



# **PanCareFollowUp**

**Recommendations for long-term  
follow-up care of childhood, adolescent  
and young adult cancer survivors**

April 2024

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## Abbreviations

ACTHD	=	adrenocorticotrophic hormone deficiency
BMI	=	body mass index
CAYA	=	childhood, adolescent and young adult
CCLG	=	Children's Cancer and Leukaemia Group
CMV	=	cytomegalovirus
CNS	=	central nervous system
COG	=	Children's Oncology Group
CPP	=	central precocious puberty
DCOG	=	Dutch Children's Oncology Group
EBV	=	Epstein-Barr virus
ECG	=	electrocardiogram
FNA	=	fine needle aspiration
FSHD	=	follicle stimulating hormone deficiency
ft4	=	free thyroxine
GHD	=	growth hormone deficiency
GvHD	=	graft-versus-host disease
HBV	=	hepatitis B virus
HCP	=	health care provider
HCV	=	hepatitis C virus
HP	=	hypothalamic-pituitary
HSCT	=	haematopoietic stem cell transplantation
IGF-1	=	insulin-like growth factor-1
IGHG	=	International Late Effects of Childhood Cancer Guideline Harmonization Group
LHD	=	luteinising hormone deficiency

NSAIDs = non-steroidal anti-inflammatory drugs  
SDS = standard deviation score  
SIGN = Scottish Intercollegiate Guidelines  
TBI = total body irradiation  
TSHD = thyroid stimulating hormone deficiency  
ULN = upper limit of normal

## Preamble

These long-term follow-up and surveillance recommendations are intended to guide CAYA cancer survivors and the healthcare professionals involved in their follow-up care. They combine existing evidence-based IGHG guidelines (adopting their strong and moderate, but not their weak, recommendations) and PanCare guidelines with PanCareFollowUp consensus-based surveillance recommendations. In addition, other topics are included where awareness is important.

The recommendations are presented in four categories:

- Late effects that benefit from awareness only
- Late effects for which surveillance by awareness, history and/or a physical examination, but no surveillance test is recommended
- Late effects for which surveillance with a potential surveillance test should be discussed
- Late effects for which surveillance with a surveillance test is recommended

When using these recommendations, it is important to take note of the cross-references that are indicated at certain recommendations.

We acknowledge that the sequence of referral and diagnostic tests might vary according to the local and national healthcare system logistics. Some measures of surveillance (e.g. weight, height, BMI, blood pressure, fasting glucose or lipid profile) may be performed in primary care in appropriate circumstances.

It is recognised that survivors and their healthcare professionals have the final responsibility for making decisions concerning their long-term follow-up care. As such, they may choose to either adopt these recommendations or not to do so after individual informed discussion. Although specific surveillance testing is only recommended for survivors at-risk as defined in the specific recommendations, clinicians are at liberty to recommend surveillance or diagnostic tests for other survivors based on clinical indication and presence of other incidental medical conditions that may alter the balance of risks versus benefits from testing. It is good practice to document this decision.

In addition to regular surveillance, real-time awareness and prompt reporting of new symptoms and signs is essential to the early detection and timely treatment of late effects.

When using recommendations defining radiotherapy doses, please be aware that radiotherapy dose estimations based on the mean dose received to the specific organ at risk is preferred over the prescribed dose since the latter may not reflect radiation exposure to that organ as accurately. It is recognised that it may be difficult to access accurate and relevant radiotherapy doses for organs or structures at risk in some patients (especially those treated in the past). A pragmatic approach to making recommendations may be necessary in such cases.

For further information or questions about these recommendations, please see [www.pancarefollowup.eu](http://www.pancarefollowup.eu), [www.pancare.eu](http://www.pancare.eu) or [www.ighg.org](http://www.ighg.org).

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## Methods

These long-term follow-up and surveillance recommendations combine existing evidence-based IGHG guidelines and PanCare guidelines, as well as PanCareFollowUp consensus-based recommendations.

### *Evidence-based IGHG guidelines*

Regarding the evidence-based IGHG guidelines, a consensus decision was taken to adopt the strong (green) and moderate (yellow) recommendations to do surveillance investigations, as well as the strong recommendations not to do (red), but not the weak (orange) recommendations to do. The IGHG recommendations have been adapted with respect to their lay-out and/or title, but not their content.

### *Consensus-based PanCareFollowUp recommendations*

For topics that are considered relevant, but where evidence-based efforts are still ongoing or not yet initiated, PanCareFollowUp consensus-based surveillance recommendations were developed. For the development of consensus-based recommendations, a European expert panel of specialists and survivors involved in PanCareFollowUp as well as external experts and survivors was formed. Four existing national long-term follow-up guidelines (United Kingdom CCLG, Dutch DCOG, Scottish SIGN, and the COG from the United States) were used to identify, extract and compare existing recommendations. Recommendations that were in agreement between the guidelines were adopted. Recommendations that were in disagreement were discussed during biweekly teleconferences.

A face-to-face meeting including all of the participating experts was held to discuss more complex topics and find agreement. The refined recommendations were further reviewed in a consultation round by e-mail. The feedback was discussed during a second, smaller face-to-face core group meeting, which was also aimed at allowing discussion of lay-out, structure, overarching topics, cross-references and further dissemination.

A final consultation round included all participants of the expert panel, as well as 18 additional European late effects specialists from 14 European countries that already participate in guideline development or long-term follow-up care, in order to optimise the consensus-based recommendations for clinical use. In total, 19 European countries were represented in this effort.

This guideline was updated in April 2024. The modification that were made and the explanations are documented in Appendix F.

## Consensus decisions

In the process of developing consensus-based recommendations, some consensus decisions were taken regarding identification of at-risk populations or appropriate surveillance.

### *Frequency of surveillance*

For some late effects, the surveillance frequency is very specific. For others, a frequency “at least every 5 years, starting at entry into long-term follow-up” was used to accommodate the wide range of survivorship care models across Europe. In these recommendations, local preferences may guide the decision to choose a frequency between 1 and 5 years.

### *General population risk factors*

The occurrence of several late effects is known or suspected to be influenced by lifestyle factors or familial risk in addition to treatment-related risk factors. These PanCareFollowUp recommendations are intended to inform about treatment-related risk factors and therefore do not specify the lifestyle, hereditary and other risk factors that may be present. However, these general population risk factors may be considered when providing recommendations for surveillance to the individual survivor.

### *Age limit*

Some late effects occur more often if the survivor was exposed at a younger age. When the four supporting guidelines were inconclusive or did not mention a specific age threshold, we decided not to specify it in these consensus-based recommendations. More systematic evidence-based approaches are needed for informed recommendations on age thresholds. The HCP may make an individual decision whether he or she considers the survivor to be at risk based on a certain exposure at a young age.

### *Dose limit*

The risk of late effects after radiotherapy or chemotherapy often depends on the dose that is given. However, for many late effects, no threshold was defined in the four guidelines that were used as a starting point for these consensus-based recommendations. It was decided not to define a new threshold based on consensus or single studies, since larger studies or systematic reviews are needed to appropriately address the question above which threshold a certain late effect occurs.

### *Corticosteroid exposure*

The definition of relevant corticosteroid use as “corticosteroids as anti-cancer treatment, at least 4 weeks continuously” was based on consensus. Our aim was to include only clinically relevant exposure to corticosteroids. The expertise of the HCP may be used to assess whether the exposure in the individual survivor is relevant in order to use the corresponding recommendation.

### *Subsequent neoplasms*

It is of importance that all CAYA cancer survivors are aware of their potential increased risk of subsequent neoplasms and the importance of reporting new symptoms or masses promptly. However, specific recommendations for awareness and surveillance could only be formulated for a subset of the cancers known to occur in CAYA cancer survivors and that were included in the four supporting guidelines.

- Existing COG recommendations for testicular and prostate cancer surveillance were not included in this booklet because there is no evidence that surveillance in the general population by self-examination and PSA respectively reduces morbidity and mortality from these causes.
- Existing COG recommendations for endometrial cancer surveillance were not included because the benefit of surveillance in those at risk (with a history of hereditary non-polyposis colorectal cancer or HNPCC) is not clear and surveillance is not uniformly accepted across Europe.
- Existing COG recommendations for cervical cancer surveillance were not included in this booklet because they did not differ from the general population.

## Awareness only

### Consensus-based recommendation for higher risk groups

Some high-risk survivors, for example some CNS tumour survivors, have a greater risk of being affected in different areas simultaneously, such as in their physical health, mental health, social skills, activities of daily living, school or work. A comprehensive approach should be used to identify and address these problems.

In addition, survivors treated with allogeneic HSCT and their HCPs should be aware of the risk of chronic GvHD, which may affect any organ system, especially the skin, mouth, eyes, liver, lungs, gastro-intestinal tract, joints and muscles.

It should be noted that greater caution for late effects is warranted in those survivors who have suffered significant acute toxicity during treatment.

Sometimes, supportive treatment may contribute to long-term adverse effects (for example, increased risk of non-melanoma skin cancer after prolonged voriconazole treatment, or renal toxicity after aminoglycoside use).

Survivors with, or with a suspicion of, a hereditary cancer syndrome should receive additional consultation by a clinical geneticist to determine individualised surveillance methods and frequency based on current available knowledge.

### Consensus-based recommendation for awareness of alopecia

#### Who is at risk for alopecia?

- Some CAYA cancer survivors treated with chemotherapy, radiotherapy and/or HSCT may experience poor hair re-growth or alopecia

#### What should be done if the survivor experiences any distress?

- Discuss the availability of cosmetic solutions and/or psychological support

### Consensus-based recommendation for awareness of cerebrovascular problems

#### Who is at risk for and should be aware of cerebrovascular problems?

CAYA cancer survivors treated with

- radiotherapy to a volume exposing the head, brain or neck, including TBI

#### What cerebrovascular problems might occur?

- Carotid artery disease
- Cerebrovascular accidents
- Aneurysms
- Cavernomas

**What should be done if abnormalities are identified?**

- Discuss the importance of controlling cardiovascular and stroke risk factors (e.g. hypertension, overweight, diabetes, dyslipidaemia, smoking and low levels of physical activity)
- Perform imaging as appropriate and/or refer to a neurologist, neurosurgeon or vascular specialist

**Consensus-based recommendation for awareness of dental and oral problems<sup>a, b, c</sup>**

**Who is at risk for and should be aware of dental and oral problems?**

CAYA cancer survivors

- treated with radiotherapy to a volume exposing the oral cavity or salivary glands, including TBI
- treated with allogeneic HSCT
- treated with chemotherapy

**What dental and oral problems might occur?**

- Dental caries
- Dental developmental problems<sup>d</sup>
- Xerostomia
- Periodontal disease

**What should be done if abnormalities are identified?**

- Refer to specialist dental care or orthodontist if there are significant dental problems related to previous treatment

<sup>a</sup> Further recommendations regarding dental hygiene and exams are specified in the Consensus-based recommendation for health promotion.

<sup>b</sup> Further recommendations regarding craniofacial growth problems are specified in the Consensus-based recommendation for surveillance of craniofacial growth problems.

<sup>c</sup> Further recommendations regarding oral cancer are specified in the Consensus-based recommendation for surveillance of subsequent neoplasms.

<sup>d</sup> Especially if treated at a young age or suffered from poor nutritional condition

### Consensus-based recommendation for awareness of gastro-intestinal problems <sup>a, b</sup>

#### Who is at risk for and should be aware of gastro-intestinal problems?

CAYA cancer survivors

- treated with radiotherapy to a volume exposing the gastro-intestinal tract, including TBI
- treated with oesophageal or abdominal surgery
- with a history of chronic GvHD

#### What gastro-intestinal problems might occur?

- Bowel stenosis or obstruction
- Cholelithiasis
- Chronic enterocolitis
- Faecal incontinence
- Gastro-intestinal fistula
- Malabsorption
- Oesophageal stenosis or stricture
- Neurogenic bowel

#### What should be done if abnormalities are identified?

- Perform appropriate diagnostic tests and/or refer to a surgeon or gastro-enterologist

<sup>a</sup> Further recommendations regarding liver problems are specified in the Evidence-based recommendation for surveillance of liver problems.

<sup>b</sup> Further recommendations regarding colorectal cancer are specified in the Consensus-based recommendation for surveillance of colorectal cancer.

### Consensus-based recommendation for awareness of peripheral neuropathy

#### Who is at risk for and should be aware of peripheral neuropathy?

CAYA cancer survivors treated with

- vinca-alkaloids
- cisplatin or carboplatin

#### What should be done if abnormalities are identified?

- Refer to the appropriate HCP
- Consider medication for painful neuropathy

## Awareness, history and/or physical examination without surveillance test

### Consensus-based recommendation for health promotion<sup>a, b, c, d</sup>

#### Who should receive advice regarding health promotion?

All CAYA cancer survivors might benefit from health promotion

#### What surveillance modality should be used and at what frequency should it be performed?

- Height, weight and BMI  
every year in survivors ≤ 18 years of age, and at least every 5 years in survivors > 18 years of age
- Blood pressure
- Ensure that appropriate immunisations<sup>e</sup> have been given on recovery from active anti-cancer treatment, and that necessary booster immunisations are planned, according to local and national policies at least every 5 years, starting at entry into long-term follow-up

#### What other advice should be given?

- Maintain a physically active lifestyle
- Maintain a healthy weight
- Eat a healthy diet, according to the current national guidelines
- Use adequate sun protection measures
- Attend regular six-monthly or yearly dental examinations
- Quit smoking and/or reduce exposure to second-hand smoke
- Avoid alcohol excess

#### What could be done to promote health?

- Consider referral to a physical or occupational therapist if the survivor has special needs and might need to adapt the physical activities for success
- Consider referral to a dietician or refer for a combined lifestyle intervention for weight management
- Consider referral to the appropriate HCP depending on the possible cause of the hypertension
- Refer for healthy lifestyle interventions if the survivor wants to participate and if such interventions are available

<sup>a</sup> Further recommendations regarding dental and oral problems are specified in the Consensus-based recommendation for dental and oral problems.

<sup>b</sup> Further recommendations regarding height are specified in the Evidence-based recommendation for surveillance of hypothalamic-pituitary problems, Evidence-based recommendation for surveillance of central precocious puberty and Evidence-based recommendation for surveillance of male fertility problems and sexual dysfunction.

<sup>c</sup> Further recommendations regarding weight and BMI are specified in the Consensus-based recommendation for surveillance of overweight and obesity.

<sup>d</sup> Further recommendations regarding blood pressure are specified in the Consensus-based recommendation for surveillance of hypertension.

<sup>e</sup> Booster immunisations after standard chemotherapy, re-immunisation after HSCT.

### **Consensus-based recommendation for surveillance of subsequent neoplasms<sup>a, b, c, d, e, f</sup>**

#### **Who is at risk for and should be aware of subsequent neoplasms?**

All CAYA cancer survivors are at a potential increased risk of subsequent neoplasms depending on the treatment that they have received and their genetic risk profile.

