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Signature:

Matthew Daniel Ramirez

Date

**Yield of Screening Urinalysis in Pediatric Cancer Survivors using the Children's
Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood,
Adolescent, and Young Adult Cancers**

By

Matthew Daniel Ramirez
Master of Science
Clinical Research

Ann Mertens, Ph.D.
Advisor

Mitchel Klein, Ph.D.
Committee Member

Amita Manatunga, Ph.D.
Committee Member

John E. McGowan, Jr., M.D.
Committee Member

Accepted:

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

Date

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Matthew Daniel Ramirez
B.S., Texas Tech University, 2004
M.D., The University of Texas Medical Branch at Galveston, 2008

Advisor: Ann Mertens, Ph.D.

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Abstract

Yield of Screening Urinalysis in Pediatric Cancer Survivors using the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers

By Matthew Daniel Ramirez

Background: Over the past decades, improvements have been made in pediatric cancer treatment outcomes. High survival rates are the product of intensive therapies which place pediatric cancer survivors at risk for treatment related morbidity. In 2003, the Children's Oncology Group published the *Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers* with the intention of increasing survivor quality of life through early identification of treatment related morbidities. These guidelines recommend annual screening urinalysis for pediatric cancer survivors exposed to therapies associated with bladder and/or renal late effects. We sought to estimate the yield and cost of this recommended screening, as well as identify possible risk factors for abnormal screening in a survivor population.

Methods: A database of pediatric cancer survivors evaluated at the Children's Healthcare of Atlanta Cancer Survivor Program was queried for survivors at risk for bladder and renal late effects evaluated between January 2008 and March 2012. The frequency of abnormal urinalyses (protein \geq 1+ and/or \geq 5 red blood cells per high power field) was estimated. Multivariable analysis identified risk factors associated with abnormal screening, using logistic regression. The cost of screening the survivor cohort was estimated.

Results: Chart review identified 758 survivors (57% male; 67% Caucasian; 60% leukemia/lymphoma survivors; mean age at diagnosis, 5.8 years [range, birth to 17 years]; time from diagnosis, 7.6 years [range, 2 to 21 years]) who underwent urinalysis screening. Abnormal results were found in 67 (4.6%) of 1461 total urinalyses. Univariate analysis identified statistical associations between abnormal urinalysis findings and sarcoma diagnosis, screening occurring 10-14 years after completion of therapy, and ifosfamide chemotherapy exposure. Multivariable analysis revealed high dose ifosfamide exposure (OR=6.1, 95% CI 2.2-16.7) and age \leq 4 at time of diagnosis (OR=1.8, 95% CI 1.0-3.2) as significant risk factors for abnormal urinalysis screening, after adjusting for hematopoietic stem cell transplantation, cisplatin chemotherapy and bladder/kidney radiation exposures.

Conclusion: Pediatric cancer survivors are in need of targeted screening for therapy late effects. Survivors \leq 4 years of age at diagnosis and those exposed to high ifosfamide chemotherapy doses may be at higher risk of abnormal findings on urinalysis.

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Table of Contents

Introduction	1
Background	2
Methods	6
Results	13
Discussion	18
References	25

Tables and Figures

Table 1.	Treatment exposures placing study subjects at risk for genitourinary late effects and recommended screening parameters <i>per</i> the Children’s Oncology Group Long-Term Follow-Up Guidelines	30
Table 2.	Demographic characteristics for survivors at risk for genitourinary complications evaluated at the Children’s Healthcare of Atlanta (CHOA), Cancer Survivor Program (CSP)	31
Table 3.	Treatment exposures for survivors at risk for genitourinary complications evaluated at the CHOA CSP	32
Table 4.	Demographic characteristics for survivors at risk for genitourinary complications who underwent urinalysis screening at the CHOA CSP	33
Table 5ab.	Treatment exposures for survivors at risk for genitourinary complications who underwent urinalysis screening at the CHOA CSP	34-35
Table 6.	Results of urinalysis screening in at risk survivors evaluated at the CHOA CSP	36
Table 7.	Point estimates and 95% confidence intervals for significant predictor variables using multivariable logistic regression model	37
Table 8.	Cost estimates for laboratory testing ordered among survivor cohort	38
Figure 1.	Survivors evaluated at the CHOA CSP during study period	39
Figure 2.	Flowchart detailing results of subsequent urinalysis findings after an initial normal urinalysis screen	40
Figure 3.	Flowchart detailing results of subsequent urinalysis findings after an initial abnormal urinalysis screen	41

Introduction

Cancer diagnoses and treatment among children and adolescents represent a substantial cause of morbidity and mortality (1-4). Paradoxically, while the incidence rate of pediatric cancer in the United States has steadily increased, a decrease in mortality has been demonstrated (5). Improvements in treatment outcomes are the consequence of a pervasive research focus in the field of pediatric oncology and intensive multi-modal therapies, including surgery, radiation and combination chemotherapy (6). Overtime, a population of pediatric survivors has emerged who have undergone extensive treatments and are at-risk for morbidities related to their prior therapies “late effects”. Prompted by a report from the Institute of Medicine, in 2003 the Children's Oncology Group (COG) published clinical guidelines (*Long-Term Follow-Up (LTFU) Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*) to screen pediatric cancer survivors for treatment-related morbidity (7, 8).

Several commonly used treatment modalities in pediatric cancer therapy have been associated with genitourinary late effects (9, 10). The COG LTFU Guidelines recommend annual screening urinalysis for genitourinary late effects among pediatric cancer survivors who were exposed to certain therapies (Table 1). It is unknown if urinalysis screening of this population is clinically beneficial or cost-effective. This study will address the following: yield of the COG LTFU Guidelines recommended urinalysis screening to identify genitourinary late effects, variables which may make urinalysis screening in this population more effective, and cost of urinalysis screening a survivor population.

Background

Over the last several decades, considerable improvements have been made in childhood cancer treatment outcomes, with current estimates of five year survivorship rates exceeding 80% (11). Since 1975, the death rate among pediatric cancer patients has decreased by more than 50% (12); consequently, an increasing population of survivors exposed to cancer therapies has emerged. There were an estimated 379,100 survivors of pediatric cancer alive in the United States as of January 1, 2010, and these numbers will approach 500,000, by some projections, before 2020 (13). Improving survival rates in pediatric cancer patients are the product of intensive multi-modal therapies, including surgery, radiation and combination chemotherapy, which place survivors at risk for treatment related late effects. Therapy related late effects in pediatric cancer survivors are common (14-17). The incidence of having at least one chronic medical condition in the survivor population has been reported as high as 62%, and 28% have a severe or life-threatening condition (18). Recognizing the need for ongoing surveillance of treatment-related late effects in the pediatric cancer survivor population, in 2003, the Institute of Medicine called for development of a "system of care and method of care" for pediatric cancer survivors (7). Due to uncertainty of how best to care for survivor patients, in its report, the Institute of Medicine placed a priority on creation of evidence-based clinical practice guidelines to guide medical providers in caring for pediatric cancer survivors (7).

