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## Communication and ethical considerations for fertility preservation for patients with childhood, adolescent, and young adult cancer

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## Fertility Preservation in Childhood, Adolescent, and Young Adult Cancer 3

### Communication and ethical considerations for fertility preservation for patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group

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Patients with childhood, adolescent, and young adult cancer who will be treated with gonadotoxic therapies are at increased risk for infertility. Many patients and their families desire biological children but effective communication about treatment-related infertility risk and procedures for fertility preservation does not always happen. The PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group reviewed the literature and developed a clinical practice guideline that provides recommendations for ongoing communication methods for fertility preservation for patients who were diagnosed with childhood, adolescent, and young adult cancer at age 25 years or younger and their families. Moreover, the guideline panel formulated considerations of the ethical implications that are associated with these procedures. Grading of Recommendations Assessment, Development and Evaluation methodology was used to grade the evidence and recommendations. In this clinical practice guideline, existing evidence and international expertise are combined to develop transparent recommendations that are easy to use to facilitate ongoing communication between health-care providers and patients with childhood, adolescent, and young adult cancer who might be at high risk for fertility impairment and their families.

#### Introduction

Damage to the reproductive organs as a result of cancer treatment in patients with childhood, adolescent, and young adult (CAYA) cancer (ie, diagnosed aged  $\leq 25$  years) can affect future fertility. With current 5-year survival rates exceeding 80% in the USA and Europe for patients with CAYA cancer,<sup>1,2</sup> many patients who are treated with gonadotoxic therapy could have subfertility and hypogonadism.<sup>3,4</sup>

Provision of information and ongoing communication about infertility risk and existing procedures for fertility preservation is essential to support patients and their families in making informed decisions about fertility preservation.<sup>5</sup> Although health-care professionals have increasingly recognised the importance of fertility preservation and have introduced counselling about fertility preservation as part of patient management,<sup>6-8</sup> communication about treatment-related infertility risk and methods for fertility preservation are suboptimal for many patients and their families.<sup>9</sup> With fertility

preservation being a primary concern for survivors of cancer,<sup>10-13</sup> barriers to communicating the options for fertility preservation are of importance.

Evidence-based and uniform guidance for the provision of information and ongoing communication is needed about treatment-related infertility risk and fertility preservation between health-care providers and patients and their families. Furthermore, fertility preservation raises important ethical issues (eg, counselling with minors, counselling about experimental procedures, and posthumous use of stored gametes) that are not always covered in detail in existing clinical practice guidelines (CPGs).<sup>14</sup> Existing CPGs are not always produced by use of high-quality methodologies and do not uniformly address communication and ethical issues that are associated with fertility preservation.<sup>14</sup> The EU-funded project, PanCareLIFE, recognised the need for global consensus on fertility preservation and established an international effort to develop transparent CPGs for fertility preservation in patients with CAYA cancer in collaboration with the

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This is the third in a Series of three papers about fertility preservation in childhood, adolescent, and young adult cancer

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We provide a systematic review and recommendations for ongoing communication about treatment-related infertility risk and fertility preservation in patients with CAYA cancer, including guidance on the ethical implications that are associated with these procedures.

## Data collection

### Guideline panel formation

A multidisciplinary panel of 38 international specialists in paediatric oncology and haematology, radiation oncology, endocrinology (including paediatric endocrinology), reproductive medicine, gynaecology, nursing, psychology, psycho-oncology, oncofertility, ethics, epidemiology, and guideline methodology was convened (appendix pp 1–2). Members of the panel were selected (by MMH, LBK, MDvdW, LCMK, JL, and WJET) because of their experience, publications, and knowledge in the fields of paediatric and reproductive medicine, psychology, and ethics. An overview of the process and structure of guideline development is presented in the appendix (appendix pp 4–5).

### Scope and definitions

The aim of this CPG is to help health-care providers to communicate the potential risk for infertility and options for fertility preservation on an ongoing basis to patients who are diagnosed with childhood cancer tumour types aged 25 years or younger and to their parents, caregivers, or partners (hereafter referred to as families), while taking into account the ethical implications that are associated with these procedures.

### Systematic literature review

The experts formulated clinical questions covering the following key issues: what are the facilitators of and barriers to communication of treatment-related infertility risk and options for fertility preservation, and what are the ethical considerations related to fertility preservation (appendix p 6). Formulation of clinical questions was based on discordant areas in recommendations that were identified in existing CPGs for fertility preservation in patients with CAYA cancer, as described by Font-Gonzalez and colleagues,<sup>14</sup> and on controversial issues that were identified within the guideline panel from discussions between panel members. Full details on the search strategies and inclusion criteria that were used to answer each clinical question are provided in the (appendix pp 7–10).

### Search strategy and selection criteria

We did systematic literature searches in collaboration with Cochrane Childhood Cancer. We searched MEDLINE (through PubMed) for literature that was published between Jan 1, 1993, and Feb 21, 2020, using combinations of the search terms “childhood cancer”,

“fertility preservation”, “attitudes”, “beliefs”, “decision making”, “communication”, “barriers”, “decision tools”, and “education”. Additionally, for ethical considerations in fertility preservation, we searched Web of Science, Ethics in Medicine (through Livivo), and Bioethics Literature Database for literature that was published between Jan 1, 1993, and Feb 21, 2020, using combinations of the search terms “childhood cancer”, “fertility preservation”, “oocyte donation”, “surrogacy”, “ethics”, and “legal”. We consulted experts to establish whether additional evidence was missing, and we crosschecked references of relevant literature reviews and reports that were identified in our searches. Only reports published in English were reviewed. Eligible study populations were patients with cancer in which 75% or more of patients had been diagnosed with cancer at age 25 years or younger. All study designs were included. Eligible study outcomes were outcomes on involvement in decision making, satisfaction with and desire for information and decision aids, information needs, other facilitators for and barriers to communication, and any outcome covering ethical issues in fertility preservation.

