Evidence in CAYA cancer survivors

Year	Bibliography
2023	Wu et al. Development and validation of a prediction model for kidney failure in long-term survivors of childhood cancer. *J Clin Oncol*. 2023;41:2258-2268.
2023	Poppe et al. Kidney disease in childhood cancer survivors treated with radiation therapy: A comprehensive PENTEC Genitourinary Review. *Int J Radiation Oncol Biol Phys*. 2023; 119:560-574.
2022	Kooijmans et al. The Dutch Childhood Cancer Survivor Study (DCCSS)-LATER 2 kidney analysis examined long-term glomerular dysfunction in childhood cancer survivors. *Kidney Int.* 2022;102:1136-1146.
2022	Kooijmans et al. Long-term tubular dysfunction in childhood cancer survivors; DCCSS-LATER 2 Renal study. *Cancers*. 2022;14:2754.
2021	Dieffenbach et al. Late-onset kidney failure in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *European Journal of Cancer*. 2021;155:216-226.
2021	Latoch et al. Urine NGAL and KIM-1 tubular injury biomarkers in long-term survivfors of childhood solid tumors: a cross-sectional cohort study. *Journal of clinical medicine*. 2021;10:399.
2021	Green et al. Kidney function after treatment for childhood cancer: a report from the St. Jude Lifetime Cohort Study. *JASN.* 2021;32(4):983-93.
2020	Green et al. Long-term renal function after treatment for unilateral, nonsyndromic Wilms tumor. A report from the St. Jude Lifetime Cohort Study. *Pediatr Blood Cancer*. 2020;67:e28271
2019	Dietz et al. Solid organ transplantation after treatment for childhood cancer: a retrospective cohort analysis from the Childhood Cancer Survivor Study. *Lancet Oncol*. 2019;20:1420-31.
2019	Kooijmans et al. Early and late adverse renal effects after potentially nephrotoxic treatment for childhood cancer. Cochrane Database Syst Rev. 2019; Issue 3, art. No CD008944.
2019	Park et al. Acute kidney injury in pediatric cancer patients. *The Journal of Pediatrics*. 2019;208:243-50.
2018	Cozzi et al. Renal function up to the 5th decade of life after nephrectomy in childhood: a literature review. Nephrology. 2018;23:397-404.
2017	Cozzi et al. Renal function recovery after nephrectomy or nephron-sparing surgery in children with unilateral renal tumor. Eur J Pediatr Surg. 2017;27:74-80.
2017	Sullivan et al. Late effects of chemotherapeutic agents on renal function in childhood cancer survivors. Ir J Med Sci. 2017;186:49-55.
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2016	Ramirez et al. Yield of urinalysis screening in pediatric cancer survivors. Pediatr Blood Cancer. 2016;63:893-900.
2015	Arga et al. Risk factors for cisplatin-induced long-term nephrotoxicity in pediatric cancer survivors. Pediatrics International. 2015;57:406-413
2015	Janeczko et al. Evaluation of Renal Function in Pediatric Patients After Treatment for Wilms' Tumor. *Adv Clin Exp Med*. 2015;24 (3):497-504.
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2013	Dekkers et al. Long-Term Nephrotoxicity in Adult Survivors of Childhood Cancer. *Clin J Am Soc Nephrol*. 2013;8:922-9.
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2012	Knijnenburg et al. Renal function and elevated blood pressure in long-term childhood cancer survivors. *Clin J Am Soc nephrol*. 2012;7:1416-27.
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2009	Oberlin et al. Long-term evaluation of ifosfamide-related nephrotoxicity in children. *J Clin Oncol.* 2009;27:5350-5355.
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2008	Grönroos et al. Long-term follow-up of renal function after high-dose methotrexate treatment in children. Pediatr Blood Cancer. 2008;51:535-539.
2008	Jones et al. Renal Late Effects in Children Treated for Cancer in Childhood: A Report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2008;51:724-31.
2007	Grönroos et al. Long-term renal function following bone marrow transplantation. *Bone Marrow Transplantation*. 2007;39:717-723.
2007	Stohr et al. Nephrotoxicity of cisplatin and carboplatin in sarcoma patients: a report from the late effects surveillance system. *Pediatr Blood Cancer*. 2007;48:140-47.
2007	Stohr et al. Ifosfamide-induced nephrotoxicity in 593 sarcoma patients: a report from the late effects surveillance system. *Pediatr Blood Cancer*. 2007;48:447-52.
2005	Cozzi et al. Renal function adaptation in children with unilateral renal tumors treated with nephron sparing surgery or nephrectomy. The Journal of Urology. 2005;174:104-8.
2004	Yetgin et al. Evaluation of Kidney Damage in Patients With Acute Lymphoblastic Leukemia in Long-Term Follow-Up: Value of Renal Scan. *Am J Hem*. 2004;77:132-139.
2002	Frisk et al. Renal function after autologous bone marrow transplantation in children: a long-term prospective study. *Bone Marrow Transplant*. 2002;29:129-36.
2001	Patzer et al. Renal function in long-term survivors of stem cell transplantation in childhood. A prospective trial. *Bone marrow transplantation*. 2001;27:319-327 .
1999	Rossi et al. Development of ifosfamide-induced nephrotoxicity: prospective follow-up in 75 patients. *Medical and Pediatric Oncology*. 1999;32:177-182.
1991	Brock et al. Partial reversibility of cisplatin nephrotoxicity in children. *J Pediatr*. 1991;118:531-4.
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Evidence from evidence-based guidelines in other populations

Year	Bibliography
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2021	Delgado et al. A Unifying Approach for GFR Estimation: Recommendation of the NFK-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. *JASN.* 2021;32:2994-3015
2020	Unger et al. International Society of Hypertension. Global hypertension practice guideline. *Hypertension*. 2020;75:1334-57
2019	NICE. Hypertension in adults: diagnosis and Management. Clinical guideline. Published: 24 August 2011, http://www.nice.org.uk/guidance/cg127. Last updated august 2019.
2018	Tobe et al. Diabetes Canada Clinical Practice Guidelines Expert Committee. Treatment of hypertension. *Canadian Journal of Diabetes*. 2018:S186-189.
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2017	Flynn et al. American Academy of Pediatrics. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140:e20171904
2017	Whelton PK et al. The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *Hypertension*. 2018;71:e13-e115. DOI: 10.1161/HYP.0000000000000065
2017	De Boer et al. American Diabetes Association. Diabetes and Hypertension: A position statement by the American Diabetes Association. *Diabetes Care.* 2017;40:1273-1284

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2012	Toussaint N et al. CARI Guidelines. Screening for early chronic kidney disease. *Early Chronic Kidney Disease*. 2012: 1-32
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Evidence tables

Who needs glomerular dysfunction surveillance?

Who needs glomerular dysfunction surveillance?				
Cozzi et al. Renal function up to the 5th decade of life after nephrectomy in childhood: a literature review. Nephrology. 2018;23:397-404.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Systematic review, meta-analysis Treatment era: NM, included articles published between 1985 – 2015 Follow-up: Follow up spanned 0.06-32 years across all oncology papers reviewed	22 papers included reporting on glomerular function in adolescent and adults who underwent nephrectomy during childhood (oncological and non-oncological) Group-non: nephrectomy for non-oncological causes (7 articles) Group-onc: nephrectomy for oncological causes (15 articles) Type and number of participants: A total of 1035 pts in 22 articles Group-non: 416 pts Group-onc: 619 pts Diagnoses: Unilateral Nephrectomy for "oncologic causes", not further specified Age at diagnosis: childhood, not further specified	Nephrectomy: unilateral nephrectomy 1035/1035 (100%) Chemotherapy: NM RT renal area: NM	Outcome definitions No defined outcome definitions of abnormal for each paper, descriptive combined outcomes 1. Renal dysfunction (GFR <90/ml/min/1.73m^2) 2. Hypertension 3. Albuminuria Results for <30 yrs or ≥ 30 yrs at time of follow-up Results Renal dysfunction *Group-onc* <30 yrs: 97/398 (24%) ≥ 30 yrs: 74/178 (41%) P <0.0001 *Group-non* <30 yrs: 32/269 (14.4%) ≥ 30 yrs: 46/120 (38.3%) P < 0.0001 Group-onc vs group-non <30 yrs p= 0.07 Group-onc vs group-non ≥30 yrs p= 0.63 Total <30 yrs (20.3%) vs ≥30 yrs (40%) p= 0.0001 Hypertension *Group-onc* <30 yrs: 28/369 (7.5%) ≥ 30 yrs: 27/146 (18.4%)	Strengths: - Large combined sample size of reviewed papers - Long term follow Limitations: - Unknown treatment details aside from nephrectomy. - Outcome definitions not specified - Heterogeneity of included studies - No information regarding risk factors **Risk of bias** A. Selection bias: unclear Reason: not reported for each article in the review B. Attrition bias: low risk Reason: Long term follow up for >75% of patients included C. Detection bias: unclear Reason: No descriptions of how measurements of outcomes of each paper were assessed D. Confounding: high risk

	Age at follow-up: Range 2.1 – 49 yrs Controls: Not given for each individual article reviewed Combined outcomes from literature review of oncology patients were compared to the 416 patients with unilateral nephrectomy for non-oncologic causes identified in 7 papers published from 1985-2013. Age at follow up range: 8.6-48 years. Length of Follow up: 8.2-33 years		P= 0.0007 *Group-non* <30 yrs: 66/244 (27%) ≥ 30 yrs: 28/108 (25.6%) P= 0.89 Group-onc vs group-non <30 yrs p< 0.001 Group-onc vs group-non ≥30 yrs p > 0.05 Total <30 yrs (15%) vs ≥30 yrs (21%) p= 0.02 Albuminuria *Group-onc* <30 yrs FU: 60/283 (21%) ≥ 30 yrs FU: 32/177 (18%) P= 0.47 *Group-non* <30 yrs FU: 63/256 (24%) ≥ 30 yrs FU: 33/101 (32.6%) P= 0.14 Group-onc vs group-non <30 yrs p= 0.35 Group-onc vs group-non ≥30 yrs p= 0.007 Total <30 yrs (22%) vs ≥30 yrs (23%) p>0.05	Reason: Information on other prognostic treatment factors not taken into account in analysis

Footnote 1: More detailed results regarding risk factors are shown in the evidence table of the included studies for this guideline.
Abbreviations: GFR, glomerular filtration rate; NM, non-onc, non-onoclogy; not mentioned; onc, oncolyg; pts, patients; yrs, years.

Who needs glomerular dysfunction surveillance?				
Dekkers et al. Long-Term Nephrotoxicity in Adult Survivors of Childhood Cancer. Clin J Am Soc Nephrol. 2013;8:922-9.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design: Cross-sectional cohort study Treatment era: 1964-2005 Follow-up: Median 18.3 yr (range 5.0–58.2)	Type and number of participants: 763 CCS with a survival of ≥ 5 years since diagnosis, and aged ≥ 18 years at study entry. Eligible cohort 885 CCS. Diagnoses: ALL/T-NHL 216 (28.3%), AML 26 (3.4%), B-NHL 68 (8.9%), HL 80 (10.5%), bone tumour 35 (4.6%), renal tumour 85 (11.1%), NB 50 (6.6%), LCH 14 (1.8%), germ cell tumour 18 (2.4%), malignant mesenchymal tumour 67 (8.8%), brain tumour 76 (9.9%), other 28 (3.7%) Age at diagnosis: Median 7.3 yr (range 0.0-18.0) Age at follow-up: Median 26.9 yr (17.8-65.8) Controls: NA	Ifosfamide: 75/763 (10%) Cisplatin: 51/763 (7%) Carboplatin: 16/763 (2%) Cyclophosphamide: 305/763 (39.9%) MTX: 319/763 (41.8%), details: intrathecal 277 (29.8%), IV 236 (30.9%), oral 250 (32.8%) Unilateral nephrectomy: 85/763 (11%) RT renal area: 47/763 (6.2%), RT field: abdominal 47 (6.2%), TBI 26 (3.4%)	Outcome definitions 1. Decreased GFR: GFR < 60 mL/minute/1.73 m² (by MDRD equation) 2. Proteinuria: Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men) GFR < 60 mL/minute/1.73 m² 21/763 (2.8%) Risk factors decreased GFR No hypertension at time of study, adjusted mean 96, 95% CI 83.00 – 110.00 Hypertension at time of study, adjusted mean 96, 95% CI 82.00 - 109.00, p=0.82 No cisplatin adjusted mean 101 , 95%CI 89.00 – 113.00 Cisplatin ≤ 450 mg/ m² Adjusted mean 96, 95%CI 82.00 - 109.00, P=0.54 Cisplatin > 450 mg/ m² Adjusted mean 83, 95% CI 66.00 - 100.00, p=0.004 No ifosfamide adjusted mean 98 , 95% CI 85.00 – 112.00 Ifosfamide ≤ 16000 mg/m² Adjusted mean 102, 95% CI 86.00 - 117.00, p= 0.42 Ifosfamide > 16000 mg/m² Adjusted mean 88, 95% CI 73.00 - 103.00, p= 0.02	Strengths: Large study sample **Risk of bias** A. Selection bias: low risk Reason: the study group consisted of more than 75% of the original cohort B. Attrition bias: GFR: low risk Reason: the outcome was assessed for more than 75% of the study group Proteinuria: High risk Reason: the outcome was assessed for less than 75% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: important prognostic factors were taken adequately into account

			No carboplatin adjusted mean 94, 95% CI 81-106 Carboplatin adjusted mean 98, 95% CI 81.00 - 115.00, p=0.50 No cyclophosphamide Adjusted mean 96, 95% CI 82.00 – 110.00 Cyclophosphamide ≤ 3500 mg/m² Adjusted mean 96, 95%CI 83.00 - 110.00, p=0.98 Cyclophosphamide > 3500 mg/m² Adjusted mean 95, 95%CI 81.00 - 109.00, p=0.74 No MTX adjusted mean 97, 95%CI 84.00 - 110.00 MTX Adjusted mean 95, 95% CI 81.00 - 109.00, p=0.36 No TBI adjusted mean 93, 95%CI 81.00 – 106.00 TBI Adjusted mean 99, 95% CI 83.00 - 115.00, p=0.29 No nephrectomy/ no abdominal RT adjusted mean 106, 95%CI 95.00 -119.00 Nephrectomy, no abdominal RT, Adjusted mean 91, 95% CI 76.00 - 106.00, p <0.001 Abdominal RT, no nephrectomy Adjusted mean 96, 95% CI 78.00 - 113.00, p=0.09 Nephrectomy and abdominal RT Adjusted mean 90, 95% CI 74.00 - 106.00, p <0.001 <u>Proteinuria</u> 56/496 (11.3%) Microalbuminuria	

			10/496 (2.0%) Macroalbuminuria <u>Risk factors proteinuria</u> Hypertension at time of study OR 1.71, 95% CI 0.86 - 3.40, p > 0.05 Cisplatin ≤ 450 mg/m² OR 1.73, 95% CI 0.44 - 6.85, p > 0.05 Cisplatin > 450 mg/m² OR 5.19, 95% CI 1.21 - 22.21, p < 0.05 Ifosfamide ≤ 16000 mg/m² OR 1.35, 95% CI 0.34 - 5.33, p > 0.05 Ifosfamide >16000 mg/m² OR 1.49, 95% CI 0.49 - 4.54, p > 0.05 Carboplatin OR 2.18, 95% CI 0.45 - 10.54, p > 0.05 Cyclophosphamide ≤ 3500 mg/m² OR 0.54, 95% CI 0.21 - 1.39, p > 0.05 Cyclophosphamide > 3500 mg/m² OR 0.84, 95% CI 0.35 - 2.00, p > 0.05 MTX OR 0.94, 95% CI 0.49 - 2.16, p > 0.05 TBI OR 3.28, 95% CI 0.88 - 12.22, p > 0.05 Nephrectomy, no abdominal RT OR 2.12, 95% CI 0.21 - 21.21, p > 0.05 Abdominal RT, no nephrectomy OR 3.29, 95% CI 0.69 - 15.67, p > 0.05 Nephrectomy and abdominal RT OR 3.14, 95% CI 1.02 - 9.69, p < 0.05	

Footnote 1: Possible overlap in patients with Knijnenburg 2012 and Mulder 2013.

Abbreviations: 95% CI, 95% confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; B-NHL, B-cell non Hodgkin lymphoma; CCS, childhood cancer survivors; Cr, creatinine; GFR, glomerular filtration rate; HL, Hodgkin lymphoma; IV, intravenous; LCH, Langerhans cell histiocytosis; MDRD, modification of diet in renal disease; MTX, Methotrexate; NA, not applicable; OR, odds ratio; RT, radiotherapy; TBI, total body irradiation; T-NHL; T-cell non Hodgkin lymphoma; U-ACR, urinary albumin to creatinine ratio; yr, year.

Who needs glomerular dysfunction surveillance?				
Dieffenbach et al. Late-onset kidney failure in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. European Journal of Cancer. 2021;155:216-226.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Multi-institutional retrospective cohort study with prospective follow-up Treatment era: 1970-1999 Follow-up: Median 22.4 years (IQR 17.4-28.8)	Type and number of participants: 25,530 CCS Diagnoses: Resp. no kidney failure / kidney failure ALL 6542 (36%) / 42 (27%) AML 911 (3%) / 8 (4%) Other leukemia 323 (3%) / 8 (4%) CNS tumour 4465 (15%) / 17 (8%) Hodgkin lymphoma 3087 (11%) / 17 (8%) Wilms tumour 2204 (8%) / 46 (21%) Neuroblastoma 1922 (7%) / 19 (8%) Soft tissue sarcoma 1744 (6%) / 10 (4%) Ewing sarcoma 2061 (7%) / 23 (10%) Osteosarcoma 727 (2%) / 7 (3%) Other bone cancer 1233 (4%) / 15 (7%) Age at diagnosis: Median 6.1 years (IQR 3.0-12.4) Age at follow-up: Follow-up until development primary outcome, death, or most recent questionnaire completion (censoring). Total 35 year follow-up. Controls:	Ifosfamide: 1168/25,530 (4.6%) Cisplatin: 2465/25,530 (9.7%) Carboplatin: NM HD-cyclophosphamide: NM Methotrexate: 4919/25,530 (19.3%) Nephrectomy: 1999/25,530 (7.8%) (unilateral) RT renal area: 12,361/25,530 (48.4%) Other cancer treatment: Anthracycline: 10,460/25,530 (41.0%)	Outcome definitions 1. Late-onset kidney failure (self-reported: grade 4 (life-threatening; initiation dialysis or renal transplantation) or grade 5 (fatal renal condition)) Results Late-onset kidney failure 35-year cumulative incidence CCS 1.7% (95% CI 1.4-1.9), siblings 0.2 (95% CI 0.1-0.4) CCS 206/25,530. Siblings 10/5045 Risk factors late-onset kidney failure Male vs female OR 1.3, 95% CI 0.9-1.9 *Race/ethinicity* Non-hispanic black vs non hispanic white OR 1.8, 95% CI 0.9-3.5 Hispanic/latino vs non-hispanic white OR 0.8, 95% CI 0.4-1.6 Other vs non-hispanice white OR 1.2, 95% CI 0.5-2.5 *Age at initial cancer diagnosis (yr)* 4-9 vs 0-3 OR 1.4, 95% CI 0.9-2.0 5-14 vs 0-3 OR 0.8, 95% CI 0.5-1.5 ≥15 vs 0-3 OR 1.7, 95% CI 0.9-3.3 *Medical comorbidities* Known genitourinary condition vs none OR 1.7, 95% CI 0.7-4.1	Strengths: - large study sample - long follow-up period - taking into account controls Limitations - self reported outcome **Risk of bias** A. Selection bias: unclear Reason: unclear if study group consists of more than 75% original cohort B. Attrition bias: low risk Reason: outcome was assessed in more than 75% of study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: important prognostic factors were taken adequately into account

	5,045 siblings Median age 6.7 years (IQR 3.0-13.2)		Diabetes vs none OR 2.2, 95% CI 1.2-4.2 Hypertension during follow-up and no nephrectomy vs none OR 5.9, 95% CI 3.3-10.5 Hypertension during follow-up and prior nephrectomy vs none OR 14.4, 95% CI 7.1-29.4 *Treatment exposures* *Anthracycline dose (mg/m^2)* 0.1-249 vs none OR 1.5, 95% CI 1.0-2.3 ≥250 vs none OR 1.6, 95% CI 1.0-2.6 *Cisplatin dose (mg/m^2)* 0.1-499 vs none OR 1.6, 95% CI 0.8-2.9 ≥500 vs none OR 1.5, 95% CI 0.7-3.0 *Ifosfamide dose (g/m^2)* 0.1-59 vs none OR 2.4, 95% CI 1.3-4.6 ≥60 vs none OR 3.0, 95% CI 1.0-9.2 *Methotrexate dose (IV, mg/m^2)* 0.1-3999 vs none OR 0.6, 95% CI 0.3-1.4 ≥4000 vs none OR 0.6, 95% CI 0.3-1.2 *Kidney dose from RT (Gy)* 0.1-9.9 vs none OR 0.8, 95% CI 0.5-1.3 10-14.9 vs none OR 1.6, 95% CI 0.8-3.3 ≥15 vs none OR 4.0, 95% CI 2.1-7.4	

			Unilateral nephrectomy vs none OR 1.9, 95% CI 1.0-3.4 *Subsequent malignant neoplasm (SMN)* Non-renal SMN vs none OR 1.2, 95% CI 0.5-3.3 Renal SMN vs none OR 15.1, 95% CI 4.2-55.0 Alternative model including ifosfamide with platinum agents (ref no ifosfamide or platinum) Platinum agent only OR 1.5, 95% CI 0.8-2.7 Ifosfamide only OR 2.6, 95% CI 1.2-5.7 Ifosfamide and platinum agent OR 3.8, 95% CI 1.8-8.0	

Abbreviations: 95% CI, 95% confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CCS, childhood cancer survivors; CNS, central nervous system; IQR, interquartile range; IV, intravenous; NA, not applicable; NM, not mentioned; OR, odds ratio; ref, reference; resp, respectively; RT, radiotherapy; SMN, subsequent malignant neoplasm; vs, versus; yr, year.

Who needs glomerular dysfunction surveillance?				
Dietz et al. Solid organ transplantation after treatment for childhood cancer: a retrospective cohort analysis from the Childhood Cancer Survivor Study. Lancet Oncol. 2019;20:1420-31.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: retrospective cohort study Treatment era: 1970 – 1986 Follow-up: follow-up until Dec 31, 2013	Type and number of participants: Total CCSS cohort: 13,318 survivors treated before the age of 21 yrs for childhood cancer and who survived at least 5 yrs after diagnosis. Diagnoses: Leukemia 4502 (33.8%) CNS tumour 1639 (12.3%) Hodgkin lymphoma 1846 (13.9%)	Chemotherapy: Cisplatin 604/11595 (3.4%) Cyclophosphamide 5132/11554 (44.4%) Ifosfamide 62/11602 (0.5%) MTX iv or im 2501/11574 (21.6%) RT renal area: *Kidney* No 3849 (34.1%) >0-10 Gy 6832 (60.4%)	Outcome definitions Solid organ (kidney) transplantation Results Kidney transplantation 50 received 21 waiting list Cumulative incidence after 35 yrs for kidney transplantation or	Strengths: - linkage of two large databases - clear methods Limitations - **Risk of bias** A. Selection bias: low risk Reason: Study group consisted of more than 75% of original cohort

	Non-Hodgkin lymphoma 1022 (7.7%) Kidney (Wilms') tumor 1162 (8.7%) Neuroblastoma 866 (6.5%) Soft tissue sarcoma 1167 (8.8%) Bone tumor 1114 (8.4%) <u>Age at diagnosis:</u> Median 6 yrs (IQR 3-13) 0-4 yrs 5295 (39.8%) 5-9 yrs 2922 (21.9%) 10-14 yrs 2687 (20.2%) 15-20 yrs 2414 (18.1%) <u>Age at follow-up:</u> Median 39 yrs (IQR 33 – 46) 7 unknown < 20 yrs 612 (4.6%) 20-29 yrs 989 (7.4%) 30-39 yrs 5147 (38.7%) 40-49 yrs 4805 (36.1%) ≥ 50 yrs 1758 (13.2%) <u>Controls:</u> NA	>10-20 gy 546 (4.8%) >20 Gy 76 (0/7%) Unknown 2015 *TBI* No 11,196 (98.4%) Yes 185 (1.6%) Unknown 1937 <u>Nephrectomy:</u> Only reported from group that received kidney transplant (n=71, 8 unknown) No 39 (62%) Yes (unilateral) 24 (38%)	being on waiting list = 0.49 %, 95% CI 0.36 – 0.62. 5 year overall survival after kidney transplantation was 93.5%, 95% CI 81.0 – 97.9 <u>Risk factors kidney transplantation</u> Unilateral nephrectomy HR 4.2, 95% CI 2.3-7.7, p <0.0001 Ifosfamide HR 24.9, 95% CI 7.4-83.5, p < 0.0001 TBI vs. no RT renal area HR 6.9, 95% CI 2.3-21.1, p = 0.007 RT renal area >0-10 Gy vs. none HR 0.4, 95%CI 0.2-0.7, p=0.0040 >10-15 Gy vs. none HR 1.6, 95%CI 0.6-4.0, p=0.35 15-20 Gy vs. none HR 3.6, 95% CI 1.5-8.5, p= 0.0041 >20 Gy vs. none HR 4.6, 95% CI 1.1-19.6, p= 0.040 MTX HR 0.6, 95% CI 0.3-1.5, p= 0.30 Age at diagnosis. p >0.05 Cisplatin, p > 0.10 Cyclophosphamide, p >0.10	<u>B. Attrition bias:</u> low risk Reason: Follow-up was complete for more than 75% of study group <u>C. Detection bias:</u> unclear Reason: not applicable <u>D. Confounding:</u> low risk Reason: all important factors were taken into account in MV analyses

Abbreviations: 95%CI, 95% confidence interval; CCSS, childhood cancer survivor study; CNS, central nervous system; Dec, december; Gy, gray; HR, hazard ratio; im, intramuscular; IQR, interquartile range; iv, intravenous; MTX, methotrexate; MV, multivariable; NA, not applicable; TBI, total body irradiation; yrs, years

Who needs glomerular dysfunction surveillance?				
Frisk et al. Renal function after autologous bone marrow transplantation in children: a long-term prospective study. Bone Marrow Transplant. 2002;29:129-36.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design: Prospective once center cohort study Treatment era: 1985-1997 Follow-up: At least 6 months Median: 120 months (group TBI +) Median: 54 months (group TBI -)	Type and number of participants: 40 patients, less than 18 years, treated with autologous BMT. 26 received TBI (TBI+), 14 did not (TBI-) Diagnoses: TBI +: ALL 23, LBL 3, TBI -:AML 9, HL.3 and LCAL 2 Age at diagnosis: Not known. Age at BMT: TBI +: Median 8.4 yr (range 3.6-17.7) TBI -: Median 13.2 yr (range 1.9 – 17.9) Age at follow-up: NM Controls: Patients are their own controls (GFR before / after BMT)	Chemotherapy: Prednisolone, teniposide, daunorubicin, vincristine, cyclophosphamide, cytarabin, busulfan. Details not stated. Nephrectomy: No RT renal area: TBI: Single fraction, maximum dose to the kidneys 7.5 +/- 5% (4/26 patients received fractionated TBI 12 Gy in 6 fractions, renal dose not known in these patients) Other: In the TBI+ group respectively 50, 29 and 29% received iv vancomycin, aminoglycosides or both. In the TBI- the figures were 42, 62 and 42%	Outcome definitions 1. Decreased GFR: GFR < 70 mL/minute/1.73 m² (estimated by single-injection clearance using 51Cr-EDTA, except in the first year of the program, when GFR was measured by endogenous creatinine clearance) GFR < 70 mL/minute/1.73 m² 7/26 (27%) after 6 months Risk factors decreased GFR CCS treated with TBI: Concomitant treatment with aminoglycosides and vancomycin, Beta: 32mL/min/1.73m², 95% CI 54 - 10, p < 0.01 CCS treated without TBI: Concomitant treatment with aminoglycosides and vancomycin, p = 0.22	Strengths: -clear methods for measuring renal function Limitations: - Gender was not taken into account in multivariable analysis - Effect size multivariable risk analysis CCS treated without TBI not mentioned. - Short follow-up period **Risk of bias** A. Selection bias: low risk Reason: the study group consisted of more than 75% of the original cohort B. Attrition bias: high risk Reason: After 1 year 75% of the pts were studied, but the number reduced quickly: at 2 years 60% were left, at 5 years 65%, 10 years 43% C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: high risk Reason: Not all important prognostic factors (gender) were taken adequately into account

Abbreviations: 95% CI, 95% confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMT; bone marrow transplantation; CCS, childhood cancer survivors; GFR, glomerular filtration rate; HL, Hodgkin lymphoma; LBL, lymphoblastic lymphoma; LCAL, large cell anaplastic lymphoma; NM; not mentioned; pts, patients; RT, radiotherapy; TBI, total body irradiation.

