Evidence tables cardiomyopathy surveillance

WG1: Who needs cardiomyopathy surveillance?				
Sorensen et al. Late anthracycline cardiotoxicity after childhood cancer: a prospective longitudinal study. Cancer 97:1991-8, 2003				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Prospective longitudinal cohort study Treatment era 1970-1990 Follow-up First evaluation: ALL mean 6.2 ±2.0 Wilms mean 6.7 ±3.7 Second evaluation: ALL mean 10.3±2.1 Wilms mean 11.1 ±4.7	Type and number of participants ALL 101/120 included Wilms 97/110 included 2 Echo's, mean 4 years apart. Diagnoses (%) 101 ALL 83 Wilms Tumor Age at diagnosis ALL mean 4.8 +/-2.7 Wilms mean 4.1 +/-2.3 Age at follow-up First evaluation: ALL mean 10.9 ± 3.6 Wilms mean 11.9 ± 4.7 Second evaluation: ALL mean 14.8 ± 3.7	Chemotherapy Anthracyclines 100% ALL mean 180 +/-73 mg/m2 WT mean 301 +/-78 mg/m2 Radiotherapy Not reported Surgery only none HSCT Not reported	Outcome definitions Comprehensive echo. FS, LVPWS, LVPWD, LVID, circumferential fiber shortening (VCF), ESWS, SVI (stress-velocity index) Results All indices were worse in ALL and wilms compared to controls Multivariable linear regression *FS evaluation 2:* **Anthracycline dose per 100 mg: B -1.77 (-2.7, -0.9)** Wilms vs ALL B 0.55 (0.12, 0.97) Follow up/year B -0.16 (-2.74, 0.69) Age treatment/year -0.03 (-0.39, 0.07) Height at evaluation 2 per SD B -0.09 (-1.08, 0.22) Female vs Male B -0.73 (-2.07, 0.60) *Difference FS (evaluation 1-2):* **Anthracycline dose per 100 mg: B -1.48 (-2.4, -0.5)**	Homogeneous populations: ALL and Wilm's Essentially comparing high dose vs. low-dose anthracycline with no heterogeneity **Risk of bias** A. Selection bias: Low risk Reason: >88% included, no difference in gender or stage of disease between included and original cohort. B. Attrition bias: low risk Reason: low drop out between evaluation 1 and evaluation 2. Unclear how many were lost to follow-up from the full cohort at evaluation 1. C. Detection bias: low risk Reason: sonographers were blinded

	Wilms mean 16.3 ± 4.6 Controls (if applicable) 100 normal children		Wilms vs ALL B -0.02 (-1.61, 2.03) Follow up/year B -0.01 (-0.25, 0.23) Age treatment/years 0.18 (-0.09, 0.45) Height at evaluation 2 per SD B -0.19 (-0.87, 0.49) Female vs Male B -1.38 (-2.78, 0.03) Average FS E1 and E2 to avoid regression to the mean: -0.02 (-0.20, 0.18)	D. Confounding: low risk Reason: Multivariable regression adjusted for sex, follow-up, age during treatment. Did not mention chest RT dose.

WG1: Who needs cardiomyopathy surveillance?				
Kremer et al. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. Ann Oncol 13:819-29, 2002				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Review of Frequency and Risk Factors of anthracycline-induced sub*clinical* cardiotoxicity Medline: 1966-2001 >50 children/study Follow-up Range across studies 0.1-23 years	Type and number of participants 25 articles included (2563 patients) Limitations in 14 studies: Missing info Non-rep. populations Non-original research 10 studies with RF analyses 6 studies which defined an abnormal SF with validity score>5	Chemotherapy 8 studies doxorubicin 2 studies daunorubicin 15 studies combination 11 studies mean/median dose <300 mg/m2 Radiotherapy Not reported Surgery only None HSCT Not reported	Outcome definitions Abnormal FS (<28 to <30%, 15 studies) or EF, VCFc, afterload (i.e. ESWS) or SVI Frequency of abnormal SF (6 studies with validity score >5) <300 mg/m2 (0-15.2%) >300 mg/m2 (15.5%-27.8%) Risk factor analysis for abnormal FS/EF Steinherz (1991) N=201: Anth – median 450 (200-1275) >cumulative dose x f/up, mediastinal radiation (no dose effect calculation) Silber (1993) N=150:	Several studies with associations with age and other indices (ie: ESWS, SVI, wall thickness) **Risk of bias** A. Selection bias: high risk in most studies, low risk in 4 studies Reason: representative sample in only 4/25 included studies. B. Attrition bias: unclear Reason: not reported if all patients had outcome assessment in the included studies. C. Detection bias: unclear

	Diagnoses (%) Not reported Age at diagnosis Range 0-28.9 years Age at follow-up Range 3.9–36.9 years		Anth – mean 307 (50-750) >anthracycline dose, <age at tx, female sex Sorensen 1997 >age at tx Lipshultz (1995) N=87: Anth- median 390 (224-550) >dosage in w3 wks x diagnosis >cumulative dose, <age at dx Nysom (1998) N=189: Anth range 0-550 >cumulative dose	Reason: blinding of investigators not mentioned D. Confounding: unclear Reason: multivariable regression was performed in the individual studies, however the covariates used for adjustments were not mentioned in the review.

WG1: Who needs cardiomyopathy surveillance?

Kremer et al. Frequency and risk factors of anthracycline-induced clinical heart failure in children: a systematic review. Ann Oncol 13:503-12, 2002

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Review of Frequency and Risk Factors of anthracycline-induced *clinical* heart failure Medline search: 1966-2000	71 articles reviewed (12507 anthracycline treated children) Limitations in many: Missing information Lack of risk factor analysis Non-representative populations	Chemotherapy Cumulative anthracycline dose range across studies: 50-1275 mg/m2 Radiotherapy Range across studies 0-32% of the participants (all fields)	Outcome definitions Heart failure as reported by the authors Risk factor analysis within studies with 2x2 table Risk factor analysis across studies with multivariable regression with backward selection on p value (p<0.10). Results Frequency of heart failure 0-16%	Review is driven by anthracycline exposure Few with XRT dose quantification and none with careful heart dosimetry calculation Unclear if lack of association with age in the other 9 studies was because age was

Follow-up Range across studies 0.9-7.3 years	Diagnoses (%) Various Age at diagnosis Range across studies: 0.8-15 years Age at follow-up Not reported Controls (if applicable) -	Surgery only none HSCT Not reported	Multivariable regression with backward selection on p value: Predictors evaluated: study design, validity score, doxorubicin vs daunorubicin, cumulative anthracycline dose, maximal anthracycline dose within 1 week. **Selected predictors:** **maximal anthracycline dose within 1 week >45 mg/m2 RR 5.8 (95% CI 1.7-14.1)** **Daunorubicin vs Doxorubicin: RR 3.1 (95% CI 0.6-11.2), not significant** Univariate analysis (heart failure): **Risk with chest RT reported in 4 out of 10 studies (3 out of 4 significant):** Gilladoga (1976) N=50 XRT to heart: RR 5.2 (1.6-16.8) Dearth (1984) N=116 XRT to heart: RR13.5 (3.4-53.3) Bu'Lock (1996) N=226 XRT to heart: 11.1 (3.7-33.5) Krischer (1997) N=6493 XRT to heart: RR 0.7 (0.3-1.9) **Risk with anthracycline dose in 5 out of 10 studies:** Goorin (1981), N=382 ≤500 mg/m2 (Ref) >500 mg/m2: RR 4.8 (1.6-14) Dearth (1984), N=112 ≤400 mg/m2 (Ref) >400 mg/m2: RR 26.1 (3.2-210) Sallan (1984), N=379 Maximal dose/wk <45 mg/m2 (Ref)	not evaluated or non-significant. **Risk of bias** A. Selection bias: high risk Reason: selection bias was present in 8 the included studies B. Attrition bias: unclear Reason: loss to follow-up was not clearly stated in individual studies included in the review C. Detection bias: High risk Reason: Only 1 included study clearly defined heart failure. None reported blinding of investigators for risk factors for heart failure. D. Confounding: High risk Reason: Only 2 of the included studies did a multivariable adjusted risk factor analysis.

			Maximal dose/wk ≥45 mg/m2 RR: 7.7 (2.1-28.1) Godoy (1997), N=120 ≤300 mg/m2 (Ref) >300 mg/m2 – HR 1.5 (0.3-3.9), NS Krischer (1997) <500 mg/m2 (Ref) ≥500 mg/m2: RR 2.6 (1.1-6) 1 out of 10 studies: Age <4 years as predictor of CHF Godoy (1997), N=69 RR = 11.7 (1.4-96.4)	

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?				
Feijen et al. Risk and Temporal Changes of Heart Failure Among 5-Year Childhood Cancer Survivors: a DCOG-LATER Study. JAHA, 2019; 8: e009122				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks** **e.g. risk of bias**
Study design Cohort study Treatment era 1963-2001 Follow-up Median 19.9 years (range 5-50.4)	Type and number of participants 5-year Childhood cancer survivors n=5845 Diagnoses Leukemias, myeloproliferative	Chemotherapy Chemotherapy+/-surgery 2882 (49.3%) Chemotherapy and Radiotherapy +/- surgery 1854 (31.7%) Cardiotoxic chemotherapy only 2304 (39.4%) Cardiotoxic chemotherapy and chest RT 434 (7.4%)	Outcome definitions Heart failure CTCAE (2010 version) grade 3-5 Results N=116/5845 (2%) symptomatic heart failure Cumulative incidence 40 years after diagnosis 4.4% (95% CI 3.4%–5.5%) in all survivors Cumulative incidence among survivors treated in the	Overlap Feijen 2015 and 2 Feijen 2019 studies Potential heart failure was validated following a standardized method 3 cases without potential cardiotoxic treatment (all

	diseases, and myelodysplastic diseases 2034 (34.8%) Lymphomas and reticuloendothelial neoplasms 1019 (17.4%) CNS and miscellaneous intracranial and intraspinal neoplasms 749 (12.8%) Neuroblastoma and other peripheral nervous cell tumors 306 (5.2%) Retinoblastoma 29 (0.5%) Renal tumors 571 (9.8%) Hepatic tumors 46 (0.8%) Bone tumors 355 (6.1%) Soft tissue and other extraosseous sarcomas 422 (7.2%) Germ cell tumors, trophoblastic tumors, and neoplasms of gonads 219 (3.7%) Other malignant epithelial neoplasms	Anthracyclines median dose 175 (IQR 114–272) No anthracyclines 3099 (53.0%) 1 to 100 mg/m2 491 (8.4%) 100 to 250 mg/m2 1402 (24.0%) >250 mg/m2 720 (12.3%) Missing 133 (2.3%) (94 anthracyclines yes but dose missing) Mitoxantrone median dose 40 (IQR 20–60) No mitoxantrone 5660 (96.8%) <40 mg/m2 81 (1.4%) >40 mg/m2 58 (1.0%) Missing 46 (0.7%) (7 mitoxantrone yes but dose missing) Cyclophosphamide (intravenous) None 3674 (62.8%) Any 2132 (36.5%) Unknown 39 (0.7%) Cisplatin None 5363 (91.8%) Any 443 (7.6%) Unknown 39 (0.7%) Ifosfamide None 5107 (87.4%) Any 699 (12.0%) Unknown 39 (0.7%)	more recent treatment periods was higher compared with survivors treated earlier (Gray test, P=0.05). Mortality due to heart failure decreased in the more recent treatment periods (Gray test, P=0.02). Cumulative incidence among all survivors at age 50 years 5.3% (95% CI 3.7-6.9); increasing with higher attained age <u>Multivariable analyses:</u> Multivariable Cox proportional hazards model with attained age as the time scale. The model was adjusted for age at childhood cancer diagnosis, sex, and calendar year of childhood cancer diagnosis. HR (95% CI) Age at primary childhood diagnosis (per year) 0.8 (0.8–0.9) Sex (reference=male) 0.9 (0.6–1.3) Year of childhood cancer diagnosis (per year) 1.0 (1.01–1.1) Anthracycline (per 1 mg/m2, splines) significant result (no HR provided) Mitoxantrone (per 1 mg/m2, splines) significant result (no HR provided) Cyclophosphamide (per 100 mg/m2, splines) significant result (no HR provided) Chest radiotherapy (reference =no chest radiotherapy):	with conditions known to predispose to heart failure: Duchenne muscular dystrophy, noncompaction cardiomyopathy, and Tetralogy of Fallot). Long-term follow-up <u>Risk of bias</u> <u>A. Selection bias:</u> Low risk Reason: 5845/6165 eligible survivors (94.8%) included <u>B. Attrition bias:</u> Low risk Reason: cardiac follow-up complete for all included participants <u>C. Detection bias:</u> Unclear Reason: not reported if outcome assessors were blinded <u>D. Confounding:</u> Low risk Reason: all important prognostic factors taken into account

	and malignant melanomas 88 (1.5%) Other and unspecified malignant neoplasms 7 (0.1%) <u>Age at diagnosis</u> Median 5.5 years (IQR 2.8-10.5) <u>Age at follow-up</u> Median 27.3 years (range 5.1-65.2) Cardiovascular risk factors Not reported Cardioactive Meds Not reported <u>Controls (if applicable)</u> NA	Vincristine None 1642 (28.1%) Any 4164 (71.2%) Unknown 39 (0.7%) <u>Radiotherapy</u> Radiotherapy+/-surgery 445 (7.6%) RT involving the heart only 211 (3.6%) Cardiotoxic chemotherapy and chest RT 434 (7.4%) Radiotherapy field involving the heart No chest radiotherapy 4575 (78.3%) Radiotherapy potentially involving the heart 588 (10.1%) Radiotherapy involving the heart <20 Gy 275 (4.7%) Radiotherapy involving the heart ≥20 Gy 363 (6.2%) Unknown 44 (0.7%) <u>Surgery</u> Surgery only n=587 (10%)) <u>HSCT</u> Not reported	Radiotherapy potentially involving the heart 1.0 (0.4–2.0) Radiotherapy involving the heart <20 Gy 2.0 (1.1–3.6) Radiotherapy involving the heart ≥20 Gy 2.1 (1.1–4.0) Cisplatin (per 1 mg/m2) 1.0 (1.0–1.0) Ifosfamide (per 1 mg/m2) 1.0 (1.0–1.0) Vincristine (per 1 mg/m2) 1.0 (1.0–1.0) No significant interaction term between anthracycline and radiotherapy involving the heart identified	

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?

Dietz et al. Solid organ transplantation after treatment for childhood cancer: a retrospective cohort analysis from the Childhood Cancer Survivor Study. 2019
The lancet oncology

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design retrospective cohort of individuals who survived at least 5 years after childhood cancer, from one of 25 institutions in the USA. Exclusion if solid organ transplantation before cancer Linkage to the Organ Procurement and Transplantation Network—a database of all US organ transplants. Treatment era between Jan 1, 1970, and Dec 31, 1986, Follow-up	Type and number of participants 13318 from the Childhood Cancer Survivor Study (CCSS) Female 6177 (46·4%) Male 7141 (53·6%) Diagnoses Leukaemia 4502 (33·8%) CNS tumour 1639 (12·3%) Hodgkin lymphoma 1846 (13·9%), Non-Hodgkin lymphoma 1022 (7·7%), Kidney (Wilms') tumour 1162 (8·7%), Neuroblastoma 866 (6·5%), Soft tissue sarcoma 1167 (8·8%), Bone tumour 1114 (8·4%) Age at diagnosis diagnosed < 21 years of age Median 6 years (IQR 3–13) 0–4y 5295 (39·8%) 5–9y 2922 (21·9%) 10–14y 2687 (20·2%) 15–20y 2414 (18·1%)	Chemotherapy Anthracycline 4574/11548 (39·6%) Data about other chemotherapy are taken into account (of whom cyclophosphamide…) Radiotherapy Heart, mean dose, Gy None 3853/11 320 (34·0%) >0 to 10 4847/11 320 (42·8%) >10 to 20 939/11 320 (8·3%) >20 to 30 627/11 320 (5·5%) >30 1054/11 320 (9·3%) Unknown 1998 Surgery - HSCT -	Outcome definitions Two primary endpoints for each type of organ transplant : date of first registration of a transplant candidate on the waiting list for an organ & the date of the first transplant received. Cumulative incidence of being placed on a waiting list or receiving a solid organ transplantation, hazard ratios (HRs) for identified risk factors, and 5-year survival following transplantation. Results -37 heart transplantations, 25 waiting list -Age at heartx: median 28, IQR 21-32 years -Time to heartx: median 17, IQR 13-26 years -Cumulative incidence of heartx or waiting list at 35 years from diagnosis: 0.49% (0.36–0.62) (2nd place after kidney) -40% with heartx had received > 450 mg/m2 Risk factors for heartx in multivariable Cox regression (95% CI) -Anthracycline dose, mg/m2 (none=ref) >0-150: HR 8.4 (2.2-32.6) >150-300: HR 5.0 (1.3-19.5) >300-450: HR 26.5 (9.9-71.0)	Data about anthracycline : total anthracycline dose (doxorubicin equivalent dose) was calculated with doxorubicin doses equivalent to daunorubicin doses and idarubicin doses multiplied by 3. Data about radiotherapy (unknown for 15% = 1998 patients) reconctructed doses with age-specific computational phantoms, mean organ doses were estimated by averaging all the calculation points in the organ with blocking taken into account using standarised blocking by field Risk of bias A. Selection bias: Low risk Reason: All eligible survivors were included B. Attrition bias: Low risk Reason: Outcome was assessed in all patients C. Detection bias: Unclear

Not reported, median ±23 years	Age at follow-up Median 39, IQR 33–46 yrs <20y 612/13 311 (4·6%) 20–29y 989/13 311 (7·4%) 30–39y 5147/13 311 (38·7%) 40–49y 4805/13 311 (36·1%) ≥50y 1758/13 311 (13·2%) Controls (if applicable)		>450: HR 94.2 (35.3-251.2) -Mean heart dose, Gray (none=ref) >0-10: HR 2.2 (1.0-4.8), p=0.050 >10-20: HR 1.9 (0.5-7.3), p=0.33 >20-30: HR 6.1 (1.8-20.6), p=0.0035 >30: HR 19.7 (7.1-54.2), p<0.0001 -Cyclophosphamide, mg/m2 (none=ref) >0-10,000: HR 0.3 (0.1-0.6), p=0.0018 >10,000-20,000: HR 0.8 (0.4-1.7), p=0.57 >20,000: HR 1.3 (0.5-3.7), p=0.61 -Model also adjusted for sex, age at diagnosis, cisplatin, busulphan but HR not shown (not significant) -5-year survival after heartx: 80·6% (95% CI 63·6–90·3)	Reason: Blinding not reported D. Confounding: Low risk Reason: Multivariable adjusted analysis

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?

Bates et al. Therapy-Related Cardiac Risk in Childhood Cancer Survivors: An Analysis of the Childhood Cancer Survivor Study. JCO 2019 1090-1102

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks e.g. risk of bias**
Study design Multi-institutional retrospective cohort study Treatment era 1970-1999	Type and number of participants 24,214, five years survivors of common childhood cancers diagnosed before age 21 years at	Anthracycline dose, mg/m2, n(%) None 11,615 (49.6) 1-249 6,305 (35.6) ≥ 250 3,455 (14.8) Cisplatin, mg/m2, n(%) None 20,132 (92.6)	Outcome definitions Cardiac disease: any of the following conditions: CAD, HF, valvular disease, pericardial disease and arrhuthmias (grade 3-5) according to the NCICTC Results - Cumulative incidence of cardiac disease after 30 years: 4.8% (95% CI, 4.3 to 5.2).	Large cohort study, no report on EF etc Self-reported outcomes Cardiac disease was self-reported Risk of bias

Follow-up Median follow-up 20.3, range 5.0-39.3 years	any of the 27 participating institutions across the United States and Canada Diagnoses n(%) Leukemia 7,282 (38.4) CNS tumors 4,313 (15.7) Hodgkin lymphoma 2,985 (10.9) Non-Hodgkin lymphoma 1,976 (7.2) Wilms tumor 2,141 (7.8) Neuroblastoma 1,837 (6.7) Soft tissue sarcoma 1,693 (6.2) Bone cancer 1,987 (7.2) Age at diagnosis Median: 7 years (0-20.9) Age at follow-up Median: 27.5 years (range, 5.6 to 58.9 years) Controls (if applicable) 5046 untreated siblings	1-299 558 (2.2) ≥ 300 1,300 (5.2) Alkylating agents, n(%) Yes 11,929 (54.8) No 10,094 (45.2) Radiotherapy Chest RT in 51.6% Mean cardiac RT dose, Gy, n(%) None 9,569 (48.4) <0-9.9 7,399 (32.6) 10-19.9 1,912 (8.3) 20-29.9 1,364 (5.5) ≥ 30 1,285 (5.2) HSCT not reported	- The overall AER compared with the sibling population was 1.28 events per 1,000 person-years. Multivariable piecewise exponentional models estimating RR(95% CI) for Grade 3 to 5 for Any Cardiac Disease / HF -Also adjusted for attained age (spline), race, smoking history, year of diagnosis. Sex Male vs. female 0.9 (0.8 to 1.1) / 0.7 (0.5 to 0.9) Race/ethnicity BNH vs. WNH 1.7 (1.2 to 2.4) / 2.0 (1.3 to 3.1) Hispanic vs. WNH 1.0 (0.7 to 1.5) / 0.7 (0.4 to 1.3) Other vs. WNH 1.1 (0.7 to 1.8) / 1.8 (1.1 to 2.9) History of smoking Yes vs. no 1.1 (0.9 to 1.3) / 1.0 (0.7 to 1.3) Mean cardiac RT dose, Gy 0.1-9.9 vs. None 0.8 (0.6 to 1.1) / 0.7 (0.5 to 1.0) 10-19.9 vs. None 2.2 (1.6 to 2.9) / 1.7 (1.1 to 2.7) 20-29.9 vs. None 2.8 (2.0 to 3.8) / 2.9 (1.9 to 4.6) ≥ 30 vs. None 6.4 (4.8 to 8.5) / 6.7 (4.6 to 9.9) ***Cumulative anthracycline dose, mg/m2*** 1-249 vs. None 1.7 (1.1 to 2.5) / 2.9 (1.6 to 5.3) ≥ 250 vs. None 2.4 (1.7 to 3.5) / 6.5 (4.0 to 10.6) Alkylating agents Yes vs. no 1.2 (1.0 to 1.4) / 1.1 (0.8 to 1.4) ***Interaction-Anthracycline dose, 0 mg/m2; age at diagnosis, years*** < 4 vs. > 13yrs 1.1 (0.6 to 1.8) / 1.3 (0.6 to 2.9) > 4 to ≤ 13 vs. > 13yrs 1.1 (0.8 to 1.5) / 1.3 (0.8 to 2.2) ***Interaction-***Anthracycline dose, 1-249 mg/m2; age at diagnosis, years ≤ 4 vs. > 13yrs 2.1 (1.3 to 3.5) / 2.1 (1.0 to 4.2)	A. Selection bias: Low risk Reason: 99.4% of the original cohort of childhood cancer survivors were included. B. Attrition bias: low risk Reason: Patients who dropped out of the study group were censored in time to event analysis. C. Detection bias: unclear Reason: unclear if outcome assessors were blinded. D. Confounding: Low risk Reason: Adjusted for potential confounders

			>4 to ≤ 13 vs. > 13yrs 1.4 (0.9 to 2.2) / 1.5 (0.8 to 2.8) ***Interaction-Anthracycline dose ≥ 250 mg/m2; age at diagnosis, years*** ≤ 4 vs. > 13yrs 4.0 (2.5 to 6.4) / 4.6 (2.7 to 7.9) > 4 to ≤ 13 vs. > 13yrs 2.4 (1.7 to 3.5) / 2.5 (1.7 to 3.8) -No clinically significant association between age at diagnosis and cardiac irradiation on the rate of cardiac disease -Association of anthracycline dose with rate of cardiac disease was not modified by cardiac RT dose <u>Thirty-Year Cumulative Incidence % (95%CI) for Grade 3 to 5 for Any Cardiac Disease/ HF</u> Sex Male 4.5 (3.9 to 5.1) / 2.1 (1.7 to 2.5) Female 5.1 (4.4 to 5.8) / 3.0 (2.5 to 3.6) Race/ethnicity White non-Hispanic 4.6 (4.1 to 5.1) / 2.4 (2.0 to 2.7) Black non-Hispanic 8.4 (5.0 to 11.7) / 5.4 (2.5 to 8.3) Hispanic 4.1 (2.4 to 5.7) / 2.0 (0.9 to 3.1) Other 5.2 (2.8 to 7.7) / 4.4 (2.0 to 6.8) History of smoking Yes 5.5 (4.6 to 6.4) / 2.6 (2.0 to 3.3) No 4.4 (3.8 to 4.9) / 2.4 (2.0 to 2.8) Mean cardiac radiotherapy dose, Gy None 3.4 (2.6 to 4.2) / 2.5 (1.8 to 3.2) 0.1-9.9 2.6 (2.0 to 3.1) / 1.4 (1.0 to 1.7) 10-19.9 5.8 (4.2 to 7.4) / 2.6 (1.6 to 3.6) 20-29.9 7.7 (5.2 to 10.2) / 4.7 (2.7 to 6.7) ≥ 30 17.3 (14.5 to 20.0) / 6.9 (5.2 to 8.7) ***Cumulative anthracycline dose, mg/m2*** None 3.7 (3.1 to 4.2) / 1.2 (0.9 to 1.5)	

			1-249 4.3 (3.2 to 5.4) / 1.9 (1.3 to 2.5) ≥ 250 8.4 (6.9 to 9.9) / 7.2 (5.7 to 8.6) Alkylating agents No 3.6 (3.0 to 4.2) / 1.8 (1.4 to 2.2) Yes 5.9 (5.1 to 6.7) / 3.1 (2.6 to 3.7) ***Anthracycline dose, 0 mg/m2; age at diagnosis, years*** < 4 yrs 1.2 (0.9 to 1.6) / 0.8 (0.5 to 1.1) >4 to ≤ 13 yrs 3.9 (2.5 to 5.3) / 3.1 (1.7 to 4.5) >13 yrs 5.5 (3.6 to 7.3) / 3.9 (2.3 to 5.5) ***Anthracycline dose, 1-249 mg/m2; age at diagnosis, years*** < 4 yrs 2.7 (1.8 to 3.6) / 1.6 (0.9 to 2.3) >4 to ≤ 13 yrs 2.6 (1.8 to 3.3) / 1.2 (0.7 to 1.6) >13 yrs 2.2 (1.1 to 3.4) / 1.4 (0.5 to 2.4) ***Anthracycline dose ≥ 250 mg/m2; age at diagnosis, years*** < 4 yrs 4.7 (2.3 to 7.1) / 2.7 (0.8 to 4.5) >4 to ≤ 13 yrs 3.8 (2.1 to 5.5) / 2.8 (1.4 to 4.3) >13 yrs 12.7 (6.9 to 18.5) / 2.1 (0.4 to 3.8) <u>RR(95%CI) Percentage Volume of Heart Receiving Specific RT Doses for Any Cardiac Disease / HF</u> ***Volume of heart receiving 5 GY when V20 = 0% (V5V20=0%), %*** 0† vs. No RT to heart 0.8 (0.6 to 1.0) / 0.6 (0.5 to 0.9) 0.1-49.9 vs. No RT to heart 0.7 (0.3 to 1.5) / 0.7 (0.3 to 1.8) ≥ 50 vs. No RT to heart 1.6 (1.1 to 2.3) / 1.3 (0.8 to 2.2)	

			Volume of heart receiving >20 Gy (V20), % 0‡ vs. No RT to heart 0.9 (0.7 to 1.1) /0.8 (0.6 to 1.0) 0.1-29.9 vs. No RT to heart 2.4 (1.4 to 4.2) / 2.3 (1.1 to 4.8) 30-79.9 vs. No RT to heart 3.3 (2.3 to 4.8) / 3.4 (2.1 to 5.6) ≥ 80 vs. No RT to heart 4.5 (3.5 to 5.7) / 4.5 (3.2 to 6.2) *†Indicates maximum RT dose to heart of 0.1 to 4.9 Gy.* *‡Indicates maximum RT dose to heart of 0.1 to 19.9 Gy*. Absolute excess risk in survivors compared with siblings: Any cardiac disease per 1000 py for 0, 1-249, ≥250 / HF per 1000 py for 0, 1-249, ≥250 *mg/m2* . *Mean cardiac RT dose, Gy* None 0.09, 0.40, 3.08 / 0.04, 0.47, 2.81 >0-9.9 0.17, 0.67, 2.01 / 0.05, 0.34, 1.85 10-19.9 1.16, 2.26, 4.38 / 0.21, 1.20, 4.05 20-29.9 1.67, 1.79, 8.10 / 0.62, 1.57, 5.39 ≥ 30 6.82, 10.3, 13.8 / 2.43, 4.96, 10.5 ***Volume of heart receiving 5 Gy when maximum heart dose is < 20 Gy (V5V20=0%), %*** No cardiac RT 0.09, 0.40, 3.08 / 0.04, 0.47, 2.81 0* 0.18, 0.52, 2.01 / 0.05, 0.19, 1.87 0.1-49.9 0.31, 0.94, 0.99 / 0.07, 1.08, 1.15 ≥ 50 0.52, 1.54, 4.13 / 0.00, 0.78, 3.69 ***Volume of heart receiving ≥20 Gy (V20), %*** 0 and dose 0 Gy 0.09, 0.40, 3.08 / 0.04, 0.47, 2.81 0† 0.24, 0.77, 2.22 / 0.05, 0.36, 2.05 0.1-29.9 0.80, 6.25, 4.05 / 0.27, 4.20, 3.13 30-79.9 2.08, 5.02, 8.25 / 0.60, 4.12, 7.50 ≥ 80 4.80, 3.68, 9.65 / 1.73, 2.10, 6.60 **Indicates maximum RT dose to heart of 0.1 to 4.9 Gy.* *†Indicates maximum RT dose to heart of 0.1 to 19.9 Gy*.	

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?				
Chellapandian et al. Congestive heart failure among children with acute leukemia - Leukemia & Lymphoma 2019 385-394				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks** **e.g. risk of bias**
Study design Retrospective matched cohort study from 5 tertiary pediatric cancer centers in Canada Treatment era 1992-2010 Follow-up Median follow-up in surviving patients without CHF 10.4 years (range 5.9-16.0)	Type and number of participants 2053 survivors of ALL and AML Diagnoses AML and ALL Age at diagnosis 50% of the population was diagnosed < 4 years of age No median age was mentioned Age at follow-up 0-24 years after diagnosis Controls (if applicable) General population cohort matched on age and geography (postal code)	Chemotherapy 77% of population received anthracyclines Radiotherapy 10.5% received chest RT Surgery - HSCT -	Outcome definitions CHF according to ICD 9 and 10 codes Results Cumulative incidence of CHF after 10 years: 1.7% (ALL) and 7.5% (AML) ALL: 14/32 CHF events (43.8%) within 3 years from cancer diagnosis AML: 9/20 CHF events within 0.5 years from cancer diagnosis Risk factors for CHF in multivariable Cox regression (prespecified predictors): ALL CHF n=32 -Female gender HR 3.26 (95% CI 1.49-7.14) -Age <1 year at cancer diagnosis HR 3.82 (1.09-13.31) -chest RT yes/no HR 6.26 (2.93-13.4) -Cumulative anthra >=250 mg/m2 3.04 (1.41-6.55) AML CHF N=20 -Female gender HR 0.99 (not sign) -Age <1 year at cancer diagnosis HR 0.93 (ns) -chest RT yes/no HR 4.67 (1.77-12.28) -Cumulative anthra >=250 mg/m2 not available as all patients with CHF were treated with doses >=250mg/m2.	Patients with Down syndrome were included (4% of study population) **Risk of bias** A. Selection bias: Low risk Reason: 96-98% of childhood cancers diagnosed <14 years of age included B. Attrition bias: Low risk Reason: Outcome was assessed in all patients C. Detection bias: unclear risk Reason: blinding not mentioned D. Confounding: Low risk Reason: multivariable adjusted analysis with important predictors included.