Two primary reviewers independently selected the studies (AF-G and JI), which were crosschecked by 24 expert panel members. Detailed information from each eligible study was extracted into evidence tables and summary of findings tables. The quality of the evidence of non-qualitative studies was appraised by use of the Grading of Recommendations Assessment, Development and Evaluation<sup>17</sup> (GRADE) approach and the evidence of qualitative studies was appraised by use of an adapted GRADE and Confidence in the Evidence from Reviews of Qualitative Research methodology.<sup>18</sup> For the ethics working group, we used the evidence tables to extract overarching themes and subthemes of ethical arguments, principles, and issues. The evidence was carefully reviewed by the ethics experts in the working group (NWP and JI). Due to the nature of the studies covering ethical themes around fertility preservation (ie, indirect literature that is reported in descriptive studies or narrative or theoretical papers), we did not formally appraise the quality of empirical evidence but the quality of ethical reasoning was appraised by the ethics experts in the working group (NWP and JI).<sup>19,20</sup>

### Recommendations

Regarding the communication of infertility risk and options for fertility preservation, final recommendations were based on scientific knowledge combined with other considerations, including clinical judgment, costs, and the need to maintain flexibility across health-care systems. We followed the criteria for the strength of recommendations according to published evidence-based methods (appendix p 11).<sup>21,22</sup>

The recommendations regarding ethical considerations were formulated as Good Practice Statements (GPSs) according to GRADE criteria<sup>23</sup> and were the result of the

evidence and arguments that were identified combined with the ethical considerations in fertility preservation that were indicated by the working group. Consensus was reached among all members of the guideline panel that the recommendations had unequivocal benefits. The recommendations were critically appraised by five independent external experts in the field (Teresa Woodruff, Anja Borgmann-Staudt, Zoltan Antal, Adam Glaser, and Rosalind McDougall; appendix p 2) and four patient or survivor representatives (AB, Jaap den Hartogh, Eline van der Meulen, and Joyce Reinecke; appendix p 3).

## Findings

Of 935 articles identified, 299 were subjected to full-text review and 147 were included (figure). The conclusions of evidence are shown in panel 1 and the recommendations are presented in panels 2 and 3. We present the evidence and recommendations for the two key issues described.

### What are facilitators of and barriers to the communication of treatment-related infertility risk and options for fertility preservation?

#### Evidence

Evidence concerning facilitators to communication of infertility risk and options for fertility preservation showed varying levels of quality. Very low-quality evidence from one study showed that some parents of male patients diagnosed with cancer before 18 years wanted to control whether physicians should discuss sperm banking with their child.<sup>24</sup> Regarding the involvement of health-care providers, one study reported that some male childhood patients with cancer considered medical support by doctors to be an important consideration, whereas only a few patients considered nursing support to be important (very low-quality evidence).<sup>25</sup> In another study, most doctors felt confident in providing up-to-date information about fertility preservation and taking a lead role in providing this information to patients and to parents, whereas most nursing staff did not feel confident in providing up-to-date information and would only take a helping role in the discussion (very low-quality evidence).<sup>26</sup>

Regarding decision making, one study found that most male adolescents and young adults reported that the decision for sperm banking is a personal one and many patients reported being influenced by their parents (very low-quality evidence).<sup>27</sup> We did not find any studies that investigated the views of female patients on decision making about procedures for fertility preservation.

Decision tools and educational materials can help to facilitate communication. However, health-care providers reported that existing educational materials about fertility preservation are sometimes scarce and that the existing materials need to be improved and adapted to the patient population with CAYA cancer (moderate-quality evidence).<sup>28–34</sup> New studies have evaluated the effects of brochures for fertility preservation;<sup>37,38</sup> a decision aid for

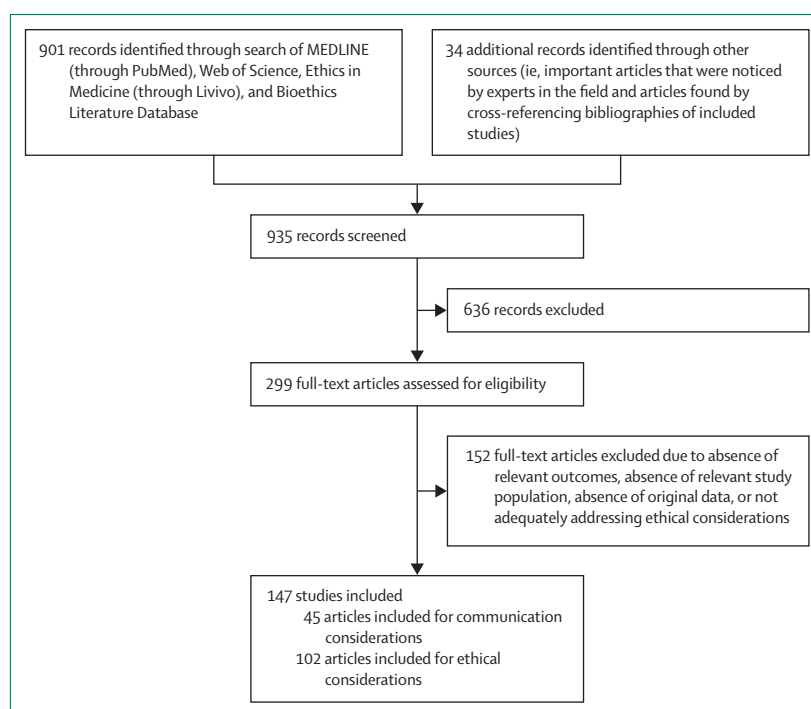


Figure: Flow diagram for selection of studies

patients and families;<sup>35</sup> toolkits for health-care providers, including educational materials, checklist, referral forms, and handouts for patients;<sup>26,39</sup> and clinical decision support systems to assist clinical discussions and decision making.<sup>36,40</sup> These studies suggest that tools to support communication about infertility and fertility preservation have potential benefits to oncofertility care related to knowledge, empowerment, confidence levels, adherence to standards of care, and the making of informed decisions about fertility by patients and families (very low-quality evidence).<sup>26,35–40</sup> On the basis of the available data, it is unclear which intervention is most effective in communicating infertility risk and options for fertility preservation.