Concurrent with publication of the Institute of Medicine's report, the Children's Oncology Group, a national pediatric cancer research consortium, was developing practice guidelines for care of the survivor population integrating available medical

literature with opinions from experts in the field of pediatric oncology (19). These evidence-based consensus recommendations underwent a stringent review processes prior to their initial release (19). The resulting document (*Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers*) was released by the Children's Oncology Group in 2003. The LTFU Guidelines identify pediatric cancer survivors for targeted late effects screening based upon their previous treatment exposures. The goal of this screening is to increase the quality of life of pediatric cancer survivors through early identification of treatment-related morbidities (19). Optimal late effects screening in the survivor population is unknown, thus the authors of the COG LTFU Guidelines opted for conservative and broad screening that would be refined overtime, as further evidence became available (19). The ambition of the COG LTFU Guidelines are to eventually focus screening tests to specific survivors at highest risk for treatment-related morbidities and thus minimize the potential harms, including cost, procedure-related risks, anxiety, and false reassurance related to wide based survivor screening (20, 21).

The genitourinary tract is one of several organ systems identified within the COG LTFU Guidelines (8) with well-documented susceptibility to pediatric cancer therapy exposures (9, 10). The kidney is vulnerable to acute and chronic functional and/or structural damage from several chemotherapy medications (ifosfamide, cisplatin, carboplatin, methotrexate), radiation and nephrectomy (22-53). Treatment-related kidney toxicity may manifest in several ways, including loss of protein (proteinuria) or other electrolytes in the urine (10). Similarly, the bladder is sensitive to acute and chronic damage from

commonly-used pediatric cancer treatments, including chemotherapy (cyclophosphamide, ifosfamide), radiation and surgical manipulation (54-70). Treatment-related bladder toxicity may manifest as blood in the urine (hematuria), which could lead to a diagnosis of hemorrhagic cystitis (urinary complaints associated with blood in the urine) or a bladder malignancy (9). The COG LTFU Guidelines recommend annual screening for proteinuria and hematuria via urinalysis among survivors who were exposed to treatment modalities which place them at risk for treatment-related kidney and/or bladder toxicity (8).

More than ten years have elapsed since the initial publication of the COG LTFU Guidelines without modification to the genitourinary late effect screening recommendations. Unfortunately, since their publication, few studies have addressed the usefulness of the screening urinalysis recommendation contained within the guidelines (71, 72), and neither of these studies focused on a pediatric aged population. No author has commented on the cost of the urinalysis screening recommended in the LTFU Guidelines, which may aggregate quickly among a large cohort of pediatric cancer survivors. Landier *et al.*, documented a low yield of urinalysis screening in their survivor cohort (71). Their study showed 0.2% (2 of 933) of screening urinalyses were positive for proteinuria and 1.4% (12 of 845) were positive for hematuria (71). Hudson *et al.*, identified a low prevalence of genitourinary late effect diagnoses in survivors screened at least ten years after completion of cancer-related therapies (72). Their results showed 2.3% (33 of 1410) of survivors at risk screened with blood and/or urinalysis tests were diagnosed with kidney dysfunction (72). Only 0.4% (4 of 1130) of survivors at risk were

diagnosed with hemorrhagic cystitis after urinalysis screening (72). Landier *et al.* has questioned the need for continued urinalysis screening in the survivor population based on the poor yield described in their study (71). Reviewing the published reports, it is obvious that a focused study of urinalysis screening in the survivor population is needed to better identify survivors for urinalysis screening, as well as to provide evidence to refine the current COG LTFU Guidelines recommendation.

Methods

The Children's Healthcare of Atlanta (CHOA) Cancer Survivor Program (CSP) operates multidisciplinary clinics for pediatric cancer survivors who are under the age of 21 and at least 24 months from completion of cancer therapies. While the majority of survivors seen through the CHOA CSP underwent cancer therapy at Children's Healthcare of Atlanta, the survivor program also follows survivors treated at other institutions. Referrals to the CSP are typically made by the survivor's primary oncology team. At the time of referral, the survivor's available medical records (demographic data, medical history and information related to their cancer diagnosis/treatment) are gathered and summarized into a clinical database, by members of the CSP staff. A summary document "Survivor Healthcare Plan" is produced from the information in the database for each patient seen at the CHOA CSP clinics. This document provides survivors with a personalized synopsis of their medical history, and includes individualized surveillance recommendations from the COG LTFU Guidelines. The database and Survivor Healthcare Plan are continually updated by clinic staff with new diagnoses and results of screening tests obtained at each subsequent CHOA CSP clinic visit.

Study Goals

- 1) Estimate the frequency of hematuria and/or proteinuria on urinalysis screening obtained in survivors evaluated through the CHOA CSP *per* the COG LTFU Guidelines.

- 2) Identify factors related to demographics, diagnosis or treatment exposures in survivors evaluated through the CHOA CSP that may place them at increased risk of abnormal findings on urinalysis screening.
- 3) Estimate the cost of urinalysis screening of a survivor population *per* the COG LTFU Guidelines.

Subjects

The pediatric cancer survivor cohort evaluated in this study was identified through retrospective review of the clinical database maintained through the Children's Healthcare of Atlanta (CHOA) Cancer Survivor Program (CSP). Survivors included in this study were previously evaluated by the CHOA CSP, 21 years of age or younger at their CSP clinic visits, and had undergone treatment exposures for malignant diseases placing them at risk for kidney or bladder complications *per* the COG LTFU Guidelines. Survivors with incomplete demographic ($n = 1$) or treatment exposure information ($n = 18$) and missing urinalysis data ($n = 8$) in their medical records were excluded (Figure 1). Inclusion criteria included survivors evaluated by the CHOA CSP between January 1, 2008 and March 31, 2012 with at least one treatment exposure identified in the COG LTFU Guidelines (Table 1) placing them at risk for genitourinary complications. Eligible screened subjects had to have results of at least one urinalysis screening documented in either their paper or electronic medical record. Exclusion criteria included survivors evaluated through the CHOA CSP outside the study dates, older than

21 years of age at their clinic visit, with known renal diagnosis prior to screening or not at risk for genitourinary late effects *per* the COG LTFU Guidelines.

Survivors identified as meeting study criteria had their demographic, diagnosis and treatment exposure information collected and deposited into a study database. A chart review of the paper and electronic medical record was subsequently undertaken to identify whether urinalysis screening had occurred, the results of urinalysis screening and follow-up evaluations/referrals prompted by the findings. The study database was housed on a secure and password-protected server located at CHOA.

Urinalysis Screening

Urinalysis can identify the presence of several abnormalities in the urine, including the presence of blood, leukocyte esterase, nitrites, protein, and glucose. The presence of hematuria and/or proteinuria constituted an abnormal urinalysis finding in this analysis. Hematuria was defined as urinalysis results with greater than 5 red blood cells per microscopic high power field on at least one occasion. Proteinuria was defined as urinalysis results with $\geq 1+$ protein via urine dipstick or automated analysis on at least one occasion. Urinalysis results documenting a value for both urine protein and number of red blood cells on microscopy were considered evaluable for this study. Abnormal urinalysis results obtained from menstruating female survivors were not analyzed.

