Reproductive Health: From Diagnosis Through Survivorship – Resources and Perspectives From the Children’s Oncology Group

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COG Educational Track at APHON 2020
Disclosure

- Dr. Brooke Cherven and Dr. Barbara Lockart have no industry relationships.
- Off label use will not be discussed.
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Learning Outcomes

- The learner will be able to
  - describe options for preserving fertility prior to gonadotoxic treatment, utilizing risk-based assessment.
  - articulate strategies to promote sexual health among adolescents and young adults during and after cancer treatment.
Why does this matter?

- Sexuality and reproduction is a normal part of the being human.
- Adults have developmental milestones!

Having cancer does not diminish the normal expression of personhood.
Why fertility preservation matters

- 75% of young adults who are childless at the time of diagnosis report a desire to parent in the future (Schover, 1999)
- Cancer survivors reports PTSD symptoms related to infertility as long as 10 years post-treatment (Schover, 2009)
- Male survivors report sperm banking helped psychological recovery from cancer. (Saito, Suzuki, Iwasaki, Yumura, Kubota, 2005)

Implications of infertility may be even more significant for certain cultural, ethnic or religious groups.
Is fertility preservation a patient right?

- Justice
- Autonomy
- Beneficence
- Non-maleficence
## This is what the experts say

<table>
<thead>
<tr>
<th>Organization</th>
<th>Position Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAP</td>
<td>“The impact of the treatment on fertility should be discussed.”</td>
</tr>
<tr>
<td>ASCO</td>
<td>“HCPs caring for adult and pediatric patients with cancer… should address the possibility of infertility as early as possible before treatment begins.”</td>
</tr>
<tr>
<td>ASRM</td>
<td>“Children and adolescents represent a special patient group that must be approached thoughtfully… give that this is a particularly vulnerable population, careful counseling and informed consent is especially recommended.”</td>
</tr>
<tr>
<td>APHON</td>
<td>“…discussions regarding fertility preservation and reproductive health should begin before treatment and continue throughout treatment and survivorship in a manner appropriate for the patient’s developmental stage.”</td>
</tr>
</tbody>
</table>
Risk for infertility

Fertility

- Treatment
- Patient's age & individual biology
- Gender
- Disease
When to have the conversation?

- From the time of diagnosis through cancer trajectory
  - Developmentally and culturally appropriate language
    - Must be comfortable with “slang”
  - Understanding will change as pt matures
    - Conversations should match current emotional needs
  - Puberty/pre-menopause discussions
    - May not “click” that future fertility may impact
      - Menstruation
      - Sexual function
Conversations throughout the cancer care trajectory

- **Survivorship**
  - COG LTFU Guidelines

- **Referrals to**
  - Reproductive Medicine
  - Endocrinology for hormone management

- **FP choices should not be limited by**
  - Gender
  - Sexual orientation/identity

- **Plan for disposal of banked tissue if death occurs**
Challenges

- Urgency to start treatment
- Provider Bias
- Care Coordination
- Limited Options
- Family Bias
Additional Challenges

- No guarantees of fertility
  - Status at end of treatment
  - That preservation attempts will be successful

Standard fertility preservation for post-pubertal males is cheaper, easier, and less time consuming than fertility preservation options available to females!
## Assessing Risk

<table>
<thead>
<tr>
<th>Therapy</th>
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</table>
| **Chemotherapy** | • Alkylator doses are not equivalent  
|             | • Cyclophosphamide Equivalent Dose (CED) (see Appendix I)  
|             | • Risk with new agents unclear  |
| **Radiation** | • Increased dose = increased risk  
|             | • Younger age protective to females?  
|             | • Pituitary XRT not associated with infertility  
|             | • XRT to gonads = high risk of infertility  
|             | • Proton beam therapy not protective if gonads in field  |

*It takes decades for us to understand infertility risk in pediatric cancer patients!*
How do we manage reproductive health?
Options - females

- Established – pubertal or older
  - Embryo/oocyte cryopreservation
  - Ovarian transposition

- Investigational – pre or post pubertal
  - Ovarian tissue preservation

- Supportive evidence lacking
  - GnRHa

**Process of Oocyte Cryopreservation**

Oocyte Cryopreservation - a process in which a woman's ovaries are stimulated in order to extract, freeze and store multiple oocytes. The oocytes can then be used after the thawing months or years later. At that point, the thawed oocytes are fertilized in the laboratory setting with sperm to create embryos. These embryos are then transferred to the uterus in an attempt to achieve a pregnancy.