#### **What general advice should be given?**

- Discuss the importance of prompt reporting of new symptoms or masses
- Discuss healthy lifestyle recommendations
- Encourage reduction of risk behaviour (smoking, alcohol consumption, drug use, sun exposure)
- Encourage HPV vaccination (according to national guidelines) and consider advising safe sexual practices
- Encourage participation in the national cancer screening programmes, unless more intensive or earlier surveillance is specified in the guidelines<sup>b</sup>

#### **What subsequent neoplasms might occur?**

- Acute myeloid leukaemia or myelodysplasia (after alkylating agents, anthracyclines, mitoxantrone, epipodophyllotoxins or autologous HSCT)
- Bladder cancer<sup>c</sup> (after radiotherapy to a volume exposing the bladder, including TBI, and after cyclophosphamide or ifosfamide, particularly if they have a history of severe haemorrhagic cystitis)
- Bone cancer and sarcomas<sup>d</sup> (after any radiotherapy, including TBI)
- Breast cancer (after radiotherapy  $\geq 10$  Gy to a volume exposing the breasts or upper abdominal field radiation that can extend above the diaphragm likely exposing breast tissue at a young age)
- CNS neoplasms (after radiotherapy to a volume exposing the head or brain, including TBI)
- Colorectal cancer (after radiotherapy to a volume exposing the colon and rectum, including TBI)
- Lung cancer (after radiotherapy to a volume exposing the lungs, including TBI)
- Oral cancer<sup>e</sup> (after radiotherapy to a volume exposing the oral cavity, including TBI, and after HSCT with a history of oral GvHD)
- Melanoma and non-melanoma skin cancer (after any radiotherapy, including TBI, predominantly in the radiotherapy field or after allogeneic HSCT, especially with a history of skin GvHD)

- Thyroid cancer (after radiotherapy to a volume exposing the thyroid gland, including TBI, or therapeutic <sup>131</sup>I-MIBG)

**What surveillance modality should be used and at what frequency should it be performed?**

All survivors:

- Perform a family history of malignancies at least every 5 years, starting at entry into long-term follow-up

Survivors with, or with a suspicion of, a hereditary cancer syndrome<sup>f</sup>:

- Additional consultation by a clinical geneticist to determine individualised surveillance methods and frequency at entry into long-term follow-up

Survivors at risk for breast cancer, colorectal cancer, CNS neoplasms, skin cancer or thyroid cancer:

- Consult the separate recommendations for breast cancer, colorectal cancer, CNS neoplasms, skin cancer or thyroid cancer<sup>b</sup>

**What should be done if abnormalities are identified?**

If there is a suspicion of a subsequent neoplasm:

- Perform the appropriate diagnostic tests
- Refer to the appropriate HCP

Survivors at risk for breast cancer, colorectal cancer, CNS neoplasms, skin cancer or thyroid cancer:

- Consult the separate recommendations for breast cancer, colorectal cancer, CNS neoplasms, skin cancer or thyroid cancer<sup>b</sup>

<sup>a</sup> The working group considered guidelines for the following subsequent malignant neoplasms that can occur in CAYA cancer survivors: acute myeloid leukaemia, bladder cancer, breast cancer, bone cancer, cervical cancer, CNS neoplasms, endometrial cancer, gastro-intestinal cancer, lung cancer, melanoma and non-melanoma skin cancer, oral cancer, prostate cancer, thyroid cancer, and testicular cancer. No recommendations could be formulated for cervical, endometrial, prostate and testicular cancer. We acknowledge that there might also be an increased risk of other subsequent neoplasms, but no recommendations can be made for surveillance at this time.

<sup>b</sup> Surveillance tests are specified in the IGHG guidelines for subsequent breast cancer, thyroid cancer and CNS neoplasm surveillance, and in the consensus-based recommendations for colorectal cancer and melanoma and non-melanoma skin cancer surveillance.

<sup>c</sup> Further recommendations regarding lower urinary tract problems are specified in the Consensus-based recommendation for lower urinary tract problems.

<sup>d</sup> Further recommendations regarding surveillance of bone problems are specified in the Consensus-based recommendation for bone problems.

<sup>e</sup> Further recommendations regarding dental and oral exams are specified in the Consensus-based recommendation for dental and oral problems and the Consensus-based recommendation for health promotion.

<sup>f</sup> For example, but not limited to: Fanconi anaemia, dyskeratosis congenita, Li-Fraumeni syndrome (TP53 mutation), neurofibromatosis type I, hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome).

### Consensus-based recommendation for surveillance of subsequent melanoma and non-melanoma skin cancer

#### Who is at risk for melanoma and non-melanoma skin cancer?

CAYA cancer survivors treated with

- any radiotherapy, including TBI, predominantly in the radiotherapy field
- allogeneic HSCT, especially with a history of skin GvHD

#### What problems might occur?

- Basal cell carcinoma
- Squamous cell carcinoma
- Melanoma

#### What surveillance modality should be used and at what frequency should it be performed?

- Self-examination for new spots and changing moles, at least every 6 months
- History at least every 2 years, starting at entry into long-term follow-up
- Skin exam at least every 2 years, starting at entry into long-term follow-up

#### What should be done if abnormalities are identified?

- Refer to a dermatologist

### Evidence-based recommendation for surveillance of cancer-related fatigue<sup>a</sup> (IGHG<sup>b</sup>)

#### Who is at risk for cancer-related fatigue?

All CAYA cancer survivors are at risk for cancer-related fatigue<sup>c</sup>

#### What surveillance modality should be used and at what frequency should it be performed?

All CAYA cancer survivors:

- Medical history focused on survivors' feelings of tiredness and exhaustion<sup>d</sup> regularly (at every long-term follow-up visit, or at general medical check-ups)

#### What should be done if there is an indication for cancer-related fatigue from the medical history?

- Perform further testing with a validated fatigue measure<sup>e</sup>
- Screen for physical problems that may cause fatigue<sup>f</sup>

#### What should be done if abnormalities are identified?

- Refer to a specialist in fatigue (or more generic specialist such as a psychologist, physiotherapist, or other relevant specialist)
- Discuss useful interventions<sup>g</sup>

<sup>a</sup> Cancer-related fatigue is defined as “a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning”.

<sup>b</sup> This recommendation reflects the content of the IGHG Cancer-related fatigue guideline (*Recommendations for the surveillance of cancer-related fatigue in childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group*, Journal of Cancer Survivorship, 2020; accessible through <https://www.ighg.org/guidelines/topics/fatigue/>).

<sup>c</sup> Main risk factors for cancer-related fatigue in CAYA cancer survivors are psychological distress, late effects or health problems, pain, older age at follow-up and radiotherapy.

<sup>d</sup> Questions to ask: “Do you get tired easily?”, or “Are you too tired or exhausted to enjoy the things you like to do?”

<sup>e</sup> Ideally, the [PROMIS Pediatric Fatigue Measure](#) or the [PedsQL Multidimensional Fatigue Scale](#).

<sup>f</sup> For example other late effects like cardiac dysfunction, endocrine dysfunction, pulmonary dysfunction, and renal dysfunction (IGHG guidelines under development); and/or other general causes like anaemia, arthritis, neuromuscular complications, pain, fever and/or infection, and nutritional deficiencies (list not conclusive).

<sup>g</sup> Physical activity, education about cancer-related fatigue, relaxation and mindfulness, cognitive behavioural therapy, adventure-based training.

### Evidence-based recommendation for surveillance of psychosocial problems (IGHG<sup>a</sup>)

#### Who is at risk for psychosocial problems?

All CAYA survivors are at risk for psychosocial problems

#### What psychosocial problems might occur?

- Dependent living
- Educational problems
- Relationship problems
- Social withdrawal
- Under-employment or unemployment

#### What surveillance modality should be used and at what frequency should it be performed?

All CAYA cancer survivors:

- A history focused on educational progress<sup>b</sup> and/or vocational planning and employment status<sup>c</sup>, and social withdrawal at every long-term follow-up visit or general medical check-up<sup>d</sup>, at least annually until education is completed

#### What should be done if abnormalities are identified?

- Educational and/or vocational problems should be documented in the survivor’s medical records and shared with all members of the survivor’s team

- Refer to a psychologist for further diagnostic testing and treatment
- Refer to appropriate social worker, or educational professional or vocational counselor as required

<sup>a</sup> This recommendation reflects the recommendations of the IGHG Psychosocial problems guideline (*Recommendations for the surveillance of education and employment outcomes in survivors of childhood, adolescent and young adult cancer: A Report from the International Late Effects of Childhood Cancer Guideline Harmonization Group, Cancer, 2022*; accessible through <https://www.ighg.org/guidelines/topics/psychosocial-problems/>)

<sup>b</sup> Questions to ask: “Do you have any problems keeping up at school?”, “Has your performance been affected in any way? In what way?”, “Are there certain areas/subjects you struggle with?”, “Are there areas of your education that cause you stress or anxiety?”.

<sup>c</sup> Questions to ask: “What profession would you like to pursue?”, “Have you had difficulties when applying for a job?”, “Do you have any problems keeping up with your work?”, “Do you have any problems keeping a full time job?”.

<sup>d</sup> If survivors are not scheduled for annual visits, screening can be done via phone or telehealth, or can be delegated to a suitable professional in the school of the survivor.

### Evidence-based recommendation for surveillance of mental health problems (IGHG<sup>a</sup>)

#### Who is at risk for mental health problems?

All CAYA survivors are at risk for mental health problems

#### What mental health problems might occur?

- Anxiety
- Behavioural problems
- Depression
- Post-traumatic stress
- Suicidal ideation

#### What surveillance modality should be used and at what frequency should it be performed?

All CAYA cancer survivors:

- A history with focus on survivors’ mental health<sup>b</sup> at every long-term follow-up visit or general medical check-up<sup>c</sup>

#### What should be done if abnormalities are identified?

- Survivors who indicate suicidal ideation: immediate referral to psychiatrist, psychologist, or local mental health crisis services
- Survivors who indicate mental health symptoms: prompt referral to psychiatrist, psychologist, or social worker for further diagnostic and risk assessment

<sup>a</sup> This recommendation reflects the recommendations of the IGHG Mental Health Problems guideline (*Recommendations for the surveillance of mental health problems in childhood, adolescent and young adult cancer survivors: a report from the International Late Effects of Childhood*

Cancer Guideline Harmonization Group, The Lancet Oncology, 2022; accessible through <https://www.ighg.org/guidelines/topics/mental-health-problems/>)

<sup>b</sup> Questions to ask: Have you ... “Been feeling sad, angry, or less interested in things than usual?”, “Been feeling worried, tense, stressed, or overwhelmed?”, “Had trouble coping with thoughts, memories, or reminders of the cancer experience?”, “Had thoughts of harming yourself or ending your life?”, “Considered connecting with a healthcare provider to support your mental health?”

<sup>c</sup> If survivors are not scheduled for annual visits, screening can be done via phone or telehealth, or can be delegated to a suitable professional in the school of the survivor.

### Consensus-based recommendation for surveillance of chronic pain

#### Who is at risk for chronic pain?

All CAYA cancer survivors

#### What surveillance modality should be used and at what frequency should it be performed?

- A history with specific attention to pain, asking for the presence of (chronic) pain at least every 5 years, starting at entry into long-term follow-up

#### What should be done if abnormalities are identified?

- Perform a more extensive pain history (including location, intensity, relation to cancer treatment, changes over time and interference with daily or social activities), for example using the Brief Pain Inventory
- Refer to the appropriate HCP

### Consensus-based recommendation for surveillance of osteonecrosis <sup>a</sup>

#### Who is at risk for osteonecrosis?

CAYA cancer survivors treated with or with a history of

- prolonged corticosteroids as anti-cancer treatment<sup>b</sup>
- HSCT, especially with any history of GvHD
- high dose radiotherapy involving any part of the skeleton

#### What surveillance modality should be used and at what frequency should it be performed?

- A history for symptoms of osteonecrosis at least every 5 years, at entry into long-term follow-up

#### What should be done if abnormalities are identified?

- Suspicion of osteonecrosis should always be followed by a timely referral to an orthopaedic surgeon

<sup>a</sup> Further recommendations regarding surveillance of bone cancer are specified in the Consensus-based recommendation for surveillance of subsequent neoplasms.

<sup>b</sup> At least 4 weeks continuously

<b>Consensus-based recommendation for surveillance of neurocognitive problems</b>
<p><b>Who is at risk for neurocognitive problems?</b> CAYA cancer survivors treated with or with a history of</p> <ul style="list-style-type: none"><li>• a CNS tumour, excluding spinal cord tumours</li><li>• any brain surgery</li><li>• radiotherapy to a volume exposing the brain, including TBI</li><li>• high dose cytarabine IV</li><li>• high dose methotrexate IV</li><li>• any chemotherapy IT especially if the survivor was treated at a young age</li></ul>
<p><b>What neurocognitive problems might occur?</b> Problems in the following cognitive domains:</p> <ul style="list-style-type: none"><li>• Academic and school performance</li><li>• Attention</li><li>• Executive functions (eg, problem solving, abstraction, planning)</li><li>• Intelligence</li><li>• Language</li><li>• Memory</li><li>• Processing speed</li><li>• Visual-motor integration</li></ul>
<p><b>What surveillance modality should be used and at what frequency should it be performed?</b></p> <ul style="list-style-type: none"><li>• A <u>history</u> with specific attention to educational and/or vocational progress or decline at least every 2 years in survivors ≤ 18 years of age, and at least every 5 years in survivors &gt; 18 years of age</li></ul>
<p><b>What should be done if abnormalities are identified?</b></p> <ul style="list-style-type: none"><li>• Refer to a (neuro)psychologist for a formal neuropsychological evaluation</li></ul>

IV = intravenous, IT = intrathecal

### Consensus-based recommendation for surveillance of eye problems

#### Who is at risk for eye problems?

CAYA cancer survivors treated with

- radiotherapy to a volume exposing the eye and orbit, including TBI
- radioiodine therapy (I-131 ablation therapy)<sup>a</sup>
- prolonged corticosteroids as anti-cancer treatment (only for cataract)<sup>b</sup>

#### What eye problems might occur?

- Cataract (after prolonged corticosteroids as anti-cancer treatment<sup>b</sup> or radiotherapy to a volume exposing the lens)
- Other problems of the eye and orbit, such as lacrimal duct atrophy, xerophthalmia, keratitis, telangiectasias, retinopathy, optic chiasm neuropathy, chronic painful eye, maculopathy, papillopathy, visual field deficits and glaucoma (after radiotherapy to a volume exposing the eye and orbit or radioiodine therapy)

#### What surveillance modality should be used and at what frequency should it be performed?

- A history with specific attention to symptoms of cataract and/or other problems of the eye and orbit
- A physical eye exam for external eye abnormalities at least every 5 years, starting at entry into long-term follow-up

#### What should be done if abnormalities are identified?

- Refer to an ophthalmologist or ocular specialist

<sup>a</sup> Associated with a risk of lacrimal duct atrophy

<sup>b</sup> At least 4 weeks continuously

### Consensus-based recommendation for surveillance of craniofacial growth problems <sup>a</sup>

#### Who is at risk for craniofacial growth problems?

CAYA cancer survivors treated with

- radiotherapy to a volume exposing the craniofacial area, including TBI, especially after higher doses and at a young age
- surgery to the face, especially at a young age

#### What problems might occur?

- Craniofacial growth disturbance
- Orbital hypoplasia
- Psychological adjustment difficulties due to craniofacial growth problems

**What surveillance modality should be used and at what frequency should it be performed?**

- A physical examination for craniofacial growth problems at least every 5 years, starting at entry into long-term follow-up

**What should be done if abnormalities are identified?**

- Refer to a reconstructive craniofacial surgeon if craniofacial growth problems are identified
- Perform a psychosocial history with specific attention to adjustment difficulties and refer to a psychologist if clinically indicated

<sup>a</sup> Further recommendations regarding dental and oral problems are specified in the Consensus-based recommendation for surveillance of dental and oral problems.

