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

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ABSTRACT

Purpose
Female survivors of childhood, adolescent, and young adult (CAYA) cancer who were treated with alkylating agents and/or radiation, with potential exposure of the ovaries, have an increased risk of premature ovarian insufficiency (POI). Clinical practice guidelines can facilitate these survivors’ access to optimal treatment of late effects that may improve health and quality of survival; however, surveillance recommendations vary among the existing long-term follow-up guidelines, which impedes the implementation of screening.

Patients and Methods
The present guideline was developed by using an evidence-based approach and summarizes harmonized POI surveillance recommendations for female survivors of CAYA cancer who were diagnosed at age < 25 years. The recommendations were formulated by an international multidisciplinary panel and graded according to the strength of the evidence and the potential benefit gained from early detection and intervention. The harmonized POI surveillance recommendations were developed by using a transparent process and are intended to facilitate care for survivors of CAYA cancer.

Results and Conclusion
The harmonized set of POI surveillance recommendations is intended to be scientifically rigorous, to positively influence health outcomes, and to facilitate the care for female survivors of CAYA cancer.

INTRODUCTION

The 5-year survival rate for childhood, adolescent, and young adult (CAYA) cancer currently exceeds 80% as a result of the advances that have been achieved in our understanding of cancer biology and cancer therapeutics.1-3 A prominent concern is the substantially elevated risk of ovarian dysfunction among female survivors who were treated with alkylating agents and/or radiotherapy.4

The risk of nonsurgical premature ovarian insufficiency (POI)—also referred to as primary ovarian insufficiency, premature ovarian failure or premature menopause—among survivors of CAYA cancer is increased compared with sibling controls, with a cumulative incidence of approximately 8% by age 40 years.5 POI is associated with infertility but also with other sequelae secondary to estrogen...
deficiency, such as osteoporosis, cardiovascular disorders, impaired psycho-social well-being, and compromised sexual health. Survivors who are at risk for ovarian dysfunction related to their cancer treatment, and their health care providers, will benefit from clinical practice guidelines that address long-term surveillance for POI to assure survivors’ timely access to interventions that may preserve health and quality of survival.\textsuperscript{11-14}

A number of clinical practice guidelines have already been developed by groups in North America and Europe to facilitate the early detection and management of POI.\textsuperscript{13-19} These guidelines differ in the definition of at-risk populations, surveillance modality, and frequency, as well as in their recommendations for interventions. These differences impose barriers to the implementation of screening across a spectrum of clinical settings.

Recognizing the importance of a global consensus in the approach for POI surveillance, an international effort was organized to harmonize the existing screening recommendations for female survivors of CAYA cancer.\textsuperscript{20} Herein, we present a summary of the evidence of and recommendations for POI surveillance in survivors of CAYA cancer who were diagnosed at age < 25 years that have been proposed by the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) in collaboration with the European Union–funded PanCareSurFup (PCSF) consortium.\textsuperscript{21}

**PATIENTS AND METHODS**

Detailed information regarding the international guideline harmonization effort and methodology has been previously presented.\textsuperscript{20} The current effort evaluates long-term follow-up guidelines for survivors of CAYA cancer that were developed after systematic evaluation of the quality of late effects literature that links cancer treatment with adverse outcomes. The working group consisted of 33 experts from seven countries who represented all relevant disciplines, including pediatric and adolescent oncology and hematology, radiation and medical oncology, gynecology, reproductive endocrinology and infertility, pediatric and adult endocrinology, survivorship care, epidemiology, and guideline methodology, as well as survivors of CAYA cancer. We evaluated concordances and discordances across previously published long-term follow-up guidelines.\textsuperscript{15-18} To achieve consensus, we formulated clinical questions to address areas of discordance for POI surveillance that covered the following key issues: Who needs surveillance? What surveillance modality should be used? At what frequency and for how long should surveillance be performed? When should survivors be referred and what should be done when abnormalities are identified? What should be done when the potential for future fertility is questioned?

