SPECIAL REPORT

White paper: Oncofertility in pediatric patients with Wilms tumor

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Abbreviations: AAD, alkylating agent dose; AMH, anti-Müllerian hormone; AYA, adolescent and young adult; CCS, childhood cancer survivors; CCSS, Childhood Cancer Survivor Study; CED, cyclophosphamide equivalent dose; CI, confidence interval; COG, Children's Oncology Group; CR, complete remission; CYP, cytochrome; DA, diffuse anaplastic; DOR, diminished ovarian reserve; DFS, event free survival; FHWT, favorable histology Wilms tumor; FP, fertility preservation; GWAS, genome wide association study; HARMONIzation and CollAboration; HR, high risk; IGHG, International Guideline Harmonization Group; IR, intermediate risk; LOH, loss of heterozygosity; NWTSG, National Wilms Tumor Study Group; OC, oocyte cryopreservation; OP, oophoropexy; OR, odds ratio; OS, overall survival; OTC, ovarian tissue cryopreservation; PESA, percutaneous epididymal sperm aspiration; POL, premature ovarian insufficiency; RR, relative risk; RT, radiotherapy; RTSG, SIOP-Renal Tumor Study Group; SIOP, Societe Internationale D’oncologie Pediatrique; SNPs, single nucleotide polymorphisms; TESE, testicular sperm extraction; VMAT, Volumetric-Modulated Arc Therapy; WART, whole abdominal radiation therapy; WT, Wilms tumor.

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Abstract

The survival of childhood Wilms tumor is currently around 90%, with many survivors reaching reproductive age. Chemotherapy and radiotherapy are established risk factors for gonadal damage and are used in both COG and SIOP Wilms tumor treatment protocols. The risk of infertility in Wilms tumor patients is low but increases with intensification of treatment including the use of alkylating agents, whole abdominal radiation or radiotherapy to the pelvis. Both COG and SIOP protocols aim to limit the use of gonadotoxic treatment, but unfortunately this cannot be avoided in all patients. Infertility is considered one of the most important late effects of childhood cancer treatment by patients and their families. Thus, timely discussion of gonadal damage risk and fertility preservation options is important. Additionally, irrespective of the choice for preservation, consultation with a fertility preservation (FP) team is associated with decreased patient and family regret and better quality of life. Current guidelines recommend early discussion of the impact of therapy on potential fertility. Since most patients with Wilms tumors are prepubertal, potential FP methods for this group are still considered experimental. There are no proven methods for FP for prepubertal males (testicular biopsy for cryopreservation is experimental), and there is just a single option for prepubertal females (ovarian tissue cryopreservation), posing both technical and ethical challenges. Identification of genetic markers of susceptibility to gonadotoxic therapy may help to stratify patient risk of gonadal damage and identify patients most likely to benefit from FP methods.

KEYWORDS
fertility preservation, gonadal damage, pediatric cancer, Wilms tumor

What’s new?

Wilms tumor (WT), a childhood kidney cancer, has a survival rate of around 90%. Because most patients survive to reproductive age, treatment decisions must take into account the risk of gonadal damage. Discussing infertility risk and fertility preservation (FP) is associated with decreased patient and family regret and better quality of life. Here, the authors present an overview of the evidence regarding the future fertility after WT treatment, collected through a unique global collaboration between Children’s Oncology Group (COG) and Societe Internationale D’oncologie Pediatrique (SIOP). They describe options for FP as well as ethical and genetic considerations, which may guide personalized risk prediction and selection of patients at risk of chemotherapy or radiotherapy induced gonadal impairment.
diagnosed with WT are prepubertal, fertility preservation (FP) options have
recently become available for young patients. However, since some of
these FP methods are still experimental, they have been largely reserved
for patients at high risk of gonadal damage.14-19 This manuscript aims to
provide an overview of the available evidence on the risk of gonadal dam-
age after WT treatment, including the patient perspective, the options
for fertility preservation, ethical and genetic considerations and
recommendations concerning FP in patients with WT.

2 | OVERVIEW OF THE ISSUE OF
FERTILITY IMPORTANCE TO CANCER
PATIENTS

When considering FP for pediatric cancer patients, it is vital to under-
stand the patient and family vantage point (Table S1). While future
fertility is generally important to most patients and caregivers, FP is
not universally discussed nor undertaken prior to initiation of oncolo-
getic therapy, as the immediate focus is on achieving cure. Unfortu-
nately, if FP is not discussed prior to treatment, this may negatively
impact the utilization and success rate of FP techniques.

Several surveys have identified attitudes of parents of children
with cancer as well as the adolescent and young adult (AYA) patient
population toward FP in the setting of a cancer diagnosis.20-22 These
surveys uncovered that nearly all AYA patients and parents are aware
of a significant risk of infertility related to cancer therapy, and that FP
is important to most of this population. However, only about 20%
were willing to take actions toward preserving fertility.21 This finding
is known as the intention-behavior gap. Nearly half of AYA patients
reported limited access, such as being unaware of the options and/or
cost concerns, as the reason for not making FP arrangements despite
financial support by philanthropic organizations, or public or private
health plans being regionally variably available. Insurance coverage of
FP costs is usually limited to the procedure and not the storage of
gametes, and some insurance plans may not cover all of the procedure
costs. Health-related concerns are prevalent and impair access to FP,
noted by about one third of male AYA patients, and over half of
female AYAs. These concerns include personally not wanting to delay
treatment, physician advising against treatment delay, and concerns
about the effect of cancer therapy on future offspring. Personal rea-
sions such as not wanting children or feeling too young to consider
such a decision were also noted in about a third of patients.22
Research studying shared decision making in adolescents and parents
of young patients with WT is lacking.

