International Guideline Harmonization Group
for Late Effects of Childhood Cancer

Published recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group

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Content

General recommendation
Providers and female childhood, adolescent and young adult cancer survivors treated with chest radiation (level A evidence) and/or upper abdominal radiation exposing breast tissue at a young age (level B evidence) should be aware of the increased risk of breast cancer (strong recommendation).
Who needs breast cancer surveillance?
Breast cancer surveillance is recommended for female childhood, adolescent and young adult cancer survivors treated with ≥10 Gy chest radiation (level A evidence, strong recommendation).
Breast cancer surveillance is reasonable for female childhood, adolescent and young adult cancer survivors treated with upper abdominal radiation exposing breast tissue at a young age. The surveillance decision should be an individual one, taking into account additional risk factors[2] and personal values regarding the harms and benefits of surveillance (see Survivor Information Form) (level B evidence, moderate recommendation).
No recommendation can be formulated for routine breast cancer surveillance for CAYA cancer survivors treated with any type of anthracyclines in the absence of chest radiation, because there is currently inconsistent evidence. Because the evidence suggests that survivors treated with high-dose (≥250 mg/m^2) anthracyclines have a moderately to highly increased breast cancer risk and that survivors of Li-Fraumeni syndrome-associated childhood cancer types (leukemia, CNS tumor and non-Ewing sarcoma)[3] have a highly increased breast cancer risk, the decision to undertake breast cancer surveillance should be made by the CAYA cancer survivor and healthcare provider after careful consideration of the potential harms and benefits of breast cancer surveillance (see Survivor Information Form).
At what age should breast cancer surveillance be initiated?
Initiation of breast cancer surveillance is recommended at age 25 years or ≥8 years from radiation for female childhood, adolescent and young adult cancer survivors treated with ≥10 Gy chest radiation (whichever occurs last) (level A evidence, strong recommendation).
Initiation of breast cancer surveillance is reasonable at age 25 years or ≥8 years from radiation for female childhood, adolescent and young adult cancer survivors treated with upper abdominal radiation exposing breast tissue at a young age based on clinical judgment, considering additional risk factors[2] and personal values regarding the harms and benefits of surveillance (see Survivor Information Form) (level B evidence, moderate recommendation).
At what frequency should breast cancer surveillance be performed?
Annual breast cancer surveillance is recommended for at least up to 60 years of age for at risk female childhood, adolescent and young adult cancer survivors treated with ≥10 Gy chest radiation (level A evidence, strong recommendation).
Annual breast cancer surveillance is reasonable for at least up to 60 years of age for female childhood, adolescent and young adult cancer survivors treated with upper abdominal radiation exposing breast tissue at a young age (level B evidence, moderate recommendation).
At what age should continuation of intensive[1] breast cancer surveillance be stopped?
Continuation of breast cancer surveillance is reasonable for at risk female childhood, adolescent and young adult cancer survivors who are older than age 60 years based upon clinical judgement and pending availability of further data (level C evidence, moderate recommendation).
What surveillance modality should be used?
Mammography and breast MRI are recommended for breast cancer surveillance in at risk female childhood, adolescent and young adult cancer survivors (level A and B evidence, strong recommendation).
Clinical breast exam is reasonable for at risk female childhood, adolescent and young adult cancer survivors returning for follow-up medical evaluations in countries where breast cancer surveillance access is through clinical referral (expert opinion, moderate recommendation).

[1] Recommended breast cancer surveillance beyond the national breast cancer screening program.
[2] Patient age, family history, menopausal status, other previous cancer treatment.
[3] Testing for genetic cancer predisposition syndromes like Li-Fraumeni syndrome can be considered for survivors of leukemia, CNS tumor and non-Ewing sarcoma, who have been treated with high-dose anthracyclines, in order to determine if the breast cancer risk is additionally increased.

Note: Breast cancer surveillance recommendations for female childhood, adolescent and young adult cancer survivors with a genetic predisposition to breast cancer are outside the scope of this paper. For that purpose, we refer to the country-specific recommendations.

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 leukemia, central nervous system tumor 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 upper abdominal radiation exposing breast tissue, 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 upper abdominal radiation exposing breast tissue, 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 ≥250 mg/m^2 without chest radiation or if you are a survivor of leukemia, CNS tumor or 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 leukemia, CNS tumor or sarcoma (except for Ewing sarcoma) and treated with high doses of anthracyclines, testing for genetic cancer predisposition syndromes, like Li-Fraumeni syndrome, can be considered. Patients with genetic cancer predisposition syndromes, like 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.

Publication

Mulder RL, Hudson MM, Bhatia S, Landier W, Levitt G, Constine LS, Wallace WH, van Leeuwen FE, Ronckers CM, Henderson TO, Moskowitz CS, Friedman DN, Ng AK, Jenkinson HC, Demoor-Goldschmidt C, Skinner R, Kremer LCM, Oeffinger KC. Updated Breast Cancer Surveillance Recommendations for Female Survivors of Childhood, Adolescent, and Young Adult Cancer From the International Guideline Harmonization Group. J Clin Oncol. 2020 10;38(35):4194-4207.

General recommendation
CAYA cancer survivors treated with cranial radiotherapy and their health care providers should be aware of the risk of subsequent CNS neoplasms (high level evidence) and informed about the symptoms* and signs that may be related to a subsequent CNS neoplasm (expert opinion, strong recommendation).
Who needs surveillance for subsequent CNS neoplasms and what surveillance modality should be used?
A history and neurological examination focused on symptoms* and signs that may be related to subsequent CNS neoplasms is recommended for CAYA cancer survivors treated with cranial radiotherapy at every long-term follow-up evaluation, which may be at 1-5 year intervals (expert opinion, strong recommendation).
No recommendation can be formulated for routine MRI surveillance for asymptomatic CAYA cancer survivors treated with cranial radiotherapy, because there is currently insufficient evidence to determine whether early detection of subsequent CNS neoplasms reduces morbidity and mortality. The decision for 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 Brochure).

* Progressively worsening, severe, unrelenting headaches, worsening nausea and vomiting, new-onset cognitive, motor, sensory or behavioural changes, new-onset or worsening balance problems, seizures, and other focal neurologic deficits.

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

The information in this brochure may need to be adapted according to national healthcare guidelines.

Why should I be aware of the risk of developing a meningioma?

- The risk of cancer and benign tumors 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 or other benign tumor during 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 tumor called a meningioma.
- While some people treated with cranial radiation will develop a meningioma, most will not.
- Although a meningioma is most often benign (non-cancerous), it can cause serious symptoms because of its location and growth.
- It is possible to detect a meningioma early by having MRI screening, but screening for meningiomas 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 powerful magnets and

radio waves to generate images of the organs of the body. MRI does not involve X-rays or require exposure to radiation.

What are the potential advantages of having meningioma screening?

- You may feel reassured if you do not have a meningioma at this time. However, a meningioma may still develop in the future.
- You may be more likely to have a meningioma detected at an earlier timepoint when it is more easily treated and before you experience any symptoms.
- Early detection would allow doctors to monitor the size/growth of the meningioma over time, which may help determine if/when treatment is needed.
- You may have a chance for improved survival, fewer side effects, and improved quality of life if the screening finds a small early stage meningioma.

What are the potential disadvantages of having meningioma screening?

- You may experience anxiety and stress about having meningioma screening and what the test results will show.
- You may feel more like a patient rather than a healthy survivor if you decide to have meningioma screening.
- Your scan may show incidental findings of unclear clinical significance, such as treatment-related 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 (overdiagnosis).
- You may experience unnecessary anxiety and distress related to a false positive test. For example, findings on tests which are suspicious for meningioma but further testing shows no meningioma.
- If you have a meningioma or another type of tumor detected by screening, we do not know if you will have better health outcomes compared to having a tumor discovered after it causes symptoms.
- If you have a meningioma without any symptoms, the need to treat is not always clear. This depends on the location, size and growth of the meningioma. This uncertainty may cause some anxiety.
- The diagnosis of an asymptomatic meningioma or other findings may affect your ability to obtain heathcare and/or life insurance.

What are the potential disadvantages associated with MRI?

- An MRI is costly and may not be covered by your health insurance. However, your healthcare provider could write a letter of medical necessity to explain that you are at risk of meningioma after brain radiation and why you may benefit from MRI screening.
- You may feel claustrophobic and have some discomfort when lying in the MRI scanner. Imaging professionals should be able to help with positioning to minimize discomfort.
- You may have deposition of gadolinium (MRI contrast) into the brain when you have an MRI with gadolinium contrast. This gadolinium deposition does not cause symptoms, but it is not yet known whether this causes any long-term health problems.
- 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). Your healthcare provider will be able to discuss with you whether this concern should influence your decision about having a MRI scan.
- 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. If this is the case, discuss this with your healthcare provider.

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, worsening nausea and vomiting, new-onset cognitive (thinking skills), motor, sensory or

behavioral changes, balance problems, seizures, or other neurological changes.

- We cannot recommend for or against 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 healthcare providers, oncology and survivorship team, and individual support networks. Careful consideration of the potential advantages and disadvantages is advised.

Thank you for taking the time to read this information sheet. If you have any questions regarding the information included in this brochure or if you require emotional support and advice regarding your thoughts and feelings, please contact your healthcare provider for advice and support.

Publication

Bowers DC, Verbruggen LC, Kremer LCM, Hudson MM, Skinner R, Constine LS, Sabin ND, Bhangoo R, Haupt R, Hawkins MM, Jenkinson H, Khan RB, Klimo P Jr, Pretorius P, Ng A, Reulen RC, Ronckers CM, Sadighi Z, Scheinemann K, Schouten-van Meeteren N, Sugden E, Teepen JC, Ullrich NJ, Walter A, Wallace WH, Oeffinger KC, Armstrong GT, van der Pal HJH, Mulder RL. 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. Lancet Oncol. 2021 May;22(5):e196-e206.

Who should be counseled about the risk of differentiated thyroid carcinoma?
It *is recommended* that childhood, adolescent and young adult cancer survivors treated with radiation therapy that includes the thyroid gland (level A evidence) or therapeutic ^{131}I-MIBG (level C evidence) should be counseled by their healthcare provider regarding their increased risk for developing differentiated thyroid carcinoma. It *is recommended* that childhood, adolescent and young adult cancer survivors should be advised to inform their healthcare provider if they detect a thyroid mass, independent of the presence or absence of associated symptoms (expert opinion).
Who should be informed about differentiated thyroid carcinoma surveillance?
It *is recommended* that at-risk survivors (i.e., those treated with radiation therapy that includes the thyroid gland) (level A evidence) should be counseled about options for differentiated thyroid carcinoma surveillance. The decision to commence surveillance 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 (Box 1) in the context of the survivor's individual preferences.
It *may be reasonable* to inform neuroblastoma survivors who received therapeutic ^{131}I-MIBG (level C evidence) about options for differentiated thyroid carcinoma surveillance. The decision to commence surveillance 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 (Box 1) in the context of the survivor's individual preferences.
If the decision to commence surveillance is made, what surveillance modality should be used to detect a thyroid nodule that may represent a differentiated thyroid carcinoma?
It *is recommended* to use neck palpation or thyroid ultrasonography as a screening modality if surveillance for differentiated thyroid carcinoma is planned. 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 (Box 2, Figure 1) (level A evidence). The decision regarding 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 the two modalities in the context of the practice setting, the health care provider's experience, expertise of local diagnosticians (radiology), and the survivor's preferences. Ultrasound and FNA and/or biopsy *is recommended* to 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 minimize the number of unnecessary invasive and additional diagnostic procedures. When ultrasound is used for surveillance, the cervical lymph node stations should always be visualized (expert opinion).
If the decision to commence surveillance is made, at what frequency should differentiated thyroid carcinoma surveillance be performed?
It *is reasonable* to commence surveillance for differentiated thyroid carcinoma 5 years after radiation therapy that includes the thyroid gland or therapeutic ^{131}I-MIBG (level B evidence).
It *is recommended* that even when a childhood, adolescent and young adult cancer survivor does not opt for periodic surveillance with either ultrasonography or palpation, it is appropriate to include examination of the neck as part of a complete physical exam whenever a survivor is assessed by a healthcare provider (expert opinion).
If periodic thyroid palpation is chosen as the screening modality it *may be reasonable* to repeat surveillance for differentiated thyroid carcinoma every 1-2 years (expert opinion; weak recommendation). If thyroid ultrasonography is chosen as screening modality, it *may be reasonable* to repeat surveillance for differentiated thyroid carcinoma every 3-5 years if there are no abnormalities found initially (expert opinion).
What should be done when abnormalities are identified?
Consultation with a thyroid specialist *is recommended* for survivors with a thyroid nodule (detected

either by palpation or thyroid ultrasonography, or incidentally noted on other imaging studies (such as CT or MRI)) (expert opinion).

Box 1

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.

Box 2

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 to 100%) for detecting a thyroid nodule that might represent DTC (many true positives and few false negatives for nodules).
- High specificity (95 to 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.

Publication

Clement SC, Kremer LCM, Verburg FA, Simmons JH, Goldfarb M, Peeters RP, Alexander EK, Bardi E, Brignardello E, Constine LS, Dinauer CA, Drozd VM, Felicetti F, Frey E, Heinzel A, van den Heuvel-Eibrink MM, Huang SA, Links TP, Lorenz K, Mulder RL, Neggers SJ, Nieveen van Dijkum EJM, Oeffinger KC, van Rijn RR, Rivkees SA, Ronckers CM, Schneider AB, Skinner R, Wasserman JD, Wynn T, Hudson MM, Nathan PC, van Santen HM. 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;63:28-39.