We performed systematic literature searches in September 2014 to update a previous Cochrane systematic review (1966 to 2010).\textsuperscript{12} The clinical questions, inclusion criteria, search strategies, and the selection of studies are provided in the Data Supplement. We generated evidence summaries to answer the relevant clinical questions. When evidence was lacking for survivors of CAYA cancer, we carefully extrapolated evidence from other populations where applicable. In the case of concordance, we extracted and evaluated the evidence cited by the guidelines. Considering the heterogeneity of definitions used to describe ovarian dysfunction, we proposed standardized definitions that were integrated into our literature review and final formulation of recommendations. Survivors of CAYA cancer were defined as individuals who were ≥ 2 years post-treatment for a cancer that was diagnosed at age < 25 years. POI was defined as a clinical condition that developed in any adult female at age < 40 years and was characterized by the absence of menstrual cycles (amenorrhea) for ≥ 4 months and two elevated serum follicle-stimulating hormone (FSH) levels in the menopausal range (on the basis of the maximum threshold of the laboratory assay used).\textsuperscript{20} POI also may result in delayed puberty with FSH levels in the menopausal range. Delayed puberty was defined as the absence of initiation of puberty (Tanner stage 2 breast development) in girls age ≥ 13 years or experiencing a failure to progress in pubertal stage for > 12 months. We defined the hard outcome POI as having both criteria, whereas the surrogate outcome was defined as having at least one of the two POI criteria (amenorrhea or elevated serum FSH levels). Amenorrhea was defined as the absence of menstrual cycles for ≥ 4 months\textsuperscript{21-24} or primary amenorrhea by age 16 years. Irregular menstrual cycles were defined as cycles < 21 days or cycles > 35 days.\textsuperscript{25} Alkylating and similar DNA interstrand cross-linking agent chemotherapy was composed of alkylating agents (busulfan, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine [nitrogen mustard], melphalan, thiopeta), triazines (procarbazine, dacarbazine, temozolomide), nitrosoureas (carmustine, lomustine), and platinum agents (carboplatin, cisplatin). For simplicity, these are all referred to as alkylating agents throughout the article. Radiotherapy to which the ovaries were potentially exposed included any radiation in which the ovaries were likely to be in the field of treatment (lumbar, sacral, whole spine, flank/hiemiabdomen extending below the iliac crest, whole abdomen, inverted Y, pelvic, vaginal, bladder, iliac, and total body irradiation). Although radiation to which the hypothalamic-pituitary region (eg, cranial radiotherapy) was potentially exposed may cause central hypogonadism and was included in our search strategy, we did not develop surveillance recommendations because this will be evaluated in a future IGHG/PCSF guideline on pituitary dysfunction.

The quality of the evidence and the strength of the recommendations were graded according to evidence-based medicine methods that were developed by experts within the Cochrane Childhood Cancer Group\textsuperscript{20} and the IGHG\textsuperscript{26} by using existing methods, such as the Applying Classification of Recommendations and Level of Evidence criteria of the American Heart Association (Data Supplement) and the Grading of Recommendations, Assessment, Development and Evaluations Working Group.\textsuperscript{27,28}

Final recommendations were based on scientific knowledge in combination with other considerations, such as clinical judgments, decisions about thresholds, costs, potential harms from excessive screening, and the need to maintain flexibility of application across different health care systems. The harmonized POI surveillance recommendations were critically appraised by three independent external experts in the field and two patient representatives. The periodic update of the recommendations is planned.

**RESULTS**

Concordances and discordances among the existing POI surveillance recommendations are shown in Table 1. The clinical questions, evidence summaries, and conclusions of evidence tables for these areas are presented in the Data Supplement. The conclusions of the evidence and the final recommendations are summarized in Tables 2 and Figure 1.

**Who Needs POI Surveillance?**

There is evidence from cohort studies that the risk of POI is increased in female survivors of CAYA cancer who were treated with alkylating agents.\textsuperscript{9,29-31} Most studies have focused on alkylating agents as a group, rather than evaluating the risk of a single alkylating agent. Some evidence from one study suggests that cyclophosphamide and procarbazine increase the risk of POI;\textsuperscript{12} however, no studies evaluated the individual risk of busulfan, chlorambucil, ifosfamide, mechlorethamine, melphalan, or thiopeta on POI. This is not surprising because most survivors are treated with combination chemotherapy. Of importance, there seems to be no clear threshold for a safe alkylating agent dose. There is a high level of evidence that
Table 1. Concordance and Discordance Among Premature Ovarian Insufficiency Surveillance Recommendations