In addition, it is well-established that many patients regret deciding
not to pursue FP.20,23,24 The level of regret tends to be higher among
those who believe that the opportunity for FP was not discussed or was
discussed at a time when it was too late to effectively act on it.20 Over
half of surveyed patients reported feeling a moderate to high amount of
concern that infertility has negatively affected their emotions, relation-
ships, and feeling of self-worth. Additionally, patients who identified
themselves as having higher concerns about fertility were more likely to suffer
from depression and lower-quality of life.25 It has been reported that most
male cancer patients/survivors do not feel sufficiently informed and post-
pubertal boys strongly desire information on FP options.26,27 Similarly,
female cancer patients feel it is important to discuss fertility, preferably
shortly after diagnosis.28-32 A recently published guideline by the Interna-
tional Guideline Harmonization Group (IGHG) states that current standard
care should include informing all pediatric cancer patients and their families
on their relative risk of gonadal damage, including the low-risk
group.30,31,33 As such, counseling is paramount and clear discussion of the
experimental nature of any intervention must be emphasized.

Taken together, these findings underscore that FP is important to
pediatric cancer patients and survivors, and should be discussed early-
on, when options for FP are greatest. The intention-behavior gap
highlights the importance of providing adequate counseling, to sup-
port the desire for FP, and help develop that into a behavior that
accomplishes that goal when feasible. While not all children and their
parents will elect to proceed with FP, there is strong evidence that
future regret is greatly reduced when families feel that they have
made an informed decision.25,34

3 | OVERVIEW OF WT THERAPY AND
ONCOLOGIC OUTCOMES

Although most patients with WT are cured with surgery and two-drug
chemotherapy with very low gonadotoxic potential,9 almost all
patients with relapse will be exposed to intensive therapy, typically
including alkylating agents. Notably these patients require counseling
again at the time of relapse, providing an opportune time to discuss
FP options.17 Four-year event free survival (EFS) for Stages II to IV
anaplasic WT with current COG/SIOP treatment regimens is 68%,35
and long-term survival for higher risk (HR) relapsed favorable histol-
ogy Wilms tumor (FHWt) who were previously treated with the combi-
nation of vincristine, daunomycin and doxorubicin is around
50%.36 The evolution of risk stratification has outlined subgroups of
WT patients for whom reduction of therapy decreases long-term
therapy-related morbidity exemplified by patients with very low risk
favorable histology Wilms tumor (FHWt, age <2 years and tumor
weight <550 g) who achieved excellent outcomes with surgery
alone.37 On the other hand, both COG and SIOP treatment regimens
for patients identified as having HR disease can increase the possibil-
ity of infertility, with exposure to alkylators, carboplatin and radiation
therapy. COG protocols showed that augmentation of therapy leads
to improved outcomes among patients with Stage III and IV FHWt
whose tumors harbor combined loss of heterozygosity (LOH) for 1p
and 16q, with the use of regimen M (five-drug chemotherapy with
vincristine, daunomycin, doxorubicin, etoposide and cyclophospha-
mine).38 SIOP protocols use high-dose doxorubicin, cyclophospha-
mine, carboplatin and etoposide for HR patients with identified risk
factors of postchemotherapy HR histology, incomplete lung metastas-
sis response, and blastemaless-predominant histology with high blastema-
volnme. These therapy regimens have reduced the risk of relapse for
these patient groups, avoiding the use of marked intensification of
therapy at relapse, but increasing the exposure to gonadotoxic agents
### 4 | General Impact of WT Chemotherapy on Fertility

The COG treatment approach to WT comprises upfront tumor resection whenever feasible, usually followed by risk-adapted chemotherapy and, in certain circumstances, radiation treatment. In comparison, apart from specific clinical-radiological features, the SIOP-Renal Tumor Study Group (RTSG) advocates preoperative chemotherapy followed by risk-adapted treatment after surgery. The differences in the COG and SIOP treatment approaches may present different logistic (timing) opportunities for FP. SIOP usually starts preoperative chemotherapy immediately after radiological or histological confirmation. This regimen does not contain gonadotoxic agents so FP is not likely to be needed at that time. Postoperative RT and chemotherapy can usually be well anticipated, allowing a window in time to achieve FP, possibly combined with the tumor nephrectomy. Notably, COG protocols currently mandate initiating chemotherapy within 14 days after surgery/biopsy, and the stage and histology results may only be available after 10 to 12 days. This may leave only a short window for decision-making and FP prior to the start of chemotherapy, even in willing patients and parents. However, prior chemotherapy is not an absolute contra-indication for ovarian tissue cryopreservation and testicular biopsy. The impact of chemotherapy on future fertility is determined by the cumulative doses of chemotherapy agents utilized. Table 3 summarizes the chemotherapy regimens and cumulative doses used by the most recently completed and published COG studies and the current SIOP-RTSG UMBRELLA protocols. The potential effects of

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**Table 1**: Current treatment protocols and published outcomes according to COG.

