Summary of findings tables, grading of the evidence and detailed conclusions of evidence for communication considerations

1. What is the reported desire and satisfaction of who should be involved in the discussion about treatment-related fertility risks and fertility preservation in cancer patients diagnosed before 25 years?

Outcome	Study	Participants	Age at patients' diagnosis	Method	Summary of findings
1.1. Involvement in the discussion as reported by patients and/or parents (n=2 studies)	De Vries 2009	14 parents of male adolescents undergoing cancer treatment aged 11-17 years	Adolescents' age at study: 13.8 (11-17) years	In-depth semistructured interviews	*Role of parents in fertility preservation communication* More than half of parents (57%) reported that they wanted control whether physicians discussed sperm banking with their child and also what the physician discussed.
	Wyns 2015	120 prepubertal boys and adolescents aged 0–18 years diagnosed with cancer Parents gave their answers for 22 patients under 12 years of age and 3 aged 12–18yrs	Boys <12 yr: 6.05 (0-11.9) yr Boys 12-18 yr: 14.41 (12-17.7) yr	Closed-ended questionnaire	*Role of medical support in fertility preservation communication* Medical support was considered important for 50% of adolescents and 42% of children. Nursing support was relevant for 16.6% of adolescents.
GRADE Assessment:					
Methodological limitations:	Some methodological limitations in 2/2				
Coherence:	No concerns on coherence				
Adequacy of data:	Important concerns on adequacy of data in 1/2 of the studies (1 study 14 study participants)				
Relevance:	No concerns on relevance (>85% cancer patients in 2/2)				
Overall assessment of confidence in findings:	**VERY LOW confidence in the evidence**				
Conclusion:	Some parents of male cancer patients diagnosed below 18 years want to control whether physicians discuss sperm banking with their child. *(1 in-depth semistructured interview study; 14 study participants)* Some male cancer patients diagnosed below 18 years considered medical support important. A minority of male cancer patients diagnosed below 18 years considered nursing support important. (*1 questionnaire study; 348 study participants*) No studies investigated the control of parents of female patients in the discussions of fertility preservation.				

Abbreviations: NM, not mentioned; NA, not applicable

Outcome	Study	Participants	Age at patients' diagnosis	Method	Summary of findings
1.2. Involvement in the discussion as reported by health professionals (n=1 study)	Kemertzis 2018	All clinical staff involved in the care of oncology patients at the RCH Melbourne and trained on the use/content of an fertility preservation toolkit Pre intervention: n=59 2 yr after implementation: n=38	Healthcare professionals caring for childhood and adolescent cancer patients	Questionnaires survey-based study	*Participants' roles in providing fertility preservation information to patients and parents pre-toolkit implementation* 12/13 (92%) medical staff and 6/41 (14.6%) nursing staff indicated taking a leading role in FP discussion. 4/13 (30.8%) medical staff and 27/41 (65.9%) nursing staff indicated to take a helping role on FP discussion. 13/13 (100%) medical staff and 11/41 (27%) nurses staff felt confident in providing FP information. *Participants' roles in providing fertility preservation information to patients and parents post-toolkit implementation* 26/37 (70.3%) felt confident in providing up to date information. 21/31 (67.7%) often/always provided verbal information. 11/31 (35.5%) often/always provided written information.

GRADE Assessment:

Methodological limitations:	Some methodological limitations in 1/1
Coherence:	Not applicable (Only one study)
Adequacy of data:	Important concerns on adequacy of data
Relevance:	No concerns on relevance
Overall assessment of confidence in findings:	**VERY LOW confidence in the evidence**
Conclusion:	Majority of the medical staff indicated taking a leading role, while majority of the nursing staff indicated taking a helping role in providing fertility preservation information to patients and parents. Majority of the medical staff and minority of the nursing staff felt confident in providing up to date fertility preservation information to patients and parents. (*1 study; 59 participants*)

Abbreviations: NM, not mentioned; NA, not applicable

2. What is the reported desire and satisfaction of who should be involved in the decision-making of treatment-related fertility risks and fertility preservation in cancer patients diagnosed before 25 years?

Outcome	Study	Participants	Age at patients' diagnosis	Method	Summary of findings
2. Involvement in the decision-making about treatment-related fertility risks and fertility preservation as reported by patients and/or parents (n=2 studies)	Ginsberg 2008	50 male patients (including 45 who attempted banking; 38 successful, 7 not) 45 parents and 1 legal guardian	Age at study: 17.2 ± 3.0 78.4% between 15-19 years of age	Questionnaire	*Role of patients and parents in decision to bank sperm* Most parents and patients (58.3%) reported that the decision to bank was made jointly. However, no statistically significant agreement on who made the decision (61.9%, p=0.065) when matching patients to parents. *Issues considered by patients and parents when deciding to bank sperm* Most adolescents and young adults felt the decision was a personal one, and many were influenced by parents' opinion.
	Wyns 2015	120 prepubertal boys and adolescents aged 0–18 years diagnosed with cancer Parents gave their answers for 22 patients under 12 years of age and 3 aged 12–18yrs	Boys <12 yr: 6.05 (0-11.9) yr Boys 12-18 yr: 14.41 (12-17.7) yr	Closed-ended questionnaire	*Role of patients and parents in decision making* 91.4% of parents considered their adolescent child capable of participating in the decisional process, while only 26.2% of parents considered their children aged 7-12 yr capable of participating. No discrepancy between patient and parent decisions was noted, indicating that decisions were essentially made jointly. Reasons for not participating in the decision process were immaturity of the child (5.7%) and poor general health (2.9%).

GRADE Assessment:	
Methodological limitations:	Some methodological limitations in 2/2
Coherence:	All studies show similar results: FP decisions were made jointly by parents and patients
Adequacy of data:	Some concerns on adequacy of data in 2/2
Relevance:	No concerns on relevance (>85% cancer patients in 2/2)
Overall assessment of confidence in findings:	**LOW confidence in the evidence**
Conclusion:	The decision about fertility preservation were essentially made jointly by parents and patients (*2 studies; 216 participants*) Most adolescents and young male adults report the decision to be a personal one, and many report being influenced by parents in the decision to sperm bank *(1 study; 96 study participants)* Majority of parents considered their adolescent child capable of participating in the decisional process, while a minority of parents considered their children aged 7-12 yr capable of participating in the fertility preservation discussion (*1 study; 120 participants*)

No studies investigated female patients reported parental influence in the decision to pursue fertility preservation procedures.

3. What is the effectiveness of decision tools/educational materials and (educational, organizational) strategies in the discussion of treatment-related fertility risks and fertility preservation for cancer patients diagnosed before 25 years?

Effect of decision tools/educational materials for patients/families on parents/patient outcomes

PICO	Study	No. of participants	Intervention	Effect size	Risk of bias
3.1 Effect of decision tools/educational material and strategies for patients/families on parents/patient fertility preservation knowledge (n=2 studies)	Borgmann-Staudt 2019	200 parents and 214 childhood cancer patients aged 12-19 years at diagnosis. 113 patients and 111 parents who received standard patient education pre-intervention 101 patients and 99 parents who received the intervention	Information flyer at initial diagnosis in addition to standard patient education	*Knowledge about fertility impairment and preservation* Educational intervention non-significantly increased knowledge in both patients and parents compared to control group; mean difference: 1.62 (95% CI -0.73–3.96) at 3 months (t0) and 2.17 (95% CI -0.38–4.72) at 6 months (t1) for patients; 2.24(95% CI -0.108–4.583) at 3 months and 2.19 (95% CI -0.22–4.616) at 6 months for parents. *Multivariable analyses for determinants of patient knowledge at t0* Education with vs. without intervention: NS *Multivariable analyses for determinants of patient knowledge at t1* Education with vs. without intervention: NS *Multivariable analyses for determinants of parent knowledge at t0* Education with vs. without intervention: OR 1.95 (95% CI 1.03-3.71) *Multivariable analyses for determinants of parent knowledge at t1* Education with vs. without intervention: NS	SB: Low risk AB: Unclear DB: High risk CF: Low risk
	Allingham 2018	34 parents of patients with cancer (aged 0-18	Web-based Decision Aid (DA) for parents of	*Improvements in knowledge and understanding* Parents reported that the DA helped improve their	SB: High risk AB: High risk

		years) 34 completed the pre-DA survey 15/34 (44.12%) completed the pre- and post-DA survey	children and adolescents with cancer developed according to the International Patient Decision Aid Standards	understanding of cancer treatments, infertility, and FP procedures to some degree Knowledge scores increased significantly by 1.50 to average of 6.71 after reviewing the DA (p<0.04) Fertility preservation knowledge scale increased from 21% (3/14) prior to reviewing the DA to 64% (9/14) after DA review in parents who scored >70%	DB: Unclear CF: High risk

GRADE assessment:		
Study design:	+2	Observational studies
Study limitations:	-2	Limitations: Selection bias low in 1/2, high in 1/2; Attrition bias high in 1/2, unclear in 1/2; Detection bias high in 1/2; unclear in 1/2; Confounding low in 1/2, high in 1/2
Consistency:	0	No important inconsistency, all show increase in knowledge (although some were insignificant)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, sample size is less than 100 in 1/2 and above 100 in 1/2 but they did not reach required sample size calculated. Wide confidence intervals in some estimates in 1/2
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect in all studies
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Education materials (information flyer/ decision aid) for CAYA cancer patients and families increased knowledge in both patients and parents. (*1 study significant effect, 1 study non-significant effect; 429 participants*)

Web-based Decision Aid (DA)

PICO	Study	No. of participants	Intervention	Effect size	Risk of bias
3.2 Effect of decision tools/educational material and strategies for patients/families on parents/patient empowerment	Borgmann-Staudt 2019	200 parents and 214 childhood cancer patients aged 12-19 years at diagnosis. 113 patients and 111 parents who received standard patient education pre-intervention	Information flyer at initial diagnosis in addition to standard patient education	*Empowerment* Significantly improved in both patients (*p* = 0.046, d =0.27) and parents (*p* = 0.046, d = 0.48) in the intervention group *Multivariable analyses for determinants of patient empowerment at t0 (3 months)* Prior infertility information yes vs. no: OR 6.59 (95% CI 2.12-20.49) Information regarding prophylactic measures: not significant	SB: Low risk AB: Unclear DB: High risk CF: Low risk