WG1: Who needs cardiomyopathy surveillance?				
Slieker et al. Echocardiographic Assessment of Cardiac Function in Pediatric Survivors of Anthracycline-Treated Childhood Cancer. Circ Imaging 2019;12:e008869				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Cross-sectional Observational Multicenter Cohort US and Canada Treatment era 1996-2012 Follow-up median 8.5 years (IQR 6.2 – 11.4)	Type and number of participants 546 asymptomatic CCS treated with anthracyclines, in remission, >3 years after final anthracycline dose and routinely followed. alive at 5-years after diagnosis. Attained age 4-18 years. No CHD or familial CMP. No SCT. 52% males. Diagnoses Leukemia 53% Lymphoma 10% Wilms tumor 9% Neuroblastoma 10% Sarcoma 7% Other 11% Age at diagnosis Median 3.6 years (IQR 2.2 – 6.0) Age at follow-up	Chemotherapy Anthracyclines 100% (median dose 150 mg/m^2; IQR 79-300) Radiotherapy Chest directed n=66 (12%) Surgery Not reported HSCT None Dexrazoxane 5%	Outcome definitions *Echo:* Structural measurements (Z-scores) LVEF ≤50% GLS, CS, twist (continuous) CS, twist and 4Ch LS Z-scores (>2SD below mean) *Biomarker:* NT-proBNP >178 ng/L, hsTnT >8.81 pg/L Results CCS had lower FS, EF, |GLS|, but higher |CS| and twist, a thinner IVS, larger EDD, longer IVRT, a lower LV mass index, and a lower VCFS compared with healthy controls. LVEF ≤50%: 0.8% Reduced LS Z-score: 7.7% Elevated NT-proBNP: 4.9% Elevated hsTnT: 1.7% No relation between elevated biomarkers and echo abnormalities. *Multivariable linear regression::* Age at study (β -0.086) and BSA per 0.1m^2 (β-0.065) correlated to 4CH LS Z-score. Not significant: Age at Dx, sex, years since last anth dose, chest RT, cum. anth. dose, dexrazoxane (data not shown).	-Multiple imputation of 36% of biomarker data. 40 imputed echo datasets. -All asymptomatic but 7 were on cardiac meds. Still pediatric population. Recent treatment era. Relatively low cum anth. dose and %RT. Low %dexrazoxane. EF and LS of most CCS were in the normal range. The relation of age and BSA only to the z-scores might also question the calibration of the z-score (body composition?) in CCS, although in controls the relation was less steep. Time between biomarkers and echo not reported

	Median 13.8 years (IQR 10.6 – 16.2) <u>Controls (if applicable)</u> 134 local school children; median age 13.6 (IQR 8.7 – 15.6			**<u>Risk of bias</u>** <u>A. Selection bias:</u> Unclear risk Reason: Underlying cohort not described. Unclear if those who refused to participate had different characteristics. <u>B. Attrition bias:</u> Low risk, high risk for biomarkers Reason: 36% of participants did not have biomarkers available. Values were imputed to limit bias. <u>C. Detection bias:</u> Unclear Reason: Blinding of echo and biomarker assessors was not mentioned <u>D. Confounding:</u> Low risk Reason: Multivariable analysis was adjusted for important confounders

WG1: Who needs cardiomyopathy surveillance?				
Feijen et al. Derivation of Anthracycline and Anthraquinone. JAMA oncology, 2019; 5: 864-871				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks e.g. risk of bias**

Study design Cohort study Treatment era 1962-2005 Follow-up Median 20 years (range 5-40) after cancer diagnosis	Type and number of participants Childhood cancer survivors (>=5 years) n=28423 Diagnoses Leukemia 8740 (36.3%) Lymphoma 5477 (17.7%) Brain tumor 4843 (15.7%) Neuroblastoma 2023 (6.6%) Kidney tumor 2547 (8.3%) Soft-tissue sarcoma 2006 (6.5%) Bone tumor 2151 (7.0%) Other malignant neoplasm 636 (2.1%) Age at diagnosis Median 6.1 years (range 0-22.7) Age at follow-up Median 27.5 years (range 5.1-40.0) Cardiovascular risk factors Not reported Cardioactive Meds Not reported	Chemotherapy -Doxorubicin 9330 (34.8%) Median dose 181 mg/m2 (IQR 119-320) -Daunorubicin 4433 (18%) Median dose 120 mg/m2 (IQR 99-208) -Epirubicin 342 (1.1%) Median dose 300 mg/m2 (IQR 240-400) -Idarubicin 241 (1.1%) Median dose 36 mg/m2 (IQR 20-40) -Mitoxantrone 265 (0.9%) Median dose 40 mg/m2 (IQR 26-72) N=1857 (7.4%) received >1 type of anthracycline or anthraquinone N=87 (0.4%) received >2 types Radiotherapy To the chest: 6240 (21.2%) Median dose 25 Gy (IQR 15-36) Surgery Not reported HSCT Not reported Percentages may not match numbers because percentages reflect weighting	Outcome definitions CTCAEv4.03 grade 3-5 restricted to those occurring after cohort entry and by 40 years of age Results -N=399 cardiomyopathy cases (1.4%) -Cumulative incidence by 40 years of age 3.4% (95% CI 3.1%-3.8%) Multivariable analyses -adjusted for sex, age at diagnosis, chest RT dose, exposure to any other anthracycline or mitoxantrone besides the 2 being compared and stratified by cohort. -Daunorubicin (HR 95% CI) <150 mg/m2 1.4 (0.9-2.1) 150-299 mg/m2 2.8 (1.7-4.5) >=300 mg/m2 6.0 (3.8-9.3) -Doxorubicin (HR 95% CI) <150 mg/m2 1.8 (1.2-2.6) 150-299 mg/m2 4.6 (3.3-6.4) >=300 mg/m2 12.6 (9.8-16.3) -Daunorubicin to doxorubicin ratio <150 mg/m2 0.8 150-299 mg/m2 0.6 >=300 mg/m2 0.5 Mean 0.6 (95% CI 0.4-1.0) -Linear dose response model 0.5 (95% CI 0.4-0.7) -Epirubicin (HR 95% CI)	Overlap Feijen 2015 and 2 Feijen 2019 studies If a survivor developed a subsequent cancer before achieving survival for 5 or 10 years, the patient was either excluded from the analysis or the treatment was taken into account Long-term follow-up **Risk of bias** A. Selection bias: Unclear Reason: the original cohort of survivors is not reported B. Attrition bias: Low risk Reason: outcome assessed for all participants C. Detection bias: Unclear

	Controls (if applicable) NA	used in the CCSS for patients with acute lymphoblastic leukemia; reported median values and IQR also reflect weighting. Participants with missing dose data were excluded.	<150 mg/m2 1.9 (0.3-13.7) 150-299 mg/m2 2.4 (0.6-9.9) >=300 mg/m2 6.0 (2.6-13.9) -Doxorubicin (HR 95% CI) <150 mg/m2 1.5 (0.99-2.2) 150-299 mg/m2 4.2 (3.1-5.7) >=300 mg/m2 11.3 (8.8-14.4) -Epirubicin to doxorubicin ratio <150 mg/m2 1.3 150-299 mg/m2 0.6 >=300 mg/m2 0.5 Mean 0.8 (95%CI 0.5-2.8) -Linear dose response model 0.8 (95% CI 0.3-1.4) -Idarubicin (HR 95% CI) <150 mg/m2 0 150-299 mg/m2 3.8 (1.5-9.5) >=300 mg/m2 0 -Doxorubicin (HR 95% CI) <150 mg/m2 1.4 (0.9-2.1) 150-299 mg/m2 4.1 (3.0-5.7) >=300 mg/m2 11.1 (8.6-14.1) -Idarubicin to doxorubicin ratio <150 mg/m2 0 150-299 mg/m2 0.9 >=300 mg/m2 0 -Mean and linear dose response model NE -Mitoxantrone (HR 95% CI) <150 mg/m2 4.2 (1.8-9.9) 150-299 mg/m2 4.2 (1.6-11.4)	Reason: not reported if outcome assessors were blinded D. Confounding: Low risk Reason: all important prognostic factors were taken into account

			>=300 mg/m2 48.3 (24.2-96.5) -Doxorubicin (HR 95% CI) <150 mg/m2 1.5 (1.0-2.3) 150-299 mg/m2 4.4 (3.2-6.0) >=300 mg/m2 11.6 (9.1-15.0) -Mitoxantrone to doxorubicin ratio <150 mg/m2 2.8 150-299 mg/m2 1.0 >=300 mg/m2 4.2 Mean 10.5 (95% CI 6.2-19.1) -Linear dose response model 13.8 (95% CI 8.0-21.6), nonlinearity beyond >=300mg/m2. -Chest RT (based on model with daunorubicin): 15-34.9Gy vs none HR 2.1 (95%CI, 1.6-2.8) ≥35Gy vs none HR3.5 (95%CI, 2.5-4.8) -No evidence of an interaction between chest RT and doxorubicin (P = .39), daunorubicin (P = .69) or mitoxantrone (P = .97)	

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy				
Mansouri et al. The role of irradiated heart and left ventricular volumes in heart failure occurrence after childhood cancer. *European journal of heart failure* vol. 21,4 (2019): 509-518. doi:10.1002/ejhf.1376				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design Nested case-control study Treatment era Between 1945 and 2000 Follow-up Median Cases: 19.7 [range 13.7–26.9] years. Controls: 33.0 (range 27.2–39.0) years	Type and number of participants n = 1281 cases and controls, 5-year survivors of solid cancers diagnosed before age 20 between 1945 and 2000 in France. HF cases = 239 Diagnoses: Cases n (%) & controls n (%) Nephroblastoma 81 (33.9) & 321 (31) Sarcoma 61 (25.5) & 191 (18.3) Hodgkin's disease 35 (14.6) & 79 (7.6) NHL 34 (14.2) & 125 (12.0) Other 21 (8.8) & 170 (16.3) CNS 4 (1.7) & 140 (13.4) Neuroblastoma 3 (1.3) & 16 (1.5) Age at diagnosis Median	Chemotherapy *Anth: Cases n (%) & controls n (%)* 172 (72.0) & 362 (34.7) Median Dose, mg/m2 Cases: 357.3 (range 2.1–998.1) Controls: 292.4 (range 6.1–1021.8) *Doxo, Cases n (%) & controls n (%)* 157 (65.7) & 322 (30.9) Median Dose, mg/m2 Cases: 352.7 (range 2.1–860.6) Controls: 284.6 (range 6.1–619.2) *Daun, Cases n (%) & controls n (%)* 25 (2.4) & 10 (4.2) Median Dose, mg/m2 Cases: 508.2 (range 279.3–998.1) Controls: 316.2 (range 81.9–998.1) *Alkylating agents Cases n (%) & controls n (%)* 182 (76.2) & 530 (50.9) Median Dose, mg/m2	Outcome definitions Heart failure raded according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.03) Results Symptomatic HF = 85.4% (grade three HF = 46.4%, grade four HF=21.4%, died from HF=17.6%) Cumulative incidence of HF 30 years = 2.5% (95% CI 2.1–2.9%) 50 years = 5.7% (95% CI 5.0–6.6%) Conditional logistic regression Heart failure risks by exposure to chemotherapy agents and splenectomy, OR (95% CL) *Anthracycline* 0–250 vs. none: 3.4 (1.5–7.6) 250–360 vs. none: 11.4 (5.0–25.9) ≥360 84 vs. none: 15.0 (7.1–31.7) *Ptrend <0.0001* *Doxorubicin,* 0–250 vs. none: 4.2 (2.4–7.9) 250–360 vs. none: 14.8 (7.8–27.9) ≥360 vs. none: 19.6 (10.5–36.3) *Ptrend <0.0001* *Alkylating agents* 0–4.75 vs. none: 1.5 (0.7–3.3) 4.75–10.7 vs. none: 1.2 (0.6–2.6) ≥10.7 vs. none: 2.4 (1.2–4.7) *Ptrend <0.03* Splenectomy Yes vs. no 3.5 (1.5–9.2)	Risk of bias A. Selection bias: Low risk Reason: Included all the 239 cases identified from the FCCSS cohort after a median follow-up of 19.7 years, who were eligible for the study. Controls were matched. High risk for study of modifiable risk factors. B. Attrition bias: Low risk Reason: the outcome was assessed for more than 75% of the study group. Dose estimation was not done for only five participants with incomplete medical records. C. Detection bias: Unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: Low risk Reason: Matching and multivariate analysis

	Cases: 5 (IQR 2.4–9.8) years Controls: 5 (IQR 2.3–9.6) years <u>Age at follow-up</u> The median age of HF diagnosis was 25.1(range,18.3–34.2) years <u>Controls (if applicable)</u> Matched controls = 1042 5-year survivors of solid cancers diagnosed before age 20 between 1945 and 2000 in France.	Cases: 10.4 (range 0.2–367.1) Controls: 7.3 (range 0.02–140.2) *Cisplatin, Cases n (%) & controls n (%)* 33 (13.8) & 91 (8.7) 0.8 Median Dose, mg/m2 Cases: 455.4 (range 97.1–1154.7) Controls: 431.3 (range 74.3–4128.2) *Vinca alkaloids, Cases n (%) & controls n (%)* 197 (82.4) & 655 (62.9) Median Dose, mg/m2 Cases: 25 (range 1.65–10611.6) Controls: 19.6 (range 1–2556) <u>Radiotherapy</u> Radiation to the heart: *Mean dose,* Cases: median 12.3 (0.004–49.1) Gy Controls: median 2.1 (0.005–45.3) Gy *Volume (%) receiving ≥30 Gy,* Cases: median 61.1 (0.1–100) Controls: median 16.9 (0.03–100)	*Ptrend <0.006* <u>Multivariable conditional logistic regression</u> Risks of heart failure among patients exposed to doses of anthracycline and cardiac radiation Ref: no anthracycline and no cardiac radiation Anth 0–250 + none CR vs. none Anth + none CR 3.3 (1.1–9.6) Anth≥250 + none CR vs. none Anth + none CR 13.9 (6.0–32.6) None Anth + Yes CR vs. none Anth + none CR 2.6 (1.2–5.9) Anth 0–250 + yes CR vs. none Anth + none CR 7.2 (3.0–18.0) Anth ≥250 + yes CR vs. none Anth + none CR 29.7 (12.9–68.6) *Adjusted for splenectomy, type of first childhood malignancy, vinca alkaloids, alkylating agents, and other chemotherapies. <u>Multivariable conditional logistic regression</u> The risk of heart failure by mean heart dose, mean left ventricular dose, volume of the heart receiving ≥30 Gy and anthracycline. OR(95%CL) *Mean heart dose (MHD) in Gy,* MHD 0–5 + none Anth vs. none MHD + none Anth 0.7(0.2-2.0) MHD 5–15 + none Anth vs. none MHD + none Anth 2.0(0.6-6.3) MHD 15–30 + none Anth vs. none MHD + none Anth 5.2(1.9-13.8) MHD ≥30 + none Anth vs. none MHD + none Anth 20.6 (7.6–55.3) MHD 0 + Anth vs. none MHD + none Anth 11.3 (4.7–27.0) MHD 0–5 + Anth vs. none MHD + none Anth 21.5 (8.8–52.6) MHD 5–15 + Anth vs. none MHD + none Anth 23.8 (7.6–75.0) MHD 15–30 + Anth vs. none MHD + none Anth 54.4 (19.3–153) MHD ≥30 + Anth vs. none MHD + none Anth 24.6 (7.2–84.1) *Mean left ventricular dose (MLVD) in Gy,*	

		Radiation to the left ventricle *Mean dose,* Cases: median 11.9 (0.003–47.4) Gy Controls: median 2.1 (0.005–39.5) Gy *Volume (%) receiving ≥30 Gy,* Cases: Median 37.3 (0.01–100) Controls: median 23.8 (0.06–100) <u>Surgery</u> Cardiac transplantation = 25 cases at a median age of 20.3 (range 15.3–28.1) years <u>HSCT</u> Not reported	MLVD 0–5 + none Anth vs. none MLVD + none Anth 0.6 (0.2–1.8) MLVD 5–15 + none Anth vs. none MLVD + none Anth 2.1 (0.7–6.5) MLVD 5–15 + none Anth vs. none MLVD + none Anth 4.5 (1.7–12.0) MLVD ≥30 + none Anth vs. none MLVD + none Anth 42.1 (14.1–126) MLVD 0 + Anth vs. none MLVD + none Anth 11.7 (4.8–28.2) MLVD 0–5 + Anth vs. none MLVD + none Anth 23.4 (9.3–56.7) MLVD 5–15 + Anth vs. none MLVD + none Anth 31.8 (10.6–95.0) MLVD 15–30 + Anth vs. none MLVD + none Anth 39.8 (14.4–110) MLVD ≥30 + Anth vs. none MLVD + none Anth 35.8 (8.2–157) *Volume of the heart (%) receiving ≥30 Gy,* <10% + none Anth vs. 0% + none Anth 1.9 (0.7–5.5) 10–50% + none Anth vs. 0% + none Anth 5.5 (2.1–14.1) ≥50% + none Anth vs. 0% + none Anth 17 (7.6–38.0) <0% + Anth vs. 0% + none Anth 16.5 (8.5–32.1) 0–10% + Anth vs. 0% + none Anth 22.2 (7.4–66.3) 10–50% + Anth vs. 0% + none Anth 26.4 (8.7–80.0) ≥50% + Anth vs. 0% + none Anth 28.3 (9.4–85.2) *Volume of the left ventricle (%) receiving ≥30,* 0–10% + none Anth vs. 0% + none Anth 3.6(1.3–10.1) 10–50% + none Anth vs. 0% + none Anth 6.6 (2.8–15.4) ≥50% + none Anth vs. 0% + none Anth 24.6 (10.3–58.7) <0% + Anth vs. 0% + none Anth 14.7 (7.7–28.0) 0–10% + Anth vs. 0% + none Anth 37.9 (12.5–115) 10–50% + Anth vs. 0% + none Anth 26.5 (8.9–78.6) ≥50% + Anth vs. 0% + none Anth 16.9 (4.9–58.4) * adjusted for splenectomy, type of first childhood malignancy, vinca alkaloids, alkylating agents, and other chemotherapies. *Similar results were observed for the *volume of the heart (%) receiving* 20Gy and 40Gy	

			Multivariate Analysis: Risk of developing HF by type of first childhood cancer, OR(95% CI) CNS tumor vs.Nephroblastoma 0.1 (0.03-0.6) Others vs.Nephroblastoma 0.3 (0.1-0.8) *Sarcoma vs.Nephroblastoma, Hodgkin's disease vs.Nephroblastoma, Non Hodgkin's disease vs.Nephroblastoma, Neuroblastoma vs.Nephroblastoma were not significant * adjusted on anthracycline, vinca alkaloids, alkylating agents, other chemotherapies, mean dose of radiation to the heart and splenectomy <u>Modifiable CV risk factors studied in 117 cases and 353 controls</u> -Diabetes before HF diagnosis: OR 0.7 (0.1 – 3.6) -Smoking at the time of HF diagnosis: OR 0.8 (0.4-1.5) -Obesity (BMI ≥30 kg/m^2): OR 1.1 (0.4-3.1) -Physical activity (<1 h/week=reference) 1-3 h/week: OR 0.9 (0.3-2.1) ≥ 3 h/week: OR 0.9 (0.5-1.8) Evaluation of potential effect modifiers of the dose response relationship for the mean heart dose and the mean left ventricle dose: ERR/Gy (95% CI) for the MHD and MLVD Anth yes, 0.09(0.02–0.22) and 0.89(0.01–0.21) Anth no, 0.44(0.18–1.12) and 0.45(0.18–1.16) <15 0.06(0.04-0.20) and 0.08(-0.02-0.92) Attained age 15-25 0.33(0.04-2.17) and 0.06(-0.01-0.41) 25-35 0.38(0.33-2.67) and 0.10(0.09-0.43) ≥30 0.48(0.05-3.78) and 0.38 (0.12-1.09) Age at diagnosis <3 0.18(0.06-0.52) and 0.19(0.05-0.53)	

			3-5 0.38(0.10-1.17) and 0.42(0.10-1.30) 5-15 0.21(0.07-0.55) and 0.23(0.07-0.60) ≥15 0.16(0.05-0.47) and 0.15(0.04-0.44) Interaction P.value for the MHD; MLVD MHD and Anth =0.007; 0.004 MHD and Attained age = 0.12; 0.17 MHD and Age at diagnosis= >0.5; 0.14	

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?				
Khanna et al. Increased Risk of All Cardiovascular Disease Subtypes Among Childhood Cancer Survivors: Population-Based Matched Cohort Study. *Circulation 2019 1041-1043*				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks** **e.g. risk of bias**

Study design Retrospective matched cohort Treatment era - Jan 1987- Dec 2010 Follow-up - to Dec 2016 Median 10, range 0-25 years	Type and number of participants 7289 5-yr survivors of childhood cancer Diagnoses Any childhood cancer Age at diagnosis All <18. No median provided Age at follow-up - median 24 (range 5-47) Controls (if applicable) 36205 matched controls without cancer	Chemotherapy median dox equiv dose 200 mg/m2 (IQR 120-300 mg/m2). Dox equivalent dose 0, n= 4,029 (55.3%) 1-149, n=1,041 (14.3%) 150-249, n=1,105 (15.2%) 250-450, n=828 (11.4%) >450, n=196 (2.7%) Unknown, n=90 (1.2%) Radiotherapy 1027 (14.1%) had received chest RT Surgery 4012 (55.2%) HSCT 230 auto 232 allo	Outcome definitions CHF based on a published administration data algorithm using hospital discharge codes and physician billing codes Results By 15 years after 5-yr survival, cumulative incidence of heart failure was 1.8%; 95% CI 1.4-2.3%. Compared to 0.2% in the general population 10 years: 1.1% (0.8-1.4) in survivors Cause specific hazard ratio of heart failure compared to the general population: HR 9.7 (95% CI 6.8-14.0) Factors associated with increased risk of CHF in multivariable cox regression analysis: relapse or SMN (HR, 2.0; CI, 1.1–3.7) Dox equivalent dose >250 mg/m2 (HR, 8.6; CI, 4.5–16.6) Diabetes (HR, 4.3; CI, 1.8–10.7) Hypertension (HR, 3.1; CI, 1.3–7.9)	Patients with Down syndrome were included (4% of study population) **Risk of bias** A. Selection bias: Low risk Reason: All survivors were included using health administrative data B. Attrition bias: Low risk Reason: Outcome was assessed in all patients C. Detection bias: Unclear Reason: Blinding of investigators for treatment exposure was not mentioned D. Confounding: Low risk Reason: Multivariable model was adjusted for important confounders. Chest RT was tested in univariable analysis but not in multivariable model as it was not a significant predictor of HF in MV analysis.

WG1: Who needs cardiomyopathy surveillance? Genetics

Singh et al. Association of GSTM1 null variant with anthracycline-related cardiomyopathy after childhood cancer-A Children's Oncology Group ALTE03N1 report. Cancer. 2020 Sep 1;126(17):4051-4058.

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Study design Case control Treatment era Not reported Follow-up Cases: median 6.0, range 1.3-11.6 years Controls: 12.0, range 7.4-17.2 years	Type and number of participants 75 cases with anthracycline CMP 92 controls matched on primary cancer diagnosis, year of diagnosis (±5 years), and race/ethnicity Diagnoses ALL, AML, HL, NHL, bone tumors, kidney tumor, sarcoma, neuroblastoma Age at diagnosis, median (range) Cases: 7.8 (3.8-11.5) Control: 9.6 (3.3-14.8) Age at follow-up	Chemotherapy 100% anthracyclines Mg/m2 (median, range): Cases: 300, 230-375 Controls: 255, 150-368 Radiotherapy Cases: 35%, mean dose 10.4 Gray±16.4 Controls: 26%, mean dose 8.1 Gray±17.9 Surgery Not reported HSCT Not reported	Outcome definitions Heart failure according to AHA criteria Cases mean LVEF 39.4%, mean FS 22.2% Controls: mean LVEF 65.9, mean FS 36.7% GSTM1=Glutathione S-transferase μ1 Multivariable conditional logistic regression (95% CI) **GSTM1 null vs positive: OR 2.7 (1.3-5.9) p=0.007** Age at diagnosis per year: OR 0.95 (0.88-1.01) Anthracycline >=250 vs <250: OR 2.5 (0.99-6.4) Chest RT yes vs no: OR 1.5 (0.6-3.6) Female vs male: OR 1.5 (0.7-2.9) -GSTM1 gene expression (RNA) in 20 cases compared with 20 controls (average relative expression, 0.67 ± 0.57 vs 1.33 ± 1.33, respectively; P = .049). -hiPSC-CMs from patients who had cardiomyopathy (n=3) compared to 3 controls revealed reduced GSTM1 expression (P = .007).	No replication **Risk of bias** A. Selection bias: unclear Reason: underlying cohort not described. High risk for RNA analysis and hiPSC-CM. B. Attrition bias: low risk Reason: outcome assessed in all C. Detection bias: unclear Reason: blinding not reported D. Confounding: low risk Reason: matched analysis and MV adjustments

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?

Mulrooney et al. Major Cardiac Events for Adult Survivors of Childhood Cancer Diagnosed Between 1970 and 1999: Report From the Childhood Cancer Survivor Study Cohort. BMJ. 2020 Jan 15;368:l6794.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks** **e.g. risk of bias**
Study design Multi-institutional retrospective cohort study Treatment era 1970 through 31 December 1999. Follow-up Median follow-up time ranged from 11.0 years (diagnosis in the 1990s) to 29.5 years (diagnosis in the 1970s).	Type and number of participants Diagnosed before age 21 years at one of 27 participating institutions in the United States and Canada. Original cohort: n= 35 649 (46.3% female) Analyzed: n= 23 462 Diagnoses leukemia, central nervous system tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, renal tumors, neuroblastoma, soft tissue sarcomas, and bone sarcomas Age at diagnosis Median 6.1 years (range 0-20.9) Age at follow-up Median 27.7 (8.2-58.3) years Controls (if applicable)	Chemotherapy Chemotherapy only 17.4% Anthracyclines: 0 (49%), <250mg/m2 (36%), ≥250 (15%) Radiotherapy Radiation only 0.4% Mean heart radiation dose: 0 (49%), <15 (37.8%), 15 to <35 (11.3%), ≥35 (15%) Surgery Surgery only 7.8% HSCT not mentioned	Participants completed a baseline questionnaire and up to four follow-up surveys. Outcome definitions all reported cardiac conditions of CTCAE grades 3-5, including heart failure. Results -140 had cardiac event prior to cohort entry -Cumulative incidence of heart failure at 15 years from cancer diagnosis was significantly lower in the 1990s (0.54%) compared with the 1970s (0.69%) (P=0.01) and the 1980s (0.74%) (P=0.01) (fig 2). The only population where an increase was observed was for heart failure among survivors of neuroblastoma (3.22 (0.83 to 12.53) in the 1980s and 5.72 (1.58 to 20.67) in the 1990s versus the 1970s). Multivariable Cox regression including sex, treatment era, mean heart dose, cumulative anthracycline dose hypertension, dyslipidemia, hypertension, race, age at diagnosis, body mass index, smoking and exercise intensity: -Female vs male HR 1.51 (1.10-2.06) -Treatment era (1970-79=ref)	Limitation: 31% of the original cohort did not participate. Outcomes were self-reported and not validated. Strength Compared with a control group. Risk of bias A. Selection bias: High risk Reason: 31% of original cohort did not participate, significant differences in age at cancer diagnosis, tumor types and overall mortality between participants and non-participants B. Attrition bias: High risk Reason: 31% of original cohort did not participate C. Detection bias: Unclear Reason: Blinding was not reported D. Confounding: Low risk Reason: Multivariable analysis adjusted for important confounders

	random sample of siblings (n=5057)		1980-89: HR 0.89 (0.67-1.17) 1990-99: HR 0.70 (0.45-1.08) -Anthracycline dose (ref=none) <250 mg/m2 HR 2.76 (1.93-3.97). >250 mg/m2 HR 9.29 (6.01-14.37) -Mean heart dose, Gray (ref=none) 1-15 HR 0.74 (0.54-1.03) 15.1-34.99 HR 1.56 (1.05-2.33) >=35 HR 3.95 (2.87-5.43) -Diabetes: HR 2.66 (1.67-4.25) -Dyslipidemia: HR 2.32 (1.53-3.52) -Hypertension: HR 4.93 (3.61-6.72)	

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?				
Chen et al. Traditional Cardiovascular Risk Factors and Individual Prediction of Cardiovascular Events in Childhood Cancer Survivors. JNCI J Natl Cancer Inst (2020) 112(3): djz108				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Prediction model development (50%) and validation (50%) in the CCSS, retrospective cohort study. Prediction timepoints (baseline) at age 20, 25, 30 and 35 y	Type and number of participants N=22543 included No CV disease <5 years from cancer diagnosis (n=353) No self-reported outcomes n=1738 Diagnoses All childhood cancer diagnoses Age at diagnosis	Anthracyclines 43%-52% >=250 mg/m2: 14.2-19.3% Chest RT 30.7%-49.5% >=35 Gray: 8.9%-13.0% Surgery Not reported	Outcome definitions Only heart failure reported in this table CTCAE grade 3-5 Modifiable CV risk factors Prevalence of CV risk factors was limited at age 20 years (all <3%) but increased over time, with 8.8% to 9.0% of survivors reporting hypertension by age 35 years. Multivariable piecewise exponential model, RR (95% CI) Age 20 / Age 35 **-Female vs male: 1.86 (1.23-2.82)** / 1.47 (0.72-3.03)	-C-statistics by age 50: 0.79 (20y), 0.75 (25y), 0.69 (30y), 0.74 (35y). -Reasonable calibration -Prediction models for heart failure at different baseline ages (20-35 years). -Prediction of both 10y risk and risk by age 50 years, could inform risk groups and surveillance frequency

Treatment era 1970-1999 Follow-up Various, depending on prediction timepoint. Range 5->30 years Duration of follow up in the 20y cohort was 10-19y in 35% and 20-29y in 51%. In the 35y cohort: 20-29y in 53% and >30y in 40%	<5y in 40% of the 20y cohort, 30% were 5-9 and the remaining 10-14y. In the 35y cohorts 12% were <5y, 15% 5-9y, 32% 10-14 and 40% >15y Age at follow-up Not reported Controls (if applicable) 5056 siblings of CCSS survivors	HSCT Not reported	-Age at diagnosis (>=15 years=ref) <5: 0.84 (0.44-1.61) / 2.64 (0.31-22.69) 5-9: 1.44 (0.89-2.31) / 0.50 (0.07-3.90) 10-14: NA / 1.01 (0.44-2.35) -Anthracycline, mg/m2 (none=ref) <100: 1.09 (0.32-3.77) / 0 (-) **100-249: 3.67 (1.85-7.28)** / 2.11 (0.46-9.76) **>=250: 11.54 (6.85-19.45) / 5.02 (2.09-12.06)** -Chest RT, Gray (none=ref) <5: 1.36 (0.64-2.85) / 0 (-) 5-14: 1.43 (0.55-3.70) / 0 (-) **15-34: 2.56 (1.43-4.57)** / 1.11 (0.23-5.25) **>=35: 6.76 (3.89-11.76) / 6.30 (2.47-16.09)** -Diabetes: 3.78 (0.91-15.73) / 3.35 (0.75-14.95) -Dyslipidemia: 2.94 (0.67-12.84) / 0 (-) **-Hypertension: 5.66 (2.54-12.61)** / 1.44 (0.33-6.22) CI of HF (prediction baseline at age 20, 25, 30, 35) *10-year follow-up:* Siblings: 0.03%-0.2% Moderate (score <5): 0.4%-1.3% High (score >=5): 2.7%-6.3% *By age 50 years:* Siblings: 0.4%-0.6% Moderate (score <5): 1.4%-2.4% High (score >=5): 9.7%-11.8%	-Moderate risk group <3% CI by age 50, <1.3% within 10y -High risk group ±10% CI by age 50, 2.7-6.3% within 10y Risk of bias A. Selection bias: low risk Reason: 91.5% included B. Attrition bias: low risk Reason: Outcome assessed in all C. Detection bias: unclear Reason: blinding not reported D. Confounding: low risk Reason: multivariable models

WG1: Who needs cardiomyopathy surveillance?