This study complied with federal guidelines for conducting research of human subjects. Review and approval for conducting this project with a waiver of informed consent was obtained from the institutional review board at Children's Healthcare of Atlanta. This study also complied with the requirements of the Health Insurance Portability and Accountability Act.

Data collected on eligible subjects from the CHOA CSP clinical database included the following: gender, age at diagnosis (categorical; 0-4, 5-9, 10-14, 15-20), age at urinalysis screening (categorical; 0-4, 5-9, 10-14, 15-20, 20-21), years between end of therapy and urinalysis screening (categorical; 2-4, 5-9, 10-14, 15-20), race (categorical; black non Hispanic, Caucasian non Hispanic, other), and diagnosis (categorical; central nervous system tumors, germ cell tumors, leukemia/lymphoma, neuroblastoma, other solid tumors, renal tumors, sarcomas). Treatment exposure information collected for this study matched the variables identified by the COG LTFU Guidelines as placing survivors at risk for genitourinary toxicity. These variables included hematopoietic stem cell transplant (dichotomous; yes/no), as well as exposure (dichotomous; yes/no) and dose (continuous; mg/m^2) of six chemotherapeutic medications (carboplatin, cisplatin, cyclophosphamide, ifosfamide, standard dose methotrexate, and high dose methotrexate). Surgical exposure variables (dichotomous; yes/no) included renal (kidney) surgery and all other non-renal genitourinary surgery. Radiation exposure (dichotomous; yes/no) and dose (continuous; gray) information were collected for survivors exposed to total body irradiation, bladder radiation, and renal radiation.

Statistical Analysis

All analyses in this study were conducted using SAS version 9.3 (Cary, NC) with a definition of statistical significance set at $\alpha = 0.05$. Fisher's Exact Test was utilized to determine significant differences between all categorical variables except for the diagnosis variable. A Monte Carlo estimation of the exact p -value was calculated for the diagnosis variable due to the large size of the contingency table (8x2). In multivariable analysis, the potential confounding factors were identified, and estimated odds ratios with their associated 95% confidence intervals were determined using a logistic regression model.

Model Development

Several steps were undertaken to identify the final multivariable logistic regression model. First, all journal articles cited by the authors of the COG LTFU Guidelines (8) as contributing to the urinalysis screening recommendation were reviewed. During this review process, diagnosis, demographics and treatment exposure variables documented as strongly associated with genitourinary late effects were identified (≤ 4 years old at cancer diagnosis, hematopoietic stem cell transplant exposure, cyclophosphamide exposure, ifosfamide exposure, total body irradiation exposure, bladder radiation exposure, renal radiation exposure). Next, the diagnosis, demographics and treatment exposures of the study cohort were analyzed to identify significant differences between survivors who had normal and abnormal urinalysis screening (Table 4, 5). The variables

identified as significant through univariate analysis (sarcoma diagnosis, urinalysis screening occurring 10-14 years after completion of therapy, ifosfamide exposure) and/or associated with genitourinary late effects from review of the literature were available as predictors for development of a multivariable logistic regression model. Predictors were reviewed for collinearity. Total body irradiation was identified as severely collinear with both exposure to hematopoietic stem cell transplant and exposure to bladder radiation. Total body irradiation exposure was therefore, removed as a possible predictor in further model development. Hematopoietic stem cell transplant and exposure to bladder radiation were not felt to be collinear. The multivariable model was initially fit with the predictors identified from the literature review. Each predictor variable identified through univariate analysis was then tested by fitting them into the model using a stepwise approach. Predictor variables tested and not included in the final regression model were sarcoma diagnosis and urinalysis screening occurring 10-14 years after completion of therapy. Lastly, interaction terms created among each pair-wise combination of the final predictor variables in the model were tested for significance. Predictors included in the final regression model were identified by comparing alternative models using the likelihood ratio test (-2 Log L).

Cost Estimate

The cost of urinalysis screening and laboratory follow-up testing (basic metabolic panel, urine calcium, urine creatinine, urine protein) was estimated utilizing the 2014 national limit for outpatient clinical laboratory fees from the United States Centers for Medicare

& Medicaid Services published online at <http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/clinlab.html> (Table 8). This cost data was accessed on 2/3/2014 at 20:00 from the United States Centers for Medicare & Medicaid Services website listed above.

Results

Query of the CHOA CSP clinical database identified 798 at risk survivors who met study criteria and therefore constituted the cohort for this study. Demographic and diagnosis data for these 798 survivors are listed in Table 2. Among the 798 survivors at risk, 758 (95.0%) underwent at least one recommended urinalysis screening *per* the COG LTFU Guidelines' recommendation. The majority of identified survivors at risk were Caucasian non-Hispanic ($n = 529$), male gender ($n = 453$), less than 4 years of age at time of diagnosis ($n = 448$), 10-14 years of age at time of urinalysis ($n = 260$), and less than 4 years from the completion of their therapy ($n = 399$). No statistically significant demographic differences were noted between screened and unscreened survivors. Diagnoses for survivors in this study cohort were divided into seven categories based on similarities in treatment exposures. An "other solid tumor" variable included 4 separate diagnoses including hepatoblastoma ($n = 8$), nasopharyngeal carcinoma ($n = 2$), pleuropulmonary blastoma ($n = 2$) and retinoblastoma ($n = 9$). The majority of survivors in this study were treated for a leukemia/lymphoma diagnosis ($n = 469$). A significant difference was identified between screened and unscreened survivors who were treated for a malignancy of the central nervous system or leukemia/lymphoma. Analysis among survivors of a central nervous system (CNS) malignancy found no statistically significant demographic or treatment exposure differences among screened and unscreened survivors. A difference in the referral pattern for some survivors with CNS diagnoses was noted during the study period. Several CNS cancer survivors were followed for an extended time by their primary oncologists, and were only referred to the CSP clinic for a onetime visit prior to transitioning into adult care. Urinalysis screening obtained outside

of the CSP clinic was not included in this analysis, and conceivably may have impacted the screening data for the CNS diagnoses survivor group. Analysis among survivors with a leukemia/lymphoma diagnosis identified a statistically significant difference in the age at diagnosis between screened and unscreened survivors. Survivors who were diagnosed with a leukemia/lymphoma diagnosis at ≤ 4 years of age underwent urinalysis screening more frequently, 98.7%, compared to those diagnosed with a leukemia/lymphoma diagnosis at age > 4 years, 94.8% ($p = 0.02$). Paradoxically, survivors diagnosed between 5 to 9 years of age with a leukemia/lymphoma diagnosis were screened less frequently, 93.9%, when compared to those survivors diagnosed with a leukemia/lymphoma diagnosis < 5 or ≥ 10 years of age, 97.9% ($p = 0.04$).

Treatment exposures for the study cohort are listed in Table 3. Ninety-six survivors were exposed to hematopoietic stem cell transplantation. A majority of the study cohort were exposed to cyclophosphamide chemotherapy ($n = 558$). Nephrectomy (surgical removal of a portion/whole kidney), was the most common surgical treatment procedure ($n = 88$). A similar number of study participants were exposed to bladder ($n = 85$) or renal (kidney) radiation ($n = 84$). Among treatment exposures, survivors exposed to carboplatin or cisplatin chemotherapy were screened less frequently, 89.7% and 88.7%, respectively compared to the remainder of the study cohort ($p < 0.05$). Focused analysis among those with exposure to carboplatin showed only survivors with a CNS diagnosis were screened significantly less frequently, 75.0% compared to the remainder of the study cohort, 95.7% ($p = < 0.01$). Analysis among survivors exposed to cisplatin identified no

statistically significant difference in demographic, diagnosis or other treatment exposures among screened and unscreened survivors.