(n=1 study)	101 patients and 99 parents who received the intervention	*Multivariable analyses for determinants of patient empowerment at t1 (6 months)* Information on prophylactic measures yes vs. no: OR 5.55 (95% CI 1.92-15.98) Recall of risk information before treatment: not significant *Multivariable analyses for determinants of parent empowerment at t0* Prior infertility information yes vs. no: OR 4.544 (95% CI 1.351-15.28) Information on prophylactic measures yes vs. no: OR 30.53 (95% CI 6.41-145.39) *Multivariable analyses for determinants of parent empowerment at t1* Prior infertility information yes vs. no: not significant Information on prophylactic measures yes vs. no: OR 6.49 (95% CI 2.17-19.40)

GRADE assessment:		
Study design:	+2	Observational studies
Study limitations:	-1	Limitations: Selection bias low; Attrition bias unclear; Detection bias high risk; Confounding low risk
Consistency:	0	Not applicable, only one study available
Directness:	0	Results are direct, population and outcomes are broadly generalizable
Precision:	-2	Imprecision, only one study, sample size was above 100 but they did not reach required sample size calculated. In addition, wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⊖⊖⊖ VERY LOW
Conclusion:		Education materials (information flyer) for CAYA cancer patients and families increased patient and parents empowerment. (*1 study; 414 participants*)

PICO	Study	No. of participants	Intervention	Effect size	Risk of bias
3.3 Effect of decision tools/educational material and strategies on patient/parent decision regret (n=1 study)	Allingham 2018	34 parents of patients with childhood cancer (aged 0-18 years) 34 completed the pre-DA survey 15/34 (44.12%) completed the pre- and post-DA survey	Web-based Decision Aid (DA) for parents of children and adolescents with cancer developed according to the International Patient Decision Aid Standards	*Decision regret scale scores (pre- vs. post-decision aid)* All parents (n=14): 16.5 (SD 18.6) vs. 18.5 (SD 19.4) p = 0.54 Parents of boys (n=6): 5.8 (SD 12.0) vs. 10.0 (SD 16.7) p = 0.32 Parents of girls (n=8): 25.7 (SD 19.0) vs. 25.7 (SD 19.7) p = 1.0	SB: High risk AB: High risk DB: Unclear CF: High risk
GRADE assessment:					
Study design:	+2	Observational studies			
Study limitations:	-3	Limitations: Selection bias high; Attrition bias high; Detection bias unclear; Confounding high			
Consistency:	0	Not applicable, only one study available			
Directness:	0	Results are direct, population and outcomes are broadly generalizable			
Precision:	-2	Imprecision, small sample size and only one study available			
Publication bias:	0	Unlikely			
Effect size:	0	No large magnitude of effect			
Dose-response:	0	No dose response relationship			
Plausible confounding:	0	No plausible confounding			
Quality of evidence:		⊕⊖⊖⊖ VERY LOW			
Conclusion:		A web-based fertility preservation decision aid was not significantly associated with decision regret in parents of patients with childhood cancer. (*1 study; 15 participants*)			

Effect of decision tools/educational material for patients/families on oncofertility clinical practice

PICO	Study	No. of participants	Intervention	Effect size	Risk of bias
3.4 Effect of decision tools/educational material and strategies for patients/families	Balcerek 2020	214 childhood cancer patients aged 12-19 years at diagnosis 113 patients who received standard patient	Information flyer at initial diagnosis in addition to standard patient education	*Utilization of cryopreservation* Control group: 37/113 (32.7%); Intervention group: 37/101 (36.6%); Difference not statistically significant Rates of cryopreservation showed no statistically	SB: Low risk AB: Low risk DB: High risk CF: Low risk

on fertility preservation clinical practice (n=1 study)		education pre-intervention 101 patients who received the intervention		significant differences between the groups according to treatment	

GRADE assessment:		
Study design:	+2	Observational studies
Study limitations:	0	Limitations: Selection bias low risk; Attrition bias low risk; Detection bias high risk; Confounding low risk
Consistency:	0	Not applicable, only one study available
Directness:	0	Results are direct, population and outcomes are broadly generalizable
Precision:	-2	Imprecision, only one study, sample size was above 100 but they did not reach required sample size calculated
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Education materials (information flyer) for CAYA cancer patients and families was not significantly associated with utilization of cryopreservation.

PICO	Study	No. of participants	Intervention	Effect size	Risk of bias
3.5 Effect of decision tools/educational material and strategies for patients/families on fertility preservation clinical practice (n=1 study)	Borgmann-Staudt 2019	200 parents and 214 childhood cancer patients aged 12-19 years at diagnosis 113 patients and 111 parents who received standard patient education pre-intervention 101 patients and 99 parents who received the intervention	Information flyer at initial diagnosis in addition to standard patient education	*Medical consultation* 12/13 (92.3%) investigators stated that participation in PanCareLIFE patient education had influenced their medical consultation practices concerning fertility issues. Information supported study physicians in educating themselves. Implementation of new standard operating procedures (SOPs) in some centers. 3/11 (27.3%) centres established fertility cryopreservation programmes for girls during the course of the study.	SB: Low risk AB: Unclear DB: High risk CF: Low risk

GRADE assessment:		
Study design:	+2	Observational studies

Study limitations:	-1	Limitations: Selection bias low; Attrition bias unclear; Detection bias high risk; Confounding low risk
Consistency:	0	Not applicable, only one study available
Directness:	0	Results are direct, population and outcomes are broadly generalizable
Precision:	-2	Imprecision, only one study, sample size was above 100 but they did not reach required sample size calculated
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Education materials (information flyer) for CAYA cancer patients and families improved fertility preservation consultation practice.

Effect of strategies/interventions for healthcare professionals and patients/parents on healthcare professional outcomes

PICO	Study	No. of participants	Intervention	Effect size	Risk of bias
3.6 Effect of decision tools/educational material and strategies on healthcare providers confidence levels to discuss fertility preservation (n=1 study)	Kemertzis 2018	All clinical staff involved in the care of oncology patients caring for childhood cancer patients Pre-intervention (T0) n=59 2 yr post-intervention (T1) n=38	Newly developed fertility preservation toolkit consisting of clinician instruction booklet, checklist, referral forms, reference information regarding fertility risk of cancer treatments, and handouts for patients and families	*Confidence levels of clinicians in providing fertility preservation information (T0 vs. T1)* 23/57(40.3%) vs. 26/37 (70.3%); OR 0.3 (95%CI 0.1-0.9)	SB: Low risk AB: High risk DB: Unclear CF: High risk

GRADE assessment:		
Study design:	+2	Observational studies
Study limitations:	-1	Limitations: Selection bias low; Attrition bias high; Detection bias unclear; Confounding high
Consistency:	0	Not applicable, only one study available
Directness:	0	Results are direct, population and outcomes are broadly generalizable
Precision:	-2	Imprecision, small sample size and only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect

Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		A fertility preservation toolkit for healthcare providers, including educational materials, checklist, referral forms and handouts for patients, increased paediatric oncology clinician’s confidence levels. (*1 study; 38 participants*)

Effect of strategies/interventions for healthcare professionals and patients/parents on oncofertility clinical practice

PICO	Study	No. of participants	Intervention	Effect size	Risk of bias
3.7 Effect of decision tools/educational material and strategies on healthcare providers involvement in verbal/written information on fertility preservation (n=1 study)	Kemertzis 2018	All clinical staff involved in the care of oncology patients caring for childhood cancer patients Pre-intervention (T0) n=59 2 yr post-intervention (T1) n=38	Newly developed fertility preservation toolkit consisting of clinician instruction booklet, checklist, referral forms, reference information regarding fertility risk of cancer treatments, and handouts for patients and families	*Clinicians providing verbal information (T0 vs. T1)* 20/58 (34.5%) vs. 21/31 (67.7%); OR 0.3 (95% CI 0.1-0.7) *Clinicians providing written information (T0 vs. T1)* 8/57 (14%) vs. 11/31 (35.5%); OR 0.3 (95% CI 0.1-0.96) *Clinicians involved in fertility preservation discussions (T0 vs. T1)* OR 0.5 (95% CI 0.2-1.4)	SB: Low risk AB: High risk DB: Unclear CF: High risk

GRADE assessment:		
Study design:	+2	Observational studies
Study limitations:	-1	Limitations: Selection bias low; Attrition bias high; Detection bias unclear; Confounding high
Consistency:	0	Not applicable, only one study available
Directness:	0	Results are direct, population and outcomes are broadly generalizable
Precision:	-2	Imprecision, small sample size and only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW

Conclusion:	A fertility preservation toolkit for healthcare 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. There was no significant effect of the fertility preservation toolkit on the likelihood of clinicians involved in fertility preservation discussions. (*1 study; 38 participants*)

PICO	Study	No. of participants	Intervention	Effect size	Risk of bias
3.8 Effect of decision tools/educational material and strategies on fertility preservation discussion, referral and preservation outcome (n=1 study)	Bradford 2018	Adolescent and young adult cancer patients aged 14-25 yr Pre-intervention n=260 Post-intervention n=216	Bundled intervention, including establishment of quality indicators for youth cancer fertility, targeted education sessions for medical and senior nursing clinicians, provision of gender-specific patient resource packs to newly diagnosed patients, development of fertility referral pathways, procedure, and work instruction forms	*Documented risk of infertility discussion (pre- vs. post-intervention), RR (95% CI)* All cancer patients: 1.47 (1.12–1.63) 14–19 years of age: 1.45 (1.22–1.71) 20–25 years of age: 1.48 (1.29–1.70) Males: 1.35 (1.19–1.5) Females: 1.70 (1.39–2.08) Leukaemia: 1.32 (1.07–1.62) Lymphoma: 1.27 (0.99–1.63) Brain tumour: 2.15 (1.03–3.62) Bone sarcoma: 1.32 (1.03–1.69) Soft tissue sarcoma: 2.60 (1.17–5.78) Germ cell tumour: 1.49 (1.16–1.91) Carcinoma: 1.58 (1.09–2.30) *Documented referral to fertility specialist (pre- vs. post-intervention), RR (95% CI)* All cancer patients: 1.53 (1.26–1.87) Age group 14–19 years: 1.41 (1.03–1.93) Age group 20–25 years: 1.63 (1.27–2.11) Males: 1.44 (1.17–1.77) Females: 1.82 (1.15–2.89) Bone sarcoma: 1.84 (1.12-3.01) Carcinoma: 2.37 (1.15-4.88) Lymphoma, leukaemia, brain cancer, soft tissue sarcoma and germ cell tumour were not significant. *Documented fertility preservation outcome (pre- vs. post-intervention), RR (95% CI)*	SB: low risk AB: low risk DB: unclear CF: high risk

				All cancer patients: 2.56 (1.19–3.44) Age group 14–19 years: 2.01 (1.16–3.48) Age group 20–25 years: 2.60 (1.82–3.71) Males: 2.89 (2.05–4.09) Females: 1.90 (1.08–3.33) Lymphoma: 2.16 (1.32–3.54) Bone sarcoma: 3.08 (1.32–7.18) Germ cell tumor: 2.71 (1.37–5.38) Carcinoma: 3.69 (1.10–12.39) Leukaemia, brain cancer and soft tissue sarcoma were not significant.	

