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 multi-disciplinary 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.

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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.¹⁻⁴ As a result of the increasing numbers of survivors, late health outcomes research has demonstrated that a significant proportion of survivors experience chronic health sequelae that result from cancer, its treatment,

or both.⁵⁻⁷ A prominent concern is the substantially elevated risk of ovarian dysfunction among female survivors who were treated with alkylating agents and/or radiotherapy.⁸

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.⁹ 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.¹⁰ 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.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.¹⁵⁻¹⁹ 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.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.²¹

PATIENTS AND METHODS

Detailed information regarding the international guideline harmonization effort and methodology has been previously presented.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.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).²² 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).²³ 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 months²⁴ or primary amenorrhea by age 16 years. Irregular menstrual cycles were defined as cycles < 21 days or cycles > 35 days.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/hemiabdomen 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 Group²⁶ and the IGHG²⁰ 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.^{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.^{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 POI³²; 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

Who needs premature ovarian insufficiency surveillance?	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Scottish Intercollegiate Guidelines Network	Concordant/Discordant
At risk		All survivors			
Alkylating agents*	Yes	Not specified	Yes	Yes	Discordant
Procarbazine	Yes	Not specified	Yes	Yes	Discordant
Temozolomide plus dacarbazine	Yes	Not specified	Yes	Not specified	Discordant
Cytarabine	Not specified	Not specified	Yes	Not specified	Discordant
Carboplatin plus cisplatin	Yes	Not specified	Yes	Not specified	Discordant
RT exposing ovaries†	Yes	Not specified	Yes	Yes	Discordant
Oophorectomy	Yes	Not specified	Not specified	Not specified	Discordant
Highest risk					
Higher doses of alkylating agents	Yes	Not specified	Not specified	Not specified	Discordant
Alkylating agent dose	MOPP ≥ 3 cycles; busulfan ≥ 600 mg/m ² ; cyclophosphamide ≥ 7.5 g/m ² ; cyclophosphamide for HCT; ifosfamide ≥ 60 g/m ²	Not specified	Not specified	Not specified	Discordant
Combination alkylating agents	Yes	Not specified	Not specified	Not specified	Discordant
Higher doses of RT exposing ovaries	Yes	Not specified	Not specified	Not specified	Discordant
RT dose	One prepubertal: ≥ 10-15 Gy RT ovaries; pubertal: ≥ 5-10 Gy RT ovaries	Not specified	Not specified	Not specified	Discordant
Alkylating agents plus RT exposing ovaries	Yes	Not specified	Not specified	Not specified	Discordant
Unilateral oophorectomy plus RT exposing ovaries/alkylating agents	Yes	Not specified	Not specified	Not specified	Discordant
Bilateral oophorectomy	Yes	Not specified	Not specified	Not specified	Discordant
What surveillance modality should be used?					
Tanner staging	Yes	Yes	Yes	Yes	Concordant
Height	Yes (testing precocious puberty)	General recommendation	Yes	General recommendation	Discordant
Menstrual/pregnancy history	Yes	Yes	Yes	Not specified	Discordant
Inspection external genitals	No	Yes	Not specified	Not specified	Discordant
FSH	Yes	Yes	Not specified	Not specified	Discordant
LH	Yes	Yes	Not specified	Not specified	Discordant
Estradiol	Yes	Yes	Not specified	Not specified	Discordant
At what frequency should surveillance be performed?					
Tanner staging (until sexually mature)	Every 1 year	Every visit (all survivors)	Every 0.5 year (all survivors); three to four times a year (if cranial RT)	Three to four times a year (if cranial RT)	Discordant
Height	Every 1 year until sexually mature (testing precocious puberty)	N/A	Every 0.5 year (all survivors, until growth spurt established); three to four times a year (if cranial RT)	N/A	Discordant
Weight	Every 1 year until sexually mature (testing precocious puberty)	N/A	N/A	N/A	N/A
Menstrual/pregnancy history	Every 1 year	Every visit (all survivors)	When appropriate	N/A	Discordant
Inspection external genitals	N/A	Every visit (all survivors, when sexually mature)	N/A	N/A	N/A
FSH	Baseline at age 13 years and as clinically indicated	As clinically indicated	N/A	N/A	Discordant
LH	Baseline at age 13 years and as clinically indicated	As clinically indicated	N/A	N/A	Discordant