| Stage | Histology | Risk stratification | Chemotherapy | Radiation | 4-year EFS/OS (%) | Gonadotoxicity potential/risk to fertility |
|-------|-----------|---------------------|--------------|-----------|------------------|---------------------------------|
| I     | Favorable | Very low risk       | None         | None      | 89.7/100         | None                            |
|       | Standard  | Standard            | EE4A (VA) 19 weeks | None | 94/98            | Very low                        |
|       | Focal/diffuse anaplastic |            | DD4A (VAD) 25 weeks | 10.8 Gy (flank) | 100/100         | Very low                        |
| II    | Favorable | Standard            | EE4A (VA) 19 weeks | None      | 86/98            | Very low                        |
|       | Focal anaplasia |            | DD4A (VAD) 25 weeks | None | N/a             | Very low                        |
|       | Diffuse anaplasia |            | Revised UH-1 (VCDBE) 30 weeks | 10.8 Gy (flank) | 86.7/86.2 | Yes                           |
| I/II  | Favorable | High risk (LOH 1p and 16q) | DD4A (VAD) 25 weeks | None | 87.3/100 | Very low               |
| III   | Favorable | Standard            | DD4A (VAD) 25 weeks | 10.8 Gy (flank/abdomen) + 10.8 Gy boost for gross disease | 87.1/94.4 | Possible depending on radiation field |
|       | Focal anaplasia |            | DD4A (VAD) 25 weeks | 10.8 Gy (flank/abdomen) + 10.8 Gy boost for gross disease | N/a | Possible depending on radiation field |
|       | Diffuse anaplasia |            | Revised UH-1 (VCDBE) 30 weeks | 10.8 Gy (flank/abdomen) + 10.8 Gy boost for gross disease | 80.9/88.6 | Yes                           |
| III/IV| Favorable | High risk-LOH 1p and 16q: OR no CR lung nodule(s) at week 6 for Stage IV | Regimen M (VADCE) 31 weeks | 10.8 Gy (flank/abdomen) + 10.8 Gy boost for gross disease | 90.2/96.1 | Yes                           |
|       |           |                     |              | 12 Gy lungs if lung metastasis | 88.5/99.8 |                           |
| IV    | Favorable | Standard AND CR lung nodule(s) at week 6 | DD4A (VAD) 25 weeks | No lung rads | 79.5/96.1 | Very low             |
|       | Focal anaplasia |            | Revised UH-1 (VCDBE) 30 weeks | 12 Gy lungs if lung metastasis | N/a | Yes                           |
|       | Diffuse anaplasia |            | Revised UH-2 (VCDBEI) 36 weeks | 12 Gy lungs if lung metastasis | 41.7/49.2 | Yes                           |

Abbreviations: CR, complete response; EFS, event-free-survival; Gy, Gray; LOH, loss of heterozygosity; OS, overall survival; VA, vincristine, dactinomycin; VAD, vincristine, dactinomycin, doxorubicin; VADCE, vincristine, dactinomycin, doxorubicin, cyclophosphamide and etoposide; VCDBE, vincristine, carboplatin, doxorubicin, cyclophosphamide and etoposide; VCDBEI, vincristine, carboplatin, doxorubicin, cyclophosphamide, etoposide and irinotecan.

during initial therapy. Tables 1 and 2 summarize the most recent published outcomes and current treatment protocols from cooperative trials (COG and SIOP) for WT patients.
Chemotherapy on future fertility differ based on gender; hence, fertility risks are discussed separately for female and male survivors. Overall, fertility impact of chemotherapy for WT patients is largely related to the cumulative doses of cyclophosphamide received (Tables 3 and 4). Of note, patients with relapsed WT usually receive doses of cyclophosphamide, ifosfamide, doxorubicin, and radiation therapy, sometimes including a high dose chemotherapy regimen or a stem cell transplant, that places them at high risk of infertility regardless of the specific chemotherapy regimen utilized.46 Tables 4 and 5 combine the fertility risk associated with both chemotherapy and radiation modalities.

5 | FERTILITY RISKS FOR FEMALE WT SURVIVORS

In relation to the age of exposure to gonadotoxic agents, ovarian damage from chemotherapeutic agents can result in delayed/absent/arrested puberty in pre- or peripubertal patients and diminished ovarian reserve (DOR) or premature ovarian insufficiency (POI), and infertility in postpubertal individuals.37 The evidence describing effects on reproductive outcomes is mostly based on retrospective data, which makes it difficult to determine the exact effects of individual chemotherapy agents.48 However, alkylating agents, such as cyclophosphamide and ifosfamide, have a clear impact on female reproductive health in a dose-related manner when given either alone or in combination.49 The most important predictors of risk are the cumulative dose of radiotherapy and alkylating agents, and the patient's age at the time of therapeutic exposure.50 If doxorubicin was included in the treatment, survivors are additionally at risk of developing cardiomyopathy during pregnancy.51 DOR is characterized by sustained menses and normal gonadotropins, but reduced indexes of ovarian reserve for age and is important in the counseling of childhood cancer survivors (CCS), as it may represent a window for performing posttreatment fertility preservation.52 POI is defined by persistent amenorrhea combined with a follicle-stimulating level >30 IU/L before the age of 40 years. In the St. Jude...
Lifetime Cohort study of 921 female cancer survivors, POI is associated with administration of high-dose cyclophosphamide. The cyclophosphamide equivalent dose (CED) and alkylating agent dose score (AAD) are two methods used to calculate the cumulative dose of alkylating agents (Text S1). Multivariable analysis showed independent associations between POI and CED $\geq 8000$. 