GRADE assessment:

Study design:	+2	Observational studies
Study limitations:	-1	Limitations: Selection bias low , Attrition bias low, Detection bias unclear, Confounding high
Consistency:	0	Not applicable, only one study available
Directness:	0	Results are direct, population and outcomes are broadly generalizable
Precision:	-1	Imprecision, only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		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 fertility preservation outcomes of AYA cancer patients (*1 study; 476 participants*)

PICO	Study	No. of participants	Intervention	Effect size	Risk of bias
3.9 Effect of decision tools/educational material and strategies on fertility preservation attempt	Saraf 2018	161 CAYA cancer patients 69 underwent consultation and 92 no consult	Opt-out implementation: a “nudge intervention” in that the default results in an automatic consult order, providing the opportunity for more patients to receive counseling and consider fertility preservation	*Predictors of completed fertility consultation, OR (95% CI)* Opt-out mechanism: 3.64 (1.84–7.22) *Predictors of fertility preservation attempt after consultation, OR (95% CI)* Opt-out mechanism: 0.48 (0.15–1.51)	SB: unclear AB: low risk DB: unclear CF: unclear

(n=1 study)	

GRADE assessment:

Study design:	+2	Observational studies
Study limitations:	-1	Limitations: Selection bias unclear; Attrition bias low ; Detection bias unclear; Confounding unclear
Consistency:	0	Not applicable, only one study available
Directness:	0	Results are direct, population and outcomes are broadly generalizable
Precision:	-1	Imprecision, only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding

Quality of evidence:	⊕⊖⊖⊖ VERY LOW
Conclusion:	The implementation of an opt-out mechanism (default results in an automatic consult order) increased the likelihood of completing fertility preservation consultation among CAYA cancer patients. There is no significant association between the implementation of an opt-out mechanism (default results in an automatic consult order) and fertility preservation attempts after consultation among CAYA cancer patients. (*1 study; 161 participants*)

PICO	Study	No. of participants	Intervention	Effect size	Risk of bias
3.10 Effect of decision tools/educational material and strategies on health care providers perceived benefit to oncofertility clinical practice (n=1 study)	Hand 2018	39 clinicians involved in paediatric oncofertility care 10 (27.7%) nursing staff 22 (61.1%) medical staff 7 (19.4%) allied health or supportive care staff	Clinician decision support system (CDSS), including an electronic clinical oncofertility pathway, flowchart and a step-wise guidance, directing clinicians through the oncofertility pathway, E-links including detailed guidance, risk table and patient information handout	*Impact of the CDSS on perceived benefit to oncofertility clinical practice* 86.5% felt the CDSS would enable adherence to consistent clinical pathways. 81.1% felt the CDSS would enable adherence to policy and standards of care. 45.9% felt the CDSS would help improve clinician satisfaction. 65% felt the CDSS would increase clinician knowledge, improve patient and family understanding and improve their decision marking.	SB: Low risk AB: High risk DB: Unclear CF: High risk

GRADE assessment:

Study design:	+2	Observational studies
Study limitations:	-1	Limitations: Selection bias low; Attrition bias high; Detection bias unclear; Confounding high
Consistency:	0	Not applicable, only one study available
Directness:	0	Results are direct, population and outcomes are broadly generalizable

Precision:	-2	Imprecision, small sample size and only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		A clinical decision support system 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. (*1 study; 39 participants*)

4. What is the patient/parent reported satisfaction with the use of decision tools/educational materials and (educational, organizational) strategies in the discussion of treatment-related fertility risks and fertility preservation for cancer patients diagnosed before 25 years?

Intervention studies

PICO	Study	No. of participants	Intervention	Effect size	Risk of bias
4.1 Patient/ parent reported satisfaction with tools/educational material and strategies (n=1 study)	Allingham 2018	34 parents of patients with cancer (aged 0-18 years) 34 completed the pre-DA survey 15/34 (44.12%) completed the pre- and post-DA survey	Web-based Decision Aid for parents of children and adolescents with cancer developed according to the International Patient Decision Aid Standards	*Parents reported satisfaction with the decision aid design* All parents considered the length to be about right. 8/15 (53%) reported that the decision aid was very appealing to look at. 11/15 (73%) mentioned that it was very clearly presented. 9/15 (60%) were satisfied with the website format. *Parents reported satisfaction with content* 13/15 (87%) reported that the information in the decision aid was balanced and fair. 12/15 (80%) felt that the information was "sufficiently detailed". 1/15 (7%) found the decision aid to be confusing. 13/15 (87%) reported that it clearly presented their child's fertility choices. 12/15 (80%) reported that the information would have been quite/very relevant when considering fertility preservation for their child.	SB: High risk AB: High risk DB: Unclear CF: High risk
GRADE assessment:					

Study design:	+2	Observational studies
Study limitations:	-3	Limitations: Selection bias high; Attrition bias high; Detection bias unclear; Confounding high
Consistency:	0	Not applicable, only one study available
Directness:	0	Results are direct, population and outcomes are broadly generalizable
Precision:	-2	Imprecision, small sample size and only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Majority of parents of childhood cancer patients were satisfied with the design and content of a newly developed fertility preservation decision aid. (*1 study; 34 participants*)

5. What is the healthcare provider reported satisfaction with the use of decision tools/educational materials and (educational, organizational) strategies in the discussion of treatment-related fertility risks and fertility preservation for cancer patients diagnosed before 25 years?

Non-intervention studies

Outcome	Study	Participants	Method	Summary of findings
5.2. Healthcare providers reported satisfaction with decision tools/educational material and strategies available for the patient in the discussion of fertility risks and fertility preservation	Murphy 2014	Interviews with: 10 cancer patients (undergoing treatment) 10 parents 5 healthcare providers in paediatric oncology Suggestions for revisions were tested with 3 focus groups: 6 cancer patients 10 parents	Face-to-face interviews and focus groups	*Opinion of a Spanish education brochure on fertility risks and fertility preservation* Some health professionals suggested terminology was too complex, while others remarked that Spanish language families want to read the medical language The majority of health professionals stated that the brochure was likely to prompt families to have discussions with their physician
	Murphy 2012	7 cancer patients and survivors 11 parents	Face-to-face interviews	*Opinion of a paediatric fertility preservation brochure* Healthcare providers reported that the design had to look more

(n=7 studies)		6 healthcare providers in paediatric oncology		exciting and less for adults; the language had to be more hopeful stressing the return to normality after cancer; and the brochure had to cover barriers to uptake of fertility preservation methods such as misconceptions
	Quinn 2009a	24 paediatric oncologists* 28 adult oncologists	Semistructured in-depth interviews	*Use of educational material for fertility preservation* Few paediatric oncologists reported that the nationally distributed educational brochure they used was not always relevant to the local level and needed improvement
	Reebals 2006	27 haematology/oncology nurse practitioners and registered nurses caring for adolescent male cancer patients	Survey	*Use of educational material for sperm banking discussion* 67% of nurses/nurse practitioners reported that they would be more likely to offer the option if they had educational materials explaining sperm banking available for the patients and their families
	Vadaparampil 2007	115 nurses attendees of paediatric oncology conference: 111 (97%) served a paediatric population 103 (90%) primarily worked in oncology	Survey	*Use of educational material for fertility preservation discussion* 32% of nurses reported to be more likely to discuss fertility preservation options with patients if they had detailed educational materials about fertility preservation available
	Vadaparampil 2008	24 paediatric oncologists	Semistructured in depth interviews	*Use of educational materials for fertility preservation discussion* 66% of paediatric oncologists, who did not give educational material to patients on a regular basis, reported a lack of materials or felt the current materials available were not appropriate for their patient population All paediatric oncologists stated the need for low-literacy and culturally appropriate educational material

	Fuchs 2016	326 paediatric oncology providers: 157(48%) physicians 59(18%) advanced practice nurses 54(17%) nurses 56(17%) unknown	Survey	*Use of educational material for fertility preservation discussion* 51% of physicians, 54.2% of advanced practice nurses and 38.9% of nurses reported 'usually' or 'always' using educational materials Majority of providers reported using printed materials, the next greatest proportion of providers reported using Internet site referrals *Limitations of existing educational material for fertility preservation* 49% of providers stated that adult content, adult language and overall reading level were limitations of existing educational material
GRADE Assessment:				
Methodological limitations:	Some methodological limitations in 8/8			
Coherence:	No concerns on coherence			
Adequacy of data:	No concerns on adequacy of data (7 studies; 527 study participants)			
Relevance:	No concerns on relevance (healthcare providers in paediatric oncology in 7/7)			
Overall assessment of confidence in findings:	**MODERATE confidence in the evidence**			
Conclusion:	Healthcare providers report that former educational materials about fertility preservation are sometimes lacking and the existing materials need to be improved and adapted to the patient population. *(3 surveys, 3 interview studies, 1 interview and focus group study; 527 study participants)*			