(continued on following page)

Table 1. Concordance and Discordance Among Premature Ovarian Insufficiency Surveillance Recommendations (continued)

Who needs premature ovarian insufficiency surveillance?	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Scottish Intercollegiate Guidelines Network	Concordant/Discordant
Estradiol	Baseline at age 13 years and as clinically indicated	As clinically indicated	N/A	N/A	Discordant
What should be done when abnormalities are identified?					
Refer to specialist	Yes	Yes	Yes	Yes	Concordant
Consider hormonal therapy	Yes	Yes	Yes	Yes	Concordant
Consider assisted reproductive technology	Yes	Not specified	Yes	Yes	Discordant

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, thiotepa, 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.

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

Who Needs Surveillance?	Level
POI risk in survivors of CAYA cancer	
Increased risk after alkylating agents v no alkylating agents	Level A ^{9,29-31}
Increased risk after higher alkylating agent dose v lower dose	Level A ^{9,30,31}
Increased risk after cyclophosphamide v no cyclophosphamide	Level C ³²
Increased risk after higher cyclophosphamide dose v lower dose	No studies
Increased risk after procarbazine v no procarbazine	Level C ³²
Increased risk after higher procarbazine dose v lower dose	No studies
Risk after multiple alkylating agents and other chemotherapeutic agents v single alkylating agents	No studies
Risk after other alkylating agents*	No studies
Risk after platinum agents†	No studies
Increased risk after radiotherapy to which ovaries are potentially exposed v no radiotherapy	Level A ^{9,29-35}
Increased risk after higher dose of radiotherapy to which ovaries are potentially exposed v lower dose	Level A ^{30,32-34}
Increased risk after radiotherapy to which ovaries are potentially exposed and alkylating agents v either treatment in the same dose alone	Level C ⁹
Increased risk after treatment at older age v younger age	Level B ^{9,29,35}
Risk after unilateral oophorectomy	No studies
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 opinion ³⁶
AMH correlates with ovarian reserve	Expert opinion ³⁷⁻⁴⁰
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, mechlorethamine, ifosfamide, melphalan, thiotepa, carmustine, lomustine.
 †Carboplatin and cisplatin.

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 <i>is recommended</i> for survivors treated with: <ul style="list-style-type: none"> 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) <i>is recommended</i> for pre-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries (expert opinion/no literature search). ^{††}
FSH and oestradiol <i>are recommended</i> 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). ^{‡§}
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 <i>is recommended</i> for post-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries (expert opinion/no literature search).*
FSH and oestradiol <i>are recommended</i> 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). [¶]
AMH <i>is not recommended</i> as the <i>primary surveillance modality</i> 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).
AMH <i>may be reasonable</i> 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/no studies).
When should pre- and peri-pubertal survivors be referred?
Referral to paediatric endocrinology / gynaecology <i>is recommended</i> for any survivor who has <ul style="list-style-type: none"> No signs of puberty by 13 years of age. Primary amenorrhoea by 16 years of age. Failure of pubertal progression.[‡] (expert opinion/no literature search)
When should post-pubertal survivors be referred?
Referral to gynaecology / reproductive medicine / endocrinology (according to local referral pathways) <i>is recommended</i> 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).
What should be done when abnormalities are identified in pre-, peri- and post-pubertal survivors?
Consideration of sex steroid replacement therapy <i>is recommended</i> for pre-, peri- and post-pubertal survivors diagnosed with premature ovarian insufficiency <i>by referral to gynaecology/ endocrinology</i> (expert opinion/no literature search).
What should be done when potential for future fertility is questioned?
Referral to gynaecology / reproductive medicine / endocrinology (according to local referral pathways) <i>is recommended</i> 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).