Evidence concerning barriers to communication of infertility risk and fertility preservation showed varying levels of evidence. In regard to patient and family perspectives, there is moderate-quality evidence that poor physical status and a highly stressed emotional status of patients;<sup>25,41–47</sup> time constraints regarding delaying treatment;<sup>25,45–48,55</sup> costs;<sup>43,45,53</sup> absence of interest;<sup>44,45,48</sup> experimental nature of the procedure for fertility preservation with the associated risks;<sup>25,42,45,46,48,53,54</sup> highly stressed emotional status of parents;<sup>44,54,56</sup> absence of parental or medical recommendation;<sup>49,50</sup> absence of patient self-efficacy for banking;<sup>50,51</sup> absence of experience with, taboo regarding, and embarrassing feelings with masturbation;<sup>25,49</sup> cultural and religious beliefs;<sup>41,45</sup> poor success rate of the procedure for fertility preservation procedure;<sup>45,46</sup> and young age at diagnosis<sup>40,52</sup> are barriers

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### Panel 1: Conclusions of evidence for fertility preservation for patients with CAYA cancer

#### What are facilitators of and barriers to the communication of treatment-related infertility risk and options for fertility preservation?

##### *Involvement of health-care providers, patients with CAYA cancer, and their families*

- Some parents of male patients diagnosed at younger than 18 years want to control whether physicians discuss sperm banking with their child (very low-quality evidence)<sup>24</sup>
- No studies investigated the involvement of female patients and parents in the communication of fertility preservation
- Some male patients who were diagnosed with cancer at younger than 18 years considered medical support by doctors to be important and few male patients who were diagnosed with cancer at younger than 18 years considered nursing support to be important (very low-quality evidence)<sup>25</sup>
- Most doctors indicated taking a leading role, whereas most nursing staff indicated taking a helping role in providing information about fertility preservation to patients and parents (very low-quality evidence)<sup>26</sup>
- Most doctors and few nursing staff felt confident in providing up-to-date information about fertility preservation to patients and parents (very low-quality evidence)<sup>26</sup>

##### *Involvement of patients with CAYA cancer in the decision making*

- Most adolescents and young male adults (mean age 17.2 years [3-0]) reported the decision to be a personal one and many reported being influenced by parents in the decision to sperm bank (very low-quality evidence)<sup>27</sup>
- Decisions about fertility preservation are essentially made jointly between male patients with cancer and their parents (low-quality evidence)<sup>25,27</sup>
- Most parents considered their adolescent child (ie, aged 12-18 years) to be capable of participating in the decision-making process, whereas few parents considered their children aged 7-12 years to be capable of participating in the discussion about fertility preservation (low-quality evidence)<sup>25</sup>
- No studies investigated views of female patients on decision making about procedures for fertility preservation

##### *Satisfaction with the use of decision tools, educational materials, and strategies in the communication of treatment-related infertility risk and fertility preservation*

- Health-care providers reported that existing educational materials about fertility preservation are sometimes scarce and the existing materials need to be improved and adapted to the patient population (moderate-quality evidence)<sup>28-34</sup>
- Most parents of childhood patients (ie, aged 0-18 years) with cancer were satisfied with the design and content of a newly developed decision aid for fertility preservation (very low-quality evidence)<sup>35</sup>
- Most health-care providers were satisfied with newly developed decision tools, educational materials, and strategies available for the patient and health-care provider (very low-quality evidence)<sup>26,35,36</sup>

##### *Effectiveness of decision tools, educational materials, and strategies in the communication of treatment-related infertility risk and fertility preservation*

##### *Effect of interventions for patients and families on parent and patient outcomes:*

- Education materials (ie, information flyer) or decision aid for patients with CAYA cancer and families increased knowledge in both patients and parents (very low-quality evidence)<sup>35,37</sup>
- Education materials (ie, information flyer) for patients with CAYA cancer and families increased patient and parents' empowerment (very low-quality evidence)<sup>37</sup>
- A web-based decision aid for fertility preservation was not significantly associated with decision regret in parents of patients with childhood cancer (ie, aged 0-18 years; very low-quality evidence)<sup>35</sup>

##### *Effect of interventions for patients and families on oncofertility clinical practice:*

- Education materials (ie, information flyer) for patients with CAYA cancer and families was not significantly associated with use of cryopreservation (very low-quality evidence)<sup>38</sup>
- Education materials (ie, information flyer) for patients with CAYA cancer and families improved consultation practice for fertility preservation (very low-quality evidence)<sup>37</sup>

##### *Effect of interventions for health-care providers, patients, and parents on health-care outcomes:*

- A toolkit for fertility preservation for health-care providers, including educational materials, checklist, referral forms, and handouts for patients, increased paediatric oncology clinician's confidence levels (very low-quality evidence)<sup>26</sup>