Abbreviations: NM, not mentioned; NA, not applicable

* Data from pediatrics oncologists was pooled from Vadaparampil 2007

Intervention studies

PICO	Study	No. of participants	Intervention	Effect size	Risk of bias
5.1 Healthcare providers reported satisfaction with decision tools/educational material and strategies available for the patient in the	Allingham 2018	34 parents of patients with cancer (aged 0-18 years) 34 completed the pre-DA survey 15/34 (44.12%) completed the pre- and post-DA survey	Web-based Decision Aid for parents of children and adolescents with cancer developed according to the International Patient Decision Aid Standards	*Clinician acceptance of the decision aid by its perceived usefulness* All clinicians reported that they would recommend the decision aid to patients. They thought that the decision aid was well designed and easy to use; the decision aid was a good information source; and there is a need for more information and resources for patients and parents beyond the decision aid. Clinicians reported satisfaction with the design and	SB: High risk AB: High risk DB: Unclear CF: High risk

discussion of fertility risks and fertility preservation (n=2 studies)				usability of the decision aid website and regarded it as a valid and relevant source of information for clinicians, patients, and their families.	
	Kemertzis 2018	All clinical staff involved in the care of oncology patients caring for childhood cancer patients Pre-intervention (T0) n=59 2 yr post-intervention (T1) n=38	Newly developed fertility preservation toolkit consisting of clinician instruction booklet, checklist, referral forms, reference information regarding fertility risk of cancer treatments, and handouts for patients and families	*Healthcare provider reported satisfaction 8 weeks after toolkit implementation* In 7/11 (63.6%) of FP discussions, the clinician was satisfied with the toolkit. In 11/11 (100%) of FP discussions, the clinician was extremely satisfied with the FP discussion. *Reason for dissatisfaction with the toolkit 8 weeks after toolkit implementation* Missing documents within the toolkit. Organization of the documents within the toolkit. Too much written information which are not relevant for patient. *Healthcare provider reported satisfaction 2 yr after toolkit implementation* 20/37 (54.1%) were satisfied with the FP toolkit system. One participant reported a great improvement in clinical practice since the use of toolkit *Reason for dissatisfaction with the toolkit 2 yr after toolkit implementation* Inefficient. Some aspects needed tweaking. *Comparison between study populations of pre-toolkit vs. 2 yr post-toolkit* Satisfaction levels: OR 0.4 (95% CI 0.2-1.1)	SB: Low risk AB: High risk DB: Unclear CF: High risk
	Hand 2018	39 clinicians involved in paediatric oncofertility care 10 (27.7%) nursing staff 22 (61.1%) medical staff 7 (19.4%) allied health or supportive care staff	Clinician decision support system (CDSS), including an electronic clinical oncofertility pathway, flowchart and a step-wise guidance, directing clinicians through the oncofertility pathway, E-	*Perceptions on acceptability and efficiency* 94.9% said the aims of the CDSS were clear. 83.3% agreed that the CDSS was created to encourage clinicians to discuss fertility with their patients. 97.4% reported understanding of the overall fertility pathway and CDSS components. 92% stated the CDSS format was clear and understood the steps specific to their role.	SB: Low risk AB: High risk DB: Unclear CF: High risk

		links including detailed guidance, risk table and patient information handout	96.2% reported the willing to lead fertility discussions using the CDSS. 82.9% thought the CDSS was of appropriate length.

GRADE assessment:		
Study design:	+2	Observational studies
Study limitations:	-2	Limitations: Selection bias low in 2/3, high in 1/3; Attrition bias high in 3/3; Detection bias unclear in 3/3; Confounding high in 3/3
Consistency:	0	Not applicable, only one study available
Directness:	0	Results are direct, population and outcomes are broadly generalizable
Precision:	-1	Imprecision, small sample sizes
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⊖⊖⊖ VERY LOW
Conclusion:		Majority of healthcare providers were satisfied with newly developed decision tools/educational materials and strategies available for the patient and health care provider. Major reasons for dissatisfaction were discussions occurring too late, lack of clarity regarding reasons for referral and FP options, inefficiency, thus requiring improvement in some aspect**,** incomplete integration of the CDSS into (electronic medical record system and a lack of a systematic approach to FP discussions. (*3 studies; 92 participants*)

6. What are the patient and/or parents/caregivers/partners reported barriers for not pursuing fertility preservation amongst cancer patients diagnosed before 25 years?

Outcome	Study	Participants	Age at patients' diagnosis	Method	Summary of findings
5. Patient and/or parents/caregivers/ partners reported barriers for not pursuing fertility preservation (n=19 studies)	Bashore 2007	32 male patients with initial and recurrence cancer diagnosis	NM Range age at diagnosis of patients who successfully banked their sperm: 14-22 years	NM	*Barriers to sperm banking* 7(22%) patients were too ill to provide sperm sample 2(6%) parents did not consent for sons to be approached to discuss sperm banking: 1 parent due to religious beliefs; 1 parent felt that masturbation was not adequate for their son to perform

	De Vries 2009	14 parents of male patients undergoing cancer treatment	NM Patients' age at study: 11-13 years	In-depth semistructured interviews	*Barriers to sperm banking* Some parents reluctant for clinicians to have discussion with their child because conversations were ill-timed and confronting due to sensitive nature
	Diesch 2016	9 physicians (1 per each of the Swiss paediatric haematology/oncology centres)	NM	Survey	*Barriers to fertility preservation counselling (according to physicians)* Reported reasons for refusal of counselling by parents/ patients were lack of interest (66%), overwhelming nature of the situation (66%), and psychological distress in a life-threatening situation (55%)
	Ginsberg 2010	21 parents of males with cancer who were approached for testicular cryopreservation	Mean (SD): 5.5 (3.9) years (3 months-14 years)	Questionnaire	*Barriers to testicular tissue cryopreservation* 80% of parents who refused consent to the biopsy reported that they were too overwhelmed by diagnosis to hear about testicular tissue cryopreservation (vs. 31% of parents who agreed to biopsy) 60% of parents who refused biopsy reported that frozen testicular never used in humans to achieve pregnancy influenced their decision (vs. 38% of parents who agreed to biopsy)
	Ginsberg 2014	62 cancer patients facing gonadotoxic therapy 12 patients with immunodeficiencies and hematologic diseases	Accepters: Mean: 6.7 years (0.2-14.5 years) Refusers: Mean: 7.0 years (0.8-15 years)	Questionnaire	*Barriers to testicular tissue cryopreservation* Refusers felt more overwhelmed at the time of the decision (compared to accepters, p=0.0221) Refusers were more likely to weigh the risks of the testicular biopsy procedure (compared to accepters, p=0.007)
	Gupta 2016	153 parents of pre-pubertal boys with cancer 77 male childhood cancer survivors	Children: ≤12 years, median 4 years Survivors: ≤12 years, median 5 years	In-depth interviews	*Barrier to testicular tissue cryopreservation* Parents and patients perceived a >30% risk of infertility, a >25% chance of complications of testicular biopsy, a >$500 per year storage cost, and a >14% chance that technology will evolve as barriers for

					testicular tissue cryopreservation
	Köhler 2011	180 paediatric oncology health professionals	NA	Survey	*Barriers to sperm banking (according to healthcare professionals)* Patients/parents desire to initiate treatment as soon as possible, not wanting to be concerned with possible infertility, and not being concerned with parenthood at the time of treatment
	Benedict 2016	179 female cancer survivors	23.6 years (0-35 years) Subgroup: 23.4 years (0-34 years)	Survey	*Barriers to fertility preservation* 30% of patients did not know about fertility preservation; 29% of patients were feeling too distressed or overwhelmed; and 27% of patients reported cost as barrier Multivariate analysis showed a significant relation between greater unmet information needs and higher levels of decisional conflict about future fertility preservation, $p < 0.001$
	Klosky 2017a	99 male cancer patients	NM 13-21 years	Questionnaire	*Barriers to sperm banking* Adolescents who did not complete a specialized fertility preservation consultation were less likely to bank sperm relative to those with this referral: consultation yes vs no, OR 4.96 (95%CI 1.52-16.00), $p < 0.01$
	Burns 2006	50 families of female adolescents diagnosed with cancer: 39 parent/female adolescent pairs 3 parent-only 8 female adolescent-only	NM Median age at time of survey: 15 years (10 - 21 years)	Survey	*Barriers to fertility preservation* Adolescents and parents reported to not be willing to postpone cancer treatment by 1 month or more for research treatments of fertility preservation

	Klosky 2017b	144 parents (of 122 adolescent males with cancer)	NM 13-21 years	Questionnaire	*Barriers to sperm banking attempt* Adolescents who did not have a parental recommendation to bank sperm were less likely to make collection attempt relative to those who did have recommendation: parental recommendation yes vs no, OR 3.72 (95% CI 1.18-11.76), p=0.03 Adolescents who did not have a parent who coordinated/facilitated banking were less likely to make a collection attempt relative to those who did have: Parental self-efficacy yes vs no, OR 1.20; 95% CI 1.02-1.41; p=0.02
	Klosky 2017c	146 male adolescents with cancer	Mean 16.49 years	Questionnaire	*Barriers to sperm banking (adolescent report)* Adolescents who did not have a history of masturbation were less likely to bank sperm relative to those who did have a history of masturbation: masturbation yes vs no, OR 5.99 (95%CI 1.25-28.50), p= 0.025 Adolescents who did not have self -efficacy for banking coordination were less likely to bank sperm relative to those who did have self-efficacy: banking self-efficacy yes vs no, OR 1.23; 95%CI, 1.05 to 1.45; p=0.012 Adolescents who did not have parent recommendation to sperm bank were less likely to bank sperm relative to those who did have recommendation: parental recommendation yes vs no, OR 4.62 (95%CI 1.46-14.73) p=0.010 Adolescents who did not have medical team recommendation to sperm bank were less likely to bank sperm relative to those who did have recommendation: medical team recommendation yes vs no, OR 4.26 (95% CI, 1.45-12.43) p=0.008