### TABLE 3 Cumulative chemotherapy doses per treatment regimen used by COG and the SIOP Renal Tumor Study Group (SIOP-RTSG)

| COG Chemotherapy agent | Cumulative dose (mg/m² unless otherwise specified) | Regimen M | Regimen I | Revised UH-1 | Revised UH-2 |
|------------------------|--------------------------------------------|-----------|-----------|--------------|--------------|
| Vincristine            | 21                                        | 25        | 18        | 25           | 23           |
| Dactinomycin           | 0.315 mg/kg                                | 0.225 mg/kg | 0.18 mg/kg | 0.145 mg/kg | 0            |
| Doxorubicin            | 0                                          | 150       | 140       | 195          | 225          |
| Cyclophosphamide       | 0                                          | 0         | 0         | 8800         | 15 400       |
| Carboplatin            | 0                                          | 0         | 0         | 2800         | 2800         |
| Etoposide              | 0                                          | 0         | 0         | 2000         | 2000         |
| Irinotecan             | 0                                          | 0         | 0         | 0            | 800          |

| SIOP-RTSG Chemotherapy agent | Cumulative dose (mg/m² unless otherwise specified) | AV | AVD | AV-1 | AV-2 | AVD | HR |
|-----------------------------|-----------------------------------------------|----|-----|------|------|-----|----|
| Vincristine                 | 6                                            | 9  | 30  | 30   | 30   | 0   |    |
| Dactinomycin                | 0.09 mg/kg                                   | 0.135 mg/kg | 0.045 mg/kg | 0.405 mg/kg | 0.405 mg/kg | 0   |    |
| Doxorubicin                 | 0                                            | 100 | 0    | 0    | 250c | 250c |    |
| Cyclophosphamide            | 0                                            | 0   | 0    | 0    | 0    | 8100 |    |
| Carboplatin                 | 0                                            | 0   | 0    | 0    | 0    | 3600 |    |
| Etoposide                   | 0                                            | 0   | 0    | 0    | 0    | 2700 |    |

Note: In Table 2 it is specified to which risk groups the regimens AV, AVD, AV-1, AV-2 and HR are given. AVD is a preoperative regimen for bilateral Wilms tumor. Including 2 cycles of vincristine and irinotecan given during the upfront window on the COG AREN0321 clinical trial. Cumulative doxorubicin dose for both pre- and postoperative chemotherapy.

### TABLE 4 Infertility risk per treatment regimen

| Treatment regimen | Female | Male | CED score (mg/m²) |
|-------------------|--------|------|------------------|
| COG treatment regimens |        |      |                  |
| Surgery only/observation | Low risk | Low risk | 0               |
| EE4A               | Low risk | Low risk | 0               |
| DD4A               | Low risk | Low risk | 0               |
| Regimen M          | High risk | High risk | 8800            |
| Regimen I<sup>a</sup> | High risk | High risk | 15 400          |
| Regimen revised UH-1 | High risk | High risk | 14 800          |
| Regimen revised UH-2 | High risk | High risk | 14 800          |
| SIOP-RTSG treatment regimens |        |      |                  |
| AV, AV-1, AV-2     | low risk | Low risk | 0               |
| AVD                | Low risk | Low risk | 0               |
| HR                 | high risk | High risk | 8100            |

Abbreviations: AV, AV-1, AV2, regimen containing vincristine, dactinomycin; AVD: regimen containing vincristine, dactinomycin, doxorubicin; CED, cyclophosphamide equivalent dose; DD4A: regimen containing vincristine, dactinomycin, doxorubicin; EE4A, regimen containing vincristine, dactinomycin; HR, high risk regimen; Regimen I<sup>a</sup>, regimen containing vincristine, doxorubicin, cyclophosphamide, etoposide; Regimen M: regimen containing vincristine, dactinomycin, doxorubicin, cyclophosphamide, etoposide; Regimen revised UH-1: regimen containing vincristine, doxorubicin, cyclophosphamide, carboplatin, etoposide, Irinotecan; Regimen revised UH-2: regimen containing vincristine, doxorubicin, cyclophosphamide, carboplatin, etoposide, Irinotecan. Currently only used for bilateral patients and for CCSK patients.
TABLE 5  Risk of compromised fertility associated with treatment modality for Wilms tumor, according to gender (adapted from Klipstein)\textsuperscript{83}

| Risk               | Treatment predisposing to compromised fertility                                                                 | Effect on reproduction                                                                 |
|--------------------|-------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Female             | • Alkylating-agent chemotherapy (Cyclophosphamide equivalent dose 6 g/m$^2$ in women and girls <20 year, Ifosfamide, Melphalan)\textsuperscript{31}  
• Radiation affecting the female reproductive system (whole abdomen, pelvis, lumbosacral spine, total body)  
  o >10 Gy in postpubertal girls  
  o 15 Gy in prepubertal girls  
• Oophorectomy       | Acute ovarian failure (ovarian failure within 5 years of diagnosis), premature menopause (cessation of menses before age 40 years) |
| Intermediate       | Radiation affecting the uterus (whole abdomen, pelvis, lumbosacral spine, total body)                      | Uterine vascular insufficiency, uterine growth impairment. Spontaneous abortion, neonatal death, premature labor, neonate with low birth weight, fetal malposition |
| Male               | • Alkylating-agent chemotherapy (Cyclophosphamide equivalent dose 4 g/m$^2$, Ifosfamide, Melphalan)\textsuperscript{10}  
• Pelvic radiation affecting the male reproductive system (1–6 Gy scatter to testes) | Azoospermia, oligospermia                                                                 |
| Intermediate       | • Pelvic surgery (retroperitoneal node or tumor dissection, cystectomy)  
• Radiation to pelvis, bladder, or spine (1–6 Gy scatter to testes)  
• Chemotherapy with heavy metals: carboplatin >2 g/m$^2$ | Retrograde ejaculation, anejaculation  
Erectile dysfunction  
Azoospermia, oligospermia | mg/m$^2$ [8000-11 999 mg/m$^2$ [HR = 2.77; 95% CI, 1.18-6.51] and 12 000-19 999 mg/m$^2$ [HR = 3.90; 95% CI, 1.80-8.43]]\textsuperscript{53}