Nolan et al. Impact of Cancer Therapy-Related Cardiac Dysfunction on Risk of Heart Failure in Pregnancy. JACC: CardioOncology 2020;2(2):153-62.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Systematic review and meta-analysis of 6 cohort studies Criteria for review: Retrospective (n=5) or prospective (n=1) cohort studies including ≥ 10 females of reproductive age, treated with cardiotoxic therapy, who underwent ≥1 pregnancy. Review period: inception to 2020 Treatment era: 1963-2015 Follow-up: Median 25 (range: 5 – 48) years since diagnosis (5 of 6 studies)	Type and number of participants 1,137 female CCS with 2,016 pregnancies from 6 studies: Bar 2003, van Dalen 2006, Hines 2016, Thompson 2017, Liu 2018, Chait-Rubinek 2019 Diagnoses 61% hematological malignancies. Also sarcoma, Wilms tumor, embryonic tumors, hepatoblastoma, other. Age at diagnosis Median 12 (range: 0 – 41) years Age at first pregnancy Median 22 (range: 14 – 43) years Age at (last) follow-up Not specified	Chemotherapy Anthracyclines 67% mean cumulative dose 234 (range 0 – 721) mg/m^2 Radiotherapy Not specified, incomplete in studies Surgery Not specified HSCT Not specified	Outcome definitions Either - LV systolic dysfunction (reduction LVEF or FS)(4 studies) - clinical HF (3 studies) during or within 12 months after delivery Results *Incidence of endpoint:* n= 33/1,137 (2.9%), of whom n=17 (52%) had a history of cancer therapeutics related cardiac dysfunction (CTRCD) before pregnancy. Weighted incidence: Overall 1.7% (95% CI 0.9-2.7%) - If history CTRCD: 28% (95% CI 15-44%) - No history of CTRCD: 0.24% (95% CI 0-0.81%) Number-needed-to-harm: 4 Odds ratio of event for previous CTRCD versus no previous CTRCD: 47 (95% CI 18 – 126)	Studies reported no maternal cardiac death. Not all patients had cardiac evaluation before and after pregnancy. All studies were judged good quality Risk of bias A. Selection bias: Unclear risk; judged adequate by authors although not quantified. B. Attrition bias: Unclear risk; judged adequate by authors although not quantified. C. Detection bias: Unclear risk; judged adequate by authors although not quantified. D. Confounding: High risk: OR is unadjusted for important confounders, although metaregression did not reveal significant interstudy heterogeneity, within-study heterogeneity might prevent metaregression and adjustment to be feasible. Risk

				factor might thus not be independent.

WG1: Who needs cardiomyopathy surveillance?				
Green et al. Congestive heart failure after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study group. J Clin Oncol 19:1926-34, 2001				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort and nested Case-Control Treatment era National Wilms Tumor studies 1-4 1969-1998 Follow-up No descriptive statistics reported Heart failure cases range ±1-20 years. Controls matched on follow-up	Type and number of participants Treated <16 years old Cohort 1: received doxorubicin N=2,843 Cohort 2: dox as part of salvage only N=228 Diagnoses (%) Wilms tumor 100% Age at diagnosis Majority <7 years Cases range 0.8-10.4 years Age at follow-up Heart failure cases: Range 2.4-21.8 years Controls not mentioned but matched for follow-up after cancer.	Chemotherapy Doxorubicin 100% Cases median 257, range 59-485 mg/m2 Controls 1-199 mg/m2 36/143 25% 200-299 mg/m2 71/143 50% >=300mg/m2 36/143 25% Radiotherapy Lung RT cases 0 Gray 16/35 10-19.99 Gray 15/35 >=20 Gray 4/35 Lung RT controls 0 Gray: 84/143 10-19.99 Gray 51/143 >=20 Gray 8/143 Abdominal RT cases None or right 9/35 Left 29/35 Abdominal RT controls	Outcome definitions Cumulative incidence and risk factors for heart failure Results cohort study Heart failure 4.4% and 17.4 at 20 years after diagnosis in cohort 1 and cohort 2, respectively. Categorical conditional logistic regression multivariate (covariates not mentioned), relative risks (RR) were estimated with the weighted Breslow estimate. -Cumulative Doxorubicin dose (1-199 mg/m2=Reference) 200-299 mg/m2: RR 1.1 (0.3-5.1), NS ≥300 mg/m2: RR 6.0 (1.5-24), p=0.01, p trend=0.002 Female vs male: RR 3.5 (1.4-8.8), p=0.009 -Lung RT (0=reference) 10-19.99 Gray 1.5 (0.6-3.9) p=0.39 ≥ 20 Gy 4.3 (0.8-24) p=0.1, p trend=0.12	Homogeneous population due to diagnosis, the vast majority were exposed before 7 years old **Risk of bias** A. Selection bias: unclear risk Reason: it was stated that controls were randomly sampled from the cohort. However, if treatment data was unavailable another control was randomly sampled. Number of controls with missing treatment data is not stated. B. Attrition bias: High risk Reason: >20% loss to follow-up in all studies 1-4 (Figure 1) C. Detection bias: Low risk Reason: Heart failure cases were validated in medical records D. Confounding: low risk

	Controls (if applicable) Four to six controls per case matched by cohort, study and time at risk from first anthracycline administration.	None or right 73/143 Left 70/143 Surgery only none HSCT Not reported	-Abdominal radiation (none or right sided=reference) Left sided: RR 4.0 (1.4-11.6), p=0.01	Reason: Multivariable analysis and matched case-control

WG1: Who needs cardiomyopathy surveillance?				
Nolan et al. Effect of Traditional Heart Failure Risk Factors on Myocardial Dysfunction in Adult Survivors of Childhood Cancer JACC: CARDIOVASCULAR IMAGING VOL. 11, NO. 8, 2018				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Cross sectional (St. Jude Lifetime cohort study) Treatment era Around 1998 Follow-up median interval from diagnosis 23 years, range 10 to 48 years	Type and number of participants 1,807 participants (48% female; median age 32 years, range 18 to 66 years Diagnoses Different cancers Age at diagnosis they were ≥18 years of age and≥10 years from diagnosis	Chemotherapy 58% treated with anthracyclines, Radiotherapy 17% treated with chest radiotherapy, and 25% treated with both). Surgery Not reported	Outcome definitions 1. LV systolic dysfunction (LVEF <53% on 3D) 2. GLS) >2 SDs from age/ sex-based population norms 3. Diastolic dysfunction based on 2016 ASE guidelines Studied conventional heart failure risk factors A. Hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg), B. Insulin resistance (homoeostatic model assessment for insulin resistance >2.86), C. obesity (body mass index >30 kg/m2), and D. smoking status (self reported current, former, or never) Also included in the multivariate analysis - sex - antracyline cumulative dose	-unknown how many were symptomatic **Risk of bias** A. Selection bias: High risk Reason: 57% of eligible subjects underwent echocardiography B. Attrition bias: Low risk

	Age at follow-up; median age 32 years, range 18 to 66 years	HSCT Not reported	- Chest radiotherapy - Age at diagnosis - current age Results Main endpoints: LVEF <53% in 14%, Abnormal GLS in 32% and diastolic dysfunction in 32% A. Hypertension was associated with abnormal 3D-LVEF (odds ratio [OR]: 1.82; 95% confidence interval [CI]: 1.25 to 2.63; p < 0.002) and diastolic dysfunction (OR: 1.40; 95% CI: 1.0.2 to 1.93; p < 0.04). B. Insulin resistance was associated with abnormal GLS (OR: 1.72; 95% CI: 1.30 to 2.27; p < 0.001), and diastolic dysfunction (OR: 1.43; 95% CI: 1.07 to 1.91; p < 0.01). C. Obesity was associated with abnormal GLS (OR: 1.59; 95% CI: 1.19 to 2.13; p < 0.002) and diastolic dysfunction (OR: 1.92; 95% CI: 1.43 to 2.59; p < 0.001). D. Smoking was not significantly associated with any echocardiographic abnormality. Cumulative anthracycline dose significantly affected 3D-LVEF (1.51 _ 10–2; p < 0.001) and current age significantly affected GLS (ES: 0.20 _ 10–2; p ¼ 0.05). After correction of these well-known risk factors, the effect of hypertension, IR and obesity on outcome (not specified which ones precisely) were of the same order of magnitude or higher	Reason: Outcome was assessed in all participants C. Detection bias: Unclear Reason: This is not stated in this short paper, but I assume they were blinded during the analysis of the ultrasounds D. Confounding: Low risk Reason: Multivariable analysis

WG1: Who needs cardiomyopathy surveillance?

Niska et al. Radiation and the heart: systematic review of dosimetry and cardiac endpoints. EXPERT REVIEW OF CARDIOVASCULAR THERAPY 2018, 16. 12, 931–950.

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Study design Systematic review of 64 cohort studies: - 20 paediatric studies - 44 adult studies (not described here) Criteria for review Studies correlating cardiac Rt dose with cardiac toxicity or death Review period 2008–2017 Treatment era NS Follow-up Range of median: 2 to 28 years (19 of 20 paediatric studies)	Number of participants N<100: 8 studies (range: 9-90) N<1000: 4 studies (range: 119-545) N<5000: 6 studies (range: 1,132-4,122) N >10 000: 2 studies (13,060; 14,358) Diagnoses Hodgkin: 11 studies Paediatric: 9 studies Age at diagnosis NS Age at (last) follow-up NS	Chemotherapy Either Anthracyclines After Hodgkin (11 studies) 0% (1 study) 100% (3 studies) >50% (5 studies) < 50% (2 studies) Means range: 146.3-160 mg/m2 (2 studies) Anthracyclines After Pediatric (9 studies) >50% (3 studies) < 50% (4studies) Reported by categories: 13.4% < 250 mg/m2 and 19.7% ≥ 250 mg/m2 (1 study) 8.1% < 239 mg/m2 and 10%: 240–359 mg/m2 and 10.7% ≥ 360 mg/m2 (1 study) Radiotherapy endpoints Prescription dose (1 study) MedRD (8 studies) and after HL (6 of 8 studies) Heart mean (6 studies), max (4 studies), median (1 study), absolute volume (1 study) and D10 (1 study) Valve mean (1 study) LV mean (1 study), V20 (1 study), V30 (2 studies) RV V30(1 study) LA V25 (1 study), V30(1 study)	Outcome definitions CAD (2 studies) Cardiac damage (1 study) Cardiac death (1 study) Cardiac diseases (1 study) Cardiac toxicity (CTCAE) (1 study) Symptomatic cardiac event (1 study) CHF (3 studies) MI (1 study) PD (1 study) VHD (9 studies) CTA abnormality (2 studies) Cardiac MRI findings (1 study) Echocardiography GLS (1 study) Main Results Mortality after pediatric cancer Linear ↑ 60% ERR at 1 Gy. RR 12.5 for 5–14.9 Gy. VHD after Hodgkin Doses > 15 Gy increase VHD risk. This risk increased also with tumor location, smaller cardiac volumes, and smaller lung volumes The LA V25 and LV V30 predicted for mitral and aortic valve dysfunction. Cumulative anthracycline doses exceeding	8 studies included less than 100 participants **Risk of bias** A. Selection bias: Unclear B. Attrition bias: Unclear C. Detection bias: Unclear D. Confounding: Unclear if multivariable analysis of all studies Unclear adjustment variables

		Surgery Not specified HSCT Not specified	250mg/m2 increased the risk of CHF, pericardial disease, or VHD MHD > 15 Gy increased the risk of events twofold to sixfold over nonirradiated survivors For MHD 15–30 Gy RR=18.9 without anth and RR=47.1 with anth, for any CD and similar results observed for symptomatic CD (Haddy 2016) Myocardial perfusion imaging echocardiography with myocardial strain imaging, CTA, and cardiac MRI may be useful for pre-RT evaluation and in long-term surveillance.	

WG1: Who needs cardiomyopathy surveillance? Genetics				
Hildebrandt et al. Hypertension Susceptibility Loci are Associated with Anthracycline-related Cardiotoxicity in Long-term Childhood Cancer Survivors. 2017, SCiEnTifiC REPOrTS | 7: 9698 | DOI:10.1038/s41598-017-09517-2				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design nested case control study Treatment era Not described	Type and number of participants N=108 long term childhood cancer survivors >5 years post diagnosis and off therapy; treated with anthracyclines of which 46 developed cardiotoxicity during follow-up:	Chemotherapy Anthracycline cumulative dose, mean (SD): Cases: 319.5 (111.5) Controls: 273.9 (157) (all patient received Atc)	Definition of cardiotoxicity (cases): finding on 2 cardiac US of i) EF 45-50% + symptoms +/- cardiac meds or ii)EF <45% and/or iii) SF <or = 25% Controls: EF >55% and SF > 28% on 2 subsequent cardiac US obtained >5y off treatment.	Study strengths i) gene expression studies confirmed results of cohort study. ii)Multivariable analyses with adjustment for follow-up time, age at diagnosis, gender, race,

Follow-up Cases: mean 21.2 yrs (SD: 11.2) Controls: mean 15.7 yrs (SD: 7.6)	N=46 cases (with cardiotoxicity) N=62 controls (without cardiotoxicity) Diagnoses Cases: Sarcoma: n=21 (46% Leukemia: n=5 (11%) Lymphoma: n=14 (30%) Other: n=6 (13%) Controls: Sarcoma: n=20 (32%) Leukemia: n=19 (31%) Lymphoma: n=15 (24%) Other: n=8 (13%) Age at diagnosis (mean, SD) Cases: 9.2 (4.7) Controls: 9.3 (5.7) Age at follow-up Not given, but globally estimated (mean calculated from age at diagnosis and follow-up time): Cases: 30 yrs Controls: 25 yrs Additionnal study characteristics: HTA: # (%) - Cases: 19 (41) - Controls: 40 (65)	Radiotherapy Cases: n=15 (33%) Controls: n=14 (23%) No doses reported Surgery none HSCT none No other treatment data reported	Main outcome: Of 12 variants previously identified to be associated with increased risk of hypertension, two were statistically significant for risk of cardiotoxicity. PLCE1: rs932764: 64% reduction in cardiotoxicity risk (95% CI: 0.18-0.76, p=0.007) OR 0.48 (0.27-0.85) p=0.012 ATP2B1: rs17249754 was protective with carriers of at least one of the hypertension risk alleles having a 74% reduction in risk of cardiotoxiciy (CI: 0.07-96, p=0.04) OR 0.33 (0.12-0.92) p=0.034 Gene expression in iPSC-cardiomyocytes showed that expression of both PLCE1 and ATP2B1 was anthracycline-dependent Adjusted analysis: Hypertension susceptibility variants and association with cardiotox adjusted for follow-up time, age at dg, gender, race, HTA, Atc dose, chest radiat,, cancer site PLCE1: rs932764. OR 0.36 (0.18-0.76) p=0.0068 ATP2B1: rs17249754. OR 0.26 (0.07-0.96) p=0.040	hypertension, anthracycline dose, chest radiation and cancer site. iii) 2 cardiac US to confirmed cardiotoxicity Study limitations i) small study sample. Possible associations may have been remained undetected. ii) significant difference in time of FU between 2 groups iii) no other treatment characteristics/doses reported. **Risk of bias** A. Selection bias: High risk Reason: number of “cases” might be underestimated as time of follow-up is different between cases and control. B. Attrition bias: Low risk Reason: outcome was assessed in all patients C. Detection bias: Unclear Reason: blinding of investigators not reported D. Confounding: Low risk Reason: Multivariable adjusted analysis

WG1: Who needs cardiomyopathy surveillance?				
Christiansen et al. Utility of Global Longitudinal Strain by Echocardiography to Detect Left Ventricular Dysfunction in Long-Term Adult Survivors of Childhood Lymphoma and Acute Lymphoblastic Leukemia. Am J Cardiol 2016; 118:446-52.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Cross-sectional 2 studies Center Norway Self-questionnaires (comorbidities) 2-day hospital visit (clinical examination) Treatment era Not reported Follow-up 1st study: Mean 21.6 years (SD 7.9) 2nd study: Mean 21.9 years (SD 8.0)	Type and number of participants >18 years, diagnosed >5 years earlier with ALL < age 16 or lymphoma < age 18. Exclusion: 2nd cancer survivors received cardiotoxic TT *Primary study group:* n=191, after exclusion of subjects with impaired LVEF/FS, known CAD, stroke, HT or DM. *Diagnoses* ALL n=108 HL n=52 NHL n=31 *Age at diagnosis* Mean 9.2 years (SD 5.2) *Age at follow-up (exam)* Mean 30.8 years (SD 7.5) *Secondary study group:* n=231, including all available survivors	Chemotherapy *Primary study group:* Anthracyclines: 76% Median dose 135mg/m^2 (range 40 – 485) *Secondary study group:* Anthracyclines: 77% Median dose 150mg/m^2 (range 40 – 485) Radiotherapy *Primary study group:* Mediastinal 22% Median dose 36 Gy (range 13 – 44) *Secondary study group:* Mediastinal 23% Median dose 40 Gy (range 13 – 44) Surgery Not reported	Outcome definitions Systolic dysfunction: LVEF <50% or FS <27% (F)/<25%(M) Peak |GLS| < -1.96SD of controls, sex-specific. *Prevalence of impaired GLS:* Primary group 28% Secondary group 32% *Multivariable logistic regression for impaired GLS* (secondary study group includes most cases) Mediastinal RT y/n (OR 5.2; [95% CI: 2.2-12] *p* <.001) Anthracycline dose >300 mg/m^2 / compared with patients received ≤ 300 mg/m2 (OR 4.8; [95% CI: 1.7-14] *p* .003) Not significant: sex, attained age, age at Dx, daily smoking, anthracycline exposure y/n.	-No data on cardiac symptoms Not all anthracycline-treated, lower median dose than other cohort studies. Systolic dysfunction in the secondary study group was mostly detected by FS, only 6 cases had impaired LVEF. Anthracycline dose not anymore associated with impaired GLS in primary study group: potentially because of high cut-off dose and loss impaired LVEF/FS cases, whereas the more restrictive hearts caused by RT remain. Risk of bias A. Selection bias: Low risk Reason: 231/259 (89%) participated

	Diagnoses ALL n=128 HL n=65 NHL n=38 *Age at diagnosis* Mean 9.3 years (SD 5.1) *Age at follow-up (exam)* Mean 31.1 years (SD 7.8) <u>Controls (if applicable)</u> Random selection from the Nord-Trøndelag Health Study (n=1296) Matching criteria: gender, age, body weight, BSA and systolic BP (n=180) *Age at exam* Mean 32.4 years (SD 8.3)	<u>HSCT</u> Not reported	In the primary study group the association with high anthracycline dose is lost, Mediastinal RT exposure remains (OR 3.8, [95% CI: 1.8-8.0] *p* <.001)	<u>B. Attrition bias:</u> Low risk Reason: outcome was assessed in all patients <u>C. Detection bias:</u> unclear Reason: blinding not reported <u>D. Confounding:</u> High risk Reason: Multivariable model only includes those with p<0.2 in univariable regression. Forward selection can result in bias.

WG1: Who needs cardiomyopathy surveillance?				
Yu et al. Two-Dimensional Speckle Tracking Echocardiography Detects Subclinical Left Ventricular Systolic Dysfunction among Adult Survivors of Childhood, Adolescent, and Young Adult Cancer. BioMed Research International, 2016				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design Cross-sectional study Institution Single institution Screening era July 1, 2010 to December 31, 2012 Treatment era Not reported Follow-up since diagnosis Median 15 years (range 2 to 39)	Type and number of participants N = 134 AYA and CCS. No heart failure symptoms Age at diagnoses Median 15.8 years (range 0 –48.7) Age at echocardiographic follow-up Median 31 years (range, 18 to 62) Most common diagnoses Sarcoma (n=54) HL (n = 29) AL (n= 31) NHL (n=9) Prevalence of cardiac risk factors Hypertension : 9% Diabetes : 5.2% Dyslipidemia : 31.3% Treatment with beta-blockers or ACE-I : 10.4%	Anthracyclines: 100% treated *Median cum dose:* All : 300mg/m^2 (27 to 660) If mediastinal RT : 279 mg/m^2 If no mediastinal RT : 375 mg/m^2 Radiotherapy : Mediastinal RT: 39% (n=52) Median dose : 35Gy (range 2 to 56) Surgery Not reported HSCT Not reported	Outcome definitions *Conventional 2D and Doppler Echocardiography:* Abnormal LV systolic function : LVEF < 55% or FS < 27% *2D speckle tracking echocardiography (2DSTE)*: Abnormal LV systolic function : GLS ≤ |16|% Results *Prevalence of LV systolic dysfunction:* FS < 27% in 5.2% LVEF < 55% in 6.0% GLS ≤ |16|% in 23.1% GLS ≤ |16| higher than FS < 27% (*p < 0.001*) GLS ≤ |16| higher than LVEF < 55% (*p < 0.001*) No significant association between echocardiographic parameters of LV systolic or diastolic function (by 2D echocardiography or 2DSTE) and *cumulative anthracycline dose* *Prevalence of LV systolic dysfunction Mediastinal vs No Mediastinal RT :* GLS : 18% vs 19% (*p = 0.003*) GLS ≤ |16| : 36.5% vs 14.6% (*p= 0.004*) No difference in FS; LVEF; GCS or GRS between the 2 groups	Substantial agreement for measurement of GLS *Anthracycline dose* = doxorubicin + (daunorubicin × 0.833) + (epirubicin × 0.57) + (idarubicin × 5) + (mitoxantrone × 4). *Mediastinal radiotherapy* was defined as any form of radiotherapy in which the myocardium was within the prespecified radiation field Multivariable analysis are adjusted on sex, age at echocardiogram, and cumulative anthracyclines dose. There were too few events to consider FS < 27% or EF < 55% as outcomes in multivariable analysis. The prevalence of LV systolic dysfunction among long-term cancer survivors may be significantly underestimated using LVEF alone as compared to GLS by 2DSTE. **Risk of bias** A. Selection bias: High risk Reason: Only high risk cancer survivors included. heterogeneous population and limited sample size B. Attrition bias: Low risk Reason: Outcome was assessed in all patients included.

			Multivariable linear analysis including sex, current age, cumulative anthracycline dose, mediastinal RT. GLS : Mediastinal RT : β=0.923, SE= 0.444, p=0.040 Mitral E/A ratio : Mediastinal RT : β = -0.250, SE= 0.087, *p=0.005* Septal *e'* velocity : Mediastinal RT : β = -1.221, SE= 0.404, *p=0.003* LV mass index : Mediastinal RT : β = -3.459, SE= 2.085, *p=0.099* Higher doses of anthracyclines : β = 0.702, SE= 0.404 *p=0.085* *Multivariable logistic regression including sex, current age, cumulative anthracycline dose, mediastinal RT.* GLS ≤ |16|% Mediastinal RT (yes/no): OR not reported but >1 (p=0.036)	C. Detection bias: Unclear Reason: Blinding of investigators / sonographers for treatment exposures was not reported D. Confounding: High risk Reason: Less than 10% of the patients were treated with cardioprotective medications results were not substantively different when these patients were excluded. Mutivariable analyses were not adjusted for age at diagnosis **Limitations of the study :** Retrospective cross-sectional study. Prognostic significance of abnormal GLS not evaluated. Did not include a healthy control group: reference normative strain data used. Heterogeneous study population, multiple cancer types from a single cancer referral center limit the generalizability of the results.

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?				
Mulrooney et al. Cardiac Outcomes in Adult Survivors of Childhood Cancer Exposed to Cardiotoxic Therapy: A Cross-sectional Study. 2016 Jan 19;164(2):93-101.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks** **e.g. risk of bias**

Study design Cross-sectional study. Treatment era Not reported First follow-up visit at survivorship clinic before April 2013. Follow-up Median 22.6 years (range, 10 to 48 years)	Type and number of participants St. Jude Children's Research Hospital Adult survivors of childhood cancer, aged 18 years or older, who received cancer-related cardiotoxic therapy at least 10 years earlier. Original cohort: n=3054 Analysed: n=1853 (female 47.7%) Diagnoses Leukaemia or lymphoma 67.2%, sarcoma (14.0%), Wilms tumor (7.2%), neuroblastoma (4.5%), central nervous system tumors (4.3%), and other tumors (2.8%). Age at diagnosis Median 8 years (range, 0 to 24 years) Age at follow-up Median 31 years (range, 18 to 60 years) Controls (if applicable)	Chemotherapy Anthracyclines: None 332 (17.9%) <100 488 (26.3%), 100–249 647 (34.9%), ≥250 386 (20.8%) Radiotherapy Cardiac radiation None 1050 (56.7%) ≤1500 cGy 366 (19.8%), >1500 cGy 411 (22.2%) Unknown 26 (1.4%) Surgery not mentioned HSCT not mentioned	Outcome definitions Outcomes included cardiomyopathy (LVEF<50%), only this outcome is reported in this table Results Cardiomyopathy: 7.4% (4.5% was detected during the SJLIFE assessment) Cardiovascular risk factors present at the time of SJLIFE assessment included being overweight or obese (61.3%), smoking (23.7% current and 11.7% past), physical inactivity (49.6%), hypertension (23.3%), diabetes (6.8%), and dyslipidemia (61.9%). Multivariable logistic regression for cardiomyopathy **-female vs male OR 1.9 (1.1-1.3)** -Age at diagnosis (≥15 years=reference) 0-4 years: OR 0.5 (0.3–1.1) 5-9 years: OR 0.6 (0.3–1.2) 10-14 years: OR 0.9 (0.5–1.7) **-anthracycline dose ≥250 vs <250 mg/m2: OR 2.7 (1.1-6.9)** **-mean heart dose >1500 cGy: OR 1.9 (1.1-3.7)** -ever-smoker: OR 0.9 (0.5-1.5) -physical activity active vs inactive: OR 1.2 (0.7-2.0) -Excessive alcohol: OR 0.9 (0.5-1.5) **-hypertension OR 3.0 (1.7-5.2)** -diabetes: OR 2.0 (0.9-4.2) -dyslipidemia: OR 1.0 (0.6-1.7) -BMI, kg/m2 (<25=ref) 25-29: OR 1.0 (0.5-1.9) >=30: 1.2 (0.6-2.3)	-14% of the echocardiograms were missing. -Vast majority was asymptomatic (4 survivors reported intermittent chest pain, and 1 reported palpitations) **Risk of bias** A. Selection bias: High risk Reason: 61% participation rate, parameters non-participants also reported and different for sex, age at study and anthracycline dose B. Attrition bias: Low risk Reason: 14% had missing echo, thus >75% was assessed for the outcome C. Detection bias: Unclear Reason: Blinding of investigators/ sonographers was not reported D. Confounding: Low risk Reason: Multivariable analysis adjusted for important confounders.

WG1: Who needs cardiomyopathy surveillance? Genetics

Krajinovic et al. Polymorphisms of ABCC5 and NOS3 genes influence doxorubicin cardiotoxicity in survivors of childhood acute lymphoblastic leukemia The Pharmacogenomics Journal 2016

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Derivation (D): Single center cohort, Canada Replication (R): Multicenter cohort, Canada Treatment era D 1989-2005 R not reported Follow-up years median (range) D 77.3% >=5 years Mean 8.4 (1-8) R 54.5% >=5 years Mean 5.25 (3-9)	Type and number of participants D: 251 ALL patients R: 44 ALL patients Age at diagnosis D mean 6.16, range 1-18 years R mean 5.27, range 1-17 years Age at follow-up D Mean 14.61 range 2-30 years R mean 10.41 range 5-21 years	Anthracycline dose in mg/m2 D 300-360 R 300 Chest RT Not reported Dexrazoxane D 53.4% R 38.1%	Outcome definitions Compared median LVEF/FS between different polymorphisms, multiple testing FDR <5% ABCC5 A-1629 T D: LVEF TT 48.2% vs AA/AT 59.6%, P<0.0005 R: LVEF TT 54.6% vs AA/AT 61.4%, P=0.17 Significant more decrease in EF during follow-up in TT vs AA/AT, P=0.03 **All are univariate associations** NOS3 Failed to replicated and very small effect on LVEF in derivation cohort	-Limited number of CMP cases: Mean EF was 60% in derivation cohort (IQR 55-63%) and 61% (IQR 57-67 in replication cohort) -Treated with high doses **Risk of bias** A. Selection bias: Unclear Reason: Unknown whether all ALL patients were included or a representative sample. B. Attrition bias: Unclear Reason: Unknown how many survivors died or were lost to follow-up before study was conducted C. Detection bias: Unclear Reason: Blinding of investigators who performed the echo was not reported D. Confounding: High risk Reason: No multivariable analysis was performed.