	Klosky 2018	146 male adolescents with cancer	Mean 16.49 years	Questionnaire	*Barriers to sperm banking (adolescent report)* Recommendations from a provider were associated with greater likelihood to successfully bank: successful sperm banking, yes v no, OR 2.67 (95% CI, 1.05-6.77), p=0.039 Recommendations from a parent were associated with greater likelihood to successfully bank: successful sperm banking, yes v no, OR, 3.02 (95% CI, 1.1-8.10) p=0.029 Adolescents who reported higher self-efficacy to bank were more likely to be successful: successful sperm banking, yes v no, OR, 1.16 (95% CI,1.01-1.33) p=0 .034 Adolescents who consulted with a fertility specialist were more likely to successfully bank: successful sperm banking, yes v no, OR 3.44 (95% CI, 1.00-11.83) p=0.050
	Diesch 2017	38 physicians reporting 834 patients (70% with malignant disease)	NM	Survey	*Barriers to fertility preservation counselling (according to physicians)* Reported reasons for refusal of counselling of fertility preservation by parents/ patients were psychological distress in a life-threatening situation (53%), overwhelming nature of the situation (50%) and lack of interest (42%)
	Wyns 2015	120 prepubertal boys and adolescents aged 0–18 years diagnosed with cancer Parents gave their answers for 22 patients under 12 years of age and 3 aged 12–18yrs	Boys <12 yr: 6.05 (0-11.9) yr Boys 12-18 yr: 14.41 (12-17.7) yr	Closed-ended questionnaire	*Barriers to fertility preservation among boys* 46% of boys aged 12–18 years considered the fertility preservation method challenging because of poor general health, lack of experience with masturbation and its taboo or embarrassing nature. Fertility preservation acceptance rates were 74% for boys aged <12 and 78.6% for boys 12-18 years. Reasons for refusal were the urgency of cancer

					treatment, diminished general health, the procedure not being a priority, or the experimental status before puberty. Wishing to avoid an additional procedure was not an issue for FP acceptance. Satisfaction about completeness of information provided to patients and parents and hope for future parenthood positively impact decision to preserve fertility ($p<0.05$). Timing of information, healthcare provider who proved the information and anxiety were not significantly associated with decision to preserve fertility.
	Khalife 2019	70 parents of female adolescent cancer patients	Mean 12.2 ± 2.67 yr at diagnosis	Questionnaire survey	*Reason for not applying for fertility preservation* It was not necessary: 32 (45.7%) Risks of hormones on my child's health: 0 (0%) Difficulty in finding proper facilities: 16 (22.8%) Time was limited: 9 (12.9%) Expenses of the procedure: 6 (8.6%) Poor success rates of fertility preservation options: 1 (1.4%) Other or unknown: 6 (8.6%) *Reason for declining oocyte cryopreservation* Unsafe procedure (bleeding, infection risks): 18 (25.7%) My daughter should decide and it’s impossible at her age: 5 (7.1%) Cultural issue related to disruption of hymen: 20 (28.6) Delay in the chemo treatment until egg collection: 3 (4.3%) Expensive procedure: 2 (2.9%) *Reason for declining ovarian tissue cryopreservation* Still experimental; no pregnancy is guaranteed: 18

					(25.7%) Unsafe procedure (risks of bleeding, infection), unnecessary: 34 (48.6%) Risking cancer relapse at future transplantation: 6 (8.6%) *Factors affecting acceptance rate* Parents with higher educational levels were more concerned about fertility-related issues of their daughters than parents with lower educational levels ($p < 0.001$). Acceptance rate of parents for vaginal retrieval did not significantly differ between the different age groups ($p = 0.67$). 18/70 (25.6%) of Muslims, 37/70 (52.6%) of Christians, and 19/70 (27.2%) of Druze would accept their daughters to undergo transvaginal egg collection ($p < 0.001$).
	Saraf 2018	161 childhood, adolescent and young adult cancer patients	Mean 8 (range <1–31) yr	Retrospective medical record review	*Predictors of completed fertility consultation (OR (95%CI); unclear if multivariable analyses)* Age at diagnosis: 1.11 (1.06–1.17) Female gender: 0.78 (0.41–1.49) Race (white vs other races): 1.17 (0.57-2.42) Opt-out mechanism: 3.64 (1.84–7.22) Leukemia/Lymphoma vs Sarcoma: 0.69 (0.30–1.59) Embryonal vs Sarcoma: 0.61 (0.18–2.04) Neuro-oncology vs Sarcoma: 0.40 (0.14–1.12) *Predictors of fertility preservation attempt after consultation (OR (95%CI); unclear if multivariable analyses)* Age at diagnosis: 1.12 (1.03–1.22) Female gender: 1.51 (0.51–4.46) Race (white vs other races): 3.60 (0.74–17.60) Opt-out mechanism: 0.48 (0.15–1.51) Leukemia/Lymphoma vs Sarcoma: 1.67 (0.39–7.12)

					Embryonal vs Sarcoma: 1.73 (0.22–13.67) Neuro-oncology vs Sarcoma: 4.33 (0.74–25.29)
	Jayasuriya 2019	108 parents and their 30 children with cancer	Mean 14.7 ± 2.1 (range 8.6-18.6) yr	Review of oncofertility database and the patient's medical record with questionnaire surve.	*Factor associated with decline in fertility preservation* Satisfaction in decision to decline was based on the experimental nature of what was available (n = 7) and risks to their child's health exceeding the expected benefit (n = 4) *Multivariate logistic analysis factors associated with high decisional regret (OR (95%CI))* Impression that FP procedures will not be successful in this lifetime: 2.958 (1.289–6.789) Having a fertility preservation procedure: 0.178 (0.050–0.639) Having a discussion after high-risk therapy has been commenced: 40.532 (2.352–698.6) Time since diagnosis: 0.830 (0.564–1.221) Age of patient at time of discussion: 0.998 (0.645–1.544) Age of patient at time of survey: 1.046 (0.968–1.131)
	Skaczkowski 2018	941 adolescent and young adult cancer patients	15-24 yr	Retrospective review of patient medical record	*Reasons for not having fertility preservation male vs female* Patient declined to proceed with suggested FP plan: 15/333 (5%) vs 15/268 (6%) Treatment too urgent: 2/333 (0.6%) vs 6/268 (2%) Treatment had already commenced: 1/333 (0.3%) vs 3/268 (1%) Infertility risk low: not reported vs 2/268 (0.7%) No reasons documented in medical record 315/333 (95%) vs 241/268 (90%) *Factors associated with documentation of fertility preservation procedure (OR (95% CI)) in multivariable analysis* Sex Female vs Male: 0.42 (0.30–0.59) Type of cancer AML vs CNS Tumour: 10.36 (6.02–17.83) ALL vs CNS Tumour: 14.07 (8.17–24.25)

		Soft Tissue Sarcoma vs CNS Tumour: 3.57 (2.00–6.39) Primary Bone Cancer vs CNS Tumour: 18.15(9.67–34.08) Ewing's Family Tumour vs CNS Tumour: 6.97 (3.83–12.69) Risk of treatment Intermediate vs No/Low: 1.43 (0.76–2.69) High vs No/Low: 3.84 (2.64–5.60) Type of treatment centre Paediatric vs Adult non-AYA: 0.96 (0.58–1.58) Adult AYA vs Adult non-AYA: 1.74 (1.17–2.57)
GRADE CERQual Assessment (for barriers reported in more than one study):		
Methodological limitations:	Some methodological limitations in all studies	
Coherence:	No concerns on coherence	
Adequacy of data:	No concerns on adequacy of data	
Relevance:	No concerns on relevance (>85% cancer patients in all but one study)	
Overall assessment of confidence in findings:	**MODERATE confidence in the evidence**	
Conclusion:	Reported barriers for not pursuing fertility preservation amongst patients and their parents include: • experimental nature of the fertility preservation procedure with the associated risks/complications (7 studies) • time constrains regarding delaying treatment (6 studies) • patient poor emotional and/or physical status (5 studies) • costs (3 studies) • lack of interest (3 studies) • parents highly stressed emotional status (parent reported barrier) (3 studies) • lack of experience, taboo and embarrassing feelings with masturbation (2 studies) • lack of parental and/or medical team recommendation (2 studies) • lack of patient self-efficacy for banking (2 studies) • poor success rate of the fertility preservation procedure (2 studies) • cultural/ religious beliefs (parents reported barrier) (2 studies) • young age at diagnosis (2 studies)	
GRADE Assessment (for barriers reported in one study only):		
Methodological limitations:	Some methodological limitations in 6/6 studies	
Coherence:	No concerns on coherence	
Adequacy of data:	Some concerns on adequacy of data (each barrier reported in one study only)	
Relevance:	No concerns on relevance (>85% cancer patients in 5/5)	
Overall assessment of confidence in findings:	**LOW confidence in the evidence**	

Conclusion:	Reported barriers for not pursuing fertility preservation amongst patients and their parents include: • sensitive nature of the fertility preservation conversation (parents reported barrier) (1 study) • parental self-efficacy (parents reported barrier) (1 study) • lack of specific fertility specialist consultation (1 study) • difficulty in finding proper facilities (1 study) • Insufficient information (1 study) • adult AYA vs. non-adult AYA treatment center (1 study)

Abbreviations: NM, not mentioned; NA, not applicable; OR, odds ratio; CI, Confidence Interval

7. What are the healthcare provider reported barriers to discuss treatment-related fertility risks and fertility preservation amongst cancer patients diagnosed before 25 years?