**Consensus-based recommendation for surveillance of spine scoliosis and kyphosis**

**Who is at risk for spine scoliosis or kyphosis?**

CAYA cancer survivors treated with or with a history of

- surgery of the spine
- surgery of the chest<sup>a</sup>
- radiotherapy to a volume exposing the spine
- spinal or paraspinal malignancies
- malignancies of bones of the lower limbs

**What problems might occur?**

- Spine scoliosis
- Spine kyphosis

**What surveillance modality should be used and at what frequency should it be performed?**

- A physical examination of the spine every year until growth is completed, starting at entry into long-term follow-up; the surveillance frequency may be increased during puberty

**What should be done if abnormalities are identified?**

- Perform imaging and/or refer to an orthopaedic surgeon or physical therapist as clinically indicated

<sup>a</sup> Does not include central venous catheter placement

**Evidence-based recommendation for surveillance of pulmonary problems (IGHG<sup>a</sup>)**

**Who is at risk for pulmonary problems?**

CAYA cancer survivors treated with

- radiotherapy to a volume exposing the lungs, including TBI
- allogeneic HSCT
- surgery to the lung or chest wall

**What pulmonary problems might occur?**

- Pulmonary dysfunction (obstructive abnormalities, restrictive abnormalities, diffusion capacity impairment)

**What surveillance modality should be used and at what frequency should it be performed?**

- History with specific attention to pulmonary dysfunction at least every 5 years, starting at entry into long-term follow-up
- Physical pulmonary exam at least every 5 years, starting at entry into long-term follow-up
- Routine pulmonary function testing is not recommended for asymptomatic at-risk CAYA cancer survivors, due to lack of interventions to prevent the deterioration of asymptomatic pulmonary dysfunction

**What other advice should be given?**

In at-risk CAYA cancer survivors:

- Get a yearly influenza vaccination and additional vaccinations based on local or national recommendations
- Consider vaccination against viral pathogens that cause pneumonias according to local or national guidelines

For all CAYA cancer survivors:

- Avoid tobacco exposure, quit smoking, and/or reduce exposure to environmental smoke

For all CAYA cancer survivors, based on expert opinion:<sup>b</sup>

- Healthcare providers should be aware of the potential risk of worsening pulmonary fibrosis after general anaesthetic and/or high oxygen exposure (e.g. during scuba diving) in survivors treated with bleomycin
- Survivors treated with pulmotoxic therapies and potentially bleomycin who wish to undertake scuba diving should be assessed by an experienced dive physician before starting to dive

**What should be done if abnormalities are identified?**

- Perform a pulmonary function test if any abnormalities are identified in the history or pulmonary exam
- Consult with or refer to a pulmonologist if the pulmonary function tests are abnormal

<sup>a</sup> This recommendation reflects the content of the IGHG Pulmonary dysfunction guideline (*Recommendations for surveillance of pulmonary dysfunction among childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group*, EClinical Medicine, 2024; accessible through <https://www.ighg.org/guidelines/topics/pulmonary-dysfunction/>).

<sup>b</sup> These expert opinion statements are not included in the IGHG Pulmonary dysfunction guideline.

## Consensus-based recommendation for surveillance of lower urinary tract problems <sup>a</sup>

### Who is at risk for lower urinary tract problems?

CAYA cancer survivors treated with

- cyclophosphamide
- ifosfamide
- radiotherapy to a volume exposing the bladder, including TBI
- cystectomy
- hysterectomy
- pelvic surgery
- spinal cord surgery

### What lower urinary tract problems might occur?

- hemorrhagic cystitis
- bladder fibrosis
- dysfunctional voiding
- vesicoureteral reflux
- neurogenic bladder
- hydronephrosis

### What surveillance modality should be used and at what frequency should it be performed?

- A history with specific attention to urinary tract symptoms at least every 5 years, starting at entry into long-term follow-up

### What other advice should be given?

- CAYA cancer survivors with a cystectomy should be followed up by an appropriate specialist

### What should be done if abnormalities are identified?

- Perform a urinalysis including cytology and urine culture
- Refer to a urologist if the urinalysis results are abnormal

<sup>a</sup> Further recommendations regarding bladder cancer are specified in the Consensus-based recommendation for surveillance of subsequent neoplasms.

### Evidence-based recommendation for obstetric problems (IGHG<sup>a</sup>)<sup>b</sup>

#### Who is at risk for obstetric problems?

Female CAYA cancer survivors treated with

- radiotherapy to a volume exposing the uterus

#### What obstetric problems might occur<sup>c</sup>?

- Miscarriage
- Premature birth
- Low birth weight

#### What surveillance modality should be used and at what frequency should it be performed?

- High-risk obstetric surveillance<sup>d</sup>  
during pregnancy

#### What other advice should be given?

- HCPs should discuss the risk of adverse obstetric outcomes<sup>c</sup> based on radiotherapy to a volume exposing the uterus with all female CAYA cancer survivors of reproductive age

#### What should be done if abnormalities are identified?

- Refer to the appropriate HCP

<sup>a</sup> This recommendation reflects the content of the IGHG Counselling and Surveillance of obstetrical risks guideline (*Counseling and surveillance of obstetrical risks for female childhood, adolescent, and young adult cancer survivors: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group*, American Journal of Obstetrics & Gynecology, 2020; accessible through <https://www.ighg.org/guidelines/topics/obstetric-care/>)

<sup>b</sup> Further recommendations regarding cardiomyopathy surveillance before and/or during pregnancy are specified in the Consensus-based recommendation for surveillance of cardiac problems.

<sup>c</sup> There is no evidence to support that survivors have an increased risk of giving birth to a child with congenital anomalies.

<sup>d</sup> Recommended due to the risk of premature birth and low birth weight.

### Consensus-based recommendation for surveillance of spleen problems

#### Who is at risk for spleen problems?

CAYA cancer survivors treated with:

- splenectomy

- radiotherapy  $\geq 10$  Gy to a volume exposing the spleen<sup>a</sup>
- allogeneic HSCT conditioned with or without TBI
- autologous HSCT conditioned with TBI

#### **What spleen problems might occur?**

- Overwhelming infections (especially with encapsulated bacteria, e.g. Pneumococcus, Meningococcus, Haemophilus influenzae type B) that could be prevented by vaccination

#### **What other advice should be given?**

- Educate about events that necessitate immediate start of therapeutic antibiotics and prompt evaluation by an HCP
  - fever  $> 38.3$  °C
  - infective or septic symptoms including hypothermia, hypotension, chills/rigors and changes in mental status (e.g. somnolence, agitation)
  - animal or human bite with skin break
- Ensure that appropriate therapeutic antibiotics are already available or will be rapidly prescribed and dispensed “on demand”, according to local and national policies
- Follow the current local and national asplenia guidelines concerning prophylactic antibiotics
- Advise wearing a medical bracelet or carrying a patient card, if available, according to local and national policies
- Discuss the importance of seeking advice from experts (long-term follow-up team and/or travel vaccine specialists) if the survivor is planning to visit endemic areas about
  - the possible need for travel vaccines
  - the possible need for anti-malarial medications

#### **What should be done if abnormalities are identified?**

If CAYA cancer survivors at risk for spleen problems present with fever  $> 38.3$  °C, infective or septic symptoms<sup>b</sup> or an animal or human bite with skin break, it is recommended to

- Perform a physical examination
- Perform a blood count
- Perform a blood culture
- Immediately treat with therapeutic antibiotics according to local and national policies until blood culture results are available

<sup>a</sup> Radiotherapy dose estimations based on the mean dose received to the spleen is preferred over the prescribed dose since the latter may not reflect radiation exposure to the spleen as accurately.

<sup>b</sup> Including hypothermia, hypotension, chills/rigors and changes in mental status (e.g. somnolence, agitation).

## Awareness, history and/or physical examination with potential surveillance test

### Evidence-based recommendation for surveillance of subsequent thyroid cancer (IGHG<sup>a</sup>)<sup>b</sup>

#### Who is at risk for subsequent thyroid cancer?

CAYA cancer survivors treated with

- radiotherapy to a volume exposing the thyroid gland, including TBI
- therapeutic <sup>131</sup>I-MIBG

#### What surveillance modality should be used and at what frequency should it be performed?

- Counselling regarding the increased risk for developing differentiated thyroid carcinoma, to inform their healthcare provider if they detect a thyroid mass (independent of the presence or absence of associated symptoms) at least every 5 years
- Counselling regarding options for differentiated thyroid carcinoma surveillance (after radiotherapy to a volume exposing the thyroid gland) at least every 5 years
- A physical examination of the neck as part of a complete physical examination whenever a survivor is assessed by a healthcare provider

If the decision to commence surveillance is made:<sup>c</sup>

- A neck palpation, every 1-2 years starting 5 years after radiotherapy
- A thyroid ultrasonography<sup>d</sup> every 3-5 years starting 5 years after radiotherapy

#### What should be done if abnormalities are identified?

- Refer to the appropriate HCP

<sup>a</sup> This recommendation reflects the content of the IGHG Thyroid Cancer guideline (*Balancing the benefits and harms of thyroid cancer surveillance in survivors of Childhood, adolescent and young adult cancer: Recommendations from the international Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium*, Cancer Treatment Reviews, 2018; accessible through <http://www.ighg.org/guidelines/topics/thyroid-cancer/>)

<sup>b</sup> Further recommendations regarding surveillance of thyroid function problems are specified in the Consensus-based recommendation for surveillance of thyroid function problems.

<sup>c</sup> The decision to commence surveillance and which modality to use should be made by the healthcare provider in consultation with the survivor after careful consideration of the advantages and disadvantages of differentiated thyroid carcinoma surveillance in the context of the survivor's individual preferences, practice setting, the HCP's experience and expertise of local diagnosticians (radiology) (see Overview of Advantages and Disadvantages in Appendix C). Healthcare providers should be aware that both diagnostic tests have advantages and disadvantages and can identify benign as well as malignant nodules resulting in need for invasive procedures.

<sup>d</sup> Ultrasound, FNA and/or biopsy should be performed in centers where there is experience in assessment of thyroid cancers so that appropriate interpretation of radiographic features and clinical risk factors can minimise the number of unnecessary invasive and additional diagnostic procedures. When ultrasound is used for surveillance, the cervical lymph node stations should always be visualised.

## Evidence-based recommendation for surveillance of subsequent CNS neoplasms (IGHG<sup>a</sup>)

### Who is at risk for subsequent CNS neoplasms?

CAYA cancer survivors treated with

- radiotherapy to a volume exposing the head or brain, including TBI

### What subsequent CNS neoplasms might occur?

- Meningiomas
- (High-grade) gliomas
- Other CNS neoplasms<sup>b</sup>

### What surveillance modality should be used and at what frequency should it be performed?

- Inform the survivor about symptoms and signs<sup>c</sup> that may be related to a subsequent CNS neoplasm
- Neurologic history focused on symptoms<sup>c</sup> that may be related to subsequent CNS neoplasms
- Neurologic examination focused on signs<sup>c</sup> that may be related to subsequent CNS neoplasms at every long-term follow-up evaluation, which may be at 1 - 5 year intervals
- No recommendation can be formulated for routine MRI surveillance for asymptomatic survivors<sup>d</sup>

### What should be done if abnormalities are identified?

- Refer to the appropriate specialist

<sup>a</sup> This recommendation reflects the recommendations of the IGHG Subsequent CNS neoplasm guideline (*Surveillance for subsequent neoplasms of the CNS for childhood, adolescent, and young adult cancer survivors: a systematic review and recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group*, The Lancet Oncology, 2021; accessible through <https://www.ighg.org/guidelines/topics/central-nervous-system-malignancies/>).

<sup>b</sup> Pituitary tumors, neurilemmoma/schwannoma, opticus glioma, craniopharyngioma, medulloblastoma, pineal tumors, pilocytic astrocytoma, choroid plexus tumors, ependymoma, supratentorial tumor, oligodendroglioma, ganglioglioma, glioblastoma.

<sup>c</sup> Progressively worsening, severe, unrelenting headaches, new onset cognitive, motor, sensory or behavioral changes, balance problems, seizures, and other neurologic deficits.

<sup>d</sup> There is currently insufficient evidence to determine whether early detection of subsequent CNS neoplasms reduces morbidity and mortality. The decision to undertake MRI surveillance should be made by the CAYA cancer survivor and healthcare provider after careful consideration of the potential harms and benefits of MRI surveillance (see Survivor Information Form in Appendix D).

## Awareness, history and/or physical examination with surveillance test

### Evidence-based recommendation for surveillance of subsequent breast cancer (IGHG<sup>a</sup>)

#### Who is at risk for subsequent breast cancer?

Female CAYA cancer survivors treated with

- radiotherapy  $\geq 10$  Gy to a volume exposing the breasts<sup>b</sup>
- upper abdominal field radiation that can extend above the diaphragm likely exposing breast tissue at a young age<sup>c</sup>

#### What surveillance modality should be used and at what frequency should it be performed?

- A physical examination of the breasts<sup>d</sup>
- A mammography
- A breast MRI  
every year in survivors  $\geq 25$  years of age or  $\geq 8$  years from radiation, whichever occurs last

#### What should be done if abnormalities are identified?

- Refer to the appropriate HCP

<sup>a</sup> This recommendation reflects the recommendations of the IGHG Breast cancer guideline (Updated breast cancer surveillance recommendations for female childhood, adolescent and young adult cancer survivors from the International Guideline Harmonization Group, Journal of Clinical Oncology, 2020; accessible through <https://www.ighg.org/guidelines/topics/breast-cancer/>).

<sup>b</sup> Radiotherapy dose estimations based on the mean dose received to the breasts is preferred over the prescribed dose since the latter may not reflect radiation exposure to the breasts as accurately.

<sup>c</sup> For survivors treated with upper abdominal field radiation that can extend above the diaphragm likely exposing breast tissue at a young age, the surveillance decision should be an individual one, taking into account additional risk factors (patient age, family history, menopausal status, other previous cancer treatment) and personal values regarding the potential advantages and disadvantages of surveillance (see Survivor Information Form in Appendix E).

<sup>d</sup> Clinical breast exam for female survivors at risk who are returning for follow-up medical evaluations in countries where breast cancer surveillance access is through clinical referral.

### Consensus-based recommendation for surveillance of subsequent colorectal cancer

#### Who is at risk for subsequent colorectal cancer?

CAYA cancer survivors treated with or with a history of

- radiotherapy to a volume exposing the colon and rectum, including TBI

#### What surveillance modality should be used and at what frequency should it be performed?

- Faecal occult blood testing every 3 years, to start 5 years after radiation or at the age of 30 years, whichever occurs last

- As an alternative surveillance method, colonoscopy might be considered every 5 years, to start 5 years after radiation or at the age of 30 years, whichever occurs last

**What should be done if abnormalities are identified?**

- Positive faecal occult blood testing should always be followed by a timely colonoscopy

**Consensus-based recommendation for surveillance of impaired glucose metabolism and diabetes mellitus**

**Who is at risk for an impaired glucose metabolism or diabetes mellitus?**

CAYA cancer survivors treated with

- radiotherapy to a volume exposing the pancreas, including TBI

**What surveillance modality should be used and at what frequency should it be performed?**

- A fasting blood glucose with or without HbA1c at least every 5 years, starting at entry into long-term follow-up

**What should be done if abnormalities are identified?**

- Evaluate other features of metabolic syndrome (including dyslipidaemia, overweight and hypertension)
- Refer to the appropriate HCP

**Consensus-based recommendation for surveillance of dyslipidaemia**

**Who is at risk for dyslipidaemia?**

CAYA cancer survivors treated with

- TBI
- HSCT

**What surveillance modality should be used and at what frequency should it be performed?**

- A fasting lipid profile starting no later than at the age of 40 years, and at least every 5 years subsequently<sup>a</sup>

**What should be done if abnormalities are identified?**

- Evaluate other features of metabolic syndrome (including impaired glucose metabolism or diabetes mellitus, overweight and hypertension)

- Refer to the appropriate HCP

<sup>a</sup> Timing of initiation and frequency could be guided by family history, presence of co-morbid conditions associated with dyslipidaemia risk or by national cardiovascular risk management guidelines.