IGHG Cardiomyopathy surveillance recommendations **2015**

Recommendations are currently being updated

General recommendation
Survivors treated with anthracyclines or chest radiation or both and their healthcare providers should be aware of the risk of cardiomyopathy.
Who needs cardiomyopathy surveillance? ***Anthracyclines***
Cardiomyopathy surveillance *is recommended* for survivors treated with high dose (≥250 mg/m2) anthracyclines.
Cardiomyopathy surveillance *is reasonable* for survivors treated with moderate dose (≥100 to <250 mg/m2) anthracyclines.
Cardiomyopathy surveillance *may be reasonable* for survivors treated with low dose (<100 mg/m2) anthracyclines.
Who needs cardiomyopathy surveillance? ***Chest radiation***
Cardiomyopathy surveillance *is recommended* for survivors treated with high dose (≥35 Gy) chest radiation.
Cardiomyopathy surveillance *may be reasonable* for survivors treated with moderate dose (≥15 to <35 Gy) chest radiation.
No recommendation can be formulated for cardiomyopathy surveillance for survivors treated with low dose (<15 Gy) chest radiation with conventional fractionation.
Who needs cardiomyopathy surveillance? ***Anthracyclines + Chest radiation***
Cardiomyopathy surveillance *is recommended* for survivors treated with moderate to high dose anthracyclines (≥100 mg/m2) and moderate to high dose chest radiation (≥15 Gy).
What surveillance modality should be used?
Echocardiography *is recommended* as the primary cardiomyopathy surveillance modality for assessment of left ventricular systolic function in survivors treated with anthracyclines or chest radiation.
Radionuclide angiography or cardiac magnetic resonance imaging (CMR) *may be reasonable* for cardiomyopathy surveillance in at-risk survivors for whom echocardiography is not technically feasible or optimal.
Assessment of cardiac blood biomarkers (e.g., natriuretic peptides and troponins) *is not recommended* as the only strategy for cardiomyopathy surveillance in at-risk survivors.
At what frequency should surveillance be performed for *high risk* survivors?
Cardiomyopathy surveillance *is recommended* for *high risk* survivors to begin no later than 2 years after completion of cardiotoxic therapy, repeated at 5 years after diagnosis and continued every 5 years thereafter.
More frequent cardiomyopathy surveillance *is reasonable* for *high risk* survivors.
Lifelong cardiomyopathy surveillance *may be reasonable* for *high risk* survivors.
At what frequency should surveillance be performed for *moderate and low risk* survivors?
Cardiomyopathy surveillance *is reasonable* for *moderate and low risk* survivors to begin no later than 2 years after completion of cardiotoxic therapy, repeated at 5 years after diagnosis and continue every 5 years thereafter.
More frequent cardiomyopathy surveillance *may be reasonable* for *moderate and low risk* survivors Lifelong cardiomyopathy surveillance *may be reasonable* for *moderate and low risk* survivors.
At what frequency should surveillance be performed for survivors who are pregnant or planning to become pregnant?
Cardiomyopathy surveillance *is reasonable* before pregnancy or in the first trimester for all female survivors treated with anthracyclines or chest radiation.

No recommendations can be formulated for the frequency of ongoing surveillance in pregnant survivors who have normal left ventricular systolic function immediately before or during the first trimester of pregnancy.
What should be done when abnormalities are identified?
Cardiology consultation *is recommended* for survivors with asymptomatic cardiomyopathy following treatment with anthracyclines or chest radiation.
What advice should be given regarding physical activity and other modifiable cardiovascular risk factors?
Regular exercise, as recommended by the AHA and ESC, offers potential benefits to survivors treated with anthracyclines or chest radiation. Regular exercise *is recommended* for survivors treated with anthracyclines or chest radiation who have normal left ventricular systolic function. Cardiology consultation *is recommended* for survivors with asymptomatic cardiomyopathy to define limits and precautions for exercise.
Cardiology consultation *may be reasonable* for *high risk* survivors who plan to participate in high intensity exercise to define limits and precautions for physical activity.
Screening for modifiable risk factors (hypertension, diabetes, dyslipidemia and obesity) *is recommended* for all survivors treated with anthracyclines or chest radiation so that necessary interventions can be initiated to help avert the risk of symptomatic cardiomyopathy.

Publication

Armenian SH, Hudson MM, Mulder RL, Chen MH, Constine LS, Dwyer M, Nathan PC, Tissing W, Shankar S, Sieswerda E, Skinner R, Steinberger J, van Dalen EC, van der Pal HJ, Wallace WH, Levitt G, Kremer LCM. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. The Lancet Oncology 2015;16:e123-136.

General recommendation
Survivors treated with one or more potentially gonadotoxic treatments[†], and their providers, should be aware of the risk of premature ovarian insufficiency and its implications for future fertility (level A and level C evidence).
Who needs surveillance?
Counselling regarding the risk of premature ovarian insufficiency and its implications for future fertility *is recommended* for survivors treated with: • Alkylating agents in general (level A evidence) • Cyclophosphamide and procarbazine (level C evidence) • Radiotherapy potentially exposing the ovaries (level A evidence)
What surveillance modality should be used for pre- and peri-pubertal survivors?
Monitoring of growth (height) and pubertal development and progression (Tanner stage) *is recommended* for pre-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries (expert opinion and no literature search).[†‡] FSH and oestradiol *are recommended* for evaluation of premature ovarian insufficiency in pre-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries[†] who fail to initiate or progress through puberty (expert opinion and no literature search).[¶#]
What surveillance modality should be used for post-pubertal survivors?
A detailed history and physical examination with specific attention for premature ovarian insufficiency symptoms, e.g. amenorrhoea and irregular cycles *is recommended* for post-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries (expert opinion and no literature search).[†] FSH and oestradiol *are recommended* for evaluation of premature ovarian insufficiency in post-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries[†] who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency or who desire assessment about potential for future fertility. Hormone replacement therapy should be discontinued prior to laboratory evaluation when applicable (expert opinion and no studies).[#§]
AMH *is not recommended* as the *primary surveillance modality* for evaluation of premature ovarian insufficiency in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries[†] who desire assessment about potential future fertility (expert opinion and no studies).
AMH *may be reasonable* in conjunction with FSH and oestradiol for identification of premature ovarian insufficiency in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries[†] aged ≥25 years who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency or who desire assessment about potential for future fertility (expert opinion and no studies).
When should pre- and peri-pubertal survivors be referred?
Referral to paediatric endocrinology or gynaecology *is recommended* for any survivor who has • No signs of puberty by 13 years of age; • Primary amenorrhoea by 16 years of age; • Failure of pubertal progression[‖] (expert opinion and no literature search).
When should post-pubertal survivors be referred?
Referral to gynaecology, reproductive medicine or endocrinology (according to local referral pathways) *is recommended* for post-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries[†] who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency (expert opinion and no literature

search).
What should be done when abnormalities are identified in pre-, peri- and post-pubertal survivors?
Consideration of sex steroid replacement therapy *is recommended* for pre-, peri- and post-pubertal survivors diagnosed with premature ovarian insufficiency *by referral to gynaecology or endocrinology* (expert opinion and no literature search).
What should be done when potential for future fertility is questioned?
Referral to gynaecology, reproductive medicine or endocrinology (according to local referral pathways) *is recommended* for post-pubertal females treated with potentially gonadotoxic chemotherapy and/or ovarian irradiation[†] without signs and symptoms of premature ovarian insufficiency who desire assessment about potential for future fertility (expert opinion and no literature search).

Definition POI: a clinical condition developing in any adult female before 40 years of age, characterized by: (1) absence of menses for at least 4 months, and (2) two elevated serum follicle-stimulating hormone (FSH) levels in the menopausal range (based on the maximum threshold of the laboratory assay used)

[†] Treatments with evidence for causing premature ovarian insufficiency include alkylating agents in general (level A evidence), cyclophosphamide, procarbazine (level C evidence), and radiotherapy potentially exposing the ovaries (level A evidence)

[‡] At least annually, with increasing frequency as clinically indicated based on growth and pubertal progression.

[¶] At least for girls of 11 years of age and older, and for girls with primary amenorrhoea (age 16).

[#] If amenorrhoea, measure FSH and oestradiol randomly; if oligomenorrhoea, measure during early follicular phase (day 2-5).

[§] This assessment should be performed after ending oral contraceptive pill/sex steroid replacement therapy use, ideally after two months without oral contraceptive pills.

[‖] 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 ≥12 months.

Publication

van Dorp W, Mulder RL, Kremer LC, Hudson MM, van den Heuvel-Eibrink MM, van den Berg MH, Levine JM, van Dulmen-den Broeder E, di Iorgi N, Albanese A, Armenian SH, Bhatia S, Constine LS, Corrias A, Deans R, Dirksen U, Gracia CR, Hjorth L, Kroon L, Lambalk CB, Landier W, Levitt G, Leiper A, Meacham L, Mussa A, Neggers SJ, Oeffinger KC, Revelli A, van Santen HM, Skinner R, Toogood A, Wallace WH, Haupt R. 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;34:3440-3450.

Impaired spermatogenesis

General recommendation
Survivors treated with one or more potentially gonadotoxic agents, and their healthcare providers, should be aware of the risk of impaired spermatogenesis and its implications for future fertility (level C evidence and supplemental literature search and expert opinion).
Who needs surveillance?
Counselling regarding the risk of impaired spermatogenesis and its implications for future fertility *is recommended* for survivors treated with: • Cyclophosphamide, mechlorethamine, procarbazine (level C evidence), busulfan and cyclophosphamide or fludarabine and melphalan for HSCT, ifosfamide (supplemental literature search/expert opinion). • Radiotherapy potentially exposing testes (supplemental literature search and expert opinion).
What surveillance modality should be used?
In survivors who desire assessment about possible future fertility after treatment with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the testes[†], semen analysis *is recommended* as the gold standard primary surveillance modality for evaluation of spermatogenesis (expert opinion).
Clinical measurement of testicular volume and of FSH and inhibin B *may be reasonable* for identification of impaired spermatogenesis in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the testes[†] in whom semen analysis has been declined or is not possible and who desire assessment about possible future fertility. Be aware of the diagnostic limitations of these tests that may result in false positives or false negatives (level B evidence).
At what frequency and for how long should surveillance be performed?
Surveillance for impaired spermatogenesis should be performed only at the request of the survivor after informed discussion or when paternity is desired in the foreseeable future (expert opinion).
When should survivors with impaired spermatogenesis be referred?
Referral to male reproductive medicine should be offered to survivors with severely impaired spermatogenesis, defined as severe oligospermia (sperm counts $\leq 5 \times 10^6$/ml), or those who are seeking paternity after potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the testes, and to those whose attempts to conceive have been unsuccessful for 6 months or more, regardless of sperm count, for detailed specialist counselling or consideration of sperm cryopreservation if not already performed (expert opinion).

Testosterone deficiency

General recommendation
Survivors treated with a potentially gonadotoxic agent, and their healthcare providers, should be aware of the risk of testosterone deficiency and its implications for future health and fertility (supplemental literature search and expert opinion).
Who needs surveillance?
Counselling regarding the risk of testosterone deficiency and its implications for future health and fertility *is recommended* for survivors treated with radiotherapy potentially exposing the testes to ≥12 Gy or with TBI (supplemental literature search and expert opinion).
What surveillance modality should be used for pre- and peri-pubertal survivors? At what frequency and for how long?
Monitoring of growth (height) and pubertal development and progression (Tanner stage including testicular volume)[‡ ¶] *is recommended* for pre- and peripubertal survivors treated with radiotherapy potentially exposing the testes to ≥12 Gy or with TBI (expert opinion).
What surveillance modality should be used for post-pubertal survivors? At what frequency and for how long?
Measurement of testosterone concentration in an early morning blood sample at clinically appropriate intervals *is reasonable* in postpubertal survivors treated with radiotherapy potentially exposing the testes to ≥12 Gy or with TBI (expert opinion). 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, it *is reasonable* to measure LH concentration in addition to testosterone (expert opinion).
When should survivors with abnormalities of pubertal development be referred?
Referral to a paediatric endocrinologist *is recommended* for any survivor who has no signs of puberty by 14 years of age or failure of pubertal progression[#] (expert opinion).
When should postpubertal survivors with suspected testosterone deficiency be referred?
Referral to a specialist in male reproductive health, andrology, endocrinology or urology (according to local referral pathways) *is recommended* for postpubertal survivors treated with radiotherapy potentially exposing the testes to ≥12 Gy or with TBI, and in whom laboratory results suggest testosterone deficiency (expert opinion).

Physical sexual dysfunction

General recommendation
Survivors treated with one or more treatment modalities with potential to cause physical sexual dysfunction, or those who are hypogonadal, and their healthcare providers, should be aware of the risk of physical sexual dysfunction (including erectile and ejaculatory dysfunction) and its implications for future health and fertility (supplemental literature search and expert opinion).
Who needs surveillance?
Counselling regarding the risk of physical sexual dysfunction (including erectile and ejaculatory dysfunction) and its implications for future health and fertility *is recommended* for survivors: • Treated with surgery to the spinal cord, sympathetic nerves or pelvis • Treated with radiotherapy potentially exposing testes or pelvis • Who are hypogonadal (supplemental literature search and expert opinion).
What surveillance modality should be used?
Providers should take a relevant sexual history in survivors treated with surgery to the spinal cord, sympathetic nerves, or pelvis, or radiotherapy potentially exposing testes or pelvis, or those who are hypogonadal (expert opinion).
When should survivors with suspected physical sexual dysfunction be referred?
Referral to a specialist in male reproductive health, andrology, endocrinology, or urology (according to local referral pathways) *is recommended* 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, and who have symptoms suggesting physical sexual dysfunction (expert opinion).