Who needs glomerular dysfunction surveillance?

Green et al. Kidney function after treatment for childhood cancer: A report from the St. Jude Lifetime Cohort Study. JASN. 2021;32(4):983-93.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: cross-sectional cohort study Treatment era: NM, see [1] for more details Follow-up: At least 10 years from diagnosis. Median 23.2 years from diagnosis (IQR 17.6 – 29.7)	Type and number of participants: 2,753 CCS Diagnoses: ALL 934 (33.9%) AML 85 (3.1%) CNS tumor 259 (9.4%) Ewing sarcoma family of tumors 88 (3.2%) Hodgkin lymphoma 340 (12.4%) Neuroblastoma 122 (4.4%) Non-Hodgkin lymphoma 200 (7.3%) Osteosarcoma 108 (3.9%) Other 348 (12.6%) Rhabdomyosarcoma 91 (3.3%) Wilms tumor 178 (6.5%) Age at diagnosis: Median 7.3 years (IQR3.3 – 13.2) Age at follow-up: Media 31.4 years (IQR 25.8 – 37.8) Controls: NA	Ifosfamide: 195/2753 (7.1%) Cisplatin: 221/2753 (8.0%) Carboplatin: 135/2753 (4.9%) HD-cyclophosphamide: 934/2739 (33.9%) HD-methotrexate: 747/2753 (27.1%) Nephrectomy: 204/2753 (7.4%) RT renal area: 439/2753 (16.0%) Percentage of total renal mass for: - V5: 367 percentage >0 - V10: 359 percentage >0 - V15: 249 percentage >0 - V20: 197 percentage >0 Other nephrotoxic medication Current ACI 133/2645 (4.8%) Current ARB 26/2652 (0.9%) Ever cacineurin inhibitor 58/2751 (2.1%) Aminoglycoside 1069/2753 (38.8%)	Outcome definitions[2] 1. CKD stages 3-5 (based on CKD-EPI 2012 equation including creatinine) 2. Proteinuria stages A2-A3 (based on dipstick) Results CKD stages 3-5 57/2693 (2.1%) Risk factors CKD stages 3-5 4 models based on volume of kidney irradiated (V5, V10, V15 or V20 Gy) - RT only significantly increased the odds in models V5 or V10 (volume of kidney irradiated ≥5 or ≥10 Gy). V5 (per 1%): OR 1.02, 95%CI 1.01-1.02 V10 (per 1%): OR 1.02, 95%CI 1.01-1.02 V15 (per 1%): OR 1.01, 95%CI 1.00-1.02 V20 (per 1%): OR 1.01, 95%CI 0.99-1.03 - Nephrectomy only significantly increased the odds in models V15 or V20. Other significant risk factors mentioned below were significant in all 4 models.	Strengths: - large study sample - long follow-up period - clear description of cohort and outcome measures - supportive care drugs taken into account in multivariable analyses - dosimetry of radiotherapy taken into account in analyses Limitations: - potential selection bias (more Ewing sarcoma, osteosarcoma and ALL survivors in participant group) **Risk of bias** A. Selection bias: high risk Reason: study group consists of 62% original cohort and more Ewing sarcoma, osteosarcoma and ALL survivors in participant group vs. non-participant group B. Attrition bias: low risk Reason: outcome was assessed in 98% of study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk

			V5 model Race/ethnicity others vs non-hispanic white OR 1.69, 95%CI 0.85-3.36 Age at evaluation (per year) OR 1.07, 95%CI 1.03-1.12 Hypertension at time of study grade ≥2 vs. <2 OR 8.63, 95%CI 4.19-17.75 Ifosfamide (per 1000 mg/m^2) OR 1.04, 95% CI 1.02-1.05 Cisplatinum (per 100 mg/m^2) OR 1.44, 95%CI 1.25-1.65 Carboplatinum (per 100 mg/m^2) OR 1.03, 95%CI 1.00-1.06 (p<0.05) CNI use ever OR 4.60, 95%CI 1.48-14.30 RT V5 (per 1%) OR 1.02, 95%CI 1.01-1.02 V10 model Race/ethnicity others vs non-hispanic white OR 1.72, 95%CI 0.86-3.41 Age at evaluation (per year) OR 1.08, 95%CI 1.04-1.12 Hypertension at time of study grade ≥2 vs. <2 OR 8.72, 95%CI 4.25-17.92 Ifosfamide (per 1000 mg/m^2) OR 1.04, 95% CI 1.02-1.05 Cisplatinum (per 100 mg/m^2) OR 1.44, 95%CI 1.25-1.65 Carboplatinum (per 100 mg/m^2) OR 1.03, 95%CI 1.00-1.06 (p<0.05) CNI use ever OR 4.61, 95%CI 1.42-14.92 RT V10 (per 1%) OR 1.02, 95%CI 1.01-1.02 V15 model	Reason: important prognostic factors were taken adequately into account

			Race/ethnicity others vs non-hispanic white OR 1.81, 95%CI 0.91-3.60 Age at evaluation (per year) OR 1.08, 95%CI 1.04-1.12 Hypertension at time of study grade ≥2 vs. <2 OR 8.43, 95%CI 4.10-17.31 Nephrectomy (Yes/No) OR 3.55, 95%CI 1.47-8.56 Ifosfamide (per 1000 mg/m^2) OR 1.04, 95% CI 1.02-1.05 Cisplatinum (per 100 mg/m^2) OR 1.43, 95%CI 1.24-1.64 Carboplatinum (per 100 mg/m^2) OR 1.03, 95%CI 1.00-1.06 (p<0.05) CNI use ever OR 17.51, 95%CI 6.16-49.77 RT V15 (per 1%) OR 1.01, 95%CI 1.00-1.02 <u>V20 model</u> Race/ethnicity others vs non-hispanic white OR 1.83, 95%CI 0.92-3.64 Age at evaluation (per year) OR 1.08, 95%CI 1.04-1.13 Hypertension at time of study grade ≥2 vs. <2 OR 8.39, 95%CI 4.08-17.25 Nephrectomy (Yes/No) OR 3.74, 95%CI 1.56-8.94 Ifosfamide (per 1000 mg/m^2) OR 1.04, 95% CI 1.02-1.05 Cisplatinum (per 100 mg/m^2) OR 1.43, 95%CI 1.24-1.64 Carboplatinum (per 100 mg/m^2) OR 1.03, 95%CI 1.00-1.06 (p<0.05) CNI use ever OR 17.59, 95%CI 6.19-50.05	

			RT V20 (per 1%) OR 1.01, 95%CI 0.99-1.03 Not included in multivariable model based on Elastic Net: - HD-methotrexate - HD-cyclophosphamide - Current use ACEI - Current use ARB - Aminoglycoside - Doses of abelcet/ambisome - Doses of amphotericin <u>Proteinuria stages A2-A3</u> 160/2693 (5.9%) <u>Risk factors proteinuria stages A2-A3</u> Higher percentages of the kidney exposed to V5, V10, V15, V20-Gy radiation were not associated with increased odds. <u>V5 model</u> Sex (men vs. women) OR 1.43, 95%CI 1.00-2.04 Race/ethnicity others vs non-hispanic white OR 2.34, 95%CI 1.59-3.44 BMI ≥25-30 vs. >13<25 OR 0.65, 95%CI 0.39-1.09 BMI ≥30 vs. >13<25 OR 1.51, 95%CI 0.98-2.31 Hypertension at time of study grade ≥2 vs. <2 OR 2.62, 95%CI 1.81-3.79 Diabetes Mellitus grade ≥ 2 vs <2 OR 1.19, 95%CI 0.70-2.02 Nephrectomy (Yes/No) OR 2.21, 95%CI 1.25-3.90	

			Doses of abelcet/ambisome (per dose) OR 1.03, 95%CI 0.99-1.06 Doses of amphotericin B (per dose) OR 1.02, 95%CI 1.00-1.04, p =0.02 RT V5 (per 1%) OR 1.00, 95%CI 1.00-1.01 V10 (per 1%): OR 1.00, 95%CI 1.00-1.01 <u>V15 model</u> Sex (men vs. women) OR 1.42, 95%CI 1.00-2.03 Race/ethnicity others vs non-hispanic white OR 2.32, 95%CI 1.58-3.41 BMI ≥25-30 vs. >13<25 OR 0.65, 95%CI 0.39-1.08 BMI ≥30 vs. >13<25 OR 1.50, 95%CI 0.98-2.30 Hypertension at time of study grade ≥2 vs. <2 OR 2.63, 95%CI 1.82-3.81 Diabetes Mellitus grade ≥ 2 vs <2 OR 1.19, 95%CI 0.70-2.01 Nephrectomy (Yes/No) OR 2.37, 95%CI 1.38-4.07 Doses of abelcet/ambisome (per dose) OR 1.03, 95%CI 1.00-1.06 Doses of amphotericin B (per dose) OR 1.02, 95%CI 1.01-1.04 V15 (per 1%): OR 1.01, 95%CI 1.00-1.02 <u>V20 model</u> Sex (men vs. women) OR 1.41, 95%CI 0.99-2.01 Race/ethnicity others vs non-hispanic white OR 2.31, 95%CI 1.57-3.39	

			BMI ≥25-30 vs. >13<25 OR 0.65, 95%CI 0.39-1.09 BMI ≥30 vs. >13<25 OR 1.51, 95%CI 0.99-2.32 Hypertension at time of study grade ≥2 vs. <2 OR 2.61, 95%CI 1.80-3.77 Diabetes Mellitus grade ≥ 2 vs <2 OR 1.19, 95%CI 0.70-2.01 Nephrectomy (Yes/No) OR 2.36, 95%CI 1.37-4.05 Doses of abelcet/ambisome (per dose) OR 1.03, 95%CI 1.00-1.06 Doses of amphotericin B (per dose) OR 1.02, 95%CI 1.01-1.04 V20 (per 1%): OR 1.01, 95%CI 1.00-1.03 Not included in multivariable model based on Elastic Net: - Ifosfamide - HD-methotrexate - HD-cyclophosphamide - Ifosfamide - Cisplatinum - Carboplatin - Current use of ACEI - Current use of ARB - Aminoglycoside - CNI use ever	

Abbreviations: 95%CI, 95% confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ALL, acute lymphoblastic leukemia; ARB, angiotensin receptor blocker; AML, acute myeloid leukemia; BMI, body mass index; CCS, childhood cancer survivors; CKD, chronic kidney disease; CNI, calcineurin inhibitor; CNS, central nervous system; HD, high-dose; IQR, interquartile range; NA, not applicable; NM, not mentioned, OR, odds ratio.
Footnote 1: Hudson et al. Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics and feasibility of the St. Jude Lifetime Cohort Study
Footnote 2: Stages based on KDIGO 2024 guideline.

Who needs glomerular dysfunction surveillance?				
Jones et al. Renal Late Effects in Children Treated for Cancer in Childhood: A Report from the Children's Oncology Group. Pediatr Blood Cancer. 2008;51:724-31.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design: systematic review Treatment era: 1970-2004 Follow-up: Variable by manuscript reviewed, not precisely stated	42 articles included Type and number of participants: Unknown Diagnoses: 42 articles on the topic of late effects of childhood cancer, reviewed as part of the COG LTFU Guidelines (kidney) Age at diagnosis: Variable (ranges from <3 to >10 years) Age at follow-up: Variable (not all follow-up intervals given) Controls: In one paper, children undergoing nephrectomy for WT were compared with children undergoing nephrectomy for non-malignant disease (hydronephrosis). In another paper, children undergoing nephrectomy for WT +/- RT. Otherwise, no controls.	Ifosfamide: 14/42 studies Cisplatin/carboplatin: 8/42 studies Methotrexate: 2/42 studies RT renal area: 5/42 studies Nephrectomy: 12/42 studies	Outcome definitions GFR: abnormal value not defined in most studies, but <80 or <90 ml/min/1.73 m^2 in two papers. Another paper defined this as SCr >3x normal. Microalbuminuria: value not defined Decreased GFR Prevalence 12 - 92 % Risk factors ifosfamide nephrotoxicity (7 studies) Cumulative dose >60-100 g/m^2 (5 studies) Age <3-5 years (2 studies) Concurrent or previous platinum therapy (2 studies) Renal irradiation (1 study) Unilateral nephrectomy (1 study) Hydronephrosis (1 study) Microalbuminuria Prevalence 5-84% of children after nephrectomy in 2 studies. No mention of microalbuminuria relative to other therapies	Strengths: - Comprehensive search Limitations: - Lack of uniform inclusion criteria (age, therapy, cancer type), assessment and follow up duration across studies - No risk of bias assessment **Risk of bias** A. Selection bias: unclear Reason: Insufficient information provided to determine if the study group of included articles was representative B. Attrition bias: unclear Reason: Insufficient information provided to determine if outcome was assessed for more than 75% of the study group of included articles C. Detection bias: unclear Reason: Blinding not mentioned D. Confounding: unclear Reason: No information provided whether risk analyses were adjusted for important confounding factors

Footnote 1: More detailed results regarding risk factors are shown in the evidence table of the included studies for this guideline
Abbreviations: COG LTFU Guidelines, Childhood Oncology Group Long Term Follow-Up Guidelines; GFR, glomerular filtration rate; RT, radiotherapy; Scr, serum creatinine; WT, Wilms tumor.

Who needs glomerular dysfunction surveillance?				
Knijnenburg et al. Renal function and elevated blood pressure in long-term childhood cancer survivors. Clin J Am Soc nephrol. 2012;7:1416-27.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design: Cross-sectional cohort study Treatment era: 1966-2003 Follow-up: Median 12.1 yr (range 7.8-17.5)	Type and number of participants: Described study group 1442 CCS ≥ 5 years after diagnosis, of whom 1313 with a renal function test. Out of described cohort 896 treated with nephrotoxic therapy, 417 without nephrotoxic therapy. Diagnoses: Bone tumours 108 (7.5%), hepatic tumours 20 (1.4%), germ cell tumours 52 (3.6%), renal tumours 207(14.4%), soft tissue sarcoma 153 (10.6%), NB 96 (6.7%), retinoblastoma 13 (0.9%), CNS tumour 85 (5.9%), leukemia 376 (26.1%), lymphoma 302 (20.9%), other 30 (2.1%). Age at diagnosis: Median 5.9 yr (range 2.9-10.9) Age at follow-up: Median 19.3 yr (range 15.6-24.5) Controls: NA	Ifosfamide: 202/1442 (14.0%) Cisplatin: 112/1442 (7.8%) Carboplatin: 111/1442 (7.7%) HD cyclophosphamide: 124/1442 (8.6%) HD MTX: 368/1442 (25.5%) Nephrectomy: 212/1442 (14.7%) RT renal area: 125/1442 (8.7%), RT field: abdominal 103 (7.1%), TBI 22 (1.5%)	Outcome definitions 1. Decreased GFR: GFR < 90 mL/minute/1.73 m² (up to 18 years Schwartz formula, adults CKD-EPI formula) 2. Proteinuria Albuminuria based on dipstick GFR < 90 mL/minute/1.73 m² 62/1313 (4.7%) Risk factors decreased GFR Cumulative ifosfamide dose (per 10 g/ m²) OR 1.62, 95% CI 1.44 – 1.82, p < 0.05 Cumulative cisplatin dose (per 100 mg/m²) OR 1.29, 95% CI 1.08 - 1.54, p < 0.05 Cumulative carboplatin dose (per 100 mg/m²) OR 1.03, 95 % CI 1.00 - 1.07, p > 0.05 HD-cyclophosphamide (no/yes) (≥1 g/m² per course) OR 7.08, 95% CI 2.72 - 18.45, p < 0.05 HD-MTX (no/yes) (≥ 1 g/m² per course) OR 0.60, 95% CI 0.19 - 1. 85, p > 0.05 Nephrectomy (no/yes) OR 8.56, 95% CI 3.42 - 21.42, p < 0.05 TBI (no/yes) OR 1.72, 95% CI 0.20 - 15.13, p > 0.05 Abdominal RT (no/yes) OR 1.50, 95% CI 0.62 - 3.63, p > 0.05 Age at diagnosis (in years) OR 1.05, 95% CI 0.97 - 1.13, p > 0.05 Time since diagnosis (per 5 years) OR 1.3, 95% CI 1.04 - 1.72, p <0.05 Male sex OR 38.4, 95%CI 11.0 - 134.4, p > 0.05	Eligible cohort 1845 CCS. Strengths: - Large study sample - Additional multivariable risk analysis for mutually exclusive treatment groups. Limitations: - Proteinuria measured by dipstick. **Risk of bias** A. Selection bias: low risk Reason: the study group consisted of more than 75% of the original cohort B. Attrition bias: GFR: low risk Reason: the outcome was assessed for more than 75% of the study group Proteinuria: low risk Reason: the outcome was assessed for more than 75% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: important prognostic factors were taken adequately into account

			Mutually exclusive treatment groups: Ifosfamide only OR 38.4, 95% CI 11.0 –134.4, $p < 0.05$ Cisplatin only OR 15.2, 95% CI 1.5 – 54.3, $p < 0.05$ Carboplatin only OR 15.2, 95 % CI 1.5 – 155.5, $p < 0.05$ Platinum agents + ifosfamide OR 37.9, 95% CI 10.0 – 144.2, $p < 0.05$ HD-MTX only (≥ 1 g/m² per course) OR 2.0, 95% CI 0.4 – 11.8, $p > 0.05$ Nephrectomy only OR 19.3, 95% CI 5.1 – 72.9, $p < 0.05$ RT [1] only OR 4.5, 95% CI 0.5 - 41.7, $p < 0.05$ Nephrectomy + chemotherapy [2] OR 108.6, 95% CI 18.1 – 651.1, $p < 0.05$ Nephrectomy + RT [1] OR 22.0, 95% CI 6.3 – 77.1, $p < 0.05$ Nephrectomy + chemotherapy [2] + RT [1] OR 125.6, 95% CI 20.8 – 757.1, $p < 0.05$ RT [1] + chemotherapy [2] OR 21.7, 95% CI 3.6 – 131.9, $p < 0.05$ <u>Proteinuria</u> 184/1269 (14.5%) <u>Risk factors proteinuria</u> Cumulative ifosfamide dose (per 10 g/m²) OR 1.34, 95% CI 1.23 - 1.46, $p < 0.05$ Cumulative cisplatin dose (per 100 mg/m²) OR 0.95, 95% CI 0.81 - 1.12, $p > 0.05$ Cumulative carboplatin dose (per 100 mg/m²) OR 1.02, 95% CI 1.00 - 1.04, $p > 0.05$	

			HD-cyclophosphamide (no/yes) (≥ 1 g/m² per course) OR 0.82, 95% CI 0.43 - 1.57, p > 0.05 HD-MTX (no/yes) (≥ 1 g/m² per course) OR 1.37, 95% CI 0.87 - 2.14, p > 0.05 Nephrectomy (no/yes) OR 1.70, 95% CI 0.97 - 2.96, p > 0.05 TBI (no/yes) OR 2.73, 95% CI 0.95 - 7.90, p > 0.05 Abdominal RT (no/yes) OR 1.10, 95% CI 0.57 - 2.16, p > 0.05 Age at diagnosis (in years) OR 1.02, 95% CI 0.98 - 1.06, p > 0.05 Time since diagnosis (per 5 years) OR 1.13, 95% CI 0.98 - 1.31, p > 0.05 Male sex OR 0.80. 95%CI 0.58 – 1.11, p > 0.05 *Mutually exclusive treatment groups:* Ifosfamide only OR 4.50, 95% CI 2.44 – 8.31, p < 0.05 Cisplatin only OR 2.20, 95% CI 0.94 – 5.14, p > 0.05 Carboplatin only OR 6.01, 95 % CI 2.21 – 16.35, p < 0.05 Platinum agents + ifosfamide OR 2.12, 95% CI 1.03 – 4.63, p < 0.05 HD-MTX only (≥ 1 g/m² per course) OR 1.59, 95% CI 0.94 – 2.66, p > 0.05 Nephrectomy only OR 1.55, 95% CI 0.77 – 3.09, p > 0.05 RT [1] only OR 2.06, 95% CI 0.74 – 5.73, p > 0.05 Nephrectomy + chemotherapy [2] OR 6.67, 95% CI 2.01 – 22.14, p < 0.05	

			Nephrectomy + RT [1] OR 2.01, 95% CI 0.98 – 4.11, p > 0.05 Nephrectomy + chemotherapy [2] + RT [1] OR 5.35, 95% CI 1.27 – 22.63, p < 0.05 RT [1] + chemotherapy [2] OR 1.76, 95% CI 0.49 – 6.29, p > 0.05	

Footnote 1: abdominal radiotherapy and/or total body irradiation.
Footnote 2: chemotherapy included: high-dose cyclophosphamide, high-dose methotrexate, cisplatin, carboplatin, and/or ifosfamide.
Footnote 3: Possible overlap in patients with Dekkers 2013 and Mulder 2013.
Abbreviations: 95% CI, 95% confidence interval; CCS, childhood cancer survivors; CKD-EPI, chronic kidney disease epidemiology collaboration; CNS, central nervous system; GFR, glomerular filtration rate; HD, high-dose; MTX, Methotrexate; NA, not applicable; NB, neuroblastoma; OR, odds ratio; RT, radiotherapy; TBI, total body irradiation; yr, year.

Who needs glomerular dysfunction surveillance?				
Kooijmans et al. Early and late adverse renal effects after potentially nephrotoxic treatment for childhood cancer. Cochrane Database Syst Rev. 2019; Issue 3, art. No CD008944.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Systematic review Treatment era: 1931-2014 Follow-up: Median or mean survival ≥ 1 yr after end treatment, if unknown ≥ 90% had to finished treatment	61 studies included (46 prevalence, 6 prevalence & risk factors, 9 risk factors) Characteristics of 52 studies included for prevalence: Type and number of participants: 13,327 participants of interest. 4,499 underwent renal function testing. Diagnoses (n studies): Only Wilms' tumor (n=39) Only renal tumor (n=2) Only sarcoma (n=3) Only hepatoblastoma (n=1) Only leukemia/lymphoma (n=2) Only central nervous system malignancies (n=1) Miscellaneous tumors (n=4)	Cisplatin: 9/52 studies Carboplatin: 15/52 studies Ifosfamide: 21/52 studies RT renal area: 44/52 studies Nephrectomy: 44/52 studies Other treatment: 40/52 studies	Outcome definitions (as defined by authors): - chronic kidney disease - decreased glomerular filtration rate - proteinuria - hypophosphatemia - abnormal tubular phosphate reabsorption - hypomagnesemia - hypertension Chronic kidney disease (CKD) Prevalence 2.4-32%, studied in 7/52 studies including 244 participants Risk factors CKD: 1 study Increased risk for end-stage renal disease in children with non-WT1 syndromic Wilms' tumour, with predominant stromal histology,	Strengths: - Comprehensive search strategy Limitations: - Heterogeneity of included studies - No meta-analysis **Risk of bias** A. Selection bias: Low risk 26/61 studies (42.6%) High risk 19/61 studies (31.1%) Unclear 16/61 studies (26.2%) B. Attrition bias: CKD Low risk 6/7 studies (85.7%) Unclear 1/7 studies (14.3%) GFR Low risk 35/36 studies (97.2%) High risk 1/36 studies (2.8%)

	Age at diagnosis: Range 12 mo - 14 yr Age at follow-up: Range 3.6 - 29 yr Controls: NA		an age at diagnosis of less than 24 months, and intralobar nephrogenic rests. Decreased glomerular filtration rate (GFR) Prevalence overall 0 – 73.7%, studied in 36/52 studies, including 432 participants Risk factors decreased GFR: 5 studies Four studies found nephrectomy and (HD) ifosfamide as risk factors. The majority also reported cisplatin as a risk factor. Two studies showed an association of a longer follow-up period with glomerular dysfunction. One study reported concomitant treatment with aminoglycosides and vancomycin as risk factor in CCS receiving total body irradiation (TBI). Proteinuria Prevalence 3.5 – 84%, studied in 22/52 studies including 851 participants. Risk factors proteinuria: 3 studies Risk factors included HD cisplatin, (HD) ifosfamide, TBI, and a combination of nephrectomy and abdominal RT. However, studies were contradictory and incomparable. Hypertension	Proteinuria Low risk 23/23 studies (100%) C. Detection bias: Unclear 61/61 studies (100%) D. Confounding: Low risk 8/15 studies (53.3%) High risk 6/15 studies (40.0%) Unclear 1/15 studies (6.7%)

			Prevalence 0 – 50%, studied in 30/52 studies, including 2464 participants Risk factors hypertension: 5 studies Reported risk factors: 3 studies BMI, 2 studies older age at screening. Treatment-related risk factors were abdominal RT and TBI, but studies were inconsistent.	

Footnote 1: For the risk of bias, results of the Cochrane review are shown. Criteria for risk of bias assessment by Cochrane may slightly differ from the IGHG criteria.
Footnote 2: More detailed results regarding risk factors are shown in the evidence table of the included studies for this guideline.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; GFR, glomerular filtration rate; HD, high-dose; mo, months; non-WT1; non Wilms tumor 1 gene; RT, radiotherapy; TBI, total body irradiation; yr, year.

Who needs glomerular dysfunction surveillance?				
Kooijmans et al. The Dutch Childhood Cancer Survivor Study (DCCSS)-LATER 2 kidney analysis examined long-term glomerular dysfunction in childhood cancer survivors. Kidney Int. 2022;102:1136-1146.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: cross-sectional multi-center study Treatment era: 1963-2001 Follow-up: Median 25.6 years (IQR 21.1-30.1)	Type and number of participants: 1033 CCS with a survival of ≥ 5 years since diagnosis, and aged ≥ 18 years at study entry. Eligible cohort 1,881 CCS. Diagnoses: Leukemias 317 (30.7%), lymphomas 79 (7.6%), CNS tumors 62 (6.0%), neuroblastoma 65 (6.3%), retinoblastoma 1 (0.3%), renal tumors 262 (25.4%), hepatic tumors 12 (1.2%), bone tumors 78 (7.6%), soft tissue sarcomas 52 (5.1%), other tumors 13 (1.3%)	Ifosfamide: 301/1033 (29.1%) HD-cyclophosphamide: 278/1033 (27.0%) Cisplatin: 176/1033 (17.0%) Carboplatin: 152/1033 (14.7%) Nephrectomy: 272/1033 (26.3%) RT renal area: 177/1033 (17.4%) Total body irradiation 85/1033 (8.3%) HSCT: 95/1033 (9.3%)	Outcome definitions 1. Decreased eGFR (< 90 ml/min/1.73m^2) 2. Albuminuria (urinary albumin:creatinine ratio ≥ 3 mgm/mol) Results Decreased eGFR 226/943 (24.0%) Risk factors decreased eGFR *Model dichotomous treatment variables* Nephrectomy OR 3.7, 95%CI 2.1 – 6.4 Abdominal RT OR 1.8, 95%CI 1.1 – 2.9	Eligible cohort 1,881 CCS Strengths: - Large study sample - Long follow-up period - Matched control group - Comprehensive assessment glomerular function Limitations: - only 58% of eligible cohort participated **Risk of bias** A. Selection bias: high risk Reason: the study group consisted of less than 75% of the original cohort

	Age at diagnosis: Median 4.7 years (IQR 1.3-8.1) Age at follow-up: Median 32.0 years (IQR 26.6-37.4) Controls: 500 age- and sex matched controls from Lifelines cohort study		TBI OR 0.8, 95% CI 0.4 – 1.6 Ifosfamide OR 2.9, 95%CI 1.9 – 4.4 HD-cyclo OR 1.0, 95%CI 0.6 – 1.7 Cisplatin OR 1.6, 95%CI 0.9 – 2.6 Carboplatin OR 1.1, 95%CI 0.6 – 2.0 Female sex OR 1.3, 95%CI 0.9 – 1.9 Age at diagnosis OR 1.1, 95%CI 1.06 – 1.2 Follow-up duration 20-29 yr vs 10-19 yr OR 1.0, 95%CI 0.6 – 1.6 ≥30 yr vs 10-19 yr OR 2.7, 95%CI 1.6 – 4.8 Hypertension at time of study visit OR 2.5, 95%CI 1.6 – 3.9 Diabetes OR 0.7, 95%CI 0.3 – 1.8 *Model 2 cumulative doses* Abdominal RT <20 Gy vs none OR 2.5, 95%CI 1.2 – 5.1 20-30 Gy vs none OR 1.0, 95%CI 0.5 – 2.0 >30 Gy vs none OR 2.1, 95%CI 1.1 – 3.8 p-trend 0.44 Ifosfamide (mg/m^2) ≤ 12000 vs none OR 1.2, 95%CI 0.6 – 2.5 12001 – 42000 vs none OR 3.2, 95%CI 1.8 – 5.8 >42000 vs none OR 6.4, 95%CI 3.4 – 12.2 p-trend 0.006 Cisplatin (mg/m^2) ≤300 vs none OR 0.3, 95%CI 0.1 - 0.9	B. Attrition bias: low risk Reason: outcome was assessed for more than 75% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: important prognostic factors were taken adequately into account

			301-500 vs none OR 1.0, 95%CI 0.4 – 2.5 >500 vs none OR 7.2, 95%CI 3.4 - 15.2 p-trend 0.15 Carboplatin (mg/m^2) ≤1500 vs none OR 1.1, 95%CI 0.5 - 2.6 1501-2800 vs none OR 1.1, 95%CI 0.5 – 3.0 >2800 vs none OR 1.3, 95%CI 0.9 – 1.9 p-trend 0.90 *Model mutually exclusive treatment groups* Nephrectomy + RT abdominal vs controls OR 3.1, 95%CI 1.8 – 5.3 Ifosfamide + HD-cyclophosphamide vs controls OR 1.7, 95%CI 0.7 – 4.4 Ifosfamide + cisplatin vs controls OR 1.9, 95%CI 0.8 – 4.5 Ifosfamide + carboplatin vs controls OR 4.0, 95%CI 1.9 – 8.3 Cisplatin + carboplatin vs controls OR 1.0,95%CI 0.1 – 8.5 <u>Albuminuria</u> 152/929 (16.4%) <u>Risk factors albuminuria</u> Nephrectomy OR 1.1, 95%CI 0.6 – 1.9 Abdominal RT OR 1.6, 95%CI 0.96 – 2.8 TBI OR 2.3, 95% CI 1.2 – 4.4 Ifosfamide OR 1.6, 95%CI 1.01 – 2.4 HD-cyclo OR 0.8, 95%CI 0.4 – 1.4	

			Cisplatin OR 1.1, 95%CI 0.6 – 1.9 Carboplatin OR 1.5, 95%CI 0.8 – 2.6 Female sex OR 1.0, 95%CI 0.6 – 1.4 Age at diagnosis OR 1.0, 95%CI 0.9 – 1.03 Follow-up duration 20-29 yr vs 10-19 yr OR 0.8, 95%CI 0.6 – 1.6 ≥30 yr vs 10-19 yr OR 1.3, 95%CI 0.4 – 1.4 Hypertension at time of study visit OR 1.9, 95%CI 1.2 – 3.1 Diabetes OR 1.3, 95%CI 0.6 – 3.1 ACEi-ARB OR 1.2, 95%CI 0.6 – 2.4 *Model 2 cumulative doses* Abdominal RT <20 Gy vs none OR 1.2, 95%CI 0.5 – 2.9 20-30 Gy vs none OR 0.9, 95%CI 0.3 – 2.1 >30 Gy vs none OR 2.6, 95%CI 1.4 – 5.0 p-trend 0.001 Ifosfamide (mg/m^2) ≤ 12000 vs none OR 0.6, 95%CI 0.2 – 1.3 12001 – 42000 vs none OR 1.9, 95%CI 1.01 – 3.6 >42000 vs none OR 3.3, 95%CI 1.7 – 6.2 p-trend 0.11 Cisplatin (mg/m^2) ≤300 vs none OR 1.1, 95%CI 0.4 – 2.6 301-500 vs none OR 0.7, 95%CI 0.3 – 2.0	

			>500 vs none OR 1.5, 95%CI 0.7 – 3.6 p-trend 0.76 Carboplatin (mg/m^2) ≤1500 vs none OR 1.5, 95%CI 0.6 – 3.6 1501-2800 vs none OR 1.5, 95%CI 0.6 – 3.9 >2800 vs none OR 1.4, 95%CI 0.6 – 3.4 p-trend 0.10	

Abbreviations: 95%CI, 95% confidence interval; CCS, childhood cancer survivors; CNS, central nervous system; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; OR, odds ratio; RT, radiotherapy, TBI, total body irradiation; yr, years.

