthenia[mh] OR asthenia OR astheni* OR exhaustion OR exhausted OR exhaust* OR loss of energy[tiab] OR energy loss[tiab] OR loss of vitality OR (vital* AND loss) OR weary[tiab] OR weariness[tiab] OR weakness OR apathy[mh] OR apath* OR lassitude[tiab] OR lethargy[mh] OR letharg* OR sleep OR sleep deprivation OR sleepiness[tiab] OR drowsy[tiab]OR drowsiness[tiab] OR chronic fatigue syndrome OR CFS OR (CF AND syndrome[tiab])

Employment

employment [MeSH terms] OR absenteeism [MeSH Terms] OR sick leave [MeSH Terms] OR rehabilitation, vocational [MeSH Terms] OR vocational guidance [MeSH Terms] OR occupation[MeSH Terms] OR occupation* OR return to work[mh] OR work performance[mh] OR employment OR unemploy* OR job*[tiab] OR vocational OR vocation* OR career OR income OR benefits use[tiab] OR socioeconomic status[tiab] OR insurance, disability[mh] OR disability insurance[tiab] OR poverty OR salaries and fringe benefits[mh] OR salaries and fringe benefits OR social security

Education

educational status[mh] OR education[mh] OR education* OR level of education

Mental health problems

depressive disorder[mh] OR depression OR depression* OR (mental AND (distress OR health OR disorder*)) OR mental disorders[mh] OR antidepressive agents[mh] OR antidepressant OR antidepressant* OR (psychological AND (outcome OR distress OR functioning OR stress*)) OR (psychosocial AND (outcomes OR impact OR challenge* OR issue* OR difficulties OR care OR need* OR profile OR functioning OR adjustment OR problem* OR health)) OR anxiety[mh] OR anxiety OR suicide OR suicide* OR (conduct AND (disorder* OR problem*)) OR behavioral symptoms[mh] OR post traumatic stress[tiab] OR PTSS

Mental health problems diagnostic tests

Brief Symptom Inventory[tiab] OR BSI OR SCL-90 OR Pediatric Symptom Checklist OR PSC OR "Checklist/methods"[MeSH Terms] OR "Checklist/standards"[MeSH Terms] OR "Psychometrics/methods"[MeSH Terms] OR "Psychometrics/standards"[MeSH Terms] OR "Surveys and Questionnaires/methods"[MeSH Terms] OR "Surveys and Questionnaires/standards"[MeSH Terms] OR Child Behavior Checklist OR CBCL OR Emotion Thermometer[tiab] OR distress thermometer OR Depression anxiety stress scale[tiab] OR DASS OR hospital anxiety depression scale[tiab] OR HADS OR behavior assessment system[tiab] OR BASC OR ((Structured Clinical Interview[tiab] OR SCID) AND DSM) OR NIH PROMIS OR Pediatric Quality of Life Inventory[tiab] OR PedsQL OR Strengths Difficulties Questionnaire OR SDQ OR kidscreen OR SF-36 Health Survey[tiab] OR SF-12 Health Survey[tiab] OR Patient Health Questionnaire 9[tiab] OR PHQ 9[tiab] OR Child Depression Inventor* OR CDI OR (Beck Depression Inventor* AND Youth) OR BDI Youth OR beck anxiety inventor* OR BAI[tiab] OR ((Manifest Anxiety Scale[mh] OR Manifest Anxiety Scale) AND (children* AND revised)) OR RCMAS 2 OR (Multidimensional Anxiety Scale[tiab] AND children) OR MASC[tiab] OR State-Trait Anxiety Inventor* OR STAI OR phobia inventor* OR SPAI OR (Beck[tiab] AND Suicide Ideation) OR (BSS AND suicide) OR Suicidal Ideation Questionnaire OR (SIQ AND suicide) OR SNAP IV OR (Behavior Rating Inventor* AND Executive Function) OR (BRIEF AND executive function) OR Connors[tiab] OR Conduct Disorder Scale OR

Disruptive behavior disorder rating scale OR (“attention deficit and disruptive behavior disorders"[MeSH Terms] AND rating scale) OR (DBD AND disruptive) OR Impact of Event Scale-Revised[tiab] OR IES-R OR Posttraumatic Stress Disorder Reaction Index[tiab] OR PTSD-RI OR (PTSD AND Reaction Index) OR Posttraumatic Diagnostic Scale[tiab] OR (PDS AND posttraumatic) OR Somatoform Dissociation Questionnaire OR SDQ-20 OR K-SADS-PL OR Psychiatric Status Rating Scales[mh]

Neurocognitive outcomes

mental processes OR “human information processing” OR “mental process” OR “mental process*” OR “human information process*” OR neurocognitive disorders OR neurocognitive disorder OR neurocognitive disorder* OR cognitive disorders OR cognitive disorder OR cognitive disorder* OR mental disorders OR mental disorder OR mental disorder* OR reaction time OR “reaction times” OR “response time” OR “response times” OR “response latency” OR “response latencies” OR “response latenc*” OR “response speed” OR “response speeds” OR “response speed*” OR refractory period, psychological OR “psychological refractory period” OR “psychological refractory periods” OR “psychological refractory period*” OR “psychologic refractory period” OR “psychologic refractory periods” OR “psychologic refractory period*” OR cognition disorders OR cognition disorder OR cognition disorder* OR intelligence OR intellig* OR psychomotor performance OR “psychomotor performances” OR “psychomotor performanc*” OR “visual motor coordination” OR “visual motor coordinations” OR “visual motor coordinat*” OR “perceptual motor performance” OR “perceptual motor performances” OR “perceptual motor performanc*” OR “sensory motor performance” OR “sensory motor performances” OR “sensory motor performanc*” OR academic performance OR “academic performances” OR “academic performan*” OR “academic test performance” OR “academic test performances” OR “academic test performan*” OR “educational test performance” OR “educational test performances” OR “educational test performan*” OR education OR education* OR verbal behavior OR verbal behaviors OR verbal behavi* OR verbal behaviour OR verbal behaviours OR arousal OR arous* OR memory OR memor* OR neurocognit* OR neuropsychologic* OR neurodevelopment* OR neurodevelopmental disorders OR neurodevelopmental disorder or neurodevelopmental disorder* OR “developmental disorder” OR “developmental disorders” OR “developmental disorder*” OR intellect* OR intellectual disability OR intellectual disabilities OR intellectual disabil* OR mental deficiencies OR mental deficiency OR mental defic* OR attention OR attention* OR executive function OR executive functions OR executive function* OR memory, short term OR working memory OR working memories OR working memor* OR Short-Term Memories OR Short-Term Memory OR short-term memor* OR Shortterm Memories OR Shortterm Memory OR shortterm memor* OR learning OR learn* OR reading OR read* OR dyslexia OR dyslexias OR dyslex* OR dyscalculia OR dyscalculias OR dyscalcul* OR executive function OR “executive functions” OR “executive function*” OR “executive control” OR “executive controls” OR “executive control*” OR problem solving OR “problem solv*” OR processing speed OR “processing speeds” OR “processing speed*” OR vigilance OR vigilanc* OR impulsive behavior OR impulsive behaviors OR impulsive behav* OR impulsive behaviour OR impulsive behaviours OR impulsivity OR impulsivities OR impulsiveness OR impulsiv* OR cognition OR cognit* OR cognitive function OR cognitive functions OR cognitive function* OR Chemotherapy-Related Cognitive Impairment OR chemobrain OR chemo-fog OR chemo fog OR chemotherapy-related cognitive impairments OR chemotherapy-related cognitive impairm* OR chemotherapy related cognitive impairment OR chemotherapy related cognitive impairments OR chemotherapy related cognitive impairm* OR chemotherapy-related cognitive dysfunction OR chemotherapy-related cognitive dysfunctions OR chemotherapy-related cognitive dysf* OR chemotherapy related cognitive dysfunction OR chemotherapy related cognitive dysfunctions OR chemotherapy related cognitive dysfunc* OR chemotherapy-induced cognitive impairment OR chemotherapy-induced cognitive impairments OR chemotherapy-induced cognitive impair* OR chemotherapy induced cognitive impairment OR chemotherapy induced cognitive impairments OR chemotherapy induced cognitive impair* OR chemotherapy-induced cognitive dysfunction OR chemotherapy-induced cognitive dysfunctions OR chemotherapy-induced cognitive dysfunc* OR chemotherapy induced cognitive dysfunction OR chemotherapy induced cognitive dysfunctions OR chemotherapy induced

cognitive dysfunc* OR cognitive dysfunction OR cognitive dysfunctions OR cognitive dysfunct* OR cognitive impairment OR cognitive impairments OR cognitive impair*