WG1: Who needs cardiomyopathy surveillance? Genetics

Wang et al. CELF4 Variant and Anthracycline-Related Cardiomyopathy: A Children's Oncology Group Genome-Wide Association Study. J Clin Oncol 2016; 34:863-70

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Case-control Treatment era <1990-2008 Follow-up 9.4 yr (0.1-35.1) for cases, 12.9 yr (1.4 – 41) for controls	Type and number of participants 219 Diagnoses HL/ NHL N=28 ALL/AML N=27 Sarcoma N= 35 Other N = 22 Age at diagnosis Median 7.9 (0-20) Age at follow-up Median 18.3 (0.4 – 41.8) Controls (if applicable) 219 controls, CCS, non-Hispanic whites, **matched to cases in 1:1 to 4:1 on cancer diagnosis, year of diagnosis (< 5 year), race/ethnicity, longer follow-up than index case** Age at diagnosis median 7.9 (0-21), Age at follow-up median 20.5 (4.2-50.1)	Chemotherapy Anthracycline dose med -cases 319 mg/m2 (0-760), >300 mg/m2 in 59 pts -controls 180 mg/m2 (0-825), >300 mg/m2 in 76 pts Chest-directed Radiotherapy Cases 25/112 (22.3%) Controls 12.4% Dose not reported Surgery Not reported HSCT Not reported	Outcome definitions 'Cardiomyopathy' at follow up (= acute/ chronic), defined as symptoms/signs of HF OR asymptomatic and LVEF ≤40% OR FS ≤28% Results 1. Multivar logistic regression analysis without gene variants: - anthracycline dose > 300 mg/m2 OR = 5.1 (2.4-10.0) - chest RT yes/no OR = 3.2 (1.3-7.7) 2. Multivar log regression with CELF4 gene variant and interaction term gene variant * anthracycline dose, adjusted for age at diagnosis, sex, anthracycline dose and RT **-CELF4 gene*dose reached multiple testing corrected significance: P = 1.14 * 10^25** **-CELF4 GG versus GA/AA: OR = 2.26 (1.2-4.0).** **-CELF4 GG and anthracycline dose >300 mg/m2 versus GA/AA and anthracycline dose <=300 mg/m2: OR 10.16 (3.8-27.3)** -OR's of variables adjusted for: not reported 3. Replication in 54 cardiomyopathy cases Multivariable logistic regression with **high (>300 mg/m2) versus low (<=300 mg/m2) dose as the outcome**. Adjusted for age at diagnosis, sex, RT, race/ethnicity. **-CELF 4 GG versus GA/AA: OR 5.09 (1.0-25.2) for being in the >300mg/m2 group**	1.Outcome is not 100% determined by LVEF, but also by symptoms without echo, and in controls many without echocardiogram. 2. Acute and chronic cardiotoxicity were tested without distinction 3. Replication cohort did not include controls but only compared high vs low dose patients. **Risk of bias** A. Selection bias: Unclear Reason: Unclear whether all cardiomyopathy cases were included or if they were representative of the underlying cohort. B. Attrition bias: High risk Reason: Genetics variants were meaured in those alive at time of the study. Patients could have died before the study was conducted. C. Detection bias: Unclear

			4. Effect of GG variant on splicing variant TNNT2 protein in 33 healthy hearts at obductions: association of GG variant with the embryonic splicing TNNT variant (90.5% in GG versus 41.7% in GA/AA), demonstrating (possible) pathogenicity of GG variant.	Reason: Blinding of investigators for case status was not mentioned. D. Confounding: Low risk Reason: Multivariable analysis was adjusted for important confounders and cases and controls were matched.

WG1: Who needs cardiomyopathy surveillance?				
Chow et al. Individual prediction of heart failure among childhood cancer survivors. J Clin Oncol 2015				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design 4 retrospective cohort studies. Development (CCSS) and external validation (SJLIFE, EKZ, NWTS) of a risk prediction model. Treatment era Development cohort:	Type and number of participants CCSS: 13060 CCS, diagnosed ≤ 21 years, survival ≥ 5 years since diagnosis. SJLIFE: 1695 CCS, survival ≥ 10 years since diagnosis, age ≥ 18 years at study EKZ: 1362 CCS, diagnosed ≤ 18 years, survival ≥ 5 years since diagnosis. NWTS: 6760 CCS after kidney tumor, diagnosed <	Chemotherapy (%) CCSS/SJLIFE/EKZ/NWTS Anthracycline=yes 37.4%/59.2%/41.5%/50.8% Anthracycline dose, mg/m2 None= 57.5/40.8/58.7/49.2 <100= 3.2%/12.9%/2.3%/6.3% 100-249= 10.4%/32.4%/19.3%/26.1%	Outcome definitions *Heart failure* CTCAE version 4.03 or version 3 (EKZ). Grade 3 (requiring medications), grade 4 (requiring HTx) or grade 5 (fatal) were included as outcomes. Included were outcomes occurring by age 40 years. Timepoint of prediction: 5 years after cancer diagnosis Cumulative incidence: by age 40years: CHF siblings=12 (cumulative incidence, 0.3%; 95% CI, 0.1% to 0.5%), CHF CCSS =285 (cumulative incidence, 2.8%; 95% CI, 2.4% to 3.2%) SJLIFE 19/1695, EKZ 26/1362, NWTS 48/6760	No calibration. AUC and C-statistics were comparable suggesting stable estimates trough age 40 Outcome/ health conditions were self-reported in the CCSS cohort, thus there may be bias.

CCSS: 1970-1986 Validation cohorts: SJLIFE: 1962-2001 EKZ: 1966-1996 NWTS: 1969-2002 <u>Years after diagnosis, median (range)</u> CCSS: 24 (5-39) SJLIFE: not reported EKZ: 23 (5-45) NWTS: not reported	16 years, survival ≥ 5 years since diagnosis. <u>Diagnoses</u> CCSS/SJLIFE/EKZ ALL 30.5%/28.4%/22.2% Other leukemia 3.5%/4.2%/2.2% Hodgkin 13.4%/12.0%/7.6% Other lymphoma 7.4%/6.6%/12.3% Brain tumor 12.9%/12.6%/9.1% Neuroblastoma 6.7%/3.3%/6.2% Kidney tumor 8.7%/5.7%/13.7% Soft tiss sarcoma 8.7%/7.9%/9.6% Bone tumor 8.2%/5.7%/9.3% Other 0%/13.5%/7.9% NWTS cohort kidney tumor 100% <u>Age at diagnosis</u> CCSS/SJLIFE/EKZ <5 years: 40.2%/32.6%/43.8% 5-9 years: 22.1%/24.2%/27.8%	≥250= 9.8%/13.6%/19.0%/16.8% Doxorubicin hematologic toxicity equivalence: Daunorubicin, 1.0; Idarubicin, 3.0; Epirubicin, 0.67; Mitoxantrone, 4.0.1 <u>Radiotherapy</u> CCSS/SJLIFE/EKZ/NWTS Chest RT = yes 25.9%/29.5%/15.9%/43.4% Chest RT dose, Gy Chest RT none 58.0%/70.5%/60.6%/45.1% Chest RT <5 Gray 9.4%/0.2%/19.6%/11.5% Chest RT 5-14 Gray 3.4%/5.8%/1.8%/24.5% Chest RT 15-34 Gray 10.8%/15.5%/7.9%/12.1% Chest RT ≥ 35 Gray 11.3%/7.9%/5.5%/5.8%	10 with history of heart transplantation <u>Multivariable Poisson Regression CCSS Cohort:</u> Simple Model RR (95CI) / Standard Model RR (95CI) / Heart Dose Model RR (95CI) Sex Female vs. male: 1.6 (1.3 to 2.1) / 1.7 (1.3 to 2.2) / 1.7 (1.3 to 2.1) Age at diagnosis, years <5 vs. ≥15: 1.5 (1.0 to 2.3) / 2.2 (1.4 to 3.4) / 2.6 (1.6 to 4.1) 5-9 vs. ≥15: 1.2(0.8 to 1.9) / 1.6 (1.0 to 2.4) / 1.9 (1.2 to 2.9) 10-14 vs. ≥15: 1.2 (0.9 to 1.6) / 1.2 (0.9 to 1.7) / 1.4 (1.0 to 2.0) Anthracycline, mg/m2 Any *v* none: 4.9 (3.8 to 6.4) / — /— <100 vs. None: — / 1.9 (0.7 to 5.1) / 2.1 (0.8 to 5.9) 100-249 vs. None: — / 3.3 (2.1 to 5.2) / 3.7 (2.3 to 5.9) ≥250 vs. None: — / 8.6 (6.4 to 11.5) / 10.5 (7.7 to 14.4) Chest RT, Gy Any *v* none: 3.2 (2.5 to 4.1) / — / — < 5 vs. None: — / 1.0 (0.6 to 1.7) / 0.9 (0.5 to 1.6) 5-14 vs. None: —/ 2.1 (1.1 to 3.8) / 1.6 (1.0 to 2.7) 15-34 vs. None: — / 2.3 (1.6 to 3.4) / 3.1 (2.2 to 4.5) ≥ 35 vs. None: —/ 6.5 (4.6 to 9.0) / 10.5 (7.2 to 15.4) * negative sign (—) indicates that Anthracycline and RT exposures were classified as yes versus no only in simple model and as different categories in standard and heart dose model. Heart dose model used average radiation dose to the heart in lieu of chest field dose because contemporary radiotherapy plans often provide heart-specific dosimetry. *Prediction model development* Piecewise exponential (Poisson) models with backward selection, adjusted for current age. Predictors evaluated: sex, age at	Influential predictors were determined by backward selection **<u>Risk of bias</u>** <u>Selection bias:</u> Low risk, Reason: 92% (13060/(13060+1110)) participated <u>Attrition bias:</u> Unclear Reason: unclear if all included participants were assessed for an outcome variable, no time to event analysis for risk factors. <u>Detection bias:</u> Unclear Reason: unclear if outcome assessors were blinded <u>Confounding:</u> Low risk Reason: Adjusted for sex and age at diagnosis, alkylating agents, platinum agents, vinca alkaloids, neck and/or abdominal

	10-14 years: 20.1%/25.7%/22.6% ≥ 15 years: 17.6%/17.5%/5.9% <u>Age at follow-up, median (range)</u> CCSS 32 (6-59) years SJLIFE 28 (18-63) years EKZ 31 (5-56 years) <u>Controls (if applicable)</u> CCSS Random sample of 4023 siblings	Heart RT dose, Gy for CCSS/EKZ None Gy, 62.1%/80.5% <5 Gy, 6.4%/0.1% 5-14 Gy, 6.5%/2.5% 15-34 Gy, 10.6%/11.7% ≥ 35Gy, 7.1%/4.5% <u>Surgery</u> Not reported <u>HSCT</u> Included but not reported	diagnosis, alkylating agents, anthracyclines including dose, platinum agents, vinca alkaloids, neck/chest/abdominal RT including doses. Integer risk scores based on the coefficients were entered in Cox models and C-statistic and AUC calculated. <u>CHF Risk Scores (Simple model/standard model/Heart dose model)</u> *Sex* Male 0/0/0 Female 1/1/1 *Age at diagnosis(years)* <5 years: 1/2/2 5-9 years: 0/1/1 10-14 years: 0/0/1 ≥ 15 years: 0/0/0 *Anthracycline, mg/m2* None: 0/0/0 Any: 3/-/- <100: -/1/2 100-249: -/3/3 ≥250: -/4/4 Chest or heart RT, Gy None: 0/0/0 Any: 3/-/- <5: -/0/0 5-14 -/2/1 15-34: -/2/3	

			≥35 -/4/4 * negative sign (-) indicates that Anthracycline and RT exposures were classified as yes versus no only in simple model and as different categories in standard and heart dose model. *Risk scores 0, 1, 2, 3, and 4 correspond to relative risks < 1.3, 1.3 to 1.9, 2.0 to 2.9, 3.0 to 4.9, and ≥ 5.0, respectively Model Discrimination and Predictive Power AUC simple model CCSS 0.71, SJLIFE 0.63, EKZ 0.74, NWTS 0.76 AUC standard model CCSS 0.74, SJLIFE 0.68, EKZ 0.81, NWTS 0.72 AUC heart dose model CCSS 0.76, EKZ 0.74 C-statistic simple model CCSS 0.72, SJLIFE 0.63, EKZ 0.75, NWTS 0.79 C-statistic standard model CCSS 0.76, SJLIFE 0.68, EKZ 0.80, NWTS 0.82 C-statistic heart dose model CCSS 0.77, EKZ 0.78 <u>Standard Model Risk Score for conventional risk factors in CCSS participants (</u>182 patient cases of CHF.<u>)</u> Obesity 1, Diabetes 0, Dyslipidemia 0, Hypertension 2 Updated model = AUC 0.75 and C-index 0.77 <u>Classification of CHF Risk Groups Within CCSS Cohort Based on Summed Risk Scores:</u> *Simple model:* Low risk <3pts cum inc 0.5% (0.2-0.8) Moderate 3-4pts 3.1% (2.5-3.7) High≥5pts 9.2% (6.8-11.6%) *Standard model:*	

			Low risk <3pts cum inc 0.5% (0.2-0.8) Moderate 3-5pts 2.4% (1.8-3.0) High ≥ 6pts 11.7% (8.8-14.5%)	

CCSS, Childhood Cancer Survivor Study; CHF, congestive heart failure; CTCAE, Common Terminology Criteria for Adverse Events; EKZ/AMC, Emma Children's Hospital and Academic Medical Center; NWTS, National Wilms Tumor Study; RT, radiotherapy; SJLIFE, St Jude Lifetime Cohort

WG1: Who needs cardiomyopathy surveillance?				
Armstrong et al. Comprehensive Echocardiographic Detection of Treatment-Related Cardiac Dysfunction in Adult Survivors of Childhood Cancer: Results From the St. Jude Lifetime Cohort Study. JACC 2015 2511-2522				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks e.g. risk of bias**
Study design SJLIEFE cohort of survivors of adult childhood cancer Quastionnaire and medical screening Treatment era Not reported Follow-up Median 22.6 years (range 10.4-48.3)	Type and number of participants 1820 adult childhood cancer survivors Diagnoses All childhood cancer diagnoses Age at diagnosis 0-21 years, median not reported Age at follow-up Median 31 (18-65) Controls (if applicable) -	Chemotherapy 83% anthracyclines Cumulative anthracycline dose, no mean/median reported Radiotherapy 41% chest RT RT doses given per range, no median/mean Surgery - HSCT	Outcome definitions LV Systolic dysfunction: -3D LVEF <50%, n=106 (5.8%) -GLS >2SD, n=579 (31.8%) -LV Diastolic dysfunction according to ASE recommendations grade 1-3 n=158 (8.7%) Results Multivariable poisson regression 3D LVEF<50% **-Anthracycline dose, mg/m2 (none=reference)** **1-100: RR 1.74 (0.66 - 4.61)** **101-200: RR 2.80 (1.24 - 6.31)** **201-300: RR 3.80 (1.59 - 9.10)** **301-400: RR 4.76 (2.16 - 10.50)** **>400: RR 7.71 (3.04 - 19.57)** **-Female vs male: RR 0.54 (0.36-0.83)** -Age at diagnosis (≥15 years=reference), p>0.05 for all 0-4 years: RR 0.66 (0.35 - 1.27) 5-9 years: RR 0.67 (0.36 - 1.25)	These findings suggest that traditional echocardiographic evaluation of cardiac function with LVEF may be insensitive Evidence of cardiac dysfunction (strain and diastolic function) in 1 of 3. **Risk of bias** A. Selection bias: high risk Reason: 1820/3029 (60%) participated, differences in sex, time since diagnosis.

		-	10-14 years: RR 1.02 (0.59 - 1.76) **-Chest RT dose, Gray (none=reference)** **1-19.9: RR 1.24 (0.70-2.22)** **20-29.9: RR 1.86 (1.00-3.45), p<0.05** **>=30: RR 7.99 (3.88-16.48)** -Non-hispanic white vs other race: RR 1.53 (0.93-2.52) -Current age, years(18-30=reference) 31-40: RR 1.38 (0.81-2.35) >40: RR 0.98 (0.52-1.84) <u>Modifiable CV risk factors and 3D LVEF<50%</u> -Poisson models adjusted for current age, age at diagnosis, race/ethnicity, sex, chest RT and anthracycline exposure -Metabolic syndrome: RR 1.07 (0.74-1.53) -Abdominal obesity: 1.34 (0.99-1.82) -Triglyc >=150 mg/dl: RR 1.01 (0.70-1.44) -Low HDL: RR 1.01 (0.74-1.38) **-Hypertension: RR 1.44 (1.22-1.70)** -Fasting glucose >=100 mg/dl: RR 1.02 (0.75-1.39) <u>Multivariable poisson regression GLS >2D</u> **-Anthracycline dose, mg/m2 (none=reference)** **1-100: RR 1.38 (1.05-1.82)** 101-200: RR 1.16 (0.89-1.50) 201-300: RR 1.06 (0.78-1.45) **301-400: RR 1.72 (1.31-2.26)** **>400: RR 1.73 (1.19-2.50)** **-Female vs male: RR 1.55 (1.34-1.79)** -Age at diagnosis (≥15 years=reference), p>0.05 for all 0-4 years: RR 1.02 (0.82-1.27) 5-9 years: RR 0.92 (0.74-1.15) 10-14 years: RR 1.03 (0.83-1.24)	<u>B. Attrition bias:</u> Low risk Reason: Outcome was assessed in all patients <u>C. Detection bias:</u> unclear Reason: blinding not reported <u>D. Confounding:</u> Low risk Reason: Multivariable models adjusted for important confounders

			-Chest RT dose, Gray (none=reference) **1-19.9: RR 1.38 (1.14-1.66)** **20-29.9: RR 1.65 (1.31-2.08)** **>=30: RR 2.39 (1.79-3.18)** **-Non-hispanic white vs other race: RR 1.22(1.03-1.46)** **-Current age, years(18-30=reference)** **31-40: RR 1.25 (1.05-1.48)** **>40: RR 1.49 (1.20-1.85)** Modifiable CV risk factors and GLS >2D **-Metabolic syndrome: RR 1.94 (1.66-2.28)** **-Abdominal obesity: RR 1.73 (1.48-2.01)** **-Triglyc >=150 mg/dl: RR 1.65 (1.40-1.95)** **-Low HDL: RR 1.40 (1.23-1.59)** **-Hypertension: RR 1.48 (1.33-1.65)** **-Fasting glucose >=100 mg/dl: RR 1.37 (1.19-1.59)** -Abnormal GLS related to reduced exercise capacity	

WG1: Who needs cardiomyopathy surveillance?				
Armstrong et al. Modifiable Risk Factors and Major Cardiac Events Among Adult Survivors of Childhood Cancer. JCO 2013				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks e.g. risk of bias**
Study design CCSS cohort of survivors of adult childhood cancer Self-reported medical conditions Treatment era	Type and number of participants 10724 adult childhood cancer survivors Diagnoses All childhood cancer diagnoses	Chemotherapy 38.9% anthracyclines Cumulative anthracycline dose, no mean/median reported	Outcome definitions Self reported major cardiovascular events, CTCAE v4.03 Grade 3-5. Only heart failure reported in this table. Self reported presence of modifiable CV risk factors and taking medications for the condition. Multivariable poisson regression for heart failure	Interaction of hypertension and anthracycline dose **Risk of bias** A. Selection bias: high risk

January 1, 1970, and December 31, 1986 Follow-up median of 25.6 years (range, 7.4 to 39.3 years) from cancer diagnosis	Age at diagnosis 0-21 years, median not reported Age at follow-up Median age at last follow-up of survivors was 33.7 years (range, 11.0 to 58.9 years) Controls (if applicable) Siblings 3159	Radiotherapy 26.4% chest RT RT doses given per range, no median/mean Surgery - HSCT -	-Cumulative incidence of grade 3 to 5 heart failure by 45 years of age was 4.8% (95% CI, 4.1% to 5.6%) *Survivors exposed to chest RT* **-Hypertension in 14.9%, RR 19.4 (11.4-33.1)** -Dyslipidemia in 8.9%, RR 1.1 (ns) **-Diabetes in 3.7%, RR 5.7 (1.3-24.3)** -Obesity, BMI>=30, in 21.7%, RR 0.9 (ns) **-Hypertension+dyslipidemia RR 7.8 (2.6-23.1)** **-Hypertension+diabetes RR 35.3 (12.1-103)** **-Hypertension+obesity RR 18.4 (8.8-38.6)** *Survivors exposed to anthracyclines* **-Hypertension RR 12.4 (7.6-20.1)** -Dyslipidemia RR 1.1 (ns) **-Diabetes RR 4.3 (1.0-17.8)** -Obesity RR 1.6 (ns) **-Hypertension+dyslipidemia RR 11.3 (4.6-27.5)** **-Hypertension+diabetes RR 16.9 (5.1-55.7)** **-Hypertension+obesity RR 6.5 (2.5-16.5)** **-Survivors treated with chest-directed RT who developed two or more cardiovascular risk factors of which one was hypertension, demonstrated a statistically significant increased RERI for development heart failure (RERI, 18.3; 95% CI, 7.6 to 37.4).** **-Survivors treated with anthracyclines who developed two or more cardiovascular risk factors of which one was hypertension, demonstrated a statistically significant increased RERI for development heart failure (RERI, 11.9; 95% CI, 0.3 to 29.6).**	Reason: 69% completed baseline questions B. Attrition bias: low risk Reason: 75% available for cardiac follow-up C. Detection bias: unclear Reason: blinding not reported D. Confounding: Low risk Reason: Multivariable models adjusted for important confounders

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?				
Ramjaun et al. Echocardiographic Detection of Cardiac Dysfunction in Childhood Cancer Survivors: How Long Is Screening Required? Pediatr Blood Cancer 2015;62:2197–2203				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort Treatment era Not specified Follow-up Median 15.8 (range 5.0–47.9) yrs	Type and number of participants 333 adult 5-year survivors of childhood (diagnosed <18 years) cancer treated with anthracyclines and/or radiation therapy involving heart Males - 49.2% Diagnoses Hodgkin lymphoma 35.4 %, ALL 43.5% Wilms tumor 10.2% Others 11% Age at diagnosis Median 8 years (range 1.5-18 years) Age at follow-up Not specified Cardiovascular risk factors Smoking (former) 3.3 %	Anthracyclines Any anthracycline dose -306 (91.8%) Anthracycline Dose <250 mg/m^2 -232 (69.6%) Anthracycline Dose >250 mg/m^2 -74 (22.2%) Platinum - Radiotherapy Radiotherapy involving heart 130 (39%) Median prescribed dose 15Gy (range 10-45 Gy) Mediastinal RT dose >=25 Gy: not specified Surgery	Outcome definitions Primary Abnormal echocardiogram: LVEF <55% or SF <28% or valvular abnormalities described as more than "trivial." Any abnormality: at least one abnormal echocardiogram, regardless of subsequent results. Sustained abnormality: an abnormal echocardiogram followed by one or more consecutive abnormal echocardiograms. Proportion with outcome -Abnormal echo at least once: n=49 (14.7%) -Median time to first abnormal echocardiogram: 11.7, range 1.8–42.0 years post-treatment -29 (8.7%) had sustained abnormal findings. -Continued increase over time in incidence of sustained abnormality in patients treated with >250mg/m^2 doxorubicin at age <5 years (43% at 20 years post treatment). -No sustained abnormality after 10 years of therapy in survivors treated with < 250mg/m^2 at age >5 years. Mean doxorubicin dose (295 mg/m^2) significantly higher in patients with sustained abnormal findings.	-32.6% of pts with abnormal echo had meds, symptoms not reported -Echocardiography is subjective, only 72% of patients with abnormal echocardiography in this cohort had reproducible results. -Variable number of echocardiograms per patient, median -2 (range 1-13). -Median dose of thoracic RT in this cohort was low. -Need to relook the duration of echocardiographic screening for childhood cancer survivors who received lower anthracycline doses after 5 years of age. **Risk of bias** A. Selection bias: Low risk 333 out of 421 (79%) eligible survivors of original cohort participated, representative of original cohort by cumulative anthracycline dose

	Smoking (current) 10.2 % Hypertension (ever) 3.6% Diabetes (ever) 2.1 % <u>Cardioactive Meds</u> 16 (4.8% of entire cohort, 32.6% of those with abnormal echo) <u>Controls (if applicable)</u> -	- <u>HSCT</u> -	thoracic RT not significantly association with sustained echo abnormalities at 20 years post treatment. <u>Multivariable regression analysis</u> Anthracycline dose >250 mg/m^2 and age <5 years at treatment were associated with significantly greater risk of having any abnormal echocardiogram as well as sustained abnormality. Stratified by age and dose, highest risk of sustained abnormality in those who were <5years AND received doxo dose >250mg/m^2 (20 years' risk: 54%, 95% CI=27-70%).	<u>B. Attrition bias:</u> Low risk, although only single echocardiogram was available in 9 (2.7%) participants outcomes were available for all <u>C. Detection bias:</u> Unclear, blinding not reported <u>D. Confounding: High</u> risk Multivariable analysis not adjusted for sex

WG1: Who needs cardiomyopathy surveillance?

Feijen et al. Equivalence Ratio for Daunorubicin to Doxorubicin Relation to Late Heart Failure in Survivors of Childhood Cancer. Journal of clinical oncology, 2015, 33, 774-3780

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks** **e.g. risk of bias**
<u>Study design</u> Cohort study <u>Treatment era</u> 1963-2002 <u>Follow-up</u>	<u>Type and number of participants</u> Childhood cancer survivors (>=5 years after diagnosis) N=15,851 <u>Diagnoses</u> Acute lymphoblastic leukemia 4561 (29.5%) Other leukemia 535 (3.5%)	<u>Chemotherapy</u> Doxorubicin No=10653 (67.4%) Yes=5144 (32.5%) Not reported=54 (0.3%) Median dose 255mg/m2 (IQR 144 to 365) Daunorubicin	<u>Outcome definitions</u> Heart failure defined as CTCAEv4.03 grade 3-5 that occurred after cohort entry by age 40 years <u>Results</u> N=271 heart failure cases included in the analyses.	Patients with heart failure excluded from analysis: second malignancy before heart failure n=48; heart failure occurrence after age 40 years n=56 15 or 16 heart failure cases received no known

Median 17.3 years (range 5-35) after cohort entry	Hodgkin lymphoma 1978 (12.5%) Other lymphoma 1190 (7.5%) Brain tumor 1941 (12.3%) Neuroblastoma 966 (6.1%) Kidney tumor 1713 (10.8%) Soft tissue sarcoma 1351 (8.5%) Bone tumor 1245 (7.9%) Other malignant neoplasm 335 (2.1%) <u>Age at diagnosis</u> Median 6.7 years (range 0.0-24.8) <u>Age at follow-up</u> Median 30.5 years (range 5.6 to 40.0) Cardiovascular risk factors Not reported Cardioactive Meds Not reported <u>Controls (if applicable)</u> NA	No=13554 (85.7%) Yes=2243 (14.2%) Not reported=54 (0.3%) Median dose 111 mg/m2 (IQR 91 to 271) Epirubicin No=15680 (99.1%) Yes=135 (0.9%) Median dose 300 mg/m2 (IQR 200-420) Idarubicin No=15798 (99.9%) Yes=18 (0.1%) Not reported=35 (0.2%) Median dose 20 mg/m2 (IQR 11-36) Mitoxantrone No=15771 (99.7%) Yes=44 (0.3%) Median dose 34.6 mg/m2 (IQR 12-50) N=742 (4.7%) received more than one type of anthracycline <u>Radiotherapy</u> To the chest: No=11340 (71.7%) Yes=4044 (25.6%) Not reported=467 (2.9%)	Overall cumulative incidence of heart failure at the age of 40 years 3.2% (95% CI, 2.8% to 3.7%). <u>Multivariable Cox regression</u> -adjusted for sex; age at diagnosis; chest radiotherapy dose; and exposure to another anthracycline besides doxorubicin or daunorubicin, such as epirubicin, idarubicin, or mitoxantrone, stratified by cohort. -Daunorubicin (HR 95% CI) None reference <=0.1 to <200 mg/m2 1.09 0.57 to 2.08 <= 200 to <300 mg/m2 3.16 1.16 to 8.61 <= 300 to <400 mg/m2 4.33 1.73 to 10.84 >=400 mg/m2 10.72 5.13 to 22.42 -Doxorubicin (HR 95% CI) None reference <=0.1 to <200 mg/m2 2.80 1.75 to 4.49 <= 200 to <300 mg/m2 6.31 4.11 to 9.69 <= 300 to <400 mg/m2 13.19 9.04 to 19.25 >=400 mg/m2 18.43 12.82 to 26.50 -Daunorubicin-to-Doxorubicin Ratio (Ratio 95% CI) <=0.1 to <200 mg/m2 0.39 0.04 to 0.78 <= 200 to <300 mg/m2 0.50 0.00 to 1.12 <= 300 to <400 mg/m2 0.33 0.03 to 0.62 >=400 mg/m2 0.58 0.09 to 1.12 **Mean ratio of HRs: 0.45 (95%CI 0.23 to 0.73)**	potential cardiotoxic treatment (both numbers reported) Long-term follow-up Only 5% of participants exposed to anthracyclines received doses in excess of 500mg/m2 Overlap Feijen 2015 and 2 Feijen 2019 studies **<u>Risk of bias</u>** <u>A. Selection bias:</u> Unclear Reason: the original cohort of survivors is not reported <u>B. Attrition bias:</u> Low risk Reason: outcome assessed for all participants <u>C. Detection bias:</u> Unclear Reason: not reported if outcome assessors were blinded <u>D. Confounding:</u> Low risk Reason: All important prognostic factors were taken into account

		Median dose 30 Gy (IQR 20 to 38) <u>Surgery</u> Not reported <u>HSCT</u> Not reported	<u>Dose response analysis</u> -Linear dose response model was chosen **DAU to DOX ratio: 0.49 (95% CI 0.28 to 0.70)** -Model contained baseline covariates: sex, age at diagnosis, chest radiotherapy dose, current age, cohort, and exposure to another anthracycline besides doxorubicin or daunorubicin (eg, epirubicin, idarubicin, or mitoxantrone).	

WG1: Who needs cardiomyopathy surveillance? Genetics				
Aminkeng et al. A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer. Nat Genet. 2015				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design</u> Retrospective?? Multi center (recruitment from 3 defined sites/countries. Unknown if this was a selection or all patient) <u>Treatment era</u> - Canadian patients 2005-2011	<u>Type and number of participants</u> - Canadian patients 44 patients – 293 controls - Dutch patients 22 patients – 74 controls - US patients 19 patients – 61 controls - All aged <18y at time of treatment - patients treated with anthracyclines for “childhood cancer”. <u>Diagnoses</u> In all groups leukemia, lymphoma, sarcoma, etc	<u>Chemotherapy</u> Cumulative anthracycline exposure (anthracycline type was doxorubicine in >50% - Canadian patients Patients:260 (177-365) Controls: 175 (140-295) - Dutch patients Patients 407 (270-480) Controls 277 (180-364) - US patients: Mixed groups per ethnicity	<u>Outcome definitions</u> Cases were defined as exhibiting shortening fractions (SFs) of ≤24% or signs and symptoms of cardiac compromise requiring intervention on the basis of Common Terminology Criteria for Adverse Events version 3 Controls had SFs of ≥ 30% and no symptoms of cardiac compromise for at least 5 years after treatment <u>Results</u> The exploratory study showed 18 variants tagging 9 distinct linkage diseauilibruim blocks which were used in the GWAS.	Extremely difficult study design. Took me ages to comprehend how this was done. Interpretation of findings should be checked by somebody familiar with genetic studies. Releavively small number of patients with a very heterogenous background regarding

- Dutch patients 2009-2011 - US patients 2008-2010 Follow-up Not reported	Age at diagnosis - Canadian patients Patients: 9 (2.5-14) Controls: 4 (2-7.5) - Dutch patients Patients 7.5 (5-12) Controls 11 (6-14) - US patients Mixed groups per etnicity Duration of follow-up - Canadian patients Patients: 7.5 (2.5-15.5) Controls: 9 (7-12) - Dutch patients Patients 22 (19-25) Controls 17 (14-22) - US patients Mixed groups per etnicity Controls (if applicable) See above	Radiotherapy (%) - Canadian patients Patients: 37.5 Controls: 16 - Dutch patients Patients 27 Controls 24 - US patients: Mixed groups per etnicity Surgery n.a. HSCT Not reported	The GWAS showed an association with RARG (p=0.0043, OR 4.1 (1.5-11.5)) The rs2229774 SNP in RARG was associated with ACT in stages 1 and 2 and in the combined analysis at both low to moderate (P = 4.1 × 10-4, 0.0036 and 9.8 × 10-6, respectively) and high (P = 0.0021, 0.084 and 8.7 × 10- 4, respectively) anthracycline doses.	underlying disease and treatment. Large discrepancy between cases and controls regarding the dose of chemo There was a correction (how?) done on age, dose, radiotherapy and disease. Overall, rs2229774 carriers (AA or AG genotype) had significantly increased odds of developing ACT in comparison to non-carriers (OR = 5.2 (3.0–9.0), P = 5.9 × 10-10).