**Steps of Oocyte Cryopreservation using Vitrification**

1. The oocytes are thawed in a solution that融化s the cryoprotectant and avoids the formation of crystals.
2. The thawed oocytes are then placed in a culture medium at 37°C.
3. The culture medium is warmed to 37°C over 30 seconds.
4. The oocytes are transferred to a culture solution containing 10% FBS, 1% glutamine, and 1% penicillin/streptomycin.
5. The culture solution is warmed to 37°C over 30 seconds.
6. The culture medium is then removed, and the oocytes are placed in a culture dish.
7. The oocytes are then incubated at 37°C for 30 minutes.
8. The culture medium is then removed, and the oocytes are placed in a culture dish.
9. The culture medium is then removed, and the oocytes are placed in a culture dish.
10. The culture medium is then removed, and the oocytes are placed in a culture dish.
11. The culture medium is then removed, and the oocytes are placed in a culture dish.
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Simone

- **14-yr-old female**
  - Menstruating for 2 years
- **Localized pelvic EWS – treated on AEWS0031**
  - Chemotherapy
    - Cyclophosphamide equivalency dosing
      - $23.7 \text{ gm/m2} = > 80\%$ relative risk of infertility
  - Radiation
    - $55.80 \text{ Gy to pelvis}$
- **Options**
  - Oocyte harvesting
  - Ovarian tissue cryopreservation
Options - Male

- **Established**
  - Testicular shielding
  - Orchiopexy

- **Investigational**
  - Testicular tissue cryopreservation
Options - Males

- Masturbation
- Electro-ejaculation
- Post-masturbation void
- Sperm Banking → tanner 2
- Testicular sperm extraction
Daniel – Initial Diagnosis

- 13-yr-old male,
  - Tanner stage 3
- Metastatic osteosarcoma of the right femur
  - Too numerous to count pulmonary nodules
  - Treated on AOST0031
- Chemotherapy
  - Infertility risk with cisplatin
- Local control
  - Limb salvage and wedge resection
- Family declined sperm banking
  - Did not qualify for testicular tissue cryopreservation
Daniel-Relapsed

- Pulmonary relapse - 21 months off tx
  - Now age 15-yrs
  - Tanner stage 4
- Chemotherapy
  - Ifosfamide/Etoposide
- Local control
  - Wedge resection
- He wants to sperm banking
Children’s Oncology Group: Focus on Fertility
COG Supportive Care Endorsed Guidelines

- Fertility preservation
  - Recommend discussion prior to treatment
  - Refer to fertility preservation as request
- Recommendations are not evidence based
- Investigation procedures
  - Testicular/ovarian tissue cryopreservation
  - Should only be provided under clinical trials
- Encourage participation in clinical trials
- Provide psychological support

Guideline for Fertility Preservation for Patients with Cancer

Click [here](#) to see all the COG Supportive Care Endorsed Guidelines.
COG Trials

- ALTE16C1 – Effects of Modern Chemotherapy Regimens on Spermatogenesis and Steroidogenesis in AYA Survivors of Osteosarcoma (open to accrual)
- ALTE11C1 – Longitudinal Assessment of Ovarian Reserve in Adolescents with Lymphoma (closed to accrual)
Reproductive Health Among Survivors of Childhood and Adolescent Cancer
Sexual Health Among Adolescents/Young Adults

AYA Sexual Health

- Relationships/Development
- Unplanned Pregnancy Prevention
- STI Prevention

Cancer Survivors Report Unmet Sexual Health Needs
AYA Cancer and Sexual Health

- AYA can experience a delay in sexual milestones compared with peers
  - Challenges with romantic relationships
- AYA with cancer are sexually active
  - One-third of AYA patients sexually active during treatment
- AYA cancer survivors participate in risky sexual behaviors
  - Increasing their risk for STIs and unplanned pregnancy
- AYA cancer survivors experience sexual dysfunction
  - 20-60% of AYA survivors report sexual dysfunction