##### *Effect of interventions for health-care providers, patients, and parents on oncofertility clinical practice:*

- A toolkit for fertility preservation for health-care providers, including educational materials, checklist, referral forms, and handouts for patients, increased the likelihood of paediatric oncology clinicians providing verbal and written information about fertility preservation; no significant effect of the toolkit for fertility preservation on the likelihood of clinicians being involved in discussions about fertility preservation (very low-quality evidence)<sup>26</sup>
- A bundled intervention, including educational material for clinicians and patients and a referral pathway, increased documented risk of fertility discussion, documented referral to fertility specialist, and documented outcomes for fertility preservation of patients with adolescent and young adult cancer (ie, aged 14-25 years; very low-quality evidence)<sup>39</sup>
- The implementation of an opt-out mechanism (where default results in an automatic consult order) increased the likelihood of completing consultation for fertility preservation among patients with CAYA cancer; no significant association between the intervention and attempts for fertility preservation after consultation in patients with CAYA cancer (very low-quality evidence)<sup>40</sup>

(Continues on next page)

(Panel 1 continued from previous page)

- A clinical support system for decision making, including electronic clinical oncofertility pathways and handouts for patients, provided perceived benefit to oncofertility clinical practice as reported by clinicians involved in paediatric oncofertility care (very low-quality evidence)<sup>36</sup>

*Barriers to pursuing fertility preservation as reported by patients with CAYA cancer and their families*

Patient-related barriers:

- Patient with poor emotional or physical status, or both (moderate-quality evidence)<sup>25,41-47</sup>
- Absence of interest (moderate-quality evidence)<sup>44,45,48</sup>
- Scarcity of experience with, taboo related to, and embarrassing feelings with masturbation (moderate-quality evidence)<sup>25,49</sup>
- Absence of patient self-efficacy for banking (moderate-quality evidence)<sup>50,51\*</sup>
- Young age at diagnosis (moderate-quality evidence)<sup>40,52</sup>
- Insufficient information (low-quality evidence)<sup>43</sup>

Procedure-related barriers:

- Experimental nature of the procedure for fertility preservation with the associated risks or complications (moderate-quality evidence)<sup>25,42,45,46,48,53,54</sup>
- Time constraints regarding delaying treatment (moderate-quality evidence)<sup>25,45-48,55</sup>
- Costs (moderate-quality evidence)<sup>43,45,53</sup>
- Poor success rate of the procedure for fertility preservation (moderate-quality evidence)<sup>45,46</sup>

Parent-related barriers:

- Parents have a highly stressed emotional status (moderate-quality evidence)<sup>44,54,56</sup>
- Absence of parental or medical team recommendation, or both (moderate-quality evidence)<sup>49,50</sup>
- Cultural or religious beliefs (moderate-quality evidence)<sup>41,45</sup>
- Sensitive nature of the conversation about fertility preservation (parent-reported barrier; low-quality evidence)<sup>24</sup>
- Absence of parental self-efficacy (low-quality evidence)<sup>49</sup>

Barriers related to health-care providers and institutions:

- Absence of specific consultation by fertility specialist (low-quality evidence)<sup>57</sup>
- Difficulty in finding proper facilities (low-quality evidence)<sup>45</sup>
- Adult treatment centre versus non-adult treatment centre (low-quality evidence)<sup>47</sup>

*Barriers to communicating treatment-related infertility risk and fertility preservation with patients with CAYA cancer as reported by health-care providers*

Patient-related barriers:

- Patient's poor prognosis, poor health status, and risks (moderate-quality evidence)<sup>31,32,44,48,52,53,58-63</sup>
- Patient's young age (moderate-quality evidence)<sup>31,52,58,63</sup>
- Patient's potential disinterest (moderate-quality evidence)<sup>60,62</sup>
- Patient already has children (moderate-quality evidence)<sup>59,60</sup>
- Positive HIV status (moderate-quality evidence)<sup>31,32</sup>

- Patient's cultural or religious beliefs (moderate-quality evidence)<sup>30,64</sup>
- Patient's emotional state and the perceived additional stress with fertility topic (moderate-quality evidence)<sup>58,62</sup>
- No current partner (low-quality evidence)<sup>59</sup>
- Difficulty of establishing sense of trust with patient (low-quality evidence)<sup>30</sup>
- Patient has few language skills (low-quality evidence)<sup>62</sup>
- Patient's sexual orientation (low-quality evidence)<sup>31</sup>

Parent-related barriers:

- Parent has highly stressed emotional status (moderate-quality evidence)<sup>33,58</sup>
- Real or perceived parental absence of interest or knowledge (moderate-quality evidence)<sup>63,64</sup>
- Absence of parental consent (moderate-quality evidence)<sup>44,48</sup>
- Families' socioeconomic status (low-quality evidence)<sup>30</sup>

Barriers related to health-care providers and institutions:

- Scarcity of knowledge, training, and educational materials, or unfamiliarity with or low availability of relevant guidelines, or both (moderate-quality evidence)<sup>30,31,33,34,59,61-66</sup>
- Scarcity of time and time pressure to start treatment (moderate-quality evidence)<sup>32,44,48,56,58-61,64,67</sup>
- Little access or inadequate referral pathways with relevant facilities and specialists (moderate-quality evidence)<sup>30,33,58,64-68</sup>
- Difficulties completing consent forms (low-quality evidence)<sup>64</sup>
- A problem with the cooperative system with the paediatrics department (low-quality evidence)<sup>65</sup>
- Cost of procedure and storage (moderate-quality evidence)<sup>30,31,33,44,52,53,59,62,65,68</sup>
- Experimental nature of the procedure for fertility preservation with the associated risks and complications (moderate-quality evidence)<sup>52,53,59,61</sup>
- Adoption system is popular, potentially discouraging discussion or promotion of fertility preservation (low-quality evidence)<sup>65</sup>