Fertility preservation general
(preservation AND (sperm OR ovarian OR semen OR fertility OR oocyte)) OR (cryopreservation AND (sperm OR ovarian OR semen OR oocyte)) OR (vitrification AND (sperm OR ovarian OR semen OR oocyte)) OR ovarium transposition OR ovarian transposition OR Gonadotropin-releasing hormone OR GNRH OR (suppression AND (ovarian OR hormonal OR hormone OR gonadotropin OR gonadotrophin)) OR fertility preservation[mh]

Fertility preservation male
(preservation AND (sperm OR semen)) OR (cryopreservation AND (sperm OR semen)) OR (vitrification AND (sperm OR semen)) OR (suppression AND (hormonal OR hormone OR gonado)) OR fertility preservation[mh] OR (cryopreserv* AND (masturbation OR testicular tissue)) OR electroejaculation OR electro ejaculation OR EEJ OR testicular sperm extraction OR TESE[tiab] OR sperm banks[mh] OR sperm banking OR sperm bank* OR penile vibration OR penile vibrat* OR (spermatogonial AND (stem cell* OR stem cells[mh])) OR SSC* OR testicular shield* OR Testis/radiation effects[mh] OR Radiation Protection/methods[mh]

Fertility preservation female: ovarian, embryo and oocyte cryopreservation
ovarian cryopreservation OR embryo cryopreservation OR oocyte cryopreservation OR ((cryopreservation[mh] OR cryopreservation) AND ovarian[tiab]) OR ((cryopreservation[mh] OR cryopreservation) AND (female[mh] OR female*[tiab])) OR ((vitrification[mh] OR vitrification) AND (ovarian OR embryo OR oocyte)) OR ((freezing[mh] OR freezing) AND (ovarian OR embryo OR oocyte))

Fertility preservation female: in vitro maturation
in vitro techniques[mh] OR (in vitro AND maturation) OR in vitro maturation OR in vitro maturation* OR (in vitro AND (maturation OR techniques)) OR Reproductive Techniques, Assisted[mh]

Gonadotropin-releasing hormone (GnRH) analogues
gonadotropin-releasing hormone[MeSH Terms] OR (gonadotropin-releasing AND hormone) OR gonadotropin-releasing hormone OR (gonadotropin AND releasing AND hormone) OR gonadotropin releasing hormone OR gonadal hormone* OR gonadotropin-releasing hormone* OR gonadotropin-releasing hormone analogue* OR GnRH analogue* OR GnRHa OR GnRH-a OR Luteinizing Hormone-Releasing Hormone OR LH-FSH Releasing Hormone OR LH-Releasing Hormone OR Gonadoliberin OR Gonadorelin

Immunomodulators
immunologic factors[MeSH Terms] OR immunomodulator* OR adjuvants, immunologic[MeSH Terms] OR AS101 OR sphingosine 1-phosphate OR sphingosine kinase* OR S1P OR biological response modifiers

Oral contraceptive pill
contraceptive OR contraceptive* OR contraceptive agents,female[mh] OR contraceptives,oral[mh] OR birth control pill OR birth control pill* OR hormonal contraception OR ((mini OR hormone) AND (pill OR pills))

Donor eggs
Donor, ovum[mh] OR Donors,ovum[mh] OR donor eggs OR oocyte donation

Surrogacy
Surrogacy OR surrogate pregnancy OR surrogate mother[mh]

Complications
Complication* OR side effect* OR side-effect* OR complications[sh] OR sequelae* OR adverse effect* OR adverse effect[sh]

Complications to pregnancy
((Preterm OR premature OR still) AND birth) OR stillbirth OR fetal death OR pregnancy outcome[mh] OR perinatal outcome OR gestational age[mh] OR premature birth[mh] OR stillbirth[mh] OR infant, low birth weight[mh] OR low birth weight OR gestational age[mh] OR gestational age* OR SGA OR fetal macrosomia[mh] OR fetal macrosomia* OR ((intrauterine growth OR fetal growth) AND retardation OR restriction) OR preeclampsia OR eclampsia

Ace inhibitor
ace inhibitor OR ace-inhibitor OR ace inhibitor* OR ace-inhibitor* OR Angiotensin-Converting Enzyme InhibitorsOR Angiotensin-Converting Enzyme Inhibitors[Pharmacological Action] OR Angiotensin Converting Enzyme Inhibitors OR Angiotensin-Converting Enzyme Antagonists OR Angiotensin Converting Enzyme Antagonists OR Enzyme Antagonists, Angiotensin-Converting OR Antagonists,
Angiotensin-Converting Enzyme OR Antagonists, Angiotensin Converting Enzyme OR Antagonists, Kininase II OR Inhibitors, Kininase II OR Inhibitors, ACE OR ACE Inhibitors OR Kininase II Inhibitors OR Kininase II Antagonists OR Angiotensin I Converting
Enzyme Inhibitors OR Angiotensin I Converting Enzyme Inhibitors OR Inhibitors, Angiotensin-Converting Enzyme OR Enzyme Inhibitors, Angiotensin-Converting OR Inhibitors, Angiotensin Converting Enzyme OR Angiotensin-Converting Enzyme
Inhibitor* OR Angiotensin Converting Enzyme Inhibitor* OR Angiotensin-Converting Enzyme Antagonist* OR Angiotensin Converting Enzyme Antagonist* OR Kininase II Inhibitor* OR Kininase II Antagonist* OR Angiotensin I-Converting Enzyme Inhibitor*
OR Angiotensin I Converting Enzyme Inhibitor* OR captopril OR enalapril OR fosinopril) OR (peptidyl dipeptidase OR Peptidyl Dipeptidase A OR Angiotensin I-Converting Enzyme OR Angiotensin I Converting Enzyme OR Carboxycathepsin OR Kininase A OR CD143 Antigen OR CD143 Antigens OR Dipeptidyl Peptidase A OR Antigens, CD143 OR Angiotensin Converting Enzyme OR Kininase II

Angiotensin receptor blocker
angiotensin receptor blocker OR angiotensin receptor blockers OR angiotensin receptor blocker* OR Angiotensin II Type 1 Receptor Blockers OR Angiotensin II Type 1 Receptor Antagonists OR Type 1 Angiotensin Receptor Antagonists OR Type 1 Angiotensin Receptor Blockers OR Selective Angiotensin II Receptor Antagonists OR Sartans OR Angiotensin II OR Angiotensin Receptors/antagonists & inhibitors OR Angiotensin II Type 1 Receptor Blocker* OR Type 1 Angiotensin Receptor Antagonist* OR Type 1 Angiotensin Receptor Blocker* OR Selective Angiotensin II Receptor Antagonist* OR losartan OR valsartan