Who needs glomerular dysfunction surveillance?				
Mudi et al. Pediatric cancer survivors demonstrate a high rate of subclinical renal dysfunction. Pediatr Blood Cancer. 2016;63:2026-32.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional cohort study Treatment era: NM Follow-up: Median 2 yr	Type and number of participants: 130 CCS aged 2-18 years who completed treatment. Diagnoses: Leukemias 26%, lymphomas 22%, renal tumours 20%, sarcomas 8%, germ cell tumours 8%, hepatoblastoma 4%, others 12% Age at diagnosis: NM Age at follow-up: 2-18 yr Controls: NA	Ifosfamide: NM, at least 1 Cisplatin: NM, at least 1 Carboplatin: NM, at least 1 Nephrectomy: NM, at least 1 RT renal area: NM, at least 1	Outcome definitions 1. Decreased GFR: GFR < 90 mL/minute/1.73 m² (by modified Schwartz formula) GFR < 90 mL/minute/1.73 m² Prevalence 23/130 (17.7%) Risk factors decreased GFR Ifosfamide OR 5.01, 95% CI 1.46 - 17.17, p < 0.05 Carboplatinum OR 3.25, 95% CI 0.83 - 12.59, p > 0.05 Nephrectomy OR 6.35, 95% CI 1.84 - 21.89, p < 0.05 RT OR 3.31, 95% CI 0.55 - 19.98, p > 0.05 Duration after treatment (years) OR 1.20. 95% CI 1.00 –	Limitations: - Treatment not specified - Age and gender were not take into account in multivariable risk analysis. **Risk of bias** A. Selection bias: low risk Reason: the study group consisted of more than 75% of the original cohort B. Attrition bias: low risk Reason: the outcome was assessed for more than 75% of the study group C. Detection bias: unclear

			1.44, p > 0.05	Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: high risk Reason: Not all important prognostic factors were taken adequately into account

Abbreviations: 95% CI, 95% confidence interval; CCS, childhood cancer survivors; GFR, glomerular filtration rate; NA, not applicable; NM; not mentioned; OR, odds ratio; RT, radiotherapy; yr, year.

Who needs glomerular dysfunction surveillance?				
Mulder et al. Glomerular function time trends in long-term survivors of childhood cancer: a longitudinal study. Cancer Epidemiol Biomarkers Prev. 2013;22:1736-46.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective cohort study Treatment era: 1966-2003 Follow-up: Median 21 yr (range 5.0 – 42.0) after cancer diagnosis until last GFR test	Type and number of participants: 1122 CCS with a survival of ≥ 5 years since diagnosis, aged ≥ 18 years at glomerular function testing, and treated with potentially nephrotoxic therapy. 251 treated without potentially nephrotoxic therapy. Years of assessment 1996-2010 Diagnoses: 1122 treated with potentially nephrotoxic therapy: leukemia 267 (23.8%), lymphoma 259 (23.1%), brain/CNS tumour 77 (6.9%), bone tumour 99 (8.8%), soft tissue sarcoma 125 (11.1%), renal tumour 144 (12.8%), hepatic tumour 10 (0.9%), germ cell tumour 45 (4%), NB 57 (5.1%), retinoblastoma 11 (1%), other 28 (2.5%)	Ifosfamide: 155/1122 (13.8%) Cisplatin: 88/1122 (7.8%) Carboplatin: 64/1122 (5.7%) HD-cyclophosphamide* 134/1122 (11.9%) HD-methotrexate** 253/1122 (22.5%) Nephrectomy: 147/1122 (13.1%), partial 7 (0.6%), complete 140 (12.5%) RT renal area: 116/1122 (10.3%) RT field: abdominal 95 (8.5%), TBI 21 (1.9%) *(≥1 g/m^2/course or a total cumulative dose of ≥ 10 g/m^2) ** (≥1 g/m^2/course)	Outcome definitions 1. Decreased GFR: GFR < 90 mL/minute/1.73 m² (by CKD-EPI formula) GFR < 90 mL/minute/1.73 m² Prevalence NM Risk factors decreased GFR Age at diagnosis, p < 0.0001 Gender effect, p=0.63 Ifosfamide, p < 0.001 Ifosfamide cumulative dose effect p < 0.001 Ifosfamide by time interaction, P= 0.32 Ifosfamide dose by time interaction, p= 0.28 Cisplatin, p < 0.001 Cisplatin cumulative dose effect p < 0.001 Cisplatin by time interaction, p = 0.005	Eligible cohort 1502 CCS. Out of 1122 CCS treated with potentially nephrotoxic treatment and having a renal function test, 920 had repeated observations. Median follow up from first until last glomerular function test 7.3 yr (range 0.8-14.3) Strengths: - Longitudinal analysis - Large study sample - Long follow-up period Limitations: - Only p-values provided for multivariable risk analyses - No information regarding co-medication (e.g., nephrotoxic antibiotics) or predisposition (e.g., WT1 mutations) **Risk of bias**

	Age at diagnosis: 0-18 yr Age at follow-up: 2-18 yr Controls: 251 CCS treated without potentially nephrotoxic therapy		Cisplatin dose by time interaction, $p < 0.001$ Carboplatin $p < 0.05$, Carboplatin cumulative dose effect p=0.28, Carboplatin by time interaction p =0.003, Carboplatin dose by time interaction p=0.26 HD-cyclophosphamide (≥ 1 g/m²/ course or a total cumulative dose of ≥ 10 g/m²), p = 0.09 HD-cyclophosphamide by time interaction, p = 0.73 HD-MTX (≥ 1 g/m²/course), P=0.91 RT, p= 0.13 Nephrectomy, $p < 0.001$ Nephrectomy by time interaction, p=0.002 Nephrectomy age at diagnosis, p = 0.29	A. Selection bias: low risk Reason: the study group consisted of more than 75% of the original cohort B. Attrition bias: low risk Reason: the outcome was assessed for more than 75% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: All important prognostic factors were taken adequately into account

Footnote 1: Possible overlap in patients with Dekkers 2013 and Knijnenburg 2012.

Abbreviations: CCS, childhood cancer survivors; CKD-EPI, chronic kidney disease epidemiology collaboration; CNS, central nervous system; GFR, glomerular filtration rate; HD, high-dose; MTX, Methotrexate; NA, not applicable; NB, neuroblastoma; NM; not mentioned; RT, radiotherapy; TBI, total body irradiation; yr, year.

Who needs glomerular dysfunction surveillance?				
Oberlin et al. Long-term evaluation of ifosfamide-related nephrotoxicity in children. J Clin Oncol 2009;27:5350-5355.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: cross-sectional multicenter cohort study Treatment era: 1984 – 2000 Follow-up: minimal 5 years after completion of therapy. Median 10.3 years (range 5 – 20.7) after end of therapy	Type and number of participants: 183 pediatric sarcomas survivors treated with ifosfamide Diagnoses: Rhabdomyosarcoma 77 (42.1%) Ewing sarcoma 39 (21.3%) Soft tissue sarcoma 39 (21.3%) Osteosarcoma 28 (15.3%)	Ifosfamide: 183/183 (100%), median cumulative dose 54 g/m² Cisplatin: 0/183 (excluded) Carboplatin: 0/183 (excluded) Methotrexate: Some, exact number NM	Outcome definitions Reduced GFR (< 90 ml/min/1.73 m²) measured by Schwartz formula for patients < 18 years, and by Cockroft-Gaults formula for older patients. GFR < 90/ml/min/1.73m² 39/181 (21.5%)	Strengths: - clear description of study cohort - relative long follow up period Limitations: - multicenter; different labs doing tests **Risk of bias**

	Age at diagnosis: Median 9.3 years (range 0.4 – 27.2) Age at follow-up: median 18.3 years (range 7.1 – 44.2) Controls: NA	Nephrectomy: 0/183 (excluded) RT renal area: 1/183 (0.01%), small posterior area of the right kidney HSCT: 0/183 (excluded)	Grade 1, 60-89: 38 (21%) Grade 2, 40-59: 1 (0.5%) Risk factors decreased GFR Age at treatment (years) RR 1.08, 95% CI 1.00 – 1.17, p=0.05 Ifosfamide dose (g/m^2) RR 1.02, 95% CI 0.99-10.04, p=0.3 Interval from therapy to investigations (years) RR 1.09, 95% CI 1.01 – 1.19, p = 0.03 Not included in model (based on univariate analysis): Methotrexate RR 0.76, 95% CI 0.27 – 2.15, p =0.6	A. Selection bias: low risk Reason: study group consisted of 72% of the original cohort, but was a random sample B. Attrition bias: low risk Reason: outcome was assessed for 85% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: important prognostic factors were adequately taken into account

Abbreviations: 95% CI, 95% confidence interval; GFR, glomerular filtration rate; HSCT, hematological stem cell transplantation; NA, not applicable; NM, not mentioned; RR, relative risk; RT, radiotherapy

Who needs glomerular dysfunction surveillance?				
Park et al. Acute kidney injury in pediatric cancer patients. The Journal of Pediatrics. 2019;208:243-50.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: retrospective cohort study Treatment era: 2004 – 2013 Follow-up: Median 5 yrs (IQR 2.26-6.16). 1093 CCS (58.5%) were followed up for more than 5 years	Type and number of participants: 1868 CCS for primary assessment (AKI) 1096 CCS for secondary assessment (renal function) Diagnoses: ALL 314 (16.8%) AML 147 (7.9%) Lymphoma 173 (9.3%) NBL 114 (6.1%) WT 47 (2.5%) Brain tumor 507 (27.2%)	Chemotherapy: Ifosfamide 205/1096 (18.7%) Cyclophosphamide 687/1096 (62.7%) Cisplatin 310/1096 (28.2%) Carboplatin 335/1096 (30.6%) Methotrexate 425/1096 (38.8%) Nephrectomy: 46/1096 (4.2%) RT renal area: NM	Outcome definitions eGFR <18 yrs by bedside Schwartz formula, ≥18 yrs CKD-EPI formula. Development of AKI - stage 1 (rise Cr by 0,3 mg/dL in 2 days or by 1.5 times) - stage 2 (rise Cr by 2 times) - stage 3 (rise Cr above 4 mg/dL or by 3 times) Development of renal impairment = eGFR < 90 ml/min/1.73m^2	Strengths: - large sample size Limitations: - qualitative proteinuria measurement - retrospective study design Timing Cr levels measured at least twice in first year after diagnosis. Serum Cr either 1 year after completion

	Ewing sarcoma 38 (2.0%) Extracranial germ cell tumor 70 (3.7%) Hepatoblastoma 53 (3.8%) Nonrhabdomyosarcoma soft tissue sarcoma 59 (3.2%) Osteosarcoma 102 (5.5%) Retinoblastoma 109 (5.8%) Rhabdomyosarcoma 43 (2.3%) Other 92 (4.9%) Age at diagnosis: Median 7.9 yrs (IQR 2.5-12.7) Age at follow-up: NM Controls: NA		Prevalence 248/1096 (22.6%) Development of proteinuria = albumin dipstick >1+ Results Risk factors renal impairment (eGFR<90 ml/min/1.73m^2) Female OR 0.65 (95% CI 0.52-0.81) Initial eGFR 73m^2 at diagnosis < 60 ml/min/1.73m^2 OR 1.80 (95% CI 1.08-2.95) Cancer group: ALL OR 0.70 (95% CI 0.43-1.14) AML OR 0.52 (95% CI 0.25-1.03) Lymphoma OR 0.63 (95% CI 0.35-1.10) NBL OR 0.61 (95% CI 0.28-1.24) WT OR 0.43 (95% CI 0.10-1.80) Brain tumor OR 1.0 (ref) Cyclophosphamide OR 0.69 (95% CI 0.47-1.02) AKI episodes: 1 time OR 1.04 (95% CI 0.72-1.50) 2-3 times OR 1.19 (95% CI 0.77-1.82) ≥ 4 times OR 2.12 (95% CI 1.09-4.03) Renal replacement therapy OR 1.56 (95%CI 0.80-2.96) Nephrectomy OR 3.68 (95% CI 1.05-13.72) Cancer relapse OR 1.29 (95%CI 0.78-2.06) Not significant in univariate analyses (p value >0.25): Carboplatin, Cisplatin, Ifosfamide, Methotrexate, HSCT, AKI stage,	of therapy or 5 yrs after diagnosis was the final measurement. **Risk of bias** A. Selection bias: unclear Reason: study group consisted of 86% of original cohort for primary assessment and 50.5% for secondary assessment and unclear if it was a random sample. B. Attrition bias: high risk Reason: outcome was assessed for 58.7% of the study group C. Detection bias: unclear Reason: unclear if assessors were blinded D. Confounding: high risk Reason: Not all important prognostic factors were taken into account

			time point at first onset of AKI, TLS	

Abbreviations: 95% CI, 95% confidence interval; AKI, acute kidney injury; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CCS, childhood cancer survivors; CKD-EPI, chronic kidney disease epidemiology collaboration; Cr, creatinine; eGFR, estimated glomerular filtration rate; HSCT, hematological stem cell transplantation; IQR, interquartile range; NA, not applicable; NBL, neuroblastoma; NM, not mentioned; OR, odds ratio; RT, radiotherapy; TLS, tumor lysis syndrome; WT, Wilms tumor; yrs, years.

Who needs glomerular dysfunction surveillance?				
Poppe et al. Kidney disease in Childhood Cancer Survivors Treated with Radiation Therapy: A Comprehensive PENTEC Genitourinary Review. Int J Radiation Oncol Biol Phys. 2023; 119:560-574.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Systematic review, meta-analysis Treatment era: Wilms tumor studies occured between 1968 – 2011 TBI studies occurred between 1969 – 2004 Follow-up: All CCS finished treatment with radiotherapy Wilms tumor studies mean follow-up 8 – 15 years TBI studies mean follow-up 4 months to 16 years	13 studies included (4 studies on WAI for Wilms tumor, 8 on TBI for HSCT and 1 for partial renal RT exposure) Characteristics of 13 studies included: Type and number of participants: 1191 pediatric patients; WAI 86, TBI 666, and 439 partial kidney Diagnoses (n studies): Only leukemia (n=6) Only Wilms tumor (n=4) Only neuroblastoma (n= 1) Various tumours (n= 1) Age at diagnosis:	WAI 4/13 studies TBI 8/13 studies Partial renal RT data 1/13 studies	Outcome definitions Risk of kidney dysfunction by RT dose and grade of toxicity according to national kidney foundation (NKF) grades. NKF Grade 1= GFR ≥ 90 Grade 2= GFR 60 -89 Grade 3= GFR 30 -59 Grade 4= GFR 15 – 29 Grade 5= GR <15 or dialysis Toxicity according to NKF Total dose if given in 2 Gy per fx (95% CI) predicted to be associated with 5% rates of various levels of toxicity NKF grade ≥1 = 8.5 Gy (7.1 – 10.2)	Strengths: - Comprehensive search strategy - Meta-analysis after strict selection criteria Limitations: - Heterogeneity of included studies - Inconsistencies in dosimetric reporting of included studies - insufficient data on dosimetry in combination with chemotherapy **Risk of bias** A. Selection bias: Low risk 9/13 studies (69.2%) High risk 0/13 studies (0%) Unclear 4/13 studies (30.8%)

	Range 1 mo – 18 years, median 2 – 11 years <u>Age at follow-up:</u> NM <u>Controls:</u> NA		NKF grade ≥2= 10.2 Gy (9.3 – 11.2) NKF grade ≥3= 14.5 (12.2 – 19.0) Conventional Wilms WAI of 10.5 Gy in 6 fx had risks of ≥ grade 2 toxicity 4% and ≥ grade 3 toxicity 1%. Fractionated TBI of 12 Gy had risks of ≥ grade 2 toxicity 8% and ≥ grade 3 toxicity <3%. Data did not support whole kidney modeling with chemotherapy. <u>Partial kidney modeling combination RT with chemotherapy:</u> 5 or 10 Gy to 100% kidney gave a <5% risk of grades 3 to 5 toxicity with 1500mg/m2 carboplatin or no chemo. With 480mg/m2 cisplatin a 3% risk of ≥grade 3 toxicity occurred without RT and a 5% risk when 26% kidney received ≥10Gy. With 63g/m2 of ifosfamide, a 5% risk of ≥grade 3 toxicity occurred with no RT, and a 10% toxicity risk occurred when 42% kidney received ≥10Gy.	<u>B. Attrition bias:</u> Low risk 9/13 studies (69.2%) High risk 1/13 studies (7.7%) Unclear 3/ 13 studies (23.1%) <u>C. Detection bias:</u> Not reported <u>D. Confounding:</u> Low risk 4/13 studies (30.8%) High risk 8/13 studies (61.5%) Unclear 1/13 studies (7.7 %)

Footnote 1: For the risk of bias, results of the review are shown. Criteria for risk of bias assessment may slightly differ from the IGHG criteria.
Footnote 2: More detailed results regarding risk factors are shown in the evidence table of the included studies for this guideline.
Abbreviations: CCS, childhood cancer survivors; HSCT, hematopoietic stem cell transplantation; NA, not applicable; NKF, national kidney foundation; NM, not mentioned; RT, radiotherapy; TBI, total body irradiation; WAI, whole abdomen irradiation; WT, Wilms tumor.

Who needs glomerular dysfunction surveillance?				
Ramirez et al. Yield of urinalysis screening in pediatric cancer survivors. Pediatr Blood Cancer. 2016;63:893-900.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Treatment era: NM Follow-up: Abnormal urinalysis group: mean 7.2 yr (range 2.9-13.3) after cancer diagnosis Normal urinalysis group: mean 7.6 yr (range 2.3-21.5) after cancer diagnosis	Type and number of participants: 773 CCS with a survival of ≥ 2 years after cancer treatment. Eligible cohort 822. Diagnoses: Leukemia/lymphoma 460 (59.5%), CNS tumour 48 (6.2%), germ cell 13 (1.7%), NB 62 (8.0%), other solid tumours 21 (2.7%), renal tumour 83 (10.7%), sarcomas 86 (11.1%) Age at diagnosis: Abnormal urinalysis mean 6.2 yr (range < 1.0-15.8), normal urinalysis mean 5.7 yr (range < 1.0- 7.7) Age at follow-up: Abnormal urinalysis mean 13.3 yr (range 6.0-20.6), normal urinalysis mean 13.3 yr (range 2.8-21.8) Controls: NA	Ifosfamide: 95/773 (12.3%) Cisplatin: 108/773 (14.0%) Carboplatin: 93/773 (12.0%) Cyclophosphamide 546/773 (70.6%) MTX 409/773 (52.9%) Nephrectomy: 87/773 (11.3%) RT renal area: 222/773 (28.7%) RT field, renal 83 (10.7%) TBI 53 (6.9%), bladder 86 (11.1%)	Outcome definitions 1. Abnormal urinalysis ≥ 1+ protein and/or presence of glucose and/or ≥ 5 red blood cells per high power field via urine dipstick or automated analysis Abnormal urinalysis 37/773 (4.8%) Risk factors abnormal urinalysis Ifosfamide <30 g/m² vs. no ifosfamide OR 0.5, 95%CI 0.1 - 4.1, p=0.56 Ifosfamide ≥30 g/m² vs. no ifosfamide OR 6.8, 95% CI 2.9 – 16.0, p<0.01 TBI OR 3.0, 95% CI 1.0 - 8.4, P= 0.04 Age 10-14 years at diagnosis OR 0.7, 95% CI 0.3 - 1.4 p=0.26	Strengths: - Large sample size Limitations: - Wide definition of abnormal urinalysis, not specific proteinuria. Measured by dipstick - Retrospective cohort study **Risk of bias** A. Selection bias: low risk Reason: the study group consisted of more than 75% of the original cohort B. Attrition bias: low risk Reason: the outcome was assessed for more than 75% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: All important prognostic factors were taken adequately into account

Abbreviations: 95% CI, 95% confidence interval; CCS, childhood cancer survivors; CNS, central nervous system; HD, high-dose; MTX, Methotrexate; NA, not applicable; NM; not mentioned; OR, odds ratio; RT, radiotherapy; TBI, total body irradiation; yr, year.

Who needs glomerular dysfunction surveillance?

Skinner et al. Persistent nephrotoxicity during 10-year follow-up after cisplatin or carboplatin treatment in childhood: relevance of age and dose as risk factors. European Journal of Cancer. 2009;45:3213-3219.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: prospective single-center longitudinal cohort study Treatment era: 1981- 1996 Follow-up: at least 10 years, the 1 and 10 year studies at median 1.1 years (range 0.7-2.3) and 10.3 years (range 9.0-12.3)	Type and number of participants: 63 CCS aged 18 years at treatment, treated with platinum and who survived at least 10 years after completion of therapy Diagnoses: *Cisplatin alone (n=27):* Osteosarcoma 12 (44.4%) Germ cell tumor 4 (14.8%) Brain tumor 3 (11.1%) Liver tumor 3 (11.1%) Epithelial carcinoma 1 (3.7%) Ewing's sarcoma 1 (3.7%) Nasopharyngeal carcinoma 1 (3.7%) Neuroblastoma 1 (3.7%) Salivary gland carcinoma 1 (3.7%) *Carboplatin alone (n=24):* Germ cell tumor 9 (37.5%) Medulloblastoma 5 (20.8%) Other brain tumor 5 (20.8%) Neuroblastoma 3 (12.5%) CCSK 1 (4.2%) Retinoblastoma 1 (4.2%) *Cisplatin and carboplatin (n=12):* Neuroblastoma 9 (75%) Brain tumor 3 (25%) Age at diagnosis: *Cisplatin alone:* Median 7.7 years (range 0.6-17.8) *Carboplatin alone:* Median 4.4 years (range 0.4-15.8)	Ifosfamide: 0/63 (0%) Cisplatin alone: 27/63 (42.9%), total median dose 500 mg/m^2 (range 300-960) Carboplatin alone: 24/63 (38.1%), total median dose 2400 mg/m^2 (range 560-8800) Cisplatin and carboplatin: 12/63 (19.0%), total median dose cisplatin 473 mg/m^2 (range 240-739), total median dose carboplatin 1500 mg/m^2 (range 750-4200) HD-melphalan 9/63 (14.3%) MTX 8/63 (12.7%) (intermediate 1 g/m^2 of high-dose 8 g/m^2) Nephrectomy: NM RT renal area: 3/63 (4.8%) and 5/63 received a small amount of scatter. Other Actinomycin D, bleomycin, cyclophosphamide, doxorubicin, etoposide, 5-fluorouracil, teniposide, vincristine. Supportive care: aminoglycosides, amphotericin.	Outcome definitions 1. Decreased GFR <90 ml/min/1.73m^2, measured by ^{51}Cr-EDTA plasma clearance Results GFR % normal results (95%CI) *Cisplatin alone* 10 years: 60 (39-70), median 96 (29-142) *Carboplatin alone* 10 years: 79 (58-93), median 110 (66-171) *Cisplatin and carboplatin* 10 years: 55 (22-83), median 92 (66-135) Risk factors After cisplatin, older age at treatment was correlated with lower GFR at 10 years ($p = 0.005$) After carboplatin, older age was associated with lower GFR at all times ($p < 0.03$)	Strengths: - long-term follow-up - clear description of study cohort Limitations: - due to small numbers in subgroups multivariable risk analyses not possible Timing Evaluation at 1 month (end), 1 year and 10 years after end of therapy **Risk of bias** A. Selection bias: low risk Reason: study group consisted of 93% of original cohort B. Attrition bias: low risk Reason: outcomes were assessed for >75% of study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: high risk Reason: not all important risk factors were adequately taken into account

	Cisplatin and carboplatin: Median 1.9 years (range 0.1-6.2) Age at follow-up: NM Controls: NA			

Abbreviations: ^{51}Cr-EDTA, ^{51}Cr-labelled ethylenediaminetetraacetic acid; 95%CI, 95% confidence interval; CCS, childhood cancer survivors; FU, follow-up; GFR, glomerular filtration rate; HD, high-dose; MTX, methotrexate; NA, not applicable; NM, not mentioned; RT, radiotherapy.

Who needs glomerular dysfunction surveillance?				
Sullivan et al. Late effects of chemotherapeutic agents on renal function in childhood cancer survivors. Ir J Med Sci. 2017;186:49-55.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Systematic review Treatment era: Not reported, articles published between 1990 - 2015 Follow-up: At least median of 6 months after and of therapy. Range 6-120 months.	15 studies included Type and number of participants: Not stated for every article included Diagnoses: Miscellaneous tumors, no details stated Age at diagnosis: Not stated Age at follow-up: Not stated Controls: Not stated	Chemotherapy: Details not stated. 6 studies included patients treated with Ifosfamide 6 studies included patients treated with carboplatin and/or cisplatin 4 studies included patients treated with methotrexate. Nephrectomy: Not stated RT renal area: Not stated	Outcome definitions Nephrotoxicity (proteinuria, decreased GFR, hypophosphatemia, hypomagnesemia, hypertension) as defined by authors Ifosfamide induced nephrotoxicity Prevalence 1-50% in 6 studies Risk factors ifosfamide nephrotoxicity (4 studies) Age < 3 years at time of treatment (2 studies) Age <4 year at time of diagnosis (1 study) Cumulative ifosfamide dose >45 g/m^2, >119 g/m^2, >80 g/m^2, high cumulative dose (1 study each) Previous or concurrent cisplatin (1 study) Previous unilateral nephrectomy 1 study)	Strengths: clear search strategy Limitations: - No risk of bias assessment performed for included articles - No detailed information regarding diagnoses / treatment regimens of included articles - No meta-analysis - Only included studies reported in English **Risk of bias** A. Selection bias: Unclear Reason: Insufficient information provided to determine if the study group of included articles was representative B. Attrition bias: Unclear Reason: Insufficient information provided to determine if

			Pre-existing renal impairment or tumor invasion (1 study) <u>Carboplatin and cisplatin induced nephrotoxicity</u> Prevalence hypomagnesemia 7-29% in 6 studies Risk of hypomagnesemia is higher with combined ifosfamide and cisplatin exposure (25% vs. 4% with ifosfamide alone) <u>Methotrexate induced nephrotoxicity</u> Prevalence mentioned in 1 study: 1,8%, and completely reversible in 4 studies	outcome was assessed for more than 75% of the study group of included articles <u>C. Detection bias:</u> Unclear Reason: Unclear if outcome assessors were blinded for important determinants related to the outcome of included articles <u>D. Confounding:</u> Unclear Reason: No information provided whether risk analyses were adjusted for important confounding factors

Footnote 1: More detailed results regarding risk factors are shown in the evidence table of the included studies for this guideline
Abbreviations: GFR, glomerular filtration rate.