Demographic and treatment exposures for survivors who underwent at least one urinalysis screening ($n = 758$) are listed in tables 4 and 5. Abnormal urinalysis findings were seen in 31 (4.1%) of the study participants at their initial urinalysis screening within the study period. Twenty three (3.0%) survivors had proteinuria, 10 (1.3%) had hematuria and 2 (0.3%) had both abnormal findings. Among the 31 survivors with abnormal initial screening test results, 3 survivors were referred directly to a nephrologist, and 1 survivor was diagnosed with a urinary tract infection. Fifteen of the remaining survivors had a documented plan for follow-up testing prompted by their abnormal screening test, and the other 12 survivors had no documented plan for further testing. Of the survivors who underwent follow-up testing ($n = 15$), 4 had normal findings, 1 was referred to nephrology for continued abnormal results, and the remaining 10 had no results documented. The yield of abnormal findings for the initial urinalysis screening in this study was 4.1% (31/758).

Subsequent urinalysis screenings among the study cohort showed varied results (Figure 2, 3). Thirty-six abnormal urinalysis findings were documented in 30 survivors on 2nd through 5th urinalyses. Five of these 30 survivors had more than 1 abnormal urinalysis screening result documented while the remaining 25 had only one abnormal urinalysis screening result documented. Of the 5 survivors with > 1 abnormal urinalysis result on

2nd through 5th screening, 1 survivor was referred to nephrology for continued abnormal findings, 1 survivor's findings normalized on follow-up testing and the remaining 3 had either no results or plan for follow-up testing documented. Of the 25 survivors with only one abnormal urinalysis result on 2nd through 5th screening, 2 were referred to a nephrologist directly, 1 was diagnosed with a urinary tract infection, 8 had no plan documented and 14 underwent follow-up testing. Among the survivors ($n = 14$) who underwent follow-up testing, 1 survivor was subsequently diagnosed with orthostatic proteinuria, 1 survivor had continued abnormal results, 6 survivors' results normalized on follow-up testing and 7 had no documentation of follow-up results.

An overall urinalysis screening yield of 4.6% (67/1461) was obtained during the study period (urinalyses 1 through 5) for the entire cohort. A total of 9 survivors had > 1 abnormal urinalysis finding during the study period. Of these 9 survivors 3 were eventually referred to a nephrologist, 3 were found to have normal results on re-testing, and the final 3 had no plan or results documented. Among survivors with only 1 abnormal screening urinalysis obtained in the study period, a total of 3 were referred to nephrology, 2 were diagnosed with urinary tract infections, 1 was diagnosed with orthostatic proteinuria, 20 had no plan or results of further testing documented and 22 underwent further testing. On further testing these 22 survivors had normal results 7 times, and only 1 abnormal finding. Fourteen of the 22 survivors with a plan for repeat testing had no results documented. In addition to 34 total repeat urinalysis tests, a basic metabolic panel was ordered in 3 survivors, urine calcium to creatinine ratios were ordered in 3 survivors and a single survivor underwent protein to creatinine urine testing.

Univariate analysis of demographic, diagnosis and treatment exposures among the screened study cohort identified statistically significant associations ($p < 0.05$) between abnormal urinalysis findings and a sarcoma diagnosis, survivors screened 10-14 years after completion of therapy and ifosfamide chemotherapy exposure. Estimated odds ratios and their associated 95% confidence intervals for the predictor variables included in the final multivariable logistic regression model are listed in Table 7. Multivariable logistic regression analysis identified age at cancer diagnosis ≤ 4 (O.R. 1.8; 95% C.I. 1.0-3.2) and high dose ifosfamide chemotherapy exposure (O.R. 6.1; 95% C.I. 2.2-16.7) as variables placing survivors at increased odds of abnormal screening urinalysis results.

Estimated cost of laboratory testing in the state of Georgia during 2014 using the data published by the United States Centers for Medicare and Medicaid Services are listed in Table 8. The cost of urinalysis screening for the 758 survivors over the study period is estimated at \$6,311.52. An estimate of the cost to screen the study cohort per abnormal urinalysis findings was \$94.20. Additional laboratory testing prompted by an abnormal urinalysis screening added approximately \$239.70 to the cost of laboratory evaluation of the study cohort.

Discussion

The latest version of the Children's Oncology Group (COG) *LongTerm Follow-up (LTFU) Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* (8) was published in 2008, based on evidence of cancer treatment exposure risks and known associated long-term outcomes. In the recent literature, two studies have reported on the yield of the urinalysis screening recommendation for survivors at risk for renal or bladder late effects (71, 72). Neither study performed a detailed analysis of screened survivors and screening yield based on demographic and exposure risks, nor focused on a pediatric aged population. In this analysis, we found screening urinalyses to be of highest yield in children with a history of ifosfamide chemotherapy exposure, especially in high cumulative doses ($\geq 60 \text{ g/m}^2$). High-dose ifosfamide exposure and young age at cancer diagnosis (≤ 4 years) were identified as independent risk factors for an abnormal urinalysis screening result. Among treatment exposures where surveillance urinalysis is recommended, relatively more abnormal results were found in survivors with radiation exposure compared to chemotherapy exposure (methotrexate; cyclophosphamide) and genitourinary/renal surgery; however, radiation as a risk factor did not reach statistical significance in multivariable analysis. This study also demonstrates that urinalysis screening *per* current LTFU Guidelines results in a modest (4.6%) yield of abnormal findings.

This study's finding that high dose ifosfamide chemotherapy exposure places survivors at higher relative risk for abnormal urinalysis screening was not unexpected; several studies (10, 39, 45, 49) have correlated higher ifosfamide doses with an increased incidence of

renal damage in pediatric cancer survivors. Loebstein *et al.* identified cumulative ifosfamide dose (median 45.5 gm/m²) as a significant predictor of nephrotoxicity (including proteinuria) among 174 exposed pediatric cancer survivors (39). Likewise, Skinner *et al.* found that increasing total ifosfamide doses correlated with greater glomerular and tubular toxicity in a pediatric survivor cohort (45). Stohr *et al.* found the incidence of tubulopathy increased with rising cumulative doses of ifosfamide exposure among 648 pediatric sarcoma survivors at a median of 19 months off therapy (49). Furthermore, Stohr *et al.* estimated a 5.6 and 18.6 fold increased risk of tubulopathy among survivors exposed to cumulative ifosfamide doses between 24-60 g/m² and greater than 60 g/m², respectively, when compared to those who received less than 24 g/m² (49).