WG1: Who needs cardiomyopathy surveillance? Genetics				
Sagi et al. Possible roles of genetic variations in chemotherapy related cardiotoxicity in pediatric acute lymphoblastic leukemia and osteosarcoma. 2018.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study	Type and number of participants 680 pediatric patients enrolled retrospectively period 1989–2015.	Chemotherapy cumulative anthracycline (i.e.	Outcome definitions Fractional shortening (FS) and ejection fraction (EF)	Small sample study only 20/680 with pathological FS The worst heart function of each patient was used to define patients

Treatment era 1989-2015 Follow-up To >15 years after diagnosis for a proportion of the included patients	Type and number of participants 680 pediatric patients enrolled retrospectively period 1989–2015. 399 (60%) male and 262 (40%) female Diagnoses 622 pediatric acute lymphoblastic leukemia (ALL) and 39 osteosarcoma (OSC) Age at diagnosis aged 0–18 years, mean 6.6 +- 4.3 y 7 (1%) < 1y and 138 (21%) > 10y Controls For the case-control study : Patients who received the same chemotherapy as the cases but never had FS ≤ 28% were regarded as controls (n = 641) + Patients with decreased FS were compared to those with increased FS Additional comments Some patients were excluded from the analysis because of Down syndrome (n = 7), previous cardiac problems or any	doxorubicin equivalent) is used Cumm doses of dox ranging from 180-380 mg/m2 Radiotherapy 29% of the ALL patients received 12 Gy cranial radiotherapy Surgery HSCT …	Case = those who had FS ≤ 28% at any time point during the follow-up (n = 20) 70 single nucleotide polymorphisms (SNPs) in 26 genes were genotyped Results variations in - **ABCC2** (ABCC2 rs3740066 GG genotype had lower FS during the acute phase of therapy and 5–10 years) - after treatment (p = 7.38E-03, p = 7.11E-04, respectively)., - **CYP3A5** (CYP3A5 rs4646450 TT was 17% among ALL cases with FS lower than 28, and 3% in ALL patients without pathological FS (p = 5.60E-03; OR = 6.94 (1.76–27.39))), - **NQO1** (NQO1 rs1043470 rare T allele was associated with lower left ventricular function in the acute phase and 5–10 years after the diagnosis (p = 4.28E-03 and 5.82E-03, respectively) - **SLC22A6 (**SLC22A6 gene rs6591722 AA genotype was associated with lower mean FS (p = 1.71E-03), 5–10 years after the diagnosis) - **SLC28A3** (SLC28A3 rs7853758AA was 12% in ALL cases population, while only 1% among controls (p = 6.50E-03; OR = 11.56 (1.98–67.45)).	for the case-control type study so if it is just a single event, the patient is considered as a “case” Number of cases per SNP is not precised, particularly for the case control study Precisions are given for the CYP3A5 rs4646450 genotype for ALL patients or when compared increased/decreased FS for ALL patients Follow-up quite short <50% over 10 years so results are expressed as 5-10 years after diagnosis Candidate gene analysed based on the litterature **Risk of bias** A. Selection bias: Low risk Reason: all eligible participated B. Attrition bias: high risk Reason: follow-up 5-10 y is 74% for ALL and 92% for OSC but over 10 years respectively for 37% and 49% C. Detection bias: unclear risk Reason: blinding not reported D. Confounding: low risk Reason: multivariable analyses

	concomitant disease with potential cardiac complications (adrenoleukodystrophy, agenesia renis, cardiac arrhythmia, congenital hypothyroidism, cystic fibrosis, ventricular septal defect, VACTERL) (n = 12).			

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?

Spewak MB. Yield of screening echocardiograms during pediatric follow-up in survivors treated with anthracyclines and cardiotoxic radiation. Pediatric blood & cancer 2017

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective single center study. Large cohort for screening pedriatic cancer survivors seen between 2001-2013 Treatment era Between 1989 and 2010 Follow-up ≥2 years after completion of therapy. median	Type and number of participants 853 (out of 911) participants (43% female; mean age at diagnosis 7±5 years. Diagnoses Different "pediatric malignancies" - Leukemia/lymphoma: 70.6% - Sarcoma 10.3% - Other: 19.1%	Chemotherapy 95.2% treated with anthracyclines (<100mg/2 16%, 100-199mg/m2 35.15, 200-299mg/m2 20.9%, 300-399mg/m2 16.9%, >400mg/m2 in 6.2%) Radiotherapy	Outcome definitions 4. LV systolic dysfunction (LVEF <55% and/or FS <28% Studied risk factors E. Anthracycline dose F. Chest radiotherapy G. Age at diagnosis H. Sex I. Race Results Main endpoints: 1. LV systolic dysfunction seen in 37pt (4.3%) 2. Median time from diagnosis to first abnormal echo 6.5 years (range 2.9–14.6 years) E. Pt recommended for echo every 5y; n=249 patients 4 abnormal (1.3%)	-42 were symptomatic -Restricted to those with a first screening echo before age 22 (n=4 excluded) -some had cardiotoxicity prior to this study (within 2 years from cancer diagnosis), exact number not reported **Risk of bias**

follow up 7.5 (range 2.4-19.9y) years	<u>Age at diagnosis</u> mean age at diagnosis 7±5 years. <u>Age at follow-up</u>; Not reported <u>Controls (if applicable)</u> none	28.2% treated with chest radiotherapy, cumulative RT dose <10 in 1.2%, 10-29 in 19.9% and >30Gy in 7.1% Antracycline only 71.8% Radiotion only 4.8% Both 23.5% <u>Surgery</u> Not reported <u>HSCT</u> 14.2%	F. Pt recommended for echo every 2y; n=331 abnormal in, the yield was 1.6%, G. Patients with the most frequent screening (N 270) had the highest yield of screening echocardiograms (3.1%). H. Using the Cow screening criteria: 149 survivors included in our analysis were classified as lowrisk (yield 1.5%), 374 as moderate risk (yield 2.7%), and 327 as high risk (yield 1.9%). I. Pt who received <100/m2 cumulative dose of anthracycline therapy, none had an abnormal screening echocardiogram J. patients who received 300 mg/m2 cumulative anthracyclines and > 30 Gy cumulative cardiotoxic radiation were 7.0 times more likely (95% CI: 1.6–31.9) to have an abnormal screening echocardiogram K. No statistical differences were found between sexes or races <u>Multivariable logistic regression at least one echo abnormality</u> -Anthracycline, mg/m2 (100-199=reference) 200-299: OR 1.3 (0.5-3.4) >=300: OR 3.1 (1.3-7.2) -Female vs male: OR 0.5 (0.2-1.1), p>0.05 -Age at diagnosis (<1 year=reference) 1-4 years: OR 1.3 (0.2-10.9), p>0.05 >=5 years: OR 1.6 (0.2-12.3), p>0.05 -Race/ethnicity Black vs white: OR 0.9 (0.4-2.1) Other vs white: OR 0.6 (0.2-2.2) -Chest RT dose, Gray (none=reference) <30: OR 1.2 (0.5-2.9), NS >=30: OR 2.5 (0.9-7.1), NS	<u>A. Selection bias:</u> Low risk Reason: Excluded patients (6%) were well classified in table 1 <u>B. Attrition bias:</u> Low risk Reason: In majority the outcome was assessed <u>C. Detection bias:</u> Unclear Reason: This is not stated in this paper <u>D. Confounding:</u> Low risk Reason: See main outcomes

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?

Markman et al. Electrophysiological effects of anthracyclines in adult survivors of pediatric malignancy. Pediatric blood & cancer 2017

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective single center study. Data subtracted from routine care (EPD) Treatment era Between 1984 and 2015 Follow-up At least 1 year (?). mean follow up 14±7years	Type and number of participants 134 (out of 147) participants (48% female; mean age 30±5.6 years, range unknown Diagnoses Different "pediatric malignancies" Age at diagnosis <18y Age at follow-up; Aged >18y during follow up. mean age 30±5.6 years, range unknown Controls (if applicable) None	Chemotherapy 72% treated with anthracyclines (cumulative dose 216±100mg/m2) Doxorubicin equivalence according to Feijen 2015. Radiotherapy 21% treated with chest radiotherapy, cumulative RT dose 16.6±24.8Gy Surgery Not reported HSCT Not reported	Outcome definitions -LV systolic dysfunction (LVEF <55% or FS Z-=score 2SD below the mean for age) -Arrhytmias (although this is not clearly defined) Studied risk factors: -QTc using the Bazetts formula -Other ECG timing parameters Also included in the multivariate analysis: -sex, antracyline cumulative dose, Chest radiotherapy, Age Results -LV dysfunction on echo in 33 (24%), 8 of them already during cancer treatment. -Mean time to LV dysfunction 3.7 ± 4.7 years Multivariable logistic regression (95% CI)* Male vs female: OR 1.027, p=0.53 Caucasian vs other: OR 0.98, p=0.12 Anthracycline dose per 1 mg/m2: OR 1.001, p=0.054 Chest RT dose per 1 Gray: OR 1.002, p=0.027 PR interval per msec: OR 0.998, p=0.17 QRS interval per msec: OR 0.999, p=0.87	-42% of cases used ACEi, unknown how many symptomatic Several significant limitations: - Retrospective design, follow up examinations not harmonized. Inconsistent reporting of arrythmias. - PAC and PVC`s were also considered arrythmias (not stated how many these were) - Time between the ECG and the ultrasound was 349 days (3 to 1448days) - Study group is far to small for the multivariate analysis they performed **Risk of bias** A. Selection bias: Low risk Reason: 134/147 (91%) participated B. Attrition bias: Low risk Reason: outcome was assessed in all participants C. Detection bias: Unclear Reason: This is not stated in this paper

			QTc interval per msec: OR 1.007, p<0.001 *ORs calculated from reported coefficients by exponentiating them	D. Confounding: Low risk Reason: MV model included important confounders

WG1: Who needs cardiomyopathy surveillance? Genetics				
Visscher et al. Genetic variants in SLC22A17 and SLC22A7 are associated with anthracycline-induced cardiotoxicity in children. Pharmacogenomics 2015				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Identification of novel SNPs with extended GWAS for cardiotoxicity in development cohort (CPNDS) and 2 independent replication cohorts (CPNDSrepl and Dutch-EKZ). EKZ: matched case control design Treatment era CPNDS recruitment of survivors between 2005-2010 CPNDSrepl rectruitment between 2010-2011	Type and number of participants *Development (n=344)* Anthracycline treated CCS from the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) *Replication cohorts (n=218)* 90 anthracycline treated children from the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) 128 CCS from the Dutch-EKZ. EKZ matched for age at treatment, gender, dose, follow-up time. No age at follow-up or survival time restrictions	Anthracyclines 100% of CCS Median dose (range) mg/m2 CPNDS cases 300 (36-540) CPNDS controls 175 (60-600) EKZ cases 360 (100-720) EKZ controls 280 (50-720) CPNDSrepl cases 300 (175-550) CPNDSrepl controls 150 (50-540) Chest RT	Outcome definitions Anthracycline induced cardiotoxicity cases: FS≤26% and/or CTCAE grade ≥3 (symptomatic events requiring intervention, Htx or fatal events). Controls: anthracycline treated with FS≥30% Proportion with cardiotoxicity during follow-up Development 78/335 Replication 44/185 Extended GWAS for 4500 SNPs. Significant when p<0.01 in development cohort and p<0.05 in replication cohort (none reached the conservative Bonferroni threshold p < 1.7×10^{-5}). Multivariable logistic regression **adjusted for anthracycline dose, age at treatment, sex, radiotheraoy (yes/no), the first 2 principal components for ethnicity and previously identified SNPs SLC28A3 and UGT1A6**	Overlap of cohort with 2012 JCO and 2013 pedtr blood cancer paper. Novel extended GWAS **Risk of bias** A. Selection bias: Unclear Reason: unclear if cohort included all patients who visited the outpatient clinic or a representative sample B. Attrition bias: Unclear

EKZ treatment between 1966-1996 Follow-up years median (range) CPNDS cases 6.5 (0.1-21.2) CPNDS controls 7.8 (5.0-17.9) EKZ cases 21.3 (7.4-28.5) EKZ controls 16.8 (5-31.6) CPNDSrepl cases 6.8 (0.4-27.2) CPNDSrepl controls 7.4 (5.0-23.1)	16 samples removed from genotype analysis Diagnoses Not reported for full cohorts (only for cases/controls separately), various tumours mostly ALL and NHL Age at diagnosis median (range) CPNDS cases 5.5 (0.04-17) CPNDS controls 3.9 (.5-16.5) EKZ cases 9.1 (0.5-16.8) EKZ controls 11.2 (1.8-17.7) CPNDSrepl cases 12.6 (0.9-17.0) CPNDSrepl controls 4.9 (0.5-16) Age at follow-up Not reported	CPNDS cases 16% CPNDS controls 7% EKZ cases 20% EKZ controls 23% CPNDSrep cases 33% CPNDSrep conts 23% Surgery Not reported HSCT Not reported	**-SLC22A17 rs4982753 combined OR 0.50 (0.33–0.75)** **-SLC22A7 rs4149178 comb OR 0.45 (0.26–0.75)** Additional non replicated SNPs, enriched in antioxidant and oxidative stress pathways SULT2B1 rs10426628 1.92 (1.19–2.50) Numerous others in table Not replicated SNP that was found in other cohorts (Blanco et al): Carbonyl reductase gene: CBR3 rs1056892 (p = 0.67, OR: 0.93) **SLC22A17 and SLC22A7 added to previous developed multimarker prediction model with rs7853758, rs17863783, rs10426377, rs2305364, rs4148808 (Visscher et al 2013)** ***development*** **Previous: AUC 0.76 (0.70–0.82)** **New: AUC 0.79 (0.74–0.85), p=0.035** ***Replication*** **Previous: AUC 0.74 (0.66–0.82)** **New: AUC 0.76 (0.68–0.83) p=0.45**	Reason: Patients could have died before study was conducted. This was not mentioned C. Detection bias: Unclear Reason: Blinding of sonographers for genetic status was not mentioned D. Confounding: Low risk Reason: multivariable analysis

WG1: Who needs cardiomyopathy surveillance?				
Christiansen et al. Left Ventricular Function in Long-Term Survivors of Childhood Lymphoma. Am J Cardiol 2014;114:483-90.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Cross-sectional	Type and number of participants	Chemotherapy	Outcome definitions Systolic dysfunction:	-No data on cardiac symptoms

Case-control Nationwide, Norway <u>Treatment era</u> 1970 - 2000 <u>Follow-up</u> Mean 20.4 years (SD 8.6)	125 childhood lymphoma survivors, diagnosed <18 years, attained age >18 years, follow-up >5 years. 54% male. <u>Diagnoses</u> Lymphoma <u>Age at diagnosis</u> Median 14 years (IQR 10.5 – 16.4) <u>Age at follow-up</u> Median 33 years (IQR 26.8 – 39.6) <u>Controls (if applicable)</u> 1:1 match for sex, age, body weight and systolic BP from healthy population study (n=1296)	Anth, no RT 40% Anth + RT 34% Median cum. dose (IQR) 160 mg/m^2 (102 – 214) Alkylating agent 80% <u>Radiotherapy</u> Mediastinal, no anth 18% Mediastinal + anth 34% No anth, no RT 7% <u>Surgery</u> Not reported <u>HSCT</u> Not reported	LVEF <50% or FS <27% (F)/<25%(M) Diastolic dysfunction: Septal e' <8cm/s or lateral e' <10cm/s Left-sided valve dysfunction: ≥mild or before valve surgery <u>Results</u> Prevalence (vs controls) LVEF <50% 4% (10% ;n.s.) FS <27%/25% 8% (3% ;n.s.) Diastolic dysfunction 29% (4%; p <.001) Valve dysfunction 31% (n.m.) Syst. or diast. or valve dysfunction 50% (n.m.) NO reduced wall dimensions after anth treatment. Reduced internal dimensions after RT treatment. <u>Multivariable logistic regression:</u> (corrected for sex, diagnosis, age, age at Dx, RT and anthracycline treatment) - Systolic dysfunction: none significant - Diastolic dysfunction: attained age (OR 1.1) - Valve dysfunction: RT exposure (OR 27.8) and attained age (OR 1.2) RT dose dependency for aortic valve disease (p <.001) and trend towards dose dependency for mitral valve disease (p 0.135)	-High degree of categorization for the LV structural measurements (tables 3 and 4) and subgroup analyses (table 5). Refer to the paper. -Relatively low cumulative anthracycline doses, 74% anthracycline exposure. In contrast, more RT than most cohort studies. -Diastolic function simplified, but the most correct parameter seems used for this young population. -RT seems to have caused smaller hearts, normative values of atrial size might not apply. **<u>Risk of bias</u>** <u>A. Selection bias:</u> High risk Reason: 125/220 participated <u>B. Attrition bias:</u> Low risk Reason: Outcome was assessed in all included. <u>C. Detection bias:</u> Low risk Reason: sonographer was blinded for clinical and exposure status <u>D. Confounding:</u> Low risk Reason: Multivariable model

WG1: Who needs cardiomyopathy surveillance?

Armenian et al. Screening for Cardiac Dysfunction in Anthracycline-Exposed Childhood Cancer Survivors. Clin Cancer Res; 2014;24:6314–23.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**
Study design Observational (cross-sectional) Treatment era Recruitment October 2010 to September 2012 Date of diagnosis: HR (high-risk): (≥300mg/m^2 doxorubicin or equivalent) 31 (31%) ≤ 1994 36 (36%) 1995-2001 33 (33%) ≥2002 LR (low-risk): (<300mg/m^2 doxorubicin or equivalent) 17 (34%) ≤ 1994 19 (38%) 1995-2001 14 (28%) ≥2002 Follow-up Time from diagnosis: median [range] HR: 12.0y [2.6-37.9y] LR: 13.2y [5.3-28.6y] (p=0.8)	Type and number of participants 203 screened 1 (HR) refused 2 (1 HR, 1 HC) did not complete tests 200 recruited – all asymptomatic with LVEF EF ≥50% on echocardiography HR (high-risk): n=100 ≥300mg/m^2 anthracyclines LR (low-risk): n=50 <300mg/m^2 anthracyclines Age at diagnosis HR: median 13.1y [range 0.4–21.7y] LR: median 6.1y [range 1.2–21.9y] p<0.01 for comparison Age at follow-up HR: median 26.6y [range 6.7–55.8y] LR: median 20.8y [range 10.2–44.4y] HC: median 28.6y [range 14.9–57.9y] Cancer treatment 100% anthracyclines, doxorubicin cardiotoxic equivalent doses.	Diagnostic test(s) -Echocardiography: Two-dimensional, M-mode, and Doppler evaluations, as per the AHA/ACC task force practice guidelines: EDD, systole; EDD, diastole; PWS; PWD; thickness-dimension ratio; ESWS; LV Mass; IVRT; IVCT; ejection time; MPI; E wave; A wave; E/A ratio -Biomarkers: BNP; NT-proBNP; Troponin-T; Galectin-3; ST-2 Outcome definitions Abnormal LV end-systolic wall stress (>2SD normal).	Diagnostic outcomes (sensitivity, specificity, PPV, NPV, ROC) -Diagnostic values not reported **Biomarkers:** -NT-proBNP higher in HR (71 pg/dL) vs LR (37 pg/dL, P = 0.02) and HC (26 pg/dL, P < 0.01). -No differences in BNP, Troponin-T, galectin-3, and ST-2 levels among the three groups. -NT-proBNP correlated with ESWS (r=0.28, P < 0.01). BNP, troponin-T, galectin-3, ST-2 not correlated. **Echocardiography:** The echo indices were significantly different between HR and LR, and HR and HC for: LVESD, LVEDD, LVPWS, LVPWD, LV thickness-dimension ratio, ESWS, MPI and ejection time. They were not significantly different for: mean arterial pressure, LV mass, velocity of circumferential shortening, IVRT, IVCT, E-wave, A-wave or E/A ratio. Multivariable logistic regression analysis -adjusting for sex, age at examination, race/ethnicity, and chest radiation exposure -HR had 8.15-fold risk of having LV dysfunction (controls, referent group with	Only asymptomatic survivors with LVEF>50% included. **Risk of bias** A. Selection bias: Low risk Reason: The sample is representative of asymptomatic cancer survivors with LVEF≥ 50% on echocardiography but not of all survivors. B. Index test bias: Low risk Reason: Echo cardiologist was blinded to the risk or control status of the study participant. Unclear if also blinded to biomarkers C. Reference test bias: Low risk Reason: Echo cardiologist was blinded to the risk or control status of the study participant. Unclear if also blinded to biomarkers D. Verification bias: Low risk

HC: N/A	-HR (high-risk): median 375mg/m^2 [range 300-642] -LR (low-risk): median 120mg/m^2 [range 25-225] doxorubicin or equivalent. -Chest RT: not reported HC (healthy controls): no anthracycline exposure or cancer diagnosis.		no exposure to anthracyclines or chest radiation): HR, OR = 8.15 (P < 0.01); LR, OR = 2.13 (P=0.36). -dose dependent increasing risk by cumulative exposure: 1–99 mg/m2, OR = 1.43; 100–299 mg/m2, OR = 2.71; 300–399 mg/m2, OR =4.13; ≥400 mg/m2, OR =12.81; P = 0.01 (trend).	Reason: Biomarkers and echo were performed on the same day E. Attrition bias: Low risk Reason: All of the study group received the same tests. Confounding: Low risk Reason: multivariable model

WG1: Who needs cardiomyopathy surveillance? Genetics

Wang et al. Hyaluronan synthase 3 variant and anthracycline-related cardiomyopathy: a report from the children's oncology group. J Clin Oncol 2014;32:647-53

Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Case-control Treatment era < 1990-2008 Follow-up (median) 10yr (0.1-35.1) for cases, 11.3 yr (0.9 – 41) for controls	Type and number of participants 93 cases, < 21 yr at diagnosis, CCS, non-Hispanic whites, "alive at follow up". Diagnoses HL/ NHL N=22 ALL/AML N=20 Sarcoma N= 9 Bone tumor N = 22 Other N = 20 Age at diagnosis Median 6.9 (0-20.2)	Chemotherapy Anthracycline median dose 300 mg/m2 (0-630), >300 mg/m2 in 45/93 pts, dose = 0 in 7 pts. Radiotherapy Y in 23/93 (24.7%) cases, dose median 36 Gy (12-54) Surgery	Outcome definitions 'Cardiomyopathy' at follow up (= acute/ chronic), defined as symptoms/signs of HF AND any type of cardiac dysfunction OR asymptomatic and LVEF ≤40% OR FS ≤28% Results 1. Multivar Logistic regression analysis without gene variants: - AC ≤ 250 mg/m2 OR = 7.3 - AC > 250 mg/m2 OR = 49.5 - RT was in the model, OR not provided 2.Multivar Log regression with HAS3 gene variant and interaction term gene variant X AC dose: significant interaction; after adjustments for age at	1.Outcome not 100% determined on LVEF, but also on symptoms with other dysfunctions on echo, and in controls many without echocardiogram. What about asymptomatic patients with LVEF < 50%^? 2. Acute and chronic cardiotoxicity were tested without distinction 3. Relationship tested in whole cohort was negative for this variant. Only in patients treated

	Age at follow-up Median 19.4 (0.4 – 41.7) Controls (if applicable) 194 controls, CCS, non-Hispanic whites, matched to cases in 1:1 to 4:1, on cancer diagnosis, on year of diagnosis (< 5 year), on race/ethnicity = non-Hispanic whites. Age at diagnosis median 6.3 (0-20.6), Age at follow-up median 18.5 (3.5-49.2) Cumul AC dose median 152 mg/m2 (0-825), >300 mg/m2 in n=45 pts; RT in 22 pts (11.3%), dose median 35 (7.5 – 55.8)	Not reported HSCT Not reported …	diagnosis, sex, AC dose and RT, AA/AG variant in a model with continuous AC dose is not significant. In a Multiv Log regression with ONLY patients with > 250 mg/m2, adjusted for age, sex and RT dose: for the AA variant OR = 8.9, for the AG variant OR = 4.7 3. Of 34912 SNP tested on Illumina Omni-Express 12 platform, one SNP is significantly associated with outcome, *P* = 5.3 x 10-7, (threshold for multiple comparison = P = 5 x 10-6), and shows that this AA/AG variant (at risk) is present in 80 cases (88%) and in 155 controls (80.4%) 4. A replication set of 76 patients tested the risk of being in a high dose AC group for AA and AG carriers: significantly increased risk. 5. In 9 human hearts, the AA and AG types were tested for HAS3 mRNA levels: lower in AA compared to AG (*P* = 0.09).	with > 250 mg/m2 an association was found. 4. Patients who were cases but without AC included n=7. 5. relationship between AC dose and risk of cardiotox ONLY present in AA-carriers, barely in GA and no longer present in non-A carriers ? This suggests bias (by selecting the SNP with the highest association for CMP, you will find many with CMP), or a SINGLE-gene hypothesis for AC cardiotoxicity, which is not very likely. What you expect is a SHIFT in the dose-reponse curve, but a dose response curve should still be present in non-AA carriers.

WG1: Who needs cardiomyopathy surveillance? Genetics

Visscher et al. Validation of variants in SLC28A3 and UGT1A6 as genetic markers predictive of anthracycline-induced cardiotoxicity in children. Pediatr Blood Cancer 2013

Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Replication of 23 SNPs previously found in 2012 JCO paper in two independent cohorts. CPNDS: cohort study	Type and number of participants 90 anthracycline treated children from the Canadian Pharmacogenomics Network for Drug Safety (CPNDS)	Anthracyclines 100% of CCS Median dose (range) mg/m2 EKZ cases 360 (100-720)	Outcome definitions Anthracycline induced cardiotoxicity cases: FS≤26% and/or CTCAE grade ≥3 (symptomatic events requiring intervention, Htx or fatal events). Controls: anthracycline treated with FS≥30% Proportion with cardiotoxicity during follow-up	Overlap of cohorts with JCO 2012 publication. Replication of SLC28A3 rs7853758 failed in one cohort

EKZ: Matched case control design <u>Treatment era</u> CPNDS1 recruitment of survivors between 2005-2010 CPNDSrepl rectruitment between 2010-2011 EKZ treatment between 1966-1996 <u>Years follow-up median (range)</u> EKZ cases 21.3 (7.4-28.5) EKZ controls 16.8 (5-31.6) CPNDS cases 6.8 (0.4-27.2) CPNDS controls 7.4 (5.0-23.1)	128 CCS from the Dutch-EKZ. EKZ matched for age at treatment, gender, dose, follow-up time. No age at follow-up or survival time restrictions Only patients that received doxorubicin or daunorubicin were included and in total 177 were genotyped <u>Diagnoses</u> Not reported for full cohorts (only for cases/controls separately), various tumours mostly ALL and NHL <u>Age at diagnosis</u> EKZ cases 9.1 (0.5-16.8) EKZ controls 11.2 (1.8-17.7) CPNDS cases 12.6 (0.9-17.0) CPNDS controls 4.9 (0.5-16) <u>Age at follow-up</u> Not reported	EKZ controls 280 (50-720) CPNDS cases 300 (175-550) CPNDS controls 150 (50-540) <u>Chest RT n, %</u> EKZ cases 9, 20% EKZ controls 19, 23% CPNDS cases 4, 33% CPNDS controls 18, 23% <u>Surgery</u> Not reported <u>HSCT</u> Not reported	EKZ 44/128 (case control design) CPNDS 12/19 <u>Replication of 23 SNPs previously found in development cohort 2012 JCO paper in EKZ and CPNDS cohorts (n=177, 46 cases)</u> UGT1A6 rs17863783 P=0.0062 OR 7.98 (1.85–34.4) SLC28A3 rs7853758 P=0.058 OR 0.46 (0.20–1.08) SLC28A3 rs885004 P=0.058 OR 0.42 (0.16–1.10) SULT2B1 rs10426377 P=0.054 OR 0.52 (0.26–1.04) <u>SNPs significant in combined cohort with JCO 2012 paper n=521, 124 cases</u> *P<1.5x10^{-4}* SLC28A3 rs7853758 P=1.6x10^{-5} OR 0.36 (0.22–0.60) SLC28A3 rs885004 P=3.0x10^{-5} OR 0.34 (0.20–0.60) *Trend (P>multiple testing threshold)* UGT1A6 rs17863783 OR 4.30 (1.97–9.36) SULT2B1 rs10426377 OR 0.56 (0.38–0.81) SLC28A1 rs2305364 OR 1.60 (1.18–2.17) ABCC1 rs4148350 OR 2.40 (1.33–4.33) <u>SNPs associated with cardiotoxicity by gender</u> ABCB4 rs1149222 OR females 2.18 (1.31–3.60); OR males 0.89 (0.56–1.44) ABCB4 rs4148808 OR females 2.53 (1.47–4.36); OR males 1.07 (0.62–1.85) SULT2B1 rs10426377 OR females 0.82 (0.50–1.34); OR males 0.35 (0.20–0.64) <u>SNPs associated with cardiotoxicity by age Dx group</u> HNMT rs17583889 <5.3yrs OR 3.53 (1.79–6.93); ≥5.3yrs OR 1.13 (0.72–1.79) SLC22A2 rs316019 OR <5.3yrs 0.16 (0.03–0.71); OR ≥5.3yrs 1.16 (0.68–2.00)	

			Replication of prediction model with 9 SNPs that was previously developed in JCO 2012 paper Clinical model: age Dx, anthracycline dose, sex, chestRT, ethnicity. AUC 0.67 (0.58–0.75) 9 SNPs only: 0.57 (0.47–0.67) Clinical+9 SNPs: 0.67 (0.58–0.76) Revised prediction model including 5 replicated SNPs (rs7853758, rs17863783, rs10426377, rs2305364, rs4148808), model development and predictor selection with forward selection in original cohort form JCO 2012 paper Clinical model: AUC 0.69 (0.61–0.77) 5 SNPs only: 0.65 (0.56–0.74) Clinical+5 SNPs: 0.77 (0.69–0.85), compared to clinical only p=0.060	

WG1: Who needs cardiomyopathy surveillance? Genetics

Lipshultz et al. Impact of hemochromatosis gene mutations on cardiac status in doxorubicin-treated survivors of childhood high-risk leukemia. Cancer 2013.