Who needs glomerular dysfunction surveillance?				
Van Why et al. Renal insufficiency after bone marrow transplantation in children. Bone Marrow Transplant. 1991;7:383-8.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design:</u> Retrospective cohort study <u>Treatment era:</u> 1975-1988 <u>Follow-up:</u> Mean 17 mo (range 2 mo-11 yr)	<u>Type and number of participants:</u> 64 CCS that survived 60 days post-BMT. <u>Diagnoses</u>: Hematological malignancies 36 (56%), solid tumours 64 (8%), immunodeficiency/other non-malignancies 64 (36%) <u>Age at diagnosis:</u> Mean age 7.6 years (range 1 month-18 years)	<u>Ifosfamide:</u> NM <u>Cisplatin:</u> NM <u>Carboplatin:</u> NM <u>Nephrectomy:</u> NM <u>RT renal area:</u> 39/64 (61%) RT field: TBI 39 (61%)	<u>Outcome definitions</u> 1. Decreased GFR: GFR < 50 mL/minute/1.73 m² (Schwartz formula) <u>GFR < 50 mL/minute/1.73 m²</u> 18/64 (28%) after 60 days, 9/64 ((14%) persistent 3 mo – 3 yr <u>Risk factors decreased GFR</u> Cyclosporin A use beyond day 60, $p < 0.05$ Amphotericin B use, $p < 0.05$ Conditioning with TBI, $p < 0.05$	<u>Limitations:</u> - Treatment not specified - No separate data / results for CCS treated with nephrotoxic therapy - Confounders taken into account for multivariable risk analyses NM - Only p-values provided for multivariable risk analyses - Retrospective cohort study **Risk of bias** <u>A. Selection bias:</u> low risk

	Age at follow-up: NM Controls: NA		Conditioning with chemotherapy, p > 0.05 Renal insufficiency in first 60 days post-BMT, p > 0.05	Reason: the study group consisted of more than 75% of the original cohort B. Attrition bias: low risk Reason: the outcome was assessed for more than 75% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: high risk Reason: Not all important prognostic factors were taken adequately into account

Abbreviations: BMT; bone marrow transplantation; CCS, childhood cancer survivors; GFR, glomerular filtration rate; mo, months; NA, not applicable; NM; not mentioned; RT, radiotherapy; TBI, total body irradiation; yr, year.

Who needs glomerular dysfunction surveillance?				
Wu et al. Development and validation of a prediction model for kidney failure in long-term survivors of childhood cancer. J Clin Oncol. 2023;41:2258-2268.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Multi-institutional retrospective cohort study with prospective follow-up Treatment era: 1970-1999 Follow-up: Median 22.2 years (IQR 16.4-29.7)	Type and number of participants: 25,483 CCS Diagnoses: Leukemia 7,832 (40.2%) Lymphoma 5,187 (176%) CNS tumor 4,482 (15.2%) Kidney tumor 2,250 (7.6%) Neuroblastoma 1,901 (6.4%) Sarcoma or bone tumor 3,831 (13.0%) Age at diagnosis:	Ifosfamide: 1,163/25,483 (4.6%) Platinum: 2,703/25,483 (9.9%) HD-cyclophosphamide: NM Methotrexate: NM Nephrectomy: 1952/25,483 (7.2%) RT renal area: 5,306/25,483 (21.0%) Other cancer treatment: Anthracycline: 11,240/25,483 (53.0%)	Outcome definitions 1. Late kidney failure (self-reported: grade 4 (life-threatening; requiring dialysis or kidney transplantation) or grade 5 (fatal; death due to kidney disease)) Results Late kidney failure CCS 204/25,483 (0.8%).	Strengths: - large study sample - long follow-up period - taking into account controls Limitations - self reported outcome **Risk of bias** A. Selection bias: unclear Reason: unclear if study group consists of more than 75% original cohort

	0-9 yr 15,867 (66.4%) 10+ yr 9,616 (33.6%) <u>Age at follow-up:</u> Follow-up until development primary outcome, death, or most recent questionnaire completion (censoring). Total follow-up until age 40 years. <u>Controls:</u> 5,045 siblings Median follow-up 27.0 years (IQR 19.8-34.7)		Cumulative incidence by age 40 years CCS 1.0%, 95% CI 0.8-11 Cumulative incidence by age 40 years siblings 0.2%, 95% CI 0.1-0.5 <u>Risk factors late kidney failure</u> Black non-hispanic vs all others OR 1.7, 95% CI 0.9-3.3 Nephrectomy (yes vs no) RR 2.9, 95% CI 1.7-5.0 Ifosfamide (yes vs no) RR 2.2, 95% CI 1.2-4.1 Platinum (yes vs no) RR 1.7, 95% CI 1.0-2.8 Anthracycline (yes vs no) RR 1.7 95% CI 1.2-2.4 Abdominal radiation (yes vs no) RR 1.5, 95% CI 1.0-2.3 Genitourinary anomalies (yes vs no) RR 2.7, 95% CI 1.1-6.6 Hypertension within 5 years of diagnosis (yes vs no) RR 8.1, 95% CI 4.3-15.6 *Dose-specific model* *Ifosfamide dose (g/m^2)* 0.1-59 vs none RR 1.7, 95% CI 1.0-3.5 ≥60 vs none RR 3.4, 95% CI 1.2-9.5 *Mean kidney radiation dose (Gy)* 0.1-11.9 vs none RR 1.1, 95% CI 0.7-1.5 ≥12 vs none RR 3.0, 95% CI 1.7-5.3	<u>B. Attrition bias:</u> low risk Reason: outcome was assessed in more than 75% of study group <u>C. Detection bias:</u> unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome <u>D. Confounding:</u> low risk Reason: important prognostic factors were taken adequately into account

Abbreviations: 95% CI, 95% confidence interval; CCS, childhood cancer survivors; HD, high-dose; CNS, central nervous system; IQR, interquartile range; NM, not mentioned; ref, reference; RR, risk ratio; RT, radiotherapy; vs, versus; yr, year.

Who needs glomerular dysfunction surveillance?				
Yetgin et al. Evaluation of Kidney Damage in Patients With Acute Lymphoblastic Leukemia in Long-Term Follow-Up: Value of Renal Scan. Am J Hem. 2004;77:132-139.				
Study design **Treatment era**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Years of follow-up				
Study design: Single institution cohort study Treatment era: March 1991-March 1998 Follow-up: median 35 months after therapy (range 18-96 months); 48-132 months after diagnosis	Type and number of participants: 116 CCS (334 were eligible); 74 males, 42 females Diagnoses: acute lymphoblastic leukemia (100%) Age at diagnosis: mean 6.5 ± 4.2 years (range 6 months-16 years) Age at follow-up: Not reported Controls: 29 patients for DMSA scan only; characteristics not reported	Chemotherapy: St. Jude Total XI—74/116 (63.8%) St. Jude Total XIII—42/116 (36.2%) LR—10/42 (23.8%) HR—32/42 (76.2%) XI and XIII HR includes HD-MTX, cyclophosphamide XIII LR includes HD-MTX CNS therapy includes triple intrathecal therapy with MTX, prednisolone and cytarabine. Nephrectomy: 0 RT renal area: 0 Received nephrotoxic antimicrobials—101/116 (87.1%) Amikacin---100/116 (86.2%) Amphotericin B—60/116 (51.7%) Received G-CSF—70/116 (60.3%)	Outcome definitions 1. Reduced DMSA uptake DMSA uptake < 16 2. Reduced GFR GFR < 85 mL/min/1.73m^2 (by Schwartz formula) Abnormal DMSA scan Abnormal DMSA—36/84 (42.9%) Abnormal MAG—9/27 (33.3%) Risk factors abnormal DMSA Patients with Hgb <10 g/dL → 3.23x increased risk of abnormal renal scan (p=0.05; 95% CI 1.00-10.48) Reduced GFR 22/116 (19.0%) Risk factors reduced GFR: Age <2 yr at dx → 5.02x increased risk of abnormal GFR (p=0.006; 95% CI 1.58-15.89) Use of nephrotoxic antimicrobials not associated with adverse renal outcomes (not significant in univariate analysis and therefore not included in multivariable model)	Strengths: - Treatment was relatively homogenous. - Data appears to be prospective. - Relatively large sample size. Limitations: - 50% response rate to survey. - Median duration of follow-up was not very long. **Risk of bias** A. Selection bias: high risk Reason: only 50% response rate of CCS B. Attrition bias: low risk for all outcomes except renal scans Reason: <75% of group was assess for renal scans C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: multiple possible confounders were included in regression

Abbreviations: 95% CI, 95% confidence interval; CCS, childhood cancer survivors; DMSA, dimercaptosuccinic acid; GFR, glomerular filtration rate; (HD-)MTX, (high-dose) methotrexate; HR, high risk; LR, low risk; yr, year.

Who needs tubular dysfunction surveillance?

Who needs tubular dysfunction surveillance?

Dekkers et al. Long-Term Nephrotoxicity in Adult Survivors of Childhood Cancer. Clin J Am Soc Nephrol. 2013;8:922-9.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional cohort study Treatment era: 1964-2005 Follow-up: Median 18.3 yr (range 5.0–58.2)	Type and number of participants: 763 CCS with a survival of ≥ 5 years since diagnosis, and aged ≥ 18 years at study entry. Eligible cohort 885 CCS. Diagnoses: ALL/T-NHL 216 (28.3%), AML 26 (3.4%), B-NHL 68 (8.9%), HL 80 (10.5%), bone tumour 35 (4.6%), renal tumour 85 (11.1%), NB 50 (6.6%), LCH 14 (1.8%), germ cell tumour 18 (2.4%), malignant mesenchymal tumour 67 (8.8%), brain tumour 76 (9.9%), other 28 (3.7%) Age at diagnosis: Median 7.3 yr (range 0.0-18.0) Age at follow-up: Median 26.9 yr (17.8-65.8) Controls: NA	Ifosfamide: 75/763 (10%) Cisplatin: 51/763 (7%) Carboplatin: 16/763 (2%) Cyclophosphamide: 305/763 (39.9%) MTX: 319/763 (41.8%), details: intrathecal 277 (29.8%), IV 236 (30.9%), oral 250 (32.8%) Unilateral nephrectomy: 85/763 (11%) RT renal area: 47/763 (6.2%), RT field: abdominal 47 (6.2%), TBI 26 (3.4%)	Outcome definitions 1. U-β2MCR: ≥ 0.04 mg/mmol Cr U-β2MCR 130/496 (26.2%) Risk factors U-β2MCR Hypertension at time of study OR 2.05, 95% CI 1.17 - 3.61, p < 0.05 Cisplatin < 450 mg/m² OR 0.58, 95% CI 0.15 – 2.26, p > 0.05 Cisplatin > 450 mg/m² OR 0.52, 95% CI 0.08 – 3.29, p > 0.05 Ifosfamide < 16000 mg/m² OR 1.34, 95% CI 0.48 – 3.76, p > 0.05 Ifosfamide >16000 mg/m² OR 6.19, 95% CI 2.45 – 15.67, p < 0.05 Carboplatin OR 2.93, 95% CI 0.68 – 12.64, p > 0.05 Cyclophosphamide < 3500 mg/m² OR 1.09, 95% CI 0.56 – 2.15, p > 0.05 Cyclophosphamide > 3500 mg/m² OR 1.61, 95% CI 0.81 – 3.20, p > 0.05 MTX OR 1.07, 95% CI 0.59 – 1.92, p > 0.05 TBI OR 0.48, 95% CI 0.12 – 1.96, p > 0.05 Nephrectomy, no abdominal RT OR 1.69, 95% CI 0.67 – 4.31, p > 0.05 Abdominal RT, no nephrectomy OR 1.12, 95% CI 0.23 – 5.55, p > 0.05	Strengths: - Large study sample **Risk of bias** A. Selection bias: low risk Reason: the study group consisted of more than 75% of the original cohort B. Attrition bias: high risk Reason: the outcome was assessed for less than 75% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: important prognostic factors were taken adequately into account

			Nephrectomy and abdominal RT OR 1.31, 95% CI 0.43 – 3.99, p > 0.05	

Footnote 1: Possible overlap in patients with Knijnenburg 2012 and Mulder 2013.

Abbreviations: 95% CI, 95% confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; B-NHL, B-cell non Hodgkin lymphoma; CCS, childhood cancer survivors; Cr, creatinine; HL, Hodgkin lymphoma; IV, intravenous; LCH, Langerhans cell histiocytosis; MTX, Methotrexate; NA, not applicable; OR, odds ratio; RT, radiotherapy; TBI, total body irradiation; T-NHL; T-cell non Hodgkin lymphoma; U- β2MCR, Urinary β2-microglobulin creatinine ratio; yr, year.

Who needs tubular dysfunction surveillance?				
Jones et al. Renal Late Effects in Children Treated for Cancer in Childhood: A Report from the Children's Oncology Group. Pediatr Blood Cancer. 2008; 51: 724-31.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: systematic review Treatment era: 1970-2004 Follow-up: Variable by manuscript reviewed, not precisely stated	42 articles included Type and number of participants: Unknown Diagnoses: 42 articles on the topic of late effects of childhood cancer, reviewed as part of the COG LTFU Guidelines (kidney) Age at diagnosis: Variable (ranges from <3 to >10 years) Age at follow-up: Variable (not all follow-up intervals given) Controls: In one paper, children undergoing nephrectomy for WT were compared with children undergoing nephrectomy for non-malignant disease (hydronephrosis). In another	Ifosfamide: 14/42 studies Cisplatin/carboplatin: 8/42 studies Methotrexate: 2/42 studies RT renal area: 5/42 studies Nephrectomy: 12/42 studies	Outcome definitions Tubular dysfunction/tubulopathy: not otherwise defined Fanconi syndrome (operationally defined as proximal tubule dysfunction) Magnesium wasting (not defined) Results Ifosfamide: 20% had persistent tubulopathy, 5% have clinically significant Fanconi syndrome (1 study) 25% of ifosfamide-treated children have subclinical magnesium wasting (1 study) Cisplatin: almost every child develops acute magnesium	Strengths: - Comprehensive search Limitations: - Lack of uniform inclusion criteria (age, therapy, cancer type), assessment and follow up duration across studies - Outcome definitions not specified - No risk of bias assessment **Risk of bias** A. Selection bias: unclear Reason: Insufficient information provided to determine if the study group of included articles was representative B. Attrition bias: unclear Reason: Insufficient information provided to determine if outcome was assessed for more

	paper, children undergoing nephrectomy for WT +/- RT. Otherwise, no controls.		wasting. This persists in one- to two-thirds (2 studies)	than 75% of the study group of included articles C. Detection bias: unclear Reason: Blinding not mentioned D. Confounding: unclear Reason: No information provided whether risk analyses were adjusted for important confounding factors

Footnote 1: More detailed results regarding risk factors are shown in the evidence table of the included studies for this guideline.
Abbreviations: COG LTFU Guidelines, Childhood Oncology Group Long Term Follow-Up Guidelines; RT, radiotherapy; WT, Wilms tumor.

Who needs tubular dysfunction surveillance?				
Knijnenburg et al. Renal function and elevated blood pressure in long-term childhood cancer survivors. Clin J Am Soc nephrol. 2012;7:1416-27.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional cohort study Treatment era: 1966-2003 Follow-up: Median 12.1 yr (range 7.8-17.5)	Type and number of participants: Described study group 1442 CCS ≥ 5 years after diagnosis, of whom 1313 with a renal function test. Out of described cohort 896 treated with nephrotoxic therapy, 417 without nephrotoxic therapy. Diagnoses: Bone tumours 108 (7.5%), hepatic tumours 20 (1.4%), germ cell tumours 52 (3.6%), renal tumours 207(14.4%), soft tissue sarcoma 153 (10.6%), NB 96 (6.7%), retinoblastoma 13 (0.9%), CNS tumour 85 (5.9%), leukemia 376 (26.1%), lymphoma 302 (20.9%), other 30 (2.1%). Age at diagnosis: Median 5.9 yr (range 2.9-10.9)	Ifosfamide: 202/1442 (14.0%) Cisplatin: 112/1442 (7.8%) Carboplatin: 111/1442 (7.7%) HD cyclophosphamide: 124/1442 (8.6%) HD MTX: 368/1442 (25.5%) Nephrectomy: 212/1442 (14.7%) RT renal area: 125/1442 (8.7%), RT field: abdominal 103 (7.1%), TBI 22 (1.5%)	Outcome definitions 1. Hypophosphatemia: Serum phosphate adults, <0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement 2. Hypomagnesemia: Serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement Hypophosphatemia 17/572 (3.0%) Risk factors hypophosphatemia Cumulative ifosfamide dose (per 10 g/ m²) OR 1.02, 95% CI 0.82 – 1.27, p > 0.05	Eligible cohort 1845 CCS. Strengths: - Large study sample - Additional multivariable risk analysis for mutually exclusive treatment groups. Limitations: - Low attrition for tubular outcomes **Risk of bias** A. Selection bias: low risk Reason: the study group consisted of more than 75% of the original cohort B. Attrition bias: Hypophosphatemia: high risk

	Age at follow-up: Median 19.3 yr (range 15.6-24.5) Controls: NA		Cumulative cisplatin dose (per 100 mg/m²) OR 1.00, 95% CI 0.77 - 1.30, p > 0.05 Cumulative carboplatin dose (per 100 mg/m²) OR 1.00, 95 % CI 0.92 - 1.07, p > 0.05 HD-cyclophosphamide (no/yes) (≥1 g/m² per course) OR 0.63, 95% CI 0.08 – 5.22, p > 0.05 HD-MTX (no/yes) (≥ 1 g/m² per course) OR 0.34, 95% CI 0.07 - 1.76, p > 0.05 Nephrectomy (no/yes) OR 0.70, 95% CI 0.06 – 8.26, p > 0.05 Abdominal RT (no/yes) OR 1.16, 95% CI 0.11 – 12.47, p > 0.05 Age at diagnosis (in years) OR 1.10, 95% CI 0.98 - 1.24, p > 0.05 Time since diagnosis (per 5 years) OR 0.97, 95% CI 0.61 - 1.55, p > 0.05 Male sex OR 0.36, 95%CI 0.12 – 1.05, p > 0.05 *Mutually exclusive treatment groups:* Ifosfamide only OR 1.32, 95% CI 0.22 – 7.89, p > 0.05 Cisplatin only OR 1.21, 95% CI 0.19 – 7.69, p > 0.05 Platinum agents + ifosfamide OR 1.71, 95% CI 0.34 –8.76, p > 0.05 HD-MTX only (≥ 1 g/m² per course) OR 0.58, 95% CI 0.10 – 3.46, p > 0.05 Nephrectomy only OR 2.12, 95% CI 0.20 – 22.39, p > 0.05 RT [1] only OR 3.77, 95% CI 0.36 – 39.40, p > 0.05 Hypomagnesemia	Reason: the outcome was assessed for less than 75% of the study group Hypomagnesemia: high risk Reason: the outcome was assessed for less than 75% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: important prognostic factors were taken adequately into account

			36/534 (8.8%) <u>Risk factors hypomagnesemia</u> Cumulative ifosfamide dose (per 10 g/m²) OR 1.08, 95% CI 0.87 - 1.34, p > 0.05 Cumulative cisplatin dose (per 100 mg/m²) OR 1.66, 95% CI 1.34 – 2.05, p > 0.05 Cumulative carboplatin dose (per 100 mg/m²) OR 0.97, 95% CI 0.87 - 1.07, p > 0.05 HD-cyclophosphamide (no/yes) (≥ 1 g/m² per course) OR 2.98, 95% CI 0.92 – 9.63, p > 0.05 HD-MTX (no/yes) (≥ 1 g/m² per course) OR 1.32, 95% CI 0.43 – 4.05, p > 0.05 Nephrectomy (no/yes) OR 17.46, 95% CI 4.63 – 65.79, p < 0.05 Abdominal RT (no/yes) OR 0.30, 95% CI 0.06 – 1.47, p > 0.05 Age at diagnosis (in years) OR 1.05, 95% CI 0.96 - 1.16, p > 0.05 Time since diagnosis (per 5 years) OR 1.55, 95% CI 1.09 – 2.20, p < 0.05 Male sex OR 0.97. 95%CI 0.46 – 2.05, p > 0.05 *Mutually exclusive treatment groups:* Ifosfamide only OR 5.53, 95% CI 0.42 – 72.94, p > 0.05 Cisplatin only OR 96.31, 95% CI 12.68 – 731.36, p < 0.05 Platinum agents + ifosfamide OR 75.53, 95% CI 9.75 – 584.89, p < 0.05 HD-MTX only (≥ 1 g/m² per	

			course) OR 2.17, 95% CI 0.17 – 27.61, p > 0.05 Nephrectomy only OR 121.85, 95% CI 15.97 – 929.97, p < 0.05 Nephrectomy + RT [1] OR 14.80, 95% CI 2.25 – 97.12, p < 0.05	

Footnote 1: abdominal radiotherapy and/or total body irradiation
Footnote 2: Possible overlap in patients with Dekkers 2013 and Mulder 2013.
Abbreviations: 95% CI, 95% confidence interval; CCS, childhood cancer survivors; CNS, central nervous system; HD, high-dose; Mg, magnesium; MTX, Methotrexate; NA, not applicable; NB, neuroblastoma; OR, odds ratio; RT, radiotherapy; TBI, total body irradiation; yr, year.

Who needs tubular dysfunction surveillance?				
Kooijmans et al. Early and late adverse renal effects after potentially nephrotoxic treatment for childhood cancer. Cochrane Database Syst Rev. 2019; Issue 3, art. No CD008944.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Systematic review Treatment era: 1931-2014 Follow-up: Median or mean survival ≥ 1 yr after end treatment, if unknown ≥ 90% had to finished treatment	61 studies included (46 prevalence, 6 prevalence & risk factors, 9 risk factors) Characteristics of 52 studies included for prevalence: Type and number of participants: 13,327 participants of interest. 4,499 underwent renal function testing. Diagnoses (n studies): Only Wilms' tumor (n=39) Only renal tumor (n=2) Only sarcoma (n=3) Only hepatoblastoma (n=1) Only leukemia/lymphoma (n=2) Only central nervous system malignancies (n=1) Miscellaneous tumors (n=4) Age at diagnosis: Range 12 mo - 14 yr	Cisplatin: 9/52 studies Carboplatin: 15/52 studies Ifosfamide: 21/52 studies RT renal area: 44/52 studies Nephrectomy: 44/52 studies Other treatment: 40/52 studies	Outcome definitions (as defined by authors): - chronic kidney disease - decreased glomerular filtration rate - proteinuria - hypophosphatemia - abnormal tubular phosphate reabsorption - hypomagnesemia - hypertension Hypophosphatemia Prevalence 0 – 36.8%, studied in 8/52 studies including 287 participants Risk factors hypophosphatemia: 1 study No treatment related risk factors were identified. Tubular phosphate reabsorption (TPR)	Strengths - Comprehensive search strategy Limitations - Heterogeneity of included studies **Risk of bias** A. Selection bias: Low risk 26/61 studies (42.6%) High risk 19/61 studies (31.1%) Unclear 16/61 studies (26.2%) B. Attrition bias: Hypophosphatemia Low risk 8/8 studies (100%) TPR Low risk 6/6 studies (100%) Hypomagnesemia Low risk 3/4 studies (75%) High risk ¼ studies (25%)

	Age at follow-up: Range 3.6 - 29 yr Controls: NA		Prevalence overall 0 – 62.5%, studied in 6/52 studies, including 246 participants Risk factors TPR: None of the included studies performed MV analysis. Hypomagnesemia Prevalence 13.2 – 28.6%, studied in 4/52 studies including 128 participants. Risk factors hypomagnesemia: 2 studies Both studies identified cisplatin as a risk factor. Carboplatin, nephrectomy and follow-up time were other reported risk factors.	C. Detection bias: Unclear 61/61 studies (100%) D. Confounding: Low risk 8/15 studies (53.3%) High risk 6/15 studies (40.0%) Unclear 1/15 studies (6.7%)

Footnote 1: For the risk of bias, results of the Cochrane review are shown. Criteria for risk of bias assessment by Cochrane may slightly differ from the IGHG criteria.
Footnote 2: More detailed results regarding risk factors are shown in the evidence table of the included studies for this guideline.
Abbreviations: mo, months; MV analysis, multivariable analysis; RT, radiotherapy; TBI, total body irradiation; TPR, tubular phosphate reabsorption; yr, year.

Who needs tubular dysfunction surveillance?				
Kooijmans et al. Long-term tubular dysfunction in childhood cancer survivors; DCCSS-LATER 2 Renal study. Cancers. 2022;14:2754.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: cross-sectional multi-center study Treatment era: 1963-2001 Follow-up: Median 25.5 years (IQR 21.4-30.3)	Type and number of participants: 1024 CCS with a survival of ≥ 5 years since diagnosis, and aged ≥ 18 years at study entry. Eligible cohort 1,881 CCS. Diagnoses: Leukemias 317 (31.0%), lymphomas 79 (7.7%), CNS tumors 62 (6.1%), neuroblastoma 65 (6.3%), retinoblastoma 1	Ifosfamide: 278/1024 (27.2%) HD-cyclophosphamide: 175/1024 (17.1%) Cisplatin: 175/1024 (17.1%) Carboplatin: 151/1024 (14.7%) Nephrectomy: 264/1024 (25.8%) RT renal area:	Outcome definitions 1. Tubular magnesium loss, Serum magnesium <1.7 mg/dL + increased fractional excretion or supplementation 2. Tubular potassium loss Serum magnesium <3.6 mEq/L + increased fractional excretion or supplementation 3. Tubular phosphate loss	Eligible cohort 1,881 CCS Strengths: - Large study sample - Long follow-up period - Comprehensive assessment tubular function Limitations: - only 54% of eligible cohort participated

	(0.3%), renal tumors 254 (24.8%), hepatic tumors 12 (1.2%), bone tumors 78 (7.6%), soft tissue sarcomas 52 (5.1%), other tumors (12 (1.2%) Age at diagnosis: Median 4.7 years (IQR 2.4-9.2) Age at follow-up: Median 32.5 years (IQR 27.7-38.0) Controls: 500 age- and sex matched controls from Lifelines cohort study	175/1024 (17.1%) HSCT: 95/1024 (9.3%)	Serum magnesium <2.2 mg/dL + abnormal TmP/GFR or supplementation 4. LMWP, defined as α1-microglobulin:creatinine ratio >15mg/g Results Tubular magnesium loss 56/999 (5.6%) Risk factors tubular magnesium loss Nephrectomy OR 1.2, 95%CI 0.4 – 3.7 Abdominal RT OR 1.0, 95%CI 0.4 – 2.7 TBI OR 0.9, 95% CI 0.2 – 4.6 Ifosfamide OR 0.3, 95%CI 0.1 – 0.7 HD-cyclo OR 0.5, 95%CI 0.2 – 1.8 Cisplatin OR 10.1, 95%CI 3.9 – 26.0 Carboplatin OR 1.2, 95%CI 0.4 – 3.4 Tubular potassium loss 45/1003 (4.5%) Risk factors tubular potassium loss Nephrectomy OR 0.6, 95%CI 0.2 – 2.1 Abdominal RT OR 1.9, 95%CI 0.7 – 5.2 TBI OR 0.8, 95% CI 0.2 – 3.8 Ifosfamide OR 2.4, 95%CI 1.2 – 4.7 HD-cyclo OR 0.5, 95%CI 0.1 – 1.5 Cisplatin OR 3.5, 95%CI 1.6 – 7.5 Carboplatin OR 1.6, 95%CI 0.7 – 3.8	**Risk of bias** A. Selection bias: high risk Reason: the study group consisted of less than 75% of the original cohort B. Attrition bias: low risk Reason: outcome was assessed for more than 75% of the study group C. Detection bias: unclear Reason: : unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: : important prognostic factors were taken adequately into account

			Tubular phosphate loss 55/997 (5.5%) Risk factors tubular phosphate loss Nephrectomy OR 0.7, 95%CI 0.4 – 1.2 Abdominal RT OR 1.2, 95%CI 0.7 – 2.0 TBI OR 1.1, 95% CI 0.6 – 2.0 Ifosfamide OR 2.8, 95%CI 2.0 – 4.1 HD-cyclo OR 0.8, 95%CI 0.5 – 1.3 Cisplatin OR 0.8, 95%CI 0.5 – 1.3 Carboplatin OR 1.2, 95%CI 0.7 – 2.0 LMWP 187/931 (20.1%) Risk factors LMWP Nephrectomy OR 1.2, 95%CI 0.4 – 3.7 Abdominal RT OR 1.0, 95%CI 0.4 – 2.7 TBI OR 0.9, 95% CI 0.2 – 4.6 Ifosfamide OR 0.3, 95%CI 0.1 – 0.7 HD-cyclo OR 0.5, 95%CI 0.2 – 1.8 Cisplatin OR 10.1, 95%CI 3.9 – 26.0 Carboplatin OR 1.2, 95%CI 0.4 – 3.4	

Abbreviations: 95%CI, 95% confidence interval; CCS, childhood cancer survivors; CNS, central nervous system; HD, high-dose; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; LMWP, low molecular weight proteinuria; OR, odds ratio; RT, radiotherapy, TBI, total body irradiation.