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 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. 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 chemotherapeutic 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 treatment 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 modeling 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 evidence, 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 recommended 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 recommendations 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 oophorectomy 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 menopausal 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 reserve^{37,50-52}; however, 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

Fig 2. The effective (shown in blue) sterilizing 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 population to below 1,000. Reprinted with permission from Anderson et al.⁴¹

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.⁹

Overbeek et al³⁶ 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.^{37,58,59} There is a wide range of AMH levels in healthy young adult women, but low AMH levels are indicative of incipient ovarian insufficiency.⁴⁷ In survivors of childhood cancer, AMH has been frequently used as marker of ovarian reserve^{42,49,60,61} and may be useful to distinguish women with POI who have little to no follicles remaining from those who are at risk for POI but still have a reasonably sized follicle pool ($\text{AFC} \geq 3$).⁴⁷ AMH may be of additive value for survivors of CAYA 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

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.^{62,63} Of importance, puberty initiation varies by race and ethnicity.⁶² By age 11 years, most girls have Tanner stage 2 breast development. The working group has

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,⁶⁴ and cardiovascular health.⁶⁵ Although POI reduces the risk of radiation-associated breast cancer,^{66,67} 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 investigative 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.⁶⁸ Direct measurement of the ovarian reserve is not possible, and methods to directly determine the number of primordial follicles have yet to be identified.⁴⁷ 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.^{37,38,58} 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.^{49,69-72}

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).

DISCUSSION

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 population⁷³⁻⁷⁶ and in survivors of childhood cancer,⁶⁰ polymorphisms 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

Table 3. Gaps in Knowledge and Future Directions for Research

Knowledge Gap
Effect of different types of alkylating agent chemotherapy on the risk of POI in female survivors of CAYA cancer
Safe alkylating agents dose with regard to the risk of POI in female survivors of CAYA cancer
Safe radiotherapy dose to which the ovaries are potentially exposed with regard to the risk of POI in female survivors of CAYA cancer
Diagnostic value of AMH to detect POI in female survivors of CAYA cancer
Prognostic value of AMH to predict POI in female survivors of CAYA cancer
Diagnostic value of AFC to detect POI in female survivors of CAYA cancer
Prognostic value of AFC to predict POI in female survivors of CAYA cancer
Prognostic value of FSH and estradiol to predict POI in female survivors of CAYA cancer
Lifetime risk of POI in survivors of CAYA cancer treated with alkylating agents and/or radiotherapy to which the ovaries are potentially exposed
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
Use of FSH, estradiol, AFC, and AMH in the prediction of fertility in female survivors of CAYA cancer
Efficacy of oral v transdermal estrogen replacement for puberty induction on final height and sexual development in female survivors of CAYA cancer with gonadal failure
Efficacy of oral v transdermal hormone replacement therapy on bone health, cardiovascular health, and mental health in female survivors of CAYA cancer with POI
Risk of secondary malignancies in female survivors of CAYA cancer treated with HRT
Risk of secondary malignancies in female survivors of CAYA cancer using HRT and treated with radiotherapy to which the breasts are potentially exposed
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

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.

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 its 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 in females age < 25 years. Thus far, data do not support routine AMH testing for preconception counseling in young, fecund women⁷⁸; therefore, on the basis of the currently available data, the recommendation for AMH testing is more tempered (may be reasonable) and limited to women of age ≥ 25 years for whom validated normative data are available.

There is agreement across previously published guidelines that referral to the appropriate specialist (pediatric endocrinologist and/or gynecologist in prepubertal; gynecologist and/or reproductive endocrinologist in postpubertal) is recommended if abnormalities are found during POI surveillance. When POI has been diagnosed, sex steroid therapy may be necessary to initiate and complete progression through puberty, and in the postpubertal survivor ongoing hormone-replacement therapy offers potential benefits to sexual function, bone health, and cardiovascular health.^{64,65}

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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Disclosures provided by the authors are available with this article at www.jco.org.

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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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