The Childhood Cancer Survivor Study (CCSS) evaluated fertility outcomes in 20 720 previously untreated patients age <21 years at diagnosis, who survived for at least 5 years, and who were diagnosed with an eligible cancer at 27 participating institutions between 1970 and 1986.\textsuperscript{55} Four-hundred and ninety-eight patients with WT were included in the analysis. For all patients, when controlled for education level, marital status, age at diagnosis, ethnicity, and smoking status, multivariate models demonstrated lower chance of pregnancy for those treated with cyclophosphamide (RR = 0.8; 95% CI, 0.68-0.93; $P = .005$).\textsuperscript{55} The impact was dose related, with fertility decreasing with increased dose. When CED was categorized by quartile, female survivors diagnosed between 1970 and 1999 who were exposed to the upper quartile ($\geq 11.295$ mg/m$^2$) had a lower likelihood of pregnancy than those not exposed (HR = 0.85; 95% CI, 0.74-0.98; $P = .023$).\textsuperscript{56} Notably, the evidence regarding the threshold for ovarian damage is scarce, and ranges from 6000 to 12 000 mg/m$^2$.\textsuperscript{11} Currently a CED score of $> 6000$ mg/m$^2$ is classified as high risk.\textsuperscript{10,11,17}

6  | FERTILITY RISKS FOR MALE WT SURVIVORS

In general, Leydig cell function is preserved, but germ cell failure is very common in men treated with high cumulative doses of cyclophosphamide ($\geq 7500$ mg/m$^2$).\textsuperscript{57} To date in the SIOP-RTSG, no retrospective analyses have been done to correlate childhood WT treatment with gonadal function in adulthood. However, within the CCSS, 1622 survivors completed the Male Health Questionnaire, with a self-reported prevalence of infertility of 46% (defined as taking $> 1$ year to get a female pregnant).\textsuperscript{58} Forty-nine male patients with kidney tumors were included in this analysis. In addition, a report from the St. Jude Lifetime Cohort Study found laboratory-evaluated impaired gonadal function in 55.6% of 304 male survivors of childhood cancer.\textsuperscript{59} In the CCSS multivariable analysis, an AAD of $\geq 3$ (RR = 2.13; 95% CI, 1.69-2.68) was associated with a high risk for infertility vs an AAD $<3$.\textsuperscript{58} Male survivors who received cumulative cyclophosphamide doses of $\geq 7412$ mg/m$^2$ reported a significantly decreased likelihood of fathering a child compared with those not exposed.\textsuperscript{56} Notably, although irreversible gonadal impairment may occur, in some patients with azoospermia before or after treatment, recovery is seen over time in sperm production.\textsuperscript{60,61}

7  | IMPACT ON FERTILITY AFTER RADIOTHERAPY FOR WT

Radiotherapy (RT) is an established, efficacious modality for treating select WT patients. NWTS-3 demonstrated that EFS of patients with Stage III FHWT treated with 1000 cGy of abdominal radiation was not significantly different from that of patients who received 2000 cGy.\textsuperscript{62} Standard of care RT in the COG and SIOP protocols is described in Table 6. AREN0321 established 1980 cGy flank RT is beneficial in cases of diffuse anaplastic (DA) WT Stage III tumors.\textsuperscript{42,63} Whole lung RT is standard of care for treating pulmonary metastases in the COG protocol, excepting cases of favorable histology with lung-only metastases who have complete response to chemotherapy by week 6 (Table 6). While the impact of whole lung RT on gonadal damage is expected to be minimal since ovaries and testes are not located in the radiation field, increased risk of complications during pregnancy and labor may
TABLE 6 Cumulative radiotherapy doses used by COG and SIOP RTSG

|                  | Local Stage II | Local Stage III | Intraabdominal dissemination | Macroscopic residual tumor | Lung metastasis |
|------------------|----------------|-----------------|------------------------------|----------------------------|----------------|
| COG              | 1080 cGy flank RT (6 fractions) | 1080 cGy flank RT (6 fractions) | 1050 cGy WART | >12 months: 1200 cGy (8 fractions) | <12 months: 1050 cGy (7 fractions) |
| SIOP             | 14.4 Gy flank RT (8 fractions) | WART: 15 Gy (10 fractions) | Boost 10.8 Gy | 12 Gy |
| IR               | DA: 25.2 Gy flank RT (14 fractions) | WART: 19.5 Gy (13 fractions) | Boost 10.8 Gy | 15 Gy |
| HR               | DA: 25.2 Gy flank RT (14 fractions) | WART: 19.5 Gy (13 fractions) | Boost 10.8 Gy | 15 Gy |

Abbreviations: CR, complete response; DA, diffuse anaplastic type; Gy, Gray; HR, high risk; IR, intermediate risk; RT, radiotherapy; WART, whole abdomen RT.

*Exception: favorable histology + lung-only metastases (CR at week 6).

*IR (no CR after preoperative chemotherapy and/or metastasectomy).

occur due to radiation and anthracycline induced cardiotoxicity. In SIOP-RTSG, approximately 25% of patients receive abdominal RT. In most patients the pelvic area is not included in the radiation field but 20% of irradiated patients (5% of the total number of patients with WT) are also treated on a HR protocol which includes cyclophosphamide. A radiation boost is delivered to any micro- or macroscopic residual abdominal disease. Whole lung RT is given for intermediate risk (IR) tumors with no complete remission (CR) after preoperative chemotherapy and/or metastasectomy and to all HR tumors. (Table 6).