Publication

Skinner R, Mulder RL, Kremer LCM, Hudson MM, Constine LS, Bardi E, Boekhout A, Borgmann-Staudt A, Brown MC, Cohn R, Dirksen U, Giwercman A, Ishiguro H, Jahnukainen K, Kenney LB, Loonen JJ, Meacham L, Neggers S, Nussey S, Petersen C, Shnorhavorian M, van den Heuvel MM, van Santen HM, Green DM. Recommendations for gonadotoxicity surveillance for 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;18:e75-e90.

IGHG Ototoxicity surveillance recommendations 2019

Hearing loss

General recommendation
Survivors treated with cisplatin (level B evidence), with or without high-dose carboplatin (>1500 mg/m^2), or head or brain radiotherapy ≥30 Gy (expert opinion*) and their healthcare providers should be aware of the risk of hearing loss.
Who needs surveillance and how often should surveillance be performed?
Surveillance for hearing loss *is recommended* for survivors treated with cisplatin (level A and B evidence), with or without high-dose carboplatin (>1500 mg/m^2), or head or brain radiotherapy ≥30 Gy (expert opinion*) to begin no later than the end of treatment and to be performed annually for children younger than 6 years of age, every other year for children 6-12 years of age, and every 5 years for adolescents and young adults older than 12 years of age (level C evidence and expert opinion).
Hearing loss surveillance *may be reasonable* for survivors who had placement of cerebrospinal fluid shunts (level B evidence) to begin no later than the end of treatment and repeated every 5 years thereafter (level C evidence and expert opinion).
What surveillance modality should be used?
Pure tone conventional audiometry testing *is recommended* for survivors ≥6 years of age at 1000–8000 Hz, and additional testing with high frequency audiometry at >8000 Hz *is recommended* whenever equipment is available (evidence-based guidelines and expert opinion). Referral to an audiologist for more extensive testing *is recommended* for survivors <6 years of age (evidence-based guidelines and expert opinion).
What should be done when abnormalities are identified?
Referral to an audiologist or auditory clinic *is recommended* for any survivor who has symptoms suggesting hearing loss or abnormal audiological test results showing a loss of more than 15 dB absolute threshold level (1000–8000 Hz) (expert opinion*).

Tinnitus

General recommendation
Survivors treated with cisplatin, with or without high-dose carboplatin (>1500 mg/m^2) (level C evidence), or head or brain radiotherapy ≥30 Gy (expert opinion) and their healthcare providers should be aware of the risk of tinnitus. Referral to an audiologist is recommended for survivors who have symptoms of tinnitus (expert opinion*).

*Based on evidence that does not meet the inclusion criteria.

Publication

Clemens E, van den Heuvel-Eibrink MM, Mulder RL, Kremer LCM, Hudson MM, Skinner R, Constine LS, Bass JK, Kuehni CE, Langer T, van Dalen EC, Bardi E, Bonne NX, Brock PR, Brooks B, Carleton B, Caron E, Chang KW, Johnston K, Knight K, Nathan PC, Orgel E, Prasad PK, Rottenberg J, Scheinemann K, de Vries ACH, Walwyn T, Weiss A, Am Zehnhoff-Dinnesen A, Cohn RJ, Landier W; International Guideline Harmonization Group ototoxicity group. 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. The Lancet Oncology 2019;20:e29-e41.

IGHG Obstetric care recommendations: Counseling and surveillance in pregnancy 2020

General recommendation
Health care providers should discuss the risk of adverse obstetric outcomes based on the specific cancer treatment exposures with all female CAYA cancer survivors of reproductive age.
Who needs preconception counseling?
Female CAYA cancer survivors and their health care providers should be aware that there is no evidence to support that survivors have an increased risk of giving birth to a child with congenital anomalies (high quality evidence). Female CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus and their health care providers should be aware of the risk of adverse obstetric outcomes including miscarriage (moderate quality evidence), premature birth (high quality evidence) and low birth weight (high quality evidence).
Who needs specific obstetric surveillance during pregnancy?
High risk obstetric surveillance is recommended for CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus due to the risk of premature birth and low birth weight (high quality evidence).

Who needs specific cardiac surveillance during pregnancy? *Based on IGHG cardiomyopathy guideline*
Cardiomyopathy surveillance is reasonable prior to pregnancy or in the first trimester for all female survivors treated with anthracyclines and/or chest radiation (moderate level recommendation, moderate quality evidence).
No recommendations can be formulated for the frequency of ongoing surveillance in pregnant survivors who have normal left ventricular systolic function immediately prior to or during the first trimester of pregnancy (moderate level recommendation, low quality evidence).

Publication

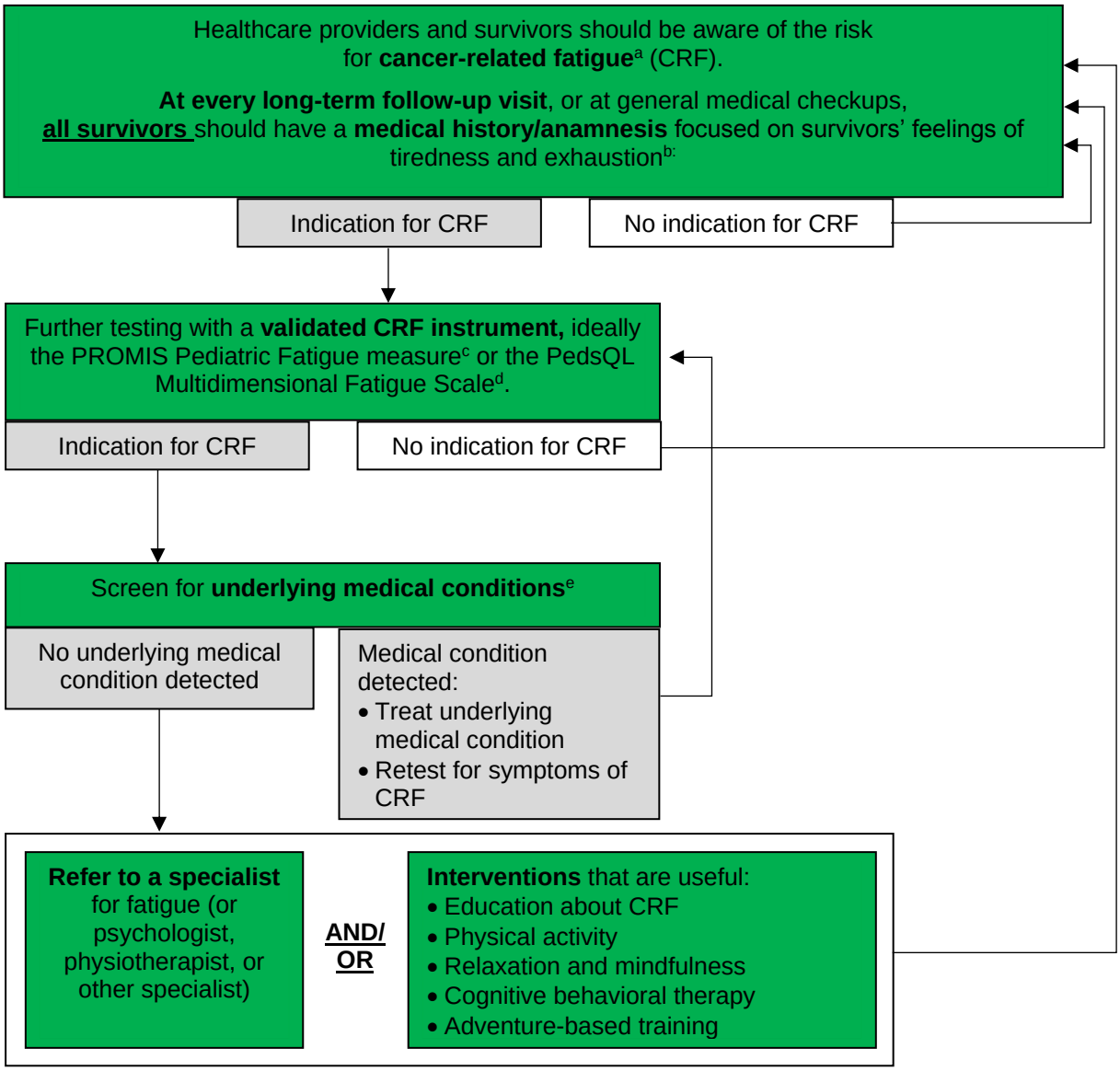
van der Kooi ALF, Mulder RL, Hudson MM, Kremer LCM, Skinner R, Constine LS, van Dorp W, van Dulmen-den Broeder E, Falck-Winther J, Wallace WH, Waugh J, Woodruff TK, Anderson RA, Armenian SH, Bloemenkamp KWM, Critchley HOD, Demoor-Goldschmidt C, Ehrhardt MJ, Green DM, Grobman WA, Iwahata Y, Krishna I, Laven JSE, Levitt G, Meacham LR, Miller ES, Mulders A, Polanco A, Ronckers CM, Samuel A, Walwyn T, Levine JM, van den Heuvel-Eibrink MM. 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:S0002-9378(20)30614-1.

Who needs surveillance?
Healthcare providers and survivors of childhood, adolescent and young adult (CAYA) cancers *should be aware* that CAYA cancer survivors are risk for cancer-related fatigue[a] (CRF; Level A evidence). Main risk factors for CRF in CAYA cancer survivors are: • Psychological distress (Level A evidence), • Late effects or health problems, pain, relapse, older age at follow-up (Level B evidence), • Radiotherapy (Level C evidence).
What surveillance modality should be used and how often should surveillance be performed?
For all CAYA cancer survivors: A medical history/anamnesis focused on survivors' feelings of tiredness and exhaustion *is recommended* to be performed regularly (at every long-term follow-up visit, or at general medical checkups) (expert opinion). • Questions to ask: "Do you get tired easily?", or "Are you too tired or exhausted to enjoy the things you like to do?" For CAYA cancer survivors with an indication for CRF from medical history/anamnesis: • Further testing with a validated fatigue measure[b] *is recommended* (Level B evidence, expert opinion). • Screening for underlying medical conditions[c] that may cause fatigue *is recommended* (expert opinion, existing guidelines)
What should be done if abnormalities are identified?

If CRF is diagnosed with a validated fatigue measure and if no underlying medical condition is identified:
• Referral to a specialist in fatigue (or more generic specialist such as psychologist, physiotherapist, or other relevant specialist) *is recommended* for CAYA cancer survivors (expert opinion).
• Interventions that *are useful*:
  ○ Physical activity (Level B evidence);
  ○ Education about CRF (Level B evidence);
  ○ Relaxation and mindfulness (Level C evidence, existing guidelines);
  ○ Cognitive behavioral therapy (Level C evidence, existing guidelines);
  ○ Adventure-based training (Level C evidence).

[a] CRF 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".
[b] Ideally the PROMIS Pediatric Fatigue measure (http://www.healthmeasures.net/index.php?Itemid=992 [accessed August 29th 2019]) or the PedsQL Multidimensional Fatigue Scale (https://eprovide.mapi-trust.org/instruments/pediatric-quality-of-life-inventory-multidimensional-fatigue-scale [accessed August 29th 2019]); see Table S13 for list of all measures validated in CAYA cancer patients and survivors.
[c] e.g. other late effects like cardiac dysfunction, endocrine dysfunction, pulmonary dysfunction, and renal dysfunction (IGHG guidelines under development); and/or other general causes like anemia, arthritis, neuromuscular complications, pain, fever and/or infection, and nutritional deficiencies (list not conclusive).

Process of screening and interventions for cancer-related fatigue in survivors of childhood, adolescent and young adult cancers



Publication

Christen S, Roser K, Mulder RL, Ilic A, Lie HC, Loonen JJ, Mellblom AV, Kremer LCM, Hudson MM, Constine LS, Skinner R, Scheinemann K, Gilleland Marchak J, Michel G; IGHG psychological late effects group. 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;14:923–938.

Education

Who needs surveillance?
Healthcare providers, teachers, caregivers, and survivors of childhood, adolescent and young adult (CAYA) cancers, and survivors' schools *should be aware* that, on a group level, survivors of CAYA cancer are at risk for: • lower educational achievement (Level C evidence) • experiencing a delay in completing their education (Level B evidence) • requiring educational accommodations (Level B evidence) Particular attention is needed for survivors of CAYA cancer with the following risk factors[a] for **lower educational achievement**: primary diagnosis of CNS tumor (Level B evidence), CNS-directed therapies (concordant in existing guidelines, expert opinion), impaired neurocognitive functioning (Level A evidence), non-white race or immigration status (Level A evidence for specific geographical regions), and parents' lower level of education (Level B evidence). (Strong recommendation)
At what age or time from exposure should surveillance be initiated?
Surveillance of educational outcomes *is recommended* for all ages to begin at diagnosis and continue through survivorship until young adulthood (expert opinion, strong recommendation).
What surveillance modality should be used and at what frequency should surveillance be performed?
Regular assessment of educational outcomes[b] via parent- or self-report *is recommended* at every long-term follow-up visit or general medical checkup at least annually[c] until education is completed (expert opinion, strong recommendation).
What should be done if abnormalities are identified?
Documentation of educational problems in the survivor's medical record *is recommended* to facilitate sharing with all members of the care team (expert opinion, strong recommendation).
Referral[d] to an educational specialist, psychologist, and/or social worker for assessment and implementation of relevant educational and/or disability services *is recommended* for survivors who report educational problems upon screening (expert opinion, strong recommendation).

