Childhood Cancer Survivor Study
Study Proposal: Male Health Questionnaire (MHQ)
November 19, 2010
Concept # 10-24

1. **STUDY TITLE:** Male Infertility and fertility preservation in childhood and adolescent cancer survivors diagnosed from 1970-1986: A report from the Childhood Cancer Survivor Study

2. **WORKING GROUP AND INVESTIGATORS:** This proposed publication will be within the Chronic Disease Working Group. Proposed investigators will include:

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3. **BACKGROUND AND RATIONALE**

Infertility

Survival from pediatric cancer has increased significantly over the last several decades. However, survival may come at the price of long-term side effects from cancer treatment such as infertility. Many cancer therapies such as alkylator-type chemotherapy, radiation to the testes, and therapies that affect the hypothalamic/pituitary axis can result in male infertility. Most data on male infertility as a result of cancer treatment have come from patients treated during adulthood. The literature on male infertility in survivors of childhood cancer is limited.

A previous CCSS publication sought to determine the effect of diagnosis and treatment on pregnancy outcome in male survivors of childhood cancer [1]. In this large study of over 4000 sexually active males, the proportion of pregnancies ending in live birth was significantly lower than for male siblings of survivors; however there were no significant differences in pregnancy outcomes by treatment and, pregnancies from assisted technology were excluded. In the analysis of male fertility in the CCSS cohort, the "hazard of pregnancy" was compared in male survivors and their sibling control with an endpoint of "ever having sired a pregnancy.[2]" Factors affecting fertility included testicular radiation dose of ≥ 7.5 Gy, an alkylating agent dose score of ≥ 2 [3], and exposure to procarbazine or higher-dose cyclophosphamide. This report differs from the proposed study in that fertility as oppose to infertility was analyzed. The fertility analysis was not able to take into consideration personal choices such as the decision to try to become pregnant, difficulties in becoming pregnant despite the ultimate outcome of a pregnancy, and the utilization of cryopreservation or sperm.

To better understand male reproductive function following childhood cancer treatment, including the need for assisted technology, a more detailed questionnaire was developed. The Male Health Questionnaire (MHQ), funded by the Lance Armstrong Foundation, was designed to ascertain information about testicular function, infertility and sexual function in pediatric cancer survivors. The MHQ was similar to a questionnaire employed in a previous ancillary study which ascertained detailed information on female reproductive and sexual function in the female survivors in the CCSS cohort. This concept will help determine the frequency of problems of infertility in male survivors of childhood or adolescent cancer as well as the effect of childhood and adolescent cancer treatment on infertility in male survivors. This will differ from previous analyses on male fertility and

pregnancy outcomes of male survivors in that the population will only include male survivors and their male sibling controls who have tried to become pregnant with a partner. The primary outcome will be difficulty in becoming pregnant, or infertility, as opposed to fertility defined as either having sired a pregnancy or having sired a pregnancy resulting in a live birth.

The American Society of Reproductive Medicine (ASRM) describes "infertility" as "a disease defined by the failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse" [4]. This definition does cause some confusion, as the majority of those labeled as infertile per the standard definition above will eventually conceive. Sterility, a zero chance of conceiving spontaneously, only occurs in 3-5% of couples in the general population [5]. Though the ASRM definition of infertility has been argued by some for this very reason, it remains the most consistent way of defining infertility both clinically and in the literature. Infertility is a complex problem with innumerable physiologic explanations with dysfunction originating in the male, female or both. In this report, we will focus on infertility originating in the male survivors and use the standard definition of "infertility" to guide our analysis..

Infertility can be further subdivided into primary infertility, never having been able to conceive, versus secondary infertility, difficulty conceiving after having already conceived with the same partner. Though birth data are available from the *Follow-Up 2007 Questionnaire* and previous baseline and follow-up questionnaires, the sequence of any pregnancies and the report of a fertility problem is not known and therefore will not be analyzed in this report. However, what can be described is the number of survivors with reported "infertility" per the definition above who had previously reported a partner with either a conception or a live birth.