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>At risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylating agents*</td>
<td>Yes</td>
<td>All survivors</td>
<td>Yes</td>
<td>Yes</td>
<td>Discordant</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Yes</td>
<td>Not specified</td>
<td>Yes</td>
<td>Yes</td>
<td>Discordant</td>
</tr>
<tr>
<td>Temozolomide plus dacarbazine</td>
<td>Yes</td>
<td>Not specified</td>
<td>Yes</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Yes</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>Carboplatin plus cisplatin</td>
<td>Yes</td>
<td>Not specified</td>
<td>Yes</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>RT exposing ovaries†</td>
<td>Yes</td>
<td>Not specified</td>
<td>Yes</td>
<td>Yes</td>
<td>Discordant</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>Yes</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>Highest risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher doses of alkylating agents</td>
<td>Yes</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>Alkylating agent dose</td>
<td>MOPP ≥ 3 cycles; busulfan ≥ 600 mg/m²; cyclophosphamide ≥ 7.5 g/m²; cyclophosphamide for HCT; ifosfamide ≥ 60 g/m²</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>Combination alkylating agents</td>
<td>Yes</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>Higher doses of RT exposing ovaries</td>
<td>Yes</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>RT dose</td>
<td>One prepubertal: ≥ 10-15 Gy RT ovaries; pubertal: ≥ 5-10 Gy RT ovaries</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>Alkylating agents plus RT exposing ovaries</td>
<td>Yes</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>Unilateral oophorectomy plus RT exposing ovaries/alkylating agents</td>
<td>Yes</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>Bilateral oophorectomy</td>
<td>Yes</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>What surveillance modality should be used?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner staging</td>
<td>Yes</td>
<td>Yes (testing precocious puberty)</td>
<td>Yes</td>
<td>Yes</td>
<td>Discordant</td>
</tr>
<tr>
<td>Height</td>
<td>Yes</td>
<td>Yes (testing precocious puberty)</td>
<td>Yes</td>
<td>Yes</td>
<td>Discordant</td>
</tr>
<tr>
<td>Menstrual/pregnancy history</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Discordant</td>
</tr>
<tr>
<td>Inspection external genitals</td>
<td>No</td>
<td>Yes</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>FSH</td>
<td>Yes</td>
<td>Yes</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>LH</td>
<td>Yes</td>
<td>Yes</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Yes</td>
<td>Yes</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Discordant</td>
</tr>
<tr>
<td>At what frequency should surveillance be performed?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner staging (until sexually mature)</td>
<td>Every 1 year</td>
<td>Every visit (all survivors)</td>
<td>Every 0.5 year (all survivors); three to four times a year (if cranial RT)</td>
<td>Three to four times a year (if cranial RT)</td>
<td>Discordant</td>
</tr>
<tr>
<td>Height</td>
<td>Every 1 year until sexually mature (testing precocious puberty)</td>
<td>N/A</td>
<td>Every 0.5 year (all survivors, until growth spurt established; three to four times a year (if cranial RT)</td>
<td>N/A</td>
<td>Discordant</td>
</tr>
<tr>
<td>Weight</td>
<td>Every 1 year until sexually mature (testing precocious puberty)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Menstrual/pregnancy history</td>
<td>Every 1 year</td>
<td>Every visit (all survivors)</td>
<td>When appropriate</td>
<td>N/A</td>
<td>Discordant</td>
</tr>
<tr>
<td>Inspection external genitals</td>
<td>N/A</td>
<td>Every visit (all survivors, when sexually mature)</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>FSH</td>
<td>Baseline at age 13 years and as clinically indicated</td>
<td>As clinically indicated</td>
<td>N/A</td>
<td>N/A</td>
<td>Discordant</td>
</tr>
<tr>
<td>LH</td>
<td>Baseline at age 13 years and as clinically indicated</td>
<td>As clinically indicated</td>
<td>N/A</td>
<td>N/A</td>
<td>Discordant</td>
</tr>
</tbody>
</table>

(continued on following page)
suggests that women who are exposed to higher doses of alkylating agents have an increased risk of POI compared with patients who are treated with a lower dose.9,30,31 The different methods used to score a total alkylating agent dose precludes comparing doses and defining a threshold for ovarian dysfunction. In addition, no studies reported on the risk of POI in female survivors of CAYA cancer who were

<table>
<thead>
<tr>
<th>Table 1. Concordance and Discordance Among Premature Ovarian Insufficiency Surveillance Recommendations (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who needs premature ovarian insufficiency surveillance?</td>
</tr>
<tr>
<td>Estradiol Baseline at age 13 years and as clinically indicated</td>
</tr>
<tr>
<td>What should be done when abnormalities are identified?</td>
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<tr>
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</table>

Abbreviations: FSH, follicle-stimulating hormone; HCT, hematopoietic cell transplantation; LH, luteinizing hormone; MOPP, mustargen, oncovin, procarbazine, prednisone; RT, radiotherapy.
*Busulfan, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine (nitrogen mustard), melphalan, thiopeta, carmustine, lomustine.
†Radiotherapy exposing the ovaries: lumbar, sacral, whole spine, flank/hemiabdomen extending below iliac crest, whole abdomen, inverted Y, pelvic, vaginal, bladder, iliac, total lymphoid irradiation, total body irradiation.