### What are ethical issues related to fertility preservation (ungraded)?

*Ethical issues regarding informed consent*

- Informed consent to procedures for fertility preservation in minors and young adults<sup>5,64,67,69-97</sup>
- Safeguarding and protecting patients' best interests when making decisions about fertility preservation<sup>67,71,72,76,78,82-87,91-94,98-107</sup>

*Ethical issues regarding communication*

- Communication between health-care providers and patients and their parents, caregivers, and partners<sup>5,52,67,70,71,73-78,81,84-86,89,92,93,96,98-100,105-113</sup>

*Ethical issues regarding potential risks of procedures for fertility preservation*

- Harms versus benefits of procedures for fertility preservation<sup>5,54,67,69-73,75,76,79,80,83,85-87,89,90,92-94,96,97,100-103,105-112,114-116</sup>

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(Panel 1 continued from previous page)

- Experimental nature of procedures for fertility preservation<sup>69,71,72,76,82–84,91,93,109,110,117</sup>
  - Psychological issues surrounding decisions about procedures of fertility preservation<sup>70,72,74,79–83,87,93,97,106,107,109</sup>
  - Ethical issues regarding storage of patients' material
  - Decisions on use and disposal of stored tissue for fertility preservation<sup>71,73,74,78–81,85,93,102,114–116,118</sup>
  - Decisions on posthumous use of stored material for fertility preservation<sup>5,64,69,71–74,79–81,83–85,88–90,92,93,99–103,108–111,114,115</sup>
- Ethical issues regarding access to procedures for fertility preservation*
- Offering access to procedures for fertility preservation considering patients' cultural or religious background<sup>91,106,108,112</sup>
  - Restoring patients' reproductive autonomy with procedures for fertility preservation<sup>69–74,108,114,118</sup>
- Differences in services for fertility preservation across countries<sup>70,79,80,93,95,103,111,113,115</sup>
  - Ethical issues regarding financial costs in procedures for fertility preservation
  - Expenses linked to procedures for fertility preservation, potential complications, storage of cryopreserved material, post-treatment assisted reproductive technology, adoption, or surrogacy<sup>69,78–80,87,89,108,109,111,113,118</sup>
- Ethical issues regarding post-treatment adoption in survivors of cancer*
- Discrimination during post-treatment adoption<sup>106</sup>

CAYA=childhood, adolescent, and young adult. \*Potential overlap in patients.

to discussing treatment effects on fertility and options for fertility preservation. Additionally, low-quality evidence exists that the sensitive nature of conversations about fertility preservation,<sup>24</sup> absence of parental self-efficacy,<sup>49</sup> absence of specific fertility specialist consultation,<sup>57</sup> difficulty in finding proper facilities,<sup>45</sup> and insufficient information<sup>43</sup> are also barriers for the communication of fertility preservation.

Similarly, health-care providers experience barriers to counselling about infertility risk and fertility preservation that are related to related to patients, parents, health-care providers and institutions, and procedures (low-quality to moderate-quality evidence).<sup>30–34,44,48,52,53,56,58–64,66–68</sup> The most reported barriers by health-care providers were patients' poor cancer prognosis, unstable health status and low infertility risk,<sup>31,32,44,48,52,53,58,59–63</sup> scarcity of knowledge and training, unfamiliarity with relevant guidelines,<sup>30,31,33,34,59,61–66</sup> time pressure to start treatment,<sup>32,44,48,56,58–61,64,67</sup> restricted access to or inadequate referral pathways with relevant facilities and specialists,<sup>30,33,58,64,66–68</sup> and costs of the procedure and storage.<sup>30,31,33,44,52,53,59,62,65,68</sup>

### Recommendations

Existing studies describe some of the facilitators for and barriers to providing information or communicating about treatment-related infertility risk and fertility preservation in patients with CAYA cancer. Our recommendations are based on existing knowledge about potential facilitators and barriers and the consensus of the guideline panel (appendix pp 15–17). The panel formulated recommendations regarding provision of information and communication about treatment-related infertility risk and options for fertility preservation (panel 2; recommendations about patient risk groups that should receive information and counselling were formulated by the male and female fertility preservation guideline panels).

Generally, multiple studies indicated that health-care providers were uncomfortable discussing fertility

preservation because they did not have adequate training and relevant educational materials, and they had difficulty keeping up to date with the latest reproductive health science.<sup>30,31,33,34,59,61–66</sup> As such, we strongly recommend that health-care providers become familiar with the latest evidence-based recommendations, institutional policies, and professional educational resources on infertility risk and procedures for fertility preservation and that they maintain their knowledge with relevant, up-to-date training as appropriate (low-quality to moderate-quality evidence). Interdisciplinary meetings and networks between paediatric oncologists or oncology nurses and reproductive medicine specialists (ie, gynaecologist, endocrinologist [including paediatric endocrinologist], urologist, andrologist, fertility physician, and specialised nurses) can overcome knowledge gaps and ensure high-quality patient care by continuous learning and teaching. The choice of who should be involved in the communication process depends on the provider's knowledge, patient's disease state, and local access to fertility specialists, rather than identifying a particular discipline to assume this role. Possibilities of whom should assume this role include the paediatric oncologist, endocrinologist (including paediatric endocrinologist), fertility specialist, specialised nurse, or another relevant health-care provider. The panel also recommend that it is of crucial importance that a system is in place to identify who is responsible for having the discussion.