Angiotensin neprilysin inhibitor
angiotensin neprilysin inhibitor OR angiotensin neprilysin inhibit* OR ARNI OR sacubitril* OR sacubitril/valsartan OR sacubitril-valsartan OR valsartan/sacubitril OR valsartan-sacubitril OR Entresto

Beta blocker
beta blocker OR beta blockers OR beta-blockers OR beta-blocker OR beta-blocker* OR beta blocker* OR Adrenergic beta Antagonists OR adrenergic beta-antagonists OR adrenergic beta-antagonists[Pharmacological Action] OR beta-Antagonists, Adrenergic OR Adrenergic beta-Receptor Blockaders OR Adrenergic beta Receptor Blockaders OR Blockaders, Adrenergic beta-Receptor OR beta-Receptor Blockaders, Adrenergic OR beta-Adrenergic Receptor Blockaders OR Blockaders, beta-Adrenergic Receptor OR Receptor Blockaders, beta-Adrenergic OR beta Adrenergic Receptor Blockaders OR beta-Adrenergic Blocking Agents OR Agents, beta-

Adrenergic Blocking OR Blocking Agents, beta-Adrenergic OR beta Adrenergic Blocking Agents OR beta-Adrenergic Blockers OR Blockers, beta-Adrenergic OR beta Adrenergic Blockers OR beta-Blockers, Adrenergic OR Adrenergic beta-Blockers OR beta Blockers, Adrenergic OR Sympatholytics OR Sympatholytics[Pharmacological Action] OR Sympathetic-Blocking Agents OR Agents, Sympathetic-Blocking OR Sympathetic Blocking Agents OR Sympatholytic Agents OR Agents, Sympatholytic OR Sympatholytic Drugs OR Drugs, Sympatholytic OR Sympatholytic* OR Adrenergic beta Antagonist* OR Adrenergic beta-Receptor Blockader* OR Adrenergic beta Receptor Blockader* OR beta-Adrenergic Receptor Blockader* OR beta Adrenergic Receptor Blockader* OR beta-Adrenergic Blocking Agent* OR beta Adrenergic Blocking Agent* OR beta Adrenergic Blocker* OR beta-Adrenergic Blocker* OR Adrenergic beta-Blocker* OR Sympathetic-Blocking Agent* OR Sympathetic Blocking Agent* OR Sympatholytic Agent* OR Sympatholytic Drug* OR carvedilol OR atenolol OR metoprolol OR propranolol

MRA

aldosteron antagonist OR aldosteron antagonists OR aldosterone antagonist OR aldosterone antagonists OR aldosterone antagonist* OR aldosteron antagonist* OR Antagonists, Aldosterone OR spironolactone

Ivabradine

Ivabradine[mh] OR ivabradine OR Corlentor OR Procoralan

Hydralazine, nitrates

Vasodilator OR vasodilators OR vasodilator* OR vasodilator agents OR vasodilator agents[Pharmacological Action] OR Agents,Vasodilator OR Vasodilator Drugs OR Drugs, Vasodilator OR Vasoactive Antagonists OR Antagonists, Vasoactive OR Vasoactive Antagonist* OR vasodilator agent* OR Vasodilator Drug* OR nitroglycerin OR Glyceryl Trinitrate OR Trinitrate, Glyceryl OR Nitroglycerin* OR diazoxide OR adenosine OR hydralazine

Digoxin

digoxin OR digoxin* OR Lanoxin

Diuretics

diuretic OR diuretics OR diuretic* OR diuretics[Pharmacological Action] OR furosemide

ICD/CRTD

Cardiac Resynchronization Therapy[mesh] OR Cardiac Resynchronization Therapy OR CRT OR CRTD OR Defibrillators, Implantable[Mesh] OR Defibrillators, Implantable OR ICD OR Implantable Cardioverter Defibrillator

Rehabilitation programs and physical activity

Rehabilitation[mesh] OR Exercise Therapy[mesh] OR sports[mesh] OR Physical Exertion[mesh] OR Exercise[mesh] OR (physical* AND (fitness or train* or therap* or activit*)) OR (train* AND (strength* OR aerobic OR exercise)) OR ((exercise* or fitness) AND (treatment or intervent* or program*)) OR Healthy Lifestyle

Physical activity

Exercise OR exercises OR exercis* OR physical activity OR physical activities OR physical activ* OR physical exercise OR physical exercises OR physical exercis* OR exercise training OR exercise train* OR sports OR sport OR sport* OR athletic OR athletics OR athletic* OR motor activity OR motor activities OR motor activ* OR total activ* OR energy expenditure OR energy expen* OR exercise therapy OR exercise therapies OR exercise

therap* OR Physical Education and Training OR physical education OR physical education* OR sedentary behavior OR sedentary behaviors OR sedentary behav* OR sedentary behaviour OR sedentary behaviours OR sedentary behav* OR sedentary lifestyle OR sedentary lifestyl* OR physical inactivity OR physical inactiv* OR sedentary times OR sedentary time OR inactivity OR inactiv* OR active lifestyle OR active lifestyl* OR active commuting OR active commut* OR resistance training OR resistance train* OR strength training OR strength train* OR exercise program OR exercise programs OR exercise program* OR accelerometry OR accelerometr* OR exergaming OR exergam* OR exergame OR exergames OR active-video gaming OR active-video game* OR active-video gami* OR active video gaming OR active video game* OR active video gami* OR fitness trackers OR fitness tracker OR fitness track* OR activity tracker OR activity trackers OR activity track* OR pedometer OR pedometers OR pedomet* OR metabolic equivalent OR metabolic equival* OR exercise movement techniques OR exercise movement technique OR exercise movement techn* OR heart rate monitor* OR recreational activities OR recreational activity* OR recreational activ* OR occupational activities OR occupational activity OR occupational activ* OR walking OR endurance training OR endurance train* OR yoga OR swimming

Diet/nutrition

Diet OR diets OR diet* OR nutrition OR nutri* OR vitamins OR vitamin OR vitamin* OR nutrients OR nutrient OR nutrition OR malnutrition OR “nutritional deficiency” OR “nutritional deficiencies” OR food OR foods OR food* OR eating OR “food intake” OR “food intakes” OR “macronutrient intake” OR “macronutrient intakes” OR “micronutrient intake” OR “micronutrient intakes” OR “dietary intake” OR “dietary intakes” OR “feed intake” OR “feed intakes” OR “nutrient intake” OR “nutrient intakes” OR “nutritional intake” OR “nutritional intakes” OR eat OR feeding OR sugar OR sugars OR sugar* OR mineral OR minerals OR fruit OR fruits OR fruit* OR vegetable OR vegetables OR bean OR beans OR legume OR legumes OR nuts OR soy OR grain OR meat OR meats OR beef OR pork OR poultry OR chicken OR fish OR seafood OR shellfish OR “dairy products” OR “dairy product” OR dairy OR milk OR yogurt OR yoghurt OR cheese OR cheeses OR juice OR juices OR soda OR coffee OR tea OR beverages OR beverage OR “diet quality” OR “dietary quality” OR “dietary pattern” OR “dietary patterns” OR “diet pattern” OR “diet patterns” OR “eating pattern” OR “eating patterns” OR “food pattern” OR “food patterns” OR “eating habit” OR “eating habits” OR “dietary habit” OR “dietary habits” OR “food habit” OR “food habits” OR “diet habit” OR “diet habits” OR “dietary profile” OR “dietary profiles” OR “food profile” OR “food profiles” OR “diet profile” OR “diet profiles” OR “eating profile” OR “eating profiles” OR “dietary guideline” OR “dietary guidelines” OR “diet guideline” OR “diet guidelines” OR “eating guideline” OR “eating guidelines” OR “food guideline” OR “food guidelines” OR “dietary recommendation” OR “dietary recommendations” OR “diet recommendation” OR “diet recommendations” OR “food recommendation” OR “food recommendations” OR “eating recommendation” OR “eating recommendations” OR “food intake pattern” OR “food intake patterns” OR “dietary intake pattern” OR “dietary intake patterns” OR “eating style” OR “eating styles” OR vegan* OR vegetarian* OR “dietary approach” OR “dietary approaches” OR “diet approach” OR “diet approaches” OR “dietary score” OR “diet score” OR “food score” OR energy intake OR “calorie intake” OR “caloric intake” OR caloric restriction OR “calorie restriction” OR “low calorie” OR low-calorie