Table 2. Conclusions of Evidence for POI Surveillance for Female Survivors of CAYA Cancer

<table>
<thead>
<tr>
<th>Who Needs Surveillance?</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>POI risk in survivors of CAYA cancer</td>
<td></td>
</tr>
<tr>
<td>Increased risk after alkylating agents v no alkylating agents</td>
<td>Level A9,29-31</td>
</tr>
<tr>
<td>Increased risk after higher alkylating agent dose v lower dose</td>
<td>Level A9,30,31</td>
</tr>
<tr>
<td>Increased risk after cyclophosphamide v no cyclophosphamide</td>
<td>Level C32</td>
</tr>
<tr>
<td>Increased risk after higher dose of cyclophosphamide v lower dose</td>
<td>No studies</td>
</tr>
<tr>
<td>Increased risk after procarbazine v no procarbazine</td>
<td>Level C32</td>
</tr>
<tr>
<td>Increased risk after higher dose of procarbazine v lower dose</td>
<td>No studies</td>
</tr>
<tr>
<td>Risk after multiple alkylating agents and other chemotherapeutic agents v single alkylating agents</td>
<td>No studies</td>
</tr>
<tr>
<td>Risk after other alkylating agents*</td>
<td>No studies</td>
</tr>
<tr>
<td>Risk after platinum agents†</td>
<td>No studies</td>
</tr>
<tr>
<td>Increased risk after radiotherapy to which ovaries are potentially exposed v no radiotherapy</td>
<td>Level A9,29-35</td>
</tr>
<tr>
<td>Increased risk after higher dose of radiotherapy to which ovaries are potentially exposed v lower dose</td>
<td>Level C32-34</td>
</tr>
<tr>
<td>Increased risk after radiotherapy to which ovaries are potentially exposed and alkylating agents v either treatment in the same dose alone</td>
<td>Level C32</td>
</tr>
<tr>
<td>Increased risk after treatment at older age v younger age</td>
<td>Level B9,29,35</td>
</tr>
<tr>
<td>Risk after unilateral oophorectomy</td>
<td>No studies</td>
</tr>
</tbody>
</table>

What surveillance should be used?
Diagnostic value of endocrine measurement and ovarian ultrasound to detect POI in survivors of CAYA cancer
Diagnostic value of AMH | No studies |
Diagnostic value of antral follicle count | No studies |
Prognostic value of endocrine measurements and ovarian ultrasound to predict POI in survivors of CAYA cancer
Prognostic value of FSH | No studies |
Prognostic value of estradiol | No studies |
Prognostic value of AMH | No studies |
Prognostic value of antral follicle count | No studies |
Diagnostic value of endocrine measurements to detect POI in the general population
Diagnostic value of AMH | No studies |
Prognostic value of endocrine measurements to predict POI in the general population
Prognostic value of AMH | No studies |
Prognostic value of endocrine measurements to predict menopause and ovarian reserve in the general population
AMH predicts time to menopause | Expert opinion36 |
AMH correlates with ovarian reserve | Expert opinion37-40 |
At what frequency should surveillance be performed?
POI risk in survivors of CAYA cancer
Changes in POI risk (deterioration or recovery of gonadal function) during the fertile life span | No studies |

Abbreviations: AMH, anti-Müllerian hormone; CAYA, childhood, adolescent, and young adult; FSH, follicle-stimulating hormone; Level A, high level of evidence; Level B, moderate/low level of evidence; Level C, very low level of evidence; POI, premature ovarian insufficiency.
*Busulfan, chlorambucil, mechloretamine, ifosfamide, melphalan, thiopeta, carmustine, lomustine.
†Carboplatin and cisplatin.
<table>
<thead>
<tr>
<th>General recommendation</th>
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<tbody>
<tr>
<td>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).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Who needs surveillance?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counselling regarding the risk of premature ovarian insufficiency and its implications for future fertility is recommended for survivors treated with:</td>
</tr>
<tr>
<td>- Alkylating agents in general (level A evidence)</td>
</tr>
<tr>
<td>- Cyclophosphamide and procarbazine (level C evidence)</td>
</tr>
<tr>
<td>- Radiotherapy potentially exposing the ovaries (level A evidence)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What surveillance modality should be used for pre- and peri-pubertal survivors?</th>
</tr>
</thead>
<tbody>
<tr>
<td>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/no literature search).</td>
</tr>
<tr>
<td>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/no literature search).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What surveillance modality should be used for post-pubertal survivors?</th>
</tr>
</thead>
<tbody>
<tr>
<td>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/no literature search).</td>
</tr>
<tr>
<td>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/no studies).</td>
</tr>
<tr>
<td>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/no studies).</td>
</tr>
<tr>
<td>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 ≥26 years who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency or who desire assessment about potential future fertility (expert opinion/no studies).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>When should pre- and peri-pubertal survivors be referred?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral to paediatric endocrinology/gynaecology is recommended for any survivor who has:</td>
</tr>
<tr>
<td>- No signs of puberty by 13 years of age.</td>
</tr>
<tr>
<td>- Primary amenorrhoea by 16 years of age.</td>
</tr>
<tr>
<td>- Failure of pubertal progression.† (expert opinion/no literature search)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>When should post-pubertal survivors be referred?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral to gynaecology/reproductive medicine/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/no literature search).</td>
</tr>
<tr>
<td>What should be done when abnormalities are identified in pre-, peri- and post-pubertal survivors?</td>
</tr>
<tr>
<td>Consideration of sex steroid replacement therapy is recommended for pre-, peri- and post-pubertal survivors diagnosed with premature ovarian insufficiency by referral to gynaecology/endocrinology (expert opinion/no literature search).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What should be done when potential for future fertility is questioned?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral to gynaecology/reproductive medicine/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/no literature search).</td>
</tr>
</tbody>
</table>