On the basis of the evidence indicating the patients' scarcity of information or interest,<sup>43–45,48,49,53</sup> a patient's prognosis<sup>25,31,32,41–48,52,53,58–63</sup> and age,<sup>31,40,52,58,63</sup> and the experimental nature of the fertility preservation procedures and associated risks,<sup>25,42,45,46,48,52–54,59,61</sup> we strongly recommend that health-care providers deliver clear, comprehensive, and age-appropriate information, and that they provide up-to-date written or online educational resources, or both, to patients and their families in appropriate languages and health-literacy levels (very low-quality to

moderate-quality evidence). Additionally, we strongly recommend that health-care providers deliver the information in a professional, neutral, and empathetic manner (low-quality to moderate-quality evidence).

We strongly recommend that health-care providers actively involve patients or their families, or both (on the basis of expert opinions in the absence of evidence). Additionally, we strongly recommend that health-care providers have a private conversation with the patient and a separate conversation with families regarding treatment-related infertility risk and procedures for fertility preservation, taking into consideration a patient's age, developmental status, and the family's cultural and religious beliefs (low-quality to moderate-quality evidence). We also strongly recommend that health-care providers provide emotional support to patients and their families during counselling about treatment-related infertility risk and fertility preservation and offer prompt psychosocial specialist referrals (eg, social workers and psychologists) as appropriate. This support is especially important in view of the patient's and family's highly stressed emotional status (low-quality to moderate-quality evidence). In relation to time constraints regarding treatment delay, we strongly recommend that health-care providers initiate counselling as early as possible after a cancer diagnosis is established and when a change in disease status occurs that requires treatment intensification with gonadotoxic agents or methods (low-quality to moderate-quality evidence). The panel recognises the need to offer counselling on an ongoing basis during treatment and throughout survivorship because the patient's wishes can change (low-quality to moderate-quality evidence). Finally, to overcome barriers that are related to the scarcity of specific fertility specialist consultation, inadequate referral pathways for accessing relevant facilities and specialists, and health-care providers' perceived discomfort with the fertility topic and high workload, we strongly recommend that hospitals establish referral pathways for accessing fertility specialists or fertility specialist centres where appropriate (low-quality to moderate-quality evidence).

### What are the ethical considerations related to fertility preservation?

From the systematic literature review, we identified evidence related to ethical considerations in fertility preservation with the following overarching themes: informed consent, communication between health-care providers and patients, caregivers, and partners, potential risks of procedures for fertility preservation, gamete storage, access to fertility preservation procedures, financial cost of procedures for fertility preservation and post-treatment assisted reproductive technology, and adoption or surrogacy in patients with cancer (appendix pp 53–64). On the basis of the evidence and expert opinions, we formulated GPSs (panel 3). Notably, all ethical deliberations should be considered within the context of the relevant national legal framework.

### Panel 2: Recommendations regarding ongoing communication of treatment-related infertility risk and fertility preservation in patients with childhood, adolescent, and young adult cancer

#### General

*Health-care providers should (strong recommendations; very low-quality to moderate-quality evidence):*

- Be familiar with the latest evidence-based recommendations, institutional policies, and professional educational resources on infertility risk and procedures for fertility preservation
- Maintain education with training where appropriate

#### Provision of information about treatment-related infertility risk and fertility preservation

*Health-care providers should (strong recommendations; very low-quality to moderate-quality evidence):*

- Deliver clear, comprehensive, and age-appropriate information in a professional, neutral, and empathetic manner
- Provide up-to-date written or online educational resources to patients and their parents, caregivers, or partners in appropriate languages and health-literacy levels

#### Communicating treatment-related infertility risk and fertility preservation

*Health-care providers\* should (strong recommendations; very low-quality to moderate-quality evidence):*

- Involve patients or their parents, caregivers, or partners, or both
- Offer a private conversation with the patient depending on age
- Offer a separate conversation with parents, caregivers, or partners after consent or assent of the patient
- Consider the patient's age, developmental status, and the family's cultural and religious beliefs
- Provide emotional support to patients and their parents, caregivers, or partners during counselling about treatment-related infertility risk and fertility preservation and prompt psychosocial specialist referrals (eg, social workers and psychologists) as appropriate
- Initiate counselling as early as possible after a cancer diagnosis and a treatment plan have been established, or when a change in disease status occurs that requires treatment intensification with gonadotoxic agents or methods
- Offer counselling on an ongoing basis during treatment and throughout survivorship because the infertility risk or patient's ideas might change

*Hospitals should (strong recommendation; very low-quality to moderate-quality evidence):*

- Establish referral pathways for accessing fertility specialists or fertility specialist centres where appropriate

\*The panel recommend that a system should be in place to identify who is responsible for having the discussion, considering the provider's knowledge, patient's disease state, and local access to fertility specialists.

Fertility preservation aims to give patients future reproductive autonomy. However, because of the risks of cancer treatment to fertility, the potentially scarce availability of fertility preservation, and the personal and social effects of fertility decisions, conflicts can exist between respect for patient autonomy and other medical values.<sup>69–74,108,114,118</sup> Health-care providers need to assist patients and their families in the decision-making process by fostering the patient's autonomy in the context of future parenthood decisions before decisions regarding procedures for fertility preservation can be made, while



**Panel 3: Recommendations regarding ethical issues about treatment-related infertility risk and fertility preservation in patients with childhood, adolescent, and young adult cancer**

**Ethical issues related to fertility preservation: good practice statements**

*Health-care providers should:*

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

also encouraging them to consider their personal notions of parenthood (GPS; panel 3). It is also important that health-care providers establish whether patients are emotionally, psychologically, and mentally competent to consent or assent to fertility preservation options.<sup>5,70,75-80</sup> Taking these factors into consideration, the guideline panel recommends that health-care providers assess a patient's emotional, psychological, and intellectual status as part of the process for informed consent (GPS; panel 3). National legal regulations for procedures for informed consent with minors need to be met.