Sun exposure

sun exposure OR sun expos* OR sun protection factor OR sun protection factors OR sun protection factor* OR sun protection OR sun protect* OR sunscreening agents OR sunscreening agent OR sunscreening agent* OR sunscreens OR sunscreen OR sunscreen* OR sunburn OR sunburns OR sunburn* OR sun prevention OR sun prevent* OR ultraviolet radiation OR ultraviolet radiations OR ultraviolet radiat* OR UV radiation OR UV radiations OR UV radiat* OR ultra-violet radiation OR ultra-violet radiations OR ultra-violet radiat* OR ultra violet radiation OR ultra violet radiations OR ultra violet radiat* OR ultraviolet rays OR ultraviolet ray OR UV rays OR UV ray OR ultra-violet rays OR ultra-violet ray OR ultra violet rays OR ultra violet ray OR ultraviolet light OR UV light OR ultra-violet light OR ultra violet light OR ultraviolet light* OR UV light* OR ultra-violet light* OR

ultra violet light* OR tanning OR tanning beds OR tanning bed OR sunshine OR sunlight OR sun OR sun care OR suncare OR suncar*

Alcohol

Alcohol abstinence OR alcohol abstinen* OR alcoholics OR alcoholic OR alcoholic* OR alcoholism OR alcoholism* OR alcohol dependence OR alcohol dependen* OR alcohol addiction OR alcohol addict* OR alcohol abuse OR alcohol abus* OR alcohol intoxication OR alcohol intoxicat* OR alcoholic intoxication OR alcoholic intoxicat* OR alcohol use disorder OR alcohol use disorders OR alcohol use disorder* OR drunk OR drunkenness OR drunkennesses OR drunk OR alcohol misuse OR alcohol misus* OR alcohol use OR alcohol drinking OR alcohol drink* OR alcohol consumption OR alcohol consum* OR alcohol intake OR alcohol intakes OR alcohol intak* OR alcohol drinking habits OR alcohol drinking habit OR alcohol drinking habit* OR binge drinking OR binge drink* OR "excessive drinking" OR alcoholic beverages OR alcoholic beverage OR alcoholic beverag* OR beer* OR wine* OR absinth* OR alcohol drinking behaviours OR alcohol drinking behaviour OR alcohol drinking behav* OR alcohol drinking behaviors OR alcohol drinking behavior OR "alcohol drinking pattern" OR "alcohol drinking patterns"

Drug use

"drug use disorders" OR "drug use disorder" OR "drug dependence" OR "drug dependent" OR "drug addiction" OR "drug addict" OR "drug abuse" OR hallucinogens OR hallucinogen OR hallucinogen* OR "hallucinogenic agent" OR "hallucinogenic agents" OR psychedelic OR psychedelics OR psychedel* OR "hallucinogenic substances" OR "hallucinogenic substance" OR "hallucinogenic drug" OR "hallucinogenic drugs" OR "psychedelic agent" OR "psychedelic agents" OR drug misuse OR "drug misuses" OR drug misus* OR "drug use" OR cocaine OR cocain* OR amphetamine OR amphetamin* OR amfetamine OR amfetamin* OR heroin OR heroin* OR opioid OR opioid* OR opiate OR opiat* OR cannabis OR cannabi* OR marihuana OR marihuan* OR marijuana OR marijuan* OR hashish OR hash OR crack OR illicit drugs OR "illicit drug" OR "illegal drugs" OR "illegal drug" OR "recreational drug" OR "recreational drugs" OR stimulant OR stimulants OR stimulant* OR hypnotics and sedatives OR hypnotic* OR sedativ* OR psilocybin OR psilocybin* OR psilocybin OR psilocybin* OR narcotics OR narcotic OR narcotic* OR thc OR cbd OR water pipe smoking OR "waterpipe smoking" OR hookas OR hooka OR hookah OR hookahs OR shisha OR shishas OR sheeshas OR sheesha OR waterpipe OR waterpipes OR narghiles OR narghile OR arghiles OR arghile OR oxycodone OR oxycodon*

Smoking

Smoking OR smok* OR smoking behaviours OR smoking behaviour OR smoking behav* OR smoking behaviors OR smoking behavior OR smoking habit OR smoking habits OR smoking habit* OR smoking cessation OR smoking cessat* OR nicotine OR nicotin* OR vaping OR vape OR vapes OR E-cigarette OR E-cigar* OR E cigar* OR E cigarette OR Ecigar* OR Ecigarette OR electronic cigarette OR electronic cigar* OR cigarette OR cigar* OR cigar OR cigarette smoking OR cigarette smok* OR smoker OR smokers OR tobacco products OR tobacco product OR tobacco produc* OR cigarillos OR cigarillo OR cigarill* OR pipe tobacco OR pipe tobaccos OR pipe tobacco* OR tobacco OR tobaccos OR tobacc* OR tobacco use OR tobacco uses OR tobacco chewing OR tobacco chew* OR pipe OR pipe smoking OR pipe smok* OR tobacco smoking OR tobacco smok*

General terms substance abuse

substance-related disorders OR substance-related disorder OR substance-related disor* OR "substance related disorders" OR "substance related disorder" OR substance related disor* OR substance abuse OR substance abuses OR substance abus* OR substance dependence OR substance depend* OR substance addiction OR substance addict* OR substance use OR substance uses OR "substance use disorder" OR "substance use disorders" OR substance use disor*