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Fig 1. Harmonized recommendations for POI surveillance in survivors of CAYA cancer. Premature ovarian insufficiency (POI) is defined as a clinical condition developing in any adult female before age 40 years that is characterized by the absence of menses for ≥4 months and two elevated serum follicle-stimulating hormone (FSH) levels in the menopausal range (on the basis of the maximum threshold of the laboratory assay used). *Treatments with evidence of causing POI include alkylating agents in general (level A evidence), cyclophosphamide, procarbazine (level C evidence), and radiotherapy to a field that includes 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 pills/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. AMH, anti-Müllerian hormone; CAYA, childhood, adolescent, and young adult; Level A, high level of evidence; Level B, moderate/low level of evidence; Level C, very low level of evidence.
treated with a combination of alkylating agents and other chemo-
therapeutic agents compared with single agent chemotherapy. We did
not identify studies that assessed the effects of platinum agents on
gonadal function in female survivors of CAYA cancer. As a result, no
recommendations could be made regarding surveillance after treat-
ment with platinum agents in the absence of other alkylating agents.

Women who were treated with radiotherapy to which the
ovaries were potentially exposed are also at an increased risk for
developing POI.9,29-35 This risk is especially high for women who
were treated with higher doses, but a clear threshold for a safe
radiotherapy dose could not be defined.30,32-34 Mathematic mod¬
elling on the basis of data on the rate of oocyte decline suggests that the
effective sterilizing dose is 20.3 Gy in infants, 18.4 Gy at age 10 years,
and 16.5 Gy at age 20 years (Fig 2).41 Moreover, some evidence from
one study suggests that treatment with a combination of alkylating
agents and radiotherapy to which the ovaries are potentially exposed
increases the risk of POI compared with each of these treatments with
the same dose alone (Fig 3).9 On the basis of the available evi¬
dence, female survivors of CAYA cancer who were treated with
alkylating agents and/or radiotherapy to which the ovaries were
potentially exposed and their health care providers should be
aware of the risk of POI and its implications for future fertility
(strong recommendation). Consequently, counseling regarding
the risk of POI and its implications for future fertility is rec¬
ommended for these females (strong recommendation).

Whereas some studies have reported that the age of treatment
had no influence on POI,9,42,43 other studies have found an increased
risk of POI in individuals who were treated at an older age.29,35 The
inverse relationship of radiation dose to age is likely a consequence of the
decline in the primordial follicle pool observed with advancing age.32,33 As a result of the inconsistency of the literature, no rec¬
ommendations could be made regarding surveillance intensity by
age at which cancer treatment was started.

Obviously, bilateral oophorectomy results in POI and, therefore,
surveillance is unnecessary, but counseling by a health professional is
mandatory in view of the POI consequences. We did not identify
studies that investigated the association between unilateral oopho¬
rectomy and POI. Some evidence in survivors of childhood cancer
and women in the general population showed a limited effect of
unilateral oophorectomy on anti-Müllerian hormone (AMH) levels
and earlier age at menopause.44,45 Because of the lack of evidence, no
recommendations could be formulated regarding surveillance after
treatment with unilateral oophorectomy.

What Surveillance Modality Should Be Used?
The existing guidelines were concordant with the use of a
detailed menstrual history and physical examination, with specific
attention given to the failure to initiate or progress through puberty
and POI symptoms such as hot flashes. Of importance, because
POI presents with primary or secondary amenorrhea, standard
laboratory evaluation is not recommended as a form of primary
surveillance in at-risk female survivors without any symptoms
of POI. The monotropic rise in FSH is the hallmark of the men¬
opausal transition46; thus, FSH is important for diagnosing POI.24,47
Antral follicle count (AFC) by transvaginal ultrasound is the most
established method for assessing ovarian reserve in adult women,
but is not part of the current clinical criteria of POI.48,49 In survivors
of childhood cancer, the additive value of AFC on the current clinical
criteria of POI has not been studied.