Low age at cancer diagnosis, a surrogate variable for age at therapy, has likewise been well-reported as a risk factor for renal damage (39, 42, 44, 49, 53). Loebstein *et al.* correlated increasing severity of renal toxicity with decreasing age of ifosfamide exposed children in their study cohort (39). Raney *et al.* found younger sarcoma patients (age < 3 years old) were more likely to develop renal tubular dysfunction compared to their older counterparts (42). Moreover, Stohr *et al.* estimated an 8.7 fold increased risk for tubulopathy among 593 ifosfamide exposed children less than 4 years of age when compared to older children in their cohort (49). Increased risk of renal damage with younger age at diagnosis has also been demonstrated among survivors without exposure to ifosfamide chemotherapy. Yetgin *et al.* reported a 5 fold increased risk of abnormal glomerular filtration in pediatric cancer survivors who were diagnosed with acute lymphoblastic leukemia at less than 2 years of age (53).

In regard to the yield of urinalysis screening in a survivor population, the most comparable study was published by Landier *et al.* (71). In that study, the results of 370 pediatric cancer survivors screened *per* the COG LTFU Guidelines in an outpatient setting are reported. Urinalysis samples from subjects who had previously been diagnosed with a disease being screened (ex. renal insufficiency) or if the urinalysis was “inevaluable” (ex. due to menstrual blood contamination) were removed from calculation of screening yield. Landier *et al.* identified 2 of 933 total urinalyses (0.2%) with proteinuria and 31 of 845 total urinalyses (3.7%) with hematuria. Multivariable analysis of subgroups that underwent urinalysis screening was not performed. Given their low yield on screening urinalysis, Landier *et al.* concluded that elimination of screening urinalysis in the survivor population should be considered.

It is important to note several differences between the study by Landier *et al.* and the current analysis. The survivors who underwent urinalysis screening in that study were predominantly male, Hispanic and represented an older population. Median age at urinalysis screening for proteinuria and hematuria was 23 (range 5-57) and 22.1 (range 5.3-57.2) years, respectively. Median time from diagnosis to proteinuria and hematuria screening was also longer in their cohort at 10 (range 5-55.8) and 9.5 (range 5-55.8) years, respectively. Lastly and perhaps most importantly, Landier *et al.* used a more stringent criterion for proteinuria ($\geq 2+$ protein on urinalysis) than the current analysis, which likely influenced the yield of the urinalysis screening in their cohort. Adjusting

the current analysis yield for the definition of proteinuria ($\geq 2+$ protein) described by Landier *et al.*, a comparable screening yield of 0.6% (9 of 1461) is calculated.

Hudson *et al.* indirectly addressed the yield of urinalysis screening by reporting prevalence rates of kidney dysfunction and hemorrhagic cystitis in a survivor population *per* the COG LTFU Guidelines (72). Their study enrolled 1713 predominately white, female pediatric cancer survivors who had survived at least 10 years from their original diagnosis and followed them prospectively for 5 years in an outpatient clinical setting. All participants in that study, including those not at risk for genitourinary late effects *per* the COG LTFU Guidelines underwent baseline urinalysis screening. The authors report a 2.3% (33/1410 at risk) rate of kidney dysfunction diagnosed during clinic follow-up. A diagnosis rate of 0.4% (4/1130 at risk) for hemorrhagic cystitis is reported during clinic screening.

Several discrepancies between the work by Hudson *et al.* and the current analysis make it difficult to compare findings. Similar to the participants in the Landier *et al.* study, the cohort of Hudson *et al.* also represented an older survivor population. Mean age at study recruitment was 33.1 (range 18-60) years old, and participants were on average 25.6 (range 10.9-47.9) years from diagnosis at study entry. Their study utilized different screening methods and definitions than the current analysis. Screening for "kidney dysfunction" utilized both blood and urinalysis tests; therefore, a subject could be diagnosed with kidney dysfunction with normal urinalysis findings. No details on the

number of red blood cells which constituted a positive urinalysis test for hemorrhagic cystitis were given; consequently, one might assume that any number of red blood cells would constitute a positive screen. Specifics regarding the results of urinalysis screening for kidney dysfunction or hemorrhagic cystitis are not available for direct comparison.

Age of the survivor cohort studied has been a major difference between the before mentioned studies (71, 72) and the current analysis. It's worth noting that 7 of the 11 survivors diagnosed with hemorrhagic cystitis and 4 of the 37 survivors diagnosed with kidney dysfunction in the Hudson *et al.* study were described as having no identifiable cancer treatment related risk factors for these diagnoses. Scant data exists regarding genitourinary late effects of cancer related treatment exposures among very long term pediatric cancer survivors (44, 46, 47, 74). Currently, it is unclear what impact, if any, older age at screening or prolonged time after cancer diagnosis/treatment may have on the yield of screening urinalyses, especially in the setting of a normal decline in renal function with age (73).

No known previous studies have commented on the cost of urinalysis screening *per* the COG LTFU Guidelines in a pediatric cancer survivor population. The reference reimbursement rate of \$4.32 per urinalysis test used in this study likely represents a gross underestimation of the cost of urinalysis at most healthcare facilities in the United States. Unfortunately, due to competition between healthcare facilities, charges for services such as a urinalysis with microscopy are not routinely published. A current estimate from the

CHOA laboratory (personal communication) places the charge for an uninsured, cash-paying customer at approximately \$75.00 per urinalysis (Table 8). Using this estimate, the cost of screening the current study population increases to \$109,575 or \$1,635 per abnormal urinalysis. Additional laboratory testing prompted by the abnormal urinalysis screenings in this study would add approximately \$3,367 to the cost of laboratory evaluation of this study cohort. Given the potentially high cost of urinalysis screening per abnormal finding in this survivor population, it is clear that refinements are needed to identify target populations with the highest yield for screening.

The findings of this analysis must be appraised acknowledging some limitations. First, this is a retrospective analysis and therefore relies upon data collection from information contained within subjects' medical charts documented by different providers over a wide time frame. Time spans between urinalysis screenings within the study cohort were sometimes variable. The majority of urinalysis tests were conducted at the CHOA laboratory department; however, some testing occurred at primary care offices or private laboratory companies. Urinalysis is a commonly performed laboratory test, but it is impossible to verify that testing was performed correctly on each sample analyzed in this study. The large number of subjects who were lost to follow-up during the study period is another recognized weakness. This censorship limited the ability for extended analysis of abnormal findings on subsequent urinalysis screening tests. Different variables from the literature review may have been identified for inclusion in the logistic regression model by another researcher, and several possible regression models could be identified to describe the data contained in this study. While this study focused on analyzing the

urinalysis screening recommendation contained within the COG LTFU Guidelines, other laboratory test(s) may offer a more sensitive screen for genitourinary late effects in pediatric cancer survivors. Lastly, this study did not analyze the contribution of other potentially genitourinary toxic therapies (ex. aminoglycoside antibiotics), which are commonly used in pediatric cancer patients during cancer therapy.

This study represents the first known focused analysis of pediatric cancer survivors who underwent urinalysis screening *per* the COG LTFU Guidelines recommendations. These results suggest targeted screening of higher risk populations, such as those with younger age at diagnosis and with a history of ifosfamide exposure, may be beneficial and more cost-effective. Further analysis among combinations of risk factors and long-term outcomes of survivors with abnormal results are needed to fully define risk and benefit of screening. Additional research into the recommendations contained within the COG LTFU Guidelines is needed to further identify the most beneficial and cost-effective means of screening the pediatric cancer survivor population.