General terms health behaviour interventions

lifestyle intervention OR lifestyle interventions OR lifestyle interven* OR life style OR life styles OR life styl* OR lifestyle OR lifestyles OR lifestyl* OR healthy lifestyle OR health promotion Or health promotions OR health promot* OR “promotion of health” OR health campaign OR health campaigns OR health campaign* OR health counseling OR health councel* OR health coaching OR health coach OR health coach* OR health behavior intervention OR health behavior interventions OR health behavior interven* OR health behaviour intervention OR health behaviour interventions OR health behaviour interven* OR health behavior change intervention OR health behavior change interventions OR health behavior change interven* OR health behaviour change intervention OR health behaviour change interventions OR health behaviour change interven* OR modifiable lifestyle intervention OR modifiable lifestyle interventions OR modifiable lifestyle interven* OR self-management intervention OR self-management interventions OR self-management interven* OR weight loss intervention OR weight loss interventions OR weight loss interven* OR BMI change intervention OR BMI change interventions OR BMI interven* OR weight control intervention OR weight control interventions OR weight control interven* OR weight management intervention OR weight management interventions OR weight management interven* OR obesity intervention OR obesity interventions OR obesity interven* OR weight reduction programs OR weight reduction program OR weight reduction program* OR weight loss program OR weight loss programs OR weight loss program* OR obesity management OR obesity manag* OR health behavior adherence OR health behaviour adherence OR health behaviour adher* OR health behavior adher* OR multiple health behavior change interventions OR multiple health behavior change interven* OR multiple health behaviour change interventions OR multiple health behaviour change interven* OR health education OR health educations OR health educat* OR behavior change technique OR behaviour change technique OR behavior change techniques OR behaviour change techniques OR behavior change techniq* OR behaviour change techniq* OR mindfulness OR mindful* OR meditation OR meditat* OR relaxation OR relaxation* OR “progressive relaxation” OR yoga OR “lifestyle coach” OR “lifestyle coaches” OR “lifestyle coaching” OR lifestyle coach* OR “combined lifestyle intervention” OR “combined lifestyle interventions” OR “health behaviour change support” OR “health behavior change support” OR Ehealth lifestyle intervention OR Ehealth lifestyle interventions OR Ehealth lifestyle interven* OR E-health lifestyle intervention OR E-health lifestyle interventions OR E-health lifestyle interven* OR Mhealth lifestyle intervention OR Mhealth lifestyle interventions OR Mhealth lifestyle interven* OR M-health lifestyle intervention OR M-health lifestyle interventions OR M-health lifestyle interven*

Cost-effectiveness

(Cost-Benefit Analysis[mesh] OR ((cost OR economic) AND (benefit OR effectiveness OR efficacy OR impact)) OR cost-effectiveness)

Risk factors

(Risk factors OR predictors OR clinical characteristics OR patient characteristics OR clinical symptoms OR ultrasound features OR ultrasound characteristics OR age[tiab] OR gender OR sex OR family history OR stridor OR cough OR lymphadenectomy OR firm texture OR fixed mass OR hoarse voice OR pain OR shortness of breath OR dysphagia)

Screening

(screening[tiab] OR "diagnosis"[Subheading] OR "diagnosis"[All Fields] OR (tool OR tools) AND (diagnostic OR screening OR assessment) OR questionnaire OR test[tiab] OR measure[tiab] OR scale[tiab]

Validation

validation OR reliability OR validity OR sensitivity OR specificity OR psychometric* OR psychometrics[mh]

Treatment
"therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR treatment OR intervention*

Attitudes, information needs, satisfaction
Attitudes[mh] OR belief* OR perception* OR attitude of health personnel[mh] OR choice behavior[mh] OR cooperative behavior[mh] OR decision making[mh] OR clinical decision making[mh] OR informed consent[mh] OR professional-family relations[mh] OR Physician-Patient Relations[mh] OR psychology[sh] OR choice behavio* OR clinical support technique* OR cognitive aspect* OR collaboration* OR compliant behavio* OR consensus OR informed consent* OR cooperative behavio* OR co-operative behavio* OR disput* OR dissent* OR doctor patient relation* OR doctor-patient relation* OR educational technology OR emotional aspect* OR health attitude* OR health education OR health information OR health literacy OR illness behavio* OR informed choice* OR informed decision* OR negotiati* OR nursing role* OR (nurse* AND role*) OR professional* patient* communic* OR patient professional communic* OR patient acceptance OR patient adherence OR patient attitude* OR patient compliance OR patient cooperation OR patient co-operation OR patient education OR patient education[mh] OR patient involvement OR patient non adherence OR patient non compliance OR patient nonadherence OR patient non-adherence OR patient noncompliance OR patient non-compliance OR patient participation OR patient* preference* OR patient preference[mh] OR patient satisfaction OR patient satisfaction[mh:noexp] OR physician attitude OR physician patient relation* OR physician patient relation* OR professional family disagreement* OR professional family relation* OR professional patient disagreement* OR professional-family disagreement* OR professional-family relation* OR professional-patient disagreement* OR shared decision* OR sharing decision* OR staff attitude* OR treatment refusal* OR uncertainty OR health priorities[mh]

Barriers (social, legal, ethical, financial, religious, access) in general
((Barrier OR barrier*) AND (treatment* OR therapeutic[mh])) OR perceived barrier* OR ((barrier* OR obstacle* OR issue* OR impediment*) AND (social OR legal OR ethic* OR financ* OR cost* OR insurance OR resource* OR religious OR access OR patient* OR famil* OR institution* OR organization* OR hospital* OR cancer center* OR cancer centre* OR cultural OR education* OR psycholog* OR practical OR clinician* OR oncolog* OR nurs* OR fertility specialist* OR referral* OR referral and consultation[mh] OR health care professional*)) OR communication barriers[mh] OR communic* barrier* OR written communication[mh] OR verbal communication[mh] OR refusal participat* OR patient nonadherence OR patient non-adherence OR patient noncompliance OR patient non-compliance

Decision tools, educational strategies, organizational strategies
decision making,computer assistance[mh] OR decision support OR decision support system OR (Decision AND (making OR tool* OR technique* OR management OR aid* OR toolkit* OR instrument* OR framework OR strateg*)) OR decision-aid* OR pamphlet* OR brochure* OR booklet* OR patient education[mh] OR teaching material[mh] OR educational strateg* OR organizational strateg* OR (online OR web-based OR educational OR organizational AND (decision-aid* OR decision aid* OR tool OR instrument OR framework OR strateg*))

Ethical considerations
Autonom* OR personal autonomy [mh] OR principle-based ethics[mh] OR beneficienc* OR maleficence OR informed consent OR declaration helsinki OR ethic* OR ethics[mh] OR ethic*[tiab] OR ethics[sh] OR ethics, medical[mh] OR medical oncology,ethics[mh]

Legal considerations
legal OR legal guardians[mh] OR social justice[mh] OR future death OR terminally ill OR postmortem paternity OR postmortem maternity OR posthumous sperm procurement OR legislation[pt] OR legal cases[pt] OR social control, formal[mh]

Transition of care
transition of care OR (transition* AND care) OR transition to adult care[mh] OR patient transfer[mh] OR care transition OR health care transition OR healthcare transition

(Randomized) controlled trials filter:
(Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab]) NOT (animals [mh] NOT humans [mh])

Systematic review
systematic review[tiab] OR review literature[mh] OR review[tiab] OR reviews[tiab] OR review[pt] OR systematic literature review[tiab] OR systematic literature review[tiab] OR meta analysis[pt] OR meta analysis[mh] OR meta analysis[tiab] OR metaanalysis[tiab] OR meta analyses[tiab]

Clinical practice guidelines
guideline[pt] OR guideline OR guideline* OR Guidelines as Topic[Mesh] OR Health Planning Guidelines[Mesh]

Appendix 3. Evidence tables

Template

Topic / Clinical question				
Author et al. Title. Journal year;volume:pages				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Treatment era Follow-up	Type and number of participants Diagnoses Age at diagnosis Age at follow-up Controls (if applicable)	Chemotherapy Radiotherapy Surgery HSCT Other treatments	Outcome definitions Results	Risk of bias A. Selection bias Low risk/High risk/Unclear Reason: B. Attrition bias Low risk/High risk/Unclear Reason: C. Detection bias Low risk/High risk/Unclear Reason: D. Confounding Low risk/High risk/Unclear Reason: Additional remarks (if applicable)