Outcome	Study	Participants	Method	Summary of findings
6. Healthcare providers reported barriers to discuss infertility risks and fertility preservation (n=21 studies)	Anderson 2008	Paediatric oncologists completed forms for 1030 patients	Survey	*Barriers to discussing treatment impact on fertility* Reported barriers included patient's infertility risk regarded as 'not significant' (300, 79%); patients seen as too young (93, 15%); patients' poor prognosis 48(13%); severity of patient's illness (19, 5%); unproven fertility preservation techniques (9, 2%); and inadequate facilities and/or funding (2, 0.5%) *Barriers to discussing fertility preservation methods* Barriers to the discussion included that patients were too young (299, 56%), patients 'not at significant risk' (258, 48%), unproven fertility preservation techniques (133, 25%), severity of patient's illness (69, 13%) and unlikely to survive (13, 2.4%), inadequate funding and/or facilities (62, 12%)
	Campbell 2016	1492 health professionals members of the COG: clinicians and investigators dedicated to paediatric cancer research	Survey	*Barriers to discussing fertility preservation* Barriers for not counselling patients were financial (47%), lack of knowledge (39%), perceived poor success rate (35%), lack of current partner (28%), poor patient prognosis (28%), lack of time (12%), and the patient already had children (5%)
	Chong 2010	15 medical professionals with an interest in fertility	Survey	*Barriers to sperm banking*

		preservation: 14 (93%) paediatric oncologists 1 (6.7%) specialist nurse		Main barriers to sperm banking included the need to start therapy, restricted access to sperm banking units, and lack of appropriate adolescent approach
	Clayton 2008	210 paediatric oncology nurses	Survey	*Barriers to discussing fertility preservation* Barriers to the discussion included low availability of guidelines for fertility preservation and established links with service providers
	Crawshaw 2004	22 health and social work professionals	Semistructured interviews	*Barriers to discussing fertility preservation* Barriers for paediatric oncologists included little prior knowledge of patient/family, no time to establish a relationship with a patient and time pressure Barriers for staff at the conception units included difficulties to complete consent forms and to facilitate provision of samples at first visit Many professionals reported ethnicity as a possible barrier when offering sperm banking to Asian men (in relation to marriage-ability) Barriers included difficulties in professionals in building and maintaining a relevant, adequate knowledge and skills base; lack of appropriate training about the legal and consent frameworks
	Forman 2009	36 oncologists: 22(61%) medical oncologists 8(22%) paediatric oncologists 6(17%) radiation oncologists	NR	*Barriers to discussing treatment impact on fertility* Barriers included patient poor prognosis (53%), the need for immediate therapy (24%) and patient already having children (24%) *Barriers to referring patients to fertility specialist* Barriers included patient disinterest in preserving fertility (39%) and limited time because of emergent need to start therapy (13%)
	Goodwin 2007	30 healthcare providers in paediatric haematology/	Survey	*Barriers to fertility preservation*

		oncology department		More than half of the healthcare providers (18, 64.3%) reported as barrier for fertility-related practices the difficulty in finding for their patients the proper facilities and specialists for fertility preservation 34.4% and 10.3% of providers reported that the success rates for female fertility preservation and for male sperm banking respectively were too low to justify pursuing gamete preservation 14.8% and 7.1% of providers reported that costs for infertility treatment for females and males respectively were too high to justify
	Gupta 2016	30 paediatric oncology health professionals	In-depth interviews	*Barriers to testicular tissue cryopreservation* Health professionals perceived a >29% risk of infertility, a >13.5% chance of complications, a >14% chance that that technology will evolve, and >$391 storage cost per year as barriers for testicular tissue cryopreservation
	Köhler 2011	180 paediatric oncology health professionals	Survey	*Barriers to sperm banking* Barriers for not recommending sperm banking was poor survival prognosis, aggressive disease requiring immediate initiation of treatment, and no consent provided by patients' parents
	Overbeek 2014	37 paediatric oncologists	Survey	*Barriers to discussing fertility and fertility preservation* 33 (89.2%) of paediatric oncologists cited insufficient time, 12 (32.4%) cited lack of knowledge about fertility preservation, 8 (21.6%) cited lack of data, and 9 (24.3%) cited patient's poor prognosis
	Quinn 2009a	24 paediatric oncologists	Semistructured in-depth interviews	*Healthcare system related barriers to discussing fertility preservation* The most common reported barrier was the financial cost of fertility preservation (fertility preservation was not included by insurance); the next most common reported barrier was a combination of lack of resources and lack of training or guidelines for paediatric oncologists

				Patient characteristics related barriers to discussing fertility preservation Barriers included perceived families' cultural or religious differences and families' socioeconomic status Barriers included the difficulty of establishing a sense of trust with the adolescent patient while not excluding parents
	Quinn 2009b	26 paediatric oncologists * 28 adult oncologists	Semistructured in-depth interviews	*Barriers to discussing fertility preservation* Barriers included little relevant training resulting in feelings of not having necessary skills for fertility preservation discussion; patients with limited English skills; belief that the fertility topic would cause additional distress and burden; perception that parents of children would not want to hear about fertility preservation or sterility; financial costs; patients with poor prognosis or with advanced disease
	Reebals 2006	27 haematology/oncology nurse practitioners and registered nurses who care for adolescent male cancer patients	Survey	*Knowledge about sperm banking as barrier to discussing fertility preservation* 92.6% of nurses had a lack of knowledge regarding cost of banking sperm; 70% of nurses had the mistaken impression that a patient needed to collect 3 to 6 semen samples before cancer treatment; almost 52% of nurses believed that birth defects would increase if children were conceived from semen collected during first week of chemotherapy or radiation; 48% were aware that infertility after treatment is more common in boys than in girls *Patient characteristics as barriers to discussing sperm banking* 78% of nurses reported a less likelihood of offering sperm banking to a HIV patient; 40.7% of nurses reported a less likelihood of offering sperm banking to a patient with aggressive disease; 33% of nurses reported a less likelihood of offering sperm banking to a patient open about being homosexual and 11.1% of nurses reported a less likelihood

				of offering sperm banking to with a patient under 19 years of age
	Vadaparampil 2007	115 nurses attendees of paediatric oncology conference 111 (97%) served a paediatric population 103 (90%) primarily worked in oncology	Survey	*Barriers to discussing fertility preservation* Reported factors that may have decreased the likelihood of discussing fertility preservation were positive HIV status (23%), poor patient prognosis (28%), and the inability to delay treatment because of aggressive disease (37%)
	Vadaparampil 2008	24 paediatric oncologists	Semistructured in depth interviews	*Barriers to discussing fertility preservation* Paediatric oncologists that felt less conformable discussing fertility preservation reported needing better educational materials and more established fertility preservation facilities to make them more comfortable *Parent/patient-related barriers to discussing fertility preservation* Physicians reported that parental emotional status was a barrier to the parent/patient receiving information 75% of physicians reported that patient health status was a barrier when patients were too ill to bank sperm or explore options; 33% of physicians reported that parents' culture/religion regarding masturbation influenced the discussion of fertility preservation *Institutional related barriers to discussing fertility preservation* 50% of physicians had no established relationship with any type of fertility clinic or specialist; 100% of physicians were not aware of guidelines for fertility preservation; majority of physicians reported that costs were a barrier to initiate fertility preservation and cost of long-term storage; 66% of physicians reported a lack of patient educational materials

				or felt the current materials available were not appropriate for their patient population
	Armuand 2017	58 physicians working within paediatric oncology	Survey	*Barriers to the fertility related discussions* The most frequently reported barriers included: patient being of pre-school age (50%); poor prognosis (47%); need for immediate treatment start (28%); patient or parent appearing anxious (26%); overwhelmed by the diagnosis (24%); high workload (24%); unclear referral paths for fertility preservation (22%) *Multivariate analysis*: Physicians were less likely to discuss the treatment's impact on fertility with patients/parents if: • they worked at a non-university hospital (male patients: OR 11.49, CI 1.98–66.67;female patients: OR 33.18, CI 4.06–271.07) • believed the subject would cause worry (male patients: OR 8.23, CI 1.48–45.89; female patients: OR 12.38, CI 1.90–80.70) • perceived parents as anxious (male patients: OR 7.18, CI 1.20–42.85, female patients: OR 11.65, CI 1.32–103.17)
	Diesch 2016	9 physicians (1 per each of the Swiss paediatric haematology/oncology centres)	Survey	*Barriers to discussing fertility preservation* 33% of the physicians reported that lack of time was the most frequently provided reason for the lack of counselling
	Fuchs 2016	326 paediatric oncology providers: 157(48%) physicians 59(18%) advanced practice nurses 54(17%) nurses 56(17%) unknown	Survey	*Knowledge about fertility preservation as a barrier to discussing fertility preservation* 26% of physicians, 35.6% of advanced practice nurses and 64.8% of nurses reported to be unfamiliar with 2006 ASCO recommendations on fertility preservation 48.7% physicians reported being unfamiliar with ICSI technique, compared with 52.5% of APNs and 81.1% of nurses (P<0.05)
	Panagiotopoulou 2017	48 adolescent and paediatric oncology healthcare professionals: 26% oncology doctors	Survey	*Barriers to fertility preservation discussion* 85% of healthcare professionals reported patient's age and patient's medical condition to be the most likely reason for not having a discussion on fertility; 82% reported the

		65% nurses 9% allied healthcare professionals		patient's or family's lack of interest in fertility discussions; and 77% reported their own knowledge gaps
	Diesch 2017	38 physicians reporting 834 patients (70% with malignant disease)	Survey	*Barriers to discussing fertility preservation* Physicians cited lack of time (59%), refusal by parents (35%), poor prognosis of the primary disease and financial considerations (5.9%) as the most frequently provided reasons for the lack of counselling
	Takae 2019	Medical professionals in 11 Asian countries who were members of the Asian Society of Fertility Preservation (ASFP)	Questionnaire survey	*Barriers that inhibit promotion of fertility preservation for children and adolescents cancer patients* 9/11 identified low recognition among medical staff. 7/11 identified low recognition in society. 8/11 indicated that information is insufficient. 6/11 indicated problems with the cooperative system within the pediatrics department. 3/11 selected "There is technology, but we don't know how to provide it". 3/11 said it is economically impossible. Only one participant from Thailand chose "It is not necessary because the adoption system is popular." Three participants from Australia mentioned "weakness of evidence for FP for pediatrics." Limited numbers of FP treatment facilities for C-A patients. Not enough information for physicians, oncologists, patients and family. Lack of public awareness.