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Table 1. Treatment exposures placing study subjects at risk for genitourinary late effects and recommended screening parameters *per* the COG LTFU Guidelines.

Treatment Exposure	Proteinuria <i>Renal Toxicity</i>	Hematuria^a <i>Hemorrhagic Cystitis</i>	Hematuria^a <i>Bladder Cancer</i>
Chemotherapy			
Cyclophosphamide		*	*
Ifosfamide	*	*	
Carboplatin	*		
Cisplatin	*		
Methotrexate	*		
Surgery			
Nephrectomy	*		
Radiation			
Abdominal fields	*	* ^b	*
Total body irradiation	*	* ^b	
Pelvic fields		* ^b	*
Sacral/Whole spine		* ^b	*

^a > 5 red blood cells per high power field on 2 occasions

^b Doses \geq 30 Gray

Table 2. Demographic characteristics for survivors at risk for genitourinary complications evaluated at the CHOA CSP.

	Screened <i>n</i> (%)	Unscreened <i>n</i> (%)	Fisher's <i>p</i>-value
Total Subjects	758 (95.0%)	40 (5.0%)	-
Gender	-	-	0.87
Male	431 (95.1%)	22 (4.9%)	
Female	327 (94.8%)	18 (5.2%)	
Race	-	-	0.14
Black non-Hispanic	151 (92.6%)	12 (7.4%)	
Caucasian non-Hispanic	508 (96.0%)	21 (4.0%)	
Other	99 (93.4%)	7 (6.6%)	
Mean age at diagnosis, years (range)	5.8 (< 1-17)	7.0 (< 1-17)	0.14 ^a
Mean age at urinalysis, years (range)	13.4 (3-21)	-	0.97 ^a
Mean time from diagnosis to urinalysis, years (range)	7.6 (2-21)	-	-
Mean time off therapy at time of urinalysis, years (range)	6.0 (2-20)	-	0.33 ^a
Diagnosis	-	-	< 0.01 ^b
Central nervous system	47 (77.1%)	14 (22.9%)	
Germ cell	13 (86.7%)	2 (13.3%)	
Leukemia/lymphoma	454 (96.8%)	15 (3.2%)	
Neuroblastoma	58 (95.1%)	3 (4.9%)	
Other solid tumors	20 (95.2%)	1 (4.8%)	
Renal tumors	83 (97.6%)	2 (2.4%)	
Sarcomas	83 (96.5%)	3 (3.5%)	

^a Analyzed as a categorical variable^b Monte Carlo estimation for exact test

Table 3. Treatment exposures for survivors at risk for genitourinary complications evaluated at the CHOA CSP.

		Screened <i>n</i> (%)	Unscreened <i>n</i> (%)	Fisher's <i>p</i>-value
Total Subjects		758 (95.0%)	40 (5.0%)	-
HSCT^a	Yes	92 (95.8%)	4 (4.2%)	1.0
	No	666 (94.9%)	36 (5.1%)	
Chemotherapy				
Carboplatin	Yes	87 (89.7%)	10 (10.3%)	0.02
	No	671 (95.7%)	30 (4.3%)	
Cisplatin	Yes	102 (88.7%)	13 (11.3%)	< 0.01
	No	656 (96.0%)	27 (4.0%)	
Cyclophosphamide	Yes	534 (95.7%)	24 (4.3%)	0.16
	No	224 (93.3%)	16 (6.7%)	
Ifosfamide	Yes	90 (95.7%)	4 (4.3%)	1.0
	No	668 (94.9%)	36 (5.1%)	
Methotrexate	Yes	405 (96.2%)	16 (3.8%)	0.10
	No	353 (93.6%)	24 (6.4%)	
High dose methotrexate	Yes	147 (97.3%)	4 (2.7%)	0.21
	No	611 (94.4%)	36 (5.6%)	
Surgery				
Other genitourinary	Yes	11 (100.0%)	0 (0.0%)	1.0
	No	747 (94.9%)	40 (5.1%)	
Renal	Yes	85 (96.6%)	3 (3.4%)	0.61
	No	673 (94.8%)	37 (5.2%)	
Radiation				
Total body irradiation	Yes	48 (96.0%)	2 (4.0%)	1.0
	No	710 (94.9%)	38 (5.1%)	
Bladder radiation	Yes	81 (95.3%)	4 (4.7%)	1.0
	No	677 (95.0%)	36 (5.0%)	
Renal radiation	Yes	79 (94.0%)	5 (6.0%)	0.60
	No	679 (95.1%)	35 (4.9%)	

^aHematopoietic stem cell transplant

Table 4. Demographic characteristics for survivors at risk for genitourinary complications on initial urinalysis screening at the CHOA CSP.

	Abnormal Urinalysis <i>n</i> (%)	Normal Urinalysis <i>n</i> (%)	Fisher's p-value
Total Subjects	31 (4.1%)	727 (95.9%)	-
Gender	-	-	0.20
Male	14 (3.3%)	417 (96.7%)	
Female	17 (5.2%)	310 (94.8%)	
Race	-	-	0.89
Black non-Hispanic	7 (4.6%)	144 (95.4%)	
Caucasian non-Hispanic	20 (3.9%)	488 (96.1%)	
Other	4 (4.0%)	95 (96.0%)	
Mean age at diagnosis, years (range)	6.0 (< 1-15)	5.8 (< 1-17)	0.51 ^a
Mean age at urinalysis, years (range)	13.0 (6-20)	13.4 (3-21)	0.76 ^a
Mean time from diagnosis to urinalysis, years (range)	6.9 (3-11)	7.6 (2-21)	-
Mean time off therapy at time of urinalysis, years (range)	5.4 (2-9)	6.0 (2-20)	0.07 ^a
Diagnosis	-	-	0.37 ^b
Central nervous system	1 (2.1%)	46 (97.9%)	
Germ cell	0 (0.0%)	13 (100.0%)	
Leukemia/lymphoma	16 (3.5%)	438 (96.5%)	
Neuroblastoma	2 (3.5%)	56 (96.5%)	
Other solid tumors	1 (5.0%)	19 (95.0%)	
Renal tumors	3 (3.6%)	80 (96.4%)	
Sarcomas	8 (9.6%)	75 (90.4%)	

^a Analyzed as a categorical variable^b Monte Carlo estimation for exact test

Table 5a. Treatment exposures for survivors at risk for genitourinary complications who underwent initial urinalysis screening at the CHOA CSP.