Example

Who needs premature ovarian insufficiency surveillance?				
Byrne et al. Early menopause in long-term survivors of cancer during adolescence. Am J Obstet Gynecol 1992;166:788-793				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Multi-center cohort study Treatment era: 1945-1974 Follow-up: >19 yr after cancer diagnosis	Type and number of participants 1048 female CCS ≥21 years of age at study entry; 954 were menstruating before study entry and 94 became menopausal before they were eligible for the cohort Primary cancer diagnoses: Female genital cancer (n=90), Hodgkin's disease (n=206), non-Hodgkin's lymphoma (n=31), soft tissue sarcoma (n=115), leukaemia (n=15), brain or CNS tumour (n=133), bone cancer (n=65), other (n=393) Age at diagnosis: Mean 13.6 yr Age at follow-up: Mean 32.3 yr Controls: 1596 menstruating siblings at age 21 yr; Mean age at follow-up 33.0 yr	Chemotherapy only: 68 (6.5%) Alkylating agents and radiotherapy above diaphragm: 38 (3.6%) Alkylating agents and radiotherapy below diaphragm: 79 (7.5%) Radiotherapy only: 261 (24.9%) Surgery only: 493 (47.0%) Sterilizing surgery and chemotherapy and radiotherapy: 25 (2.4%) Other treatments: 84 (8.0%)	Outcome definitions: - Amenorrhea: woman's report of whether she was still having menstrual periods Amenorrhea: - 123/954 (12.9%) menopausal after study entry - 831/954 (87.1%) still menstruating Age-specific relative risks for amenorrhea survivors vs. controls: - All survivors aged 21-25: RR 4.32, 95% CI 2.28-8.17 - All survivors aged 26-30: RR 1.61, p>0.05 - All survivors aged 31-40: RR 0.78, p>0.05 - All survivors aged 41+: RR 0.98, p>0.05 - Alkylating agents alone aged 21-25: RR 9.17, 95% CI 2.67-31.49 - Radiotherapy below diaphragm and alkylating agents aged 21-25: RR 27.39, 95% CI 12.42-60.35 - Radiotherapy below diaphragm and alkylating agents aged 26-30: RR 4.64, p<0.01 - Radiotherapy alone aged 21-25: RR 3.66, 95% CI 1.34-9.99 - Radiotherapy alone aged 26-30: RR 2.41, p<0.05 - Radiotherapy alone aged 31-40: RR 0.90, p>0.05 - Radiotherapy alone aged 41+: RR 1.22, p>0.05 - Aged 0-12 at diagnosis aged 21-30 at follow-up: RR 0.62, p>0.05 - Aged 13-19 at diagnosis aged 21-30 at follow-up: RR 2.32, 95% CI 1.63-3.291	**Risk of bias** A. Selection bias: Unclear Reason: unclear how many patients were included in the original cohort of survivors B. Attrition bias: Low risk Reason: 90% of eligible survivors completed follow-up assessment. At follow-up, 10% of the survivors and 1% of the controls had died C. Detection bias: Unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: High risk Reason: Controls not matched to cases Strengths - study sample Limitations - Self-reported outcome - Control group not representative for general population

Appendix 4. Risk of bias assessment

Risk of bias assessment criteria for randomized clinical trials

	Internal validity
Study group	Selection bias - Low risk/high risk/unclear Is the study group representative? yes/no/unclear Low risk if: • there was random sequence allocation and allocation concealment
Follow-up	Attrition bias - Low risk/high risk/unclear Is the follow-up adequate? yes/no/unclear Low risk if: • the outcome was assessed for more than 90% in each treatment arm
Outcome	Performance bias - Low risk/high risk/unclear Are the participants and personnel blinded from knowledge of which intervention was received? yes/no/unclear Low risk if: • the participants and personnel were blinded from knowledge of which intervention was received Detection bias - Low risk/high risk/unclear Are the outcome assessors blinded from knowledge of which intervention was received? yes/no/unclear Low risk if: • the outcome assessors were blinded from knowledge of which intervention was received

Risk of bias assessment criteria for observational studies

	Internal validity
Study group	Selection bias - Low risk/high risk/unclear Is the study group representative? Low risk if: • the study group consisted of more than 75% of the original cohort of childhood cancer survivors • *or* it was a random sample with respect to certain prognostic factors (e.g. cancer treatment)
Follow-up	Attrition bias - Low risk/high risk/unclear Is the follow-up adequate? Low risk if: • the outcome was assessed for more than 75% of the study group
Outcome	Detection bias - Low risk/high risk/unclear Are the outcome assessors blinded for important determinants related to the outcome? Low risk if: • the outcome assessors were blinded for important determinants related to the outcome
Risk estimation	Confounding - Low risk/high risk/unclear Are the analyses adjusted for important confounding factors? Low risk if: • important prognostic factors (i.e. ….) were taken adequately into account

Risk of bias assessment criteria for diagnostic studies

	Internal validity
Study group	Selection bias - Low risk/high risk/unclear Is the study group representative? yes/no/unclear Low risk if: • the study group consisted of more than 75% of the original cohort of childhood cancer survivors • *or* it was a random sample
Index test	Index test bias - Low risk/high risk/unclear Are the index test results interpreted without knowledge of the results of the reference standard? yes/no/unclear Low risk if: • the index test results were interpreted without knowledge of the results of the reference standard in all patients
Reference test	Reference test bias - Low risk/high risk/unclear Are the reference test results interpreted without knowledge of the results of the index test? yes/no/unclear Low risk if: • the reference test results were interpreted without knowledge of the results of the index test in all patients
Flow and timing	Verification bias - Low risk/high risk/unclear Was there an appropriate interval (to be determined by the group) between index test(s) and reference standard? yes/no/unclear Low risk if: • there was an appropriate interval between the index test(s) and reference standard in all patients Attrition bias - Low risk/high risk/unclear Did all patients receive the same tests (i.e. same reference standard and same index test)? yes/no/unclear Low risk if: • More than 75% of the study group received the same tests

Risk of bias assessment criteria for qualitative studies

1. Was the research design appropriate to address the aims of the research? Yes/unclear/no Consider for example: • The researcher has justified the research design (e.g. have they discussed how they decided which method to use?)
2. Was the recruitment strategy appropriate to the aims of the research? Yes/unclear/no Consider for example: • The researcher has explained how the participants were selected, and • They explained why the participants they selected were the most appropriate to provide access to the type of knowledge sought by the study
3. Was the data collected in a way that addressed the research issue? Yes/no/unclear Consider for example: • It is clear how data were collected (e.g. focus group, semi-structured interview etc), and • The researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews are conducted, or did they use a topic guide), and • The researcher has explained how and why methods were modified during the study (if applicable), and • If the researcher has discussed saturation of data
4. Has the relationship between researcher and participants been adequately considered? Yes/no/unclear Consider for example: • The researcher critically examined their own role, potential bias and influence during (a) formulation of the research questions and (b) data collection, including sample recruitment, and • It was reported how the researcher responded to events during the study and whether they considered the implications of any changes in the research design (only when applicable)

Based on the CASP checklist for qualitative research (section A: are the results of the study valid; https://casp-uk.net/images/checklist/documents/CASP-Qualitative-Studies-Checklist/CASP-Qualitative-Checklist-2018_fillable_form.pdf)

Appendix 5. Summary of findings table

Example of a Summary of findings table of the body of evidence for the risk of premature ovarian insufficiency after procarbazine