Decision making about future fertility can be challenging for patients who have been newly diagnosed with cancer. Patients might have difficulty making life-changing decisions for the future, especially when having physical and psychological trauma. Additionally, patients might feel uncertain about their future desires and struggle with balancing the short-term and long-term advantages and disadvantages of fertility preservation. Patients often make decisions together with their families. Parents might be driven by their own interest and emotions, but they need to contemplate what the child might desire when they are an adult and what is in the interest of their child.<sup>98</sup> Hence, we recommend that

health-care providers ensure that decisions about fertility preservation are not driven by their own interest or interest of parents, caregivers, or partners but are made in the patients' best interest instead (GPS; panel 3).

The literature emphasised that a patient's decision to pursue fertility preservation can be influenced by projected advances in technology.<sup>81</sup> This influence is especially important when offering procedures with little or unknown efficacy to prepubertal children. Similarly, fertility preservation measures should not create unrealistic or false expectations (ie, raising hope and not fulfilling expectations) as fertility preservation does not guarantee future reproductive potential.<sup>72,74,79-83,109</sup> It is important to balance realistic expectations, including the likelihood of success of gamete thawing, gamete transplantation, and future livebirths, with costs that are associated with fertility preservation procedures and post-treatment assisted reproductive technology, surrogacy, or adoption, with allowing hope for successful family building in the future. To balance the risks and benefits that are associated with experimental procedures that are available for prepubertal children, interventions for fertility preservation should be done within a research setting with appropriate participant approval. Ethical reflection can be built into the care pathway for each individual by undertaking a case-by-case ethical analysis, if necessary.<sup>109</sup> Therefore, we recommend that health-care providers address the uncertainty of future technologies during patient counselling about infertility risk and procedures for fertility preservation.

The process for informed consent should be dynamic, ongoing, and adapted as new information becomes available.<sup>83-85</sup> The document regarding informed consent should disclose the risks and potential benefits of procedures for fertility preservation.<sup>69,81,86</sup> Additionally, it is important that the consent process is divided in two stages: at diagnosis when the decision about harvesting and storing tissue is made and after therapy at a developmentally appropriate age (which might vary depending on the patient) when the decision of whether and how to use the stored material is made.<sup>69,70,72,73,77,79,80,82,85,87-89</sup> We recommend that health-care providers emphasise this fact, pointing out that the decision to preserve gametes or tissue does not obligate them to use this material in the future. This discussion can be held at a later date, such as at a developmentally appropriate age after therapy (GPS; panel 3).

Regarding posthumous use of stored gametes, evidence from this systematic review emphasises the need to consider two issues: disposal of gametes and preserved tissue in the event of a patient's death<sup>5,64,69,71-74,79,80,85,88-93,99,100-102,108-111,114,115</sup> and potential disagreement among family members about gamete disposal in the event of a patient's death.<sup>72,92,103</sup> Hence, we recommend that health-care providers should be aware of the need to discuss and obtain approval by patients and their families regarding the disposal of stored gametes in the event of a patient's

death and that such stored material can be donated for scientific research (GPS; panel 3). Of importance is the communication of local, national, and international regulations about researcher access to stored gametes. In terms of possible conflicts of interest between the needs of patients, the potential financial costs involved in procedures for fertility preservation and storage, and the long-term costs associated with pursuing family building necessitated by fertility preservation,<sup>78</sup> we recommend that health-care providers consider these issues and offer referrals for charity or other programmes that might help to offset costs, when available (GPS; panel 3).

## Discussion

We present a systematic review of the evidence and recommendations regarding ongoing communication about, and ethical considerations related to, fertility preservation in patients with CAYA cancer. The evidence-driven recommendations were derived from the consensus of an international multidisciplinary group of experts following critical analysis of the scientific knowledge from the published literature by use of the GRADE methodology. This CPG harmonises efforts across Europe, Canada, Australia, New Zealand, and the USA as part of the PanCareLIFE Consortium and in collaboration with the IGHG.<sup>15,16</sup> The global dissemination of this guideline aims to assist health-care providers to effectively communicate with patients with CAYA cancer and their families about potential infertility risk and procedures for fertility preservation while considering ethical issues. This CPG is one of the three CPGs that we have developed in this Series, with the other two Series papers focusing on fertility preservation options for male<sup>119</sup> and female<sup>120</sup> patients with CAYA cancer.

The systematic literature review disclosed a paucity of data related to facilitators of and barriers to communication about fertility preservation that was limited to evidence of very low to moderate quality. Our strong recommendations were based on the clinical expertise of the guideline panel on how to communicate treatment-related infertility risk and options for fertility preservation to patients and their families. It is important that future studies focus on interventions to facilitate communication about fertility preservation between health-care providers and patients and their families and to overcome identified barriers.

There is a scarcity of knowledge about or unfamiliarity with relevant guidelines, creating barriers for communicating about fertility preservation as reported by health-care providers.<sup>30,31,33,34,59,61,63–66,103,121,122</sup> These barriers are in line with the main findings from a systematic review focusing on children and young adults with cancer<sup>9</sup> and also from literature reviews including adult patients with cancer who are of reproductive age.<sup>123,124</sup> This deficit in knowledge is closely related to the institutional barriers reported by health-care providers that we also identified. These barriers include the difficulties for health-care providers in building

and maintaining a knowledge base and the scarcity of appropriate training about legal and consent frameworks.<sup>64</sup> Clinician training in communication skills is recommended in the adult population as part of the American Society of Clinical Oncology CPG to optimise patient–clinician communication<sup>125</sup> and has also been recommended as an area for training and development for health-care providers caring for adolescents and young adults with cancer.<sup>126</sup> Web-based training for communication skills that has improved nurses' knowledge about the fertility needs of adolescents and young adults with cancer is an example of encouraging results in this area.<sup>127</sup> To overcome barriers in communicating infertility risk and fertility preservation, interventions have been developed to promote and facilitate discussions between health-care providers and patients and families.<sup>26,35–40</sup> Studies have shown that including fertility preservation discussions in the clinical care pathway (with all relevant documentation easily accessible, such as electronic flowcharts, instruction booklets, checklists, referral forms, and handouts for patients and families) increased discussion rates and the health-care providers' confidence in providing up-to-date knowledge to patients.<sup>26,36</sup>