Abbreviations: CAYA, childhood, adolescent and young adult; CNS, central nervous system.

[a] Main risk factors were all factors that were associated with increased risk for lower educational achievement with at least Level B evidence, demonstrating statistically significantly increased risk in >50% of studies, or with concordance in existing guidelines. A complete list of all risk factors is presented in the conclusions of evidence table.

[b] Questions to ask: "How are you doing in 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?", "Have you ever received or asked for any support?"

[c] 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.

[d] The referring healthcare professional is responsible for following up with the referred survivor regarding receipt of support, and documenting progress of educational outcomes in the survivor's medical records. The referring healthcare professional can transfer this responsibility to another person, e.g. the educational specialist or school, but it needs to be communicated clearly to the survivor, the referring healthcare professional, and the educational specialist who is responsible for this.

Employment

Who needs surveillance?
Healthcare providers, caregivers, and survivors of childhood, adolescent and young adult (CAYA) cancers *should be aware* that, on a group level, survivors of CAYA cancer are at risk for unemployment (Level C evidence). Particular attention is needed for survivors of CAYA cancer with the following risk factors[a] for **unemployment**: female sex (Level B evidence), lower educational achievement (Level A evidence), primary diagnosis of CNS tumor (concordant in existing guidelines, Level A evidence), CNS-directed therapies (concordant in existing guidelines, Level A evidence), any adverse long-term side effects (Level A evidence), impaired neurocognitive functioning (Level A evidence), second malignancy or recurrence (Level B evidence), psychological distress (Level B evidence), and physical disability (Level B evidence). (Strong recommendation)
At what age or time from exposure should surveillance be initiated?
Vocational planning and employment surveillance *is recommended* beginning in adolescence to support survivors to transition from education to employment (expert opinion, strong recommendation).
What surveillance modality should be used and at what frequency should surveillance be performed?
Regular assessment of vocational planning[b] and employment status via parent- or self-report *is recommended* at every long-term follow-up visit or general medical checkup (expert opinion, strong recommendation).
What should be done if abnormalities are identified?
Documentation of vocational problems in the survivor's medical record *is recommended* to facilitate information sharing with all members of the care team (expert opinion, strong recommendation).
Referral[c] to a vocational counselor, psychologist, and/or social worker for assessment and implementation of relevant vocational and/or disability services *is recommended* for survivors who report vocational problems upon screening (expert opinion, strong recommendation).

Abbreviations: CAYA, childhood, adolescent and young adult; CNS, central nervous system.
[a] Main risk factors were all factors that were associated with increased risk for unemployment with at least Level B evidence, demonstrating statistically significantly increased risk in >50% of studies, or with concordance in existing guidelines. A complete list of all risk factors are presented in the conclusions of evidence table.
[b] 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?", "Have you ever received or asked for any support?"
[c] The referring healthcare professional is responsible for following up with the referred survivor regarding receipt of support, and documenting progress of vocational outcomes in the survivor's medical records. The referring healthcare professional can transfer this responsibility to another person, e.g. the vocational counselor or rehabilitation specialist, but it needs to be communicated clearly to the survivor, the referring healthcare professional, and the vocational specialist who is responsible for this.

Publication

Devine KA, Christen S, Mulder RL, Brown MC, Ingerski LM, Mader L, Potter E, Sleurs C, Viola A, Waern S, Constine LS, Hudson MM, Kremer LCM, Skinner R, Michel G, Gilleland Marchak J, Schulte F on behalf of the IGHG psychological late effects group. 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; 128:2405-2419.

Who needs surveillance?

Healthcare providers and survivors of childhood, adolescent and young adult (CAYA) cancer *should be aware* that survivors are at risk for mental disorder symptoms. For all survivors, surveillance *is recommended* for:

- **Depression and mood disorders** (Level A-C evidence)
- **Anxiety** (Level A-C evidence)
- **Psychological distress** (Level C evidence)
- **Post-traumatic stress** (Level B evidence)
- **Behavioral problems** (Level C evidence)
- **Suicidal ideation** (Level C evidence)

The main risk factors[a] for mental disorders and symptoms in survivors of CAYA cancer are unemployment[b], lower educational achievement[c], late effects[d], experiencing pain[e], and female sex[f].

(Level A-C evidence, strong recommendation)

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

Healthcare providers *should be aware* that mental disorders and symptoms can be present at diagnosis or arise during treatment for CAYA cancer. Mental health surveillance is important for patients throughout treatment for CAYA cancer (expert opinion, strong recommendation).

Mental health surveillance *is recommended* for survivors of all ages to begin at the first follow-up visit and continue throughout the lifespan (Level C evidence, strong recommendation).

At what frequency should surveillance be performed?

Mental health surveillance *is recommended* for all survivors of CAYA cancers at every follow-up visit (or at general medical check-ups) (Level C evidence, strong recommendation).

What surveillance modality should be used?

A medical history focused on survivors' mental health *is recommended* during follow-up care visits.
Suggested questions to screen for mental health problems: "Have you [has your child[g]]...

- "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?"

(expert opinion, strong recommendation)

For survivors of CAYA cancer with an indication for mental health problems from medical history: Further testing with a validated parent- and/or self-report measure[h] by a mental health professional (e.g. psychologist, psychiatrist, or other suitable specialist) *is recommended* (Level A-C evidence, expert opinion, strong recommendation).

What should be done if abnormalities are identified?

Healthcare providers and survivors of CAYA cancer *should be aware* of standardly recommended care:

- Prompt referral of survivors reporting mental health symptoms to a mental health professional (e.g. psychologist, psychiatrist, or other suitable specialist) for diagnostic and risk assessment (expert opinion).
- Immediate referral of survivors with severe mental health problems that may significantly interfere with their safety (e.g. psychosis, severe depression, suicidal ideation, self-harming

behaviors or impulses) to a mental health professional (e.g. psychiatrist, psychologist, or local mental health crisis services; expert opinion).

- Cognitive behavioral therapy for the treatment of survivors of CAYA cancer with anxiety, depression, and post-traumatic stress symptoms (Level B evidence).

(Strong recommendation)

[a] Risk factors with at least Level B evidence.
[b] Level A evidence for psychological distress; Level B evidence for anxiety and post-traumatic stress.
[c] Level A evidence for post-traumatic stress; Level B evidence for depression, anxiety and psychological distress.
[d] Level B evidence for depression, anxiety, psychological distress, and post-traumatic stress.
[e] Level B evidence for depression, anxiety.
[f] Level B evidence for anxiety, psychological distress, and post-traumatic stress.
[g] if parent-report is indicated.
[h] Recommended measures for children to assess mental health problems: Benefit and Burden Scale for Children, Beck Youth Inventories-II, Distress Screening Tool, Strengths and Difficulties Questionnaire; Recommended measures for adults: Brief Symptom Inventory-18, Posttraumatic stress response Diagnostic Scale, Distress Thermometer, General Health Questionnaire.

Publication

Gilleland Marchak J, Christen S, Mulder RL, Baust K, Blom JMC, Brinkman TM, Elens I, Harju E, Kadan-Lottick NS, Khor JWT, Lemiere J, Recklitis C, Wakefield CE, Wiener L, Constine LS, Hudson MM, Kremer LCM, Skinner R, Vetsch J, Lee J, Michel G on behalf of the IGHG psychological late effects group. 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. Lancet Oncol 2022;23:e184-96.

1. Coronary artery disease

General recommendation
Health care providers and childhood, adolescent and young adult cancer survivors treated with radiotherapy exposing the heart should be aware of the increased risk of coronary artery disease (moderate level evidence and expert opinion, strong recommendation).

2. Surveillance for coronary artery disease

Who need coronary artery disease surveillance and what modality should be used?
Due to insufficient evidence, currently, no recommendation can be formulated for routine primary CAD surveillance of childhood, adolescent and young adult cancer survivors treated with radiotherapy involving the heart*.

** Insufficient evidence to determine the diagnostic value of surveillance options for asymptomatic abnormalities of the coronary arteries and whether early detection reduces morbidity and mortality (no studies/expert opinion).*

3. Modifiable cardiovascular disease risk factors

Who needs surveillance of modifiable cardiovascular disease risk factors?
Surveillance for modifiable cardiovascular disease risk factors according to national or local guidelines, which may involve referral to a cardiovascular specialist, is recommended for childhood, adolescent and young adult cancer survivors treated with radiotherapy exposing the heart (existing guidelines and expert opinion, strong recommendation).
When should surveillance for modifiable cardiovascular risk factors be initiated and at what frequency?
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, but at least by age 40 years and at a minimum of every 5 years (very low to high level evidence, existing guidelines and expert opinion, strong recommendation).
What can be done when modifiable cardiovascular disease risk factors have been identified?
Timely management of all modifiable cardiovascular disease risk factors (such as hypertension, dyslipidaemia, diabetes, overweight/obesity and smoking) is recommended due to the increased risk of coronary artery disease in childhood, adolescent and young adult cancer survivors treated with radiotherapy exposing the heart (existing guidelines and expert opinion, strong recommendation).

Publication

van Dalen EC, Mulder RL, Suh E, Ehrhardt MJ, Aune GJ, Bardi E, Benson BJ, Bergler-Klein J, Chen MH, Frey E, Hennewig U, Lockwood L, Martinsson U, Muraca M, van der Pal HJ, Plummer C, Scheinemann K, Schindera C, Tonorezos ES, Wallace WH, Constine LS, Skinner R, Hudson MM, Kremer LCM, Levitt G, Mulrooney DA. 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. Eur J Cancer 2021;156:127-137.

General recommendations

CAYA cancer survivors with a history of:

- Radiation therapy exposing the HP region (high-quality evidence for GHD, moderate-quality evidence for ACTHD, low-quality evidence for TSHD, LH/FSHD, CPP).
- A CNS tumor near or within the HP region (high-quality evidence for all HP disorders and expert opinion)
- Surgery near or within the HP region (expert opinion)
- Hydrocephalus or cerebrospinal fluid shunt (low-quality evidence and expert opinion for GHD and CPP)

and their health-care providers should be aware of the risk of HP dysfunction (i.e., GHD, TSHD, LH/FSHD, ACTHD or CPP) (strong recommendation).

CAYA cancer survivors with a history of:

- Exposure to high dose radiation therapy to the HP region°
- Surgery near or within the HP region
- A CNS tumor near or within the HP region

should be referred to an (pediatric) endocrinologist, whenever feasible, or followed by a multidisciplinary team including an (pediatric) endocrinologist due to the high risk of developing HP dysfunction (expert opinion, strong recommendation).

Who needs surveillance for HP dysfunction?

Surveillance for HP dysfunction is recommended for CAYA cancer survivors with a history of:

- Radiation therapy exposing the HP region†
  Note: this also applies for radiation therapy to a non-CNS/solid tumor of the head and neck
- A CNS tumor near or within the HP region†
- Surgery near or within the HP region†

(strong recommendation).

Surveillance for GHD is reasonable for CAYA cancer survivors with a history of:

- TBI (very low-quality evidence and expert opinion)
- Hydrocephalus or cerebrospinal fluid shunt (low-quality evidence and expert opinion)

Surveillance for CPP†† is reasonable for CAYA cancer survivors with a history of:

- Hydrocephalus or cerebrospinal fluid shunt (low-quality evidence and expert opinion)

(moderate recommendation).

When should surveillance for HP dysfunction be initiated?

All at-risk* CAYA cancer survivors, caregivers and/or parents should be counselled about signs and symptoms of HP dysfunction and offer psychosocial support if preferred, and late effects health care providers should be educated on the risk and consequences of HP dysfunction, to prevent delay in diagnosis and treatment (expert opinion, strong recommendation).

Initiation of surveillance for HP dysfunction is recommended:

- For any HP dysfunction: 1 year after completion of radiation therapy even in the absence of symptoms‡, or from diagnosis in CAYA cancer survivors with CNS tumors or surgery near or within the HP region (expert opinion, strong recommendation).
- For GHD and CPP††: from occurrence of hydrocephalus or cerebrospinal fluid shunt (expert opinion, strong recommendation)

At what frequency should surveillance for HP dysfunction be performed?

Surveillance with physical examination, including height and pubertal status is recommended every 6 months for at-risk* pre- and peri-pubertal CAYA cancer survivors, and every year for at risk* adult CAYA cancer survivors (expert opinion, strong recommendation).

Annual laboratory surveillance for HP dysfunction is recommended for all at-risk* CAYA cancer survivors (expert opinion, strong recommendation).

For how long should surveillance for HP dysfunction be performed?

Surveillance for HP dysfunction (*i.e.,* ACTHD, GHD, LH/FSHD and TSHD) is reasonable for at-risk* CAYA cancer survivors for at least 15 years after cancer diagnosis or from treatment exposure (moderate-quality evidence and expert opinion, moderate recommendation).º
However, HP dysfunction may still occur after 15 years. Continuation of surveillance should be a shared decision between survivor and healthcare provider considering available healthcare resources (expert opinion, moderate recommendation).

Surveillance for CPP is recommended for at-risk* childhood cancer survivors until age 8 years in girls and 9 years in boys (expert opinion, strong recommendation).

What surveillance modality should be used for HP dysfunction for all at-risk* CAYA cancer survivors?

For all at-risk* CAYA cancer survivors**,** the following evaluation is recommended:

- A relevant patient and familial clinical history
- A physical examination assessing signs and symptoms suggestive of HP dysfunction
- FT4 measurement
- TSH measurement
- Morning cortisol measurement

(existing guidelines and expert opinion, strong recommendation).