AMH has been used as a marker of ovarian reserve37,50-52; how¬
ever, there are no studies that describe the value of AMH in the
diagnosis of POI in both survivors of childhood cancer and the
general population. In healthy women, AMH represents the best
endocrine marker to assess the age-related decline in ovarian reserve,53
although a recent validated model of AMH throughout life describes a
transition period in early adult life.38 Previous studies have found that
AMH is correlated with AFC in the general population.37-39 Unlike
FSH and estradiol, the majority of studies indicate that AMH is
relatively stable through the menstrual cycle.54-57 A recent analysis by

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**Fig 2.** The effective (shown in blue) steriliz¬
ing doses of radiation are illustrated for a
known age at treatment. Above the gold/blue
boundary, doses to the ovary will cause
immediate POI for most patients due to
depletion of the non-growing follicle pop¬
ulation to below 1,000. Reprinted with per¬
mission from Anderson et al.41
recommendation). This assessment should be performed after or laboratory evaluation of FSH and estradiol is recommended (strong POI or who desire assessment of potential future fertility, lab-

present with menstrual cycle dysfunction that is suggestive of development of POI (strong recommendation). In females who example, amenorrhea, but also irregular cycles as a examination, with speci-

agents and/or radiotherapy to which the ovaries were potentially exposed, we recommend detailed menstrual history and physical examination, with specific attention paid to POI symptoms, for example, amenorrhea, but also irregular cycles as a first sign of the development of POI (strong recommendation). In females who present with menstrual cycle dysfunction that is suggestive of POI or who desire assessment of potential future fertility, laboratory evaluation of FSH and estradiol is recommended (strong recommendation). This assessment should be performed after discontinuing sex steroid hormone replacement or contraceptive hormone therapy when applicable, with careful advice to prevent unwanted pregnancy. The evidence is conflicting on how long a female should discontinue sex steroids before ovarian function is assessed. We have therefore not made a firm recommendation as to how long sex steroids should be omitted before testing, but for practical purposes we would recommend ≥ 2 months. In the case of amenorrhea, FSH and estradiol can be measured at any time. In the case of oligomenorrhea, FSH and estradiol should be measured, ideally, during early follicular phase (days 2 to 5). In addition, AMH is not recommended as the primary surveillance modality for evaluation of POI in survivors of CAYA cancer; however, on the basis of evidence in the general population, laboratory evaluation of AMH in conjunction with FSH and estradiol may be reasonable for the identification of POI in at-risk survivors age ≥ 25 years who present with menstrual cycle dysfunction that is suggestive of POI or who desire assessment of potential future fertility (weak recommendation).

At What Frequency and For How Long Should Surveillance Be Performed?

Data to support changes in POI risk during the fertile life span is lacking in female survivors of CAYA cancer; therefore, recommendations regarding the initiation and frequency of surveillance are largely based on the consensus of multidisciplinary late effects experts. For postpubertal females, surveillance by laboratory evaluation should only be performed on the basis of clinical indication or when the patient desires assessment of potential future fertility.

In the general population, girls initiate puberty, on average, between the age of 8 and 10 years. Of importance, puberty initiation varies by race and ethnicity. By age 11 years, most girls have Tanner stage 2 breast development. The working group has

Overbeek et al has described possibly significant fluctuations in AMH throughout the menstrual cycle, in particular, in young women. It is clear that in patients age ≥ 25 years, AMH is inversely correlated with increasing age, which implies that AMH may be a clinically useful marker of ovarian reserve in these women. There is a wide range of AMH levels in healthy young adult women, but low AMH levels are indicative of incipient ovarian insufficiency. AMH may be of additive value for survivors of childhood cancer who were treated with alkylating agents and/or radiotherapy to which the ovaries were potentially exposed, but if assessed before age 25 years, one should exercise extra caution when interpreting AMH values.

On the basis of the evidence and consensus, the working group has agreed that for at-risk pre- and peripubertal survivors, the monitoring of growth and pubertal development and progression is recommended (strong recommendation). Laboratory evaluation of FSH and estradiol is recommended for prepubertal girls who experience a failure to initiate or progress through puberty normally as part of the current clinical criteria of POI (strong recommendation).

For postpubertal females who were treated with alkylating agents and/or radiotherapy to which the ovaries were potentially exposed, we recommend detailed menstrual history and physical examination, with specific attention paid to POI symptoms, for example, amenorrhea, but also irregular cycles as a first sign of the development of POI (strong recommendation). In females who present with menstrual cycle dysfunction that is suggestive of POI or who desire assessment of potential future fertility, laboratory evaluation of FSH and estradiol is recommended (strong recommendation). This assessment should be performed after

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Fig 3. The cumulative incidence of nonsurgical menopause in female survivors of childhood cancer demonstrating increasing incidence of menopause with advancing age and relationship to gonadotoxic cancer therapy. (A) Treatment with alkylating agents (AA); (B) treatment with abdominal-pelvic radiotherapy (A-P RT) only; and (C) treatment with AA plus A-P RT, which was associated with the highest incidence. NOTE. Study cohort does not include females who developed ovarian failure within the first 5 years. Reprinted with permission from Sklar et al.
agreed that surveillance should be performed at least annually, with increasing frequency as clinically indicated on the basis of growth and pubertal progress as measured by physical examination. Moreover, it is recommended that, for prepubertal females age ≥ 11 years who experience a failure to initiate or progress through puberty, laboratory evaluation should be performed. No recommendations could be made for how long surveillance should be performed.