Fertility Preservation

Sperm banking is often recommended to/for pubertal males at risk for infertility due to cancer treatment. The first successful human pregnancy using banked sperm occurred in 1953 [6] and successful cyropreservation became possible in the mid-1970's [7]. Sperm banking became widely available to patients with cancer in the 1980's. The number of patients banking sperm dramatically increased with the reported successes of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) in the 1990's [7, 8]. Intrauterine insemination (IUI) requires high sperm numbers. In ICSI, one sperm is directly injected into an oocyte requiring only a viable few sperm cells after cryopreservation [7]. Prior to the advent of this new assisted reproduction technique, banking sperm in cancer patients was often not offered or encouraged due to concerns about the quality and quantity of sperm [7].

The original CCSS cohort is composed of 5-year survivors of childhood cancer diagnosed from 1970-1986, a time frame in which cryopreservation of sperm was becoming increasing available. Through the Male Health Questionnaire, we will determine the frequency in which cryopreservation of sperm was offered and utilized in the early years of its availability.

4. **Aims**:

   Aim 1:
   To determine the prevalence of infertility or difficulty in siring a pregnancy among male survivors of childhood or adolescent cancer who have tried to become pregnant with a partner in comparison to sibling controls

   Aim 2:
   To determine the effect of childhood and adolescent cancer treatment on infertility in male survivors

   Aim 3:
   To determine the frequency in which cryopreservation of sperm was offered and utilized in the early years of its availability in adolescent cancer patients

5. **Data Analysis**

- Aim 1: Prevalence of infertility

  Population:
  - Inclusion

        - All male survivors responding positively to question C6 to the MHQ – "Have you and a partner ever tried to become pregnant"
    - Exclusion
        - Recurrence
        - SMN
    - Comparison population
        - Male siblings responding to MHQ
            - Exclude siblings who have had cancer

Primary outcome variable:

- Difficulty becoming pregnant (C7)
    - Definition of "infertility" = positive answer to C6 and C7

Secondary outcome variable(s):

- Infertility due to male factors (C6+C7 = "yes" and any of the following)
    - C11 ="b" or "c" – fertility problem in me or both
    - C12 + C13 = "yes" – fertility problem was identified
    - C14 = "yes" and C15 = "low" or C16 = "low"– semen analysis done and sperm count low or motility low
- Report of a pregnancy 5+ years after diagnosis (Q1-5 on LTFU plus cumulative data on past questionnaires)
    - At least one conception
    - At least one live birth

Explanatory variables:

- Ethnicity (Baseline)
- Age at assessment (date of MHQ – dob)
- Marital status (M2 – LTFU)
- Smoking status (N7 – LTFU)
- Alcohol status (N6 – LTFU)
- Physical activity (N15 – LTFU)
- Education level (A3 – LTFU)
- Employment status (A4 – LTFU)
- Household Income (A6 – LTFU)
- Individual income (A8 – LTFU)
- Insurance coverage (B9 – LTFU)

Statistical analysis

Odds ratios comparing the risk of infertility, and of the secondary outcomes between survivors and siblings will be computed using age-adjusted generalized estimating equations (GEE) logistic regression models. We will also examine the effects of the potential explanatory variables listed above in a multivariable regression model, with final models including those that are significant at $\alpha=0.05$, or which markedly modify the effect of the comparison between survivors and siblings.

Figure 1: Infertility in Male Cancer Survivors

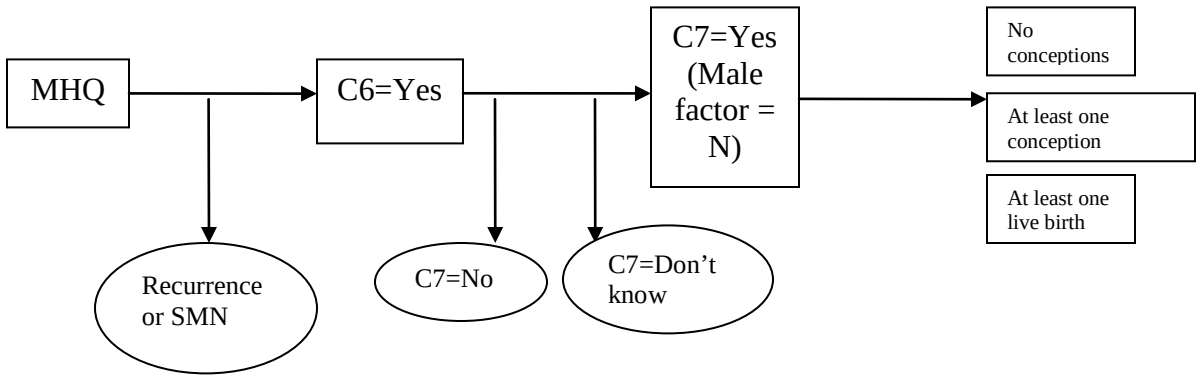


Table 1: Comparison of infertility in survivors and their male siblings who have "tried to become pregnant"