GRADE Assessment (for barriers reported in more than one study):

Methodological limitations:	Some methodological limitations in all studies
Coherence:	No concerns on coherence
Adequacy of data:	Some concerns on adequacy of data (most of the studies have sample size below 100)
Relevance:	No concerns on relevance (>85% of healthcare providers in paediatric oncology)

Overall assessment of confidence in findings:	**MODERATE confidence in the evidence**
Conclusion:	Reported barriers by healthcare providers to fertility preservation discussions and decisions about fertility risks and fertility preservation include: Patient-related barriers: • Patient's poor prognosis, poor health status and risks (12 studies) • Patient's young age (4 studies)

	• Patient’s potential disinterest (2 studies) • Patient already having children (2 studies) • Positive HIV status (2 studies) • Patient’s culture/religion beliefs (2 studies) • Patient’s emotional state and the perceived additional stress with fertility topic (2 studies) Parental-related barriers: • Parental poor emotional status (2 studies) • (Perceived) parental lack of interest and/or knowledge (2 studies) • Lack of parental consent (2 studies) Healthcare provider- and institutional-related barriers: • Lack of knowledge, training and educational materials, and/or unfamiliarity with or low availability of relevant guidelines (11 studies) • Lack of time and time pressure to start treatment (10 studies) • Restricted access or inadequate liaisons with relevant facilities and specialists (8 studies) Procedure-related barriers: • Cost of procedure and/or storage (10 studies) • Experimental nature of the fertility preservation procedure with the associated risks/complications (4 studies)
GRADE Assessment (for barriers reported in one study only):	
Methodological limitations:	Some methodological limitations in all studies
Coherence:	No concerns on coherence
Adequacy of data:	Some concerns on adequacy of data (each barrier reported in one study only)
Relevance:	No concerns on relevance (>85% of healthcare providers in paediatric oncology)
Overall assessment of confidence in findings	**LOW confidence in the evidence**
Conclusion:	Reported barriers by healthcare providers to fertility preservation discussions and decisions about fertility risks and fertility preservation include Patient-related barriers: • Lack of current partner (1 study) • Difficulty of establishing sense of trust with patient (1 study) • Patient limited language skills (1 study) • Patient sexual orientation (1 study) • Adoption system is popular (1 study) Parental-related barriers: • Families’ socioeconomic status (1 study) Healthcare provider-related barriers: • Difficulties to complete consent form (1 study) • A problem with the cooperative system with the pediatrics department (1 study)

Abbreviations: COG: Children’s Oncology Group; NM, not mentioned; NA, not applicable; ICSI, intracytoplasmic Sperm Injection

* Data from paediatric oncologists was pooled from Vadaparampil 2007.

Summary of findings ethical considerations

1. Ethical considerations regarding informed consent

1.1 Informed consent to fertility preservation procedures in minors and young adults

- The requirement in the consent process for the individual to be able to understand the information given, believes it applies to them, retains it, and uses it to make an informed choice. (8, 47, 55)
- Need of valid consent to be informed, obtained voluntarily, and given by a competent person/parents/guardian/authorized person especially if the child is not capable of consenting. (8, 9, 47,53)
- Importance to consider that healthcare providers need to be up-to-date and with accurate knowledge about fertility preservation procedures, and the legal and consent frameworks. (13, 22, 32, 14, 35)
- Consent (with/without assent in minors) should be discussed and obtained on how gametes, embryos, and gonadal tissue preserved for the patient would be managed in the event of death. If the tissue is to be discarded, used in medical research, or allowed to be utilized for posthumous reproduction and by whom (7, 56, 57,58, 61)
- Importance to consider consent as a dynamic and on-going process (not just one interview) that is adapted over a time period as new research evidence evolves and new information becomes available. (27, 48, 53)
- The need to have multiple healthcare providers involved in the consent process. (14, 35)
- Importance to include the following information in the consent (or assent in minors): the likelihood of infertility, the collection procedure, the likelihood that the preserved gametes will be useful in attaining pregnancy, the disposition of gametes in the event of patient's death. (43)
- The need for the informed consent to disclose risks and potential benefits of fertility preservation including a discussion of immediate and future physical harms related to the procedures to preserve fertility and risks related to using the tissues to have a child later. (31, 33, 46)
- The need to disclose during informed consent of the potential adverse consequences for offspring such as birth defects to ensure an informed choice. (31)
- Importance to disclose during informed consent the potential psychological harms (false hope, anxiety, or hopelessness in case pregnancy is later not achieved) to ensure an informed choice. (5, 31)
- Importance for the healthcare provider to provide age-appropriate information, carefully assess the comprehension of the patient of any age and the parent/caregiver and, determine whether they are emotionally, psychologically, and mentally competent to consent and assent. (5, 12, 23, 39, 38, 14, 35, 44)
- Importance to consider the validity of consent within the context of parents/patients being stressed and vulnerable. Informed consent for minors needs to take into account the time pressures on affected families to make the decision before cancer treatment, the anxiety

that surrounds the situation, the complexity of the procedures involved, the uncertainty of future technological capabilities, and the ability of the child to comprehend the circumstances (not necessarily related to age) in order to be valid. (7, 11, 10, 13)

- Importance to consider who decides if minors should receive fertility-preserving treatment and how the informed consent and assent should be obtained in case of children. (12, 23, 53, 61, 62)
- Importance to consider a two-stage consent process: the decision for gonadal harvesting/storage would be made at cancer diagnosis, and parents or guardians would be left to decide to consent for the procedure. At a future moment, the patient in adulthood would make the decision of how to use the gametes. (7,33, 36, 39, 14, 35, 44, 47, 53, 57, 58, 59)
- Importance for parents to understand during the consent process that preservation might be desirable (but not required), and that their child will receive optimal treatment independently of their decision for the consent. (43)
- Importance of giving minors a say in preservation of future fertility. (10, 55, 61) The need for children to be involved in the process to assent to the extent of their capacity. (3, 12, 27, 33, 53, 55) Children need to be allowed to assent (affirmative agreement) to their treatment after being provided with a full explanation including risks, discomforts, benefits, and alternatives. (20, 58)
- The issue of uncertainty of decisional capacity for children and adolescents with respect to fertility preservation. (specialized consent form should be developed for adolescents 31, 55)
- The issue that a specialized consent form should be developed for adolescents, to allow them assent to fertility preservation (61)
- The issue that the process of consenting and assenting to these procedures may not fully understood by the pediatric patient. (13, 55, 59)
- The issue that obtaining assent for posthumous tissue use from minors can be challenging considering complexity of information, level of maturity, level of understanding, vulnerability due to cancer diagnosis, treatment. (56)
- The issue that a valid consent in the context of fertility preservation is not only a legal need but an ethical need. (48)

1.2. Safeguarding and protecting patients’ best interest when making decisions about fertility preservation

- The importance that seeking to preserve the child’s reproductive potential needs to be considered a substantial benefit to the child. (7) The importance for providers and parents/caregivers to take any decision in the patient’s best interests when considering options for future fertility. (7, 8, 12, 27, 31, 36, 48, 49, 51, 37, 53, 55, 56)
- The importance of taking into account that if a minor who is deemed capable of assenting objects to a proposed treatment does not assent, that treatment should not be given. (12)
- The importance to respect patient’s autonomy by putting the patient in a position to choose what is the best option for the improvement of their own condition and quality of life. (15, 43, 52, 55)

- The issue of considering if the child is capable of making decisions to respect patient's autonomy. (44, 53, 55)
- The importance of parents' role in decision-making as future fertility may be difficult for the prepubertal child to assess. (22)
- The issue that parents are eager to preserve child's fertility and the child may not understand the concept. (19)
- The issue that a minor cancer patient may have differing opinions about fertility and reproductive health and may be influenced by his parents when deciding fertility preservation method. (41, 62)
- The importance for providers to be aware of their gaps in knowledge and missing evidence and/or criteria for success (i.e. how much tissue to collect, long-term consequences). (36)
- The issue of considering age restrictions for patients to be allowed to take fertility preservation measures. (38, 62)
- The issue of age in the disclosure of sensitive health issues such as fertility potentials. (62)
- The difficulty by parents not to be driven by own interest and emotions but to contemplate what the child will desire when they are an adult and what is in the interest of their child. (16, 57, 60)
- The issue that parents play a role in decision-making of fertility preservation procedures that also carry risks. (26, 60)

2. Ethical considerations regarding communication

2.1. Communication between healthcare providers and patients and their parents/caregivers/partners

- Importance for healthcare providers to initiate the discussion about fertility preservation and to counsel (prepubertal and postpubertal) patients about (short-term and long-term) risk of future fertility and (established and experimental) options for fertility preservation in a timely manner and appropriate for patient's age and developmental, as it is a right for the patient and parents/caregivers to have provision of information. (1, 3, 5, 10, 12, 15, 18, 22, 25, 39, 38, 52, 29, 53, 54, 55)
- The issue that lack of information and insufficient communication about fertility preservation will prevent the patients from making informed decision. (63)
- The conflict between the need of information on fertility preservation for patients and the level of knowledge by healthcare providers about how and what fertility preservation options should be offered to patients. (23, 44)
- Importance of involving the mental health professionals and/or an ethics consultant in case of conflicts between patients and families on fertility preservation. (58)
- The issue about dealing in the discussion with the patient/parents/caregiver with reasonable expectations and the distinction between standard care and experimental interventions. (23)

- Importance for family to understand that tissue cryopreservation process is largely unproven for prepubertal tissue. (54)
- It is important for healthcare providers to counsel (prepubertal and postpubertal) patients and family to understand that there will be cases in which treatment will commence immediately and fertility preservation will not be an option. (58)
- Importance to provide information in a culturally sensitive and knowledge-adjusted manner because the use of samples for research, the disposal of samples if the patients die and use of assisted reproduction may be affected by cultural and religious background of the patient and his guardians. (41, 55, 56, 58, 61)
- The issue of discussing FP with post-pubertal minors, with and without the parents/caregiver present, while considering their cultural and/or religious values and beliefs. (55, 58, 61)
- Importance to be aware that information provided to patients/ parents/ caregivers might be understood differently. (41, 59)
- Importance to provide support and information to the patient and the parents/caregivers to be included in the decision-making process about fertility preservation whenever possible. (31, 44) The need for resources, such as educational materials and support tools or referral to fertility specialists for patients to help in the decision-making process. (5, 41)
- Importance to discuss possible harms/benefit of preserving fertility with the patients and family. (15, 54, 55, 62)
- The issue of informing and subjecting the child to the choice of gamete donation procedures or surrogacy. (19)
- The issue of timing for fertility preservation discussion after families have received a cancer diagnosis, and the need for balancing the discussion of fertility preservation with the timely start of cancer treatment. (22, 27, 59)
- The issue of possible gender disparity in the discussion and treatment offered for fertility preservation. (25)
- The issue of healthcare providers attitude, personal judgement or prejudices to potentially influence fertility preservation discussions. (25)
- The need for sensitive handling of the embarrassment some adolescents may have with sperm collection. (41)
- The need to inform the patient/parents/caregiver about possible conflicts of interest for the healthcare provider. (38)
- The issue of how to include the potential adverse consequences for offspring in the information provided to the patient/families/caregivers. (31)
- The issue (of how) to communicate to patients/families/caregiver the immediate and long-term financial costs in fertility preservation options. (23, 16, 54)
- The issue of limited time available for decision-making of fertility preservation. (14, 35, 59, 60)