These established regimens result in variable gonadal exposure in male and female patients. Patients with early-stage local disease and lung metastases may require lung-only RT and have very low dose gonadal exposure from indirect internal and external scatter. Those requiring flank RT may have little to no direct exposure in males and variable exposure in females depending upon lesion size at diagnosis and age of the patient, which influences the location of the ovaries. In cases with a large primary tumor or those requiring whole abdominal radiation therapy (WART), gonadal tissue may receive full prescription dose (see Figures S1-S4 for illustrations of flank and WART dose distributions for female and male pediatric WT patients). New approaches to reducing target volumes for flank radiation by combining highly conformal target volumes with Volumetric-Modulated Arc Therapy (VMAT) will likely have a clinical benefit by dose reduction to organs of risk. In the first single center study of VMAT, excellent locoregional control could be achieved by this technique. Unfortunately, gonadal toxicity was not formally assessed in these two papers, but this risk is predicted to be reduced.

There are limited published reports detailing the impact of RT on fertility in WT survivors, and most of these include small patient numbers. In a study of 23 prepubertal children aged 6 months to >4 years following therapy for WT, 1500 to 3000 cGy hemiabdominal RT or WART resulted in serum hormone levels which indicate gonadal damage in both males and females compared with normal controls and those receiving chemotherapy only.

An analysis of testicular function of 10 young adult WT survivors who received 268 to 983 cGy to the testes from WART without chemotherapy revealed all of these men to have decreased testicular volume compared to “normal males of the same age” and eight of the nine with evaluable sperm counts had oligo- or azoospermia.

The impact of RT prior to puberty on ovarian size, based on ultrasound analysis, was conducted on 18 female WT survivors, 14 of whom were evaluated postpuberty. Of 10 postpubescent females treated with 400 to 4096 cGy flank RT, five had a small or not visible ipsilateral ovary; the ovaries of all three treated with 2100 to 3000 cGy WART were small or not seen. Of note, the uterine length was also decreased in the postpubertal females treated with WART. In general, cases with major tumor rupture that require WART are most at risk.

In a more recent questionnaire-based analysis of male fertility in a large retrospective cohort of 6224 childhood cancer survivors participating in the CCSS, 429 of whom had WT, testicular RT dose >750 cGy was significantly associated with decreased likelihood of being able to establish paternity compared with those not receiving RT. This study identified the subgroup with younger age at diagnosis (0-4 years), in which most WT subjects fall, to be associated with higher likelihood of being able to sire a child. This analysis, however, did not separate survivors by cancer type and is confounded by variable chemotherapy exposure.

In addition to potential impact on gonadal function, late effects of RT to the abdominopelvic region in young children may impair normal growth and development of the irradiated pelvic bones, vasculature and organs including the uterus, which are critical to successful gestation (Table 5). There have been several studies of pregnancy outcomes of WT survivors, including those receiving RT either to flank only or to upper abdomen/WART on NWTS 1-4. Review of 309 medical records of at least 20-week gestation pregnancies showed female WT survivors receiving >2500 cGy flank RT to have increased risk for preterm labor (OR = 2.36), fetal malposition (OR = 6.26), and birth before 36 weeks gestation (OR = 4.07) compared with nonirradiated female survivors, whereas there was
no difference noted in those receiving chemotherapy only or in pregnancies conceived with male survivors treated in NWTS 1-4.73

While radiation may result in decreased distensibility of the uterus during pregnancy, leading to preterm delivery, no correlation between birth weight in offspring and radiation dose has been found.50,74,75 RT dose to ipsilateral and contralateral ovary as well as to the uterus from flank RT was estimated to range from 2% to 7% of the prescription dose.73

Regarding radiation-dose correlations, as little as 5 Gy cumulative exposure to reproductive organs augments the risk of infertility by a factor of 1.6.50 Of female WT survivors from NWTS 1-4 cohort who received RT beyond the flank, only seven (5.5%) of 126 with known RT fields had at least one pregnancy. Nine of 10 babies were live born from five female survivors receiving upper abdominal RT only, whereas only one of four pregnancies resulted in a viable child from two female survivors who received WART. Notably, the WART dose was 1050 cGy for the live birth and 2100 cGy for the three nonviable pregnancies.76

These findings support earlier retrospective analyses of pregnancy outcomes of WT survivors, including one study by Li et al77 of 114 pregnancies in 99 WT survivors (65 female, 34 male), which showed a 30% incidence of adverse outcomes including perinatal death and low birthweight in females receiving 2000 to 3500 cGy flank RT compared with 3% in nonirradiated female survivors or wives of irradiated male survivors.77 The relative risk (RR) of perinatal mortality (RR 7.9; P < .0001) and low birthweight (RR 4.0; P < .0001) was significantly higher in the mothers irradiated for WT than expected for pregnancy outcomes for white women in the United States at that time.25 In another study of 47 WT survivors, 43 of whom received abdominal RT,78 female WT survivors had a more than 4-fold increased risk of adverse birth outcomes, including preterm birth and birth defects, compared with sibling controls and wives of male WT survivors. The addition of chemotherapy did not modify this risk. Adverse pregnancy outcomes following RT for WT in the above studies have been attributed to uterine fibrosis, impaired placentation, vascular insufficiency, altered bone growth, scarring/adhesions, and/or genitourinary malfunction.50,76-78 The most important factor for a successful pregnancy after pelvic radiotherapy is the cumulative dose to the ovaries and uterus and the age of the patient at the time of radiation.74 Prepubertal age at time of antineoplastic therapy exposure has been associated with a lower risk of ovarian failure, with mathematical models suggesting this finding may be due to increased follicular reserve in these very young patients.55,79 While younger age is considered protective for gonadal damage, the growth and function of the uterus may be impaired due to the radiation. Radiation to a prepubertal uterus may lead to incomplete pubertal growth and development. This may pose difficulties regarding embryo implantation or fetal growth (to term).