References:
Sexual Health Priorities During Cancer Treatment

- Abstain from sex during times of neutropenia/thrombocytopenia
- Reduce risk for sexually transmitted infections
  - Abstinence
  - Condoms
- Reduce risk for pregnancy
  - Abstinence
  - Contraception
- Screen for sexual dysfunction

Promote a safe and open environment to discuss sexual health with providers
### COG Long-Term Follow-Up Guidelines

#### Sexual Dysfunction

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>• Erectile dysfunction</td>
</tr>
<tr>
<td>Females</td>
<td>• Pain or vaginal dryness</td>
</tr>
<tr>
<td>Both</td>
<td>• Decreased interest, arousal, satisfaction</td>
</tr>
</tbody>
</table>

#### Chemotherapy Classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>HCT</th>
<th>XRT Field</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating Agents</td>
<td>Hx of cGVHD (females)</td>
<td>TBI</td>
<td>Cystectomy</td>
</tr>
<tr>
<td>Heavy Metals</td>
<td></td>
<td>Pelvis</td>
<td>Spinal cord</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spine</td>
<td>Pelvic surgery</td>
</tr>
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<td></td>
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<td>Testes</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Head/Brain</td>
<td>Oophorectomy/Orchiectomy</td>
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</table>

*Note: COG Track at APHON Thursday, September 3, 2020 2:30 – 3:30 PM*
HPV in Cancer Survivors

- HPV most common STI in US: ↑prevalence in 20-24 yr olds
- Cancer Survivors ↑risk for HPV-related subsequent cancers
- HPV Vaccine protects against 7 oncogenic HPV types

- >30,000 HPV-related Cancers Annually
- Females: 40% excess
- Males: 150% excess
- 75% HPV-related cancers

Ojha et al.; Plos One 2013. 8(8); e70349
HPV Vaccine for Cancer Survivors

Age 11 or 12 years

Cancer Survivors: Recommended vaccination 9 to 26 years
Consider vaccination up to age 45

3 Doses
6 Months

Illustrations by Sam Phang, 2007

Petrosky et al., MMWR 2015; 64: 300-304;
Meites et al., MMWR 2019;68: 698–702
COG Long-Term Follow-Up Guidelines: HPV Vaccination

- Counsel on the importance of HPV Vaccination
- Screen for HPV Vaccination

GENERAL HEALTH SCREENING

HEMATOPOIETIC CELL TRANSPLANT (CONT)

CANCER SCREENING GUIDELINES

CERVICAL CANCER

CANCER SCREENING GUIDELINES

ORAL CANCER

<table>
<thead>
<tr>
<th>Sec #</th>
<th>Organ</th>
<th>Standard Risk Parameters and Screening Guidelines</th>
<th>Highest Risk Parameters and Screening Guidelines</th>
<th>Health Counseling/Further Considerations</th>
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<tbody>
<tr>
<td>161</td>
<td>Oral</td>
<td>STANDARD RISK PARAMETERS</td>
<td>HIGHEST RISK PARAMETERS</td>
<td>COUNSELING</td>
</tr>
</tbody>
</table>

The world's childhood cancer experts
Children’s Oncology Group Sexual Health Task Force

**Task Force Within COG AYA Committee**

**Vision:** To improve sexual health for adolescents and young adults with cancer.

**Mission:** to explore the feasibility of a sexual health research initiative, advise on compelling research questions, deliver these within COG cooperative group setting.
Children’s Oncology Group AYA Sexual Health Task Force

Kristin Bingen, PhD
Pediatric Psychologist
Children’s Hospital of Wisconsin

Sharon Bober, PhD
Psychologist
Dana-Farber Cancer Institute

Brooke Cherven, PhD,
MPH, RN
Nurse Scientist
Emory University

Natasha Frederick, M
MPH, MST
Pediatric Oncologist
Connecticut Children’s Medical Center

David Freyer, DO
Pediatric Oncologist
Children’s Hospital of Los Angeles

Gwendolyn Quinn, PhD
Psychologist
New York University
COG Sexual Health Task Force

What is known about sexual health and AYA cancer?

What do providers need?

What do AYA patients and survivors need?