### Consensus-based recommendation for surveillance of overweight and obesity <sup>a</sup>

#### Who is at risk for overweight or obesity?

CAYA cancer survivors treated with or with a history of

- CNS tumour near or within the HP region
- radiotherapy to a volume exposing the hypothalamus or pituitary gland, including TBI
- neurosurgery of the hypothalamus or pituitary gland

#### What surveillance modality should be used and at what frequency should it be performed?

- Height, weight and BMI  
at least every 2 years and at every long-term follow-up visit

#### What should be done if abnormalities are identified in survivors at risk?

- Evaluate other features of metabolic syndrome (including dyslipidaemia, diabetes and hypertension)
- Refer to a dietician or refer for a combined lifestyle intervention for weight management
- Consider referral to the appropriate HCP for management of metabolic syndrome
- Consider referral to an endocrinologist for evaluation and management of central endocrinopathies

<sup>a</sup> Further recommendations regarding weight and BMI are specified in the Consensus-based recommendation for health promotion.

### Consensus-based recommendation for surveillance of hypertension <sup>a, b</sup>

#### Who is at risk for hypertension?

CAYA cancer survivors treated with

- radiotherapy to a volume exposing the kidneys, or to a volume exposing the heart and associated large vessels, including TBI
- nephrectomy
- ifosfamide
- platinum based chemotherapy
- nitrosoureas
- immunosuppressives<sup>c</sup>

#### What surveillance modality should be used and at what frequency should it be performed?

- Blood pressure

at least every 2 years and at every long-term follow-up visit

**What should be done if abnormalities are identified in survivors at risk?**

- Evaluate other features of metabolic syndrome (including dyslipidaemia, overweight and diabetes mellitus)
- Refer to the appropriate HCP depending on the possible cause of the hypertension

<sup>a</sup> Further recommendations regarding blood pressure are specified in the Consensus-based recommendation for health promotion.

<sup>a</sup> Further recommendations regarding renal problems are specified in the Consensus-based recommendation for surveillance of renal problems.

<sup>c</sup> For example, cyclosporine, tacrolimus.

**Evidence-based recommendation for surveillance of reduced bone mineral density (BMD)<sup>a</sup> (IGHG<sup>b</sup>)**

**Who is at risk for reduced BMD?<sup>b</sup>**

CAYA cancer survivors treated with or with a history of

- Cranial or craniospinal radiotherapy
- TBI

**What surveillance modality should be used and at what frequency should it be performed?**

- A history with specific attention to risk factors<sup>c</sup> and symptoms (back pain, fractures) of reduced bone mineral density at least every 5 years, starting at entry into long-term follow-up
- A DXA scan<sup>d</sup> once at entry into long-term follow-up (between two to five years following completion of therapy), to be repeated at 25 years of age when peak bone mass should be achieved, and thereafter as clinically indicated

**What other advice should be given?**

- Be aware of other potential risk factors for low and very low bone mineral density for survivors, including corticosteroids as anti-cancer treatment,<sup>e</sup> hypogonadism, growth hormone deficiency, low BMI or underweight, male sex, white race, lack of physical activity,<sup>f</sup> smoking
- Due to insufficient evidence, no recommendation can be formulated for or against BMD surveillance for survivors with these potential risk factors for reduced BMD
- Counsel about lifestyle habits that are important to maintain or improve bone health: adequate calcium and vitamin D intake, abstinence from smoking and alcohol, and adequate physical activity according to guidelines for the general population

**What should be done if abnormalities are identified?**

In CAYA cancer survivors with a BMD Z-score  $\leq -2$ :

- Refer to (or consult) a medical bone health specialist<sup>g</sup> for further (endocrine) evaluation, interpretation of BMD findings, treatment, and follow-up

In CAYA cancer survivors with a BMD Z-score  $\leq -1$  and  $> -2$ :

- Evaluate for the presence of endocrine defects and consult a medical bone health specialist<sup>g</sup> for further evaluation and interpretation of BMD findings as clinically indicated
- Repeat DXA after 2 years, and thereafter as clinically indicated based on BMD change (i.e. in case of BMD decline more than the DXA machine's least significant change) and ongoing risk assessment

<sup>a</sup> Further recommendations regarding surveillance of bone cancer are specified in the Consensus-based recommendation for surveillance of subsequent neoplasms.

<sup>b</sup> The bone mineral density recommendations reflects the content of the IGHG Bone Mineral Density guideline (*Bone mineral density surveillance for childhood, adolescent, and young adult cancer survivors: evidence-based recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group*, Lancet Diabetes & Endocrinology, 2021; accessible through <https://www.ighg.org/guidelines/topics/bone-abnormalities/>).

<sup>c</sup> Poor intake of vitamin D, poor intake of calcium, minimal weight-bearing exercise, comorbidities.

<sup>d</sup> The pubertal stage of the survivor should be taken into account when deciding to perform a DXA scan. It might be considered to postpone the DXA scan in pre-pubertal and pubertal survivors.

<sup>e</sup> At least 4 weeks continuously.

<sup>f</sup> The WHO global recommendation on physical activity for health for adults is 150 minutes of moderate-intensity activity (or equivalent) per week, measured as a composite of physical activity undertaken across multiple domains: for work (paid and unpaid, including domestic work); for travel (walking and cycling); and for recreation (including sports). For adolescents, the recommendation is 60 minutes of moderate- to vigorous-intensity activity daily.

<sup>g</sup> A medical bone health specialist is defined as any specialist who is caring for BMD deficits in CAYA cancer survivors, such as an endocrinologist (most settings), internist, pediatrician, rheumatologist, family physician, or general practitioner, depending on country and setting.

### **Evidence-based recommendation for surveillance of hypothalamic-pituitary (HP) axis problems (IGHG<sup>a</sup>)<sup>b, c</sup>**

#### **Who is at risk for HP axis problems?**

CAYA cancer survivors treated with or with a history of

- radiotherapy to a volume exposing the HP region, including TBI
- surgery near or within the HP region
- CNS tumours near or within the HP region
- hydrocephalus or cerebrospinal fluid shunt (risk factor for growth hormone deficiency)

#### **What HP axis problems might occur?**

- Growth hormone deficiency (GHD)
- TSH deficiency (TSHD)
- LH/FSH deficiency (LH/FSHD)
- ACTH deficiency (ACTHD)

### **Who should be referred directly to a (paediatric) endocrinologist or seen in a multidisciplinary team?**

CAYA cancer survivors treated with or with a history of

- suprasellar and sellar tumours
- surgery near or within the HP region
- $\geq 30$  Gy radiotherapy exposing the HP region<sup>d</sup>

### **When should surveillance for HP axis problems be initiated?**

For survivors treated with radiotherapy to a volume exposing the HP region, including TBI:

- Initiate surveillance for any HP axis problem at  $\geq 1$  year from the end of radiotherapy, even in the absence of symptoms<sup>e</sup>

For survivors with a history of hydrocephalus or cerebrospinal fluid shunt:

- Initiate surveillance for GHD from occurrence of hydrocephalus or cerebrospinal fluid shunt

### **What surveillance modality should be used and at what frequency should it be performed?**

Pre-pubertal and peri-pubertal survivors:

Every 6 months:

- Height velocity (height, expressed as standard deviation and plotted on a growth chart) in relation to parental height
- Tanner stage<sup>f</sup> (pubertal development and pubertal progression)

Every year:

- Relevant clinical history for HP axis problems
- Physical examination for symptoms and signs suggestive of HP axis problems
- Laboratory surveillance
  - fT4, TSH, morning cortisol

Post-pubertal survivors:

- Relevant clinical history for HP axis problems
- Evaluation of menstrual cycle in females
- Physical examination for symptoms and signs suggestive of HP axis problems
- Laboratory surveillance
  - fT4, TSH, morning cortisol, IGF-1<sup>g</sup>
  - Morning testosterone (10 AM) (or free testosterone in case of overweight) and LH in males
  - Estradiol, LH and FSH in females

every year

### **For how long should surveillance for HP axis problems be performed?**

Surveillance should be continued for at least 15 years from radiotherapy exposure or after diagnosis. However, HP axis problems may still occur after 15 years. Continuation of surveillance should be a shared decision between survivor and HCP considering available healthcare resources. If the decision is made to stop surveillance, the survivor should be educated about possible signs and symptoms of HP axis problems.

### **What should be done if abnormalities are identified?**

- Refer to a (paediatric) endocrinologist
  - All CAYA cancer survivors with clinical symptoms or laboratory results suggestive for HP axis problems
  - Pre- and peri-pubertal CAYA cancer survivors experiencing decline in height velocity or lack of acceleration of growth velocity in case of signs of puberty or a height SDS below their target height range SDS, which cannot be explained by other causes
- Refer directly to a (paediatric) endocrinologist in case of a low morning cortisol<sup>h</sup>
- Counsel survivors with (a suspicion for) HP axis problems regarding the benefits of hormonal replacement therapy on overall health, as well as the risks associated with untreated HP axis problems, and assist them with coordinating and obtaining an early referral when appropriate<sup>i</sup>

<sup>a</sup> This recommendation reflects the recommendations of the IGHG Hypothalamic-pituitary dysfunction guideline (*Hypothalamic-Pituitary and Other Endocrine Surveillance Among Childhood Cancer Survivors*, Endocrine Reviews, 2021; accessible through <https://www.ighg.org/guidelines/topics/hypothalamic-pituitary-dysfunction/>).

<sup>b</sup> Further recommendations regarding height are specified in the Consensus-based recommendation for health promotion.

<sup>c</sup> Further recommendations regarding male fertility and male sexual dysfunction are specified in the Evidence-based recommendation for male fertility problems and sexual dysfunction.

<sup>d</sup> Radiotherapy dose estimations based on the mean dose received to the HP region is preferred over the prescribed dose since the latter may not reflect radiation exposure to the HP region as accurately.

<sup>e</sup> Monitoring height and pubertal status at six months from the end of radiotherapy is desirable, as interpretation of growth and pubertal development requires multiple measurements over time. Oncology and primary care clinicians involved in the follow-up care of CAYA cancer survivors should be aware that growth hormone deficiency may already present in the first year after radiotherapy exposure.

<sup>f</sup> Boys exposed to gonadotoxic therapy (e.g. alkylating agents and radiotherapy to the testes) may have testes small for pubertal stage while in puberty.

<sup>g</sup> Measure IGF-I with the understanding that an IGF-I level up to 0 SDS does not rule out the diagnosis of growth hormone deficiency.

<sup>h</sup> These survivors should be counselled regarding the risks associated with untreated ACTH deficiency. A hydrocortisone stress scheme should be provided in case of doubt of an adequate functioning ACTH axis.

<sup>i</sup> Thyroid hormone treatment should be started only after evaluation and approval of function of the ACTH axis.

## Evidence-based recommendation for surveillance of central precocious puberty (CPP) (IGHG<sup>a</sup>)<sup>b</sup>

### Who is at risk for central precocious puberty (CPP)?

CAYA cancer survivors below age 8 years (girls) or 9 years (boys) treated with or with a history of

- radiotherapy to a volume exposing the HP region, including TBI
- surgery near or within the HP region
- CNS tumours near or within the HP region
- hydrocephalus or cerebrospinal fluid shunt

### When should surveillance for CPP be initiated?

For survivors treated with radiotherapy to a volume exposing the HP region, including TBI:

- Initiate surveillance at 1 year from start of radiotherapy, even in the absence of symptoms<sup>c</sup>

For other survivors at risk for central precocious puberty:

- Initiate surveillance from diagnosis of CNS tumour, surgery near or within the HP region, or occurrence of hydrocephalus or cerebrospinal fluid shunt

### What surveillance modality should be used and at what frequency should it be performed?

All survivors at risk for CPP:

- Relevant clinical history for symptoms of CPP
- Physical examination for signs of CPP
- Height velocity (height, expressed as standard deviation and plotted on a growth chart) in relation to parental height
- Tanner stage (pubertal development and pubertal progression)<sup>d</sup>  
every 6 months

### For how long should surveillance for central precocious puberty be performed?

- Until age 8 years in girls
- Until age 9 years in boys

### What should be done if abnormalities are identified?

- Refer to a paediatric endocrinologist if there are clinical symptoms and signs suggestive for CPP
- Counsel survivors with (a suspicion for) CPP regarding the benefits of treatment for central precocious puberty on overall health as well as the risk for short stature associated with untreated CPP, and assist them with coordinating and obtaining an early referral when appropriate

<sup>a</sup> This recommendation reflects the recommendations of the IGHG Hypothalamic-pituitary dysfunction guideline (*Hypothalamic-Pituitary and Other Endocrine Surveillance Among Childhood Cancer Survivors*, Endocrine Reviews, 2021; accessible through <https://www.ighg.org/guidelines/topics/hypothalamic-pituitary-dysfunction/>).

<sup>b</sup> Further recommendations regarding height are specified in the Consensus-based recommendation for health promotion.

<sup>c</sup> Monitoring height and pubertal status at six months from the end of radiotherapy is desirable, as interpretation of growth and pubertal development requires multiple measurements over time. Oncology and primary care clinicians involved in the follow-up care of CAYA cancer survivors should be aware that central precocious puberty may already present in the first year after radiotherapy exposure, necessitating early referral.

<sup>d</sup> Boys exposed to gonadotoxic therapy (i.e., alkylating agents and radiotherapy to the testes) may have testes small for pubertal stage while in puberty. Instead, morning testosterone (before 10.00 AM) should be used as screening modality as testicular volume may be unreliable.

### **Evidence-based recommendation for ear problems (IGHG<sup>a</sup>)**

#### **Who is at risk for ear problems?**

CAYA cancer survivors treated with

- cisplatin (with or without carboplatin > 1500 mg/m<sup>2</sup>)
- head or brain radiotherapy ≥ 30 Gy<sup>b</sup>

#### **What ear problems might occur?**

- Hearing loss
- Tinnitus

#### **What surveillance modality should be used and at what frequency should it be performed?**

For survivors ≥6 years of age at risk:

- Pure tone conventional audiometry testing at 1000–8000 Hz, and additional testing with high frequency audiometry at >8000 Hz (whenever equipment is available) every other year for children 6-12 years of age, and every 5 years for adolescents and young adults ≥ 12 years of age, to begin no later than the end of treatment

For survivors <6 years of age at risk:

- Extensive testing by audiologist every year, to begin no later than the end of treatment

#### **What should be done if abnormalities are identified?**

- Refer to audiologist or auditory clinic if there are symptoms suggesting hearing loss or abnormal audiological test results showing a loss of more than 15 dB absolute threshold level (1000–8000 Hz) or if there are symptoms of tinnitus

<sup>a</sup> This recommendation reflects the content of the IGHG Ototoxicity guideline (*Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium*, Lancet Oncology, 2019; accessible through <http://www.ighg.org/guidelines/topics/ototoxicity/>).

<sup>b</sup> Radiotherapy dose estimations based on the mean dose received to the head or brain is preferred over the prescribed dose since the latter may not reflect radiation exposure to the head or brain as accurately.

### **Consensus-based recommendation for surveillance of thyroid function problems<sup>a</sup>**

#### **Who is at risk for thyroid function problems?**

CAYA cancer survivors treated with

- radiotherapy to a volume exposing the thyroid gland, including TBI
- radioiodine therapy (I-131 ablation therapy)
- MIBG therapy (I-131 MIBG therapy)<sup>b</sup>
- allogeneic HSCT
- total thyroidectomy<sup>c</sup>

#### **What thyroid function problems might occur?**

- Hypothyroidism (after radiotherapy to a volume exposing the thyroid gland, including TBI, radioiodine therapy, MIBG therapy, allogeneic HSCT or total thyroidectomy)
- Hyperthyroidism (after radiotherapy to a volume exposing the thyroid gland, including TBI, or allogeneic HSCT)

#### **What surveillance modality should be used and at what frequency should it be performed?**

- A history with specific attention to hypothyroidism and/or hyperthyroidism
- Measurement of TSH and ft4 every year in survivors ≤ 18 years of age, and at least every 2-3 years in survivors > 18 years of age

#### **What other advice should be given?**

- For female CAYA cancer survivors at risk for hypothyroidism, discuss the importance of measuring TSH and ft4 prior to attempting pregnancy and periodically during pregnancy at least every 5 years, starting at entry into long-term follow-up or more often at the request of the survivor and/or their family (after informed discussion) or when maternity is desired in the foreseeable future

#### **What should be done if abnormalities are identified?**

- Repeat TSH and ft4 within 3 months if the results are (borderline) abnormal
- Refer to an endocrinologist if the results are repeatedly abnormal

<sup>a</sup> Further recommendations regarding surveillance of thyroid cancer are specified in the Evidence-based recommendation for surveillance of thyroid cancer.