	All MHQ Survivors	MHQ Siblings
	n/y (%)	n/y (%)
Total (C6 = yes)		
Infertility (C7 = Yes)		
Yes		
No		
Don't know		
Able to have all the children you wanted (C8)		
Yes		
No (C8a)		
• Subject wanted more		
• Partner of subject wanted more		
• Both subject and partner wanted more but could not		
Reasons for not having more children (C9)		
Male infertility		
Health issues related to cancer treatment		
Health issues not related to cancer treatment		
Female infertility		
Partner had health issues		
Tried but reason unknown		
Issues other than health		
Evaluation for infertility of subject or female partner (C10)		
Yes		
No		
Don't know		

Fertility problem identified (C11)		
Fertility problem in partner		
Fertility problem in subject		
Fertility problem in partner and subject		
No		
Don't know		
Subject personally evaluated for fertility problem (C12)		
Yes		
No		
Age at fertility evaluation (mean; range) (C12)		
Problem identified by personal fertility evaluation (C13)		
Yes		
No		
Semen Analysis (C14)		
Yes		
No		
Don't know		
Sperm Count (C15)		
Normal		
Low		
Don't know		
Sperm Motility (C16)		
Normal		
Low		
Don't know		

(Some features of Table 1 may be better illustrated in figure form)

Table 2: Characteristics of Male Childhood Cancer Survivors with Infertility

	Total in MHQ	**Survivors with Reported Infertility (C7=Yes)**	**Survivors not Reporting Infertility (C7=No)**	**Siblings with Reported Infertility**	**Siblings Not Reporting Infertility**
Ethnicity					
Non-Hispanic White					
Hispanic					
Non-Hispanic Black					
Other					
Age at Assessment					
Mean (range)					
20-29					
30-39					
40-49					
50-59					
60+					

Marital Status					
Single; never married					
Married					
Living as married					
Widowed					
Divorced					
Separated					
Smoking Status (N7)					
Never					
Current					
Former					
Alcohol Use (N1)					
Yes					
No					
Alcohol Abuse (5+ drinks) (N6)					
One day/week or more					
Less than one day per week					
Physical Activity (N15)					
Yes					
No					
Moderate or Vigorous activity (N17; N20)					
< 3 days per week					
3+ days per week					
Highest Level of Education (A3)					
Did not complete HS					
Completed HS or GED					
Non-college training after HS					
Some college					
College graduate					
Post graduate					
Employment (A4)					
Full time (30+ hours/wk)					
Part time (< 30 hr/wk)					
Caring for home/family					
Unemployed looking for work					
Unable to work					
Retired					
Student					

Household Income (A6)					
< $20,000					
$20,000-39,999					
$40,000-59,999					
$60,000-79,999					
$80,000-99,999					
>$100,000					
Don't know					
Individual Income (A8)					
None					
< $20,000					
$20,000-39,999					
$40,000-59,999					
$60,000-79,999					
$80,000-99,999					
>$100,000					
Don't know					
Insurance (B9)					
Yes					
No					
Canadian resident					

- Aims 2: Effect of treatment on infertility

  Population (s):
  - All male survivors responding to the MHQ and responding positively to question C6; recurrence and SMN excluded as above

  Outcome
  - Infertility (C6=yes and C7=yes)

  Comparison population
  - No fertility problem (C6=yes and C7=no)

  Exposure variables:
  - Oncology
    - Age at diagnosis (MRAF)
    - Primary diagnosis (MRAF) – preliminary analysis with 14; may need to consolidate based on numbers; acknowledged confounding with treatment but will look at first-pass
    - At risk based on the COG Long-Term Follow-Up Guidelines (Yes/No) – Summary category with any of the following exposures
      - Alkylating agents (including heavy metals) - any
      - Cranial radiation (> 40 Gy)
      - Testicular radiation - any
      - TBI
      - Orchiectomy
    - Alkylator exposure (MRAF)
      - Summed AAD (0-11) – per Green et al. JCO June 2009, 27 (16):2677-2685
      - *Cyclophosphamide equivalent scores if available for analysis*
      - Individual chemotherapy agents (yes/no exposure)
        - Include at first pass all alkylating agents, heavy metals, and any other agent to which > 5% of the population was exposed
    - Radiation exposure by dosimetry (MRAF & Dosimetry)
      - Testicular radiation in Gy
        - None