Who needs tubular dysfunction surveillance?				
Latoch et al. Urine NGAL and KIM-1 tubular injury biomarkers in long-term survivors of childhood solid tumors: a cross-sectional cohort study. Journal of clinical medicine. 2021;10:399.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design: cross-sectional cohort study Treatment era: 1995-2016 Follow-up: median 8.35 yr (IQR 4.95 – 12.55)	Type and number of participants: 60 survivors pediatric solid tumors Diagnoses: Wilms tumor 17 (28%) Sarcoma 14 (23%) Hodgkin lymphoma 10 (17%) Neuroblastoma 9 (15%) Hepatoblastoma 4 (7%) Germ tumors 3 (5%) Langerhans cell histiocytosis 3 (5%) Age at diagnosis: median 4.61 yr (IQR 4.95 – 12.55) Age at follow-up: median 15.5 yr (IQR 9.25 – 19.00) Controls: 53, median age 11.5 yr (IQR 8.04 – 16.5)	Ifosfamide 12/60 (20%) Cisplatin 16/60 (26.7%) Carboplatin NM Cyclophosphamide 19/60 (31.7%) Methotrexate 5/60 (8.3%) Nephrectomy: NM RT renal area: 19/60 (31.7%)	Outcome definitions 1. NGAL/creatinine ratio (ng/mg creatinine) ratio Risk factors NGAL/creatinine ratio (continuous) Cisplatin (cum dose g/m^2) coefficient 0.108, 95% CI 0.005-0.211) Age at diagnosis (yr) coefficient 3.162, 95% CI -1.702-8.033 Nephrectomy (no vs yes) coefficient 5.009, 95% CI -47.18-147.3 Factors not included in multiple linear regression because not significant ($p<0.05$) in univariate analyses: Follow-up time, cum dose of cyclophosphamide, ifosfamide and methotrexate, and abdominal radiotherapy	Strengths: - control group Limitations: - small study sample - number of some nephrotoxic agents missing **Risk of bias** A. Selection bias: high risk Reason: study group consisted of less than 75% of original cohort and was not a random sample B. Attrition bias: low risk Reason: outcome was assessed for more than 75% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: high risk Reason: important prognostic factors were not taken adequately into account

Abbreviations: 95% CI, 95% confidence interval; cum dose, cumulative dose; IQR, interquartile range; NGAL, neutrophil gelatinase-associated lipocalin; NM, not mentioned; RT, radiotherapy; yr, year

Who needs tubular dysfunction surveillance?				
Oberlin et al. Long-term evaluation of ifosfamide-related nephrotoxicity in children. J Clin Oncol. 2009;27:5350-5355.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design: cross-sectional multicenter cohort study Treatment era: 1984 – 2000 Follow-up: minimal 5 years after completion of therapy. Median 10.3 years (range 5 – 10.7)	Type and number of participants: 183 pediatric sarcomas survivors treated with ifosfamide Diagnoses: Rhabdomyosarcoma 77 (42.1%) Ewing sarcoma 39 (21.3%) Soft tissue sarcoma 39 (21.3%) Osteosarcoma 28 (15.3%) Age at diagnosis: Median 9.3 years (range 0.4 – 27.2) Age at follow-up: median 18.3 years (range 7.1 – 44.2) Controls: NA	Ifosfamide: 183/183 (100%), median cumulative dose 54 g/m^2 Cisplatin: 0/183 (excluded) Carboplatin: 0/183 (excluded) Methotrexate: Some, exact number NM Nephrectomy: 0/183 (excluded) RT renal area: 1/183 (0.01%), small posterior area of the right kidney HSCT: 0/183 (excluded)	Outcome definitions Reduced TmP/GFR, definition based on previously outlined normal ranges used for age. Reduced TmP/GFR Reduced 38/156 (24%) Grade 1: 24 (15%) Grade 2: 12 (8%) Grade 3: 1 (0.5%) Risk factors reduced TmP/GFR Lineal multivariable regression: Age at treatment (years) β -0.0047, SE 0.0033, p= 0.2 Ifosfamide dose (g/m^2) β -0.0028, SE 0.001, p =0.02 Interval from therapy to investigations (years) β -0.013, SE 0.0036, p= 0.0005 Not included in model (based on univariate analysis): Methotrexate β 0.0049, SE 0.046, p=0.9	Strengths: - clear description of study cohort - relative long follow up period Limitations: - multicenter; different labs doing tests **Risk of bias** A. Selection bias: low risk Reason: study group consisted of 72% of the original cohort, but was a random sample B. Attrition bias: low risk Reason: outcome was assessed for 85% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: important prognostic factors were adequately taken into account

Abbreviations: 95% CI, 95% confidence interval; HSCT, hematological stem cell transplantation; NA, not applicable; NM, not mentioned; RR, relative risk; RT, radiotherapy; TmP/GFR, renal tubular threshold for phosphate.

Who needs tubular dysfunction surveillance?				
Skinner et al. Persistent nephrotoxicity during 10-year follow-up after cisplatin or carboplatin treatment in childhood: relevance of age and dose as risk factors. European Journal of Cancer. 2009;45:3213-3219.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: prospective single-center longitudinal cohort study	Type and number of participants: 63 CCS aged 18 years at treatment, treated with platinum	Ifosfamide: 0/63 (0%) Cisplatin alone:	Outcome definitions 1. Hypocalcemia, based on age-related reference ranges	Strengths: - long-term follow-up - clear description of study cohort

Treatment era: 1981- 1996 Follow-up: at least 10 years, the 1 and 10 year studies at median 1.1 years (range 0.7-2.3) and 10.3 years (range 9.0-12.3)	and who survived at least 10 years after completion of therapy Diagnoses: *Cisplatin alone (n=27):* Osteosarcoma 12 (44.4%) Germ cell tumor 4 (14.8%) Brain tumor 3 (11.1%) Liver tumor 3 (11.1%) Epithelial carcinoma 1 (3.7%) Ewing's sarcoma 1 (3.7%) Nasopharyngeal carcinoma 1 (3.7%) Neuroblastoma 1 (3.7%) Salivary gland carcinoma 1 (3.7%) *Carboplatin alone (n=24):* Germ cell tumor 9 (37.5%) Medulloblastoma 5 (20.8%) Other brain tumor 5 (20.8%) Neuroblastoma 3 (12.5%) CCSK 1 (4.2%) Retinoblastoma 1 (4.2%) *Cisplatin and carboplatin (n=12):* Neuroblastoma 9 (75%) Brain tumor 3 (25%) Age at diagnosis: *Cisplatin alone:* Median 7.7 years (range 0.6-17.8) *Carboplatin alone:* Median 4.4 years (range 0.4-15.8) *Cisplatin and carboplatin:* Median 1.9 years (range 0.1-6.2) Age at follow-up: NM Controls: NA	27/63 (42.9%), total median dose 500 mg/m^2 (range 300-960) Carboplatin alone: 24/63 (38.1%), total median dose 2400 mg/m^2 (range 560-8800) Cisplatin and carboplatin: 12/63 (19.0%), total median dose cisplatin 473 mg/m^2 (range 240-739), total median dose carboplatin 1500 mg/m^2 (range 750-4200) HD-melphalan 9/63 (14.3%) MTX 8/63 (12.7%) (intermediate 1 g/m^2 of high-dose 8 g/m^2) Nephrectomy: NM RT renal area: 3/63 (4.8%) and 5/63 received a small amount of scatter. Other Actinomycin D, bleomycin, cyclophosphamide, doxorubicin, etoposide, 5-fluorouracil, teniposide, vincristine. Supportive care: aminoglycosides, amphotericin.	2. Hypomagnesemia, defined as <0.75 mmol/l <2 years, and <0.70 ≥ 2 years. Results Calcium % normal results (95%CI) *Cisplatin alone* 10 years: 100 (89-100), median 2.38 (2.18-2.53) *Carboplatin alone* 10 years: 100 (88-100), median 2.39 (2.28-2.59) *Cisplatin and carboplatin* 10 years: 100 (76-100), median 2.36 (2.23-2.53) Magnesium % normal results (95%CI) *Cisplatin alone* 10 years: 63 (42-81), median 0.73 (0.37-0.83) *Carboplatin alone* 10 years: 83 (61-95), median 0.77 (0.54-0.94) *Cisplatin and carboplatin* 10 years: 91 (59-100), median 0.81 (0.68-0.92) Risk factors Higher cisplatin dose was not associated with lower Mg at 10 years (p>0.05) Higher carboplatin dose was not associated with lower Mg at 10 years (p>0.05)	Limitations: - due to small numbers in subgroups multivariable risk analyses not possible Timing Evaluation at 1 month (end), 1 year and 10 years after end of therapy **Risk of bias** A. Selection bias: low risk Reason: study group consisted of 93% of original cohort B. Attrition bias: low risk Reason: outcomes were assessed for >75% of study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: high risk Reason: not all important risk factors were adequately taken into account

Abbreviations: 95%CI, 95% confidence interval; CCS, childhood cancer survivors; HD, high dose; Mg, magnesium; MTX, methotrexate; NA, not applicable; NM, not mentioned; RT, radiotherapy.

Who needs tubular dysfunction surveillance?				
Stohr et al. (a) Nephrotoxicity of cisplatin and carboplatin in sarcoma patients: a report from the late effects surveillance system. Pediatr Blood Cancer. 2007;48:140-47.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective multicenter cohort study Treatment era: Registered on a GPOH trial between 1-1-1998 and 1-1-2002 Follow-up: Median follow-up 2 years. Follow-up to most recent renal examination in 435 survivors with information on serum magnesium was median 23 months (IQR 10-35; range 0-59).	Type and number of participants: Described study group with complete information on magnesium is 435 sarcoma CCS. Eligible cohort 651 sarcoma patients younger than 18 years at diagnosis; follow-up minimal at end of treatment. Diagnoses: Osteosarcoma 139/435 (31.9%), soft tissue sarcoma 167/435 (38.4%), Ewing's sarcoma 109/435 (25.1%) Age at diagnosis: Median 11.6 yr (range 6.5 – 14.9) Age at follow-up: NM Controls: From within cohort: survivors not treated with any platinum derivative (i.e., Ewing and some soft tissue sarcoma patients)	Ifosfamide: 410/435 (94.3%) Cisplatin: 158/435 (36.3%) Carboplatin: 60/435 (13.8%) MTX: NM Nephrectomy: NM RT renal area: 53/435 (12.2%), RT field: abdominal 53 (12.2%) Other chemotherapeutic agents: Combination of actinomycin D, busulfan, doxorubicin, epirubicin, melphalan, methotrexate, or vincristine Other treatments: Magnesium supplementation as prophylaxis during treatment; no further information provided.	Outcome definitions 1. Hypomagnesemia Serum Mg < 0.7 mmol/L; CTCEv3 or receiving Mg supplementation unless this was reported as prophylaxis. Hypomagnesemia Overall prevalence 30/339 (8.9%) after +/- 6 months cessation of therapy Overall prevalence 30/339 (8.9%) after +/- 6 months cessation of therapy Overall prevalence 9/286 (3.1%) at last examination Adjusted mean (95% CI) for magnesium Cisplatin (yes vs no) adjusted mean (95% CI): First examination[1] yes 0.77 (0.74 – 0.81), no 0.82 (0.80 – 0.84) Last examination yes 0.82 (0.79 – 0.85), no 0.86 (0.84 – 0.88) Overall effect $p < 0.05$, interaction with time[2] $p > 0.05$ Carboplatin (yes vs no) adjusted mean (95%CI): First examination[1] 0.78 (0.74 – 0.81), no 0.82 (0.80- 0.84)	Strengths: - Longitudinal study Limitations: - Only very few survivors available for longitudinal information. - Relatively short follow-up. - Information on over-the-counter magnesium might not be available for all survivors, possibly leading to an underestimation of hypomagnesemia and the effect of cisplatin. **Risk of bias** A. Selection bias: unclear Reason: unclear if the study group was a random sample of the original cohort B. Attrition bias: high risk Reason: the outcome was assessed for 68% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk for longitudinal analysis

			Last examination yes 0.82 (0.79 – 0.86), no 0.86 (0.83 – 0.88) Overall effect p < 0.05, interaction with time[2] p > 0.05 Abdominal RT (yes vs no) adjusted mean (95%CI) First examination[1] yes 0.79 (0.75 – 0.83), no 0.80 (0.79-0.82) Last examination yes 0.84 (0.80 – 0.88), no 0.84 (0.82 – 0.86) Overall effect p > 0.05, interaction with time[2] p > 0.05	Reason: All important confounding factors were taken into account. High risk for all other analyses: Reason: Important confounding factors not taken into account.

Footnote 1: the first examination took place approximately 6 months after cessation of therapy. The last examination took place at a median follow-up of 23 months.
Footnote 2: A non-significant P-value of ''interaction with time'' means that the effect of a particular factor does not differ between the two examinations.
Abbreviations: 95% CI, 95% confidence interval; CCS, childhood cancer survivors; Mg, magnesium; MTX, Methotrexate; NM, not mentioned; RT, radiotherapy; yr, year.

Who needs tubular dysfunction surveillance?				
Stohr et al. (b) Ifosfamide-induced nephrotoxicity in 593 sarcoma patients: a report from the late effects surveillance system. Pediatr Blood Cancer. 2007;48:447-52.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective cohort study Treatment era: 1998-2002 Follow-up: Median 19 mo (range 8-36)	Type and number of participants: Described study group 593 sarcoma CCS. Eligible cohort 754 CCS Diagnoses: Osteosarcoma 217 (36.6%), soft tissue sarcoma 222 (37.4%), Ewing's sarcoma 154 (26.0%) Age at diagnosis: Median 11.7 yr (range 0.4 – 17.6) Age at follow-up: NM Controls: NA	Ifosfamide: 593/593 (100%) Cisplatin: 217/593 (36.6%) Carboplatin: 84/593 (14.2%) MTX: NM Nephrectomy: 0/593 (0%) RT renal area: 63/593 (10.6%), RT field: abdominal 63 (10.6%)	Outcome definitions 1. Tubulopathy Having at least 2 out of 3 criteria: - hypophosphatemia - glucosuria - proteinuria At least at 2 consecutive examinations 4 weeks apart Tubulopathy 27/593 (4.6%) Tubulopathy Cumulative ifosfamide dose (24-60 g/m^2) vs ifosfamide dose (≤ 24 g/m^2) HR 5.6 (0.7 - 45.4)	Strengths: - Longitudinal study Limitations: - Relatively small follow-up period The Cox's proportional hazards model is adjusted for gender, concomitant treatment with carboplatin and abdominal irradiation, but no HR shown. **Risk of bias** A. Selection bias: low risk Reason: the study group consisted of more than 75% of the original cohort and was not a random sample

			Cumulative ifosfamide dose (>60 g/m^2) vs ifosfamide dose (≤ 24 g/m^2) HR 18.6 (2.4 - 143.2) Age at diagnosis HR 8.7, 95% CI 3.5 – 21.8, p < 0.05	B. Attrition bias: low risk Reason: the outcome was assessed for more than 75% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: important prognostic factors were taken adequately into account

Abbreviations: CCS, childhood cancer survivors; HR, hazard ratio; mo, months; MTX, methotrexate; NA, not applicable; NM, not mentioned; RT, radiotherapy; yr, year.

Who needs glomerular dysfunction surveillance?				
Sullivan et al. Late effects of chemotherapeutic agents on renal function in childhood cancer survivors. Ir J Med Sci. 2017;186:49-55.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Systematic review Treatment era: Not reported, articles published between 1990 - 2015 Follow-up: At least median of 6 months after and of therapy. Range 6-120 months.	15 studies included Type and number of participants: Not stated for every article included Diagnoses: Miscellaneous tumors, no details stated Age at diagnosis: Not stated Age at follow-up: Not stated Controls: Not stated	Chemotherapy: Details not stated. 6 studies included patients treated with Ifosfamide 6 studies included patients treated with carboplatin and/or cisplatin 4 studies included patients treated with methotrexate. Nephrectomy: Not stated RT renal area: Not stated	Outcome definitions Nephrotoxicity (proteinuria, decreased GFR, hypophosphatemia, hypomagnesemia, hypertension) as defined by authors Ifosfamide induced nephrotoxicity Prevalence 1-50% in 6 studies Risk factors ifosfamide nephrotoxicity (4 studies) Age < 3 years at time of treatment (2 studies) Age <4 year at time of diagnosis (1 study)	Strengths: clear search strategy Limitations: - No risk of bias assessment performed for included articles - No detailed information regarding diagnoses / treatment regimens of included articles - No meta-analysis - Only included studies reported in English **Risk of bias** A. Selection bias: Unclear Reason: Insufficient information provided to determine if the study

			Cumulative ifosfamide dose >45 g/m^2, >119 g/m^2, >80 g/m^2, high cumulative dose (1 study each) Previous or concurrent cisplatin (1 study) Previous unilateral nephrectomy 1 study) Pre-existing renal impairment or tumor invasion (1 study) <u>Carboplatin and cisplatin induced nephrotoxicity</u> Prevalence hypomagnesemia 7-29% in 6 studies Risk of hypomagnesemia is higher with combined ifos and cis exposure (25% vs. 4% with ifos alone) <u>Methotrexate induced nephrotoxicity</u> Prevalence mentioned in 1 study: 1,8%, and completely reversible in 4 studies	group of included articles was representative <u>B. Attrition bias:</u> Unclear Reason: Insufficient information provided to determine if outcome was assessed for more than 75% of the study group of included articles <u>C. Detection bias:</u> Unclear Reason: Unclear if outcome assessors were blinded for important determinants related to the outcome of included articles <u>D. Confounding:</u> Unclear Reason: No information provided whether risk analyses were adjusted for important confounding factors

Footnote 1: More detailed results regarding risk factors are shown in the evidence table of the included studies for this guideline.
Abbreviations: GFR, glomerular filtration rate.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Brock et al. Partial reversibility of cisplatin nephrotoxicity in children. J Pediatr. 1991;118:531-4.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design: cohort: constructed using retrospective data at time of treatment and a subsequent cross-sectional measurement among long-term survivors. Treatment era: 1979 to 1988 Follow-up: Median 2 years 6 months (range 18 months – 7 years)	Type and number of participants: 40 patients from single centre at least 18 months post therapy that included cisplatin (potential cohort of 55 children). Diagnoses: Neuroblastoma 27 (67.5%), germ cell tumor 8 (20%), hepatoblastoma 3 (7.5%) osteogenic sarcoma 2 (5%). Age at diagnosis: Median 15 months (range 13 days – 13 years 8 months) Age at follow-up: NM Controls: NA	Chemotherapy: Cisplatin 40/40 (100%) - median cumulative dose 500 mg/m^2 (range 120 to 1860). Other agents: Neuroblastoma – cyclophosphamide, vincristine, teniposide-etoposide, and high-dose melphplan; Germ cell tumor – bleomycin, and vinblastine-etoposide; Hepatoblastoma – doxorubicin; Osteosarcoma – doxorubicin and methotrexate. Nephrectomy: 0/40 (0%) RT renal area: 0/40 (0%)	Outcome definitions Change in GFR (ml/min/1.73m^2) measured by 51Cr-EDTA clearance Results longitudinal GFR: *End of treatment GFR* Median 74 (range 13 to 184) GFR >80: 16/40 (40%) GFR 60-80: 13/40 (32.5%) GFR < 60: 11/40 (27.5%) *Follow-up GFR* Median 90 (range 27 to 135) GFR > 80: 23/40 (57.5%) GFR 60 to 80: 15/40 (37.5%) GFR <60: 2/40 (5%) Compared to EoT, GFR at FU increased in all but 4 patients. GFR improved at 1, 2 and 4 year FU with respect to EoT GFR ($p < 0.05$) CCS with EoT GFR 60-80 had better chance of regaining GFR 80 at median FU time than CCS with EoT GFR <60 ($p< 0.01$) No association between GFR and total cisplatin dose, age, gender, tumor type or associated nephrotoxic treatment. In one patient with long-term GFR <60, the deterioration in GFR was considered to be caused after melphalan consolidation dose (not cisplatin). The follow-up GFRs 13 CCS who received HD-melphalan were	Strengths: measured GFR (EDTA) Limitations: Limited modelling of the association between prognostic factors and outcome. Timing single measurement taken at median of 2 years 6 months post treatment. **Risk of bias** A. Selection bias: low risk Reason: random sample with respect to cancer treatment, with 73% of eligible patients recruited, authors state difference between those participating and not B. Attrition bias: low risk Reason: Cross-sectional measurement of recruited long-term survivors, i.e., all included patients had long-term measure reported C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: unclear Reason: some prognostic factors such as dose and age accounted for, but reporting incomplete and unclear if multivariable models used to examine these associations.

			compared with who had not received melphalan; no significant correlation was found	

Abbreviations: CCS, childhood cancer survivors; EoT, end of treatment; FU, follow-up; GFR, glomerular filtration rate; HD, high-dose; NA, not applicable; NM, not mentioned; RT, radiotherapy.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Cozzi et al. Renal function adaptation in children with unilateral renal tumors treated with nephron sparing surgery or nephrectomy. The Journal of Urology. 2005;174:104-8.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective & cross-sectional cohort study Treatment era: 1992-2003 Follow-up: Mean (SD): nephrectomy group 71.9 mo (41.0), NSS group 65.3 mo (38.6) postoperative	Type and number of participants: 26 patients with unilateral renal tumors - 16 in Group 1 nephrectomy (6 Male, 10 Female) - 10 in Group 2 NSS (3 Male, 7 Female) Diagnoses: 23 WT (Stage I/II, 1 local stage 1 with lung metastases) 1 Renal Cell Carcinoma 1 cystic nephroma 1 oncocytoma Age at diagnosis: Nephrectomy group mean 60.0 mo (40.7) NSS group mean 42.7 mo (42.0) Age at follow-up: NM Controls: NA	Nephrectomy: 26/26 (100%), unilateral 16 (61.5%), NSS 10 (38.5%) Co-medication: Group 1: 12/16 Vincristine + actinomycin D 2; Vincristine + actinomycin D + epirubicin 10 Group 2: 7/10 Vincristine + actinomycin D 2; Vincristine + actinomycin D + epirubicin 5 Radiotherapy: No RT used	Outcome definitions 1. Mean serum creatinine SDS Longitudinal change in serum creatinine SDS Significant increase of mean serum creatinine SDS in total group with increasing postoperative follow up ($p < 0.05$), $r^2 = 0.49$. For each year of postoperative follow up 5 CCS in group 1 and 2 CCS in group 2 had higher serum creatinine SDS. The 7 CCS treated with surgery alone had no significant postoperative difference in serum creatinine SDS compared to the 19 CCS treated with postoperative chemotherapy (1.13 ± 0.66 vs 1.03 ± 0.78, p=0.38)	Group 1= nephrectomy unilateral (16 CCS) Group 2= NSS (10 CCS) Strenghts: long follow-up period Limitations - Small study sample Timing Yearly measurements for total 9 years Follow-up years (number CCS evaluated): 1 (26), 2 (26), 3 (26), 4 (23), 5 (17), 6 (17), 7 (14), 8 (12), 9 (9) **Risk of bias** A. Selection bias: low risk Reason: the study group consisted of more than 75% of the original cohort B. Attrition bias: low risk Reason: the outcome was assessed for more than 75% of the study group

				C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: NA Reason: no MV analysis

Footnote 1: Possible overlap in patients with Cozzi 2012, Cozzi 2013 and Cozzi 2017.
Abbreviations: CCS, childhood cancer survivors; mo, months; MV analysis, multivariable analysis; NA, not applicable; NM, not mentioned; NSS, nephron sparing surgery; SD, standard deviation; SDS, stand deviation scores; WT, Wilms tumor.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Cozzi et al. Chronic kidney disease in children with unilateral renal tumor. Pediatric urology. 2012;187:1800-5.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional & longitudinal cohort study, single-center. Comparative study unilateral nephrectomy (UN) and nephron sparing surgery (NSS) Treatment era: 1992-2003 Follow-up: Mean (SD): group 1: 148.6 mo (48.5), group 2: 147.9 mo (48.5) postoperative	Type and number of participants: 25 renal tumor CCS Diagnoses: Wilms tumor 20 (80%), renal cell carcinoma 1 (4%), cystic nephroma 3 (12%), oncocytoma 1 (4%) Age at diagnosis: Group 1: mean 55.4 mo (41.4 SD) Group 2: mean 42.7 mo (42.0 SD) Age at follow-up: NM 10 pts ≥ 18 yrs 15 pts ≤ 17 yrs Controls: NA	Chemotherapy 18/25 (72%) pts received chemotherapy 4 pts: vincristine + doxorubicin 13 pts: vincristine + doxorubicin + epirubicin 1 pt: vincristine +epirubicin + carboplatin Carboplatin 1/25 (4%) Nephrectomy: 25/25 (100%), unilateral 15 (60%) NSS 10 (40%) RT renal area: 0/25 (0%)	Outcome definitions 1. Chronic kidney disease (CKD) based on eGFR 2. change in eGFR (ml/min/1.73m^2); pts ≤ 17 yrs Schwartz equation and pts ≥ 18 yrs MDRD equation Results Chronic kidney disease *Group 1 (UN):* CKD stage 1: 7/15 CKD stage 2: 8/15 *Group 2 (NSS)* CKD stage 1: 9/10 CKD stage 2: 1/10 Longitudinal change in eGFR *Group 1 with stage 2 CKD (n=8)* eGFR diagnosis 75.70 ± 25.5 eGFR last follow-up 79.49 ± 3.9	Group 1= UN (15 CCS) Group 2= NSS (10 CCS) Strengths - Long follow-up period Limitations - Small study sample Timing Sequential measurements during a period of at least 12 years postoperatively (range 12-17). Measurements every 2 years. **Risk of bias** A. Selection bias: low risk Reason: the study group consisted of 34 pts; 4 died of disease. Of the remaining 30 survivors the study group consisted of more than 75%

			slope 1.35 – 2.04, p >0.05, r^2 0.05 *Group 1 with stage 1 CKD (n=7)* eGFR diagnosis 81.16 ± 24.74 eGFR last follow-up 102.3 ± 3.6 slope 0.30 – 2.93, p < 0.05, r^2 0.65 *Group 2 (n=10)* eGFR diagnosis 88.74 ± 26.74 eGFR last follow-up 107.41 ± 14.39 slope 0.71 – 2.44, p < 0.05, r^2 0.81 No significant differences in eGFR at diagnosis among the 3 groups. At last follow-up significant difference group 1 (UN) with stage 2 CKD vs. stage 1 CKD: 79.49 ± 3.9 vs 102. 3± 3.6, p < 0.05. Group 1 (UN) had a significant lower mean eGFR compared to group 2 (NSS) at last follow up.	B. Attrition bias: low risk Reason: the outcome was assessed for more than 75% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: NA Reason: no risk estimation done

Footnote 1: Possible overlap in patients with Cozzi 2005, Cozzi 2013 and Cozzi 2017.