When Should Survivors Be Referred and What Should Be Done When Abnormalities Are Identified?

The recommendations outlined in this article are for primary surveillance rather than for treatment options; however, because of the health problems induced by estrogen deprivation in patients with POI in the general population, it is important to consider sex hormone replacement therapy for survivors of CAYA cancer with POI because of its benefit to sexual function, bone health, and cardiovascular health. Although POI reduces the risk of radiation-associated breast cancer, the harms of sex steroid replacement therapy on breast cancer risk and the risk of other secondary malignancies in survivors of CAYA cancer is not yet known.

Because the recommendations outlined in this article are for primary surveillance, they do not address all the investigatory steps necessary for the diagnosis of POI, such as excluding Turner syndrome or other causes of ovarian insufficiency. As such, endocrinology and gynecology consultation is recommended for prepubertal females who have no signs of puberty by age 13 years and with elevated FSH levels at laboratory screening, primary amenorrhea by age 16 years in the presence of other evidence of puberty, or who experience a failure to initiate or progress through puberty (strong recommendation). For postpubertal females who were treated with alkylating agents and/or radiotherapy to which the ovaries were potentially exposed and who present with menstrual cycle dysfunction that is suggestive of POI, gynecology, endocrinology, and/or reproductive endocrinology consultation is recommended (strong recommendation). In addition, the working group recommends gynecology and endocrinology referral of all survivors who are diagnosed with POI for the consideration of sex steroid replacement therapy and its potential harms and benefits (strong recommendation).

What Should Be Done When Potential For Future Fertility Is Questioned?

Assessment of the ovarian reserve is important in estimating future fertility. Ovarian reserve is a term used to determine the capacity of the ovary to produce mature eggs that are capable of fertilization. The human ovary is believed to contain a finite population of primordial follicles. At 18 to 22 weeks postconception, the female ovary contains its peak number of follicles, approximately 300,000 in the average case, but individual peak populations range from 35,000 to 2.5 million. Direct measurement of the ovarian reserve is not possible, and methods to directly determine the number of primordial follicles have yet to be identified. The size of the primordial follicle pool is reflected by the number of early, growing follicles. AMH is a product of these growing ovarian follicles and can be reliably used as an indirect marker of the ovarian reserve in women age ≥ 25 years. There is evidence for reduced AMH levels in survivors of CAYA cancer who were treated with alkylating agents and/or radiotherapy to which the ovaries were potentially exposed.

Although POI presents with amenorrhea, survivors with regular menstrual cycles who were treated with gonadotoxic therapy are still at risk for a decreased ovarian reserve and may therefore be at risk for reduced fertility. At-risk postpubertal females without signs and symptoms of POI who desire assessment of the potential for future fertility should be referred for gynecology, endocrinology, and/or reproductive endocrinology consultation (strong recommendation).

In female survivors of CAYA cancer, gonadal dysfunction is one of the most prevalent long-term adverse effects of treatment that includes alkylating agents and radiotherapy to which the ovaries are potentially exposed. Compelling evidence suggests that female survivors of CAYA cancer who were treated with alkylating agents and/or radiotherapy to which the ovaries are potentially exposed are at an increased risk of POI; however, there is no clear evidence to indicate which type of alkylating agent chemotherapy increases the risk. Although there is evidence that a higher treatment dose is associated with an increased risk of POI, there is virtually no information regarding a safe threshold dose. This, at least in part, might be explained by the complexity of factors that influence the ovarian reserve.

Important limitations of previous studies on the impact of alkylating agents and radiotherapy doses include the use of different scoring models, which preclude the comparison of study results. To effectively estimate POI risk as it relates to radiotherapy, the exact dose received by the ovaries should be on the basis of accurate dosimetry derived from information of the total dose and the specific radiotherapy technology. So far, most literature, and, therefore, our conclusions, are based on studies that include survivors who were treated in eras during which dosimetry was not easily achievable. Therefore, we recommend that future studies use consistent methods to comprehensively calculate treatment doses, including modern radiotherapy dose-volume histograms.

Elaborating on the latter, some survivors develop POI at relatively low gonadotoxic treatment doses and others do not seem to be affected, which suggests that other factors, such as the age of a patient at treatment, cumulative chemotherapy and radiotherapy dose, combinations of these modalities, and genetic variation may play a role in the pretreatment primordial follicle pool. In both the general population and in survivors of childhood cancer, poly-morphisms have been associated with post-treatment ovarian reserve, even independently from the administered gonadotoxic cancer treatment. Genetic variation, when further elucidated, could advance our understanding of the pathogenesis of treatment-related POI and may improve patient-tailored counseling and surveillance throughout life.