For all at-risk* CAYA cancer survivors, the following evaluation is not recommended:

- TRH test or nocturnal TSH surge for the diagnosis of TSHD

(very low-quality evidence and expert opinion, strong recommendation).

For pre- and peri-pubertal at-risk* CAYA cancer survivors, additional monitoring recommended include:

- Height velocity (*i.e.,* height plotted on a growth chart) in relation to parental height, and
- Pubertal development and pubertal progression (*i.e.,* Tanner stage)¶

(high-quality evidence and expert opinion, strong recommendation).

For adult at-risk* CAYA cancer survivors, additional evaluation that is reasonable includes:

- IGF-I measurement, with the understanding that an IGF-I level >0 SDS does not rule out the diagnosis of GHD

(expert opinion, moderate recommendation).

For adult at-risk* CAYA cancer survivors, additional evaluation recommended include:

- In males: measurements of morning testosterone§ (assay measuring free testosterone if overweight) and LH
- In females: measurements of estradiol, FSH and LH

(existing guidelines and expert opinion, strong recommendation).

What should be done when abnormalities are identified?
Referral to an (pediatric) endocrinologist is recommended: • For pre- and peri-pubertal CAYA cancer survivors experiencing decline in height velocity or lack of acceleration of height velocity in case of signs of puberty or with a height SDS below their target height range SDS, which cannot be explained by other causes (expert opinion, strong recommendation). • For all CAYA cancer survivors with clinical symptoms or laboratory results suggestive for HP dysfunction (expert opinion, strong recommendation).
Referral to an (pediatric) endocrinologist is recommended: • For all CAYA cancer survivors with low morning cortisol (expert opinion, strong recommendation). These survivors should be counselled regarding risks associated with untreated ACTHD. Ideally, an interim management plan should be agreed upon by the referring provider and the endocrinologist who is receiving the referral until provocative testing has established adequate ACTH axis function. This plan may involve initiating hydrocortisone replacement at maintenance or stress doses depending on the level of suspicion and the survivor's clinical presentation.
CAYA cancer survivors with (a suspicion for) HP dysfunction should be counseled regarding the benefits of hormonal replacement therapy‖ (or treatment in case of CPP) on overall health, as well as the risks associated with untreated HP dysfunction, and should be assisted in coordinating and obtaining an early referral when appropriate (expert opinion, strong recommendation).

Abbreviations: ACTHD= adrenocorticotropic hormone deficiency, CAYA= childhood and young adult, CCP= central precocious puberty, CNS= central nervous system, FT4= free thyroxine, FSH= follicle stimulating hormone, GHD= growth hormone deficiency, HP= hypothalamic-pituitary, IGF-I= insulin-like growth factor, LH= luteinizing hormone, SDS= standard deviation score, LH/FSHD= luteinizing hormone/follicle-stimulating hormone deficiency, TBI= total body irradiation, TRH= thyrotropin releasing hormone, TSH= thyroid stimulating hormone, TSHD= thyroid stimulating hormone deficiency.
In this table, recommendations for surveillance of HP dysfunction are given. If clinical symptoms or laboratory findings suggest HP dysfunction (for example signs of puberty not appropriate for the age or low FT4), the CAYA cancer survivor should be referred to a (pediatric) endocrinologist for further counseling and to discuss the benefits and harms of starting specific treatment.
† Concerning radiation therapy exposing the HP region; there is high-quality evidence for GHD, moderate-quality evidence for ACTHD, and low-quality evidence for TSHD, LH/FSHD and CPP. Concerning surgery near or within the HP region; there is high-quality evidence for all HP disorders, supported with expert opinion. Concerning surgery near or within the HP region; there is expert opinion for all HP disorders.
º The panel agreed that the risk for HP dysfunction increases, with higher doses of radiation therapy. When the RT dose exceeds 30 Gy, there is a higher risk for HP disorders including ACTHD, LH/FSHD and TSHD.
†† Surveillance for CPP should include monitoring for onset of puberty in CCS below age 8 years (girls, based on thelarche) or 9 years (boys, based on testicular enlargement).
*At-risk CAYA cancer survivors include survivors treated with radiation therapy exposing the HP region, with CNS tumors or surgery near or within the HP region. For GHD and CPP, history of hydrocephalus or cerebrospinal fluid shunt may also be a risk factor.
º In CAYA cancer survivors treated with neurosurgery outside the HP region only, one-time surveillance post-surgery suffices in the absence of other risk factors.
‡ Monitoring height and pubertal status at six months after RT is desirable, as interpretation of growth and pubertal development requires multiple measurements over time. Clinicians involved in

the follow-up care of CAYA cancer survivors should be aware that CPP may already present in the first year after RT exposure, necessitating early referral.
[¶] 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.
[§] Measuring morning testosterone before 10.00 AM, preferably by tandem mass spectroscopy and not in an immunoassay.
[‖] Thyroid hormone replacement therapy should be started only after evaluation of function of the hypothalamic-pituitary-adrenal axis.

Publication

van Iersel L, Mulder RL, Denzer C, Cohen LE, Spoudeas HA, Meacham LR, Sugden E, Schouten-van Meeteren AYN, Hoving EW, Packer RJ, Armstrong GT, Mostoufi-Moab S, Stades AM, van Vuurden D, Janssens GO, Thomas-Teinturier C, Murray RD, Di Iorgi N, Neggers SJCMM, Thompson J, Toogood AA, Gleeson H, Follin C, Bardi E, Torno L, Patterson B, Morsellino V, Sommer G, Clement SC, Srivastava D, Kiserud CE, Fernandez A, Scheinemann K, Raman S, Yuen KCJ, Wallace WH, Constine LS, Skinner R, Hudson MM, Kremer LCM, Chemaitilly W, van Santen HM. Hypothalamic-Pituitary and Other Endocrine Surveillance Among Childhood Cancer Survivors. Endocr Rev 2021:bnab040.

General recommendation
CAYA cancer survivors and their healthcare providers should be aware of the risk of low (Z-score ≤-1 and >-2) and very low (Z-score ≤-2) bone mineral density, and pay specific attention to possible consequences (e.g. acute and chronic back pain, vertebral and non-vertebral low-trauma fractures, and loss of height due to vertebral fractures) after treatment with: • Cranial or craniospinal radiotherapy (high-quality evidence for very low BMD) • Total body irradiation (high-quality evidence for low BMD, unknown effect for very low BMD) • Corticosteroids as anti-cancer treatment (moderate-quality evidence for low BMD, no significant effect for very low BMD) Other risk factors for low and very low bone mineral density in CAYA cancer survivors include[1]: • Hypogonadism (moderate-quality evidence for very low BMD; BMD assessment is recommended according to standard endocrine care, which is best done by a medical bone health specialist[2]) • Growth hormone deficiency (moderate-quality evidence for low BMD; BMD assessment is recommended according to standard endocrine care, which is best done by a medical bone health specialist[2]) • Low BMI or underweight (high-quality evidence for very low BMD) • Male sex (moderate-quality evidence for very low BMD) • White race (moderate-quality evidence for low BMD) • Lack of physical activity[3] (moderate-quality evidence for low BMD) • Current or prior smoking (moderate-quality evidence for low BMD)
Who needs bone mineral density surveillance?
Bone mineral density surveillance is recommended for CAYA cancer survivors treated with cranial or craniospinal radiotherapy (high-quality evidence for very low BMD).
Bone mineral density surveillance is reasonable for CAYA cancer survivors treated with TBI (high-quality evidence for low BMD).
Due to insufficient evidence[4], no recommendation can be formulated for or against BMD surveillance for CAYA cancer survivors treated with corticosteroids as anti-cancer treatment. The surveillance decision should be made by the CAYA cancer survivor and healthcare provider together, after careful consideration of the potential harms and benefits (see Survivor Information Brochure) and additional risk factors.
What surveillance modality should be used?
A DXA scan of the lumbar spine (posterior-anterior L1-L4), total body less head (in children and adolescents), and total hip (in adolescents and adults) are recommended for surveillance of bone mineral density (evidence-based guidelines).
QCT is not recommended for surveillance of bone mineral density (evidence-based guidelines and expert opinion).
When should surveillance be initiated and at what frequency should it be performed?
BMD surveillance is recommended at entry into LTFU (between two to five years following completion of therapy), and if normal (Z-score >-1), it is recommended to repeat surveillance at 25 years of age when peak bone mass should be achieved. Between these two measurements and thereafter, BMD surveillance should be performed as clinically indicated based on BMD and ongoing risk assessment (expert opinion).
What should be done when abnormalities are identified?
In CAYA cancer survivors with a BMD Z-score ≤-2, referral to (or consultation of) a medical bone health specialist[2] is recommended for further (endocrine) evaluation, interpretation of BMD findings, treatment, and follow-up (expert opinion).
In CAYA cancer survivors with a BMD Z-score ≤-1 and >-2, it is recommended to: • Evaluate for the presence of endocrine defects (hypogonadism, GHD etc.), and consult a medical bone health specialist2 for further evaluation and interpretation of BMD findings as clinically

indicated (very low-quality evidence and evidence-based guidelines) • 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 (expert opinion)
In all at-risk CAYA cancer survivors[5], regardless of their BMD Z-score, it is recommended to counsel about lifestyle habits that are important to maintain or improve bone health: • Engage in regular physical activity3, especially weight-bearing and fall prevention activities (evidence-based guidelines and expert opinion) • Abstain from smoking (moderate-quality evidence for low BMD and evidence-based guidelines) • Limit or avoid alcohol intake (evidence-based guidelines) • Consume adequate dietary vitamin D (at least 400 IU/day) and calcium (at least 500 mg/day) irrespective of vitamin D status, and advise vitamin D supplementation in survivors with 25OHD levels <20 ng/ml6 (plus calcium if the recommended amount of dietary calcium is not met) as per local or national guidelines (evidence-based guidelines and expert opinion) • Advise nutritional supplementation for CAYA cancer survivors with low BMI or underweight (expert opinion)
It is reasonable to refer at-risk CAYA cancer survivors[5] with a history of low-trauma vertebral and non-vertebral fractures (from entry into LTFU onwards) to a medical bone health specialist[2] for further evaluation and treatment (expert opinion).

Abbreviations: BMD=bone mineral density; BMI=body mass index; CAYA=childhood, adolescent and young adult; DXA=dual energy X-ray absorptiometry; LTFU=long-term follow-up; PBM=peak bone mass; TBI=total body irradiation.

[1]As in the general population (except for sex; female sex in the general population); [2]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; [3]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; [4]Insufficient evidence to determine if early detection of low BMD after treatment with corticosteroids reduces morbidity in CAYA cancer survivors, and whether the risk of very low BMD is increased in the long-term; [5]Survivors treated with C(S)RT (high-quality evidence), TBI (high-quality evidence), or corticosteroids (moderate-quality evidence); [6]Target 25OHD levels should be >20 ng/ml.

Potential advantages and disadvantages of bone mineral density surveillance for childhood, adolescent and young adult cancer survivors – A Survivor Information Brochure

Why should I be aware of the risk of low bone mineral density (weak bones)?

- Bone mineral density is an important determinant of bone strength. This means that if you have low bone mineral density (weak bones), you probably break your bones more easily.
- Having weak bones around the age of 25 (when your bones should be the heaviest) predicts for osteoporosis and bone fractures later in life.
- As a survivor of childhood, adolescent or young adult cancer you may have a higher risk of developing weak bones 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 (cranial[spinal] irradiation), or if you were treated with total body irradiation, you have an increased risk of developing weak bones.
- If you were treated with corticosteroids (as anti-cancer treatment) you may have an increased risk of weak bones as well. However, it is unclear if corticosteroids can lead to weak bones in the long term.

- While some people treated with cranial(spinal) irradiation, total body irradiation, and/or corticosteroids will develop weak bones at a young age, most will not.
- However, among those who develop weak bones, detecting it early can possibly prevent bone fractures and may therefore reduce consequences such as pain, surgery, and temporary immobilization.
- It is possible to detect weak bones early by having bone mineral density screening, but bone mineral density screening has advantages and disadvantages.
- This information sheet can be used to help you and your healthcare provider decide if having bone mineral density screening is the right choice for you.

What is bone mineral density screening?

- Bone mineral density screening is performed with a bone scan that uses low dose X-rays to see how strong your bones are.

What are the potential advantages of having bone mineral density screening?

- You may feel reassured if you have normal bone mineral density at this time. However, weak bones may still develop in the future, and your fracture risk may still be increased due to other reasons.
- Early detection would allow doctors to monitor the bone mineral density course over time. In addition, early detection would allow referral to a specialized bone doctor who can further evaluate your bone health, which may both help to determine if/when treatment is needed.
- You may be more likely to have weak bones detected at an earlier time point when certain interventions may be most effective (before the end of puberty), and as a result, bone fractures may be prevented.

What are the potential disadvantages of having bone mineral density screening?

- You may experience anxiety and stress about having bone mineral density screening and what the test results will show.
- You may feel more like a patient rather than a healthy survivor if you decide to have bone mineral density screening.
- You may be incorrectly diagnosed with weak bones (misdiagnosis), or diagnosed with weak bones that never would have caused fractures (overdiagnosis), although your doctor carefully considers treatment.
- We do not know if early treatment of weak bones leads to better health (no further weakening of the bones or prevention of fractures) in childhood, adolescent and young adult cancer survivors. However, in the general population, we know that this is the case.
- The diagnosis of weak bones may affect your ability to obtain healthcare and/or life insurance.