Abbreviations: CCS, childhood cancer survivors; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; mo, months; NA, not applicable; NM, not mentioned; NSS, nephron sparing surgery; pts, patients; UN, unilateral nephrectomy; RT, radiotherapy; SD, standard deviation; yrs, years.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Cozzi et al. Renal function adaptation up to the fifth decade after treatment of children with unilateral renal tumor: a cross-sectional and longitudinal study. Pediatr Blood Cancer. 2013;60:1534-1538.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional and longitudinal study Treatment era: 1962 - 2011 Follow-up:	Type and number of participants: 72 survivors of unilateral renal tumor Group A= 12 pts ≤ 30 yrs old who underwent NSS	Nephrectomy: 60 (83.3%) unilateral nephrectomy, 12 (16.7%) NSS *Group A (n=12)* Surgery only 3 (25%)	Outcome definitions 1. Change of eGFR (ml/min/1.73m^2) ≤ 17 yrs the updated bedside Schwartz formula was used, for ≥ 18 yrs the MDRD equation	Strengths: - long-term follow up Limitations: - retrospective data collection for longitudinal part

Post-operative follow-up Group A mean 11.7 yrs ± 6.5 SD Group B mean 11.38 yrs ± 7.8 SD Group C mean 38.44 yrs ± 4.9 SD	Group B= 42 pts ≤ 30 yrs old who underwent nephrectomy Group C= 18 pts ≥ 30 yrs old who underwent nephrectomy Diagnoses: *Group A (n=12)* Wilms tumor 10 (83.3%) Cystic nephroma 1 (8.3%) Oncocitoma 1 (8.3%) *Group B (n=42)* Mesoblastic nephroma 2 (4.8%) Wilms tumor 32 (76.2%) Cystic nephroma 3 (7.1%) Renal cell carcinoma 3 (7.1%) Clear cells sarcoma 1 (2.4%) Rabdoid tumor 1 (2.4%) *Group C (n=18)* Mesoblastic nephroma 1 (0.6%) Wilms tumor 17 (94.4%) Age at diagnosis: Age at surgery Group A mean 3.9 yrs ± 3.2 SD Group B mean 3.6 yrs ± 2.9 SD Group C mean 4.47 yrs ± 3.1 SD Age at follow-up: Group A mean 15.18 yrs ± 6.6 SD Group B mean 15.8 yrs ± 8.0 SD Group C mean 42.7 yrs ± 5.7 SD Controls: healthy subjects with two kidneys from Rowe [1]	Two drugs 4 (33.3%) Three drugs/radiotherapy 5 (41.7%) Preoperative chemotherapy 12 (100%) *Group B (n=42)* Surgery only 7 (16.7%) Two drugs 14 (33.3%) Three drugs/radiotherapy 21 (50%) Preoperative chemotherapy 33 (78.6%) *Group C (n=18)* Surgery only 2 (11.1%) Two drugs 4 (22.2%) Three drugs/radiotherapy 12 (66.7%) Preoperative chemotherapy 4 (22.2%)	Results eGFR < 90 at last follow-up Group A 1 (8.3%), mean eGFR 109.8 ± 18.4 SD Group B 18 (42.8%), mean eGFR 95.1 ± 18.5 SD Group C 14 (77.8%), mean eGFR 76.1 ± 16.3 SD Longitudinal changes in eGFR Group A preop – 1st – 2nd decade: slope 0.28 to 1.55, r^2= 0.99, p= 0.03 (significant increase eGFR) Group B preop – 1st – 2nd decade: Slope -8.80 to 9.40, r^2= 0.51, p=0.74 Group C 3rd – 4th – 5th decade: slope -1.28 to -0.47, r^2= 0.99, p=0.02 (significant decrease in eGFR) Preop no significant differences were found between mean eGFR of Groups A (NSS) and B (UN) patients. Postop the mean eGFR of Group A (NSS) was higher than of Group B (UN) patients (P=0.01). Group C (UN) patients showed a progressive decrease in mean eGFR from 88.1 ± 22.6 SD during the third decade postop to 66.6 ± 15.6 SD during the fifth decade postop (p=0.02) Comparison with healthy subjects The longitudinal analysis of eGFR in relation to age showed that	- small sample size in the 4th – 5th decade Timing Cross-sectional data collection for last follow-up, other data retrospective from hospital records. Total over 1,675 measurements **Risk of bias** A. Selection bias: high risk Reason: study group consists of 73% of original cohort and is not a random sample B. Attrition bias: low risk Reason: at last follow- up the outcome was assessed for 78% of the total study group, but please note that in subgroup C this was only 59% C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: NA Reason: No MV analysis

			patients undergoing nephrectomy experience a progressive decrease of renal function that parallels the physiological decline of renal function in subjects with two healthy kidneys. However, the mean ± SEM value of eGFR in patients with an age between 45 and 54 years was significantly lower than that of normal subjects (70.28 ± 6.1 vs. 128.1 ± 1.6; P<0.001)	

Footnote 1: Rowe et al. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. J. Gerontol 1976;31:155-163
Footnote 2: Possible overlap in patients with Cozzi 2005, Cozzi 2012 and Cozzi2017.
Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; MV, multivariable; NA, not applicable; NSS, nephron sparing surgery; postop, post-operative; preop, pre-operative; SD, standard deviation; UN, unilateral nephrectomy; yrs, years.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Cozzi et al. Renal function recovery after nephrectomy or nephron-sparing surgery in children with unilateral renal tumor. Eur J Pediatr Surg. 2017;27:74-80.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: retrospective cohort study Treatment era: January 1992 – December 2015 Follow-up: NM, last follow-up > 13 yrs post-operative	Type and number of participants: 36 CCS of unilateral renal tumor Cohort stratified by PRD (eGFR <90 ml/min/1.73m^2) and surgical extent Diagnoses: *Group without PRD (n=19)* Wilms tumor 18 (94.7%) Oncocytoma 1 (5.3%) *Group with PRD (n=17)* Wilms tumor 12 (70.6%) Adenocarcinoma 3 (17.6%) Renal sarcoma 1 (5.9%)	Nephrectomy: *Group without PRD* Nephrectomy 12/19 (63.2%) NSS 7/19 (36.8%) *Group with PRD* Nephrectomy 13/17 (76.5%) NSS 4/17 (23.5%) Chemotherapy: *Group without PRD* Preop chemo 19/19 (100%) *Group with PRD* Preop chemo 15/17 (88.2%) RT renal area: NM	Outcome definitions 1. Change in eGFR (ml/min/1.73m^2) For patients ≤ 17 yrs the updated bedside Schwartz formula was used. For patients ≥18 yrs the MDRD equations was used. Results *Group without PRD (n=19)* Preop eGFR 110.5 ± 17.9 SD Postop eGFR 103.0 ± 20.8 SD *Group with PRD (n=17)* Preop eGFR 66.7 ± 17.4 SD Postop eGFR 96.2 ± 19.1 SD	Strengths: - Long follow-up period Limitations: - no treatment details provided besides type of surgery - small study group, especially the NSS group - retrospective study design Timing Retrospective design, different creatinine measurements for each year were averaged **Risk of bias**

	Age at diagnosis: Age at surgery *Group without PRD* Mean 4.7 years ± 3.6 SD *Group with PRD* Mean 5.1 years ± 3.2 SD Age at follow-up: *Group without PRD* Mean 14.5 years ± 7.5 SD *Group with PRD* Mean 17.7 years ± 4.6 SD Controls: NA		Longitudinal *Nephrectomy* - pts with PRD: Significant eGFR increase over time after puberty, slope 0.095 to 1.785 (p=0.03) - pts without PRD: Non-significant eGFR decline, slope -1.832 to 0.827 (p=0.4) *NSS* - pts with PRD: Significant eGFR increase over time after puberty, slope 1.973 to 5.871 (p=0.002) - pts without PRD: Non-significant eGFR decline, slope -1.497 to 1.253 (p=0.83)	A. Selection bias: low risk Reason: the study group consisted of more than 75% of the original cohort of childhood cancer survivors B. Attrition bias: low risk Reason: the outcome was assessed for more than 75% of the study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: NA Reason: No risk analyses performed

Footnote 1: Possible overlap in patients with Cozzi 2005, Cozzi 2012 and Cozzi 2013.
Abbreviations: CCS, childhood cancer survivors; eGFR, estimated glomerular filtration rate; NM, not mentioned; NSS, nephron sparing surgery; PRD, pre-operative renal dysfunction; RT, radiotherapy; yrs, years.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Dietz et al. Solid organ transplantation after treatment for childhood cancer: a retrospective cohort analysis from the Childhood Cancer Survivor Study. Lancet Oncol. 2019;20:1420-31.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: retrospective cohort study Treatment era: 1970 – 1986 Follow-up: follow-up until Dec 31, 2013	Type and number of participants: Total CCSS cohort: 13,318 survivors treated before the age of 21 years for childhood cancer and who survived at least 5 years after diagnosis. Diagnoses: Leukemia 4502 (33.8%)	Chemotherapy: Cisplatin 604/11595 (3.4%) Cyclophosphamide 5132/11554 (44.4%) Ifosfamide 62/11602 (0.5%) MTX iv or im 2501/11574 (21.6%) RT renal area: *Kidney*	Outcome definitions Solid organ (kidney) transplantation Results Kidney transplantation 50 received 21 waiting list	Strengths: - linkage of two large databases - clear methods Limitations - Timing

	CNS tumour 1639 (12.3%) Hodgkin lymphoma 1846 (13.9%) Non-Hodgkin lymphoma 1022 (7.7%) Kidney (Wilms') tumor 1162 (8.7%) Neuroblastoma 866 (6.5%) Soft tissue sarcoma 1167 (8.8%) Bone tumor 1114 (8.4%) <u>Age at diagnosis:</u> Median 6 yrs (IQR 3-13) 0-4 yrs 5295 (39.8%) 5-9 yrs 2922 (21.9%) 10-14 yrs 2687 (20.2%) 15-20 yrs 2414 (18.1%) <u>Age at follow-up:</u> Median 39 yrs (IQR 33 – 46) 7 unknown < 20 yrs 612 (4.6%) 20-29 yrs 989 (7.4%) 30-39 yrs 5147 (38.7%) 40-49 yrs 4805 (36.1%) ≥ 50 yrs 1758 (13.2%) <u>Controls:</u> NA	No 3849 (34.1%) >0-10 Gy 6832 (60.4%) >10-20 gy 546 (4.8%) >20 Gy 76 (0/7%) Unknown 2015 *TBI* No 11,196 (98.4%) Yes 185 (1.6%) Unknown 1937 <u>Nephrectomy:</u> Only reported from group that received kidney transplant (n=71, 8 unknown) No 39 (62%) Yes (unilateral) 24 (38%)	Cumulative incidence after 35 yrs for kidney transplantation or being on waiting list = 0.49 %, 95% CI 0.36 – 0.62. 5 year overall survival after kidney transplantation was 93.5%, 95% CI 81.0 – 97.9	Linkage of CCSS cohort to OPTN database to obtain data regarding solid organ (kidney) transplantation from Oct 1, 1987 until Dec 31, 2013 **Risk of bias** <u>A. Selection bias:</u> low risk Reason: Study group consisted of more than 75% of original cohort <u>B. Attrition bias:</u> low risk Reason: Follow-up was complete for more than 75% of study group <u>C. Detection bias:</u> unclear Reason: not applicable <u>D. Confounding:</u> low risk Reason: all important factors were taken into account in MV analyses

Abbreviations: 95%CI, 95% confidence interval; CCSS, childhood cancer survivor study; CNS, central nervous system; Dec, december; Gy, gray; im, intramuscular; IQR, interquartile range; iv, intravenous; MTX, methotrexate; MV, multivariable; NA, not applicable; OPTN, The Organ Procurement and Transplantation Network; TBI, total body irradiation; yrs, years.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Frisk et al. Renal function after autologous bone marrow transplantation in children: a long-term prospective study. Bone Marrow Transplantation. 2002;29:129-136.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design: Prospective once center cohort study Treatment era: October 1985 – August 1997 Follow-up: -At least 6 months - Median: 120 months (group TBI +) - Median: 54 months (group TBI -)	Type and number of participants: 40 patients, less than 18 years, treated with autologous BMT. 26 received TBI (TBI+), 14 did not (TBI-) Diagnoses: TBI +: ALL 23, LBL 3, TBI -:AML 9, HL.3 and LCAL 2 Age at diagnosis: Not known: Age at BMT: TBI +: Median 8.4 yr (range 3.6-17.7) TBI -: Median 13.2 yr (range 1.9 – 17.9) Age at follow-up: NM Controls: Patients are their own controls (GFR before / after BMT)	Chemotherapy: Prednisolone, teniposide, daunorubicin, vincristine, cyclophosphamide, cytarabin, busulfan. Details not stated. Nephrectomy: No RT renal area: TBI: Single fraction, maximum dose to the kidneys 7.5 +/- 5% (4/26 patients received fractionated TBI 12 Gy in 6 fractions, renal dose not known in these patients) Other: In the TBI+ group respectively 50, 29 and 29% received iv vancomycin, aminoglycosides or both. In the TBI- the figures were 42, 62 and 42%	Outcome definitions - Statistically significant reduce in GFR or ERPF at the follow-up compared to GFR or ERPF before BMT -chronic renal impairment: GFR <70 ml/min/1.73m^2 (estimated by single-injection clearance using 51Cr-EDTA, except in the first year of the program, when GFR was measured by endogenous creatinine clearance) Results -GFR in TBI+ group reduced from 124 (114 - 134) to 99 (82 - 115) in 6 months (p<0.001) -ERPF in TBI+ group reduced from 1110 (830 - 1390) to 760 (580 - 940) in 6 months (p=0.064). - No significant changes in TBI- group in 6 months (GFR 129 (117-143) to 121 (105-136)). -7 patients in TBI+ group (27%) developed chronic renal impairment, in all pts the lowest GFR was recorded 6 months after BMT (mean 56, range 38-67). After improving to some extent the GFR stabilized to reduced level. The mean GFR after median of 60 months (range 67-85) was 76 ml/min/1.73m^2, the ERPF had the same pattern. Serum creatinine normalized within 1st year. Microscopic hematuria (4 pts) and proteinuria (3 pts) persisted	Strengths: - clear methods for measuring renal function Limitations: - no controls - age at diagnosis and age at follow-up not known - short time-points (3 and 6 months) - the data on long-term follow-up is lacking for the whole group - the frequency of the measurements was not same for all patients, and the time-points are not presented - the radiation dose on kidneys is not known for all patients Timing - the timing is clear on acute phase (3 and 6 months), but after that there are no clear time-points **Risk of bias** A. Selection bias: low risk Reason: the study group consisted of more than 75% of the original cohort B. Attrition bias: high risk Reason: After 1 year 75% of the pts were studied, but the number reduced quickly: at 2 years 60% were left, at 5 years 65%, 10 years 43% C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for

				important determinants related to the outcome D. Confounding: high risk Reason: Not all important prognostic factors (gender) were taken adequately into account

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMT; bone marrow transplantation; GFR, glomerular filtration rate; HL, Hodgkin lymphoma; LBL, lymphoblastic lymphoma; LCAL, large cell anaplastic lymphoma; NM; not mentioned; pts, patients; RT, radiotherapy; TBI, total body irradiation.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Grönroos et al. Long-term renal function following bone marrow transplantation. Bone Marrow Transplantation. 2007;39:717-723.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Treatment era: 1980 – 2000 Follow-up: Unclear, at least 1 year. By the time of last clearance 63 (34%) had died. Causes: transplantation related 28 (44%), disease progression/relapse 35 (56%).	Type and number of participants: 187 children who underwent BMT Diagnoses: Allogenic BMT 169 Group 1: hematological malignancies 108 (57.8%) ALL 54, AML 33, lymphomas 6, MDS 8, CLL 7 Group 2: aplastic anemias 28 (15.0%) Aplastic anemia 19, Fanconi's anemia 9 Group 3: non-malignant diseases 33 (17.6%) Immunodeficiencies 10, hemoglobinopathies 5, inborn errors 18 Group 4: Autologous BMT 18 (no details reported regarding diagnosis) Age at diagnosis:	BMT Allogenic 169 (90%) Autologous 18 (10%) Conditioning TBI 115/169 (68%) Cyclophosphamide 129/187 (69%) Leukemia pts cyclophosphamide total dose 120 mg/kg, busulfan total dose 16 mg/kg or TBI 10Gy single fraction, or 12-14.4 Gy fractionated. ATG in case of unrelated donors SAA cyclophosphamide total dose 200 mg/kg and ATG. Inborn errors cyclophosphamide total dose 200 mg/kg, busulfan total dose 16 mg/kg HLH or Philadelphia positive ALL etoposide 900 mg/m^2 was added	Outcome definitions Changes in GFR and ERPF determined by the clearance of inulin Results 1. Renal function by type of BMT No differences in GFR or ERPF between auto and allo before or after BMT 2. Renal function by cyclo No differences in GFR or ERPF in pts treated with/without cyclo before BMT and during follow up. 3. Renal function between allo groups before BMT Mean GFR and ERPF (in ml/min/1.73m^2) Group 1: GFR 108 ± 33, ERPF 590 Group 2: GFR 114 ± 38, ERPF 574 Group 3: GFR 130 ± 50, ERPF 587 Controls: GFR 116 ± 11, ERPF 611	Strengths: - GFR measurement by inulin clearance Limitations: - decrease in study sample during longer follow-up period Timing Renal function tests were performed 1-13 times per patient. Total of 415 testes in 187 patients. **Risk of bias** A. Selection bias: low risk Reason: no information original cohort, but random sample with respect to treatment B. Attrition bias: low risk Reason: >75% participated until 1 year follow up, for the longer period follow up high risk

	Age at time of BMT was median 8.0 years (range 0.04 – 17.6) <u>Age at follow-up:</u> <u>Controls:</u> 50 healthy children. Median age 11 years (range 3-22)		Group 1 had significantly lower GFR compared to controls (p=0.02) 4. <u>Changes in renal function pre-BMT to 1 year after total group</u> Both GFR and ERPF reduced 1 year after BMT compared to pre-BMT (p<0.0001), and compared to 1 year GFR of controls (p<0.001) Pre-BMT: GFR 114± 39, ERPF 586± 222 1 yr post BMT: GFR 85± 26, ERPF 508± 189 GFR was decreased significantly in all groups, ERPF only in group 1 (hematological malignancies) 5. <u>Changes renal function over time</u> 3 years after transplantation a slight recovery in GFR after the initial fall was seen (P=0.04) , after which it remained stable. Renal impairment post BMT: 3 yrs 31%, 7 yrs 11% and 10 yrs 23% In pts with hematological malignancies GFR was significantly lower in those with non-malignant diseases (p=0.01) 6. <u>Influence TBI</u> In the TBI + group, the fall in GFR and ERPF after BMT was more profound than in the TBI- group at all time points (p=0.02)	<u>C. Detection bias:</u> unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome <u>D. Confounding:</u> high risk Reason: Analyses were not corrected for possible confounders

Abbreviations: ALL, acute lymphoblastic leukemia; allo, allogenic; AML, acute myeloid leukemia; ATG, anti thymocyte globulin; auto, autologous; BMT, bone marrow transplantation, CLL, chronic lymphoblastic leukemia; cyclo, cyclophosphamide; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; MDS, myelodysplastic syndrome; pts, patients; SAA, severe aplastic anemia; TBI, total body irradiation.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Grönroos et al. Long-term follow-up of renal function after high-dose methotrexate treatment in children. Pediatr Blood Cancer. 2008;51:535-539.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective & cross-sectional cohort study Treatment era: 1992 – 2003 Follow-up: Median 6.0 years (range 1.0 – 10.0 years)	Type and number of participants: 28 CCS Diagnoses: ALL 25 (89%), lymphoma 3 (11%) Age at diagnosis: Median 7.7 years (range 1.5 – 15.4 years) Age at follow-up: NM Controls: NA	Chemotherapy: HD-MTX 28 (100%) Dose 5 g/m^2 n=16 Dose 8 g/m^2 n=12 Other agents NM Nephrectomy: NM RT renal area: NM Other Amphoterisin B 9 (32.1%) Vancomycin 8 (28.6%) Gentamycin 6 (21.4%)	Outcome definitions Change in iGFR in ml/min/1.73m^2 (during follow up evaluated by ^{5}Cr-EDTA or ^{99m}Tc-DTPA, pre-treatment in 17 pts isotope and in 11 pts by Schwartz formula) Results Pre-treatment Mean GFR isotope method 136.7 (range 87 – 237) Mean GFR by Schwartz 109.4 (range 79.5 – 152.3) Follow up: Mean iGFR 113.9 (SD 24.2, range 75.7 – 185.6) iGFR ≥ 115 n=11 (39%) iGFR 90-114 n=14 (50%) iGFR ≤ 89 n=3 (11%) Change in GFR The iGFR declined significantly with increasing follow-up time (p=0.02) In subgroup of 17 pts with isotope GFR measurement pre—treatment and during follow-up the mean iGFR dropped from 136.7 (pre-treatment) to 118.8 (follow-up), but not significantly.	Strengths: - homogeneous study population - majority isotope GFR measurements - taking into account nephrotoxic antibiotics Limitations: - only 1 follow-up measurement with variation in follow-up duration among patients - small study sample - differences in GFR measurement Timing Single measurement taken at median of 6.0 post treatment and compared with pre-treatment measurement. **Risk of bias** A. Selection bias: unclear Reason: Not reported how many childhood cancer survivors were in the original cohort, but seems random sample with respect to cancer treatment B. Attrition bias: low risk Reason: Outcome assessed for total study group C. Detection bias: unclear

			No significant influence on change of iGFR by age at time of diagnosis, dose of MTX (5 or 8 g/m^2), cumulative MTX dose or simultaneous use of amphotericin B, vancomycin or gentamycin.	Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk Reason: Important confounding factors taken into account

Abbreviations: ^{51}Cr-EDTA, chromium-51-ethylenediaminetetraacetic acid; ^{99m}Tc-DTPA, ^{99m}Tc-diethylenetriaminepentaacetic acid; ALL, acute lymphoblastic leukemia; CCS, childhood cancer survivors; (i)GFR, (isotope) glomerular filtration rate; MTX, methotrexate; NA, not applicable; NM, not mentioned.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Janeczko et al. Evaluation of Renal Function in Pediatric Patients After Treatment for Wilms' Tumor. Adv Clin Exp Med. 2015;24 (3):497-504.				
Study design **Treatment era** **Years of follow-up**	Participants	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Single institution, cohort study Treatment era: 2002-2012. Follow-up: 2 years after completion of therapy	Type and number of participants: 50 children treated for Wilm's Tumour. 44% boys and 56% girls. Diagnoses: Nephroblastoma (Wilm's Tumour) (50, 100%). Stage I in 29 patients (58%), Stage II in 13 patients (26%), Stage III in 4 patients (8%) and Stage IV in 2 patients (4%). 2 (4%) patients were diagnosed with bilateral disease (Stage V). Age at diagnosis: 2 months to 12 years (median 3.1 years) Age at follow-up: Not stated (study period completed 2 years after therapy completion) Controls: NA Additional characteristics: 4 patients relapsed (1 in CNS and 3	Treatment was performed according to the SIOP 2001 protocol. Chemotherapy: Pre-operative chemotherapy was recommended in 92% of patients. Post-operative chemotherapy was given in all patients. Chemotherapy drugs used were: Vincristine, n=50(100%) Actinomycin, n=48 (96%) Doxorubicin, n=18 (36%) Etoposide, n=5 (10%) Carboplatin, n=5 (10%) Cyclophosphamide, n=5 (10%) Nephrectomy: Total nephrectomy was performed in 82% (41 children) and nephron-sparing surgery (partial nephrectomy) was performed in 18% (9 children).	Outcome definitions: Glomerular Filtration Rate (GFR) by Schwartz formula, with normal ranges defined as follows: • 1-6 months age >39mL/min/1.73m^2 • 6-12 months age >49mL/min/1.73m^2 • 12-23 months age >62mL/min/1.73m^2 • >2 years age >90mL/min/1.73m^2 Maximum serum creatinine with normal ranges defined as follows: • 7 weeks to 3 years age 0.4mg/dL • 4 to 7 years age 0.5mg/dL • 8 to 10 years age 0.8mg/dL • 10 to 13 years age 0.9mg/dL • 10 to 13 years age 0.9mg/dL	Strengths: - Uniform therapy - Clear outcome definitions Limitations: - Short follow-up time (2 years post completion of therapy). - Small numbers, particularly with more advanced or bilateral disease or use of radiotherapy. Timing During 2 year follow-up time the frequency was every 6-12 months **Risk of bias** A. Selection bias: Unclear Reason: Although apparently 'Low', the authors don't state ascertainment methods or % eligible patients enrolled. B. Attrition bias: low risk

	in Lungs). 1 of the pulmonary relapse patients suffered a CNS progression during relapse therapy and died of disease.	<u>RT renal area:</u> 'Local radiotherapy' was implemented in 12% (6 patients) and 6% (3 patients) received whole lung radiotherapy.	Serum urea was considered raised for values above 40mg/dL (regardless of the child's age) Blood pressure (using OLAF project standards for BP in Polish children and young people) was considered abnormal if the value exceeded the 95th percentile (for weight and height) <u>Results (Longitudinal)</u> <u>Abnormal GFR</u> (n) *Age 12 -13 months* EoT: 6 6 months: 2 12 months: 1 24 months: 0 *>2 years* EoT: 17 6 months: 17 12 months: 20 24 months: 7 No difference over time between CPM/Carbo and non-CPM/Carbo No difference over time between nephrectomy and nephron-sparing surgery <u>Serum Creatinine</u> (mg/dL/% raised):	Reason: Of patients enrolled, 4 patients relapsed. It appears that they were included in ongoing follow-up, but this is not overtly stated. <u>C. Detection bias:</u> unclear Reason: No information on blinding provided <u>D. Confounding:</u> high risk Reason: Important confounding factors not (all) taken into account

	Mean	Median	SD	raised n (%)

			Start Rx: 0.53; 0.54; 0.15; 30 (60%) EoT: 0.55; 0.56; 0.15; 32 (64%) 6 mnths: 0.59; 0.61; 0.12; 32 (64%) 12 mnths: 0.58; 0.60; 0.16; 24 (48%) 24 mnths: 0.58; 0.61; 0.13; 13 (26%) Hypertension: Beginning of therapy: 15 EoT: 8 6 months: 4 12 months: 5 24 months: 4	

Abbreviations: BP, blood pressure; carbo, carboplatin; CNS, central nervous system; CPM, cyclophosphamide; EoT, end of therapy; GFR, glomerular filtration rate; NA, not applicable; RT, radiotherapy.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Mulder et al. Glomerular function time trends in long-term survivors of childhood cancer: a longitudinal study. Cancer Epidemiol Biomarkers Prev. 2013;22:1736-46.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective cohort study Treatment era:	Type and number of participants: 1122 CCS with a survival of ≥ 5 years since diagnosis, aged ≥ 18 years at time of glomerular	Ifosfamide: 155/1122 (13.8%) Cisplatin: 88/1122 (7.8%)	Outcome definitions 1. Continuous GFR 2. Decreased GFR:	Eligible cohort 1502 CCS. Out of 1122 CCS treated with potentially nephrotoxic treatment and having a renal function test,

1966-2003 Follow-up: Median 21 yr (range 5.0 – 42.0) after cancer diagnosis until last GFR test	function testing, and treated with potentially nephrotoxic therapy. 251 treated without potentially nephrotoxic therapy. Years of assessment 1996-2010 Diagnoses: 1122 treated with potentially nephrotoxic therapy: leukemia 267 (23.8%), lymphoma 259 (23.1%), brain/CNS tumour 77 (6.9%), bone tumour 99 (8.8%), soft tissue sarcoma 125 (11.1%), renal tumour 144 (12.8%), hepatic tumour 10 (0.9%), germ cell tumour 45 (4%), NB 57 (5.1%), retinoblastoma 11 (1%), other 28 (2.5%) Age at diagnosis: 0-18 yr Age at follow-up: 2-18 yr Controls: 251 CCS treated without potentially nephrotoxic therapy	Carboplatin: 64/1122 (5.7%) HD-cyclophosphamide* 134/1122 (11.9%) HD-methotrexate** 253/1122 (22.5%) Nephrectomy: 147/1122 (13.1%), partial 7 (0.9%), complete 140 (12.5%) RT renal area: 116/1122 (10.3%) RT field: abdominal 95 (8.5%), TBI 21 (1.9%) *(≥1 g/m^2/course or a total cumulative dose of ≥ 10 g/m^2) ** (≥1 g/m^2/course)	GFR < 90 mL/minute/1.73 m² (by CKD-epi formula) Results linear random effects model (continuous GFR) Age at diagnosis, p < 0.001 Older age associated with a lower GFR Ifosfamide, p < 0.001, ifosfamide cumulative dose effect p < 0.001, ifosfamide by time interaction p= 0.08, ifosfamide dose by time interaction p=0.09 No significantly different GFR pattern over time for CCS treated with and without ifsofamide Cisplatin, p < 0.001, cisplatin cumulative dose effect p < 0.001 (especially ≥ 500 mg/m²), cisplatin by time interaction p = 0.002, cisplatin dose by time interaction p = 0.004 Higher deterioration rate in CCS with higher doses of cisplatin vs. lower doses up to 25 years after diagnosis Carboplatin p = 0.006, carboplatin cumulative dose effect p =0.07, carboplatin by time interaction p = 0.24, carboplatin dose by time interaction p = 0.06 HD-cyclophosphamide (≥ 1 g/m²/ course or a total cumulative dose of ≥ 10 g/m²), p = 0.005 HD-cyclophosphamide by time interaction, p = 0.006	920 CCS had repeated observations. P-value <0.01 was considered significant. Timing 920 CCS had repeated observations. The screening frequency was comparable between CCS treated with and without nephrotoxic therapy (0.96 and 0.95 per year, respectively), and between CCS with a normal and an abnormal GFR during the course of followup (0.95 and 0.94 per year, respectively). Median follow up from first until last glomerular function test 7.3 yr (range 0.8-14.3) Strengths - Longitudinal analysis - Large study sample - Long follow-up period Limitations - Only p-values provided for multivariable risk analyses - No information regarding co-medication (e.g., nephrotoxic antibiotics) or predisposition (e.g., WT1 mutations) **Risk of bias** A. Selection bias: low risk Reason: the study group consisted of more than 75% of the original cohort B. Attrition bias: low risk