<sup>b</sup> MIBG used for diagnostic purposes (e.g. MIBG scanning) does not put patients at risk for hypothyroidism if adequate preventive measures were used.

<sup>c</sup> CAYA cancer survivors treated with a total thyroidectomy should receive follow-up by an endocrinologist starting directly after surgery. These survivors and their HCPs should be aware of the risk of primary hypoparathyroidism.

### **Consensus- and evidence-based recommendation for surveillance of cardiac problems (including IGHG Cardiomyopathy<sup>a</sup>)<sup>b</sup>**

#### **Who is at risk for cardiac problems?**

CAYA cancer survivors treated with

- radiotherapy to a volume exposing the heart
- anthracyclines, including doxorubicin, daunorubicin, epirubicin, idarubicin and mitoxantrone

#### **What cardiac problems might occur?**

- Cardiomyopathy (after radiotherapy  $\geq 15$  Gy to a volume exposing the heart,<sup>c</sup> or total cumulative anthracycline dose  $\geq 100$  mg/m<sup>2</sup> <sup>d</sup>)
- Arrhythmia (after radiotherapy  $\geq 15$  Gy to a volume exposing the heart,<sup>c</sup> anthracyclines or mitoxantrone)
- Pericardial disease (after radiotherapy  $\geq 15$  Gy to a volume exposing the heart<sup>c</sup>)
- Valvular heart disease (after radiotherapy  $\geq 15$  Gy to a volume exposing the heart<sup>c</sup>)

#### **What surveillance modality should be used and at what frequency should it be performed?**

- A cardiac history at every long-term follow-up visit, at least every 5 years
- A physical cardiac exam at every long-term follow-up visit, at least every 5 years
- An ECG once at entry into long-term follow-up
- An ECG once after the age of 18 years, if entry into long-term follow-up was at a younger age
- A 2D or 3D echocardiogram with assessment of left ventricular systolic function:
  - Radiotherapy  $\geq 30$  Gy to a volume exposing the heart<sup>c</sup>: every 2 years, starting no later than 2 years after cardiotoxic therapy
  - Radiotherapy  $\geq 15$  -  $< 30$  Gy to a volume exposing the heart<sup>c</sup>: every 5 years, starting no later than 2 years after cardiotoxic therapy
  - Total cumulative anthracycline dose  $\geq 100$  -  $250$  mg/m<sup>2</sup> <sup>d</sup>: every 5 years, starting no later than 2 years after cardiotoxic therapy
  - Total cumulative anthracycline dose  $\geq 250$  mg/m<sup>2</sup> <sup>d</sup>: every 2 years, starting no later than 2 years after cardiotoxic therapy
  - Combination of radiotherapy  $\geq 15$  Gy to a volume exposing the heart<sup>c</sup> and total cumulative anthracycline dose  $\geq 100$  mg/m<sup>2</sup> <sup>d</sup>: every 2 years, starting no later than 2 years after cardiotoxic therapy
  - Total cumulative anthracycline dose  $\geq 100$  mg/m<sup>2</sup> and/or radiotherapy  $\geq 15$  Gy to a volume exposing the heart<sup>c</sup>: prior to pregnancy or in the first trimester<sup>b</sup> and continuing during pregnancy for female survivors who had a history of prior left ventricular systolic dysfunction that has resolved even in the presence of a normal baseline ejection fraction in the first trimester
- Cardiac magnetic resonance imaging:
  - In survivors at risk for cardiomyopathy for whom echocardiogram is not technically feasible or optimal
- An echocardiogram with specific attention to the pericardium and valvular structure and function

- Radiotherapy  $\geq 15$  Gy to a volume exposing the heart<sup>c</sup>: at least every 5 years, starting 2 years after cardiotoxic therapy
- **Not recommended**: assessment of cardiac blood biomarkers as the only surveillance strategy<sup>e</sup>

#### What other advice should be given?

Survivors treated with anthracyclines and/or radiotherapy exposing the heart:

- Screening for modifiable cardiovascular risk factors (hypertension, diabetes, dyslipidemia, obesity, smoking, alcohol intake and low levels of physical activity) so that necessary interventions can be initiated to help avert the risk of symptomatic cardiomyopathy
- Cardiology consultation for survivors with asymptomatic cardiomyopathy or who are at high risk to define limits and precautions for exercise

#### What should be done if abnormalities are identified?

- Refer to or consult a cardiologist if an abnormal ejection fraction or if other abnormalities are identified
- Treatment with heart failure medications (ACE inhibitors, ARBs, beta-blockers) is recommended in survivors with asymptomatic LV ejection fraction  $< 40\%$  according to guidelines from the general population
- No recommendation can be formulated about treatment with heart failure medications in survivors with asymptomatic borderline (LV ejection fraction between  $40\%$  and the upper limit of normal) cardiac function

<sup>a</sup> The recommendations for cardiomyopathy surveillance reflect the content of the IGHG Cardiomyopathy guideline (*Systematic review and updated recommendations for cardiomyopathy surveillance for survivors of childhood, adolescent, and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group*, Lancet Oncology, 2023; accessible through <http://www.ighg.org/guidelines/topics/cardiomyopathy/>).

<sup>b</sup> Further recommendations regarding surveillance in pregnancy specified in the Evidence-based recommendation for obstetric problems.

<sup>c</sup> Radiotherapy dose estimations based on the mean dose received to the heart is preferred over the prescribed dose since the latter may not reflect radiation exposure to the heart as accurately.

<sup>d</sup> Use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. Doxorubicin: multiply total dose x 1; Daunorubicin: multiply total dose x 0.6 (Feijen, 2019); Epirubicin: multiply total dose x 0.8 (Feijen, 2019); Idarubicin: multiply total dose x 5 (COG guideline); Mitoxantrone: multiply total dose x 10 (Feijen, 2019).

<sup>e</sup> Assessment of cardiac blood biomarkers (e.g., natriuretic peptides) in conjunction with imaging studies may be reasonable in instances where symptomatic cardiomyopathy is strongly suspected or in CAYA cancer survivors who have borderline cardiac function during primary surveillance.

*References:* EAM Feijen, WM Leisenring, KL Stratton et al. Derivation of anthracycline and anthraquinone equivalence ratios to doxorubicin for late-onset cardiotoxicity. *JAMA Oncology*. 2019;5(6):864-871.

EAM Feijen, A Font-Gonzalez, HJH van der Pal et al. Risk and temporal changes of heart failure among 5-year childhood cancer survivors: a DCOG-LATER study. *J Am Heart Assoc*. 2019; 8(1):e009122.

### Evidence-based recommendation for surveillance of asymptomatic coronary artery disease (IGHG<sup>a</sup>)

#### Who is at risk for asymptomatic coronary artery disease?

CAYA cancer survivors treated with

- radiotherapy to a volume exposing the heart

#### What surveillance modality should be used and at what frequency should it be performed?

- No recommendation can be formulated for routine surveillance of asymptomatic abnormalities of the coronary arteries<sup>b</sup>
- Surveillance for modifiable cardiovascular disease risk factors (hypertension, dyslipidaemia, diabetes, overweight or obesity, smoking and low levels of physical activity) according to national or local guidelines, which may involve referral to a cardiovascular specialist starting no later than at the age of 40 years, and at least every 5 years subsequently<sup>c</sup>

#### What should be done if abnormalities are identified?

- Timely management of all modifiable cardiovascular disease risk factors

<sup>a</sup> This recommendation reflects the recommendations of the IGHG Coronary artery disease guideline (*Coronary artery disease surveillance among childhood, adolescent, and young adult cancer survivors: a systematic review and recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group*, European Journal of Cancer, 2021; accessible through <https://www.ighg.org/guidelines/topics/coronary-artery-disease/>).

<sup>b</sup> There is currently insufficient evidence to determine the diagnostic value of surveillance options for asymptomatic abnormalities of the coronary arteries and whether early detection of abnormalities of the coronary arteries reduces morbidity and mortality.

<sup>c</sup> Timing of initiation and frequency should be based on the intensity of cardiotoxic treatment exposure(s), family history and presence of co-morbid conditions associated with cardiovascular disease risk.

### Consensus-based recommendation for surveillance of renal problems<sup>a</sup>

#### Who is at risk for renal problems?

CAYA cancer survivors treated with

- ifosfamide
- cisplatin
- carboplatin
- radiotherapy to volume exposing the kidney or urinary tract, including TBI
- nephrectomy
- HSCT

#### What renal problems might occur?

- Glomerular dysfunction

- Tubular dysfunction

**What surveillance modality should be used and at what frequency should it be performed?**

All survivors at risk:

- Glomerular function testing consisting of:
  - blood testing: creatinine
  - urine testing: creatinine, proteinuria
  - calculation of eGFR

at least every 5 years, starting at entry into long-term follow-up.

CAYA cancer survivors treated with ifosfamide, cisplatin or carboplatin:

- Tubular function testing consisting of:
  - blood testing: sodium, potassium, magnesium, phosphate, calcium, albumin
  - urine testing: glucose, phosphate

at least every 5 years, starting at entry into long-term follow-up

**What other advice should be given to survivors with a nephrectomy?**

- Education about caution in the use of NSAIDs
- Counselling about single kidney-related health risks at entry into long-term follow-up and periodically

**What should be done if abnormalities are identified?**

- Electrolyte supplementation as guided by serum biochemistry if an electrolyte imbalance is detected
- Refer to a nephrologist if proteinuria and/or chronic kidney disease are identified

**Evidence-based recommendation for surveillance of late liver injury (IGHG<sup>a</sup>)<sup>b</sup>**

**Who is at risk for late liver injury?**

CAYA cancer survivors treated with or with a history of

- radiotherapy to volume exposing the liver, including TBI
- HSCT (irrespective of GvHD)
- methotrexate
- mercaptopurine
- thioguanine
- dactinomycin

- busulfan
- chronic viral hepatitis<sup>c</sup>
- sinusoidal obstruction syndrome
- chronic GvHD
- liver surgery

**What late liver injury might occur?**

- Liver fibrosis or cirrhosis
- Hepatocellular liver injury
- Hepatobiliary dysfunction
- Biliary tract injury
- Liver synthetic dysfunction
- Focal nodular hyperplasia (FNH) and nodular regenerative hyperplasia (NRH)<sup>d</sup>

**What surveillance modality should be used and at what frequency should it be performed?**

All survivors at risk:

- Physical examination<sup>e</sup>
- Measurement of serum liver enzyme concentrations (ALT, AST, gGT, ALP)  
once at entry into long-term follow-up

**What should be done if abnormalities are identified?**

- In case of increased liver enzyme values between 1-2 x ULN the test should be repeated within 1 year
- In case of increased liver enzyme values >2x ULN the test should be repeated within 2 months
- If persistent liver abnormalities (> ULN) are identified:
  - Refer to a hepatologist or gastroenterologist for further examination if there is no obvious explanation (alcohol, medication, obesity)
  - Avoid or prescribe with caution potentially hepatotoxic medications and supplements
  - Evaluate body mass index and discuss healthy weight goals, especially in those with evidence of metabolic syndrome
  - Consider immunization against hepatitis A and B if not already immune
  - Counsel about importance of measures to maintain liver health:
    - Cautious use or avoidance of alcohol intake
    - Maintain a healthy weight and lifestyle
    - Precautions to reduce viral transmission to household and sexual contacts in survivors with chronic HBV/HCV infection

<sup>a</sup> This recommendation reflects the recommendations of the evidence-based IGHG Late hepatic toxicity guideline (*Late hepatic toxicity surveillance for survivors of childhood, adolescent and young adult cancer: Recommendations from the international late effects of childhood*)

cancer guideline harmonization group, Cancer Treatment Reviews, 2021, accessible through <https://www.ighg.org/guidelines/topics/hepatic-toxicity/>).

<sup>b</sup> Further recommendations regarding gastro-intestinal problems are specified in the Consensus-based recommendation for gastro-intestinal problems.

<sup>c</sup> We assume that survivors with chronic viral hepatitis are followed by an appropriate specialist (e.g. hepatologist or infectious diseases specialist). Follow-up should be performed in all survivors with a history of chronic viral hepatitis according to the hepatitis clinical practice guidelines in each country (expert opinion).

<sup>d</sup> We did not formulate surveillance recommendations for FNH and NRH due to the benign nature of FNH and because these are rare entities that are typically detected incidentally. These outcomes are written in this recommendation to increase awareness and to avoid unnecessary investigations.

<sup>e</sup> Physical examination to evaluate height, weight, and body mass index and check for signs of liver disease or bile duct injury, i.e. hepatosplenomegaly, jaundice/icterus, spider naevi, pruritus.

#### **Evidence-based recommendation for surveillance of iron overload (IGHG<sup>a</sup>)**

##### **Who is at risk for iron overload?**

CAYA cancer survivors treated with or with a history of

- HSCT (irrespective of GvHD)
- multiple red blood cell transfusions

##### **What surveillance modality should be used and at what frequency should it be performed?**

All survivors at risk:

- Serum ferritin  
once at entry into long-term follow-up

##### **What should be done if abnormalities are identified?**

- In case of increased serum ferritin >500 ng/ml the test should be repeated within 6 months in survivors
- If persistent abnormal serum ferritin levels (>500 ng/ml) are identified perform a MRI T2\* to quantify the liver iron content
- For survivors with confirmed elevated liver iron content refer to a hematologist or other specialist to start treatment, such as phlebotomy or chelation therapy

<sup>a</sup> This recommendation reflects the recommendations of the evidence-based IGHG Late hepatic toxicity guideline (*Late hepatic toxicity surveillance for survivors of childhood, adolescent and young adult cancer: Recommendations from the international late effects of childhood cancer guideline harmonization group*, Cancer Treatment Reviews, 2021, accessible through <https://www.ighg.org/guidelines/topics/hepatic-toxicity/>).