		Abnormal Urinalysis <i>n</i> (%)	Normal Urinalysis <i>n</i> (%)	Fisher's p-value
Total Subjects		31 (4.1%)	727 (95.9%)	-
HSCT^a	Yes	5 (5.4%)	87 (94.6%)	0.41
	No	26 (3.9%)	640 (96.1%)	
Chemotherapy				
Carboplatin	Yes	2 (2.3%)	85 (97.7%)	0.57
	No	29 (4.3%)	642 (95.7%)	
Cisplatin	Yes	4 (3.9%)	98 (96.1%)	1.0
	No	27 (4.1%)	629 (95.9%)	
Cyclophosphamide	Yes	22 (4.1%)	512 (95.9%)	1.0
	No	9 (4.0%)	215 (96.0%)	
Ifosfamide	Yes	8 (8.9%)	82 (91.1%)	0.02
	No	23 (3.4%)	645 (96.6%)	
Methotrexate	Yes	15 (3.7%)	390 (96.3%)	0.59
	No	16 (4.5%)	337 (95.5%)	
High dose methotrexate	Yes	7 (4.8%)	140 (95.2%)	0.64
	No	24 (3.9%)	587 (96.1%)	
Cumulative Chemotherapy Dose				
Cyclophosphamide		-	-	0.38
Dose < 3 g/m ²		5 (2.5%)	192 (97.5%)	
Dose ≥ 3 g/m ²		17 (5.0%)	320 (95.0%)	
None		9 (4.0%)	215 (96.0%)	
Ifosfamide		-	-	< 0.01
Dose < 25 g/m ²		1 (2.4%)	40 (97.6%)	
Dose 25-60 g/m ²		2 (6.3%)	30 (93.8%)	
Dose ≥ 60 gm/m ²		5 (29.4%)	12 (70.6%)	
None		23 (3.4%)	645 (96.6%)	

^aHematopoietic stem cell transplant

Table 5b. Treatment exposures for survivors at risk for genitourinary complications who underwent initial urinalysis screening at the CHOA CSP.

		Abnormal Urinalysis <i>n</i> (%)	Normal Urinalysis <i>n</i> (%)	Fisher's p-value
Total Subjects		31 (4.1%)	727 (95.9%)	-
Surgery				
Other genitourinary	Yes	0 (0.0%)	11 (100.0%)	1.0
	No	31 (4.1%)	716 (95.9%)	
Renal	Yes	3 (3.5%)	82 (96.5%)	1.0
	No	28 (4.2%)	645 (95.8%)	
Radiation				
Total body irradiation	Yes	4 (8.3%)	44 (91.7%)	0.13
	No	27 (3.8%)	683 (96.2%)	
Bladder radiation	Yes	6 (7.4%)	75 (92.6%)	0.13
	No	25 (3.7%)	652 (96.3%)	
Renal radiation	Yes	4 (5.1%)	75 (94.9%)	0.55
	No	27 (4.0%)	652 (96.0%)	

Table 6. Results of urinalysis screening in at risk survivors evaluated at the CHOA CSP.

Urinalysis Screening	Survivors Screened <i>n</i>	Normal Urinalysis <i>n</i> (%)	Abnormal Urinalysis <i>n</i> (%)	Proteinuria <i>n</i>	Hematuria <i>n</i>
First	758	727 (95.9%)	31 (4.1%)	23	10
Second	414	389 (94.0%)	25 (6.0%)	17	8
Third	212	203 (95.8%)	9 (4.2%)	7	3
Forth	74	73 (98.7%)	1 (1.3%)	1	0
Fifth	3	2 (66.7%)	1 (33.3%)	0	1
Total	1461^a	1394 (95.4%)	67 (4.6%)	48	22

^aIncludes repeat screening from same survivor

Table 7. Point estimates and 95% confidence intervals for significant predictor variables using multivariable logistic regression model ($n = 758$).

Predictor Variable	OR (95% CI)	p-value
Age ≤ 4 at Diagnosis		
No	1	-
Yes	1.8 (1.0-3.2)	0.04
Hematopoietic Stem Cell Transplant		
No	1	-
Yes	1.9 (0.8-4.5)	0.13
Cyclophosphamide Exposure		
No	1	-
Dose $< 3 \text{ g/m}^2$	1.2 (0.5-2.5)	0.70
Dose $\geq 3 \text{ g/m}^2$	1.5 (0.7-2.9)	0.28
Ifosfamide Exposure		
No	1	-
Dose $< 25 \text{ g/m}^2$	1.0 (0.4-2.9)	0.93
Dose 25-60 g/m^2	1.0 (0.2-4.2)	0.96
Dose $> 60 \text{ g/m}^2$	6.1 (2.2-16.7)	< 0.001
Bladder Radiation		
No	1	-
Yes	0.8 (0.3-2.0)	0.69
Kidney Radiation Exposure		
No	1	-
Dose $< 15 \text{ Gy}$	1.0 (0.3-2.9)	0.97
Dose $\geq 15 \text{ Gy}$	1.1 (0.4-3.1)	0.80

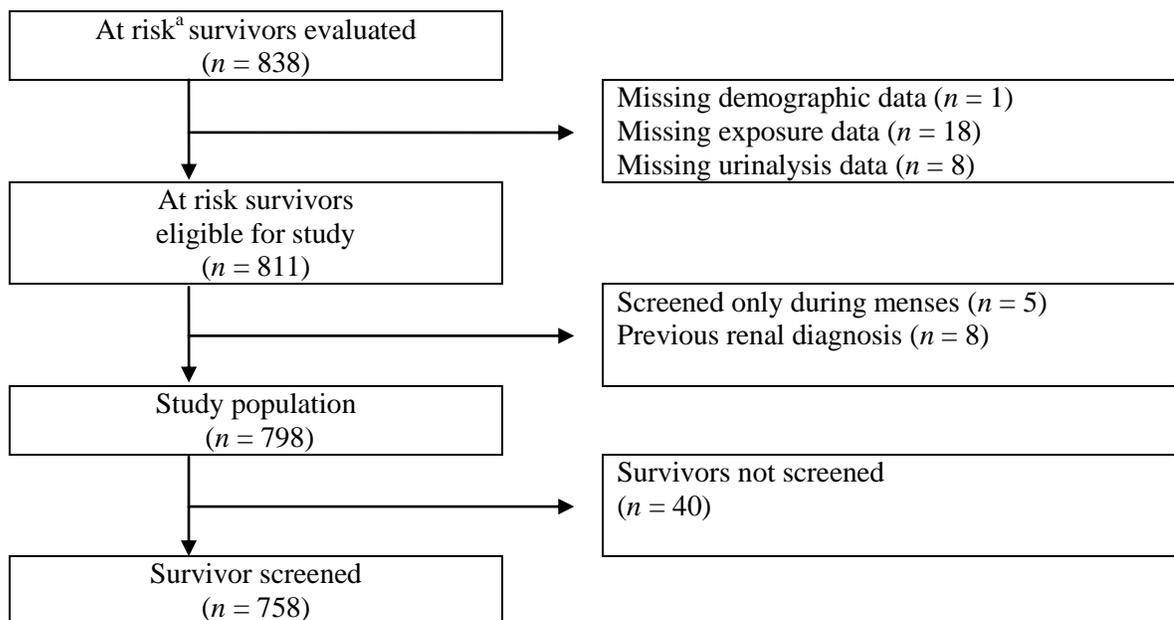
Table 8. Cost estimates for laboratory testing ordered among survivor cohort

Laboratory Test	USCMMS^a	CHOA^b
Automated urinalysis with microscopy	\$4.32	\$75.00
Basic Metabolic Panel	\$11.54	\$112.50
Urine Calcium	\$8.32	\$60.00
Urine Creatinine	\$7.06	\$60.00
Urine Protein	\$5.00	\$60.00