			CCS treated with and without HD-cyclophosphamide showed different GFR time trends, although differences were small HD-MTX (≥ 1 g/m²/course), p = 0.07, HD-MTX by time p=0.17 RT kidney region, p =0.012, RT by time interaction p =0.04 Nephrectomy, p < 0.001, Nephrectomy by time interaction p= 0.26, nephrectomy age at diagnosis p = 0.002 Faster decline in GFR in CCS nephrectomized at an older vs. younger age <u>*Comparison with controls*</u> Mean GFR in mL/min/1.73m2 (95%CI) At 5 years after diagnosis CCS with nephrotoxic treatment: 132 (130.5 – 133.6) CCS without nephrotoxic treatment: 139 (137.0 – 141.1) At 35 years after diagnosis CCS with nephrotoxic treatment: 95.2 (92.2 – 97.9) CCS without nephrotoxic treatment: 100.2 (98.1 – 102.3) GFR declined in both groups during follow up, p < 0.001. The differences in GFR between both groups were highly significant (P < 0.001), but the differences in time trends were not (P = 0.04).	Reason: the outcome was assessed for more than 75% of the study group <u>C. Detection bias:</u> unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome <u>D. Confounding:</u> low risk Reason: All important prognostic factors were taken adequately into account

Abbreviations: 95% CI, 95% confidence interval; CCS, childhood cancer survivors; CNS, central nervous system; GFR, glomerular filtration rate; HD, high-dose; MTX, Methotrexate; NB, neuroblastoma; NM; not mentioned; RT, radiotherapy; TBI, total body irradiation; yr, year.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Patzer et al. Renal function in long-term survivors of stem cell transplantation in childhood. A prospective trial. Bone marrow transplantation. 2001;27:319-327 .				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective cohort study Treatment era: 1992 – 1998 Follow-up: prospective, time points of evaluation 20 days before, and 1 and 2 years after HSCT	Type and number of participants: Survivors of HSCT 1 year after HSCT: 44 patients 2 years after HSCT: 36 patients *Group A:* 41 pts with normal renal function prior to HSCT *Group B:* 3 pts with unilateral nephrectomy Diagnoses: *Group A (41 pts):* ALL 13 (31.7%) ANLL 9 (22.0%) CML 4 (9.8%) HL 4 (9.8%) Non-HL 2 (4.9%) Ewing sarcoma 2 (4.9%) PNET 2 (4.9%) Rhabdomyosarcoma 1 (2.4%) MDS 1 (2.4%) Osteosarcoma 1 (2.4%) SAA 1 (2.4%) Neuroblastoma 1 (2.4%) *Group B (3 pts):* - Metastatic clear cell sarcoma left kidney - Metastatic nephroblastoma - Pulmonary relapse nephroblastoma Age at diagnosis:	HSCT *Group A* Allogeneical 20/41 (48.8%) Autologous 21/41 (51.2%) (6 MUD, 10 MRD, 3 Haplo, 1 MMUD) *Group B* Autologous 3/3 (100%) Ifosfamide *Group A* 23/41 (56.1%), median cumulative dose 10 g/m^2, range 2-86 *Group B* 3/3 (100%); cumulative dose 24 g/m^2, 12 g/m^2 and 43 g/m^2 Cisplatin *Group A* 0/41 (0%) *Group B* 1, cumulative dose 300 mg/m^2 Carboplatin *Group A* 0/41 (0%) *Group B* 3/3 (100%), cumulative dose 400 mg/m^2, 1.8 g/m^2, 1.4 g/m^2 Melphalan *Group A* 0/41 (0%) *Group B* 3/3 (100%), cumulative dose 180 mg/m^2, 120 mg/m^2, 180 mg/m^2 Nephrectomy: *Group A* 0/41 (0%) *Group B*	Outcome definitions 1. GFR < 90 ml/min/1.73m^2, measured by inulin clearance Longitudinal results GFR (ml/min/1.73m^2) *Group A, median* Before: 130 (range 73-217) 1 year: 123 (range 68-185)* 2 years: 105 (range 81-177)* Significantly different compared to before *GFR <90 ml/min/1.73m^2* *Group A & B* Before: 1/33 1 year: 2/28 2 years: 2/16 No significant differences with respect to: - acute renal failure within 30 days after HSCT vs no doubling of creatinine - initial disease - type of conditioning (TBI or not) - kind of HSCT (allo vs auto) - presence of GVHD at time of investigation	Strengths: - clear description of cohort - inulin clearance Limitations: - For some outcome measures important lost to follow-up Timing 20 days before, and 1 and 2 years after HSCT **Risk of bias** A. Selection bias: low risk Reason: at 2 year follow up study group consisted of 65% of original cohort of survivors without relapse, but it was a random sample with respect to treatment B. Attrition bias: high risk Reason: GFR was assessed for 39% of study group at 2 years C. Detection bias: unclear Reason: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: high risk Reason: Important confounding factors not (all) taken into account

	Group A: median 13.6 years (range 3.9-42) at time of HSCT, 10 pts >16 years *Group B:* 3.9 years, 5.6 years, 22.3 years Age at follow-up: NM Controls: NA	3/3 (100%), unilateral RT renal area: *Group A* NM *Group B* 1/3 (33%), TBI 8 x 1.5 Gy Other *Group A* 1 year after HSCT all were taking antibiotic prophylaxis (penicillin or cotrimoxazol), 7 were receiving methotrexate, 6 CyA, 1 FK506, 3 prednisolone, 4 azathioprine, 4 6-thioguanine and 4 6-mercaptopurine. 2 years after HSCT all children were off CyA.		

Abbreviations: ALL, acute lymphoblastic leukemia; allo, allogeneical; ANLL, acute non-lymphoblastic leukemia; auto, autologous; CML chronic myeloid leukemia; CyA, cyclosporine; Gy, gray; HL, Hodgkin lymphoma; GFR, glomerular filtration rate; GVHD, graft versus host disease; HSCT, hematological stem cell transplantation; MMUD, mismatch unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; NA, not applicable; Non-HL, non-Hodgkin lymphoma; NM, not mentioned; PNET, primitive neuro ectodermal tumor; pts, patients; RT, radiotherapy; TBI, total body irradiation.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Skinner et al. Persistent nephrotoxicity during 10-year follow-up after cisplatin or carboplatin treatment in childhood: relevance of age and dose as risk factors. European Journal of Cancer. 2009;45:3213-3219.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: prospective single-center longitudinal cohort study Treatment era: 1981- 1996 Follow-up: at least 10 years, the 1 and 10 year studies at median 1.1 years (range 0.7-2.3) and 10.3 years (range 9.0-12.3)	Type and number of participants: 63 CCS aged 18 years at treatment, treated with platinum and who survived at least 10 years after completion of therapy Diagnoses: *Cisplatin alone (n=27):* Osteosarcoma 12 (44.4%) Germ cell tumor 4 (14.8%) Brain tumor 3 (11.1%) Liver tumor 3 (11.1%)	Ifosfamide: 0/63 (0%) Cisplatin alone: 27/63 (42.9%), total median dose 500 mg/m^2 (range 300-960) Carboplatin alone: 24/63 (38.1%), total median dose 2400 mg/m^2 (range 560-8800) Cisplatin and carboplatin: 12/63 (19.0%), total median dose cisplatin 473 mg/m^2 (range 240-739), total median dose	Outcome definitions 1. Decreased GFR <90 ml/min/1.73m^2, measured by ^{51}Cr-EDTA plasma clearance Results GFR % normal results (95%CI) *Cisplatin alone* End: 40 (19-64), median 84 (18-197)	Strengths: - long-term follow-up - clear description of study cohort Limitations: - due to small numbers in subgroups multivariable risk analyses not possible Timing

	Epithelial carcinoma 1 (3.7%) Ewing's sarcoma 1 (3.7%) Nasopharyngeal carcinoma 1 (3.7%) Neuroblastoma 1 (3.7%) Salivary gland carcinoma 1 (3.7%) *Carboplatin alone (n=24):* Germ cell tumor 9 (37.5%) Medulloblastoma 5 (20.8%) Other brain tumor 5 (20.8%) Neuroblastoma 3 (12.5%) CCSK 1 (4.2%) Retinoblastoma 1 (4.2%) *Cisplatin and carboplatin (n=12):* Neuroblastoma 9 (75%) Brain tumor 3 (25%) <u>Age at diagnosis:</u> *Cisplatin alone:* Median 7.7 years (range 0.6-17.8) *Carboplatin alone:* Median 4.4 years (range 0.4-15.8) *Cisplatin and carboplatin:* Median 1.9 years (range 0.1-6.2) <u>Age at follow-up:</u> NM <u>Controls:</u> NA	carboplatin 1500 mg/m^2 (range 750-4200) <u>HD-melphalan</u> 9/63 (14.3%) <u>MTX</u> 8/63 (12.7%) (intermediate 1 g/m^2 of high-dose 8 g/m^2) <u>Nephrectomy:</u> NM <u>RT renal area:</u> 3/63 (4.8%) and 5/63 received a small amount of scatter. <u>Other</u> Actinomycin D, bleomycin, cyclophosphamide, doxorubicin, etoposide, 5-fluorouracil, teniposide, vincristine. Supportive care: aminoglycosides, amphotericin.	1 year: 62 (38-82), median 98 (25-130) 10 years: 60 (39-70), median 96 (29-142) *Carboplatin alone* End: 80 (56-94), median 120 (68-207) 1 year: 81 (58-95), median 109 (63-161) 10 years: 79 (58-93), median 110 (66-171) *Cisplatin and carboplatin* End: 80 (44-97), median 91 (45-160) 1 year: 75 (43-95), median 93 (55-131) 10 years: 55 (22-83), median 92 (66-135) Substantial inter-individual variability was observed with some survivors showing improvement and others deterioration in glomerular, tubular or overall renal function during follow-up. There was no significant change with time in any of the measures of nephrotoxicity in any treatment group, nor in the proportion with clinically significant complications or ongoing treatment with supplements.	Evaluation at 1 month (end), 1 year and 10 years after end of therapy **Risk of bias** <u>A. Selection bias:</u> low risk Reason: study group consisted of 93% of original cohort <u>B. Attrition bias:</u> low risk Reason: outcomes were assessed for >75% of study group <u>C. Detection bias:</u> unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome <u>D. Confounding:</u> NA Reason: no risk analyses

Abbreviations: ^{51}Cr-EDTA, ^{51}Cr-labelled ethylenediaminetetraacetic acid; 95%CI, 95% confidence interval; CCS, childhood cancer survivors; GFR, glomerular filtration rate; HD, high-dose; MTX, methotrexate; NA, not applicable; NM, not mentioned; RT, radiotherapy.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?

Skinner et al. Glomerular Toxicity Persists 10 Years After Ifosfamide Treatment in Childhood and Is Not Predictable by Age or Dose. Pediatr Blood Cancer. 2010; 54: 983-98.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective longitudinal single center cohort study Treatment era: Start ifosfamide 1986-1996 Follow-up: 1 year studies median 1.1 year (0.9-2.1) and 10 year studies median 10.5 (9.3-11.4) years after ifosfamide completion	Type and number of participants: 25 CCS who survived at least 10 years after completion of treatment; all patients had normal renal function (as demonstrated by normal serum creatinine, bicarbonate, and phosphate concentrations) prior to ifosfamide treatment or during treatment but before the onset of nephrotoxicity. Diagnoses: 12 (48%) rhabdomyosarcoma 6 (24%) soft tissue sarcoma 6 (24%) Ewing sarcoma 1 (4%) soft tissue primitive neuroectodermal tumor Age at diagnosis: Not reported (age at start ifosfamide median 6 (0.6-14.7) years) Age at follow-up: Not reported Controls: No (but age-related reference ranges of outcomes used for analyses) Additional study characteristics: 16 (64%) males	Chemotherapy: 25 (100%) ifosfamide; median total dose 106 (12-153) g/m2 IV 2 (8%) melphalan; dose not reported Actinomycin D, doxorubicin, etoposide, cyclophosphamide, vincristine: number of patients and dose not reported Nephrectomy: 0 (0%) RT renal area: 2 (8%) small area of kidney; dose not reported 1 (4%) TBI; 12 Gy	Outcome definitions: Change in GFR (ml/min/1.73m2) Clinically significant complication: GFR<60 ml/min/1.73m^2 (sometimes reported as <=60, method for measurement not reported) Hypertension (standard definition; no further information reported) Results: There was considerable interpatient variability in the severity of renal toxicity and in changes with time (GFR); some survivors showed substantial deterioration and others marked improvement. GFR <=60ml/min/1.73m2: 0% at end of treatment 4% at 1 year 13% at 10 years Hypertension: 1 (4%) received treatment for stage 2 hypertension at 10 years. No other patients required antihypertensive treatment during follow-up. No correlation between cumulative ifosfamide dose or age at treatment and GFR at any timepoint.	Strengths: Relatively long follow-up period with more than 2 measurements Limitations: - Small study size - method for GFR measurement not reported Timing: Sequential measurements at end of treatment and 1 and 10 years thereafter. **Risk of bias** A. Selection bias: low risk Reason: 25/29=86% of eligible patients included B. Attrition bias: low risk Reason: End of treatment minimal 21/25=84% follow-up 1 and 10 years: minimal 24/25=96% follow-up C. Detection bias: unclear Reason: No information on blinding provided D. Confounding: high risk Reason: Important confounding factors not (all) taken into account

Abbreviations: CCS, childhood cancer survivors; GFR, glomerular filtration rate; Gy, gray; IV, intravenous; TBI, total body irradiation.

When should glomerular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Stohr et al. Nephrotoxicity of Cisplatin and Carboplatin in Sarcoma Patients: A Report From the Late Effects Surveillance System. Pediatr Blood Cancer. 2007;48:140-7.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective multicenter study Treatment era: Registered on a GPOH trial between 1-1-1998 and 1-1-2002 Follow-up: Median follow-up 2 years. Follow-up to most recent renal examination in 435 survivors with information on serum magnesium was median 23 months (IQR 10-35; range 0-59).	Type and number of participants: 651 sarcoma patients younger than 18 years at diagnosis; follow-up minimal at end of treatment. Diagnoses: Ewing sarcoma (N not reported) Osteosarcoma (N not reported) Soft tissue sarcoma (N not reported) Age at diagnosis: <18 years Age at follow-up: Not reported Controls: From within cohort: survivors not treated with any platinum derivative (i.e., Ewing and some soft tissue sarcoma patients) Additional study characteristics: Gender not reported for complete study population	Chemotherapy: Platinum (osteosarcoma and some soft tissue sarcoma patients): Cisplatin and/or carboplatin Other chemotherapeutic agents: Ifosfamide (most patients) Combination of actinomycin D, busulfan, doxorubicin, epirubicin, melphalan, methotrexate, or vincristine Actual received cumulative doses not reported for the (complete) study population Nephrectomy: Not reported RT renal area: Abdominal RT applied when indicated in some Ewing and soft tissue sarcoma patients; no further information provided, unclear if renal area in the field. Other treatments: Magnesium supplementation as prophylaxis during treatment; no further information provided.	Outcome definitions Decreased GFR (calculated using Schwartz formula; defined according to CTCEv3) Results It was stated that "Estimation of the GFR by the Schwartz formula turned out not to be appropriate in this study population, especially in the first year after therapy, where more than 40% of all patients had an estimated GFR above the upper limit of normal. This indicated a considerable overestimation of the GFR. With further follow-up, this proportion decreased." No further information provided; information on serum creatinine was available for 618/651 (95%) survivors, but not reported if for all these survivors the GFR was also available.	Strengths: - Limitations: GFR calculated using Schwartz formula is not optimal; only very limit amount of information provided. Timing Yearly intervals after end of treatment **Risk of bias** A. Selection bias: unclear Reason: Not reported how many childhood cancer survivors were in the original cohort B. Attrition bias: unclear Reason: Not reported for how many survivors information on GFR was available. C. Detection bias: unclear Reason: No information on blinding provided. D. Confounding: NA Reason: No risk estimation done

Abbreviations: GFR, glomerular filtration rate; IQR, inter quartile range; N, number; NA, not applicable; RT, radiotherapy.

When should tubular dysfunction surveillance be initiated and at what frequency should surveillance be performed?

When should tubular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Janeczko et al. Evaluation of Renal Function in Pediatric Patients After Treatment for Wilms' Tumor. Adv Clin Exp Med. 2015;24 (3):497-504.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Single institution, cohort study Treatment era: 2002-2012. Follow-up: 2 years after completion of therapy	Type and number of participants: 50 children treated for Wilm's Tumour. 44% boys and 56% girls. Diagnoses: Nephroblastoma (Wilm's Tumour) (50, 100%). Stage I in 29 patients (58%), Stage II in 13 patients (26%), Stage III in 4 patients (8%) and Stage IV in 2 patients (4%). 2 (4%) patients were diagnosed with bilateral disease (Stage V). Age at diagnosis: 2 months to 12 years (median 3.1 years) Age at follow-up: Not stated (study period completed 2 years after therapy completion) Controls: None Additional characteristics: 4 patients relapsed (1 in CNS and 3 in Lungs). 1 of the pulmonary relapse patients suffered a CNS progression during relapse therapy and died of disease.	Treatment was performed according to the SIOP 2001 protocol. Chemotherapy: Pre-operative chemotherapy was recommended in 92% of patients. Post-operative chemotherapy was given in all patients. Chemotherapy drugs used were: Vincristine, n=50 (100%) Actinomycin, n=48 (96%) Doxorubicin, n=18 (36%) Etoposide, n=5 (10%) Carboplatin, n=5 (10%) Cyclophosphamide, n=5 (10%) Nephrectomy: Total nephrectomy was performed in 82% (41 children) and nephron-sparing surgery (partial nephrectomy) was performed in 18% (9 children). RT renal area: 'Local radiotherapy' was implemented in 12% (6 patients) and 6% (3 patients) received whole lung radiotherapy.	Outcome definitions Proximal tubular function based on serum sodium, potassium and phosphorus with ranges: Sodium 138-144mEq/L Potassium 3.4-4.7 mEq/L Phosphorus 4.49-5.51 mEq/L Results (Longitudinal) Serum electrolytes: Sodium *Decreased* Beginning treatment: 39% EoT: 17% 6 months: 21% 12 months: 6% 24 months: 0% *Increased* Beginning treatment: 0% EoT: 0% 6 months: 0% 12 months: 2% 24 months: 0% Potassium *Decreased* Beginning treatment: 4% EoT: 2% 6 months: 0% 12 months: 0% 24 months: 3% *Increased* Beginning treatment: 12%	Strengths: - Uniform therapy - Clear outcome definitions Limitations: - Short follow-up time (2 years post completion of therapy). - Small numbers, particularly with more advanced or bilateral disease or use of radiotherapy. Timing During 2 year follow-up time the frequency was every 6-12 months **Risk of bias** A. Selection bias: Unclear Reason: Although apparently 'Low', the authors don't state ascertainment methods or %eligible patients enrolled. B. Attrition bias: low risk Reason: Of patients enrolled, 4 patients relapsed. It appears that they were included in ongoing follow-up, but this is not overtly stated. C. Detection bias: unclear Reason: No information on blinding provided

			EoT: 4% 6 months: 19% 12 months: 25% 24 months: 12% <u>Phosphorus</u> *Decreased* Beginning treatment: 46% EoT: 27% 6 monhts: 57% 12 months: 18% 24 monhts: 22% *Increased* Beginning treatment: 12% EoT: 32% 6 months: 14% 12 months: 27% 24 months: 22%	<u>D. Confounding:</u> high risk Reason: Important confounding factors not (all) taken into account

Abbreviations: CNS, central nervous system; EoT, end of treatment; RT, radiotherapy.

When should tubular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Patzer et al. Renal function in long-term survivors of stem cell transplantation in childhood. A prospective trial. Bone marrow transplantation. 2001;27:319-327 .				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design: Prospective cohort study Treatment era: 1992 – 1998 Follow-up: prospective, time points of evaluation 20 days before, and 1 and 2 years after HSCT	Type and number of participants: Survivors of HSCT 1 year after HSCT: 44 patients 2 years after HSCT: 36 patients *Group A:* 41 pts with normal renal function prior to HSCT *Group B:* 3 pts with unilateral nephrectomy Diagnoses: *Group A (41 pts):* ALL 13 (31.7%) ANLL 9 (22.0%) CML 4 (9.8%) HL 4 (9.8%) Non-HL 2 (4.9%) Ewing sarcoma 2 (4.9%) PNET 2 (4.9%) Rhabdomyosarcoma 1 (2.4%) MDS 1 (2.4%) Osteosarcoma 1 (2.4%) SAA 1 (2.4%) Neuroblastoma 1 (2.4%) *Group B (3 pts):* - Metastatic clear cell sarcoma left kidney - Metastatic nephroblastoma - Pulmonary relapse nephroblastoma Age at diagnosis: *Group A:* median 13.6 years (range 3.9-42) at time of HSCT, 10 pts >16 years *Group B:* 3.9 years, 5.6 years, 22.3 years Age at follow-up: NM	HSCT *Group A* Allogeneical 20/41 (48.8%) Autologous 21/41 (51.2%) (6 MUD, 10 MRD, 3 Haplo, 1 MMUD) *Group B* Autologous 3/3 (100%) Ifosfamide *Group A* 23/41 (56.1%), median cumulative dose 10 g/m^2, range 2-86 *Group B* 3/3 (100%); cumulative dose 24 g/m^2, 12 g/m^2 and 43 g/m^2 Cisplatin *Group A* 0/41 (0%) *Group B* 1, cumulative dose 300 mg/m^2 Carboplatin *Group A* 0/41 (0%) *Group B* 3/3 (100%), cumulative dose 400 mg/m^2, 1.8 g/m^2, 1.4 g/m^2 Melphalan *Group A* 0/41 (0%) *Group B* 3/3 (100%), cumulative dose 180 mg/m^2, 120 mg/m^2, 180 mg/m^2 Nephrectomy: *Group A* 0/41 (0%) *Group B* 3/3 (100%), unilateral RT renal area: *Group A* NM *Group B* 1/3 (33%), TBI 8 x 1.5 Gy	Outcome definitions 1. TP/Cl$_{cr}$ <1.07 mmol/l 2. α1-mg >1.0 mg/mmol creat 3. β-NAG > 0.4 U/mmol creat Longitudinal results TP/Cl$_{cr}$ (mmol/l) *Group A, median* Before: 1.21 (range 0.51-1.75) 1 year: 1.11 (range 0.56-1.64)* 2 years: 1.08 (range 0.53-1.44)* Significantly different compared to before *TP/Cl$_{cr}$ <1.07 mmol/l* *Group A* Before: 13/41 1 year: 17/39 2 years: 15/33 No significant differences with respect to earlier ifosfamide therapy, kind of HSCT (allo vs auto), use of RT, occurrence of acute renal insufficiency, presence of chronic GVHD, CyA therapy 1 year after HSCT Longitudinal results α1-mg (mg/mmol creat) *Group A, median* Before: 0.98 (range 0.02-9.9) 1 year: 0.66 (range 0.03-23.2) 2 years: 0.63 (range 0.03-17.12) No significant differences *α1-mg >1.0 mg/mmol creat* *Group A* Before: 18/41 1 year: 16/40 2 years: 13/33	Strengths: - clear description of cohort - inulin clearance Limitations: - For some outcome measures important lost to follow-up Timing 20 days before, and 1 and 2 years after HSCT **Risk of bias** A. Selection bias: low risk Reason: at 2 year follow up study group consisted of 65% of original cohort of survivors without relapse, but it was a random sample with respect to treatment B. Attrition bias: TP/Cl$_{cr}$: low risk Reason: outcome assessed for >75% of study group α1-mg: low risk Reason: outcome assessed for >75% of study group β-NAG: high risk Reason: outcome assessed for 63% at 2 year follow up C. Detection bias: unclear Reason: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: high risk Reason: Important confounding factors not (all) taken into account

	Controls: NA	Other *Group A* 1 year after HSCT all were taking antibiotic prophylaxis (penicillin or cotrimoxazol), 7 were receiving methotrexate, 6 CyA, 1 FK506, 3 prednisolone, 4 azathioprine, 4 6-thioguanine and 4 6-mercaptopurine. 2 years after HSCT all children were off CyA.	No significant differences with respect to ifosfamide therapy, kind of HSCT (allo vs auto), RT use, acute renal insufficiency, presence of GVHD or CyA therapy 1 year after HSCT Longitudinal results β-NAG *Group A, median* Before: 0.45 (range 0.16-1.7) 1 year: 0.27 (range 0.05-1.4)* 2 years: 0.22 (range 0.06-1.13)* * Significantly different compared to before *β-NAG > 0.4 U/mmol creat* *Group A* Before: 17/31 1 year: 8/31 2 years: 5/26	

Abbreviations: α1-mg, α1-microglobuline; β-NAG, β-N-acetylglucosaminidase; ALL, acute lymphoblastic leukemia; allo, allogeneical; ANLL, acute non-lymphoblastic leukemia; auto, autologous; CML chronic myeloid leukemia; creat, creatinine; CyA, cyclosporine; Gy, gray; HL, Hodgkin lymphoma; GVHD, graft versus host disease; HSCT, hematological stem cell transplantation; MMUD, mismatch unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; NA, not applicable; Non-HL, non-Hodgkin lymphoma; NM, not mentioned; PNET, primitive neuro ectodermal tumor; pts, patients; RT, radiotherapy; TBI, total body irradiation; TP/Cl_{cr}, tubular phosphate reabsorption.

When should tubular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Rossi et al. Development of ifosfamide-induced nephrotoxicity: prospective follow-up in 75 patients. Medical and Pediatric Oncology. 1999;32:177-182.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design: Prospective cohort study Treatment era: NM Follow-up: Median 31 months (range 12-71)	Type and number of participants: 75 CCS Diagnoses: Sarcoma (osteo, Ewing, soft tissue) 49 (65.3%) Recurrent (lymphoma/leukemia) 13 (17.3%) Neuroblastoma 6 (8%) Brain tumor 5 (6.7%) Miscellaneous malignancies 2 (2.7%) Age at diagnosis: NM Age at follow-up: Median age at completion of therapy was 12.1 years (range 1.1 – 24.1) Controls: NA	Ifosfamide 75/75 (100%), median cumulative dose 30.0 g/m^2 (range 2-95) Cisplatin 35/75 (46.7%), median cumulative dose 402.0 mg/m^2 (range 97-600) Methotrexate 35/75 (46.7%), median cumulative dose 88.4 g/m^2 (range 3-168) Nephrectomy: 3/75 (4%), unilateral RT renal area: 3/75 (4%) Other: Gentamicin 46/75 (61.3%), median cumulative dose 32.5 mg/kg (range 4-217)	Outcome definitions 1. Fanconi syndrome, defined as the presence of hyperaminoaciduria, phosphaturia (resulting in hypophosphatemia), glucosuria and renal tubular acidosis (all pts were on phosphate and bicarbonate supplements) 2. Generalized subclinical tubulopathies, defined as the impairment of 3 or all 4 parameters of proximal tubular solute transport (amino acids, phosphate, glucose and sodium) on one and the same occasion in the absence of acidosis or metabolic bone disease 3. Reduced amino acid reabsorption, for reference see figure 1 in original article 4. Impaired phosphate reabsorption, defined as <0.84 µmol/ml Results Fanconi syndrome Total cumulative probability 9.6% (SD 4.3%) This occurred up to 3 years off therapy Generalized subclinical tubulopathies Total cumulative probability 17% (SD 4.5%) This developed within the first 2 years off therapy only Reduced amino acid reabsorption Cumulative probabilities:	Strengths: - frequent measurements per patients Limitations: - no risk analyses Timing Starting in the first year, and continued for at least 1 more examination in the second year off therapy. Total 347 examinations, median 4 (range 2-15) per patients over a median period of 31 months (range 12-71) at intervals of 6-12 months **Risk of bias** A. Selection bias: unclear Reason: size of original cohort unclear B. Attrition bias: low risk Reason: outcomes were assessed for 92-100% of study group C. Detection bias: unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: NA Reason: no risk analyses

			End of first year: 18% End of second year: 28% Total 38.3% (SD 8.5%) <u>Impaired phosphate reabsorption</u> Cumulative probabilities: End of first year: 8% End of second year: 14% Total 30.6% (SD 8.9%)	

Abbreviations: CCS, childhood cancer survivors; NA, not applicable; NM, not mentioned; pts, patients; RT, radiotherapy.