What are the potential disadvantages associated with this bone scan?

- This bone scan is associated with potential harms from radiation exposure (especially in the context of cumulative radiation dose after cancer treatment), although the dose of one scan is considered negligible (less than one chest X-ray or a short flight).
- This bone scan may be costly and may not be covered by your health insurance. However, your healthcare provider could write a letter of medical necessity to explain that you are at increased risk of weak bones and why you may benefit from a bone scan.

What are the international screening recommendations?

- If you were treated with radiotherapy to your brain or spinal cord, total body irradiation, and/or corticosteroids, it is important that you are aware of the risk of weak bones, and pay specific attention to their possible consequences (acute back pain, [spinal] fractures, and loss of height due to spinal fractures).
- If you were treated with radiotherapy to your brain or spinal cord, bone mineral density

screening is recommended at entry into long-term follow-up (beginning two or more years following completion of therapy) and at 25 years of age.
- If you were treated with total body irradiation, bone mineral density screening is reasonable at entry into long-term follow-up and at 25 years of age.
- If you were treated with corticosteroids as anti-cancer treatment, we cannot recommend for or against routine bone mineral density screening because we do not know if your health outcomes will be better if we detect weak bones early. It is important that you make the decision whether or not to screen together with your healthcare providers, oncology and survivorship team, and individual support networks. Careful consideration of the potential advantages and disadvantages is advised.

Thank you for taking the time to read this information sheet. If you have any questions regarding the information included in this brochure or if you require emotional support and advice regarding your thoughts and feelings, please contact your healthcare provider for advice and support.

Publication

van Atteveld JE, Mulder RL, van den Heuvel-Eibrink MM, Hudson MM, Kremer LCM, Skinner R, Wallace WH, Constine LS, Higham CE, Kaste SC, Niinimäki R, Mostoufi-Moab S, Alos N, Fintini D, Templeton KJ, Ward LM, Frey E, Franceschi R, Pavasovic V, Karol SE, Amin NL, Vrooman LM, Harila-Saari A, Demoor-Goldschmidt C, Murray RD, Bardi E, Lequin MH, Faienza MF, Zaikova O, Berger C, Mora S, Ness KK, Neggers SJCMM, Pluijm SMF, Simmons JH, Di Iorgi N. 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 Endocrinol 2021;9:622-637.

Late liver injury

General recommendation
Childhood, adolescent and young adult cancer survivors and their healthcare providers should be aware of the risk of late liver injury[1] after (treatment with): • radiotherapy potentially exposing the liver, including total body irradiation (moderate- to high-quality evidence) • busulfan (low-quality evidence) • thioguanine (low-quality evidence) • mercaptopurine (expert opinion)[2] • methotrexate (expert opinion)[2] • dactinomycin (expert opinion)[2] • hematopoietic stem cell transplantation (irrespective of GVHD) (expert opinion) • hepatic surgery (low-quality evidence) • chronic viral hepatitis (low-quality evidence) • sinusoidal obstruction syndrome (expert opinion)[2] (strong recommendation)
Who needs surveillance for late liver injury?
Surveillance for liver injury is recommended for childhood, adolescent and young adult cancer survivors treated with radiotherapy potentially exposing the liver, including total body irradiation (moderate- to high-quality evidence, strong recommendation).
Surveillance for liver injury is reasonable for childhood, adolescent and young adult cancer survivors treated with or with a history of: • busulfan (low-quality evidence) • thioguanine (low-quality evidence) • mercaptopurine (expert opinion)[2] • methotrexate (expert opinion)[2] • dactinomycin (expert opinion)[2] • hematopoietic stem cell transplantation (irrespective of GVHD) (expert opinion) • hepatic surgery (low-quality evidence) • chronic viral hepatitis (low-quality evidence) • sinusoidal obstruction syndrome (expert opinion)[2] (moderate recommendation).
What surveillance modality should be used, when should surveillance be initiated and at what frequency should surveillance be performed?
Physical examination[3] and measurement of serum liver enzyme concentrations (ALT, AST, gGT, ALP) is recommended once at entry into long-term follow-up, with further surveillance as clinically indicated (expert opinion/existing guidelines, strong recommendation)
What should be done when abnormalities are identified?
In case of increased liver enzyme values between 1 and 2 x ULN, the test should be repeated within 1 year in survivors (expert opinion/existing guidelines, strong recommendation).
In case of increased liver enzyme values between 2 and 5 x ULN, the test should be repeated within 3-6 months in survivors (expert opinion/existing guidelines, strong recommendation).
In case of increased liver enzyme values >5 x ULN, the test should be repeated within 2 weeks in survivors (expert opinion/existing guidelines, strong recommendation).
If persistent liver abnormalities (> ULN) or signs of advanced liver disease are identified in survivors, it is recommended to: • discuss with or refer to a hepatologist or gastroenterologist for further evaluation if there is no obvious explanation (alcohol, medication, obesity) • use potentially hepatotoxic medications[4] and supplements judiciously

- 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
    - maintenance of a healthy weight and lifestyle

(expert opinion/existing guidelines, strong recommendation).

For survivors with chronic HBV/HCV infection it is recommended to counsel about precautions to reduce viral transmission to household and sexual contacts and continue follow-up by a hepatitis specialist according to the hepatitis clinical practice guidelines in each country (expert opinion/existing guidelines, strong recommendation).

Note: No surveillance recommendations for FNH and NRH were formulated, because these are rare entities that are typically detected incidentally.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase, gGT, gamma-glutamyltransferase; ULN, upper limit of normal.
[1] Clinical outcomes: hepatocellular liver injury confirmed by liver histology; liver fibrosis or cirrhosis (compensated or decompensated) confirmed by liver ultrasound, elastography or liver histology; Subclinical outcomes: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) for cellular liver injury; gamma-glutamyltransferase (gGT), alkaline phosphatase (ALP) and bilirubin for hepatobiliary dysfunction and biliary tract injury; prothrombin time and albumin for liver synthetic function.
[2] Late liver injury is typically only seen in the context of previous acute liver injury.
[3] 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 nevi, pruritus.
[4] Potentially hepatotoxic medications are defined as those associated with elevated liver enzymes described in >1% of the general population using the drug.

Iron overload

General recommendation
Childhood, adolescent and young adult cancer survivors who have undergone hematopoietic stem cell transplantation or received multiple red blood cell transfusions and their healthcare providers should be aware of the risk of iron overload (expert opinion, strong recommendation).
Who needs surveillance for iron overload?
Surveillance for iron overload is recommended for childhood, adolescent and young adult cancer survivors who have undergone hematopoietic stem cell transplantation and/or received multiple red blood cell transfusions (very-low quality evidence/expert opinion, strong recommendation).
What surveillance modality should be used, when should surveillance be initiated and at what frequency should surveillance be performed?
Measurement of serum ferritin is recommended once at entry into long-term follow-up, with further surveillance as clinically indicated. It is important to be aware of the diagnostic limitations of serum ferritin measurement that may represent inflammation and not iron overload (expert opinion/existing guidelines, strong recommendation).
What should be done when abnormalities are identified?
In case of increased serum ferritin >500 ng/ml the test should be repeated within 6 months in survivors (expert opinion/existing guidelines, strong recommendation).
If persistently elevated serum ferritin levels (>500 ng/ml) are identified, it is recommended to perform a T2* magnetic resonance imaging (MRI) to quantify the liver iron content (expert opinion/existing guidelines, strong recommendation).
For survivors with confirmed elevated liver iron content it is recommended to refer to a hematologist or other specialist to start treatment, such as phlebotomy or chelation therapy (expert opinion/existing guidelines, strong recommendation).

Publication

Bardi E, Mulder RL, van Dalen EC, Bhatt NS, Ruble KA, Burgis J, Castellino SM, Constine LS, den Hoed CM, Green DM, Koot BGP, Levitt G, Szonyi L, Wallace WH, Skinner R, Hudson MM, Kremer LCM, Effinger KE, Bresters D. 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 Treat Rev 2021;100:102296.

Recommendations for reproductive fertility preservation for female CAYA cancer patients 2020

Who should be informed about the potential infertility risk?
We strongly recommend that healthcare providers inform all CAYA cancer patients and their parents/caregivers/partners about the expected risk of infertility and/or early menopause, which may vary in magnitude based on the specific treatment planned (very low- to moderate-quality evidence).

Who should be counselled about fertility preservation?
We strongly recommend that healthcare providers[1] discuss fertility preservation options and alternative family planning with CAYA cancer patients and their parents/caregivers/partners if planned treatment will include alkylating agents[2] (high-quality evidence), radiotherapy to volumes exposing the ovaries (high-quality evidence), HSCT (very low-quality evidence), unilateral oophorectomy (very low-quality evidence), and/or cranial radiotherapy (very low-quality evidence).
If planned treatment will not include gonadotoxic modalities[3], referral to a specialist to discuss fertility preservation options and family planning may be considered upon the request for additional information of the CAYA cancer patient and their parents/caregivers/partners (no studies).

What methods for reproductive preservation are appropriate to offer in counselling?[4]
Female CAYA cancer patients at potential risk of infertility: high-dose alkylating agents (CED ≥ 6000-8000 mg/m^2), radiotherapy to volumes exposing the ovaries or HSCT
We strongly recommend offering oocyte or embryo cryopreservation to post-pubertal[5] CAYA cancer patients in this treatment group only if cancer prognosis is not compromised by delay (existing guidelines).
We moderately recommend offering harvesting of ovarian tissue for cryopreservation to prepubertal and postpubertal[5] CAYA cancer patients in this treatment group (very low-quality evidence, existing guidelines).[6]
We moderately recommend offering oophoropexy prior to radiotherapy to volumes exposing the ovaries to prepubertal and postpubertal[5] CAYA cancer patients (very low-quality evidence).[7]
No recommendation can be formulated for offering hormone suppression during alkylating agent chemotherapy to postpubertal[5] CAYA cancer patients in clinical care, but it could be offered in a research setting (inconclusive evidence).
Female CAYA cancer patients at potential risk of infertility: low-dose alkylating agents (CED < 6000-8000 mg/m^2) or cranial radiotherapy
We moderately recommend offering oocyte or embryo cryopreservation only to postpubertal[5] CAYA cancer patients in this treatment group at high risk of cancer recurrence who may need gonadotoxic treatment[8] in the future (existing guidelines).[9]
We do not recommend offering harvesting of ovarian tissue for cryopreservation to prepubertal and postpubertal[5] CAYA cancer patients in this treatment group (very low-quality evidence, existing guidelines).
No recommendation can be formulated for offering hormone suppression during alkylating agent chemotherapy to postpubertal[5] CAYA cancer patients in clinical care, but it could be offered in a research setting (inconclusive evidence).
Female CAYA cancer patients at potential risk of infertility: unilateral oophorectomy
We moderately recommend offering oocyte or embryo cryopreservation only to postpubertal[4] CAYA cancer patients in this treatment group at high risk of cancer recurrence who may need gonadotoxic treatment[8] in the future (existing guidelines).[9]
No recommendation can be formulated for offering harvesting of ovarian tissue for

cryopreservation to prepubertal and postpubertal[5] CAYA cancer patients in this treatment group (insufficient evidence).
Female CAYA cancer patients not at risk of infertility: other treatments
We moderately recommend offering oocyte or embryo cryopreservation only to postpubertal[4] CAYA cancer patients in this treatment group at high risk of cancer recurrence who may need gonadotoxic treatment[8] in the future (existing guidelines).[9]
We do not recommend offering harvesting of ovarian tissue for cryopreservation to prepubertal and postpubertal[5] CAYA cancer patients in this treatment group (very low-quality evidence, existing guidelines).

Abbreviations: CAYA, childhood, adolescent and young adult; HSCT, hematopoietic stem cell transplantation.

Note: Patients who will be treated with bilateral oophorectomy will by definition become infertile and are therefore qualified for any of the fertility preservation options as listed in the recommendations.

The panel emphasized that shared decision making between healthcare providers and patients and their families is essential when fertility preservation (any method) and future family planning decisions are made. It is important to inform patients and their families about the potential benefits, harms, costs and logistics associated with fertility preservation in order for them to make a well-informed decision.

[1] The panel agreed that the choice of who should discuss fertility preservation and family planning options with the CAYA cancer patients and their families depends more on the provider's knowledge, patient's disease state and local access to fertility specialists than identifying a particular discipline to assume this role. Possibilities include paediatric oncologist, (paediatric) endocrinologist, fertility specialist, specialised nurse or other relevant healthcare provider. Of critical importance is that a system is in place to identify who is responsible for having the discussion.

[2] Alkylating agents: cyclophosphamide, procarbazine, busulfan, ifosfamide, mechlorethamine (nitrogen mustard), melphalan, chlorambucil, thiothepa, carmustin (BCNU), lomustine (CCNU), dacarbazine, temozolomide. A calculation formula for the cyclophosphamide equivalent dose can be found in Green et al. Pediatr Blood Cancer. 2014;61(1):53-67.

[3] Therapies that do not include alkylating agents, radiotherapy to volumes exposing the ovaries, HSCT, unilateral oophorectomy, and/or cranial radiotherapy.

[4] The panel emphasized that shared decision making between healthcare providers and patients and their families is essential when fertility preservation (any method) and future family planning decisions are made. It is important to inform patients and their families about the potential benefits, harms, costs and logistics associated with fertility preservation in order for them to make a well-informed decision.

[5] Postpubertal status was defined as females with menarche.