## Evidence-based recommendation for male fertility problems and sexual dysfunction (IGHG<sup>a</sup>)<sup>b, c</sup>

### Who is at risk for male fertility problems and sexual dysfunction?

Male CAYA cancer survivors treated with or who are

- alkylating agents
- radiotherapy to a volume exposing the testes, including TBI
- surgery to the spinal cord, sympathetic nerves or pelvis
- hypogonadal

### What problems might occur?

- Impaired fertility
- Impaired spermatogenesis (after alkylating agents or radiotherapy to a volume exposing the testes)
- Testosterone deficiency (after radiotherapy potentially exposing the testes  $\geq 12$  Gy<sup>d</sup> or TBI)
- Physical sexual dysfunction (after surgery to the spinal cord, sympathetic nerves or pelvis, or radiotherapy to volumes exposing the testes or pelvis, or who are hypogonadal)

### What surveillance modality should be used and at what frequency should it be performed?

All survivors at risk:

- Ensure that counselling has been provided regarding the risk of impaired spermatogenesis, testosterone deficiency and physical sexual dysfunction (including erectile and ejaculatory dysfunction), and its implications for future health and fertility at least every 5 years or more often at the request of the survivor and/or their family (after informed discussion) or when paternity is desired in the foreseeable future

For pre- and peri-pubertal survivors at risk<sup>e</sup>:

- Monitoring of growth (height) and pubertal development and progression (Tanner stage including testicular volume)<sup>e</sup> after radiotherapy  $\geq 12$  Gy to volumes exposing the testes<sup>d</sup> or TBI, at least every year, with increasing frequency as clinically indicated depending on growth and pubertal progress

For post-pubertal survivors at risk:

- Semen analysis for survivors who desire assessment about possible future fertility
- Measurement of testosterone in an early morning blood sample at clinically appropriate intervals after radiotherapy  $\geq 12$  Gy to volumes exposing the testes<sup>d</sup> or TBI, at least every 2-3 years; measurement of LH should be performed in the presence of clinical signs of hypogonadism, or of previous low-normal or borderline testosterone concentrations, or if it is not possible to obtain an early morning blood sample, in addition to testosterone
- A sexual history for survivors treated with surgery to the spinal cord, sympathetic nerves, or pelvis, or radiotherapy potentially exposing testes or pelvis, or those who are hypogonadal, every 5 years

**What should be done if abnormalities are identified?**

- Refer to male reproductive medicine, andrology, endocrinology or urology those survivors with severely impaired spermatogenesis<sup>f</sup>, those who are seeking paternity, those whose attempts to conceive have been unsuccessful for ≥6 months, regardless of sperm count, those whom laboratory results suggest testosterone deficiency, or who have symptoms suggesting physical sexual dysfunction

<sup>a</sup> This recommendation reflects the content of the IGHG Male Gonadotoxicity guideline (*Recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium*, Lancet Oncology, 2017; accessible through <http://www.ighg.org/guidelines/topics/male-gonadotoxicity/>). Further recommendations regarding fertility preservation can be accessed through <https://www.ighg.org/guidelines/topics/fertility-preservation/> (*Fertility preservation for male childhood, adolescent and young adult patients with cancer: recommendations from the PanCareLIFE consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group*, The Lancet Oncology, 2021).

<sup>b</sup> Further recommendations regarding height are specified in the Consensus-based recommendation for health promotion.

<sup>c</sup> Further recommendations regarding central hypogonadism are specified in the Evidence-based recommendation for hypothalamic-hypopituitary disorders.

<sup>d</sup> Radiotherapy dose estimations based on the mean dose received to the testes is preferred over the prescribed dose since the latter may not reflect radiation exposure to the testes as accurately.

<sup>e</sup> Regular growth and pubertal monitoring should be started by no later than 12 years (and no earlier than 10 years) of age. The pubertal increase in growth velocity may be impaired if growth hormone deficiency is also present in survivors who received cranial radiation.

<sup>f</sup> Severe oligospermia (sperm counts  $\leq 5 \times 10^6$ /ml).

**Evidence-based recommendation for premature ovarian insufficiency (IGHG<sup>a</sup>)****Who is at risk for premature ovarian insufficiency?**

CAYA cancer survivors treated with

- alkylating agents
- radiotherapy to a volume exposing the ovaries, including TBI

**What problems might occur?**

- Impaired fertility
- Amenorrhoea
- Premature menopause

**What surveillance modality should be used and at what frequency should it be performed?**

All survivors at risk:

- Ensure that counselling has been provided regarding the risk of premature ovarian insufficiency and its implications for future fertility at least every 5 years during the fertile lifespan or more often at the request of the survivor and/or their family (after informed discussion) or when maternity is desired in the foreseeable future

For pre- and peri-pubertal survivors at risk:

- Monitoring of growth (height) and pubertal development and progression (Tanner stage) at least every year, with increasing frequency as clinically indicated based on growth and pubertal progression
- Measurement of FSH and oestradiol for girls who fail to initiate or progress through puberty at least for girls  $\geq 11$  years of age, and for girls with primary amenorrhoea (age 16)<sup>b</sup>

For post-pubertal survivors at risk:

- History with specific attention to premature ovarian insufficiency symptoms (amenorrhoea and irregular cycles), every 5 years
- Measurement of FSH and oestradiol in females who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency or who desire assessment about potential for future fertility<sup>b, c, d</sup>

- Not recommended: measurement of AMH as the primary surveillance modality

#### **What should be done if abnormalities are identified?**

For pre- and peri-pubertal survivors:

- Refer to paediatric endocrinology or gynaecology for any survivor who has no signs of puberty by 13 years of age, primary amenorrhoea by 16 years of age, or failure of pubertal progression<sup>e</sup>
- Consider sex steroid replacement therapy by referral to paediatric endocrinology or gynaecology

For post-pubertal survivors:

- Referral to gynaecology, reproductive medicine or endocrinology in females who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency or who desire assessment about potential for future fertility
- Consider sex steroid replacement therapy by referral to endocrinology or gynaecology

<sup>a</sup> This recommendation reflects the content of the IGHG Premature Ovarian Insufficiency guideline (*Recommendations for Premature Ovarian Insufficiency Surveillance for Female Survivors of Childhood, Adolescent, and Young Adult Cancer: A Report From the International Late Effects of Childhood Cancer Guideline Harmonization Group in Collaboration With the PanCareSurFup Consortium, Journal of Clinical Oncology, 2016*; accessible through <http://www.ighg.org/guidelines/topics/premature-ovarian-insufficiency/>). Further recommendations regarding fertility preservation can be accessed through <https://www.ighg.org/guidelines/topics/fertility-preservation/> (*Fertility preservation for female childhood, adolescent and young adult patients with cancer: recommendations from the PanCareLIFE consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group, The Lancet Oncology, 2021*).

<sup>b</sup> If amenorrhoea, measure FSH and oestradiol randomly; if oligomenorrhoea, measure during early follicular phase (day 2-5).

<sup>c</sup> Hormone replacement therapy should be discontinued prior to laboratory evaluation when applicable

<sup>d</sup> This assessment should be performed after ending oral contraceptive pill/sex steroid replacement therapy use, ideally after two months without oral contraceptive pills.

<sup>e</sup> The absence of initiation of puberty (Tanner stage 2 breast development) in girls 13 years or older or failure to progress in pubertal stage for  $\geq$  12 months.

## Appendix A: Experts involved in the development of the consensus-based recommendations

### Development of the consensus-based recommendations

Edit Bardi, Austria	Rebecca van Kalsbeek, the Netherlands	Monica Muraca, Italy
Morven Brown, United Kingdom	Tomas Kepak, Czech Republic	Heleen van der Pal, the Netherlands
Rachel Effeney, Australia	Katerina Kepakova, Czech Republic	Marleen Renard, Belgium
Jeanette Falck Winther, Denmark	Leontien Kremer, the Netherlands	Harun Sabic, Bosnia and Herzegovina
Cecilia Follin, Sweden	Gill Levitt, United Kingdom	Carina Schneider, Austria
Jaap den Hartogh, the Netherlands	Jacqueline Loonen, the Netherlands	Roderick Skinner, United Kingdom
Riccardo Haupt, Italy	Marlies Mangelschots, Belgium	Anne Uyttebroeck, Belgium
Lars Hjorth, Sweden	Renée Mulder, the Netherlands	

### External review of the consensus-based recommendations

Claire Berger, France	Paivi Lahteenmaki, Finland	Hanneke van Santen, the Netherlands
Julie Byrne, Ireland	Thorsten Langer, Germany	Katrin Scheinemann, Switzerland
Charlotte Demoor, France	Anna Panasiuk, Poland	Elaine Sugden, United Kingdom
Maria Genoveva Correa, Spain	Vesna Pavasovic, United Kingdom	Monica Terenziani, Italy
Kirsi Jahnukainen, Finland	Catherine Rechnitzer, Denmark	Eva Maria Tinner, Switzerland
Katerina Katsibardi, Greece	Jelena Roganovic, Croatia	Lorna Zalatel, Slovenia

### Additional experts involved in reviewing the guideline update

Magdalena Balcerek, Germany	Ali Hall, United Kingdom	Menia Koukougiani, Greece
Andrea Beccaria, Italy	Sabine Heinrich, Germany	Sara Oberti, Italy
Laura Diaco, Italy	Gisela Michel, Switzerland	Annik Vacher-Lansonneur, France
Francesco Felicetti, Italy	Monica Murraca, Italy	Elvira van Dalen, the Netherlands

## Appendix B: Symptoms and signs glossary

In order to achieve awareness in survivors at risk for specific health problems and their health care providers, they need to know about possible symptoms and signs. We provide the following overview for the late effects that might occur and are described in the recommendations.

Late effect	Possible symptoms and signs
Cerebrovascular problems	Hemiparesis, hemiplegia, weakness, aphasia, field deficits, memory impairment, carotid bruits
Neurocognitive problems	Functional deficits in executive function (planning and organisation), sustained attention, memory (visual, sequencing, temporal memory), processing speed, visual-motor integration, fine motor dexterity, language, academic fluency, learning deficits in math and reading, diminished IQ, behavioural change
Hypothalamic-pituitary dysfunction	
Growth hormone deficiency	Reduced growth velocity, fatigue, decreased strength and exercise tolerance, weight gain, hypoglycaemia
TSH deficiency	Fatigue, weight gain, cold intolerance, constipation, dry skin, brittle hair, depressed mood, neurocognitive impairment, sleep disturbance
LH/FSH deficiency	Loss of menstrual cycles, reduced libido, vaginal dryness, reduced fertility
ACTH deficiency	Weight loss, lack of appetite, muscle weakness, nausea, vomiting, fatigue, low blood pressure
Central precocious puberty	Early sexual development (before age 8 years in girls and before age 9 years in boys)
Psychosocial problems	Family problems, behavioural problems, problems in school or work
Mental health problems	Anger, anxiety, panic attacks, depression, substance abuse, post-traumatic stress symptoms
Craniofacial growth disturbance	Aesthetic and functional complaints
Cataract	Cloudy or dazzled vision in bright lighting, difficulties in reading or in focusing images
Other eye problems	Visual changes (decreased acuity, halos, diplopia), dry eyes, persistent eye irritation, excessive tearing, light sensitivity, poor night vision, painful eye
Ear problems	Hearing difficulties (with or without background noise), tinnitus, vertigo
Hypothyroidism	Fatigue, weight gain, cold intolerance, constipation, dry skin, brittle hair, depressed mood, neurocognitive impairment, sleep disturbance
Hypoparathyroidism	Paraesthesias, muscle cramping, altered mental status, hyperreflexia, tetany, hypocalcaemia, hyperphosphataemia
Hyperthyroidism	Heat intolerance, tachycardia, palpitations, weight loss, emotional lability, muscular weakness, hyperphagia
Arrhythmia	Palpitations, dizziness, fainting
Pericardial disease	Fatigue, dizziness, shortness of breath, chest pain
Valvular heart disease	Early fatigue during exercise, dyspnoea
Cardiomyopathy	Shortness of breath, dyspnoea on exertion, orthopnoea, nocturia, ankle or lower leg oedema

Pulmonary dysfunction	Cough, wheezing, dyspnoea at rest or on exertion
Gastro-intestinal problems	Nausea, vomiting, dysphagia, heartburn, abdominal pain, abdominal distension, chronic diarrhoea, constipation
Liver problems	Fatigue, nausea, vomiting, dark-coloured urine, light-coloured bowel movements, yellow skin and eyes, loss of appetite
Premature ovarian insufficiency	Irregular or missed menstrual periods, hot flushes, night sweats, vaginal dryness, reduced libido, reduced fertility
Lower urinary tract problems	Dysuria, haematuria, urinary urgency or frequency, urinary incontinence or retention, nocturia, abnormal urinary stream
Renal problems	Reduced amount of urine, ankle or lower leg oedema, persistent nausea, confusion (note that renal toxicity is usually asymptomatic until a late stage)
Diabetes mellitus	Frequent urination (polyuria), extreme thirst and excessive fluid intake (polydipsia), extreme fatigue, blurry vision, weight loss.
Hypertension	Headache, fatigue, vision problems (note that hypertension is usually asymptomatic until a late stage)
Osteonecrosis	Pain, swelling, limited range of motion
Reduced bone mineral density	Back pain, fractures
Spine scoliosis and kyphosis	Uneven shoulder blades, leaning to one side, hump or curve in the back, back pain
Peripheral neuropathy	Numbness, prickling or tingling in hands or feet, extreme sensitivity to touch, lack of coordination and falling, areflexia, weakness, foot drop
Subsequent AML	Fatigue, pallor, purpura, bone pain
Subsequent bladder cancer	Haematuria, dysuria
Subsequent bone cancer	Bone mass, bone pain
Subsequent breast cancer	Lump or mass in the breast, skin irritation, breast or nipple pain, nipple retraction, nipple discharge or bleeding
Subsequent CNS neoplasms	Progressively worsening, severe, unrelenting headaches, new onset cognitive, motor, sensory or behavioural changes, balance problems, seizures, and other neurologic deficits
Subsequent colorectal cancer	Persistent change in bowel habits, blood in stool, feeling that the bowel does not empty completely, weakness, fatigue, unexplained weight loss
Subsequent melanoma and non-melanoma skin cancer	Suspicious new skin lesions and changing moles
Subsequent oral cancer	Suspicious intra-oral lesions or pain
Subsequent thyroid cancer	Lump or swelling in the neck, hoarseness, difficulty swallowing or breathing, constant cough (note that thyroid cancer is usually asymptomatic)

## Appendix C: Advantages and Disadvantages of Thyroid Cancer Surveillance

This overview of advantages and disadvantages of thyroid cancer surveillance was developed and provided by the International Late Effects of Childhood Cancer Guideline Harmonization Group.

### Arguments for and against DTC surveillance in at-risk CAYAC survivors (independent of surveillance modality)

#### **Advantages:**

- CAYAC survivors undergoing surveillance are likely to have DTC detected at an earlier stage. This may reduce the extent of surgery and/or need for radioiodine therapy, which could decrease overall morbidity, recurrence as well as mortality.
- CAYAC survivors who do not have a DTC detected when they undergo surveillance may benefit by being reassured that they do not have a new cancer.

#### **Disadvantages:**

- There is uncertainty about the benefit of early treatment since most DTC can be cured. There are no randomized studies that demonstrate a clear benefit of DTC surveillance.
- Detection of a benign nodule with surveillance (false positive results for DTC) can lead to repeated ultrasounds, fine needle aspiration biopsies or thyroid surgery. These interventions may result in stress and anxiety, as well as inconvenience, costs, and complications of unnecessary biopsies or surgery.
- There is a risk that surveillance will detect an indolent DTC, which may never cause clinical problems and lead to overtreatment.
- False negative results of surveillance may lead to some survivors being falsely reassured that they do not have DTC, when in fact they do.

**Abbreviations:** DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adult cancer

### **Arguments for and against DTC surveillance with neck palpation.**

#### **Advantages:**

- Quick, inexpensive and non-invasive.
- High specificity (96-100%) for detecting a thyroid nodule that might represent DTC (many true negatives and few false positives for nodules).

#### **Disadvantages:**

- Low sensitivity (17-43%) for detecting a thyroid nodule that might represent DTC (few true positives and many false negatives for nodules).
- Increase in unnecessary invasive procedures due to false positive screening results.
- Detection of DTC at a more advanced stage (compared to thyroid ultrasonography), possibly leading to increased morbidity, recurrence and mortality rate.
- Diagnostic value dependent on experience of the physician (high-interobserver variation).

### **Arguments for and against DTC surveillance with thyroid ultrasonography.**

#### **Advantages:**

- Non-invasive.
- High sensitivity (~95-100%) for detecting a thyroid nodule that might represent DTC (many true positives and few false negatives for nodules).
- High specificity (~95-100%) for detecting a thyroid nodule that might represent DTC (many true negatives and few false positives for nodules).
- Detection of DTC at an earlier stage (compared to neck palpation).

#### **Disadvantages:**

- Poor diagnostic value of ultrasound for predicting whether an identified nodule is a DTC: detection of a high number of benign thyroid nodules and indolent DTC.
- Increase in unnecessary invasive procedures due to false positive screening results.
- Diagnostic value dependent on experience of the ultrasonographer (high-interobserver variation).