When should tubular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Skinner et al. Persistent nephrotoxicity during 10-year follow-up after cisplatin or carboplatin treatment in childhood: relevance of age and dose as risk factors. European Journal of Cancer.2009;45:3213-3219.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design:</u> prospective single-center longitudinal cohort study <u>Treatment era:</u> 1981- 1996 <u>Follow-up:</u> at least 10 years, the 1 and 10 year studies at median 1.1 years (range 0.7-2.3) and 10.3 years (range 9.0-12.3)	<u>Type and number of participants:</u> 63 CCS aged 18 years at treatment, treated with platinum and who survived at least 10 years after completion of therapy <u>Diagnoses</u>: *Cisplatin alone (n=27):* Osteosarcoma 12 (44.4%) Germ cell tumor 4 (14.8%) Brain tumor 3 (11.1%) Liver tumor 3 (11.1%) Epithelial carcinoma 1 (3.7%) Ewing's sarcoma 1 (3.7%)	<u>Ifosfamide:</u> 0/63 (0%) <u>Cisplatin alone:</u> 27/63 (42.9%), total median dose 500 mg/m^2 (range 300-960) <u>Carboplatin alone:</u> 24/63 (38.1%), total median dose 2400 mg/m^2 (range 560-8800) <u>Cisplatin and carboplatin:</u> 12/63 (19.0%), total median dose cisplatin 473 mg/m^2 (range 240-739), total median dose carboplatin 1500 mg/m^2 (range 750-4200)	<u>Outcome definitions</u> 1. Hypocalcemia, based on age-related reference ranges 2. Hypomagnesemia, defined as >0.75 mmol/l <2 years, and >0.70 ≥ 2 years. <u>Results</u> <u>Calcium</u> % normal results (95%CI) *Cisplatin alone* End: 90 (70-99), median 2.45 (2.02-2.60)	<u>Strengths:</u> - long-term follow-up - clear description of study cohort <u>Limitations:</u> - due to small numbers in subgroups multivariable risk analyses not possible <u>Timing</u> Evaluation at 1 month (end), 1 year and 10 years after end of therapy

	Nasopharyngeal carcinoma 1 (3.7%) Neuroblastoma 1 (3.7%) Salivary gland carcinoma 1 (3.7%) *Carboplatin alone (n=24):* Germ cell tumor 9 (37.5%) Medulloblastoma 5 (20.8%) Other brain tumor 5 (20.8%) Neuroblastoma 3 (12.5%) CCSK 1 (4.2%) Retinoblastoma 1 (4.2%) *Cisplatin and carboplatin (n=12):* Neuroblastoma 9 (75%) Brain tumor 3 (25%) <u>Age at diagnosis:</u> *Cisplatin alone:* Median 7.7 years (range 0.6-17.8) *Carboplatin alone:* Median 4.4 years (range 0.4-15.8) *Cisplatin and carboplatin:* Median 1.9 years (range 0.1-6.2) <u>Age at follow-up:</u> NM <u>Controls:</u> NA	<u>HD-melphalan</u> 9/63 (14.3%) <u>MTX</u> 8/63 (12.7%) (intermediate 1 g/m^2 of high-dose 8 g/m^2) <u>Nephrectomy:</u> NM <u>RT renal area:</u> 3/63 (4.8%) and 5/63 received a small amount of scatter. <u>Other</u> Actinomycin D, bleomycin, cyclophosphamide, doxorubicin, etoposide, 5-fluorouracil, teniposide, vincristine. Supportive care: aminoglycosides, amphotericin.	1 year: 100 (87-100), median 2.47 (2.19-2.66) 10 years: 100 (89-100), median 2.38 (2.18-2.53) *Carboplatin alone* End: 100 (88-100), median 2.42 (2.25-2.59) 1 year: 100 (87-100), median 2.48 (2.34-2.58) 10 years: 100 (88-100), median 2.39 (2.28-2.59) *Cisplatin and carboplatin* End: 100 (76-100), median 2.39 (2.18-2.61) 1 year: 100 (80-100), median 2.46 (2.24-2.55) 10 years: 100 (76-100), median 2.36 (2.23-2.53) <u>Magnesium</u> % normal results (95%CI) *Cisplatin alone* End: 48 (26-70), median 0.68 (0.32-0.93) 1 year: 50 (28-72), median 0.70 (0.44-0.95) 10 years: 63 (42-81), median 0.73 (0.37-0.83) *Carboplatin alone* End: 74 (52-90), median 0.77 (0.42-0.89) 1 year: 73 (50-89), median 0.78 (0.51-0.90) 10 years: 83 (61-95), median 0.77 (0.54-0.94) *Cisplatin and carboplatin*	**Risk of bias** <u>A. Selection bias:</u> low risk Reason: study group consisted of 93% of original cohort <u>B. Attrition bias:</u> low risk Reason: outcomes were assessed for >75% of study group <u>C. Detection bias:</u> unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome <u>D. Confounding:</u> NA Reason: no risk analyses

			End: 55 (23-83), median 0.74 (0.62-0.98) 1 year: 92 (62-100), median 0.80 (0.69-0.89) 10 years: 91 (59-100), median 0.81 (0.68-0.92) Substantial inter-individual variability was observed with some survivors showing improvement and others deterioration in glomerular, tubular or overall renal function during follow-up. There was no significant change with time in any of the measures of nephrotoxicity in any treatment group, nor in the proportion with clinically significant complications or ongoing treatment with supplements.	

Footnote 1: No overlap in patients with Skinner 2010.
Abbreviations: 95%CI, 95% confidence interval; CCS, childhood cancer survivors; HD, high-dose; MTX, methotrexate; NA, not applicable; NM, not mentioned; RT, radiotherapy.

When should tubular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Skinner R et al. Glomerular Toxicity Persists 10 Years After Ifosfamide Treatment in Childhood and Is Not Predictable by Age or Dose. Pediatr Blood Cancer. 2010; 54: 983-98.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective longitudinal single center cohort study Treatment era: Start ifosfamide 1986-1996 Follow-up: 1 year studies median 1.1 year (0.9-2.1) and 10 year studies	Type and number of participants: 25 CCS who survived at least 10 years after completion of treatment; all patients had normal renal function (as demonstrated by normal serum creatinine, bicarbonate, and phosphate concentrations) prior to ifosfamide treatment or during treatment but before the onset of nephrotoxicity.	Chemotherapy: 25 (100%) ifosfamide; median total dose 106 (12-153) g/m2 IV 2 (8%) melphalan; dose not reported Actinomycin D, doxorubicin, etoposide, cyclophosphamide, vincristine: number of patients and dose not reported Nephrectomy:	Outcome definitions: Serum phosphate (PO4) Bicarbonate (HCO3) Renal tubular threshold for phosphate (Tmp/GFR) Hypophosphatemic rickets (HR) Renal tubular acidosis (RTA) Standard definitions no further information provided	Strengths: Relatively long follow-up period with more than 2 measurements Limitations: Small study size Timing: Sequential measurements at end of treatment and 1 and 10 years thereafter.

median 10.5 (9.3-11.4) years after ifosfamide completion	Diagnoses: 12 (48%) rhabdomyosarcoma 6 (24%) soft tissue sarcoma 6 (24%) Ewing sarcoma 1 (4%) soft tissue primitive neuroectodermal tumor Age at diagnosis: Not reported (age at start ifosfamide median 6 (0.6-14.7) years) Age at follow-up: Not reported Controls: No (but age-related reference ranges of outcomes used for analyses) Additional study characteristics: 16 (64%) males	0 (0%) RT renal area: 2 (8%) small area of kidney; dose not reported 1 (4%) TBI; 12 Gy	Results: There was considerable interpatient variability in the severity of renal toxicity and in changes with time (renal tubular threshold for phosphate); some survivors showed substantial deterioration and others marked improvement HR: 20% at end of treatment 16% at 1 year 0% at 10 years End vs 10 years p=0.06 RTA: 0% at end of treatment 8% at 1 year 0% at 10 years Electrolytes: 32% electrolyte supplements at end of treatment (28% PO4, 8% potassium) 24% at 1 year (24% PO4, 4% additional HCO3, potassium, calcium and 1α-cholecalciferol) 0% at 10 years End vs 10 years p=0.008, 1 vs 10 years p=0.03 At end of treatment: higher cumulative ifosfamide dose correlated to increased tubular toxicity (lower PO4 (P=0.03) and HCO3 (P=0.002)). An increase in cumulative ifosfamide dose of 36 g/m2 was associated with a fall in PO4 of 0.14 (95% CI 0.02–0.25) mmol/L,	**Risk of bias** A. Selection bias: low risk Reason: 25/29=86% of eligible patients included B. Attrition bias: low risk Reason: End of treatment minimal 21/25=84% follow-up 1 and 10 years: minimal 24/25=96% follow-up C. Detection bias: unclear Reason: No information on blinding provided D. Confounding: high risk Reason: Important confounding factors not (all) taken into account

			and in HCO3 of 1.18 (0.53–1.82) mmol/L. At 1 year: higher ifosfamide dose correlated to lower PO4 (P=0.02) and renal tubular threshold (P=0.008). At 10 years: no correlation between ifosfamide dose and nephrotoxicity (P=0.85, 0.69 and 0.79, respectively, for PO4, HCO3, renal tubular threshold). An increase in ifosfamide dose of 36 g/m2 was associated with much smaller falls in PO4 (0.009 mmol/L) and HCO3 (0.17 mmol/L) with 95% CI PO4 -0.081 to 0.098 and HCO3 -0.70 to 1.04. There was no significant difference between the mean age of survivors with normal and those with abnormal PO4, HCO3 and renal tubular threshold at any time point.	

Footnote 1: No overlap in patients with Skinner 2009.

Abbreviations: CCS, childhood cancer survivors; Gy, gray; HCO3, bicarbonate; HR, hypophosphatemic rickets; IV, intravenous; PO4, phosphate; RTA, renal tubular acidosis; TBI, total body irradiation; Tmp/GFR, renal tubular threshold for phosphate.

When should tubular dysfunction surveillance be initiated and at what frequency should surveillance be performed?				
Stohr et al. Nephrotoxicity of Cisplatin and Carboplatin in Sarcoma Patients: A Report From the Late Effects Surveillance System. Pediatr Blood Cancer. 2007; 48: 140-7.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design: Prospective multicenter cohort study Treatment era: Registered on a GPOH trial between 1-1-1998 and 1-1-2002 Follow-up: Median follow-up 2 years. Follow-up to most recent renal examination in 435 survivors with information on serum magnesium was median 23 months (IQR 10-35; range 0-59).	Type and number of participants: Described study group with complete information on magnesium is 435 sarcoma CCS. Eligible cohort 651 sarcoma patients younger than 18 years at diagnosis; follow-up minimal at end of treatment. Diagnoses: Osteosarcoma 139/435 (31.9%), soft tissue sarcoma 167/435 (38.4%), Ewing's sarcoma 109/435 (25.1%) Age at diagnosis: Median 11.6 yr (range 6.5 – 14.9) Age at follow-up: Not reported Controls: From within cohort: survivors not treated with any platinum derivative (i.e., Ewing and some soft tissue sarcoma patients) Additional study characteristics: Gender not reported for complete study population	Ifosfamide: 410/435 (94.3%) Cisplatin: 158/435 (36.3%) Carboplatin: 60/435 (13.8%) MTX: NM Nephrectomy: Not reported RT renal area: 53/435 (12.2%), RT field: abdominal 53 (12.2%) Other chemotherapeutic agents: Combination of actinomycin D, busulfan, doxorubicin, epirubicin, melphalan, methotrexate, or vincristine Other treatments: Magnesium supplementation as prophylaxis during treatment; no further information provided.	Outcome definitions 1. Hypomagnesemia Serum Mg < 0.7 mmol/L; CTCEv3 or receiving Mg supplementation unless this was reported as prophylaxis. Results N=435/651 (67%) information on serum magnesium available: N=325 end of treatment N= 214 at 1 year N=136 at 2 years N=76 at 3 years Magnesium supplementation after end of treatment: N=9 (2%) (4 cisplatin, 1 both platinum derivatives, 4 controls). N=8 in the first year only; no patient needed long-lasting supplementation. Hypomagnesemia: End of treatment 8.9% (30/339) (22/172 platinum group and 8/177 controls). At last examination: 3.1% (9/286) (4/130 platinum group and 5/156 controls). The prevalence of hypomagnesemia was significantly higher in patients treated with any platinum derivative; no difference between cisplatin and carboplatin. At the last available examination, there was no difference in hypomagnesemia prevalence between the groups, however,	Strengths: - Limitations: - Only very few survivors available for longitudinal information. - Relatively short follow-up. - Almost all patients received ifosfamide. - Information on over-the-counter magnesium might not be available for all survivors, possibly leading to an underestimation of hypomagnesemia and the effect of cisplatin. Timing Yearly intervals after end of treatment **Risk of bias** A. Selection bias: unclear Reason: unclear if the study group was a random sample of the original cohort B. Attrition bias: high risk Reason: For maximal 435/651 survivors=67% information available; less for longitudinal bivariate/multivariable analysis (187/651=29%), for different time points (for example 76/651=12% at 3 years) and for number of survivors who had all 3 examinations (74/651=11%). Several additional analyses were done to assess this risk of bias but only a limited amount of possible factors was taken into account.

			patients treated with cisplatin still had significantly lower serum magnesium than patients treated with neither cisplatin or carboplatin. Serum magnesium: increased during the first year after therapy and remained stable thereafter. This was confirmed in 74 patients who had three yearly examinations during 2 years of follow-up: statistically significant increase in serum magnesium by 0.03 mmol/L (95%CI 0.01–0.06 mmol/L) in the first year and remained unchanged thereafter. Absolute changes in serum magnesium over time did not differ between patients with cisplatin treatment (n=25) and patients without platinum (n=40); accordingly, serum magnesium levels were significantly lower in patients treated with cisplatin at every examination. No difference was found in comparison to carboplatin treated patients (n=6). Longitudinal analysis (only two examinations in every patient (examination in the first year and last examination) were analyzed, to maximize sample size N=187): both treatment with cisplatin and carboplatin significant	<u>C. Detection bias:</u> unclear Reason: No information on blinding provided. <u>D. Confounding:</u> low risk for longitudinal analysis Reason: All important confounding factors were taken into account. High risk for all other analyses: Reason: Important confounding factors not taken into account.

			influence factors on serum magnesium, abdominal radiation or length of follow-up had no influence. In additional analyses in osteosarcoma patients (N not reported) only no difference between different cumulative doses of cisplatin were found. No influence of ifosfamide found. See table IV below for more information.	

Abbreviations: CCS, childhood cancer survivors; IQR, inter quartile range; MTX, methotrexate; N, number; RT, radiotherapy; yr, year.

What surveillance modality should be used?

What surveillance modality should be used?				
Green et al. Long-term renal function after treatment for unilateral, nonsyndromic Wilms tumor. A report from the St. Jude Lifetime Cohort Study. Pediatr Blood Cancer. 2020;67:e28271				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study with prospective clinical follow-up Treatment era: 1961 – ongoing Follow-up: At least 10 year from diagnosis Average 26.9 years post-diagnosis for unirradiated patients versus 30.1 years among irradiated patients	Type and number of participants: 40 Wilms tumor survivors at least ≥10 years after diagnosis and ≥18 years at time of study Controls: 35 noncancer controls; age (± 5 years), sex and race/ethnicity matched. Age at diagnosis: NM Age at follow-up: Average 28.8 years for unirradiated patients Average 33.7 years for irradiated patients	Diagnostic test(s) 1. CKD-EPI 2012 creatinine based eGFR 2. CKD-EPI 2012 creatinine + cystatin C based eGFR 3. ^{99m}Tc DTPA plasma clearance (in survivors only) 4. 24-hour creatinine clearance Outcome definitions Comparison of mean eGFR between CCS and controls, and within CCS between WART and no RT group.	Diagnostic outcomes Correlation estimates Plasma ^{99m}Tc clearance did not correlate with eGFR using the creatinine only equations for either unirradiated (Pearson r = 0.323; P = 0.177) or irradiated (Pearson r = 0.284;P = 0.254) patients. Plasma ^{99m}Tc clearance did correlate well with the eGFR using the creatinine + cystatin C equations among unirradiated (Pearson r = 0.488; P = 0.034) and	Strengths: - Taking into account a control group - Comparison with exogenous GFR measurement Limitations: - small study size - Plasma ^{99m}Tc clearance not performed in controls **Risk of bias** A. Selection bias: low risk Reason: study population is random sample of original cohort B. Index test bias: NA

	Cancer treatment: Nephrectomy 40 (100%) WART 20 (50%) No RT 30 (50%). Median 11.0 Gy to 100% of the remaining kidney Nonnephrotoxic chemotherapy 40 (100%), i.e., no treatment with cisplatin, carboplatin or ifosfamide.		irradiated (Pearson r = 0.558; P = 0.020) survivors. 24-hour urine creatinine clearance did not correlate with plasma ^{99m}Tc clearance among either the unirradiated (Pearson r=0.120; P=0.625) or the irradiated (Pearson r=0.252; P = 0.314) WT participants.	Reason: comparison of different equations C. Reference test bias: NA Reason: comparison of different equations D. Verification bias: low risk Reason: there was an appropriate interval between index test(s) and reference standard in all patients E. Attrition bias: low risk Reason: Tests were performed in all participating survivors

Abbreviations: ^{99m}Tc DTPA, 99mTc-dieethylenetraiminepentaacetic acid; CCS, childhood cancer survivors; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; NA, not applicable; NM, not mentioned; RT, radiotherapy; WART, whole abdominal radiation therapy

What surveillance modality should be used?				
Stefanowicz et al. Glomerular filtration rate and prevalence of chronic kidney disease in Wilms' tumour survivors. Pediatr nephrol. 2011:26;759-766				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional cohort study Treatment era: 1987 – 2008 Follow-up: Mean 9.3 years (SD 5.4) Median 7.7 years (range 0.3 – 20)	Type and number of participants: 32 survivors of unilateral WT Controls: NA Age at diagnosis: Mean 8.5 years (SD 5.7) Median 2.9 years (range 0.08 – 11.4) Age at follow-up: Mean 13 years (SD 5.4) Median 12.2 years (range 3.6 – 24.3) Cancer treatment:	Diagnostic test(s) 1. 99Tc-DTPA clearance 2. Old Schwartz formula 3. New Schwartz formula 4. Filler formula Outcome definitions 1. Differences in mean GFR 2. Correlation rates 99Tc-DTPA clearance serum activity of 99 Tc-DTPA at 1 and 3 hour following the injection of 99 Tc-DTPA Old Schwartz formula	Diagnostic outcomes Mean GFR in mL/min/1.73 m² (SD) 1. 99Tc-DTPA clearance: mean: 94.3 (SD 10.24) 2. old Schwartz formula: mean: 122.3 (SD 19.92) 3. new Schwartz formula: mean: 94.3 (SD 10.2) 4. Filler formula: mean: 129.8 (SD 23.9) Comparison 99Tc-DPTA vs old Schwartz p<0.001 99Tc-DPTA vs new Schwartz p=0.55 99Tc-DPTA vs Filler p<0.001	Strengths: - GFR equations compared to a reference method Limitations: - no control group - small study group **Risk of bias** A. Selection bias: unclear Reason: size original cohort not mentioned B. Index test bias: NA Reason: correlation tests were performed

	Unilateral nephrectomy 32/32 (100%) RT renal area 12/32 (37.5%); 9 total abdomen, 3 remnant kidney Nephrotoxic CT 7/30 (23.3%) Ifosfamide unclear, at least 1 with maximum 7/30 Carboplatin unclear, at least 1 with maximum 7/30 <u>Decreased eGFR (<90 ml/min/1.73m^2)</u> 1. 99Tc-DTPA clearance 14/32 (44%) 2. old Schwartz formula 1/32 (3%) 3. new Schwartz formula 11/32 (34%) 4. Filler formula 0/32 (0%)	eGFR =k × height of child in cm/serum creatinine concentration in mg/dl; where the constant k was defined using published literature values: k=0.55 for children aged 2–12 or adolescent females and k=0.7 for adolescent males <u>New Schwartz formula</u> eGFR=39.2 × (height of child in m/serum creatinine concentration in mg/dl)$^{0.516}$ × (1.8/ cystatin C serum concentration)$^{0.294}$ × (30/BUN)$^{0.169}$ × (1.099^{male}/1^{female}) × (height of child in m/1.4)$^{0.188}$ <u>Filler formula</u> logGFR=1,.962+[1.123 × log(1/cystatin C)	Old Schwartz vs New Schwartz vs. p<0.0001 Old Schwartz vs Filler (p=0.26) New Schwartz vs Filler p<0.0001 <u>Correlation rate</u> 99Tc-DTPA vs old Schwartz 0.33 (p<0.05) 99Tc-DTPA vs new Schwartz 0.33 (p<0.05) 99Tc-DTPA vs Filer formula 0.44 (p<0.05) 99Tc-DTPA vs serum cys C 0.51 (p<0.05)	<u>C. Reference test bias:</u> NA Reason: correlation tests were performed <u>D. Verification bias:</u> low risk Reason: there was an appropriate interval between index test(s) and reference standard in all patients <u>E. Attrition bias:</u> low risk Reason: Total study group received the same tests

Footnote 1: possible overlap in patients with Stefanowicz 2012.
Abbreviations: 99Tc-DTPA, 99mTc-dieethylenetraiminepentaacetic acid; cys C, cystatin C; (e)GFR, (estimated) glomerular filtration rate; NA, not applicable; RT, radiotherapy; SD, standard deviation; WT, Wilms tumor.

Diagnostic studies regarding GFR equations in other populations.

Studies in children

Björk et al. Validation of standardized creatinine and cystatin C GFR estimating equations in a large multicentre European cohort of children. Pediatric Nephrology. 2019;34:1087-1098.		
Study population	**Main outcomes**	**Conclusions**
Data on measured GFR, serum creatinine, serum cystatin C, age, sex, height and weight from 5 different cohorts from Europe including 2218 children aged 2-17 years. Median (2.5 – 97.5 percentiles) Age: 12.3 years (2.6 – 17.8) Measured GFR: 90 (23 – 165)	GFR equations investigated (for more detailed information we refer to the original article): Creatinine based: - FAS_{age} - FAS_{height} - $Schwartz2009_{creat}$ - $Schwartz2012_{creat}$ - Schwartz-lyon - LMR	Arithmetic means of the best creatinine and cystatin C equations above improved bias compared to the existing composite creatinine+cystatin C equations.

	Cystatin C based: - FAS_{cys} - $Schwartz2012_{cys}$ - CAPA - $CKD\text{-}EPI_{cys}$ - Berg Combined equations: - $Schwartz2012_{creat+cys}$ - FAS combined (age & cys C) - FAS combined (height & cys C) - Andersen For most important results see table 2 and table 3 in original article.	

Den Bakker et al. Combining GFR estimates from cystatin C and creatinine - what is the optimal mix? Pediatric Nephrology. 2018;33:1553-1563.		
Study population	**Main outcomes**	**Conclusions**
Retrospective study of 408 inulin clearance tests with simultaneous measurement of creatinine, cystatin C, and urea. Participants includes children and adolescents aged 2 – 19.5 years. Mean age 12.5 years (4.9 SD). Mean GFR was 91.2 (30.3 SD) $ml/min1.73m^2$. Spectrum of diagnoses: single kidney (n= 98), malignancy (n= 96), nephritis (n= 72), urological abnormalities (n= 42), neural tube defect (n= 38), follow-up after malignancy (n= 14), and others (n= 48). No external validation has been performed.	GFR equations investigated (for more detailed information we refer to the original article): Creatinine based: - FAS_{age} Cystatin C based: - FAS_{cys} - $Schwartz_{cys}$ - CAPA Combined equations: - CKiD3 - FAScombined - arithmetic mean FAS_{age} and FAS_{cys} - geometric mean FAS_{age} and FAS_{cys} For most important results see table 1 in original article.	The mean of a cystatin-C based and a creatinine-based GFR equation improved bias, precision, and accuracy compared to single-parameter equations.

Leion et al. Estimating glomerular filtration rate (GFR) in children. The average between a cystatin-C and a creatinine-based equation improves estimation of GFR in both children and adults and enables diagnosing Shrunken Pore Syndrome. Scandinavian Journal of Clinical and Laboratory Investigation. 2017;77:338-344.		
Study population	**Main outcomes**	**Conclusions**
702 children below 18 years of age, 440 from Sweden, 262 from the Netherlands. Median (2.5^{th} – 97.5^{th} percentile): Age: 12 years (2-18) Measured GFR: 101 ml/min/1.73m^2 (23-196)	GFR equations investigated (for more detailed information we refer to the original article): Creatinine based: - FAS_{age} - FAS_{height} - $Schwartz_{original}$ - $Schwartz_{IDMS}$ - CKD-$EPIc_{creat}$ - LMR - Cockcroft-Gault - Counahan-Baratt - Gao Cystatin C based: - FAS_{cys} - $Schwartz_{cys}$ - CAPA - CKD-EPI_{cys} - Berg Combined equations: - CKD-$EPI_{creat+cys}$ - $Schwartz2012_{creat+cys}$ - Chehade Arithmetic mean equations: - LMR+CAPA - Gao + CAPA - $FASa_{ge}$ + CAPA - FAS_{height} + CAPA - $FASa_{ge}$ + FAS_{cys} - FAS_{height} + FAS_{cys} - CKD-EPI_{creat} + CKD-$EPIc_{ys}$ - $Schwartz_{IDMS}$ + CAPA - $Schwartz_{IDMS}$ + $Schwartz_{cys}$	The average of a suitable creatinine-based and a cystatin C-based equation generally displayed a better diagnostic performance than estimates obtained by equations using only one of these analytes or by complex equations using both analytes.

	For most important results see table 2 and table 3 in original article.	

Studies in children and adults

Pottel et al. Estimating glomerular filtration rate for the full age spectrum from creatinine and cystatin C. Nephrol Dial Transplant. 2017;32:497-507.		
Study population	**Main outcomes**	**Conclusions**
Data on measured GFR, serum creatinine, serum cystatin C, age, gender, height from 11 different cohorts including 6132 participants (368 children aged ≤18 years, 4295 adults and 1469 older adults aged ≥70 years). Mean (SD) measured GFR in ml/min/1.73m^2 - children aged ≤18 years: 89.2 (30.4) - adults aged 19-69 years: 80.2 (25.6) - adults aged ≥70 years: 58.5 (20.0)	GFR equations investigated (for more detailed information we refer to the original article): Creatinine based: - FAS_{age} - FAS_{height} - $Schwartz_{creat}$ - CKD-EPI_{creat} Cystatin C based: - FAS_{cys} - $Schwartz_{cys}$ - CAPA - CKD-EPI_{cys} Combined equations: - FAS combined (age & cys C) - FAS combined (height & cys C) - CKD-$EPI_{creat+cys}$ For most important results see table 6, table 7 and table 8 in original article.	In children and adolescents, the new FAS_{cys} equation showed significantly better performance [percentage of patients within 30% of mGFR (P30)=86.1%] than the CAPA equation (P30=76.6%; P<0.0001), or the $Schwartz_{cys}$ equation (P30=68.8%; P<0.0001) and the FAScombi equation outperformed all equations with P30=92.1% (P<0.0001). In adults, the FAS_{cys} equation (P30=82.6%) performed equally as well as the CKD-EPI_{cys} (P30=80.4%) and the FAScombi equation (P30=89.9%) was also equal to the combined CKD-EPI equation (P30=88.2%). In older adults, FAScys was superior (P30=88.2%) to CKDEPIcys (P30=84.4%; P<0.0001) and the FAScombi equation (P30=91.2%) showed significantly higher performance than the combined CKD-EPI equation (P30=85.6%) (P<0.0001).

Studies in adults

Zou et al. Comparison of bias and accuracy using cystatin C and creatinine in CKD-EPI equations for GFR estimation. European Journal of Internal Medicine. 2020;80:29-34.		
Study population	**Main outcomes**	**Conclusions**

Meta-analyses of 35 studies with 23,667 participants which reported the data on the bias, and/or p30, and/or R. All participants were aged > 18 years.	The difference in the bias of eGFR using CKD-EPIcys was 4.84 mL/min/1.73 m^2 (95% CI, 1.88-7.80) lower than using CKD-EPIcreat, and 1.50 mL/min/1.73 m^2 (95% CI, 0.05-2.95) lower than using CKD-EPIcreat/cys. These gaps increased in subgroups of low mGFR (<60 mL/min/1.73 m^2). CKD-EPIcreat/cys eGFR achieved the highest accuracy, 7.50% higher than CKD-EPIcreat (95% CI, 4.81-10.18), and 3.21% higher than CKD-EPIcys (95% CI, -0.43-6.85); and the best correlation with mGFR, with Fisher's z transformed R of 1.20 (95% CI, 0.89-1.50). For most important results see figure 2, figure 3, and figure 4 in original article.	CKD-EPIcreat+cys and CKD-EPIcys gave less bias and more accurate estimates of mGFR than CKDEPIcreat.

What should be done when abnormalities are identified?

No studies identified in CAYA cancer survivors.