[6] The panel agreed that transplantation of post-pubertal cryopreserved ovarian tissue can be offered as clinical care, but advises careful evaluation of outcomes of the procedure as clinical research. Transplantation of pre-pubertal cryopreserved ovarian tissue can only be offered in the context of research due to the experimental nature. The panel recognizes the potential risk of reintroduction of malignant cells during auto-transplantation of ovarian tissue, especially for survivors of leukaemia, non-Hodgkin and metastasized solid tumours and the limited data of transplantation of pre-pubertal cryopreserved ovarian tissue.

[7] Consultation with a radiation oncologist is needed to determine if oophoropexy is appropriate and to inform patients, caregivers or partners about the procedure's benefits and harms.

[8] Patients needing high-dose alkylating agents (CED ≥ 6000-8000 mg/m^2), radiotherapy to volumes exposing the ovaries and/or HSCT in the future and if the procedure delay does not compromise patient outcome.

[9] For patients not at risk of cancer recurrence, we do not recommend.

Counselling and methods for preservation of female reproductive fertility

Female patients with CAYA cancer patients before age 25 years

Strong recommendation[1] to inform all patients with CAYA cancer and their parents, caregivers, and partners about the expected risk of infertility

	At potential risk for infertility						**Not at risk for infertility**	
	High-dose alkylating agents[2], radiotherapy to ovaries, or HSCT		Low-dose alkylating agents [4], or cranial radiotherapy		Unilateral oophorectomy		Other treatment groups[5]	
	Postpubertal[3]	Prepubertal	Postpubertal[3]	Prepubertal	Postpubertal[3]	Prepubertal	Postpubertal[3]	Prepubertal
Counselling about options for fertility preservation and alternative family planning	**Strong recommendation[6]**	**Strong recommendation[6]**	**Strong recommendation[6]**	**Strong recommendation[6]**	**Strong recommendation[6]**	**Strong recommendation[6]**	**Moderate recommendation[7] only if requested**	**Moderate recommendation[7] only if requested**
Oocyte or embryo cryopreservation	**Strong recommendation only if cancer prognosis is not compromised by delay[8]**		**Moderate recommendation for only patients at high risk of cancer recurrence[8,9,10]**		**Moderate recommendation for only patients at high risk of cancer recurrence[8,9,10]**		**Moderate recommendation for only patients at high risk of cancer recurrence[8,9,10]**	
Harvesting of ovarian tissue for cryopreservation[11]	**Moderate recommendation[12]**	**Moderate recommendation[12]**	**Not recommended[12]**	**Not recommended[12]**	**No recommendation** (insufficient evidence)	**No recommendation** (insufficient evidence)	**Not recommended[12]**	**Not recommended[12]**
Oophoropexy (before radiotherapy to ovaries)	**Moderate recommendation[13, 14]**	**Moderate recommendation[13, 14]**						
Hormone suppression during alkylating agent chemotherapy	**No recommendation for clinical care, only in research setting** (insufficient evidence)		**No recommendation for clinical care, only in research setting** (insufficient evidence)					

Abbreviations: CAYA, childhood, adolescent, and young adult; HSCT, hematopoietic stem cell transplantation.
Notes: Patients who will be treated with bilateral oophorectomy will by definition become infertile and are therefore qualified for any of the fertility preservation options as listed in the recommendations. The panel emphasized that shared decision making between healthcare providers and patients and their families is essential when fertility preservation (any method) and future family planning decisions are made. It is important to inform patients and their families about the potential benefits, harms, costs and logistics associated with fertility preservation in order for them to make a well-informed decision.
[1] This recommendation is based on very low- to moderate-quality evidence.
[2] High-dose alkylating agents defined as a cumulative alkylating agent dose (cyclophosphamide equivalent dose (CED)) at or above 6000-8000 mg/m^2; A CED calculation can be found in Green et al. Pediatr Blood Cancer. 2014;61(1):53-67.
[3] Post-pubertal status was defined as females with menarche.
[4] Low-dose alkylating agents defined as a cumulative alkylating agent dose (cyclophosphamide equivalent dose (CED)) below 6000-8000 mg/m^2.
[5] Therapies that do not include alkylating agents, radiotherapy to volumes exposing the ovaries, HSCT, unilateral oophorectomy, and/or cranial radiotherapy.
[6] This recommendation is based on very low- to high-quality evidence.
[7] This recommendation is based on expert opinions; no studies were identified.
[8] This recommendation is based on evidence cited in high-quality existing evidence-based guidelines and expert opinions; no evidence in CAYA cancer patients was identified.
[9] Patients who may need high-dose alkylating agents (CED ≥6000-8000 mg/m^2), radiotherapy to volumes exposing the ovaries and/or HSCT in the future for cancer recurrence, and if prognosis will not be compromised by delay of treatment initiation.
[10] For patients not at risk of cancer recurrence, we do not recommend.
[11] The panel agreed that transplantation of post-pubertal cryopreserved ovarian tissue can be offered as clinical care, but advises careful evaluation of outcomes of the procedure as clinical research. Transplantation of pre-pubertal cryopreserved ovarian tissue can only be offered in the context of research due to the experimental nature. The panel recognizes the potential risk of reintroduction of malignant cells during auto-transplantation of ovarian tissue, especially for survivors of leukaemia, non-Hodgkin and metastasized solid tumours and the limited data of transplantation of pre-pubertal cryopreserved ovarian tissue.
[12] This recommendation is based on a combination of very low-quality evidence, evidence cited in high-quality existing evidence-based guidelines and expert opinions.
[13] Consultation with a radiation oncologist is needed to determine if oophoropexy is appropriate and to inform patients, caregivers or partners about the procedure's benefits and harms.
[14] This recommendation is based on a combination of very low-quality evidence and expert opinions.

Publication

Mulder RL, Font-Gonzalez A, Hudson MM, van Santen HM, Loeffen EAH, Burns KC, Quinn GP, van Dulmen-den Broeder E, Byrne J, Haupt R, Wallace WH, van den Heuvel-Eibrink MM, Anazodo A, Anderson RA, Barnbrock A, Beck JD, Bos AME, Demeestere I, Denzer C, Di Iorgi N, Hoefgen HR, Kebudi R, Lambalk C, Langer T, Meacham LR, Rodriguez-Wallberg K, Stern C, Stutz-Grunder E, van Dorp W, Veening M, Veldkamp S, van der Meulen E, Constine LS, Kenney LB, van de Wetering MD, Kremer LCM, Levine J, Tissing WJE; PanCareLIFE Consortium. Fertility preservation for female patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2021;22(2):e45-e56.

Recommendations for reproductive fertility preservation for male CAYA cancer patients 2020

Who should be informed about the potential infertility risk?
We strongly recommend that healthcare providers inform all CAYA cancer patients and their parents/caregivers/partners about the expected risk of infertility, which may vary in magnitude based on the specific treatment planned (very low- to moderate-quality evidence).

Who should be counselled about fertility preservation?
We strongly recommend that healthcare providers[1] discuss fertility preservation options and alternative family planning with CAYA cancer patients and their parents/caregivers/partners if planned treatment will include alkylating agents[2] (high-quality evidence), radiotherapy to volumes exposing the testes (moderate quality evidence), HSCT (expert opinion), cisplatin (low-quality evidence) orchiectomy (expert opinion), and/or cranial radiotherapy (very low-quality evidence).
If planned treatment will not include gonadotoxic modalities[3], referral to a specialist to discuss fertility preservation options and family planning may be considered upon the request for additional information of the CAYA cancer patient and their parents/caregivers/partners (no studies).

What methods for reproductive preservation are appropriate to offer in counselling?[4]
Male CAYA cancer patients at potential risk of infertility: high-dose alkylating agents (CED ≥ 4000 mg/m^2), radiotherapy to volumes exposing the testes, or HSCT
We strongly recommend offering sperm cryopreservation via masturbation or penile vibration to pubertal and postpubertal[5] CAYA cancer patients in this treatment group (very low-quality evidence, existing guidelines).
When masturbation or penile vibration is not successful due to failure to ejaculate, we strongly recommend offering sperm cryopreservation via electro-ejaculation or testicular sperm extraction to pubertal and postpubertal[5] CAYA cancer patients in this treatment group (very low-quality evidence, existing guidelines).
We moderately recommend offering harvesting of testicular tissue for cryopreservation to prepubertal CAYA cancer patients in this treatment group, only as part of clinical trials or approved protocols (very low-quality evidence, existing guidelines).[6] We moderately recommend offering harvesting of testicular tissue for cryopreservation to pubertal and postpubertal[5] CAYA cancer patients in this treatment group who cannot undergo other fertility preservation options, only as part of clinical trials or approved protocols (very low-quality evidence, existing guidelines).[6]
We do not recommend offering hormone suppression during alkylating agent chemotherapy to pubertal and postpubertal[5] CAYA cancer patients (exisiting guidelines).
Male CAYA cancer patients at potential risk of infertility: low-dose alkylating agents (CED < 4000 mg/m^2), cisplatin or orchiectomy
We strongly recommend offering sperm cryopreservation via masturbation or penile vibration to pubertal and postpubertal[5] CAYA cancer patients in this treatment group (very low quality evidence, existing guidelines).
When masturbation or penile vibration is not successful due to failure to ejaculate, we moderately recommend offering sperm cryopreservation via electro-ejaculation or testicular sperm extraction only to pubertal and postpubertal[5] CAYA cancer patients in this treatment group at high risk of cancer recurrence who may need gonadotoxic treatment[7] in the future (very low-quality evidence, existing guidelines).[8]
No recommendation can be formulated for offering harvesting of testicular tissue for cryopreservation to prepubertal, pubertal and postpubertal[5] CAYA cancer patients in this treatment

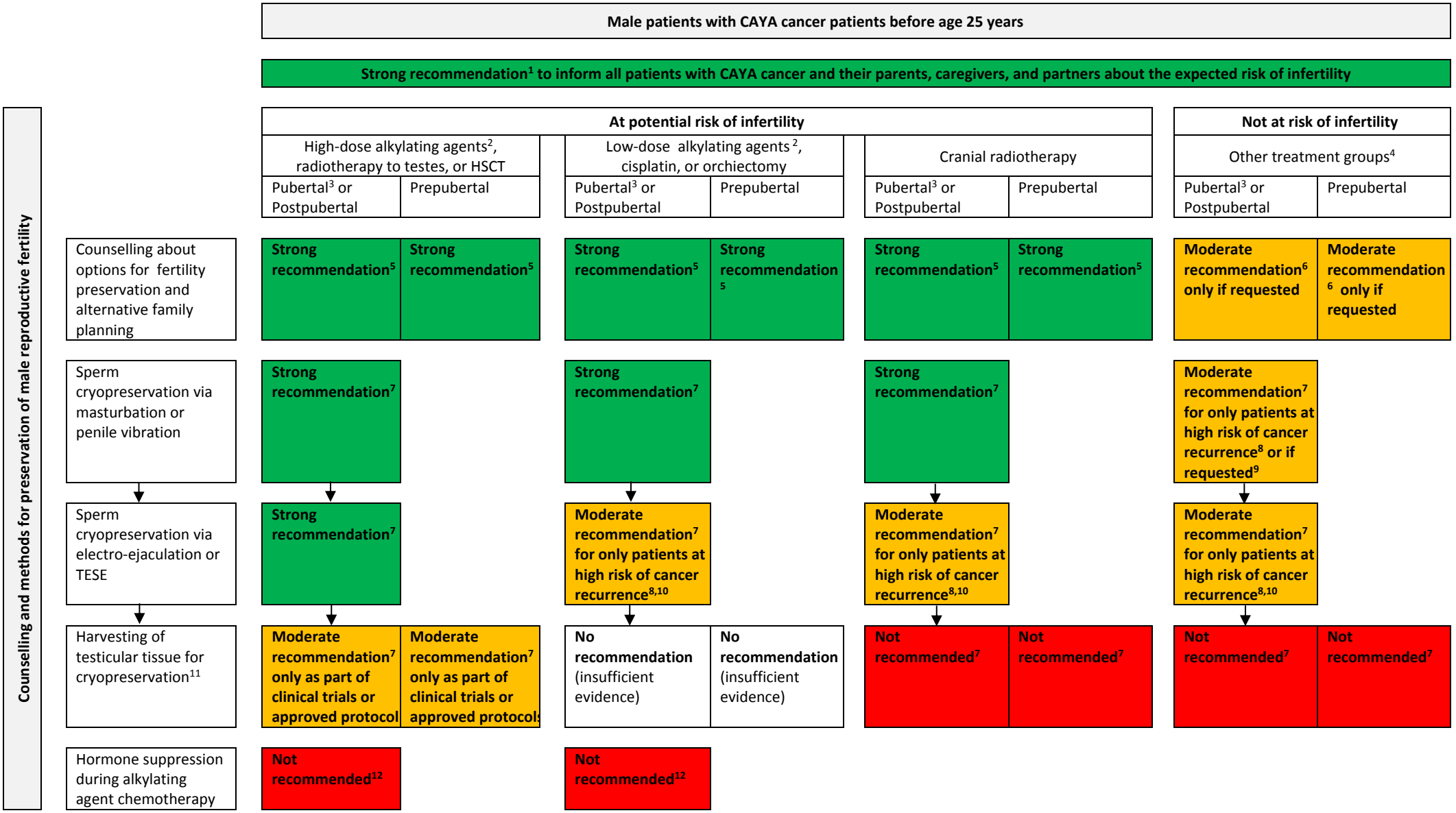
group (insufficient evidence).
We do not recommend offering hormone suppression during alkylating agent chemotherapy to pubertal and postpubertal[5] CAYA cancer patients (exisiting guidelines).
Male CAYA cancer patients at potential risk of infertility: cranial radiotherapy
We strongly recommend offering sperm cryopreservation via masturbation or penile vibration to pubertal and postpubertal[5] CAYA cancer patients in this treatment group (very low- quality evidence, existing guidelines).
When masturbation or penile vibration is not successful due to failure to ejaculate, we moderately recommend offering sperm cryopreservation via electro-ejaculation or testicular sperm extraction only to pubertal and postpubertal[5] CAYA cancer patients in this treatment group at high risk of cancer recurrence who may need gonadotoxic treatment[7] in the future (very low-quality evidence, existing guidelines).[8]
We do not recommend offering harvesting of testicular tissue for cryopreservation to prepubertal, pubertal and postpubertal[5] CAYA cancer patients in this treatment group (very low-quality evidence, existing guidelines).
Male CAYA cancer patients not at risk of infertility: other treatments
We moderately recommend offering sperm cryopreservation via masturbation or penile vibration to pubertal and postpubertal[5] CAYA cancer patients in this treatment group based on their wishes and shared decision-making with their healthcare provider (very low-quality evidence, existing guidelines).
When masturbation or penile vibration is not successful due to failure to ejaculate, we moderately recommend offering sperm cryopreservation via electro-ejaculation or testicular sperm extraction only to pubertal and postpubertal[5] CAYA cancer patients in this treatment group at high risk of cancer recurrence who may need gonadotoxic treatment[7] in the future (very low-quality evidence, existing guidelines).[8]
We do not recommend offering harvesting of testicular tissue for cryopreservation to prepubertal, pubertal and postpubertal[5] patients in this treatment group (very low-quality evidence, existing guidelines).