There is agreement across previously published long-term follow-up guidelines that POI surveillance should include Tanner stage and menstrual history. In the case of clinical symptoms of POI, such as irregular menstrual cycles, we recommend laboratory evaluation with FSH and estradiol. Because these markers vary throughout the menstrual cycle and are affected by hormonal contraceptive therapy and sex steroid replacement therapy, testing should be performed during the early follicular phase in survivors.
who are still menstruating and who are not using such hormonal therapy that may mask the diagnosis. Less is known about the diagnostic and predictive value of AFC and AMH levels for diagnosing POI in survivors of CAYA cancer. Neither AFC nor AMH are part of the definition of POI; however, they may become increasingly important in the prediction of the early decrease in ovarian reserve and the development of POI as FSH remains a late marker of ovarian dysfunction.77

AMH shows promise as a predictor of ovarian reserve and the timing of the onset of menopause in adult patients with cancer. Studies in survivors of CAYA cancer are needed to establish predictive value in estimating POI and fertility by correlation with AFC, pregnancy, and time to pregnancy. In the general population, AMH rises to a peak at approximately age 25 years,38 and there is no evidence that we are aware of that a low AMH indicates reduced fertility or low ovarian reserve.77

Table 3. Gaps in Knowledge and Future Directions for Research

<table>
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<tr>
<th>Knowledge Gap</th>
<th>Abbreviations: AFC, antral follicle count; AMH, anti-Müllerian hormone; CAYA, childhood, adolescent, and young adult; FSH, follicle-stimulating hormone; HRT, hormone replacement therapy; POI, premature ovarian insufficiency.</th>
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<tr>
<td>Effect of different types of alkylating agent chemotherapy on the risk of POI in female survivors of CAYA cancer</td>
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<td>Safe alkylating agents dose with regard to the risk of POI in female survivors of CAYA cancer</td>
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<td>Safe radiotherapy dose to which the ovaries are potentially exposed with regard to the risk of POI in female survivors of CAYA cancer</td>
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<td>Diagnostic value of AMH to detect POI in female survivors of CAYA cancer</td>
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<td>Prognostic value of AMH to predict POI in female survivors of CAYA cancer</td>
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<td>Lifetime risk of POI in survivors of CAYA cancer treated with alkylating agents and/or radiotherapy to which the ovaries are potentially exposed</td>
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<td>Potential recovery of ovarian dysfunction in female survivors of CAYA cancer treated with alkylating agents and/or radiotherapy to which the ovaries are potentially exposed</td>
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<td>Risk of secondary malignancies in female survivors of CAYA cancer treated with HRT</td>
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<td>Risk of secondary malignancies in female survivors of CAYA cancer using HRT and treated with radiotherapy to which the breasts are potentially exposed</td>
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<tr>
<td>Examination of the role of genetic susceptibility on subsequent POI risk in survivors of CAYA cancer treated with alkylating agents and/or radiotherapy to which the ovaries are potentially exposed</td>
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</table>

The highlighting of a research agenda by identifying key gaps in knowledge is an important result of the harmonization process (Table 3). The agenda may serve as the impetus for collaborative research aimed at improving POI surveillance and care of at-risk survivors of CAYA cancer. According to our findings, future studies should focus on the identification of threshold doses of both alkylating agents and radiotherapy to which the ovaries are potentially exposed, the effect of different types of alkylating agent chemotherapy, and the influence of other determinants such as genetic variation, which should finally be integrated into a risk model. Furthermore, the prognostic and predictive value of AFC and AMH for the diagnosis of POI after childhood cancer has not been established. Longitudinal studies are recommended to identify the effect of both markers. Another important topic that needs to be addressed is central hypogonadism. As mentioned, this was not included in this guideline because it will be evaluated in a future IGHG/PCSF guideline on pituitary dysfunction.

This POI surveillance harmonization endeavor was strengthened by our evidence-based approach, reliance on standardized definitions for outcomes of interest, transparent presentation of the quality of the available evidence and the strength of recommendations, and the multidisciplinary approach necessary to derive a consensus for surveillance. Of importance, we identified key gaps in the knowledge regarding safe alkylating agent and radiotherapy dose thresholds as well as for optimal surveillance frequency and modalities. These gaps should be approached in a systematic, comprehensive manner, preferably by internationally guided efforts and collaborative opportunities under the umbrella of international groups, such as International Society of Pediatric Oncology and PanCare.21,79,80

The implementation of the harmonized recommendations will be an ongoing process. Countries with or without existing long-term follow-up guidelines for survivors of CAYA cancer can use the current harmonized guidelines as a basis for an evidence-based national policy. The current international guideline harmonization effort was developed to increase collaborative research to ultimately optimize the quality of care for and minimize the burden of disease of survivors of CAYA cancer.
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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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