- 0.001-3.99
- 4.00-4.99
- 5.00-5.99
- 6.00-14.99
- 15.00-23.99
- >24

- Hypothalamic/pituitary (Cranial) in Gy
  - None
  - 0-19.99
  - 20-29.00
  - 30.00-39.99
  - >40.00

- Surgery – *Will need to review individual ICD-9 codes which fall within the parameters below*
  - MHQ (ICD-9 60-64) – *Will need to review individual answers/ICD-9 codes for what type of surgery*
    - Prostate(B3 – MHQ)
    - Pelvic(B3 – MHQ)
    - Penis(B3 – MHQ)
    - Testicular(B3 – MHQ)
      - Orchiectomy – addition data from MRAF; FU 2007 J35; J36
    - Orchiopexy – additional date from MRAF; FU 2007 J37?
  - Surgeries from other Questionnaires (MRAF; Baseline; FU 2007)
    - Operations on the male genital organs (ICD-9 60-64)
      - 60.X – prostate/seminal vesicles
      - 61.X – scrotum/tunical vaginalis
      - 62.X – testes
      - 63.X – spermatic cord, epididymis, vas deferens
      - 64.X – penis
    - Operations on the Endocrine System
      - 0.7.6X_- Hypophysectomy
      - 0.7.7X – Other operations on hypophysis
    - Operations on the Urinary System
      - 57.7 – Total cystectomy
    - Operations on the Nervous System
      - 03.X - Operations on spinal cord and spinal canal structures
      - 05.X - Operations on sympathetic nerves or ganglia

<u>Co-Variates</u>:

- General Health
  - General health status (MHQ – D1)
  - Personal care (N22;23 – LTFU)
  - Pain (L21 – L23 – LTFU)
- Cognitive/Psychological
  - Problems with learning or memory (K1 – LTFU)
  - Anxiety/fears as a result of cancer/treatment (L20 – LTFU)
  - Concern of ability to have children (O2 – LTFU)
- Neurological
  - Weakness or inability to move legs (K12; K14e - LTFU)
- Endocrine
  - Timing of puberty (C1)
  - Testosterone treatment (C8(3) LTFU; B4 MHQ)

Statistical analysis.

Separate logistic regression models utilizing each the factors listed above, along with current age will be used to generate age-adjusted odds ratios for the risk of infertility. This will serve as a "screening" step precursor to the multivariable modeling exercise described below.

Table 3: Effects of Cancer Treatment on Male Infertility in Childhood Cancer Survivors

	Total in MHQ	**Survivors with Reported Infertility (C7=Yes)**	**Survivors not Reporting Infertility (C7=No)**
General Health (D1)			
Excellent			
Very good			
Good			
Fair			
Poor			
Need Help with Personal Care (N22)			
Yes			
No			
Need Help with Routine Activities (N23)			
Yes			
No			
Somatic Pain (L21)			
None			
Very mild			
Mild			
Moderate			
Severe			
Very Severe			
Interference of Pain with Normal Work (L22)			
Not at all			
A little bit			
Moderately			
Quite a bit			
Extremely			
Location of Pain (L23)			
Head			
Neck			
Chest			
Hands/Arms			
Abdomen			
Back			
Pelvis			

Legs/Feet			
Other			
Current Problem with Learning or Memory (K1)			
No (Includes condition no longer present)			
Mild			
Moderate			
Severe			
Disabling			
Anxiety/Fears about Cancer History (L20)			
No			
Small amount			
Medium amount			
A lot			
Very many/extreme			
Concerns of Ability to Have Children (O2)			
Very			
Somewhat			
Concerned			
Not very			
Not at all			
Weakness of inability to move legs (K12)			
Yes - current			
No – includes condition no longer present			
Timing of Puberty (C1)			
Early			
Normal			
Late			
Testosterone Treatment			
Yes			
No			
Erectile Dysfunction Treatment			
Yes			
No			
Primary Diagnosis			
ALL			
AML			