Develop a toolkit/Intervention to improve sexual health

Scoping Review of Literature

COG Provider Survey
Scoping Review of Literature:
Among cancer survivors, did childhood/AYA cancer impact sexual function?

Findings:
• Wide variation in definition and measurement of sexual dysfunction
• Substantial sexual dysfunction among AYA cancer survivors
• Survivors desire education, resources, and clinical support
COG Sexual Health Provider Survey

Aims:

- Determine current pediatric oncology clinician practices around sexual health communication.
- Identify clinician-reported facilitators of and barriers to sexual health communication
- Identify clinician preferred education and resource needs to help improve sexual health communication with AYA patients
COG Sexual Health Task Force: Next Steps

- Publish Review and Provider Survey Data
- Develop Resources/Intervention
- Conduct Research within COG
- Collaborate with Professional Organizations
Communication and Considerations for Sexual Health Discussions
Considerations for Discussions of Sexual Health

- Age and Development
- Romantic History
- Cultural Factors
- Parental/Family Attitudes
- Sexual Orientation
- Gender Identity

Build Trust and Establish Open Environment
Association of Clinical Oncology Guideline:
It is recommended that there be a discussion with the patient, 
initiated by a member of the health-care team, 
regarding sexual health and dysfunction resulting from cancer or its treatment

• Conversations regarding sexual health should begin at diagnosis and continue through survivorship
• Identify resources for referral (e.g., urology, OB/GYN, psychology) for patients who report problems
Sexual Health Discussions

- **Set the stage**
  - Private setting
  - Parents/family members and other leave the room
  - Discuss confidentiality at start of the conversation

- **Ask Permission**
  - “Many AYAs worry about how cancer will affect dating and relationships. I would like to take some time today to talk about this. Is this okay with you?”
Discussing Sex with AYA Patients: *Diagnosis and During Treatment*

5 P’s (Sexual Health History)

- Previous *Partners*
- Sexual *Practices*
- Protection from STIs
- Prior History of STIs
- Prevention of *Pregnancy*

- Focus on building trust/open relationships
- Identify and address risky behaviors
- Counsel regarding safe sex practices during cancer treatment
- Continue discussions throughout treatment

CDC, 2015 STD Guidelines
Examples

- I am going to ask you a few questions about your sexual health and sexual practices. I understand that these questions are very personal, but they are important for your overall health.”

- Some of my patients your age have started having sex. Have you been sexually active? What kind of sexual contact do you have or have you had?

- What kinds of protection do you use to prevent sexually transmitted infections and pregnancy?
Discussing Sex with AYA Patients: After Treatment/Survivorship

PLISSIT
- Permission
- Limited Information
- Specific Suggestions
- Intensive Therapy

5 A’s
- Ask
- Advise
- Assess
- Assist
- Arrange Follow-Up

- Screen for sexual dysfunction
- Counsel on safe sex practices
- Refer for sexual therapy, psychology as appropriate

Park et al.; Cancer 2009; 15:74-77
Examples

- Do you have any questions about sexual health or is there anything that you are worried about that you’d like to ask me?

- “Many cancer survivors have concerns about changes in sexual function; do you have any questions or concerns you would like to ask me about?”
  - Can give examples if needed: pain with intercourse, decreased lubrication (females), or problems getting or maintaining an erection (males), decreased desire for sex.

- What other things about your sexual health and sexual practices should we discuss to help ensure your good health?
Resources

CDC Sexual Health Assessment Guide

Project ECHO
Virtual Course in Reproductive and Sexual Health for Oncology Healthcare Providers

What is ECHO?
Enriching Communication Skills for Health Professionals in Oncofertility (ECHO) is a web-based training program focusing on building communication skills

Training Topics
- Risk of infertility
- Fertility preservation
- Sexual functioning
- Body image
- Family planning
- Contraception
- Ethical, social, and cultural considerations

Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

A GUIDE TO TAKING A SEXUAL HISTORY

www.echo.rhoinstitute.org
Appendix I - Cyclophosphamide Equivalent Dose

- All the listed agents mg/m² dose are equal to 100 mg/m² of CPM
  - e.g.: BCNU 6.7 mg/m² = CPM 100 mg/m²
- To calculate CED multiply the cumulative dose of the agent by the multiplier
  - e.g.: if cumulative dose of BCNU was 220 then CED is 220 x 15 = equivalent to 3300 mg/m² CPM
  - You may also use a CED calculator such as the one found at
- CED of >7500 mg/m² = a significant risk of loss of reproductive potential