3. Ethical considerations regarding potential risks of fertility preservation procedures

3.1. Harms versus benefits of fertility preservation procedures

- Importance of ascertaining the risk of the procedure itself to the patient (including anesthetic and operative risks) in the context of the patient´s disease state. (10, 44, 54)
- Importance to consider if the patient has other procedures planned that could be performed at the same time as fertility preservation procedure. (10, 54,)
- The issue of justifying the anesthetic and operative risks for (experimental) fertility preservation methods. (19, 26, 54)
- The issue that surgical and anaesthetic risks are sometimes increased by comorbidities. (54)
- The issue of how to select patients that are candidates for fertility preservation needs consideration. (9, 22, 23, 33, 36, 53, 58). The issue of collection and storage of gonadal tissue from a child only when the doctors/specialist have evaluated and certified there is a reasonable risk of the child becoming infertile before becoming an adult. (53)
- The issue that delaying treatment for fertility preservation methods may cause harm to the patient. Fertility preservation should occur, if the delay does not affect the success of the cancer treatment. (15, 22, 23, 51, 20, 54, 55, 58, 63)
- The issue that urgency to treatment may affect decision-making capabilities for fertility preservation. (52)
- The issue that parents report not to find ethical issues of cryopreservation to be major factors in the decision-making process for their son to undergo testicular biopsy with tissue cryopreservation. (17)
- The issue to justify transplantation of ovarian tissue with the potential risk of re-introducing cancer cells. (24, 36, 20, 54, 55, 56, 59, 60)
- The issue towards testing tissue/gametes from both child and adult for presence of cancerous cell before storing it. (53)
- Importance for experimental fertility preservation strategies in children/adolescents to be offered within well-designed research studies with approved protocol (31, 55, 53, 58, 62)
- The importance that the advantages of any intervention or of an active decision not to intervene should outweigh any disadvantages, to maintain best interests of the child in the short and long term. (5, 8, 48, 37, 53, 54, 55, 56, 59)
- The issue of potential violation of children's rights with children being possible experimental objects for the medical breakthrough. (14, 35)
- The issue that the child might be forced to grow up quickly when considering fertility aspects. (52)

- The issue of a presumed decreased life span in cancer survivors needs consideration as it can result in leaving their offspring without parents in event of earlier death. (11, 14, 35, 42, 51, 55, 56, 57)
- The issue of health risks to the potential offspring after fertility preservation measures needs consideration. (10, 11, 12, 14, 19, 29, 35, 41, 42, 44, 48, 51, 54, 55, 56, 59, 62)
- The issue of potential harm to germ cells from gonadotoxic therapy (for those patients who use gametes after chemotherapy and/or radiotherapy) or reproductive technologies. (10, 30, 14, 35, 54, 55, 56, 59)
- Importance of protecting the interest of the offspring that come as a result of a fertility preservation method, and to consider the follow-up of these children and mothers. (33, 56)

3.2. Experimental nature of fertility preservation procedures

- Experimental nature of procedures refers to the uncertainty about subsequent fertility benefit or harm that intervention may cause. (7, 33, 48, 55, 57, 62)
- Importance to consider if fertility preservation experimental treatments should be offered to prepubertal children with cancer. (12, 27, 29, 54, 55)
- The issue of justifying potential risks, especially for prepubertal children. (2, 54)
- Importance to consider if fertility preservation treatments currently provided to adults should be applied to children and adolescents. (12)
- The issue of possible future selection of gametes based on testing the heritability of the original malignancy needs consideration. (43)

3.3. Psychological issues surrounding decisions of fertility preservation procedures

- The issue of psychological benefits and costs around fertility preservation procedures. (41, 61)
- The issue that providing information on fertility preservation can be a source of hope and also a great disappointment for the patient as no guarantee can be given. (18, 22 ,44, 54, 61, 62) The issue that fertility preservation measures should not raise unrealistic or false expectations (i.e. raising hope and failing to fulfil them). (7, 14, 20, 35, 48, 57)
- Importance to consider the distress among patients and families as a result of making a quick experimental fertility preservation decision (before cancer treatment), and the guilt, panic or decisional regret that may follow the choice made (especially when the decision is made by a proxy on behalf of the child). (36, 46, 54, 60)
- The issue that the decision to take fertility preservation measures may be influenced by the idea that future technology will fix the problems of today. (46)
- The issue that having stored ovarian tissue may place a psychological burden on the patient later in life knowing the tissue is present. (46, 54)
- The issue that fertility preservation might create false hope about the patients chance of survival. (54)

- The issue of heritable genetic diseases or cancers and its impact on psychological functioning. (36)

4. Ethical considerations regarding storage of patients' material

4.1. Decisions on use and disposition of stored tissue for fertility preservation

- Storage of cryopreserved material needs consideration. (9, 14, 35, 51)

- Storage of the gonadal tissue or gametes should be done only if it is the best means of preserving the fertility of the child or young person and if the risk and discomfort of the procedure can be minimised (53)

- The issue that religion plays a role in collection and use of genetic tissue for future. (14, 35, 55, 58, 61)

- The need for clinician to seek advice from an independent body whenever there is any doubt about the collection and storage of gonadal tissue or gametes for a child or young person. (53)

- The need to decide about storage of tissue, sperm, or oocytes and disposition of tissue prior to fertility preservation. (51, 61)

- The issue of stored tissue, gametes and embryos not being used needs consideration. (24, 38, 58)

- The issue of considering a registry for stored tissue, gametes, embryos. (38)

- The time elapsed between banking tissue and its use is a unique feature of pediatric tissue banking. (40)

- The issue of ownership of embryos after divorce or relationship ends needs consideration. (24, 42)

- The issue of a future partner accepting parenthood of an embryo created with a former partner or sperm donor needs consideration. (24)

- The issue that it is not justified for parents (by virtue of their parenthood) to have any decision on the use of stored ovarian tissue needs consideration. (46)

- The issue with tissue and gamete donation. Should tissue and gamete obtained from a child who does not survive into adulthood be discarded, will to a relative or donate to another person? Is collection and storage of tissue from a child be of a reproductive needs of another individual. (38, 53, 58, 61, 62)

- The issue of future use of stored tissue, gametes, embryos: to consider limiting the number of those materials, and whether material should be labelled as coming from cancer patient, and whether the material should be donated to another person. (38)

4.2. Decisions on posthumous use of stored material for fertility preservation

- Disposition of gametes and preserved tissue in the event of patients' death needs consideration. (3, 11, 13, 19, 23, 24, 26, 33, 14, 35, 42, 43, 47, 48, 51, 52, 29, 53, 54, 55, 56, 57, 58, 61, 62, 63) Importance to determine upfront what happens to stored preserved tissue in the event of patient's death. (27, 56, 54, 55, 57, 58, 59, 62) The need to have a regulation regarding disposition of the ovarian tissue in advance at the time of freezing in case of patient's death. (46)
- The issue if researchers can have access to preserved tissue needs consideration. (19, 53) 55, 57)
- The issue of family members disagreeing/ agreeing about the disposition in event of patient's death and the need for a valid written documentation of the patient's wishes in genetic continuity before parents and relatives can utilize gametes for posthumous reproduction (37, 56, 57)
- The issue of the surviving partner considering posthumous reproduction. (24, 55, 56, 57)
- There should be an appropriate grieving period prior to posthumous reproduction (57)
- The issue that patient's decision regarding use or disposal of stored tissue needs to be respected. (51, 56, 53)
- Issue of psycho-social well-being of the offspring resulting from 1). being a 'planned orphan', if the parent dies at the time of conception and 2). the fact that his caregiver used him/her as a means for maintaining a genetic link to another deceased child. (56)

5. Ethical considerations regarding access to fertility preservation procedures

5.1. Offering access to fertility preservation procedures considering patient's cultural or religious background

- The issue of justice by offering access to care to all (including fertility preservation), regardless of race, culture, ethnic background. (41, 52)
- The need to have fairness and be inclusive in the collection and storage of material when offering cryopreservation. (43)
- The issue that semen obtained via ejaculation might pose religious and moral objections for some patients/families. (18, 41)

5.2. Restoring patients' reproductive autonomy with fertility preservation procedures

- The importance of restoring personal reproductive autonomy with fertility preservation. (33)
- The issue that fertility preservation methods can preserve reproductive autonomy for the patients and help them to have an open future in which they can make their own choices. (40, 57, 55, 58, 61)
- The debate about reproductive rights and whether there is a 'positive right' to reproduce (for an intervention to be needed). (42)

5.3. Differences in fertility preservation services across countries

- The issue of disparity in access to fertility preservation technologies implies a disparity in uptake of fertility preservation procedures between those affording the procedures and those that may be denied the opportunity. (24, 37, 62)

- The issue that insurance coverage is or not variable for cryopreservation. (24, 62, 63)

- The need to reduce financial barriers in order to increase opportunities to families and afford fertility-preserving measures. (14,35, 63)

- The importance of not making a distinction due to high costs and to give information equally to all cancer patients. (44)

- The issue of differences in fertility preservation services across countries and differences in local, regional, national and federal legislation on fertility preservation methods. (25)

- Differences in countries in relation to donor treatments and gestational surrogacy. (32)

6. Ethical considerations regarding financial costs in fertility preservation procedures

6.1. Expenses linked to procedures for fertility preservation, potential complications and storage of cryopreserved material

- The issue of financial costs linked to fertility preservation procedures and who covers the cost for storage and facilities needs consideration. (33, 14, 35, 40, 52, 54, 59, 61, 63)

- To consider financial counselling that covers fertility preservation expenses (treatment and storage expenses). (25)

- The issue of possible conflicts of interest between the needs of patients and financial concerns. (38)

- The issue of potential costs of surgical complications (even when fertility preservation procedure is done at the same time as another intervention). (36)

7. Ethical consideration regarding post-treatment adoption in cancer survivors

7.1. Discrimination during post treatment adoption

- The issue of potential discrimination of cancer patients during post-treatment adoption because of their pre-existing condition needs consideration. (41)

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