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Alkylating agents Radiotherapy to ovaries	Events	Effect size	Risk of bias
Risk of POI after procarbazine (n=4 studies)	Chemaitilly 2006*	3,390 CCS	>5 yr after cancer diagnosis	Alkylating agents: 49.7%; RT to ovaries: 24.5%	215/3390 (6.3%) amenorrhea within 5 yr after their cancer diagnosis	*Odds ratio (95% CI) for amenorrhea age at diagn 0-12 yr* Procarbazine yes vs. no: OR 3.2 (1.3-7.3)	SB: high risk AB: low risk DB: unclear CF: low risk
	Thomas-Teinturier 2013*	706 CCS	>5 yr after cancer diagnosis	Any alkylating agent: 47.7%; Procarbazine: 7.2%; RT to ovaries: 56.7%	62/706 (8.9%) nonsurgical menopause; 15/706 (2.1%) nonsurgical premature menopause <age 40 yr	*Relative risk (95% CI) for nonsurgical menopause* Procarbazine dose per g/m^2: RR 2.5 (1.4-5.8)	SB: high risk AB: low risk DB: unclear CF: low risk
	Thomas-Teinturier 2015*	108 CCS	>3 yr after cancer treatment	Any alkylating agent: 100%; Procarbazine: 21.9%; RT to ovaries: 17.6%	8/108 (7.6%) altered ovarian function (↑ FSH, ↓ AMH and amenorrhoea)	*Mean FSH* Procarbazine dose: β 0.012, p<0.001; (Each unit increase in procarbazine dose, mean FSH values increased by 0.012 IU/L)	SB: high risk AB: low risk DB: unclear CF: low risk
	Levine 2018*	2,930 CCS	>5 yr after cancer diagnosis	Alkylating agents: 46.5%; Procarbazine: 201 (7.2%); RT to ovaries: 55.4%	110/2930 (3.8%) nonsurgical premature menopause <age 40 yr	*Odds ratio (95% CI) for nonsurgical premature menopause* Procarbazine dose <4000 mg/m^2 vs. 0: OR 3.07 (0.76-12.43); Procarbazine dose ≥4000 mg/m^2 vs. 0: OR 8.96 (5.02-16.00)	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Limitations: Selection bias high in 4/4; Attrition bias low in 4/4; Detection bias unclear in 4/4; Confounding low in 4/4
Consistency:	0	No important inconsistency, all show effect of procarbazine
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	+1	Dose response relationship as higher doses are associated with an increased risk as compared to lower doses
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH

Conclusion:	Increased risk of POI after procarbazine vs. no procarbazine in female childhood, adolescent and young adult cancer survivors. (4 studies significant effect; 7,134 participants; 395 events; 4 multivariable analyses)

Abbreviations: AB, attrition bias; AMH, anti-Müllerian hormone; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; FSH, follicle stimulating hormone; SB, selection bias; yr, year.
* Overlap in included patients in studies of Chemaitily 2000 and Levine 2018; and Thomas-Teinturier 2013 and 2015.

Appendix 6. GRADE assessment for grading the quality of the total body of evidence

Initial score based on type of evidence		
+4	Randomized controlled trials or systematic reviews of randomized controlled trials for intervention questions	
+2	Controlled clinical trials or observational evidence (e.g., cohort, case-control) for intervention questions	
+4	Observational studies for etiologic, prognostic and diagnostic questions	
Factors decreasing quality of evidence	**Assessment**	**Effect on quality**
1. Study limitations	Risk of bias based on the elements as defined in the risk of bias table	○ 0: No problems ○ -1: Problem with 1 element ○ -2: Problem with 2 elements ○ -3: Problem with 3 or more elements
2. Consistency of results	Degree of consistency of effect between or within studies	○ 0: All/most studies show similar results ○ -1: Lack of agreement between studies (statistical heterogeneity / conflicting result, e.g. effect sizes in different directions)
3. Directness of evidence	The generalizability of population and outcomes from each study to the population of interest	○ 0: Population and outcomes broadly generalizable ○ -1: Problem with 1 element (population different from the defined inclusion criteria OR outcomes different from the defined inclusion) ○ -2: Problem with 2 elements (population and outcomes)
4. Imprecision	The precision of the results	○ 0: No important imprecision when studies include many patients, many events and narrow confidence intervals; Determine with the chairs and advisors what is seen as a large population and events, and narrow confidence intervals. ○ -1: Important imprecision when studies include relatively few patients, few events and/or wide confidence intervals. ○ -1: If only one study is identified ○ -2: When studies include relatively few patients, few events and/or wide confidence intervals AND if only one study has been identified
5. Publication bias	If investigators fail to report studies and outcomes (typically those that show no effect)	○ 0: Publication bias unlikely ○ -1: Risk of publication bias when for example published evidence is limited to industry funded trials

Factors decreasing quality of evidence	Assessment	Effect on quality
6. Magnitude of effect	If there is a large magnitude of effect	○ +1: Large magnitude of effect if all studies show significant effect sizes (point estimate) >2 or <0.5 ○ +2: Very large magnitude of effect if all studies show significant effect sizes (point estimate) >5 or <0.2
7. Dose response gradient	If there is a dose-response relationship	○ +1: Evidence of clear relation with increases in the outcome with higher exposure levels across or within studies
8. Plausible confounding	If there is plausible confounding	○ +1: If adjustment for confounders would have increased the effect size; for example the estimate of effect is not controlled for the following possible confounders: smoking, degree of education, but the distribution of these factors in the studies is likely to lead to an underestimate of the true effect
Total score		
⊕⊕⊕⊕	High quality evidence	Further research is unlikely to change the confidence in the estimate of effect
⊕⊕⊕⊖	Moderate quality evidence	Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate
⊕⊕⊖⊖	Low quality evidence	Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate
⊕⊖⊖⊖	Very low quality evidence	Any estimate of effect is very uncertain

Appendix 7. GRADE CERQual assessment for grading the quality of the total body of qualitative evidence

Initial score based on type of evidence		
+4	Qualitative studies	
Factors decreasing quality of evidence	**Assessment**	**Effect on quality**
1. Methodological limitations	The extent to which there are concerns about the design or conduct of the primary studies that contributed evidence to an individual review finding. Assessed by risk of bias based on the elements as defined in the risk of bias table.	○ 0: No problems ○ -1: Problem with 1 element ○ -2: Problem with 2 or more elements
2. Coherence / Consistency	Degree of consistency between or within studies, assessed by (1) how clear and cogent the fit is between the data from primary studies and the overall finding and (2) the extent to which different individual themes or components of themes from studies fit into a wider network of overarching themes.	○ 0: Findings related to a theme or sub-theme are coherent ○ -1: Findings related to a theme or sub-theme are not coherent or ambiguous
3. Adequacy of data / sufficiency of saturation	An overall determination of the degree of richness and quantity of data supporting a review finding. Theme saturation or sufficiency refers to whether a theoretical point of theme saturation was achieved, at which point no further citations or observations would provide more insight or suggest a different interpretation of this theme.	○ 0: Sufficient saturation ○ -1: Insufficient saturation OR only 1 study identified
4. Relevance	The extent to which the body of evidence from the primary studies supporting a review finding is applicable to the context (perspective or population, phenomenon of interest, setting) specified in the clinical question (i.e. the generalizability)	○ 0: Relevant / generalizable ○ -1: Irrelevant, when results are not generalizable to population of outcome of the clinical question
Total score		
⊕⊕⊕⊕	High confidence in the evidence	It is highly likely that the review finding is a reasonable representation of the phenomenon of interest

⊕⊕⊕⊖	Moderate confidence in the evidence	It is likely that the review finding is a reasonable representation of the phenomenon of interest
⊕⊕⊖⊖	Low confidence in the evidence	It is possible that the review finding is a reasonable representation of the phenomenon of interest
⊕⊖⊖⊖	Very low confidence in the evidence	It is not clear whether the review finding is a reasonable representation of the phenomenon of interest