**Abbreviations:** DTC: differentiated thyroid carcinoma

## Appendix D: Survivor Information Form for Asymptomatic Meningioma Surveillance

This Survivor Information Form was developed and provided by the International Late Effects of Childhood Cancer Guideline Harmonization Group.

### **Potential advantages and disadvantages of meningioma screening options for asymptomatic childhood, adolescent and young adult cancer survivors – A Survivor Information Form**

#### **Why should I be aware of the risk of meningioma?**

- The risk of cancer increases for all people as they get older.
- As a survivor of childhood, adolescent or young adult cancer you may have a higher risk of developing a new (different) cancer in adulthood compared to people of similar age in the general population.
- If your brain and spinal cord were exposed to radiation as part of your treatment for a childhood, adolescent or young adult cancer, you have an increased risk of developing a benign tumour called a meningioma of your central nervous system that may present at a younger age than meningioma in people in the general population.
- While some people treated with cranial radiation will develop a meningioma at a young age, most will not.
- Although a meningioma is most often benign, it can result in serious symptoms because of the location and the growing nature of the tumour.
- It is possible to detect a meningioma early by having MRI screening.
- Meningioma screening has benefits and harms.
- This information sheet can be used to help you and your healthcare provider decide if having meningioma screening is the right choice for you.

#### **What type of meningioma screening test is used?**

- Magnetic resonance imaging (MRI) is a medical imaging technique that uses magnetic waves and a computer to generate detailed images of the brain.

#### **What are the potential advantages of having meningioma screening?**

- You may be more likely to have a meningioma detected at an earlier stage before you experience any symptoms.
- You may have a chance for better outcomes (improved survival and quality of life and decreased mortality, morbidity, and recurrence) if the screening finds a small early stage meningioma.
- The smaller the meningioma, the more likely it is potentially treatable with surgery, depending on the location.
- You may feel reassured that you do not have a meningioma.

**What are the potential disadvantages of having meningioma screening?**

- Your scan may show incidental findings of unclear clinical significance, like abnormalities in brain tissue and blood vessels that may lead to unnecessary stress and anxiety.
- You may be diagnosed with a small meningioma that never would have caused problems if not detected by screening (overdiagnosis).
- You may experience anxiety and stress about having meningioma screening and what the test results will show.
- You may experience unnecessary anxiety and distress related to a false positive test (findings on tests suspicious for meningioma but further testing showing no meningioma).
- You may feel more like a cancer patient rather than a healthy survivor if you decide to have meningioma screening.
- If you have a meningioma detected by screening, we do not know if you will have better health outcomes compared to having a meningioma discovered after it causes symptoms.
- If you have a meningioma without any symptoms, it is not always clear if this meningioma will be need to be treated. This depends on the location, size and growth of the meningioma.

**What are the potential disadvantages associated with MRI?**

- An MRI is costly and may not be covered by your health insurance.
- You may experience claustrophobia and some discomfort when lying in the breast MRI scanner. Imaging professionals should be able to help with positioning to minimize discomfort.
- You may have asymptomatic deposition of gadolinium into the brain when you had an MRI with gadolinium contrast. However, we do not know if this will cause any harm.
- If you have poor kidney function an MRI with gadolinium contrast may place you at risk of kidney damage (a syndrome called nephrogenic systemic fibrosis).
- You may not be able to have a MRI if you have any medical devices or metal hardware in your body. However, many modern devices are MRI compatible.

**What are the international screening recommendations?**

- If you were treated with radiotherapy to your brain or spinal cord it is very important that you are aware of possible symptoms related to a meningioma. You should contact your healthcare provider if you experience any of the following symptoms: progressively worsening, severe, unrelenting headaches, new-onset cognitive (thinking skills), motor, sensory or behavioral changes, balance problems, seizures, and other neurologic changes.
- We cannot recommend routine screening with MRI because we do not know if your health outcomes will be better if we detect a meningioma that is not causing symptoms.
- It is important that you make the decision whether or not to screen together with your oncology and survivorship team and individual support networks after careful consideration of the potential advantages and disadvantages.

*Thank you for taking the time to read this information sheet. If you have any questions regarding the information included in this form or if you require emotional support and advice regarding your thoughts and feelings, please contact your treating team, general practitioner, case manager, or nurse specialist if you have one, or another member of your oncology or survivorship team as applicable to you.*

## Appendix E: Survivor Information Form for Breast Cancer Surveillance

This Survivor Information Form was developed and provided by the International Late Effects of Childhood Cancer Guideline Harmonization Group.

### **Potential advantages and disadvantages of breast cancer screening options for female childhood, adolescent and young adult cancer survivors – A Survivor Information Form**

#### **Why should I be aware of the risk of breast cancer?**

- The risk of cancer increases for all women as they get older.
- As a survivor of childhood, adolescent or young adult cancer you have a higher risk of developing a new (different) cancer in adulthood compared to people of similar age in the general population.
- Breast cancer is one of the most common new cancers that occur in women treated for a childhood, adolescent or young adult cancer.
- If your breast region was exposed to radiation as part of your treatment (chest radiation), you have an increased risk of developing breast cancer that may present at a younger age than breast cancer in women in the general population.
- If you were treated with high doses of anthracyclines without chest radiation you may have a higher risk of breast cancer as well, especially if you had a diagnosis of leukaemia, central nervous system tumour or sarcoma (except for Ewing sarcoma).
- While some women treated with chest radiation and/or anthracyclines will develop breast cancer at a young age, most will not.
- However, among those who develop breast cancer, detecting it early can be life-saving and may reduce the amount of treatment needed.
- It is possible to detect breast cancer early by having breast cancer screening.
- Breast cancer screening has advantages and disadvantages.
- This information sheet can be used to help you and your healthcare provider decide if having breast cancer screening is the right choice for you.

#### **What types of breast cancer screening tests are used?**

- Mammography is specialized medical imaging that uses a low-dose x-ray system to see inside the breasts. Mammography is the standard breast cancer screening test in the general population.
- Magnetic resonance imaging (MRI) is a medical imaging technique that uses magnetic waves and a computer to generate detailed images of the breast.

#### **What are the potential advantages and disadvantages of having mammography?**

- Mammography has a good track record of detecting breast cancer in the general population.
- Early breast cancer detection has been shown to decrease death from breast cancer in the general population.
- A mammogram is a relatively inexpensive test to perform and should be covered by most national health service programs and insurance plans.
- You may experience pain during the mammogram due to the pressure on your breasts.

- You will be exposed to a small amount of radiation during the mammogram. For example, in a woman treated with moderate to high dose chest radiation for a childhood cancer, the additional radiation exposure that would result from 50 mammograms (annual mammogram from age 25 to 74) is less than 1% of the total amount.
- Mammography may not be as accurate for breast cancer screening in young women with dense breast tissue. Dense breast tissue means that there is less fatty tissue and more dense tissue including milk glands, milk ducts and supportive tissue, which is more common in younger women.

**What are the potential advantages and disadvantages of having a breast MRI?**

- Breast MRI is more accurate in detecting a hidden breast cancer in young women with dense breast tissue.
- You may experience claustrophobia and some discomfort when lying in the breast MRI scanner. Imaging professionals should be able to help with positioning to minimize discomfort.
- You may not be able to have a breast MRI if you have any medical devices or metal hardware in your body or if you have a MRI contrast allergy. However, many modern devices are MRI compatible.
- You may need to have the breast MRI performed during a specific time in your menstrual cycle. This may be difficult to predict and coordinate especially with lifestyle commitments and requiring time off work.
- If you have poor kidney function, an MRI with gadolinium contrast may place you at risk of kidney damage (a syndrome called nephrogenic systemic fibrosis).
- Breast MRI is costly and may not be covered by your health insurance. However, most insurance companies and national health service programs will cover an annual breast MRI for women in high risk groups such as you.

**What are potential advantages of having both a mammogram and breast MRI for breast cancer screening?**

- You have a better chance of detecting pre-cancerous changes in the breast by a mammogram.
- You have a better chance of detecting hidden breast cancer by a breast MRI if your breast tissue is dense.
- You have a higher chance of detecting a small breast cancer if you have breast cancer screening with a mammogram and breast MRI compared to mammogram or breast MRI alone.

**What are the potential advantages of having breast cancer screening?**

- You may be more likely to have a breast cancer detected at an earlier stage.
- You may need less aggressive treatment if breast cancer is detected at an earlier stage.
- You are more likely to have a good outcome if the screening finds a small early stage breast cancer.
- You may feel reassured that you do not have breast cancer.

**What are the potential disadvantages of having breast cancer screening?**

- You may feel more like a cancer patient rather than a healthy survivor if you decide to have breast cancer screening and you may experience anxiety and stress about having breast cancer screening and what the test results will show.
- You may have additional expenses related to breast cancer screening that are not covered by insurance (in some countries), including travel costs. In addition, you may have to take time off work or use annual leave to attend appointments.

- You may have a false positive test (a test result that indicates that you may have cancer even though you do not). This may lead to additional medical testing including biopsy which can cause unnecessary anxiety and distress.
- You may be diagnosed with a small and slow-growing breast cancer that never would have caused problems if not detected by screening (overdiagnosis).
- You may still have a small breast cancer that is still not detected by screening. In that case you may be falsely reassured that you do not have breast cancer.

**What are the international screening recommendations?**

- If you were treated with chest radiation doses of 10 Gy or higher or high abdominal field radiation above the diaphragm, especially at a young age, it is very important that you are aware of the risk of breast cancer. You should contact your healthcare provider if you note a change in your breasts.
- If you were treated with chest radiation doses of 10 Gy or higher yearly breast cancer screening with mammography and MRI is recommended starting at age 25 years or 8 years after radiotherapy, whichever occurs last.
- If you were treated with high abdominal field radiation above the diaphragm, especially at a young age, annual breast cancer screening with mammography and MRI is reasonable starting at age 25 years or 8 years after radiotherapy, whichever occurs last. It is important that you make the decision whether or not to screen together with your oncology and survivorship team and individual support networks after careful consideration of the potential advantages and disadvantages.
- If you were treated with any type of anthracyclines in the absence of chest radiation, we cannot recommend routine breast cancer screening because there is currently not enough data to determine if you are at increased risk.
- If you were treated with anthracycline doses of  $\geq 250$  mg/m<sup>2</sup> without chest radiation or if you are a survivor of leukaemia, CNS tumour and sarcoma (except for Ewing sarcoma) (Li-Fraumeni syndrome-associated childhood cancer types) it is important that you make the decision whether or not to screen together with your oncology and survivorship team and individual support networks after careful consideration of the potential advantages and disadvantages. In addition, if you are a survivor of leukaemia, CNS tumour or sarcoma (except for Ewing sarcoma) it is recommended to test for Li-Fraumeni syndrome. Patients with Li-Fraumeni syndrome have an increased breast cancer risk and should be screened routinely.

*Thank you for taking the time to read this information sheet. If you have any questions regarding the information included in this form or if you require emotional support and advice regarding your thoughts and feelings, please contact your treating team, general practitioner, case manager, or nurse specialist if you have one, or another member of your oncology or survivorship team as applicable to you.*

## Appendix F: Differences PanCareFollowUp Recommendations for Long-Term Follow-Up 2020 versus 2024

Changes based on newly published IGHG guidelines		
Topic	Differences 2020 vs. 2024	Reason for change
<i>Pulmonary problems</i>	Moved to the category Awareness, history and/or physical examination without surveillance test since a surveillance test is no longer recommended	Harmonization with IGHG Pulmonary dysfunction guideline ( <i>Recommendations for surveillance of pulmonary dysfunction among childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group, EClinicalMedicine, 2024</i> ; accessible through <a href="https://www.ighg.org/guidelines/topics/pulmonary-dysfunction/">https://www.ighg.org/guidelines/topics/pulmonary-dysfunction/</a> ).
	Who is at risk for pulmonary problems: <ul style="list-style-type: none"> <li>Removed: carmustine (BCNU), lomustine (CCNU), busulfan, bleomycin</li> </ul>	
	What pulmonary problems might occur: <ul style="list-style-type: none"> <li>Added: (obstructive abnormalities, restrictive abnormalities, diffusion capacity impairment)</li> <li>Removed: Worsening pulmonary fibrosis after high oxygen exposure (such as during anaesthesia) in survivors treated with bleomycin who already have evidence of pulmonary fibrosis</li> </ul>	
	What surveillance modality should be used: <ul style="list-style-type: none"> <li>Added: Routine pulmonary function testing is not recommended for asymptomatic at-risk CAYA cancer survivors, due to lack of interventions to prevent the deterioration of asymptomatic pulmonary dysfunction</li> <li>Removed: Pulmonary function tests, including a spirometry and diffusing capacity for carbon monoxide (DLCO), once at entry into long-term follow-up</li> </ul>	
	What other advise should be given changed into: <p>In at-risk CAYA cancer survivors:</p> <ul style="list-style-type: none"> <li>Get a yearly influenza vaccination and additional vaccinations based on local or national recommendations</li> <li>Consider vaccination against viral pathogens that cause pneumonias according to local or national guidelines</li> </ul> <p>For all CAYA cancer survivors:</p> <ul style="list-style-type: none"> <li>Avoid tobacco exposure, quit smoking, and/or reduce exposure to environmental smoke</li> </ul> <p>For all CAYA cancer survivors, based on expert opinion:<sup>b</sup></p> <ul style="list-style-type: none"> <li>Healthcare providers should be aware of the potential risk of worsening pulmonary fibrosis after general anaesthetic and/or high oxygen exposure (e.g. during scuba diving) in survivors treated with bleomycin</li> </ul>	

	<ul style="list-style-type: none"> <li>Survivors treated with pulmotoxic therapies and potentially bleomycin who wish to undertake scuba diving should be assessed by an experienced dive physician before starting to dive</li> <li>Footnote b: These expert opinion statements are not included in the IGHG Pulmonary dysfunction guideline</li> </ul> <p>What should be done if abnormalities are identified:</p> <ul style="list-style-type: none"> <li>Removed: Repeat the pulmonary function tests if, during subsequent follow-up visits, any abnormalities are identified in the history or pulmonary exam</li> <li>Added: Perform a pulmonary function test if any abnormalities are identified in the history or pulmonary exam</li> </ul>	
<p><i>Reduced bone mineral density (BMD)</i></p>	<p>Split bone mineral density problems and osteonecrosis</p> <ul style="list-style-type: none"> <li>Two separate recommendations instead of one recommendation named “bone problems”</li> </ul> <p>Who is at risk for bone mineral density:</p> <ul style="list-style-type: none"> <li>Removed: Methotrexate, HSCT and high dose radiotherapy</li> </ul> <p>Surveillance modality for survivors treated with cranial or craniospinal radiotherapy or TBI at risk for reduced BMD:</p> <ul style="list-style-type: none"> <li>Changed “A DXA scan once, if possible, and thereafter as clinically indicated” into “A DXA scan once at entry into long-term follow-up (between two to five years following completion of therapy), to be repeated at 25 years of age when peak bone mass should be achieved, and thereafter as clinically indicated”</li> </ul> <p>What other advice should be given:</p> <ul style="list-style-type: none"> <li>Added: Be aware of other potential risk factors for low and very low bone mineral density for survivors, including corticosteroids as anti-cancer treatment, hypogonadism, growth hormone deficiency, low BMI or underweight, male sex, white race, lack of physical activity, smoking</li> <li>Added: Due to insufficient evidence, no recommendation can be formulated for or against BMD surveillance for survivors with these potential risk factors for reduced BMD</li> <li>Added: abstinence from smoking and alcohol</li> </ul> <p>What should be done if abnormalities are identified:</p> <p>In CAYA cancer survivors with a BMD Z-score <math>\leq -2</math>:</p> <ul style="list-style-type: none"> <li>Refer to (or consult) a medical bone health specialist<sup>h</sup> for further (endocrine) evaluation, interpretation of BMD findings, treatment, and follow-up</li> </ul> <p>In CAYA cancer survivors with a BMD Z-score <math>\leq -1</math> and <math>&gt; -2</math>:</p>	<p>Harmonization with IGHG bone mineral density surveillance recommendations (<i>Bone mineral density surveillance for childhood, adolescent, and young adult cancer survivors: evidence-based recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group, Lancet Diabetes &amp; Endocrinology, 2021; accessible through <a href="https://www.ighg.org/guidelines/topics/bone-abnormalities/">https://www.ighg.org/guidelines/topics/bone-abnormalities/</a></i>)</p>