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Study design Prospective cohort study Treatment era 1991 onwards Follow-up	Type and number of participants 184 high risk ALL patients included between 2005-2007 Diagnoses High risk ALL 100% T-cell 18%, B-cell 82%	Anthracyclines 37%, median dose 300 range 204-420 mg/m2 Dexrazoxane 63% Chest RT Not reported	Outcome definitions Frequency of H63D and C282Y hemochromatosis gene mutations and associations with echocardiographic parameters. Cardiac injury: cTnT levels > 0.01 ng/mL Cardiomyopathy: NT-proBNP levels >150pg/mL in infants <1 year and ≥ 100pg/mL in the rest Results	Study was underpowered to detect differences in echo parameters between carriers and non-carriers

Median 7.0 range 1.1-17.1 years	Age at diagnosis Median 6.3 range 0-17.9 yrs Age at follow-up Median 15.2 range 3.1-31.4 Cardiac symptoms Not reported Cardiac medications Not reported Controls (if applicable) NA	Surgery Not reported HSCT Not reported	41/172 (23.8%) H63D variant carriers 18/179 (10.1%) C282Y variant carriers ≥2 cTnT levels >0.01 during treatment in 31% C282Y carriers, 6% non carriers p=0.015 NT-proBNP elevations during treatment not significantly different H63D carriers no significant cTnT/BNP elevations After median follow-up 2.2 range 1-3.99 yrs Z scores for LV mass, end-systolic posterior wall thickness, end-diastolic posterior wall thickness, FS were significanly worse compared to normal values but not significantly different between hemochromatosis gene carriers and non-carriers.	

WG1: Who needs cardiomyopathy surveillance? Genetics WG3: At what frequency should surveillance be performed?				
Visscher et al. Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. J Clin Oncol 2012				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design *Canada development:* retrospective cohort study *Canada replication:* Retrospective cohort study *EKZ replication:* nested matched case-control study Treatment era	Type and number of participants *Development:* 156 CCS from Canada *Replication:* 188 CCS from Canada and 96 CCS from the EKZ. No age at follow-up or survival time restrictions Diagnoses	Anthracyclines 100% Median dose cases 270-360, range 36-840 mg/m2 controls 175-300, range 25-720 mg/m2 Chest RT Develop/replic/EKZ Cases 16%/30%/23%	Outcome definitions Anthracycline induced cardiotoxicity cases: FS≤26% and/or CTCAE grade ≥3 (symptomatic events requiring intervention, Htx or fatal events). Controls: anthracycline treated with FS≥30% Proportion with cardiotoxicity during follow-up Development 38 (24%), Canada validation 40 (21%), EKZ validation 43 (case-control design)	Prediction model was not validated but was developed in development and replication cohorts. Model with 9 SNPs failed to replicate in future study in 2013

CPNDS1 recruitment of survivors between 2005-2010 CPNDSrepl rectruitment between 2010-2011 EKZ treatment between 1966-1996 <u>Median yrs follow-up, range</u> *Canada development* Cases 6.5, 0.1-21.2 Controls 7.8, 5-17.9 *Canada replication* Cases 7.4, 0.2-20.7 Controls 9.2, 5-18.6 *EKZ replication* Cases 20.2, 7.4-27.9 Controls 15.4, 5.1-29.8	Not reported for full cohorts (only for cases/controls separately), various tumours mostly ALL and NHL <u>Median age at diagnosis cases/controls</u> *Development* 5.5/3.9 range 0.04-17 years *Replication* 6.2/3.7 range 0.05-17.6 years *EKZ replication* 9.0/10.6 range 0.5-17.7 years <u>Age at follow-up</u> Not reported	Controls 7%/20%/25% <u>Surgery</u> Not reported <u>HSCT</u> Not reported	<u>GWAS for 2977 SNPs with significance threshold $1.5x10^{-4}$ and replicated in the Canada replication cohort</u> SLC28A3 rs7853758 combined OR 2 cohorts 0.31 95%CI 0.16-0.60. OR in EKZ replication cohort 0.69, p=0.38 Combined OR 3 cohorts: 0.35 95%CI 0.21-0.59 <u>Did not reach multiple testing significance:</u> SLC28A3 rs885004 in 2 canada cohorts OR 0.31 95%CI 0.15-0.62 *SLC28A3 rs4877847* in 2 canada cohorts OR 0.60 95% CI 0.41-0.89 <u>9 SNPs prediction model (forward selection logistic regression, p<0.01)</u> Risk enhancing: UGT1A6 rs6759892, ABCB4 rs1149222, ABCC1 rs4148350, HNMT rs17583889 Protective: SLC28A3 rs7853758, FMO2 rs2020870, SPG7 rs2019604, SLC10A2 rs9514091, SLC28A3 rs4877847. Clinical model: age Dx, anthracycline dose, sex, chestRT, ethnicity. AUC 0.68 (0.61-0.74) 9 SNPs only: AUC 0.81 (0.76-0.86) Clinical+9 SNPs: AUC 0.87 (0.82-0.91)	

WG1: Who needs cardiomyopathy surveillance? Genetics				
Semsei et al. ABCC1 polymorphisms in anthracycline-induced cardiotoxicity in childhood acute lymphoblastic leukaemia. Cell Biol. Int. (2012) 36, 79–86				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design Cohort Treatment era 1990-2002 Follow-up (median) Latest echo: Mean 6.6±2.7 years	Type and number of participants 235/337 included Diagnoses ALL Age at diagnosis Latest echo: Mean 5.7±3.8 (range 1.2–18.0) Age at follow-up Median 6.3 (range, 2.4–13.7)	Chemotherapy 100% anthracyclines High risk: 8% Medium: 66% Low: 26% Dose range 180-300 30% dexrazoxane Radiotherapy Not reported Surgery Not reported HSCT Not reported	Outcome definitions LVFS at 3 time-points: 1. Cancer diagnosis 2. end of the treatment (median 2 years after diagnosis) 3. latest follow-up echo -Genotyping for 9 SNPs in ABCC1 gene Multivariable general linear models -Adusted for gender (male–female), age at the time of diagnosis (years), clinical centre (6 centres), total anthracycline dose (mg/m2), dexrazoxane administration (yes–no), and chemotherapy protocol (ALL BFM 90–ALL BFM 95) (estimates not reported) LVFS End of treatment (median 2 years from diagnosis) -ABCC1 rs3743527: TT (34.0%) vs CC (39.5%) or CT (39.3%) (P=0.001) -ABCC1 rs246221: NS LVFS Latest echo (Mean 6.6±2.7 years) -ABCC1 rs3743527 TT (35.3%) vs CC (38.9%) or CT (38.7%), p=NS -ABCC1 rs246221 TC (38.4%) and TT (38.5%) vs CC (40.7%), p=0.027	No replication **Risk of bias** A. Selection bias: low risk Reason: 70% included, however no significant differences in pt characteristics B. Attrition bias: low risk Reason: follow-up was complete for most C. Detection bias: unclear Reason: blinding not reported D. Confounding: low risk Reason: MV adjustments

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?				
van der Pal et al. High risk of symptomatic cardiac events in childhood cancer survivors. J Clin Oncol 30:1429-37, 2012				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort	Type and number of participants 1362 5-year childhood cancer survivors	Chemotherapy Anthracyclines 457 (33.6%), cumulative dose median 250 (range 25-775) mg/m2	Outcome definitions Symptomatic cardiac events (CE) Grading: CTCAE v 3.0 grade 3-5	Clinically validated outcomes Long follow-up, large cohort Wide confidence interval for anthracyclines and RT as categorical variable (yes/no)

Treatment era 1966-1996 Follow-up Median 22.2 (range 5.0-44.5) years	Diagnoses ALL 302 (22.2%) ANLL 30 (2.2%) Non Hodgkin 167 (12.3%) Hodgkin 104 (7.6%) Nephroblastoma 186 (13.7% Soft tiss sarcoma 131 (9.6%) Ewing sarcoma 53 (3.9%) Osteosarcoma 73 (5.4%) CNS tumor 124 (9.1%) Neuroblastoma 85 (6.2%) Germcell tumor 45 (3.3%) Other 62 (4.5%) Age at diagnosis Median 5.9 (range 0-18) years 0-4: 596 43.7% 5-9: 378 27.8% 10-14: 309 22.7% 15-18: 79 5.8% Age at follow-up Median 29.1 (range 5.2-54.2) years Controls (if applicable) NA	Radiotherapy Chest RT 158 (11.6%) *Location* Thorax (31.6%) Abdomen (24.4%) Spine (33.5%) TBI (10.5%) *Doses (EQD2)* Thorax dose median 24.1 (range 9.5-88.5) Gray Abdomen dose median 26.9 (range 3.7-57.2) Gray Spine dose median 30.1 (range 8.0-50.1) Gray TBI dose median 15.8 (range 14.0-21.6) Gray Anthracyclines and chest RT 108 (7.9%) Surgery 107 (7.9%) Cardiac surgery 3 (0.2%) HSCT NA	Results 50 CEs in 42 survivors Heart failure 27 (54% of the 50 CE) Cardiac ischemia 6 (12%) Valvular heart disease 6 (12%) Arrhythmia 9 (18%) Pericarditis 2 (4.0%) Median time from diagnosis to CE: 18.6 yrs Cumulative incidence of heart failure: chestRT only: 0.7% at 30-yrs chestRT + Anth: 7.9% at 30yrs Heart failure outcome multivariable Cox regression *Model 1 (95% CI):* Sex (female v male HR 0.8 (0.4-1.8) Age at Dx (per year): HR 0.98 (0.90-1.07) Anthracycline dose (per 100 mg/m2) HR 1.8 (1.5-2.3) ChestRT (EQD2 per 10 Gy) HR 1.4 (1.1-2.0) Cyclophosphamide (yes v no) HR 1.8 (0.6-5.3) Ifosfamide (yes v no) HR 1.9 (0.7-5.2) Vincristine (yes v no) HR 1.5 (0.3-7.7) Cisplatin (yes/no) 1.7 (0.4-8.0) Congenital heart disease (yes/no) 9.9 (2.2-44) *Model 2 mutual exclusive risk factors* Sex (female/male) 0.9 (0.4-1.9) Age at diagn (per year) 0.98 (0.90-1.07) Anthracyclines only (Yes/No) HR 33.5 (4.4-254)	**Risk of bias** A. Selection bias: Low risk Reason: 81.8% of eligible survivors participated B. Attrition bias: Low risk Reason: Outcome was assessed in all patients and/or censoring was taken into account C. Detection bias: Unclear Reason: Blinding of outcome assessors for cardiotoxic exposures not mentioned. D. Confounding: Low risk Reason: Multivariable cox regression model adjusted for all important confounders

			Radiotherapy only (Yes vs. No) HR 6.6 (0.6-73) Anth + Radiotherapy (Yes vs. No) HR 55.9 (6.6-470), p<0.001 Congenital heart disease HR 6.9 (1.6-30)	

WG1: Who needs cardiomyopathy surveillance? Genetics				
Blanco et al. Anthracycline-related cardiomyopathy after childhood cancer: role of polymorphisms in carbonyl reductase genes--a report from the Children's Oncology Group. J Clin Oncol 30:1415-21, 2012				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Case-Control Treatment era 1966-2008 Follow-up Cases: 9.2 (range 0.1-35.1) Controls: 12.3 (0.4-40)	Type and number of participants Case (CHF) – N=170 Control (none) – N=317 Matching criteria: Diagnosis Year of Dx (+/-5 yrs) Race/ethnicity Follow-up (controls) Cases: heart failure symptoms and/or LVEF≤40% and/or FS≤28%	Cases vs. controls: Anthracyclines 91% of cases 71% of controls Median dose, range Cases: 300, 0-575 Controls: 140, 0-1050 Chest RT Cases: 25% Controls: 14%	Clinically validated heart failure and/or LVEF≤40% and/or FS≤28% Multivariable conditional logistic regression adjusted for chest radiation (yes or no), age at cancer diagnosis and sex Referent group – no anthracycline P for trend p<0.001; OR (95% CI) 1-100: 1.65 (0.5 to 5.6), not significant 101-150: 3.85 (1.1 to 13.9) 151-200: 3.69 (1.0 to 13.6) 201-250: 7.23 (2.3 to 22.5) 251-300: 23.5 (7.4 to 74.2) >300: 27.6 (9.3 to 82.1) Female vs male: 1.47 (0.9 to 2.4) Age at diagnosis (per year): 0.99 (0.93 to 1.04) Chest RT (yes/no): 4.29 (1.9 to 9.6) Genetic susceptibility	-Genetic susceptibility -Matching based on diagnosis -Differences in mean anthracycline dose between Cases and controls -Wide confidence interval in some estimates -Survival bias might be present as case-control studies exclude fatal end points from the patient case set **Replication of CBR3 failed in study from Visscher et al 2012.** **Risk of bias** A. Selection bias: unclear Reason: unclear how many survivors were in the original survival cohort of COG institution. B. Attrition bias: low risk Reason: Echocardiogram report unavailable for 114 controls, but exclusion of these 114

			CBR3 GG variant (rs1056892) OR 1.79 (1.08-2.96), P=0.02 Anthracycline dose stratified 1-250 mg/m2 OR 3.30 (1.41-7.73) >250 mg/m2 OR 1.37 (0.606-2.84) CBR1 not significant	controls did not alter association. Excluded 5 patients with unknown chest radiation and 9 patients with non-informative genotype. C. Detection bias: low risk Reason: laboratory personnel were blinded to case-control status, but unclear if ECHO assessors were blinded. D. Confounding: low risk Reason: Adjusted for age at diagnosis, sex, chest radiation, and cumulative anthracycline exposure.

WG1: Who needs cardiomyopathy surveillance?				
Armenian et al. Incidence and predictors of congestive heart failure after autologous hematopoietic cell transplantation. Blood 118:6023-9, 2011				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design retrospective cohort study design & nested case-control Treatment era Cohort: 1988 and 2002 Follow-up	Type and number of participants *Cohort*: patients with autologous HCT for a hematologic malignancy at City of Hope & without cardiac dysfunction before HCT (n=1244) *Case control* (1:3): Case = developed CHF (n=88)	Chemotherapy Not the same for every participant, table 3 summerizes: Anthracyclines (case: mean dose 309.4 mg/m2 (SD 105.5), control: mean dose 237.0 mg/m2 (SD 102.0)), cyclophosphamide,	Outcome definitions CHF: according to the American Heart Association /American College of Cardiology publication, Guidelines for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005). Results Cohort: cumulative incidence (±SE) of CHF at 5, 10, and 15 years after HCT was 4.8% ±0.6%, 6.8% ±0.8%, and 9.1% ±1.0%, respectively.	Predominantly adults at time of HCT **Risk of bias** A. Selection bias: low risk Reason: only 3% did not participate in cohort study. Case controls study was a good representation of the full cohort. B. Attrition bias: low risk

Cohort: median 5.3 years (range, 0.1-20.5 years)	Control = selected from within the cohort with following matching criteria: age at HCT (±5 years), year of HCT (±2 years), and length of follow-up (n=218) <u>Diagnoses</u> Hematologic malignancy <u>Age at HCT (mean, yrs)</u> Cohort: 43.5 (13.1) Case: 46.5 (13.1) <u>Age at follow-up</u> nm	ifosfamide, procarbazine, melphalan, cisplatin. <u>Radiotherapy</u> Pre-HCT chest RT: n (%) Case: 15 (17) Control: 22 (10.1) <u>HSCT</u> 100% autologous HSCT	<u>Case-control: Multivariable conditional logistic regression adjusted for sex, underlying diagnosis, and exposure to chest radiation</u> Dose response anthracyclines Reference: <150 mg/m2. 150-249: OR=3.5, not significant 250-349: OR=9.9, P=0.01; ≥350 mg/m2: OR=19.8, P=0.01 <u>Multivariate cox regression analysis:</u> Cohort: Variables in the regression model included sex, ethnicity/race, underlying diagnosis, age at HCT (<35, 35-44, 45-54, and ≥ 55 years), and subsequent HCT after initial autologous HCT. Significant: females (RR=2.4; P=.01), patients undergoing HCT for lymphoma (referent group: nonlymphoma; lymphoma RR=1.5; P= .05); the risk of CHF increased with age at HCT. <u>Multivariable conditional logistic regression, OR (95% CI) (no CV risk factor and no HD-anthracycline=ref)</u> *Model 1: CV risk factor alone; no high dose anthracycline* Hypertension: 3.5 (0.88-14.01) Diabetes: 6.2 (0.86-43.82) Dyslipidemia: 2.7 (0.56-13.40) Thyroid disease: 0.7 (0.2-4.6) *Model 3: CV risk factor and HD anthracycline* **Hypertension: 35.3 (8.30-150.18)** **Diabetes: 26.8 (4.34-165.2)** **Dyslipidemia: 5.4 (1.53-18.95)** Thyroid disease: 3.3 (0.82-13.22)	Reason: Outcome was assessed in all participants <u>C. Detection bias:</u> unclear Reason: Blinding of investigators for treatment status not mentioned <u>D. Confounding: low risk</u> Reason: Cohort study: multivariable analyses adjusted for sex, ethnicity/race, underlying diagnosis, age at HCT (<35, 35-44, 45-54, and ≥ 55 years), and subsequent HCT after initial autologous HCT. Case-control: matching on age at HCT (±5 years), year of HCT (±2 years), and length of follow-up.

			- adjusted for sex, diagnosis (lymphoma vs nonlymphoma), pre-HCT exposure to chest radiation, and individual pre-HCT comorbidity.	

WG1: Who needs cardiomyopathy surveillance? WG2: What surveillance modality should be used?				
Brouwer et al. Systolic and diastolic dysfunction in long-term adult survivors of childhood cancer. Eur J Cancer, 2011, 47:2453-62				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Cross-sectional Treatment era 1976-1999 Follow-up Median 18.2 (range 5.4-30.8) yrs	Type and number of participants 277 5-yr childhood cancer survivors diagnosed <20 yrs Diagnoses ALL 103 (%), acute non-lymphoblastic leukemia 9 (%), acute undifferentiated leukemia 1 (%), lymphoma 56 (20%), sarcoma 48 (17%), brain tumor 32 (12%), blastoma 23 (8%), germ cell tumor 5 (2%) Age at diagnosis Median 8.8 (range 0-20) years Age at follow-up	Anthracyclines 199 (72%) Cumulative dose median 183 (range 50-600) mg/m2 Platinum 22 (8%) Radiotherapy 174 (63%) Chest RT: 69 (25%) Mediastinal RT: 33 (12%) TBI: 17 (6%) Spinal RT: 19 (7%) Mediastinal RT dose >=25 Gy: 17 (6%) Surgery Not reported	Outcome definitions Primary Systolic dysfunction: FS < 29% or WMSI > 1.00 Diastolic dysfunction: TVI et mean < 8 cm/sec Secondary NT-proBNP>125 ng/L Cardiac autonomic function: Baroreflex sensitivity (BRS) in ms/mmHg (continuous outcome) Proportion with outcome FS<29%: n=100/274 (37%) WMSI >1.00: n=39/267 (15%) TVI Et <8 cm/sec: n=32/273 (12%) NT-proBNP >125 ng/L: n=32/262 (12%) BRS log mean 2.4 (SD±0.6) significantly lower than in controls (p=0.01) Multivariable logistic regression adjusted for age dx, sex, age, follow-up, hypertension, BMI, use of ACE-inhibitor, diuretic, b-blocker or GH-replacement.	Comprehensive echo screen Long term follow-up 7 clinical HF and 17 on cardmeds included in analysis Adjusted for cardmeds in multivariable regression **Risk of bias** A. Selection bias: Low risk 277 out of 401 (69%) eligible survivors of original cohort participated but was representative of the full cohort B. Attrition bias: Low risk, FS outcome was available in 274/277 CCS, WMSI in 267/277, diastolic function in 273/277, NT-proBNP in 262/277.

	Median 27.5 (range 18.1-48.2) years <u>Cardiovascular risk factors</u> Hypertension 38 (14%), overweight 91 (33%), hypercholesterolemia 80 (33%) <u>Cardioactive Meds</u> 17 (6%) <u>Controls (if applicable)</u> 130 siblings (48% female) Age median 25.9 (range 18.0-51.1 years)	<u>HSCT</u> Not reported	- *SF<29%; OR (95% CI)* **Anthracycline dose>183 mg/m2: 2.18 (1.25-3.80)** **Mediastinal RT: 3.00 (1.35-6.67)** TBI: 1.89 (0.64-5.6) Spinal RT: 1.40 (0.40-4.90) - *WMSI >1.00; OR (95% CI)* **Anthracycline dose>183 mg/m2: 2.40 (1.10-5.25)** Mediast RT: 1.61 (0.51-5.02) TBI: 0.82 (0.18-3.78) Spinal RT: 0.79 (0.11-5.57) - *TVI Et <8.0 m/sec; OR (95% CI)* **Anthracycline dose>183 mg/m2: 4.05 (1.16-14.09)** **Mediastinal RT: 15.21 (3.40-68.01)** TBI: 2.89 (0.18-46.77) Spinal RT: 1.12 (0.11-11.54)	<u>C. Detection bias:</u> Unclear. blinding of sonographers not reported <u>D. Confounding:</u> Low risk Multivariable analysis adjusted for important confounders. 7 clinical HF cases were included but it is unlikely this has changed the estimates very much.

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should surveillance be performed?				
Abosoudah et al. Echocardiographic surveillance for asymptomatic late-onset anthracycline cardiomyopathy in childhood cancer survivors. Pediatr Blood Cancer 57:467-72, 2011				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design Retrospective single center cohort Treatment era 1995-2003 Follow-up >1 year after anthracycline treatment Median 3, range 1-10 years Median 2 echo per patient (range 1-10)	Type and number of participants 603 eligible survivors (>1 year of therapy) 469 echocardiogram >1 year after therapy (77.8%) Diagnoses (%) ALL 33% AML 8% Hodgkins 18% NHL 12% Soft tissue sarcoma 4% Bone tumors 8% Renal tumors 9% Liver tumors 2% Neuroblastoma 6% Other 2 (0%) Age at diagnosis Mean 7.7, SD 4.6 years Age at follow-up Not reported Controls (if applicable) none	Chemotherapy Anthracyclines 100% Cumulative dose mean 205.0 mg/m2 (SD 114.7) Radiotherapy Chest RT 34% Surgery only None HSCT Not reported	Outcome definitions abnormal echocardiogram (EF < 55% or SF < 28% or LVED z-score > 2.0 or LVPW z-score < −2.0. Frequency of abnormal echo 79 (16.8%) with abnormal echo EF < 55% (10/79, 12%) SF 1/79 (0.01%) LVED z score >2 10/79 (10.0%) LVPW z score >2 51/79 (64.6%) 7/79 more than 1 abnormality: EF+FS 3/79 (0.04%) LVED+LVPW 3 (0.04%) SF/EF/LVPW 1 (0.01%) Median time from 1 year off therapy to abnormal echo 2.9, range 0.01-9.8 years (median time to abnormal echo in COG risk groups are reported in table) Abnormal echo's in 10/12 COG LTFU guideline risk groups (low and high risk patients) 41/48 with a follow-up echo had persistent abnormalities (85.4%) Multivariable Cox proportional hazard model **Abnormal echo during treatment HR 1.39 (0.83-2.29) NS** Female vs male HR 1.65 (1.04-2.62) Chest RT HR 1.73 (1.08-2.76) Age treatment	Time to first abnormal echocardiogram Unclear for transients Screening frequency driven by age and *anthracycline dose*, so unclear implication Implications of abnormal LVPW questionable, which was the driver of the abnormal echo's (51/79) **Risk of bias** A. Selection bias: high risk Reason: 77.8% participated, participants not different from non-participants with respect to important confounders. B. Attrition bias: high risk Reason: many lost to follow-up, however cox regression analysis takes censored patients into account C. Detection bias: unclear Reason: blinding not mentioned D. Confounding: low risk Reason: multivariable analysis. However, did not adjust for chest RT dose (only chest RT yes/no)

			<1 HR 1.16 (0.30-4.48) NS 1-4 1.89 (1.08-3.31) >5 (reference) Cumulative anthracycline dose <200 mg/m2 (reference(200-300 HR 1.32 (0.61-2.85) NS >300 HR 3.00 (1.51-5.98) <u>Cumulative incidence of abnormal echo</u> 7 years off therapy 26% 8 years off therapy 35%	

WG1: Who needs cardiomyopathy surveillance?				
Rathe et al. Long-term cardiac follow-up of children treated with anthracycline doses of 300 mg/m2 or less for acute lymphoblastic leukemia. Pediatr Blood Cancer 54:444-8, 2010				
Study design **Treatment era** **Years of follow-up**		**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design</u> Prospective cohort <u>Treatment era</u> 1986-2000 <u>Follow-up</u> 8.2 yrs (1.1-30.6)	<u>Type and number of participants</u> 1-yr survivors ALL N=80 All asymptomatic <u>Diagnoses</u> ALL <u>Age at diagnosis, median</u> 4.0 yrs (0.8-13.4)	<u>Chemotherapy</u> Median anth dose: 250 mg/m2 (120-300) <u>Radiotherapy</u> nm <u>HSCT</u> Nm	<u>Outcome definitions</u> IVS, LVPW, LVEDD, LVEDS, and ΔEF and EF measurements. Normal values derived from ref 9 and 11. <u>Results</u> At last follow-up 49 (61%) patients had an abnormally thin IVS, 21 (26%) had an abnormally thin LVPW, 11 (14%) patients had an abnormally high LVEDD, 9 (11%) had an abnormally high LVEDS while 19 (24%) had an abnormally low LVM. Nine patients had an EF below 60% with one pt <55%.	Looking specifically at cardiotoxicity at lower doses of anthracyclines (<300). **<u>Risk of bias</u>** <u>A. Selection bias:</u> high Reason: 69% of the eligible patients were included in the analysis <u>B. Attrition bias:</u> low Reason: we assume that at least 75% underwent echocardiography since they mention that the cohort

	Age at follow-up, median 13.0 yrs (2.0-30.5)		Multivariate regression analysis: ΔEF Model included: age at diagnosis, gender, cumulative dose of anthracycline, and length of follow-up. Only length of follow-up was a significant risk factor.	was followed with serial echocardiography according to the follow-up protocol until relapse or latest follow-up. C. Detection bias: unclear Reason: blinded not mentioned D. Confounding: low risk Reason: multivariable model

WG1: Who needs cardiomyopathy surveillance?				
Van der Pal et al. Cardiac function in 5-year survivors of childhood cancer: a long-term follow-up study. Arch Intern Med 170:1247-55, 2010				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Cross sectional Treatment era 1966-1997 Follow-up Median 15.4 yrs (range 5.1-40.3)	Type and number of participants 5-yr survivors 735 anthracycline-treated 675 Eligible for study 525 with echocardiogram 514 with FS Diagnoses (%) All childhood cancers Age at diagnosis Median 8.9 years (range 0.1-17.8) Age at follow-up	Chemotherapy Anthracyclines 68.8% Median dose 250 mg/m2 (range 33-720) Cyclophosphamide 45.1% Median dose 7.7 g/m2 (range 0.3-26.8) Vincristine 79.2% Ifosfamide 15.8% Radiotherapy Any 35% Median dose 25.0 Gray (range 8.0-60.0) Thorax 36.4% Abdomen 26.6%	Outcome definitions Left ventricular fractional shortening (FS) at first available echocardiogram >5 years from diagnosis, continuous and categorical (FS<30%). Graded per CTCAE 3.0 Results Median FS 33.1% (range 13-56%) FS<30% in 139 (27%) Multivariable logistic regression (FS<30%) Male vs female OR 0.73 (0.47-1.13) NS Age at diagnosis 0-5 years OR 2.94 (1.08-8.02) 5-10 years OR 1.64 NS 10-15 years 1.45 NS	-7 had previous heart failure but recovered -None had heart failure symptoms at time of presente study **Risk of bias** A. Selection bias: low risk Reason: 89% participated, 87.4 had an echocardiogram. Characteristics were not different between those with and without echo B. Attrition bias: low risk Reason: FS outcome was assessed in 514/675 (76%)

	Median 23.1, range 18.0-47.1 years <u>Controls (if applicable)</u> -	Spine 29.9% TBI 7.1 % <u>Surgery only</u> none <u>HSCT</u> Not reported	>15 (referent) P for trend 0.049 Time since diagnosis 5-10 years (referent) 10-15 years OR 0.80 (0.41-1.54) NS 15-20 years OR 0.40 (0.18-0.86) 20-25 years OR 0.48 NS >25 years OR 0.11 (0.03-0.42) P for trend 0.01 Vincristine (yes/no) OR 1.47 (0.71-3.05)NS Anthracyclines 1-150 mg/m2 (Ref) 151-300: OR 3.98 (1.58-10.01) 301-450: OR 7.77 (2.85-21.22) >450: OR 10.58 (3.35-33.40) Cyclophosphamide >10 vs <=10 g/m2 OR 1.01 NS Ifosfamide >10 vs <=10 g/m2 OR 1.50 NS Radiotherapy No Radiotherapy (Ref) Thorax: OR 3.49 (1.6-7.6) Abdomen: OR 2.66 (1.0-7.05) Spine: OR 0.64 (0.23-1.74) TBI: OR 0.53 (0.10-2.87)	<u>C. Detection bias:</u> low risk Reason: blinding of sonographers who measured FS. Measurements were performed multiple times. <u>D. Confounding:</u> Low risk Reason: Multivariable adjustments in risk factor analysis.