Abbreviations: CAYA, childhood, adolescent, and young adult; CED, cyclophosphamide equivalent dose; HSCT, hematopoietic stem cell transplantation.
Note: Patients who will be treated with bilateral orchiectomy will by definition become infertile and are therefore qualified for any of the fertility preservation options as listed in the recommendations.
[1] The panel agreed that the choice of who should discuss fertility preservation and family planning options with the CAYA cancer patients and their families depends more on the provider's knowledge, patient's disease state and local access to fertility specialists than identifying a particular discipline to assume this role. Possibilities include paediatric oncologist, (paediatric) endocrinologist, fertility specialist, specialised nurse or other relevant healthcare provider. Of critical importance is that a system is in place to identify who is responsible for having the discussion.
[2] Alkylating agents: cyclophosphamide, procarbazine, busulfan, ifosfamide, mechlorethamine (nitrogen mustard), melphalan, chlorambucil, thiothepa, carmustin (BCNU), lomustine (CCNU), dacarbazine, temozolomide. A calculation formula for the cyclophosphamide equivalent dose can be found in Green et al. Pediatr Blood Cancer. 2014;61(1):53-67.
[3] Therapies that do not include alkylating agents, radiotherapy to volumes exposing the testes, cisplatin, orchiectomy, *and*/or cranial radiotherapy.
[4] The panel emphasized that shared decision making between healthcare providers and patients and their families is essential when fertility preservation (any method) and future family planning decisions are made. It is important to inform patients and their families about the potential benefits, harms, costs and logistics associated with fertility preservation in order for them to make a well-informed decision
[5] Pubertal patients are defined as ≥ tanner stage II.
[6] The panel agreed that transplantation of cryopreserved testicular tissue should only be offered in the context of research, recognizing the experimental nature and the insufficient evidence available about

its feasibility to restore fertility and the potential risk of reintroduction of malignant cells during auto-transplantation of testicular tissue.

[7] Patients needing high-dose alkylating agents (CED ≥ *4000* mg/m^2) and/or radiotherapy to volumes exposing the testes in the future.

[8] For patients not at risk of cancer recurrence, we do not recommend.


Male patients with CAYA cancer patients before age 25 years
Strong recommendation[1] to inform all patients with CAYA cancer and their parents, caregivers, and partners about the expected risk of infertility
Counselling and methods for preservation of male reproductive fertility
At potential risk of infertility
Not at risk of infertility
High-dose alkylating agents[2], radiotherapy to testes, or HSCT
Low-dose alkylating agents [2], cisplatin, or orchiectomy
Cranial radiotherapy
Other treatment groups[4]
Pubertal[3] or Postpubertal
Prepubertal
Counselling about options for fertility preservation and alternative family planning
Strong recommendation[5]
Strong recommendation[5]
Strong recommendation[5]
Strong recommendation [5]
Strong recommendation[5]
Strong recommendation[5]
Moderate recommendation[6] only if requested
Moderate recommendation [6] only if requested
Sperm cryopreservation via masturbation or penile vibration
Strong recommendation[7]
Strong recommendation[7]
Strong recommendation[7]
Moderate recommendation[7] for only patients at high risk of cancer recurrence[8] or if requested[9]
Sperm cryopreservation via electro-ejaculation or TESE
Strong recommendation[7]
Moderate recommendation[7] for only patients at high risk of cancer recurrence[8,10]
Moderate recommendation[7] for only patients at high risk of cancer recurrence[8,10]
Moderate recommendation[7] for only patients at high risk of cancer recurrence[8,10]
Harvesting of testicular tissue for cryopreservation[11]
Moderate recommendation[7] only as part of clinical trials or approved protocol
Moderate recommendation[7] only as part of clinical trials or approved protocols
No recommendation (insufficient evidence)
No recommendation (insufficient evidence)
Not recommended[7]
Not recommended[7]
Not recommended[7]
Not recommended[7]
Hormone suppression during alkylating agent chemotherapy
Not recommended[12]
Not recommended[12]

Abbreviations: CAYA, childhood, adolescent, and young adult; HSCT, hematopoietic stem cell transplantation; TESE, testicular sperm extraction.
Note: The panel emphasized that shared decision making between healthcare providers and patients and their families is essential when fertility preservation (any method) and future family planning decisions are made. It is important to inform patients and their families about the potential benefits, harms, costs and logistics associated with fertility preservation in order for them to make a well-informed decision.
Patients who will be treated with bilateral orchiectomy will by definition become infertile and are therefore qualified for any of the fertility preservation options as listed in the recommendations.
[1] This recommendation is based on very low- to moderate-quality evidence.
[2] High-dose alkylating agents defined as a cyclophosphamide equivalent dose (CED) of ≥ 4000 mg/m^2 and low-dose alkylating agents defined as CED < 4000 mg/m^2; A CED calculation can be found in Green et al. Pediatr Blood Cancer. 2014;61(1):53-67.
[3] Pubertal patients are defined as ≥ tanner stage II (testicular volume of ≥4cc).
[4] Therapies that do not include alkylating agents, radiotherapy to volumes exposing the testes, HSCT, cisplatin, orchiectomy, and/or cranial radiotherapy. Includes patients who will be treated with major surgery to spinal cord/sympathetic nerves/pelvis.
[5] This recommendation is based on very low- to high-quality evidence.
[6] This recommendation is based on expert opinions; no studies were identified.
[7] This recommendations is based on a combination of very low-quality evidence, evidence cited in high-quality existing evidence-based guidelines and expert opinions.
[8] Patients who may need high-dose alkylating agents (CED ≥ 4000 mg/m^2), radiotherapy to volumes exposing the testes and/or HSCT in the future for cancer recurrence.
[9] Based on patient's wishes and shared decision-making with the healthcare provider.
[10] For patients who are not at risk of cancer recurrence, we do not recommend.
[11] The panel agreed that transplantation of cryopreserved testicular tissue should only be offered in the context of research, recognizing the experimental nature and the insufficient evidence available about its feasibility to restore fertility and the potential risk of reintroduction of malignant cells during auto-transplantation of testicular tissue.
[12] This recommendation is based on evidence cited in high-quality existing evidence-based guidelines and expert opinions.

Publication

Mulder RL, Font-Gonzalez A, Green DM, Loeffen EAH, Hudson MM, Loonen J, Yu R, Ginsberg JP, Mitchell RT, Byrne J, Skinner R, Anazodo A, Constine LS, de Vries A, Jahnukainen K, Lorenzo A, Meissner A, Nahata L, Dinkelman-Smit M, Tournaye H, Haupt R, van den Heuvel-Eibrink MM, van Santen HM, van Pelt AMM, Dirksen U, den Hartogh J, van Dulmen-den Broeder E, Wallace WH, Levine J, Tissing WJE, Kremer LCM, Kenney LB, van de Wetering MD; PanCareLIFE Consortium. Fertility preservation for male patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2021;22(2):e57-e67.

Recommendations regarding ongoing communication of treatment-related infertility risk and fertility preservation in patients with CAYA cancer 2020

General	Healthcare providers should: • Be familiar with the latest evidence-based recommendations, institutional policies and professional educational resources on infertility risk and fertility preservation procedures • Maintain currency with training where appropriate (strong recommendation; very low- to moderate-quality evidence)
Provision of information about treatment-related infertility risk and fertility preservation	Healthcare providers should: • Deliver clear, comprehensive and age-appropriate information in a professional, neutral and empathetic manner; • Provide up-to-date written and/or online educational resources to patients and their parents/caregivers/partner in appropriate languages and health literacy levels. (strong recommendation; very low- to moderate-quality evidence)
Communicating treatment-related infertility risk and fertility preservation	Healthcare providers[1] should: • Involve patients and/or their parents/caregivers/partners • Offer a private conversation with the patient depending on age • Offer a separate conversation with parents/caregivers/partners after consent or assent of the patient • Consider the patient's age, developmental status and the family's cultural/religious beliefs • Provide emotional support to patients and their parents/caregivers/partners during counselling about treatment-related infertility risk and fertility preservation and prompt psychosocial specialist referrals (e.g. social workers and psychologists) as appropriate • Initiate counselling as early as possible after a cancer diagnosis and treatment plan are established and when a change in disease status occurs that requires treatment intensification with gonadal toxic agents/modalities • Offer counselling on an ongoing basis during treatment and throughout survivorship because the infertility risk or patient's ideas may change (strong recommendation; very low- to moderate-quality evidence) Hospitals should: • Establish referral pathways for accessing fertility specialists or fertility specialist centres where appropriate (strong recommendation; very low- to moderate-quality evidence)

[1] A system should be in place to identify who is responsible for having the discussion, taking into account the provider's knowledge, patient's disease state and local access to fertility specialists.

Publication

Mulder RL, Font-Gonzalez A, van Dulmen-den Broeder E, Quinn GP, Ginsberg JP, Loeffen EAH, Hudson MM, Burns KC, van Santen HM, Berger C, Diesch T, Dirksen U, Giwercman A, Gracia C, Hunter SE, Kelvin JF, Klosky JL, Laven JSE, Lockart BA, Neggers SJCMM, Peate M, Phillips B, Reed DR, Tinner EME, Byrne J, Veening M, van de Berg M, Verhaak CM, Anazodo A, Rodriguez-Wallberg K, van den Heuvel-Eibrink MM, Asogwa OA, Brownsdon A, Wallace WH, Green DM, Skinner R, Haupt R, Kenney LB, Levine J, van de Wetering MD, Tissing WJE, Paul NW, Kremer LCM, Inthorn J; PanCareLIFE Consortium. Communication and ethical considerations for fertility preservation for patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2021;22(2):e68-e80.

Recommendations regarding ethical issues about treatment-related infertility risk and fertility preservation in patients with CAYA cancer patients 2020

What are the ethical issues related to fertility preservation?
Healthcare providers should: • Foster the autonomy of the patient • Assess the patient's emotional, psychological and intellectual status as part of the informed consent process • Ensure that decisions about fertility preservation are driven by patient's best interest and not by own interest and/or interest of parents/caregivers/partners • Encourage patients to consider the risks, and the medical, social and ethical contingencies of fertility preservation procedures as well as future use of frozen tissue • Address the uncertainty of future technologies during counselling about infertility risk and fertility preservation procedures • Include societal and ethical values connected to social parenthood (adoption) and the potential discrimination when applying for adoption in the discussions with the patient and parents/caregivers/partners about adoption • Include a two-stage consent process with patients and/or their families/caregivers/partners: 1) at diagnosis when the decision about harvesting and storing tissue is made and 2) after therapy at a developmentally appropriate age when the decision of whether and how to use the stored material is made • Be aware of the importance to determine upfront with patients and their families/caregivers/partners the access of researchers to their stored gametes • Be aware of the importance to determine upfront with patients and their families/caregivers/partners the disposition of gametes and/or preserved tissue in the event of patient's death • Be aware of possible conflicts of interest between the needs of patients/parents/caregivers and the potential short- and long-term financial costs involved in fertility preservation procedures and storage, as well as post-treatment costs associated with pursuing family-building (Good practice statements)

Publication

Mulder RL, Font-Gonzalez A, van Dulmen-den Broeder E, Quinn GP, Ginsberg JP, Loeffen EAH, Hudson MM, Burns KC, van Santen HM, Berger C, Diesch T, Dirksen U, Giwercman A, Gracia C, Hunter SE, Kelvin JF, Klosky JL, Laven JSE, Lockart BA, Neggers SJCMM, Peate M, Phillips B, Reed DR, Tinner EME, Byrne J, Veening M, van de Berg M, Verhaak CM, Anazodo A, Rodriguez-Wallberg K, van den Heuvel-Eibrink MM, Asogwa OA, Brownsdon A, Wallace WH, Green DM, Skinner R, Haupt R, Kenney LB, Levine J, van de Wetering MD, Tissing WJE, Paul NW, Kremer LCM, Inthorn J; PanCareLIFE Consortium. Communication and ethical considerations for fertility preservation for patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2021;22(2):e68-e80.