	<ul style="list-style-type: none"> <li>• Evaluate for the presence of endocrine defects and consult a medical bone health specialist<sup>h</sup> for further evaluation and interpretation of BMD findings as clinically indicated</li> <li>• Repeat DXA after 2 years, and thereafter as clinically indicated based on BMD change (i.e. in case of BMD decline more than the DXA machine’s least significant change) and ongoing risk assessment</li> </ul> <p>Including footnote:  “A medical bone health specialist is defined as any specialist who is caring for BMD deficits in CAYA cancer survivors, such as an endocrinologist (most settings), internist, pediatrician, rheumatologist, family physician, or general practitioner, depending on country and setting.”</p> <p>Footnote added: “The WHO global recommendation on physical activity for health for adults is 150 minutes of moderate-intensity activity (or equivalent) per week, measured as a composite of physical activity undertaken across multiple domains: for work (paid and unpaid, including domestic work); for travel (walking and cycling); and for recreation (including sports). For adolescents, the recommendation is 60 minutes of moderate- to vigorous-intensity activity daily.”</p>	
<p><i>Cardiac problems</i></p>	<p>Surveillance modality and frequency:  A 2D or 3D echocardiogram with assessment of left ventricular systolic function:</p> <ul style="list-style-type: none"> <li>• Added “2D or 3D”</li> <li>• Changed “Radiotherapy ≥ 35 Gy to a volume exposing the heart” into “Radiotherapy ≥ 30 Gy to a volume exposing the heart”</li> <li>• Changed “twice every 5 years” into “every 2 years”</li> <li>• Changed “starting 2 years after cardiotoxic therapy” into “starting no later than 2 years after cardiotoxic therapy”</li> <li>• Added “Radiotherapy ≥ 15 - &lt; 30 Gy to a volume exposing the heart: every 5 years, starting no later than 2 years after cardiotoxic therapy”</li> <li>• Added “and continuing during pregnancy even in the presence of a normal baseline ejection fraction in the first trimester” after “Anthracyclines, mitoxantrone and/or radiotherapy to a volume exposing the heart: prior to pregnancy or in the first trimester<sup>b</sup>”</li> </ul> <p>Added cardiac magnetic resonance imaging:</p> <ul style="list-style-type: none"> <li>• In survivors at risk for cardiomyopathy for whom echocardiogram is not technically feasible or optimal</li> </ul> <p>Added a footnote to blood biomarkers:</p> <ul style="list-style-type: none"> <li>• “Assessment of cardiac blood biomarkers (e.g., natriuretic peptides) in conjunction with imaging studies may be reasonable in instances where symptomatic cardiomyopathy is strongly suspected or in CAYA cancer</li> </ul>	<p>Harmonization with IGHG Cardiomyopathy guideline (<i>Systematic review and updated recommendations for cardiomyopathy surveillance for survivors of childhood, adolescent, and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group</i>, Lancet Oncology, 2023; accessible through <a href="http://www.ighg.org/guidelines/topics/cardiomyopathy/">http://www.ighg.org/guidelines/topics/cardiomyopathy/</a>).</p>

	<p>survivors who have borderline cardiac function during primary surveillance”</p> <p>What other advice should be given:</p> <ul style="list-style-type: none"> <li>• Added “alcohol intake” to cardiovascular risk factors</li> <li>• Added “Cardiology consultation for survivors with asymptomatic cardiomyopathy or who are at high risk to define limits and precautions for exercise”</li> </ul> <p>What should be done if abnormalities are identified:</p> <ul style="list-style-type: none"> <li>• Added “or consult” to “Refer to a cardiologist if an abnormal ejection fraction or if other abnormalities are identified”</li> <li>• Added “Treatment with heart failure medications (ACE inhibitors, ARBs, beta-blockers) is recommended in survivors with asymptomatic LV ejection fraction &lt; 40% according to guidelines from the general population”</li> <li>• Added “No recommendation can be formulated about treatment with heart failure medications in survivors with asymptomatic borderline (LV ejection fraction between 40% and the upper limit of normal) cardiac function”</li> </ul>	
<b>Refinements based on IGHG guidelines</b>		
<b>Topic</b>	<b>Differences 2020 vs. 2024</b>	<b>Reason for change</b>
<i>Hypothalamic-pituitary (HP) axis problems</i>	<p>When should surveillance for HP axis problems be initiated?</p> <ul style="list-style-type: none"> <li>• Changed “Initiate surveillance for any HP axis problem at ≥ 6 months from the end of radiotherapy” into “Initiate surveillance for any HP axis problem at ≥ 1 year from the end of radiotherapy”</li> </ul>	<p>Harmonization with IGHG Hypothalamic-Pituitary dysfunction guideline (<i>Hypothalamic-Pituitary and Other Endocrine Surveillance Among Childhood Cancer Survivors</i>, Endocrine Reviews, 2017; accessible through <a href="https://www.ighg.org/guidelines/topics/hypothalamic-pituitary-dysfunction/">https://www.ighg.org/guidelines/topics/hypothalamic-pituitary-dysfunction/</a>). Misinterpreted in PCFU guideline.</p>
<i>Central precocious puberty (CPP)</i>	<p>When should surveillance for CPP be initiated?</p> <ul style="list-style-type: none"> <li>• Changed “Initiate surveillance at 6 months from start of radiotherapy” into “Initiate surveillance at 1 year from start of radiotherapy”</li> </ul> <p>What surveillance modality should be used:</p> <ul style="list-style-type: none"> <li>• Removed underscored text from main recommendation and added to footnote ‘d’: Boys exposed to gonadotoxic therapy (i.e., alkylating agents and radiotherapy to the testes) may have testes small for pubertal stage while in puberty. <u>Instead, morning testosterone (before 10.00 AM) should be used as screening modality as testicular volume may be unreliable.</u></li> </ul>	<p>Harmonization with IGHG Hypothalamic-Pituitary dysfunction guideline (<i>Hypothalamic-Pituitary and Other Endocrine Surveillance Among Childhood Cancer Survivors</i>, Endocrine Reviews, 2017; accessible through <a href="https://www.ighg.org/guidelines/topics/hypothalamic-pituitary-dysfunction/">https://www.ighg.org/guidelines/topics/hypothalamic-pituitary-dysfunction/</a>). Misinterpreted in PCFU guideline.</p>

<i>Late liver injury</i>	<p>What late liver injury might occur?</p> <ul style="list-style-type: none"> <li>Added: “Focal nodular hyperplasia (FNH) and nodular regenerative hyperplasia (NRH)” including footnote: “We did not formulate surveillance recommendations for FNH and NRH due to the benign nature of FNH and because these are rare entities that are typically detected incidentally. These outcomes are written in this recommendation to increase awareness and to avoid unnecessary investigations.”</li> </ul>	Harmonization with IGHG Late hepatic toxicity guideline ( <i>Late hepatic toxicity surveillance for survivors of childhood, adolescent and young adult cancer: Recommendations from the international late effects of childhood cancer guideline harmonization group</i> , Cancer Treatment Reviews, 2021, accessible through <a href="https://www.ighg.org/guidelines/topics/hepatic-toxicity/">https://www.ighg.org/guidelines/topics/hepatic-toxicity/</a> ).
<b>Changes based on clinical expertise, and language and format changes according to the PanCareSurPass Recommendations for follow-up care from end of treatment until 5 years after diagnosis</b>		
<b>Topic</b>	<b>Differences 2020 vs. 2024</b>	<b>Reason for change</b>
<i>Subsequent melanoma and non-melanoma skin cancer</i>	<p>Who is at risk:</p> <p>Added: “allogeneic” and “especially with a history of skin GvHD” to “HSCT”</p>	Consensus in working group based on strong clinical expertise
<i>Eye problems</i>	<p>Who is at risk:</p> <ul style="list-style-type: none"> <li>Added “only for cataract” to “Prolonged corticosteroids as anti-cancer treatment”</li> </ul>	Prolonged steroids are a risk factor only for cataract
<i>Spine scoliosis and kyphosis</i>	<p>Who is at risk:</p> <ul style="list-style-type: none"> <li>Added “malignancies of bones of the lower limbs”</li> </ul>	Feedback from consultation round
<i>Alopecia, cerebrovascular problems, dental and oral problems, gastrointestinal problems, peripheral neuropathy</i>	<p>Title of recommendation:</p> <ul style="list-style-type: none"> <li>Changed “Consensus-based recommendation for surveillance of [topic]” into “Consensus-based recommendation for awareness of [topic]”</li> </ul>	No surveillance is being performed
<i>Chronic Pain</i>	<p>Surveillance modality and frequency:</p> <ul style="list-style-type: none"> <li>Change of wording: “A history with specific attention to pain” instead of “a screening question for pain”</li> </ul>	Consensus in working group; adapted only in language to be consistent with other recommendations
<i>Neurocognitive problems</i>	<p>Who is at risk:</p> <ul style="list-style-type: none"> <li>Added “excluding spinal cord tumours” to “a CNS tumour”</li> <li>Changed “brain surgery” into “any brain surgery”</li> </ul>	Consensus in working group based on strong clinical expertise
<i>CNS neoplasms</i>	<p>Footnote ‘b’ regarding CNS neoplasms:</p> <ul style="list-style-type: none"> <li>Added: “glioblastoma”</li> </ul>	Feedback from consultation round
<i>Hypothalamic-pituitary (HP) axis problems</i>	<p>Who is at risk:</p>	Feedback from consultation round

	<ul style="list-style-type: none"> <li>Changed “Hydrocephalus or cerebrospinal fluid shunt <sup>d</sup>” into “Hydrocephalus or cerebrospinal fluid shunt (risk factor for growth hormone deficiency)” (information from footnote put into brackets)</li> </ul>	
<i>Osteonecrosis</i>	Split bone mineral density problems and osteonecrosis <ul style="list-style-type: none"> <li>Two separate recommendations instead of one recommendation named “bone problems”</li> </ul>	New IGHG guideline bone mineral density
	Recommendation category: <ul style="list-style-type: none"> <li>Included as an “Awareness, history and/or physical examination without surveillance test” recommendation instead of a “Awareness, history and/or physical examination with surveillance test”</li> </ul>	No surveillance test included
<i>Overweight and obesity</i>	Who is at risk? <ul style="list-style-type: none"> <li>Changed “with a hypothalamic or pituitary tumour” to “CNS tumour near or within the HP region”</li> </ul>	Harmonization with HP axis recommendation
<i>Hypertension</i>	Footnote ‘c’ immunosuppressives: <ul style="list-style-type: none"> <li>Removed and prolonged corticosteroids as anti-cancer treatment (at least 4 weeks continuously)</li> </ul>	Feedback from consultation round
<i>Thyroid function problems</i>	What other advice should be given? (...) Discuss the importance of measuring TSH and fT4 prior to attempting pregnancy and periodically during pregnancy at least every 5 years <ul style="list-style-type: none"> <li>Added after: “or more often at the request of the survivor and/or their family (after informed discussion) or when maternity is desired in the foreseeable future”</li> </ul>	Consensus in working group; adapted only in language to be consistent with other recommendations
<i>Male fertility problems and sexual dysfunction</i>	Surveillance modality and frequency: All survivors at risk: <ul style="list-style-type: none"> <li>Changed wording from “Counselling regarding the risk of impaired spermatogenesis, testosterone deficiency and physical sexual dysfunction (including erectile and ejaculatory dysfunction), and its implications for future health and fertility at the request of the survivor after informed discussion or when paternity is desired in the foreseeable future at least every 5 years” to “Ensure that counselling has been provided regarding the risk of impaired spermatogenesis, testosterone deficiency and physical sexual dysfunction (including erectile and ejaculatory dysfunction), and its implications for future health and fertility at least every 5 years or more often at the request of the survivor and/or their family (after informed discussion) or when paternity is desired in the foreseeable future ”</li> </ul>	Consensus in working group

	Footnote added: Further recommendations regarding fertility preservation can be accessed through <a href="https://www.ighg.org/guidelines/topics/fertility-preservation/">https://www.ighg.org/guidelines/topics/fertility-preservation/</a> ( <i>Fertility preservation for male childhood, adolescent and young adult patients with cancer: recommendations from the PanCareLIFE consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group, The Lancet Oncology, 2021</i> ).	New IGHG fertility preservation guideline
<i>Premature ovarian insufficiency</i>	Surveillance modality and frequency: <ul style="list-style-type: none"> <li>Changed wording from “Counselling regarding the risk of premature ovarian insufficiency and its implications for future fertility at least every 5 years” to “Ensure that counselling has been provided regarding the risk of premature ovarian insufficiency and its implications for future fertility at least every 5 years during the fertile lifespan or more often at the request of the survivor and/or their family (after informed discussion) or when maternity is desired in the foreseeable future”</li> </ul>	Consensus in working group regarding improved wording and consistency with male fertility recommendation
	Surveillance modality and frequency: <ul style="list-style-type: none"> <li>Changed “history and physical examination with specific attention to premature ovarian insufficiency symptoms (amenorrhoea and irregular cycles)” to “history with specific attention to premature ovarian insufficiency symptoms (amenorrhoea and irregular cycles)”</li> </ul>	Not possible to physically examine amenorrhoea and irregular cycles
	Footnote added: Further recommendations regarding fertility preservation can be accessed through <a href="https://www.ighg.org/guidelines/topics/fertility-preservation/">https://www.ighg.org/guidelines/topics/fertility-preservation/</a> ( <i>Fertility preservation for female childhood, adolescent and young adult patients with cancer: recommendations from the PanCareLIFE consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group, The Lancet Oncology, 2021</i> ).	New IGHG fertility preservation guideline
<b>Refinements</b>		
<b>Topic</b>	<b>Differences 2020 vs. 2024</b>	<b>Reason for change</b>
<i>Preamble</i>	Added the following statements: <ul style="list-style-type: none"> <li>Although specific surveillance testing is only recommended for survivors at-risk as defined in the specific recommendations, clinicians are at liberty to recommend surveillance or diagnostic tests for other survivors based on clinical indication and presence of other incidental medical conditions that may alter the balance of risks versus benefits from testing.</li> <li>When using recommendations defining radiotherapy doses, please be aware that radiotherapy dose estimations based on the mean dose received to the specific organ at risk is preferred over the prescribed dose since the latter may not reflect radiation exposure to that organ as</li> </ul>	Clinical expertise from the working group

	<p>accurately. It is recognised that it may be difficult to access accurate and relevant radiotherapy doses for organs or structures at risk in some patients (especially those treated in the past). A pragmatic approach to making recommendations may be necessary in such cases.</p> <ul style="list-style-type: none"> <li>• This guideline should be cited as: PanCare Guidelines Group. PanCareFollowUp Recommendations for long-term follow-up care of childhood, adolescent and young adult cancer survivors. 2024. Available at: <a href="http://www.pancare.eu">www.pancare.eu</a>.</li> </ul>	
<i>Recommendations where radiotherapy dose thresholds are defined</i>	Footnote added: Radiotherapy dose estimations based on the mean dose received to the specific organ at risk is preferred over the prescribed dose since the latter may not reflect radiation exposure to that organ as accurately	Clinical expertise from the working group