Appendix 8. Conclusions of evidence table

Breast cancer risk in CAYA cancer survivors	GRADE level of evidence
Increased risk after *10-19 Gy chest radiation* vs. no chest radiation	⊕⊕⊕⊕ HIGH[5,18-24]
No significant effect of *1-9 Gy chest radiation* vs. no chest radiation	⊕⊕⊕⊖ MODERATE[15,18-22,25,26]
Increased risk after *TBI* vs. no TBI	⊕⊕⊕⊖ MODERATE[5,16,20,27]
Increased risk after *TBI < 10 Gy* vs. no TBI	⊕⊕⊖⊖ LOW
Increased risk after *upper abdominal radiation exposing breast tissue* vs. none	⊕⊕⊕⊖ MODERATE[5,20,23,24]
Decreased risk after *radiation to volumes exposing the ovaries* vs. no radiation to volumes exposing the ovaries in survivors treated with chest radiation at younger ages (<21 yr)	⊕⊕⊕⊕ HIGH[3,5,14,18,21,22,33]
Decreased risk after *radiation to volumes exposing the ovaries* vs. no radiation to volumes exposing the ovaries in Hodgkin lymphoma survivors treated with chest radiation at older ages (21-49 yr)	⊕⊕⊖⊖ LOW[15,26,28,30-32]
Decreased risk after *higher doses of alkylating agents* vs. no alkylating agents in survivors treated with chest radiation at younger ages (<21 yr)	⊕⊕⊖⊖ LOW[2,4,5,14,21,22,35]
Decreased risk after *higher doses of alkylating agents* vs. no alkylating agents in Hodgkin lymphoma survivors treated with chest radiation at older ages (21-49 yr)	⊕⊕⊕⊕ HIGH[15,17,26,28,30,32,34]
Decreased risk in survivors treated with chest radiation with *a younger age at menopause* vs. older age	⊕⊕⊕⊕ HIGH[14,15,28,32,38]
Decreased risk in survivors with a *shorter duration of intact ovarian function after chest radiation* vs. longer duration	⊕⊕⊕⊕ HIGH[14,15,28,32,38]
Increased risk in survivors treated with *chest radiation close to menarche* vs. longer time from menarche	⊕⊕⊕⊖ MODERATE[14,15,38]
No significant effect of *treatment of early menopause* vs. no treatment	⊕⊕⊕⊖ MODERATE[14,15,32]
Increased risk after *anthracyclines* vs. no anthracyclines in a dose-response relationship. However, the dose cut-off for survivors at low, moderate and high risk is difficult to determine.	⊕⊕⊕⊕ HIGH[16,18,21,39,40]
Increased risk after *anthracyclines* without chest radiation vs. no anthracyclines and no chest radiation in survivors of Li-Fraumeni syndrome-associated childhood cancer types (leukemia, CNS tumor and non-Ewing sarcoma)	⊕⊕⊕⊖ MODERATE[16,18,39]
Increased risk after *high-dose alkylating agents without chest radiation* vs. no alkylating agents and no chest radiation	⊕⊕⊖⊖ LOW[3,16,18,39,40]

Appendix 9. Evidence to decision (EtD) framework

	Criteria	Judgements	Research evidence	Additional considerations
PROBLEM	Is the problem a priority?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes		
BENEFITS AND HARMS	What is the overall certainty of this evidence?	☐ No included studies ☐Very low ☐ Low ☐ Moderate ☐ High		
	Is there important uncertainty about how much people value the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☐ No important uncertainty or variability ☐ No known undesirable outcomes		
	Are the desirable anticipated effects large?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		
	Are the undesirable anticipated effects small?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		
	Are the desirable effects large relative to undesirable effects?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		
RESOURCE USE	Are the resources required small?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		

	Is the incremental cost small relative to the net benefits?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐Varies		
EQUITY	What would be the impact on health inequities?	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies		
ACCEPTABILITY	Is the option acceptable to key stakeholders?	☐No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		
FEASIBILITY	Is the option feasible to implement?	☐ No ☐Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		

Overall conclusions

Balance of consequences				
Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐

Appendix 10. Criteria for grading the recommendations

Grade of Recommendation Conclusions of evidence according to GRADE	**Strong recommendation to do** Benefits >>> risk & harms	**Moderate recommendation to do** Benefits > or = risk & harms	**Recommendation not to do** No benefit / Potentially harm
High quality of evidence Consistent evidence from well performed and high quality studies or systematic reviews (low risk of bias, direct, consistent, precise).	Strong recommendation based on high quality evidence	Moderate recommendation based on high quality evidence	Recommendation not to do based on high quality evidence
Moderate quality of evidence Evidence from studies or systematic reviews with few important limitations.	Strong recommendation based on moderate quality evidence	Moderate recommendation based on moderate quality evidence	Recommendation not to do based on moderate quality evidence
Low to very low quality of evidence Evidence from studies with serious flaws, only expert opinion, or standards of care.	Strong recommendation based on expert opinion	Moderate recommendation based on (very) low quality evidence Diverging expert opinions	Recommendation not to do based on expert opinion
	Wording in recommendations:		
	Is recommended …	Is reasonable …	Is not recommended …

Gibbons RJ, Smith S, Antman E. American College of Cardiology/American Heart Association clinical practice guidelines: Part I: where do they come from? Circulation. 2003; 107(23): 2979-86.

Appendix 11. Timeline for guideline development

Tasks to be finished	By whom	Estimated time to complete task
Preparation phase		
Compose working group Identify WG leaders	Chairs, coordinators and advisors	Allow 2 months for this before:
Conference call: introduction and composition of working groups	Chairs, coordinators and advisors	
Development phase		
Step 1 – Bottleneck analysis		
Develop protocol Define scope of the guideline, i.e. outcomes and population of interest Perform bottleneck analysis	Chairs, coordinator, WG leaders and advisors	Allow 2 months for this before:
Step 2 – Formulation clinical questions		
Formulate clinical questions	Chairs, coordinator, WG leaders and advisors	Allow 1 month for this before:
Conference call: Introduction, methods, clinical questions	Total group	
Step 3 – Selection of evidence		
Finalize clinical questions Develop search strategy Define in- and exclusion criteria	Chairs, coordinator, WG leaders and advisors	Allow 2 months for this before:
Perform literature search	Princess Máxima Center	Allow 2 months for this before:
Conference call: discuss steps for evidence selection	Total group	
Select evidence	Coordinator, WG leaders and members	Allow 2-3 months for this depending on number of articles
Step 4 – Summarizing evidence		
Develop evidence tables and instructions for data-extraction	Coordinator and advisors	Allow 1 month for this before:
Conference call: discuss steps for data-extraction	Total group	
Make evidence tables	Coordinator, WG leaders and members	Allow 3 months for this before:
Agree evidence tables Each WG checks evidence tables (missing studies, completeness, etc.)	WG leader will lead discussions within WG Advisors will do a general check	Allow 1 month for this before:
Make summary of findings tables, perform GRADE assessment and formulate conclusions of evidence tables	Coordinator and advisors	Allow 3 months for this before:
Conference call: Discuss conclusions of evidence	Chairs, coordinator, WG leaders and advisors	
Conference call: Discuss conclusions of evidence	WG leader will lead discussions within WG	

Step 5 – Formulation of recommendations		
Formulation of draft recommendations	Chairs, coordinator, advisors and WG leaders	Allow 2 months before:
Conference call: discuss draft recommendations	Total group	Allow 2 months to make modifications before:
Write guideline manuscript		