Other leukemia			
Astrocytoma			
Medulloblastoma			
Other CNS			
Hodgkins			
NHL			
Kidney			
Neuoblastoma			
Soft Tissue Sarcoma			
Ewings Sarcoma			
Osteosarcoma			
Other sarcoma			
Age at Diagnosis			
0-4			
5-9			
10-14			
15+			
COG LTFUG-Defined Exposure Risk			
Yes			
No			
Alkylator exposure Summed AAD Or cyclophosphamide equivalents			
0			
1			
2			
3			
4			
5			
6+			
Radiation (in Gy)			
Cranial (Hypothalamic Radiation)			
None			
0.001-19.99			
20-29.99 Gy			
30.00-39.99			
> 40.00			
Testicular Radiation			
None			
0.001-3.99			
4.00-4.99			
5.00-5.99			
6.00-14.99			
15.00-23.99			

>24			
TBI			
Yes			
No			
Surgery			
Unilateral Orchietcomy			
Yes			
No			
Bilateral Orchiectomy			
Yes			
No			
Other testicular surgery			
Yes			
No			
Prostate surgery			
Yes			
No			
Pelvic surgery			
Yes			
No			
Penis surgery			
Yes			
No			

Table 4: Multivariate Analysis of Relative Risk of Infertility in Male Cancer Survivors
(Variables to depend on initial analysis)
Proposed variables

- Age at diagnosis
- Ethnicity
- General health
- Self-help
- COG Long-Term Follow-Up Guideline lumped category (see above for description)
- Alkylator exposure (AAD score)
- Heavy metal exposure
- Cranial radiation exposure
- Testicular radiation exposure
- TBI (if not using dosimetry)
- GU surgery

Statistical analysis
Potentially significant risk factors will be identified in the age-adjusted "univariable" analyses described above, and included in an initial multivariate logistic regression model. Parameters which do not contribute to the overall fit of the model, and/or which do not have statistically significant odds ratios, will be removed.

- Aim 3: Frequency in which cryopreservation of sperm was offered and utilized in the early years of its availability in adolescent cancer patients

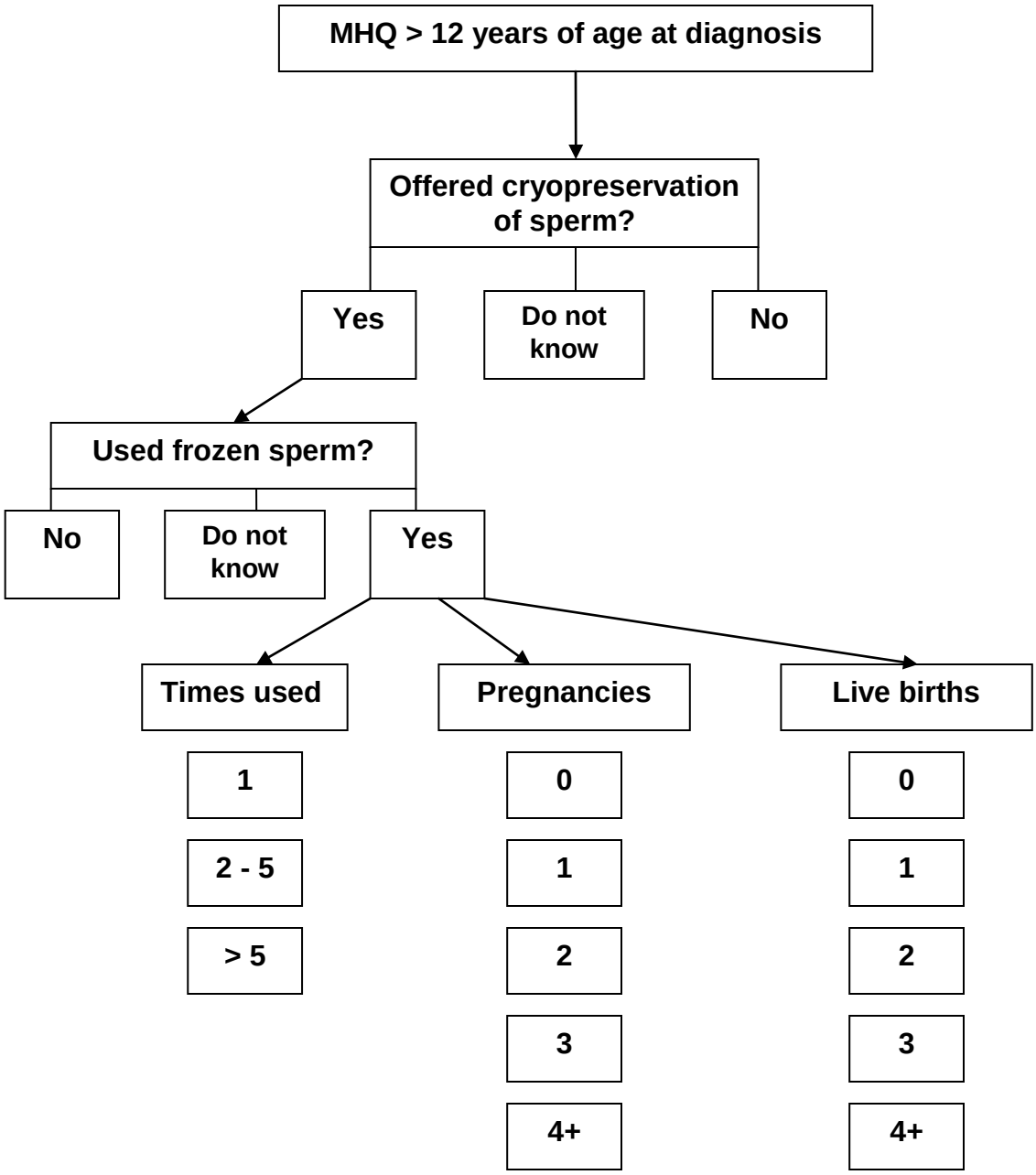
  Population
  - Answered question C17 on MHQ; age > 12 years at diagnosis