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?				
Mulrooney et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ 339:b4606, 2009				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort Treatment era 1970-1986 Follow-up 27.0 (range 8-51) years	Type and number of participants 5-yr Survivors (N=14, 358) Diagnoses (%) Leukaemia 4830 (33.6) Brain cancer 1876 (13.1) Hodgkin's lymphoma 1927 (13.4) Non-Hodgkin's lymphoma 1081 (7.5) Kidney tumour 1256 (8.7) Neuroblastoma 954 (6.6) Soft tissue sarcoma 1245 (8.7) Bone cancer 1189 (8.3) Age at diagnosis Mean 6.0 (range 0-20) yrs 0-4 yrs: 40.1% 5-9 yrs: 22.3% 10-14 yrs: 20.3% 15-20 yrs: 17.3%	Chemotherapy Anthracyclines: 33.1% <250 mg/m2 1931 (13.4) ≥250 mg/m2 2834 (19.7) Bleomycin 756 (5.3%) Cisplatin 738 (5.1%) Cyclophosphamide 5694 (39.7%) Vincristine 9031 (62.9%) Chest radiotherapy No chest RT: 29% <5 Gy: 34% 5-15 Gy: 5.8% 15-35Gy: 9.7% >=35Gy: 6.9% Surgery only 909 (7.3) HSCT Not reported	Outcome definitions Self-reported CV outcomes Graded per CTCAE v. 3.0 Results N (prevalence %) Heart failure 248 (1.7) Myocardial infarction 101 (0.7) Pericardial disease 181 (1.3) Valvular abnormalities 238 (1.6) Results cumulative incidence 30 years after cancer diagnosis % (95% CI) Heart failure 4.1% (3.2 to 5.0%) Myocardial infarction ±1.4% (1.0 to 1.8%) Pericardial disease 3.0% (2.1 to 3.9%) Valvular abnormalities 4.0% (3.1 to 4.9%) Cumulative incidence increased for all outcomes without a plateau (except possibly for MI) HR for heart failure in survivors compared to siblings, adjusted for gender, race, household income, education and tobacco use: 5.9 (95% CI 3.4-9.6)	-Long follow-up, large cohort -Cardiac XRT dosimetry calculations (Stovall et al.) -ChestRT data not mutually exclusive of anthracycline exposure. -Cardiac events are self-reported. -Did not assess subclinical disease. -No adjustment for Framingham risk factors. This might have developed over time. It may be important to assess the additional risk of cardio toxic therapy as they become adults. -Broad geographical distribution- comprises of 26 collaborating institutions. **Risk of bias** A. Selection bias: High risk Reason: 69% of eligible B. Attrition bias: Low risk Reason: outcome was assessed in all patients

	Age at follow-up Survivors: median=27.0 (8-51) years; Controls (if applicable) Siblings (N=3899) Median age 28.0 (range 3-56) years		Multivariable Cox regression with age as the time scale: Heart failure HR (95% CI) Female 1.4 (1.1-1.9) Age at diagnosis (reference 15-20 years) 0-4 years 3.9 (2.1-7.3), 5-9 years 2.3 (1.3-4.0), 10-14 years 1.2 ns. Treatment era (reference 1970-1974) 1975-1979 1.1 ns, 1980-86 1.9 (1.2-3.0) **Chest RT dose**: <5 Gy 0.9 ns, 5-<15 Gy 1.3 ns, **15-35 Gy 2.2 (1.4-3.5), 35 Gy 4.5 (2.8-7.2)** **Anthracycline dose (reference none)** **<250 mg/m2 2.4 (1.5-3.9), ≥250 5.2 (3.6-7.4)** Cisplatin yes vs no: 1.7 ns Myocardial infarction, Pericardial disease and valvular disease risk factor analysis also performed	C. Detection bias: Unclear Reason: Blinding of outcome assessors for cardiotoxic exposures not mentioned. Self-reported outcomes. D. Confounding: Low risk Reason: Multivariable regression model adjusted for all important confounders

WG1: Who needs cardiomyopathy surveillance? Genetics				
Blanco et al. Genetic Polymorphisms in the Carbonyl Reductase 3 Gene CBR3 and the NAD(P)H:Quinone Oxidoreductase 1 Gene NQO1 in Patients Who Developed Anthracycline-related Congestive Heart Failure After Childhood Cancer. CANCER June 15, 2008 / Volume 112 / Number 12				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks e.g. risk of bias**

Study design Nested case control in CCSS Treatment era 1970-1986 Follow-up (median) Not reported. >=5 years	Type and number of participants 30 cases with heart failure 115 controls matched on age at diagnosis, race/ethnicity, duration of follow-up (controls were followed at least until the case developed the event), anthracycline dose and radiation to the heart (also adjusted for RT in models) Diagnoses All childhood cancer diagnoses Age at diagnosis Cases: mean 10.3±6.5 years Controls: mean 9.1±5.8 years Age at follow-up Not reported	Chemotherapy 100% ANT No median reported Radiotherapy Cases: 60% Controls: 55% No medians Surgery Not reported HSCT Not reported	Outcome definitions Self-reporting of signs and symptoms of CHF and use of medication for CHF management. Multivariable conditional logistic regression CBR3 rs1056892: GG vs AA: OR 8.16 (0.95-70.10), p=0.056 -GA vs AA: OR 5.44 (0.76-39.14), p=0.092 Female vs male: OR 2.68 (1.07-6.73) Recurrence or not: OR 6.35 (1.13-35.75) adjusted for heart in radiation beam Univiariate analysis only NQO1 s1800566: not significant adjusted for heart in radiation beam Functional studies Recombinant CBR3 V244 (G allele) synthesized 2.6-fold more cardiotoxic doxorubicinol per unit of time than CBR3 M244 A allele.	**Risk of bias** A. Selection bias: unclear Reason: limited to patients who provided buccal sample, unknow what proportion provided this B. Attrition bias: low risk Reason: outcome assessed in all C. Detection bias: high risk Reason: self-reported outcomes, no blinding reported D. Confounding: low risk Reason: matching and MV model considered confounder with >10% effect on estimate.

WG1: Who needs cardiomyopathy surveillance?				
Hudson et al. Noninvasive evaluation of late anthracycline cardiac toxicity in childhood cancer survivors. J Clin Oncol 25:3635-43, 2007				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design Cross-sectional Treatment era Not reported Follow-up Median 9.0 (range 3.0-18.0)	Type and number of participants 1268 full cohort 223 anthracycline and or chest RT treated survivors participated Diagnoses (%) Leukemia 30% Sarcomas 26.9% Lymphoma 24.2% (Hodgkin 15%, NHL 9.0%) Embryonal tumors (18.8%) Age at diagnosis Median 5.5 (range 0-23.6) Age at follow-up Median 17.0, range 7.5-39.7 years Controls (if applicable) 55 – not received cardiotoxic treatment	Chemotherapy Anthracyclines 70.4% Median dose 202 mg/m2 (range 25-510) Radiotherapy cardiac RT: 2.7% Anth + cardiac RT: 26.9% Surgery only none HSCT Not reported	Outcome definitions Screening echo. LVSF <28%, LV Wall stress (afterload) Univariate regression (SF<28%): Male vs female OR 1.17 (0.57-2.40) Cardiac RT yes/no: OR 0.9 (0.4-2.05) Other vs white race OR 0.89 (0.34-2.33) Anthracycline mg/m2/week >=50 vs <50 OR 3.13 (1.41-6.96) Cyclophosphamide, infusion type, smoking, thyroid function, BMI, GH deficiency, dyslipidemia, QTc not significant Multivariate regression with risk factors with univariate p <0.10 (SF<28%): *Age at diagnosis* >=5 yrs – OR 2.41 (0.9-6.4), p0.08 <5 Ref *Diagnosis group* Sarcoma 5.09 (1.3-19.89) Lymphoma 2.04 (0.47-8.94) Embryonal 1.70 (0.36-8.04) Leukemia (Reference) *Years of therapy* per 5 years increase OR 1.08 (0.52-2.27) *anthracycline dose* per 50 mg/m2 increase OR 1.19 (1.01-1.39) p=0.033	Asymptomatic One time-point No cardiac dose quantification **Risk of bias** A. Selection bias: High risk Reason: only 22% of full cohort participated B. Attrition bias: low risk Reason: outcome assessed in all C. Detection bias: low risk Reason: cardiologist who performed echo was blinded for treatment status D. Confounding: low risk Reason: multivariable analysis adjusted for important covariates (after univariable selection on p value <0.1).

WG1: Who needs cardiomyopathy surveillance?

Aleman et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood 2007;109:1878-86

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort Treatment era 1965-1995 Follow-up Median 18.7 yrs (28 669 person-years for cohort)	Type and number of participants 1474 5-year survivors of HL, diagnosed before age 41 yr. Diagnoses Hodgkin lymphoma Age at start treatment <20 yo (21.3%) 20-35 yo (62.7%) >35 yo (15.9%) Median 25.7 yrs Age at follow-up <35 yo (16.6%) 35-55 yo (63.4) >55 yo (20.1%) No median given Controls (if applicable) Dutch morbidity registration (age-, sex-, period specific) Cardiovascular risk factors: 17% recent smokers	Chemotherapy Chemo only 4.8% Radiotherapy RT only 27.5% (all fields) RT + chemo (incl. anth) 29.5% RT + chemo (no anth) 37.9% 84% of RT included the mediastinum Unknown 0.2%	Outcome definitions Cumulative incidence of CHF after 25 years from medical records N=52 Results *Cumulative incidence* No RT group: 0.4% Mediastinal RT only group: 6.8% Mediast RT + CT, no anth group: 4.9% Mediast RT + CT, anth group: 7.9% Median time to heart failure: 18.5, range 5.0-39.0 *Multivariate regression (CHF):* **Model 1** Mediastinal RT (vs no) HR 7.37 (1.81 – 30.0) Anth. Containing chemo (vs no) HR 2.44 (1.37-4.33) Recent smoking (vs no) HR 1.96 (1.16-3.30) Diabetes mellitus (vs no) HR 4.45 (2.54-7.81) Not significant: hypertension (vs no) HR 1.07 (0.59-1.94) hypercholesterolemia (vs no) HR 1.48 (0.85-2.58) **Model 2**	Large pop of adult lymphoma survivors (most <35 yo at Dx) Very long follow-up Critical role of cardiovascular risk factors No dosimetry for cardiac XRT Includes older treatment era **Risk of bias** A. Selection bias: Low risk Reason: only 12 of original cohort had no medical records available B. Attrition bias: Low risk Reason: Only 6.7% had no complete follow-up C. Detection bias: Unclear if outcome assessors were blinded, however medical records need only little judgement from the assessor. D. Confounding: Low risk Reason: as sex was not corrected for after stepwise selection. However, cardiovascular risk factors were taken into account.

	10% hypertension 5% diabetes 8.5% hypercholesterolemia		Mediastinal RT only (Ref) Med. RT + CT, no anthracycline: HR 1.33 (0.79-2.24) Med. RT + CT, anthracycline: HR 2.81 (1.44-5.49) (Adjusted for recent smoking, age at diagnosis, hypertension, hypercholesterolemia, diabetes mellitus)	

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should surveillance be performed?				
Creutzig et al. Longitudinal evaluation of early and late anthracycline cardiotoxicity in children with AML. Pediatr Blood Cancer 48:651-62, 2007				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort, single centre study. Treatment era 1993-2003. *Treated in 1993-2003 according to AML-BFM-98 and 93 trial study. Follow-up AML-BFM-98 study: Median 3.6 (0.8-7.0) years.	Type and number of participants Within 1yr and ≥ 1yr survivors. N=1207 survivors <18 years at primary cancer diagnosis. Data on late cardiotoxicity (>1year after AML chemotherapy) were available for 547 (45%) patients. Diagnoses AML 100% AML with down syndrome: 121(10.02%)	Chemotherapy 1207 (100%) anthracyclines Dauno: Ida – 1:5 Dauno: Mitox – 1:5 Anthracycline dose: AML-BFM-93 study: 300-400mg/m2 AML-BFM-98 study: 420-450mg/m2 Number of patients treated & followed up for late cardiotoxicity BFM-93 study: 306/547 (55.94%)	Outcome definitions -Clinical cardiotoxicity: clinical signs and symptoms of cardiomyopathy. -Subclinical cardiotoxicity: no clinical signs and symptoms of cardiomyopathy, but with an abnormal SF of the left ventricle measured by ECHO. -Late cardiotoxicity >1 year after AML chemotherapy. Results -Late cardiotoxicity: 16/547 (2.9%) cardiomyopathy (9 clinical and 7 subclinical cardiomyopathy). - Late cardiotoxicity determined at median follow up 5.3 (0.8-11.5) years after diagnosis	**Additional remarks:** -Early and late cardiotoxicity, only late cardiotoxicity reported in table -A lot of missing information -Cumulative dose was lowered for high-risk patients eg, dose reduced by 1/3 for patients with down syndrome -Long term follow up -986/1399 (70%) of echo evaluations done within first 5yrs after diagnosis -Homogenous treated group of AML patients -Assessment of subclinical cardiac function was only by fractional shortening **Risk of bias**

AML-BFM-93 study: Median 7.5 (1.1-11.5) year.	AML without down syndrome: 1010 (83.68%) Secondary AML: 76(6.29%). <u>Age at diagnosis</u> <18 years of age. <u>Age at follow-up</u> Not Reported.	BFM-98 study: 241/547 (44.06%).	-5/9 patients with clinical cardiomyopathy had persistent abnormal SF. <u>Cumulative incidence late cardiomyopathy at 5 yrs after diagn.</u> Patient with/without down syndrome: 4% ±1% Patients with secondary AML: 60% ± 22% Early/late cardiomyopathy: 4-5% Late clinical cardiomyopathy: 2.5±1% <u>Cox Regression:</u> Early cardiotoxicity was the only predictor of late cardiotoxicity (Adjusted for early cardiotoxicity, sex, age at diagnosis, FAB M4/M5 vs. other FAB types)	<u>A. Selection bias:</u> unclear Reason: Unclear how many survivors were included in the original cohort and study group. <u>B. Attrition bias:</u> High risk Reason: Data on late cardiotoxicity were available on 547/1207 (45%) patients <u>C. Detection bias:</u> unclear Reason: unclear if outcome assessors were blinded. <u>D. Confounding:</u> Low risk Reason: Adjusted for early cardiotoxicity, sex, age <2 vs >2 years, age <10 vs >10 years, FAB M4/M5 vs other FAB types.

WG1: Who needs cardiomyopathy surveillance?				
Paulides et al. Prospective longitudinal evaluation of doxorubicin-induced cardiomyopathy in sarcoma patients: a report of the late effects surveillance system (LESS). Pediatr Blood Cancer 46:489-95, 2006				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design</u> Prospective cohort germany, Austria, switzerland <u>Treatment era</u> 1992-2004	<u>Type and number of participants</u> LESS - sarcoma 1066 non-relapse cohort 564 excluded 502 eligible 265 with echo <u>Diagnoses (%)</u>	<u>Chemotherapy</u> Doxorubicin dose mean 290 +/-91 mg/m2 <u>Radiotherapy</u> Chest RT: 6.8% Mean dose 47 +/- 10 Gray	<u>Outcome definitions</u> Subclinical FS<29% at least twice, no symptoms Clinical heart failure – per AHA <u>Results</u> 4/265 Clinical CHF 16/265 subclinical DCM	- Clinical and subclinical DCM - Low participation rate - Short follow-up, acute setting - Similar to several other low-yield studies **<u>Risk of bias</u>** <u>A. Selection bias:</u> very high risk

Follow-up Mean 3 yrs (+/-1 yr)	Sarcoma 100% Age at end of therapy mean: 13 +/- 5 yrs Age at follow-up No descriptive statistic reported Range 1-23 years Controls (if applicable) none	Surgery only none HSCT Not reported	Results multivariable regression not reported, no statistically significant results. Tested were anthracycline dose, age at diagnosis, gender, mediastinal irradiation, and longer follow-up	Reason: 237/1066 included in analysis. Comparison between 502 eligible and 237 with echo did not show differences in important confounders but data was not shown B. Attrition bias: unclear Reason: unclear how many patients were lost to follow-up. C. Detection bias: unclear risk Reason: blinding investigators/sonographers not mentioned D. Confounding: NA Reason: unclear how multivariable modeling was done and results not reported

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?				
Van Dalen et al. Clinical heart failure in a cohort of children treated with anthracyclines: a long-term follow-up study. Eur J Cancer 42:3191-8, 2006				
Study design Treatment era Years of follow-up		**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort Treatment era 1976-2001 Follow-up	Type and number of participants Children treated with anthracyclines (n=830) Diagnoses Various	Chemotherapy Mean anthracycline dose: 288 mg/m2 (range 15-900) Mitoxantrone: Any 4.1% None 95.5% Mean dose 21.8 mg/m2 (range 12–108)	Outcome definitions A-CHF = congestive heart failure, not attributable to other known causes, such as direct medical effects of the tumour, septic shock, valvular disease or renal failure. Results Cumulative incidence of A-CHF: 2.5% (21 patients; 95% CI 1.6–3.8%).	Follow-up on previous 2001 JCO study. Not limited to long-term survivors. No RT dosimetry reported. **Risk of bias** A. Selection bias: low risk Reason: 830 out of 831 eligible patients were evaluated (>75%).

Median 8.5, range 0.01-28.4	Age at anthracycline exposure Mean 8.8 years (median 8.7; range 0.1–18.0) Age at follow-up, mean 17.3 years (median 16.7; range 0.3–42.7)	Ifosfamide: Any 27.2% None 72.4% Cyclophosphamide: Any 55% None 44.8 % Radiotherapy Chest RT: Any 21.2% None 78.7%	Mean time between the first dose of anthracyclines and A-CHF: 3.7 years (median 0.84 years; range 0.1–20.9 years). Univariate analyses: Cumulative anthracycline dose of 300 mg/m2 or more (RR = 8.66, 95% CI 2.01–37.35, P = 0.004). Additional treatment with ifosfamide with a cumulative dose of more than 10 g/m2 (RR = 2.67, 95% CI 1.05– 6.82, P = 0.04). Female sex, age at first anthracycline dose 2 years or younger, RT involving the heart region, additional treatment with mitoxantrone and additional treatment with more than 10 g/m2 of cyclophosphamide) were not associated with an increased risk of A-CHF. Multivariate COX regression analyses: It was unclear which variables were included in the multivariate analyses. Cumulative anthracycline dose of 300 mg/m2 or more was the only independent risk factor. Cumulative anthracycline ≥300 mg/m2 RR: 7.78 (95% CI 1.76-34.27), p<0.01	B. Attrition bias: low risk Reason: the authors state that information on the clinical status up to at least January 2002 was available for 95.8% of the cohort. C. Detection bias: low risk Reason: the cardiologist who confirmed the diagnosis was unaware of the cumulative anthracycline dose received by the patients. D. Confounding: unclear risk Reason: it was not stated which variables were included in the multivariate model.

WG1: Who needs cardiomyopathy surveillance?				
Guldner et al. Radiation dose and long term risk of cardiac pathology following radiotherapy and anthracyclin for a childhood cancer. Radiother Oncol 2006;81:47-56				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design Retrospective cohort Cross-sectional evaluation Treatment era 1968-1985 Follow-up (n=229) Mean 18 years	Type and number of participants 447 CCS treated with anthracycline and alive at end therapy, now ≥15 years after exposure. 229 (51%) participated in study Diagnoses (of 245 who received RT) Lymphoma n=75 nephroblastoma n=46 Soft tissue sarcoma n=42 Neuroblastoma n=33 Ewing sarcoma n=25 Other n=22 Unknown n=2 Age at diagnosis (n=447) 6.2 yrs (0-21) Age at follow-up (n=229) Mean 24 yrs	Chemotherapy Anthracyclines: mean 344mg/m^2 (range 40-600) Radiotherapy 245/447 pt had RT XRT heart dose: Mean 8.1 (15.6)	Outcome definitions - heart failure, n=24 - Prevalence of asymptomatic cardiac disease (FS <25 / EF <50 / ESWS > 100) Results 218 not examined and not known cardiac failure 140 examined and healthy 24 with cardiac failure 65 with asymptomatic cardiac disease Heart radiation dose: Not examined vs healthy vs. heart failure vs asymptomatic disease: Median 0.27 Gy vs 0.6 Gy vs. 18.1 Gy vs 2.2 Gy; p <0.001 Multivariable logistic regression (heart failure) Dose-dependent increase in HF and cardiac disease risk by radiation dose RR of 19% (95% CI: 2% to 50%) per 1 Gray (adjusted for sex, age at treatment, cumulative anthracycline dose, attained age).	No XRT heart dosimetry, dosing estimated Inclusion based on anth. exposure, no RT alone population. Cohort overlap with Pein, 2004. Mixed reporting of details on the whole cohort, RT treated cohort, examined cohort and groups with(out) cardiac failure. **Risk of bias** A. Selection bias: High risk as only 51% participated and pt with known cardiac failure were added to the selection. B. Attrition bias: Low, all 205 asympt. participants had an echo C. Detection bias: Unclear if blinded assessor D. Confounding: Low risk, adequate adjustment

WG1: Who needs cardiomyopathy surveillance?

Van der Pal et al. Risk of morbidity and mortality from cardiovascular disease following radiotherapy for childhood cancer: a systematic review. Cancer Treat Rev 2005;31:173-85

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Study design Systematic review of risk of morbidity and mortality from cardiovascular disease for childhood cancer Lit Review: 1966-2002 Treatment era 1954-1997 Follow-up: Reported means /medians range from 6 to 24 years. Reported ranges range from 1 to 29 years.	Criteria for review: 1) Original report 2) English, Dutch, French, German 3) Study pop.: >50 pts. 4) Childhood CA: <=18 y. 5) XRT involving heart region 6) Outcome: Clinical cardiovascular event (CVE) or cardiovascular mortality For CVE: 9 studies selected based on validity and inclusion criteria. For CV mortality: 11 studies selected based on validity and inclusion criteria.	Chemotherapy 10 studies mentioned possible cardiotoxic co-treament (i.e. anthracyclines), ranging from 4% to 100% of the cohort. Radiotherapy Inclusion criterion	Outcome definitions All cardiac events Results **Cumulative incidence CVE** 0.3% to 22.8% **Cumulative incidence CV mortality** 0% to 3.5% Pooled standardized mortality ratio 28.4 Multiple regression from 1 case-control study (all Cardiac events), matched for anthracycline, time at risk, cohort **Continuous tx. Variables (RR; 95%CI):** Female/Male: 4.5 (1.6-12.6) Anth, 100 mg/m2: 3.2 (1.8-5.7) Lung RT, 10 Gy: 1.6 (1.1-2.7) Left abd, 10 Gy: 1.8 (1.1-2.7) **Categorical tx. Variables (RR; 95% CI):** Female/Male: 3.7 (1.4-9.3) Anth,>300 mg/m2: 5.0 (1.3-19) Left abd. RT: 3.5 (1.2-10) **Not significant:** **Continuous tx. Variables (RR; 95% CI):** Right abd. 10 Gy: 0.94 (0.66-1.3) **Categorical tx. Variables (RR; 95% CI):** Lung RT >20Gy: 3.1 (0.5 – 19)	Older treatment eras Many studies include arterial events (ie: MI) and CHF as CVE. For many, no clear delineation between RT-related systolic heart failure vs. CHF due to coronary artery disease, or MI alone. Dose-dependent Risk **Risk of bias** A. Selection bias: Low risk; 10/11 studies had more than 95% of the original cohort or a random sample. B. Attrition bias: Unclear risk. 5/11 studies assessed >90%, 3/11 assessed 60-90%, 3/11 n.m. C. Detection bias: High risk: none of the studies mentioned blind detection D. Confounding: Unclear: 6/11 studies adequately adjusted for confounders. Low risk for matched case-control study

WG1: Who needs cardiomyopathy surveillance? WG3: At what frequency should cardiomyopathy surveillance be performed?				
Pein et al. Cardiac abnormalities 15 years and more after adriamycin therapy in 229 childhood survivors of a solid tumour at the Institut Gustave Roussy. Br J Cancer 91:37-44, 2004				
Study design **Treatment era** **Years of follow-up**		**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort Treatment era 1968-1982 Follow-up 18 yrs (average)	Type and number of participants Children who received at least one dose of anthracyclines and who were alive at the end of treatment (n=229) Group I (n=205) examined according to protocol Group II (n=24) not examined but included because they had experienced a clinical cardiac failure. Diagnoses Solid tumour Age at treatment: Group I: 5.7 (0–21) Group II: 4.8 (1–13) Age at follow-up	Chemotherapy Anthracycline, mean dose mg/m2 (range): Group I: 333 (40–600) Group II: 412 (180–600) Radiotherapy Chest RT Group I: yes 106 (52%) Group II: yes 14 (58%) Mean dose chest RT Gy (range): Group I: 7.7 (0–91) Group II: 13.4 (0–46)	Outcome definitions -Heart failure, FS<25%, EF<50%, or ESWS>100, n=89 -Heart failure, n=24 Results Risk of cardiac failure increased with time since first anthra treatment. Multivariate COX regression (asymptomatic and symptomatic cardiomyopathy) Model 1: RR (95% CI) Female (male ref): 1.41 (0.8 – 2.6) Age at first treatment <7 yrs (≥8 yrs ref): 3.21 (1.63 – 6.34) Cum anthracycline dose at 100mg/m2: 1.60 (1.22 – 2.09) Average chest RT dose: 1.25 (0.99 – 1.50) Model 2: RR (95% CI) Adjusted for age at treatment of first cancer, sex, and average radiation dose received at 6 points in the heart, and stratified on the site of the cancer.	High proportion treated with chest radiation. Very long term follow-up. One of the earlier studies to demonstrate dose-response with RT. **Risk of bias** A. Selection bias: high risk Reason: there were 447 consecutive patients, <75% were included for the analyses. B. Attrition bias: low risk Reason: group II is <75% of the study group. C. Detection bias: unclear risk Reason: blinding was not mentioned by the authors. D. Confounding: low risk

	nm		Cumulative anthracycline dose 0 –150 (Ref) >150 – 250 2.0 (0.44 – 9.5) >250 – 400 4.0 (0.95 – 17) >400 3.3 (0.78 – 14) Model 3: RR (95% CI) Adjusted for age at treatment of 1st cancer, sex, and cumulative anthracyline dose, and stratified on the site of the cancer. 0 No chest RT (Ref) >0-5 Gy: 1.63 (0.82-3.26) >5-20 Gy: 6.48 (2.76-15.20) >20 Gy: 4.40 (1.11-17.48) Model 4 RR (95% CI) Adjusted for age at treatment of first cancer, and sex, and stratified on the site of the cancer. <250 mg of adriamycin + < 5Gy to the heart (ref) + ≥ 5Gy to the heart 4.9 (1.3 –18.0) ≥ 250 mg of adriamycin + < 5Gy to the heart 5.1 (1.8 –14.5) + ≥ 5Gy to the heart 6.6 (2.1 –20.6)	Reason: all the relevant variables were included in the multivariate analyses.

WG2: What surveillance modality should be used?				
Kismet et al. Serum troponin T levels and echocardiographic evaluation in children treated with doxorubicin. Pediatr Blood Cancer. 2004;42:220–224.				
Study design Treatment era	**Participants**	**Diagnostic tests**	**Main outcomes~**	**Additional remarks**

Years of follow-up				
Study design Multi-center cohort study (Turkey). Treatment era June 1982 to August 2000. Median time from last doxorubicin dose: 12 months (range 1 to 168).	Type and number of Participants 24 childhood cancer patients who received doxorubicin for treatment of Hodgkin disease (n=4), rhabdomyosarcoma (n=4), Ewing sarcoma (n=3), osteosarcoma (n=3), malignant mesenchymal tumor (n=3). Wilms tumor (n=2), neuroblastoma (n=1), hepatoblastoma (n=1), clear cell sarcoma (n=1), malignant mesothelioma (n=1) and primitive neuroectodermal tumor (n=1). 14 males/10 females Age at diagnosis Not reported Age at study median 14 years (range 3-31). Cancer treatment Median cumulative doxorubicin dose 480 mg/m² (range 400 to 840); 4 patients also received mediastinal irradiation (no further information provided)	Diagnostic test(s) Cardiac troponin T; an abnormal test result was defined as ≥ 0.010 ng/ml (n=3; prevalence 12.5%). Outcome definitions Two-dimensional, M-mode and Doppler echocardiography performed by pediatric cardiologists (number of observers nm); an abnormal test result was defined as LVEF < 55% and LVSF < 29% (n=2; prevalence 8.3%). Time between tests within 24 hours.	Diagnostic outcomes (sensitivity, specificity, PPV, NPV, ROC) When the echocardiographic result is used as the reference standard^: Sensitivity: 50% (95% CI 2.7 to 97.2) Specificity: 90.9% (95% CI 86.6 to 95.2) Positive predictive value: 33.3% (95% CI 1.8 to 64.8) Negative predictive value: 95.2% (95% CI 90.7 to 99.7) Agreement between tests (i.e. either both abnormal or both normal): 21/24 (87.5%).	None of the patients had clinical evidence of abnormal cardiac functions; patients with evidence of renal disease were excluded from the study. **Risk of bias** A. Selection bias: unclear Reason: not clear if these 24 patients were all eligible patients or a random sample thereof. B. Index test bias: unclear Reason: nm if outcome assessors were blinded. C. Reference test bias unclear Reason: nm if outcome assessors were blinded. D. Verification bias: low risk Reason: time between test <24hrs E. Attrition bias low risk Reason: all 24 patients had both tests.

^ Since echocardiography is most often used to assess cardiac function in clinical practice, we have chosen the echocardiographic results as reference standard

~ Calculated by the guideline developers based on information provided in the article (for the main outcomes we used the calculator on http://statpages.org/ctab2x2.html)

WG2: What surveillance modality should be used?				
Soker et al. Plasma concentrations of NT-pro-BNP and cardiac troponin-I in relation to doxorubicin-induced cardiomyopathy and cardiac function in childhood malignancy. Saudi Med J 26:1197-202, 2005				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes~**	**Additional remarks**
Study design Single-center study (Turkey). Cross sectional Treatment era October 2000 and December 2004. Follow-up Mean follow-up after the last anthracycline dose 9.39 months (range 1 to 42).	Type and number of participants 31 childhood cancer patients who received doxorubicin 14 males/17 females;; Diagnoses (%) ALL (n=27), AML (n=2), Hodgkin disease (n=1), NHL (n=1). Age at diagnosis median age at diagnosis nm Age at follow-up median age at study 8.16 years (range 4 to 15). Controls (if applicable)	Chemotherapy Median cumulative doxorubicin dose 240 mg/m² (range 30-600). Radiotherapy Patients who received mediastinal RT were excluded Surgery only none HSCT NA	Outcome definitions Two-dimensional, pulse-wave Doppler and M-mode echocardiography (performed by 1 experienced pediatric cardiologist); an abnormal test result was defined as LVEF < 60% and LVSF < 30% (n=4; prevalence 12.9%). Cardiac troponin I; an abnormal test result was defined as ≥ 0.50 ng/ml (n=0; prevalence 0%). Time between tests: performed simultaneously. Results When the echocardiographic result is used as the reference standard^: Sensitivity: 0% (95% CI 0 to 0) Specificity:	Tests were performed at the same time **Risk of bias** A. Selection bias: unclear Reason: not clear if these 31 patients were all eligible patients or a random sample thereof. B. Attrition bias: low risk Reason: all 31 patients had both tests. C. Detection bias: unclear Reason: unclear if outcome assessors were blinded. D. Confounding: NA Reason: no multivariable adjustments, we are interested in the crude sensitivity, specificity etc.