^aUnited States Centers for Medicare & Medicaid Services

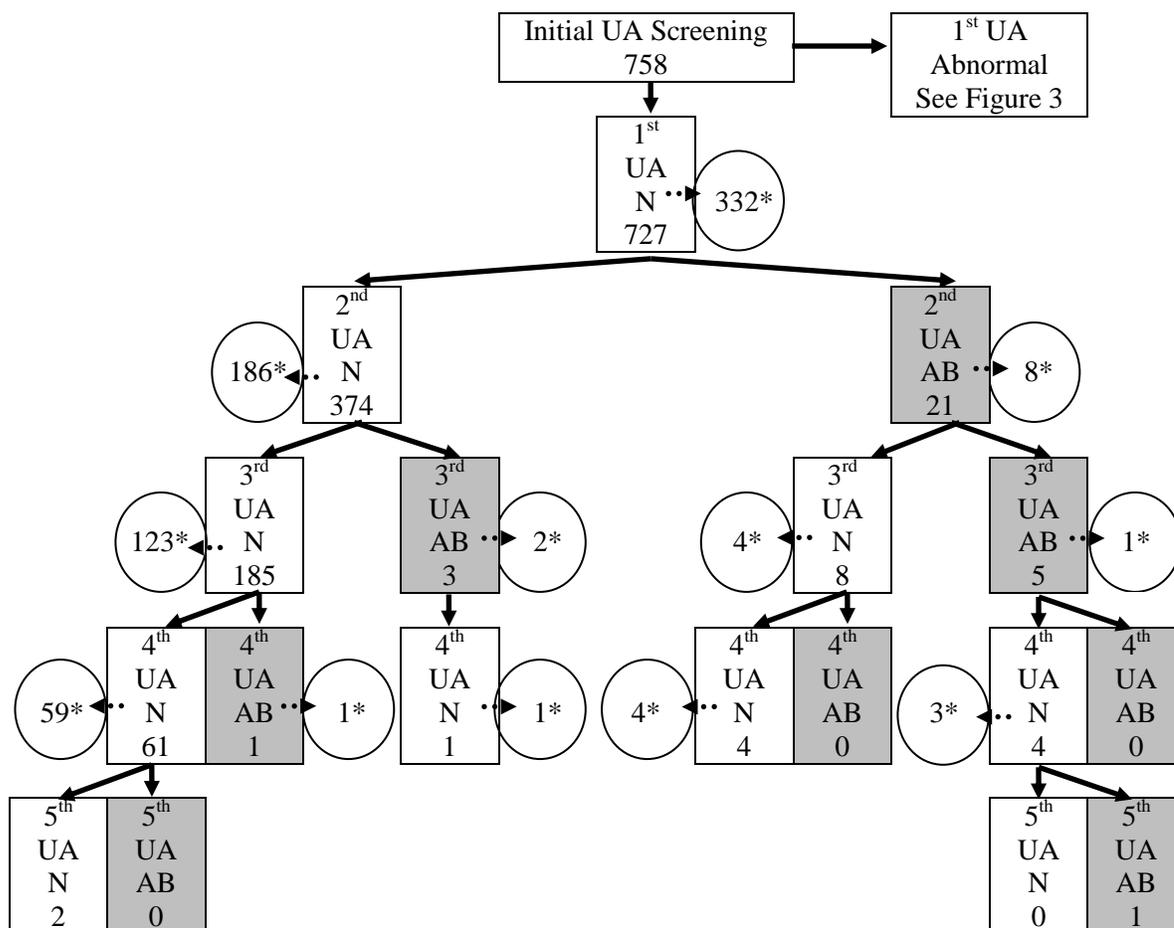
^bMean estimate from CHOA laboratory

Figure 1. Survivors evaluated at the Children's Healthcare of Atlanta Cancer Survivor Program during study period



^a per COG LTFU Guidelines (8)

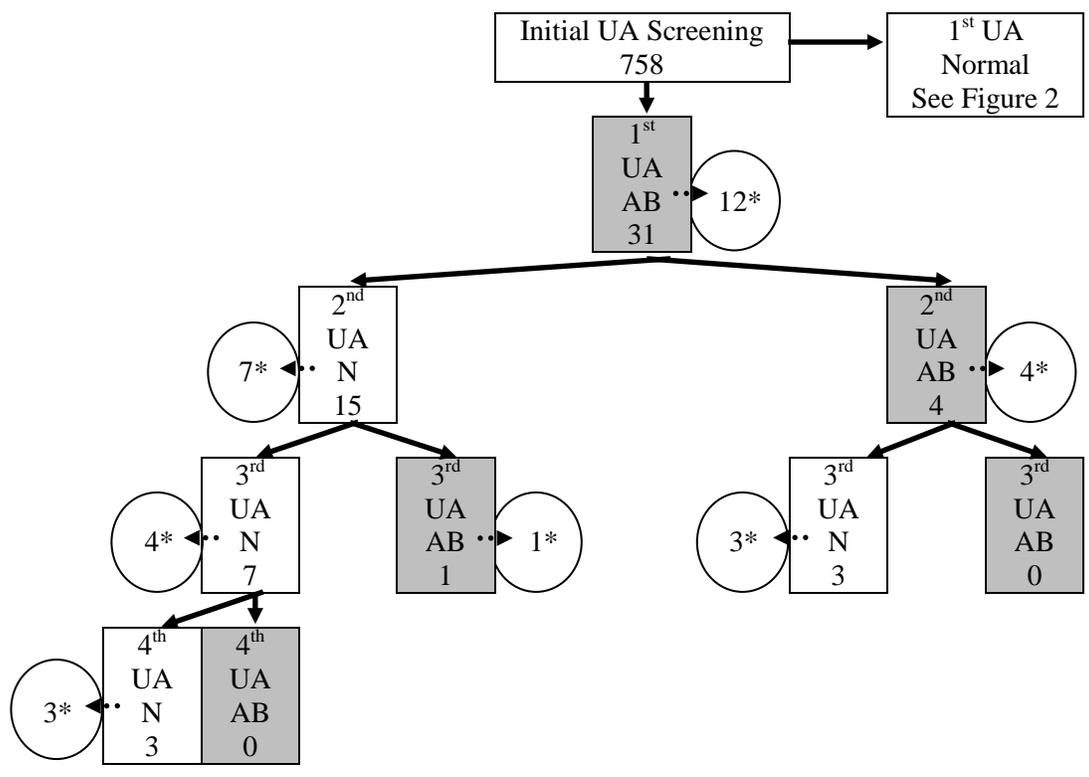
Figure 2. Flowchart detailing results of urinalysis findings after an initial **normal** urinalysis



UA – Urinalysis
*Patients censored

N – Normal Urinalysis Findings
AB – Abnormal Urinalysis Findings

Figure 3. Flowchart detailing results of urinalysis findings after an initial **abnormal** urinalysis



UA – Urinalysis
*Patients censored

N – Normal Urinalysis Findings
AB – Abnormal Urinalysis Findings