Outcome
- Answered positively to C17
- Answered positively to C18

Exposure Variables
- Age
- Diagnosis
- Treatment Era
- Treating Institution – *first pass data to see if all cases came out of specific institutions*

Statistical Analysis
The analyses for this aim will be primarily descriptive, though some associations between the factors listed above and whether cryopreservation of sperm was offered and utilized will be evaluated.

Figure 1: Cryopreservation of Sperm in Adolescent Cancer Patients Diagnosed from 1970-1986



	MHQ Survivors
Banked Sperm	
Yes	
No	
Utilized banked Sperm	
1	
2-5	
>5	
# Pregnancies	
0	
1	
2	
3	
4+	

Live Births	
0	
1	
2	
3	
4+	

Table 4: Reasons for not sperm banking or using banked sperm

	Did not bank sperm	Did not use banked sperm
Total		
Too young at diagnosis		
Told not to bank sperm		
Did not know how to utilize service		
Worried about future health and ability to be a father		
Worried about passing on cancer to my child		
Worried about having a child damaged by cancer or cancer treatment		
Too expensive		
Not the right thing to do		
Other		

Table 5: Factors in Sperm Banking for Adolescent Cancer Patients Diagnosed 1970-1986

	Sperm banked (N; %)	Did not bank sperm (N; %)	Odds Ratio
Total			
Infertility			
Survivors not reporting infertility			**1**
Survivors reporting infertility			
Age at diagnosis			
<18 years			**1**
≥ 18 years			
Diagnosis			
ALL			**1**
AML			
Other leukemia			
Astrocytoma			
Medulloblastoma			
Other CNS			
Hodgkins			
NHL			
Kidney			
Neuoblastoma			
Soft Tissue Sarcoma			
Ewings Sarcoma			
Osteosarcoma			
Other sarcoma			
Treatment Era			

1970-1973			**1**
1974-1977			
1978-1981			
1982-1986			
Treating Institution			

Table 6: Factors in Utilization of Banked Sperm for Adolescent Cancer Patients Diagnosed 1970-1986

	Sperm banked (N; %)	**Utilized bank sperm (N; %)**	**Odds Ratio**
Total			
Infertility			
Survivors not reporting infertility			**1**
Survivors reporting infertility			
Age at diagnosis			
<18 years			**1**
≥ 18 years			
Diagnosis			
ALL			**1**
AML			
Other leukemia			
Astrocytoma			
Medulloblastoma			
Other CNS			
Hodgkins			
NHL			
Kidney			
Neuoblastoma			
Soft Tissue Sarcoma			
Ewings Sarcoma			
Osteosarcoma			
Other sarcoma			
Treatment Era			
1970-1973			**1**
1974-1977			
1978-1981			
1982-1986			
Treating Institution			

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