Continued efforts to limit RT dose to the adjacent organs-at-risk, including but not limited to the gonads, is essential to improve reproductive success in this patient population. Advances in molecular biology and imaging as well as increased international collaboration between COG and SIOP will be very beneficial in this respect.80 An example of this partnership is the monthly HARMONIzation and CollAboration (HARMONICA) meetings in which SIOP and COG collaborate on numerous projects including plans for a unified approach to FP in children with renal tumors. Refining flank field and dose exposures in a manner that optimizes cancer control while concurrently limiting gonadal toxicity is also a topic amenable to international discussion. In addition, education and counseling of the parents of these young patients about the risk-benefit ratio of tumor control and late fertility risks, as well as early involvement of endocrinology/fertility experts, is critical to optimize outcomes and expectations.81

8 OPTIONS FOR FERTILITY PRESERVATION

As early as 2005, multiple international organizations, including the National Comprehensive Cancer Network, American Society of Clinical Oncology, European Society for Medical Oncology, American Academy of Pediatrics, Children's Oncology Group, and the American Society of Reproductive Medicine created strong guidelines around FP.32 For postpubertal patients, there are clear data to guide counseling and intervention. Challenges to FP efforts include patient and provider knowledge of options, as well as logistical considerations. For example, FP measures should generally precede administration of any chemotherapy or radiation treatment. If possible, the FP surgery will be combined with another surgical procedure (line placement, nephrectomy) to limit the number of times a child has to undergo anesthesia and surgery. This poses an additional logistic challenge. This time pressure often factors into decisions made by patients and families. Furthermore, not all pediatric oncology treatment centers offer all FP options, which may further delay FP and initiation of definitive oncologic therapy.17,83-87

Females with preoperative tumor rupture and most relapsed WT patients are at especially high risk of gonadal damage due to radiation and chemotherapy intensification. In these cases, fertility counseling is mandatory and FP procedures may be considered. Fertility risk is generally triaged early after initial diagnosis, however, sometimes the definitive treatment plan and subsequent gonadal damage risk is determined after the assessment of the initial treatment period. The response determines the treatment intensity and potential impact on fertility. Furthermore, treatment intensification may need to occur at any time depending on disease response or other factors. Thus, FP discussion and plan for FP intervention is needed when intensification is suggested.17

Currently, FP for patients with WT is largely experimental. Most patients are prepubertal, there are no established methods considered clinically standard for FP for prepubertal males, and just a single option for prepubertal females. As previously noted, patients report a desire to learn more about FP and regret that they were not more comprehensively counseled; as such, clinicians should proactively initiate conversations around standard and experimental options for FP. Figures 1 and 2 summarize FP options for patients, and Table S2 provides more details about each option.88-91 Other options that exist for both genders include adoption, surrogacy, and the use of donor sperm/eggs or embryos.
8.1 | Boys

Postpubertal boys are defined as Tanner stage $\geq 3$, corresponding to a testicular volume of $\geq 6$ cc. Therapy-related impaired spermatogenesis, testosterone deficiency, hypogonadotropic and hypergonadotropic hypogonadism may all lead to infertility. In prepubertal boys, options for FP are testicular biopsy, testicular sperm extraction (TESE) and percutaneous epididymal sperm aspiration (PESA). However, these procedures are not standard of care in all countries for young children. In postpubertal boys, freezing of ejaculated sperm is offered also in case of a low risk of gonadal damage. For boys who are Tanner $\geq 3$ with unsuccessful attempts at masturbation, electroejaculation can be considered. However, due to the invasive nature of the procedure, this should be considered primarily as an option for patients with high estimated risk of gonadal damage.

8.2 | Girls

Cryopreservation of ovarian tissue (OTC) is now offered around Europe and at selected centers in the United States to prepubertal and postpubertal girls with cancer who are at high risk of infertility. An ovary can be completely or partially removed and harvested tissue frozen. Oocyte cryopreservation (OC) is another FP option available in some jurisdictions for postpubertal girls in which postponement of cancer treatment for at least 2 weeks is feasible. Due to the intensive hormone therapy required and the psychological impact, this is offered to physically and emotionally mature postmenarcheal girls, usually aged 16 years and older. As most WT patients are prepubertal, this is a very rare occurrence. Nevertheless (young) adult WT patients are registered. Oophoropexy (OP), in which the ovary is surgically secured in a location outside of the planned radiation field, is rarely used in WT patients, when flank radiation reaches into the pelvis. For WART only heterotopic OP would be applicable and this has multiple limitations.