<table>
<thead>
<tr>
<th>Agent</th>
<th>Multiplier</th>
<th>CED Dose</th>
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<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>1</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>BCNU</td>
<td>15</td>
<td>6.7 mg/m²</td>
</tr>
<tr>
<td>Busulfan</td>
<td>8.823</td>
<td>11.3 mg/m²</td>
</tr>
<tr>
<td>CCNU</td>
<td>16</td>
<td>6.3 mg/m²</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>14.286</td>
<td>7 mg/m²</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>0.244</td>
<td>409 mg/m²</td>
</tr>
<tr>
<td>Melphalan</td>
<td>40</td>
<td>2.5 mg/m²</td>
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<tr>
<td>Nitrogen mustard</td>
<td>100</td>
<td>1 mg/m²</td>
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<tr>
<td>Procarbazine</td>
<td>0.857</td>
<td>117 mg/m²</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>50</td>
<td>2 mg/m²</td>
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Appendix I – using CED female case study EWS0031

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</tbody>
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- CPM 1200 mg/m² X 7 cycles = 8400 mg/m² total CPM = **CED** 8400 mg/m²
- IFOS 1800 mg/m² X 5 days X 7 cycles = 63000 mg/m² cumulative IFOS dose
- IFOS **CED** obtained by multiplying 63000 x 0.244 = 15,372 mg/m²
- CPM **CED** 8400 mg/m² + IFOS **CED** 15,372 mg/m² = **CED** 23,772 mg/m², which is considered to be a significant fertility risk for this patient
## Abbreviations

<table>
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<th>FULL TERM</th>
<th>ABBREVIATION</th>
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<tr>
<td>Adolescent and young adult</td>
<td>AYA</td>
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<td>American Academy of Pediatrics</td>
<td>AAP</td>
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<tr>
<td>American Society for Clinical Oncology</td>
<td>ASCO</td>
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<tr>
<td>American Society for Reproductive Medicine</td>
<td>ASRM</td>
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<tr>
<td>Association Pediatric Hematology Oncology Nurses</td>
<td>APHON</td>
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<tr>
<td>Carmustine</td>
<td>BCNU</td>
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<td>Children's Oncology Group</td>
<td>COG</td>
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<td>Chronic graft versus host disease</td>
<td>cGVHD</td>
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<tr>
<td>Cyclophosphamide</td>
<td>CPM</td>
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<tr>
<td>Cyclophosphamide Equivalent Dose</td>
<td>CED</td>
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<tr>
<td>Ewing's Sarcoma</td>
<td>EWS</td>
</tr>
<tr>
<td>Fertility preservation</td>
<td>FP</td>
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<tr>
<td>FULL TERM</td>
<td>ABBREVIATION</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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</tr>
<tr>
<td>Gonadotropin-releasing hormone agonist</td>
<td>GnRHa</td>
</tr>
<tr>
<td>Gram</td>
<td>gm</td>
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<tr>
<td>Gray</td>
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<tr>
<td>History</td>
<td>HX</td>
</tr>
<tr>
<td>Human Papilloma Virus</td>
<td>HPV</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Ifos</td>
</tr>
<tr>
<td>Lomustine</td>
<td>CCNU</td>
</tr>
<tr>
<td>Long-Term Follow-Up</td>
<td>LTFU</td>
</tr>
<tr>
<td>Meter square</td>
<td>m2</td>
</tr>
<tr>
<td>Number</td>
<td>N or n</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>osteo or OST</td>
</tr>
<tr>
<td>Patient(s)</td>
<td>pt(s)</td>
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### Abbreviations

<table>
<thead>
<tr>
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<th>ABBREVIATION</th>
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<tr>
<td>Post traumatic stress disorder</td>
<td>PTSD</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>XRT</td>
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<tr>
<td>Sexually Transmitted Infection(s)</td>
<td>STI(s)</td>
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<tr>
<td>Total Body Irradiation</td>
<td>TBI</td>
</tr>
<tr>
<td>Treatment</td>
<td>Tx</td>
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References


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