The current CPG recommends providing patients and their families with up-to-date written or online educational resources, or both, in appropriate languages. Findings from the systematic review have showed that health-care providers reported that educational materials about fertility preservation are sometimes scarce and existing materials need to be improved and adapted to the patient population with CAYA cancer.<sup>28–34</sup> Additionally, patients reported a scarcity of information about fertility preservation.<sup>43,48</sup> Educational materials that provide age-appropriate information and tools to facilitate shared decision making for patients with CAYA cancer and their families have been developed within the past 2 years.<sup>35,37,38,128</sup> We encourage wider dissemination of culturally sensitive print and electronic (ie, web-based and app-based) educational materials in different languages. Digital information platforms can offer novel mechanisms to facilitate access to up-to-date information based on evidence-based guidelines. In an evolving field such as fertility preservation, educational patient resources will have to be updated as new data emerge.

This systematic review identified that both patients and health-care providers endorsed concerns regarding the delay in initiation of therapy as a barrier to communication about fertility preservation and procedures for fertility preservation. As published in CPGs for fertility preservation for young adults and adults with cancer, the guideline panel recommends that health-care providers should initiate discussions about fertility preservation as early as possible after a diagnosis and treatment plan have been established.<sup>14</sup> The present CPG also specifies that health-care providers should readdress fertility preservation in the event of a change in disease status that requires treatment intensification with gonadotoxic

agents or methods and throughout survivorship to assure continued understanding about potential cancer-related and treatment-related effects on infertility risk, in agreement with the American Society of Clinical Oncology guideline in fertility preservation.<sup>6</sup> Risk perceptions are discordant from laboratory-evaluated gonadal functioning. It was observed that most survivors overestimated their infertility risk when their fertility status seemed normal.<sup>129</sup> It is therefore essential to provide ongoing communication about fertility throughout survivorship. Fertility discussions are a standard component of survivorship care. The IGHG guidelines for male and female gonadotoxicity provide information that is pertinent to risk groups and surveillance measures of reproductive function.<sup>3,4</sup> The guideline panel also recommends offering separate private conversations about treatment-related infertility risk and fertility preservation to the patient, especially with growing age and maturity of the patient, and their families. These conversations are especially important for adolescents and young adults, as they might feel more comfortable engaging in conversations in which their privacy is respected.<sup>130</sup>

The systematic review showed that some health-care providers considered patients' cultural and religious background as barriers to initiating communication about infertility risk and procedures for fertility preservation.<sup>33</sup> The guideline panel recognises the importance of integrating families' cultural and religious beliefs during discussions about treatment-related infertility risk and fertility preservation, and the need to deliver information in a professional, neutral, and empathetic manner at all times. Similarly, the guideline panel considers that health-care providers need to be prepared to address religious preferences as part of a holistic approach to patient care during counselling for fertility preservation.<sup>131</sup>

The strengths of this CPG are the evidence-based approach used, the transparency given in deriving and rating the strength of the recommendations formed, and the wide geographical representation and multi-disciplinary expertise of the guideline panel. The ongoing interactive relationship between the academics and clinicians who appraise the evidence and those who formulate recommendations also increases the validity and trustworthiness of our process for guideline development. We involved patient representatives from different countries to ensure that patient values were considered in the guideline development process. Comprehensive periodic updates of the recommendations are planned as fertility preservation is a rapidly evolving field. Acknowledging that the recommendations offered will be subjected to consideration through national entities, policies, and legislation, they have been carefully formulated to facilitate implementation in different health-care settings. Finally, in accordance with patients' and their families' desire for genetically-related children, this CPG aims to facilitate access to

fertility preservation services by patients with CAYA cancer and their families.

## Conclusion

We have developed a transparent, rigorous, and evidence-based CPG that provides guidance for ongoing communication of infertility risk and options for fertility preservation by health-care professionals to patients with CAYA cancer and their families, taking into account the associated ethical considerations of these interventions. Implementation of the present CPG can facilitate communication between patients and health-care providers and potentially fulfil patients' desire for biological offspring. Health-care professionals can tailor these recommendations to their patients' needs. With this CPG, we ultimately expect to increase future international collaborative research for patients with CAYA cancer and their families.

### Contributors

AF-G, RLM, EAHL, MMH, JL, WJET, LCMK, LBK, and MDvdW contributed to the conception and design of the study. All authors contributed to the search strategy, data extractions, and interpretation of the data. All authors and collaborators contributed to the formulation of the recommendations. AF-G, RLM, LCMK and MMH drafted the manuscript; and EvD-dB, GPQ, JPG, EAHL, KCB, HMvS, CB, TD, UD, AG, CG, SEH, JFK, JLK, JSEL, BAL, SJCMMN, MP, BP, DRR, EMET, JB, MV, MvdB, CMV, AA, KR-W, MMvdH-E, AB, WHW, DMG, RS, RH, LBK, JL, MDvdW, WJET, NWP, JI, and collaborators (for full details of the collaborators see the appendix, p 2) critically revised the manuscript. All authors and collaborators approved the final version of this Series paper.

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