Currently, future success of pregnancy after auto-transplantation of prepubertally harvested ovarian tissue is under extensive investigation. The effect of OTC on the future ovarian function is still unknown, OTC is limited to patients with a high risk of infertility. Additionally, dormant malignant cells may be present in the harvested ovarian tissue sample, which complicates auto-transplantation. However, promising preclinical research is being conducted to ensure
ovarian tissue can be used safely.\textsuperscript{103,104} GnRH antagonists use to preserve ovarian function is highly debated and currently is not considered a reliable/effective option for children and AYAs for fertility preservation according to international consensus.\textsuperscript{11}

In the United States and many other countries, FP services (including both procedural costs and storage of the procured tissue) are not universally covered by insurance programs, although some need-based financial assistance programs are available.\textsuperscript{105,106} There is a general shift toward covering these services and procedures in some states, but it is far from a universally available service. In most European countries, FP for oncologic reasons is covered by insurance programs. Notably, while FP options are available in high income nations, access to these options in middle- and low-income countries is more limited.\textsuperscript{107} Therefore, finding strategies for less gonadotoxic therapy remains important.

\section{ETHICS OF FERTILITY PRESERVATION IN PATIENTS WITH WT}

An overview of ethical considerations concerning FP has recently been published by the PanCareLIFE consortium in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG).\textsuperscript{33} It is important to consider ethical, cultural, and religious issues since available FP options for prepubertal boys and girls involve invasive procedures, the harvested tissue contains gametes, and not all FP technologies are standard of care for all patients. Most WT patients are minors, and there is no universal consensus at what age a child is competent to make medical decisions.\textsuperscript{108} Issues such as the use of stored gametes after reaching adulthood as well as handling the material after the death of a child with cancer pose ethical dilemmas. Finally, the risk of not being able to guarantee the efficacy of auto-transplanted tissue in future settings raises additional ethical challenges.\textsuperscript{33,109-115}

Since most patients diagnosed with WT are under the age of 10 years (median: 3.4 years),\textsuperscript{115} parents are typically the medical decision-makers. Yet internationally the importance of respecting the autonomy of children is reflected in the need for assent or consent for research or treatment, though these ages vary by country.\textsuperscript{108,116,117} While the parents are the primary decision-makers, the patient’s perspective should be incorporated, and clinicians should ensure that information is provided to the child in an age-appropriate manner. It is important to primarily keep the interest of the child in mind, as the

FIGURE 2 Female fertility preservation options. \textsuperscript{1}Only in selected cases receiving abdominal radiotherapy (RT) with an ovary in the RT field. \textsuperscript{*}In rare cases, older patients with a partner may want to opt for embryo cryopreservation. However, for most Wilms tumor patients this will not be an option. \textsuperscript{^}Currently, no strong evidence exists that hormonal suppression has a protective effect on gonadal damage in children. However, it can be used in addition to other fertility preservation methods.
decision made by parents may be influenced by their own interests. The possibility may arise that the view of a maturing child may differ from the view of his or her parents. Especially in the case of OTC, the fact that 50% of the ovarian reserve is removed and stored, automatically reducing that child’s ovarian reserve by 50%, and that future efficacy of use of the material is uncertain need to be considered and weighed.

10 | THE IMPACT OF GENETIC SUSCEPTIBILITY ON FP

The most important known risk factors for treatment-related gonadal damage in WT are use of alkylating agents (boys and girls) and full abdominal radiotherapy (girls). However, previously published work shows that female patients with similar oncologic treatment at the same age can have variable gonadal damage. This interindividual variability suggests that genetic factors modify gonadotoxicity of the treatment. In contrast, only two GWAS studies have been performed to explore genetic susceptibility of cancer treatment-related gonadal damage in girls. Brooke et al identified and replicated a common haplotype associated with increased prevalence of premature menopause among childhood cancer survivors exposed to ovarian RT. Results of a European GWAS study are currently pending. BRSK1 (rs11668344) appears to be a relevant SNP in childhood cancer survivors treated with 8000 mg/m² cyclophosphamide or more. It is hypothesized that the presence of the BRSK1 SNP leads to a less efficient DNA damage response system and this may result in more damage caused by the alkylating agents in healthy cells, including the gonadal cells. In addition, SNPs in cytochrome (CYP) 450 genes have been shown to be associated with cyclophosphamide metabolism and ovarian function, and recently also with anti-Müllerian hormone (AMH) levels in CCSS.

The role of genetic variation in male infertility in the general population is still unclear and has not been studied extensively in male childhood cancer patients. Although evidence is limited, it should be mentioned during counseling that genetic susceptibility may contribute to the risk of future infertility in childhood cancer when discussing fertility in newly diagnosed and especially relapsed WT patients.

11 | CONCLUSIONS

Fertility concerns in WT survivors may be related to treatment (surgical intervention, chemotherapy, and/or radiotherapy) or underlying patient-specific risk factors (including syndromes associated with WT development). Fortunately, the reproductive organs are rarely directly affected by surgical intervention for primary WT. Unfortunately, the young age of most children diagnosed with WT makes fertility preservation prior to treatment difficult, although both testicular and ovarian tissue harvest have been described. The absence of effective and widely available methods to preserve fertility in very young patients undergoing cancer treatment may place an emotional burden on families. It should not be assumed that parents will initiate a discussion about fertility preservation and thus, initiation of this discussion by the treating team together with an offer of a consult from an oncofertility team, where available, should be a standard of care for all patients with WT.

In summary, with improved survival for children treated for WT there is an associated risk of late effects including fertility impairment. Refinements in oncologic treatments and an understanding of late effects help to limit morbidity. However, patient, family, and clinician education on fertility preservation in this population is necessary to provide the best and most holistic care possible. Our goal is that this review serves as a statement that we must turn our focus to this area as stated by G.J. D’Angio, “cure is not enough.”

CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

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All authors contributed to the writing of the manuscript. All coauthors reviewed the final article. In all, this document represents a fully collaborative work. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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