	Na		100% (95% CI 100 to 100) Positive predictive value: NaN Negative predictive value: 87.1% (95% CI 87.1 to 87.1) Agreement between tests (i.e. either both abnormal or both normal): 27/31 (87.1%).	
^ Since echocardiography is most often used to assess cardiac function in clinical practice, we have chosen the echocardiographic results as reference standard ~ Calculated by the guideline developers based on information provided in the article (for the main outcomes we used the calculator on http://statpages.org/ctab2x2.html)				

WG2: What surveillance modality should be used?				
Mavinkurve-Groothuis et al. Abnormal NT-pro-BNP levels in asymptomatic long-term survivors of childhood cancer treated with anthracyclines. Pediatr Blood Cancer. 2009;52(5):631–6.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic tests**	**Main outcomes~**	**Additional remarks**
Study design Single-center cohort study (the Netherlands). Treatment era Not reported (current study executed between May 2006 and October 2007).	Type and number of Participants 122 long-term survivors of childhood cancer treated with anthracyclines for ALL (n=38), AML (n=8), ependymoma (n=1), Ewing sarcoma (n=6), hepatoblastoma (n=3), Hodgkin lymphoma (n=13), neuroblastoma (n=6), NHL (n=30),	Diagnostic test(s) **Cardiac troponin T;** an abnormal test result was defined as **≥ 0.010 ng/ml (n=0%; prevalence 0%)** **NT-pro-BNP**; an abnormal test result was defined as **males <10 pmol/L, females <18 pmol/L** and for **children age dependent** reference	Diagnostic outcomes (sensitivity, specificity, PPV, NPV, ROC) When the echocardiographic result of the **LVEF** is used as the reference standard^: Sensitivity: cTnT: 0% (95% CI 0 to 0) NT-proBNP: 22.2% (95% CI 4.0 to 57.0) Specificity: cTnT: 100% (95% CI 100 to 100)	At time of testing none of the patients had symptomatic cardiac disease (defined as < NYHA class II) or a history of cardiovascular disease or chronic renal insufficiency. **Risk of bias** A. Selection bias: unclear Reason: all consecutive patients who visited the Late Effects Clinic

Follow-up Median 13.8 years (range 5 to 28.7).	osteosarcoma (n=3), rhabdomyosarcoma (n=4) or Wilms tumor (n=10). 62 males/60 females Age at diagnosis median 5.7 years (range 0.03 to 14.4) Age at study median 21 years (range 5 to 39.4 years). Cancer treatment Median cumulative anthracycline dose (doxorubicin and/or daunorubicin) 180 mg/m² (range 50-542); 7 patients also received mediastinal irradiation (no further information provided).	values by Albers et al* **(n=16; prevalence 13.1%).** Outcome definitions Transthoracic M-mode echocardiography (performed by experienced echocardiographic technicians and supervised by 2 (pediatric) cardiologists who were unaware of the cumulative chemotherapy dose and levels of cardiac troponin T); an abnormal test result was defined as **LVEF < 55% (n=9; prevalence 7.4%) or as LVSF < 29% (n=4; prevalence 3.3%).** Time between tests Both tests were performed at the same time.	NT-proBNP: 87.6% (95% CI 86.2 to 90.4) Positive predictive value: cTnT: NaN NT-proBNP: 12.5% (95% CI 2.3 to 32.1) Negative predictive value: cTnT: 92.6% (95% CI 92.6 to 92.6) NT-proBNP: 93.4% (95% CI 91.8 to 96.3) Agreement between tests (i.e. either both abnormal or both normal): cTnT: 113/122 (92.6%). NT-proBNP: 101/122 (82.8%). When the echocardiographic result of the **LVSF** is used as the reference standard^: Sensitivity: cTnT: 0% (95% CI 0 to 0) Specificity: cTnT: 100% (95% CI 100 to 100) Positive predictive value: cTnT: NaN Negative predictive value: cTnT: 96.7% (95% CI 96.7 to 96.7) Agreement between tests (i.e. either both abnormal or both normal): cTnT: 118/122 (96.7%).	during the study period were included, but it is not stated if those patients represented a random sample of the complete cohort of survivors. B. Index test bias: low risk Reason: echocardiographic outcome assessors were blinded. C. Reference test bias low risk Reason: echocardiographic outcome assessors were blinded. D. Verification bias: low risk Reason: biomarker and echo performed at the same time E. Attrition bias low risk Reason: all 122 patients had both tests.

* Albers S, Mir TS, Haddad M, Läer S. N-Terminal pro-brain natriuretic peptide: normal ranges in the pediatric population including method comparison and interlaboratory variability. *Clin Chem Lab Med*. 2006;44(1):80–5.

^ Since echocardiography is most often used to assess cardiac function in clinical practice, we have chosen the echocardiographic results as reference standard

~ Calculated by the guideline developers based on information provided in the article (for the main outcomes we used the calculator on http://statpages.org/ctab2x2.html)

WG2: What surveillance modality should be used?				
Krawczuk-Rybak et al. Cardiac function in survivors of acute lymphoblastic leukaemia and Hodgkin's lymphoma J Paediatr Child Health, 47 (2011), pp. 455-459				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic tests**	**Main outcomes~**	**Additional remarks**
Study design Single-center cohort study (Poland). Treatment era Not reported Follow-up after treatment completion: mean 5.91 years (range 1.6 to 13.8).	Type and number of Participants 44 childhood cancer survivors treated with anthracyclines (doxorubicin, daunorubicin) for ALL (n=37) or Hodgkin lymphoma (n=7). 30 males/ 14 females; Age at diagnosis Not reported Age at study Mean 14.7 years (range 6 to 23) Cancer treatment Cumulative anthracycline dose for ALL 180 to 540	Diagnostic test(s) NT-pro-BNP; an abnormal test result was defined as > 115 ng/L (n=6; prevalence 13.6%). Outcome definitions Doppler and colour flow visualization echocardiography; M-mode for heart structures and Teicholz method for contractility and LVEF (number of observers nm); an abnormal test result was defined as indexed stroke volume < 40 ml/m² (n=16; prevalence 36.4%). Time between tests	Diagnostic outcomes (sensitivity, specificity, PPV, NPV, ROC) When the echocardiographic result is used as the reference standard^: Sensitivity: 12.5% (95% CI 2.3 to 27.9) Specificity: 85.7% (95% CI 79.9 to 94.5) Positive predictive value: 33.3% (95% CI 6.1 to 74.4) Negative predictive value: 63.2% (95% CI 58.9 to 69.6) Agreement between tests (i.e. either both abnormal or both normal): 26/44 (59.1%).	Patients had no history of heart disease and no signs of cardiac failure. **Risk of bias** A. Selection bias: unclear Reason: not stated if all eligible patients or a random sample thereof were included. B. Index test bias: unclear Reason: not reported if outcome assessors were blinded. C. Reference test bias unclear Reason: nm if outcome assessors were blinded. D. Verification bias: unclear

	mg/m²; for Hodgkin lymphoma 120 to 240 mg/m²; patients with Hodgkin lymphoma received 15 Gy of radiotherapy to the upper mediastinum (no information on number of fractions).	not reported		Reason: time between biomarker and echo was not reported E. Attrition bias low risk Reason: all 44 patients had both tests.
^ Since echocardiography is most often used to assess cardiac function in clinical practice, we have chosen the echocardiographic results as reference standard ~ Calculated by the guideline developers based on information provided in the article (for the main outcomes we used the calculator on http://statpages.org/ctab2x2.html)				

WG2: What surveillance modality should be used?				
Sherief et al. Biomarkers and early detection of late onset anthracycline-induced cardiotoxicity in children, Hematology, 17:3, 151-156, 2012				
Study design Treatment era Years of follow-up	**Participants**	**Diagnostic tests**	**Main outcomes~**	**Additional remarks**
Study design Single-center cohort study (Egypt) Treatment era Not reported Mean years of follow-up not completely clear from manuscript, but most likely 3.75 years (range 1.5 to 6)	Type and number of Participants 50 survivors of childhood acute leukemia (n=39 ALL; n=11 AML) treated with anthracyclines. 30 males/20 females; Age at diagnosis mean 8.4 years (range 3 to 15) Age at study	Diagnostic test(s) **-Cardiac troponin T;** an abnormal test result was defined as **> 0.010 ng/ml (n=0; prevalence 0%).** **-NT-proBNP, age-dependent reference values defined by Albers 2006* (n=10; prevalence 20%)** Outcome definitions Conventional echocardiography (no	Diagnostic outcomes (sensitivity, specificity, PPV, NPV, ROC) When the echocardiographic result is used as the reference standard^: Sensitivity: cTnT: 0% (95% CI 0 to 0) NT-proBNP: data to calculate not provided Specificity: cTnT: 100% (95% CI 100 to 100) NT-proBNP: data to calculate not provided Positive predictive value: cTnT: NaN	At time of testing all survivors were asymptomatic (i.e. no signs and symptoms of cardiac impairment); patients with renal or hepatic impairment were excluded as were patients with a history of cardiac disease and hypertension. **Risk of bias** A. Selection bias: unclear Reason: not clear if these 50 patients were all eligible patients or a random sample thereof. B. Index test bias: unclear

	mean 11.63 years (range 8 to 16) <u>Cancer treatment</u> n=18 cumulative anthracycline dose <150-300 mg/m²; n=32 cumulative anthracycline dose > 300 mg/m² (but elsewhere in the manuscript n=19 < 300mg/m² and n=31 > 300 mg/m² was mentioned).	further information provided; number of observers not reported); an abnormal test result was defined as **LVEF < 55% or a LVSF < 29% (n=8 prevalence 16%).** <u>Time between tests</u> Not reported	NT-proBNP: data to calculate not provided Negative predictive value: cTnT: 84% (95% CI 84 to 84) NT-proBNP: data to calculate not provided Agreement between tests (i.e. either both abnormal or both normal) cTnT: 42/50 (84%). NT-proBNP: data to calculate not provided Higher NT-proBNP levels associated with worse FS, LVEDS, LVEDD, abnormal TDI and with higher anthracycline dose.	Reason: not reported if outcome assessors were blinded. <u>C. Reference test bias</u> unclear Reason: not reported if outcome assessors were blinded. <u>D. Verification bias</u>: unclear Reason: time between tests not reported <u>E. Attrition bias</u> low risk Reason: all 50 patients had both tests.

***** Albers S, Mir TS, Haddad M, Läer S. N-Terminal pro-brain natriuretic peptide: normal ranges in the pediatric population including method comparison and interlaboratory variability. *Clin Chem Lab Med*. 2006;44(1):80–5.

^ Since echocardiography is most often used to assess cardiac function in clinical practice, we have chosen the echocardiographic results as reference standard

~ Calculated by the guideline developers based on information provided in the article (for the main outcomes we used the calculator on http://statpages.org/ctab2x2.html)

WG2: What surveillance modality should be used?				
Mladosievicova et al. Role of NT-proBNP in detection of myocardial damage in childhood leukemia survivors treated with and without anthracyclines. *J Exp Clin Cancer Res* 31, 86, 2012				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**

Study design: Cross sectional study Treatment era: not reported. Outpatient clinic visit between January 2006 to October 2010 Follow-up: Median 11, range 5-22 years from therapy	Type and number of Participants 36 asymptomatic survivors of ALL (33 ALL survivors not treated with anthracyclines are not described in this table) 100% Anthracyclines, dose not reported, 0% chest-RT Age at diagnosis: Median 8 range, 1–17 years Age at follow-up: Median 22 range 18–31 years	Diagnostic test(s): -NT-proBNP, males >75 ng/L, females >105 ng/L (n=4, 11.1%) Outcome definitions Echo 2D LVEF <50% (n=0, 0%)	-None had LVEF<50% NT-proBNP to detect LVEF <50% on echo Sensitivity: NA Specificity: 89% (95% CI 89-89%) Positive predictive value: 0% (95% CI 0-0%) Negative predictive value: 100% (95% CI 100-100%) -NT-proBNP not correlated with LVEF (rho=0.15, p=0.42)	Patients with heart failure and renal failure were excluded. Risk of bias A. Selection bias: Unclear Reason: Underlying cohort not described, not stated if all patients who visited outpatient clinic were included. B. Index test bias: Unclear Reason: Blinding of investigators for reference standard was not reported. C. Reference test bias: Unclear Reason: Blinding of investigators for index test was not mentioned. D. Verification bias: Low risk Reason: tests on same day E. Attrition bias: Low risk Reason: All patients received the same index and reference test

WG2: What surveillance modality should be used?				
Armstrong et al. Screening adult survivors of childhood cancer for cardiomyopathy: comparison of echocardiography and cardiac magnetic resonance imaging. J Clin Oncol 30:2876-84, 2012				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Single-center cohort (USA) - St. Jude Lifetime Cohort Study (SJLIFE)	134 adult childhood cancer survivors (cancer diagnosed before age 21 years; 47 men / 67 women).	Anthracyclines or chest directed radiotherapy Diagnostic tests:	Screening performance of echocardiography compared with cardiac magnetic resonance imaging (reference standard) for detection of an LVEF<50%:	**Risk of bias** A. Selection bias: high risk Reason: convenient sample from 5 pilot studies in SJLIFE

Treatment era: Not reported Follow-up: Median 27.8 (18.4-38.3) years	Primary cancer diagnosis: ALL (n=44), Hodgkin's lymphoma (n=37), osteosarcoma (n=11), non-Hodgkin's lymphoma (n=8), AML (n=6), neuroblastoma (n=3), Ewing sarcoma (n=2). Wilms tumour (n=2) and soft tissue sarcoma (n=1). Age at primary cancer diagnosis: Median 11.3 (0.02-19.0) years Age at follow-up: Median 38.5 (22.7-53.7) years Genetic predisposition: NA	Cardiac magnetic resonance imaging (analysis was supervised and/or performed by a single investigator); an abnormal test result was defined as LVEF<50% (n=16; prevalence 14%). 3D as well as a 2D echocardiogram with Doppler and time-motion mode (M-mode) (analysis was performed by a single investigator); an abnormal test result was defined as LVEF<50% (n=22/prevalence 19.3% with 3D echocardiography; n=6/prevalence 5.3% with biplane 2D echocardiography; n=8/prevalence 7% with apical 4-Chamber 2D echocardiography and n=24/prevalence 21.1% with Teichholz 2D echocardiography). Time between tests: within a 48-hour period.	3D echocardiography: Sensitivity 53% Specificity 86% Positive predictive value 36% Negative predictive value 92% Biplane 2D echocardiography: Sensitivity 25% Specificity 98% Positive predictive value 67% Negative predictive value 89% Apical 4-Chamber 2D echocardiography: Sensitivity 25% Specificity 96% Positive predictive value 50% Negative predictive value 89% Teichholz 2D echocardiography: Sensitivity 29% Specificity 79% Positive predictive value 17% Negative predictive value 88% Poor correlation between CMR and echo LVEF Teichholz LVEF, r = 0.29; apical 4CH LVEF, r = 0.34; 2D biplane LVEF, r = 0.39; 3D LVEF, r = 0.37. Bland-Altman measures of agreement with cardiac magnetic resonance imaging:	B. Index test bias: low risk Reason: blinding of investigators C. Reference test bias low risk Reason: blinding of investigators D. Verification bias: low risk Reason: MRI and echo performed within 48 hours E. Attrition bias low risk Reason: 20 out of 134 survivors that agreed to participate (15%) cardiac magnetic resonance imaging could not be completed*), *however this is <25%.* Patients with an implanted medical device or a history of congenital heart disease were excluded. Of the 114 patients that completed the evaluation, 108 were previously undiagnosed with cardiomyopathy.

			For 3D echocardiography (bias, 1%; Bland-Altman limits of agreement [± 1.96 standard deviation], −11.8% to 14.0%); For 2D echocardiography: 2D biplane (bias, −5.2%; −19.0% to 8.69%), 2D apical 4-chamber (bias, −5.4%; −22.1% to 11.4%), Teichholz M-mode (bias, −3.1%; −28.3% to 22.1%).	

WG2: What surveillance modality should be used?				
Ylänen et al. Three-Dimensional Echocardiography and Cardiac Magnetic Resonance Imaging in the screening of Long-Term Survivors of Childhood Cancer after Cardiotoxic Therapy. Am J Cardiol 2014;113:1886-1892				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic Tests**	**Main outcomes**	**Additional remarks**
<u>Study design</u> Prospective, cross-sectional, single centre <u>Treatment era</u> Not specified, study performed Feb 2010-June 2011 <u>Follow-up</u> Median 7 (range 5-18) yrs	<u>Type and number of participants</u> 76 childhood cancer survivors treated >5 yrs ago 42 female/34 male, 5 excluded (4-Cardiomyopathy and 1-suboptimal acoustic window) 71 studied participants Group I-Anthracyclines only no RT: 63 participants. Group II-AC and RT: 8 participants.	-Conventional ECHO **FS<28% (prevalence 0%)** -real-time 3-dimensional echocardiography (RT-3DE) **3D LVEF <50% (prevalence 10%)** <u>Outcome</u> -cardiac magnetic resonance **(CMR)** in 58 patients **LVEF <55% 45/58 (78%)** **LVEF <50% 29/58 (50%)**	<u>Diagnostic values with CMR LVEF<55% as reference*</u> **3D LVEF <50% (95%CI)** Sensitivity 13.3% (7.3-13.3) Specificity 100% (79.2-100) PPV 100% (55.0-100) NPV 91.2% (80.4-96.3) Agreement 32.8% (23.5-32.8) **FS<28% (95%CI)** Sensitivity 0% (0-0) Specificity 100% (100-100) PPV NA NPV 22.4% (22.4-22.4) Agreement 22.4% (22.4-22.4)	Demonstrated the RT-3DE-derived LVEF to detect more abnormalities in the systolic LV function than M-mode. Better sensitivity of the RT-3DE and MRI over that of the 2-dimensional echocardiography **<u>Risk of bias</u>** <u>A. Selection bias:</u> Low risk 76 out of 86 (88%) eligible survivors of original cohort

	Controls 71 healthy volunteers as gender-, body surface area-, age-matched Gr. I: 63, Gr. II: 8 Diagnoses Gr.I: ALL 31 (49%), AML 3 (5%), Solid tumor 29 (46%) Gr.II: AML 6(75%), Solid Tu 2 (25%) Age at diagnosis Gr.I Median 4 (range 0-14) years Gr. II Median 5 (0-13) yrs Age at follow-up Gr.I 14 ±3 years Gr. II 13± 3 years Cancer Treatment: Anthracyclines All participants (71) Gr. I Cumulative dose median 218 (range 80-386) mg/m2 Gr. II Cumulative dose median 382 (range 163-454) mg/m2	LV volumes, ejection fraction (EF), and dyssynchrony indexes for the 16 and 12 cardiac segments (Tmsv16-SD and Tmsv12-SD)	Diagnostic definitions Systolic dysfunction: FS < 28% or RT-3DE LVEF < 50% or CMR-derived LVEF < 55% CMR performed in 58 participants; Gr. I 52 and Gr. II 2 participants. No CMR in both control groups Upper normal limits for dyssynchrony indexes derived from +2 SD of 71 healthy controls: Tmsv16-SD 2.26% and Tms12-SD 2.11% Proportion with outcome None of the survivors had an abnormal fractional shortening (<28%), but 10% had an LVEF <50% by RT-3DE. An LVEF <55% was detected in 45 of 58 (78%) of those imaged with CMR. Group I: median FS 33% ± 3%; median RT-3DE LVEF 57 ± 6%; median CMR LVEF 50% ± 6% Group II: median FS 33% ± 2%; median RT-3DE LVEF 56% ± 7%; median CMR LVEF 50% ± 6% 1 case-control pair excluded from dyssynchrony analysis due to stich artifact. **7/70 (10%) survivors with M-mode normal FS found to have abnormal LVEF by RT-3DE.** **3/70 (4%) had abnormally high Tmsv16-SD** **4/70 (6%) with high Tmsv12-SD (all with normal QRS-duration in ECHO)** In Linear regression analysis: **Tmsv16-SD was predictable with the RT-3DE LVEF (p<0.001) and Cardiac Irradiation (p=0.002) with adjusted R2 of 0.28**. FS derived by M-mode and LVEF by RT-3DE and CMR in 58 survivors (all had normal FS). **6/58 (10%) LVEF<50% by RT-3DE** **45/58 (78%) LVEF<55% by CMR (even with lower cut off <50% by CMR was found in 29/58 (50%).**	participated, 5 excluded. **CMR was performed in 58/71 participants (82%)** B Index test bias: unclear Reason: Blinding not mentioned. There was not a clear reference test however. C. Reference test bias: unclear Reason: Blinding not mentioned. There was not a clear reference test however. D. Verification bias: unclear intraobserver and interobserver variability was low. Not stated if CMR and echo were performed at same time **E.** Attrition bias: Low risk, same tests were used in all 58 participants who had CMR.

	Radiotherapy All 8 participants in Gr. II (11% of study participants) Average cumulative cardiac radiation dose 10 Gy (range 3.6-12.0) HSCT Allogenic Gr. I: 0 Gr. II: 6 (75%)		**LV end-diast and end-syst volumes were larger as measured by CMR then RT-3DE (89%±14 vs 73± 11ml/m2 and 44± 9 vs 31 ± 7ml/m2, p<0.001 for both)** Group I-larger LV end-sys dimensions and lowe FS than controls. RT-3DE LV end-syst volumes larger and LVEFs lower in survivors. RT-3DE LVEF<50% in 5/63 (8%) CMR LVEF<55% in 40/52 (77%) Group II- Lower FS and M-mode derived LV mass/volume ratio than controls. Dyssynchrony indexes were higher among survivors than controls. 2/8 (25%) had RT-3DE LVEF<50% 5/6 (83%) had CMR LEF<55% All dyssynchrony indexes higher in Gr.II than Gr. I: Tmsv16-SD (p = 0.003), Tmsv16-Dif (p = 0.005), Tmsv12-SD (p = 0.001), and Tmsv12-Dif (p = 0.001), Respectively **Correlations** between the RT-3DE and the CMR were for the LV end-diastolic (r = 0.880, p <0.001) and end-systolic volumes (r = 0.831, p <0.001) and LVEF (r = 0.189, p = 0.155). **Bland altman analysis 3D LVEF - CMR LVEF (from figure)** Mean difference: 7% (higher for CMR) Lower limit [-1.96 SD]: -9% Upper limit [+1.96 SD]: 21%	
*calculated with https://statpages.info/ctab2x2.html				

WG2: What surveillance modality should be used? WG3: At what frequency should surveillance be performed?					
Yeh et al. Routine Echocardiography Screening for Asymptomatic Left Ventricular Dysfunction in Childhood Cancer Survivors: A Model-Based Estimation of the Clinical and Economic Effects. Ann Intern Med. 2014;160:661-71.					
Study Design, Treatment Era, Years of follow-up	**Participants**	**Treatment**	**Diagnostic Tests**	**Main Outcomes**	**Additional Remarks**
Study Design: Simulation of life histories using Markov health states (no ALVD, ALVD, HF or death). Treatment Era: Not reported Years of Follow-up: Not reported. Model estimates lifetime risk.	Type and no. of participants: Childhood cancer survivors ≥ 5 years from cancer diagnosis (similar to CCSS) Diagnoses: Not reported Age at diagnosis: Median age = 10 yrs Age at follow-up: Not reported CV Risk Factors: Not reported	Anthracyclines: Not reported. Assumed that all patients received anthracyclines Radiation: Not reported Surgery: Not reported HSCT: Not reported Looked at 2 risk groups based on anthracycline dose < 250 or ≥ 250 mg/m2 Lifetime risk of ALVD = 22.6%; lifetime risk of HF = 18.8%; and lifetime risk of dying from HF = 11.1% Intervention:	1. 2D-Echo: -LVEF, % Assumed sensitivity = 25% and specificity = 99% compared to CMR 2. CMR -LVEF, %	Primary Outcome: Cost-effectiveness of screening for ALVD in childhood cancer survivors at intervals of 1, 2, 5 and 10 yrs: 1. For anthracycline exposure < 250 mg/m2 – no screening w/ echo was most cost-effective (ICER/QALY gained for every 10 yrs $104,400 exceeds cut-off value of $100,000) 2. For anthracycline ≥ 250 mg/m2 – screening every 2 years w/ echo was most cost-effective (ICER/QALY gained $ 83,600) CMR more cost -effective as a screening strategy than echo: -For anthracyclines < 250 mg/m2 – every 10 years (ICER/QALY gained $78,000) -For anthracyclines ≥ 250 mg/m2- every 5 years (ICER/QALY gained 89,800) Model conclusions tested with sensitivity analyses looking at:	**Risk of bias** Model is limited by multiple assumptions: 1. Accuracy of echo to detect ALVD 2. Sensitivity of echo is constant, regardless of EF 3. Effectiveness of ACEi/BB to prevent progression to HF in pts with ALVD 4. Adherence to screening schedule 5. Adherence to ACEi/BB 6. Rate of progression to HF is same as that in adult pts 7. Rate of progression to HF is constant after age 30 yrs. in childhood survivors 8. Rate of dying from HF does not take into account modern therapies for HF such as ARNIs etc. 9. Excludes the possibility of developing HF from restrictive cardiomyopathy w/o developing ALVD first. 10. Does not take added risk of RT into account when assessing risk of ALVD Selection bias: Low risk

		ACEi and BB upon detection of ALVD (assumed efficacy = 36% and adherence = 100%)		Gender; age at cancer diagnosis; efficacy of ACEi and BB; time to progression to CHF; absolute excess risk of CHF; CHF death risk; cost of diagnostic tests, medicine, and clinical care; disutility of ACEi/BB due to adverse effects. -model affected most by efficacy of ACEi/BB, AER of HF in childhood cancer survivors and time to progression to CHF.	Reason: model simulated CCSS pts Attrition bias: Low risk Reason: Model assumes that all patients will have echocardiograms performed throughout their lifetime. Detection bias: High risk Reason: CCSS investigators were not blinded Confounding: Low risk Reason: effects measures from CCSS were adjusted in MV analysis

WG2: What surveillance modality should be used? WG3: At what frequency should surveillance be performed?					
Wong et al. Cost-Effectiveness of the Children's Oncology Group Long-Term Follow-up Screening Guidelines for Childhood Cancer Survivors at Risk for Treatment-Related Heart Failure. Ann Intern Med. 2014;160:672-83.					
Study Design, Treatment Era, Years of follow-up	**Participants**	**Treatment**	**Diagnostic Tests**	**Main Outcomes**	**Additional Remarks**
Study Design: Simulation of life histories using Markov health states (no ALVD, ALVD, HF or death). Treatment Era: 1970-1986 Years of Follow-up: Median f/u: 20 yrs within CCSS.	Type and no. of participants: N=4635 childhood cancer survivors ≥ 5 yrs from cancer diagnosis Diagnoses: As in CCSS but not specifically reported for the anthracycline treated subset included in this study	Anthracyclines: N=4635, median dose = 292.8 mg/m2 Radiation: N=1020 (22%) Surgery: Not reported HSCT: Not reported	1. 2D-Echo: -LVEF, % Assumed sensitivity = 75% and specificity = 90% compared to MUGA 2. CMR -LVEF, % (to confirm echo findings)	Primary Outcome: Cost-effectiveness of COG guidelines for ALVD screening in childhood cancer survivors: COG Guidelines: 1. Increased life expectancy by 6.1 mths 2. Increased QALY by 1.6 mths 3. Reduced HF risk at 30 ys after cancer by 18%	Model is limited by multiple assumptions: 1. Accuracy of echo to detect ALVD 2. Effectiveness of ACEi/BB to prevent progression to HF in pts with ALVD 3. Adherence to screening schedule 4. Adherence to ACEi/BB 5. Rate of progression to HF is same as that in adult pts

Model estimates lifetime risk	Age at diagnosis: Median age = 7 yrs (range 0-20 yrs) Age at follow-up: Not reported CV Risk Factors: Not reported	Looked at 12 risk profile groups based on age at diagnosis, dose of anthracyclines, and exposure to chest radiation Median prevalence of ALVD =13.3-14.2% (range 2.6-39.2%) Median prevalence of HF is 1/3 ALVD Intervention: ACEi and BB upon detection of ALVD (assumed efficacy = 30% and adherence = 76%)		4. ICER/QALY gained is $61,500 Increasing screening intervals from 1 to 2 yrs, 2 to 5 yrs, and 5 to 10 yrs retained 80% benefit with half the cost (ICER $33,200) Model conclusions tested with sensitivity analyses looking at: ALVD treatment efficacy and duration of efficacy; accuracy of echo; medication adherence rate; the cumulative incidence of HF at 20 years after cancer diagnosis; utilities for HF; discount rates; and echocardiographic screening cost. -ALVD treatment efficacy influenced the model most.	6. Rate of progression to HF is constant after age 30 yrs. in childhood survivors 7. Rate of dying from HF does not take into account modern therapies for HF such as ARNIs etc. **Risk of bias** Selection bias: Low risk Reason: model included all anthracycline treated CCSS pts Attrition bias: Low risk Reason: Model assumes that all patients will have echocardiograms performed throughout their lifetime. Detection bias: High risk Reason: CCSS investigators were not blinded Confounding: Low risk Reason: effects measures from CCSS were adjusted in MV analysis

WG2: What surveillance modality should be used?

Shah et al. Medium-term assessment of cardiac function in pediatric cancer survivors. Comparison of different echocardiographic methods, cardiac MRI and cardiac biomarker testing in adolescent cancer survivors. *Echocardiography 2017;34:250–256*

Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**
Study design Observational (cross-sectional) Treatment era Recruitment: Not stated - 2015 (extrapolated from submission date of 29 July 2016) Date of diagnosis: 1992-2009 (calculated from range of years off therapy minus submission date) Follow-up Years off therapy: median [range] 10.8y (5-21.6)	Type and number of participants 50 consecutive asymptomatic patients ≥10y attending Children's Mercy Hospital paediatric and young adult cancer survivorship program, treated with chemotherapy and/or radiation for childhood malignancies and had completed treatment more than 2 years prior to their upcoming clinic visit. All who were approached consented to the study. Exclusions: Age <10y, Pacemaker, Claustrophobia **Characteristics of the participants** (n=50) number (percentage) Male gender 25 (50%) Blood cancer 33 (66%) High anthracycline dose ≥300 mg/m2 10 (20%) Radiation therapy 19 (38%) Bone marrow transplant 7 (14%) median (range)	Diagnostic test(s) **Echocardiography:** 2D and 3D with volumetric measurements of end-diastolic volume, end-systolic volume, and EF were performed offline using the bullet method. **Cardiac MRI:** 1.5T with 16-channel phased array cardiac coil. **Biomarkers:** N-terminal pro-B-type brain natriuretic peptide (NT-proBNP) and troponin-I Outcome definitions EF of <53% was considered abnormal	Diagnostic outcomes (sensitivity, specificity, PPV, NPV, ROC) **Cardiac MRI:** Successfully performed in all 50 subjects (but the number excluded (age <10y pacemaker or claustrophobia) is not stated. 4 asymptomatic male subjects (8% of total) had mild LV dysfunction (cardiac MRI-measured LV EF of 51-52%). They had been in remission for a median duration of 10 years, 3 were ≤4 years of age, and one subject was age 6 at diagnosis. 5 other patients had LVEF 53-54% **Echocardiography:** M-mode and 2D echo were successfully performed in all 50 subjects. 4 subjects were said to have poor image quality on 2D echo but their results were used in the calculation of end-systolic volume, end-diastolic volume and LVEF (Table 2a). 3D was successfully performed in 46 of 50 subjects. Of the 4 patients with LVEF <53% on cardiac MRI, the number correctly classified as abnormal by echo was: M-mode – 0 (sensitivity 0; specificity 97.8, PPV 0, NPV 91.8) 2D echo – 0 (sensitivity 0; specificity 91.3, PPV 0, NPV 91.3) 3D echo – 1 (sensitivity 25; specificity 90.7, PPV 50, NPV 93.2 All – 1 (sensitivity 25; specificity 97.6, PPV 20, NPV 92.9) Of the 9 patients with LVEF <55% on cardiac MRI, the number correctly classified as abnormal by echo was: M-mode – 1 2D echo – 2 3D echo – 3	The paper defines cardiac MRI as the gold standard test for detection of left ventricular systolic dysfunction defined as LVEF <53%. It shows LVEF calculated by M-mode, 2D and 3D echo to have low sensitivity in this patient group. NT-proBNP and troponin-I were not correlated with LVEF. **Risk of bias** A. Selection bias: Low risk Reason: 50 consecutive patients approached and all consented to take part B. Index test bias: Unclear Reason: Blinding is not stated. It is also unclear whether the echocardiographer was aware of previous echo reports. C. Reference test bias Unclear Reason: Blinding is not stated. It is also unclear whether the MRI

	Age at diagnosis 3y (0.4-16) Years off of therapy 10.8 (5-21.6) Cumulative anthracycline dose (mg/m^2) 175 (75-450) LVEF% by MRI 58.1 (51-67) RVEF% by MRI 58 (47-70) E'/E-wave velocity ratio 5.5 (3.3-9.9) Left ventricular mass index to BSA (gm/m^2) 59.4 (40.4-92.6)		All – 4 (3D did not identify a patient identified by M-mode and/or 2D) The significance of this is unclear, as these are different imaging modalities with different reference ranges. <u>Bland altman analysis CMR - echocardiography</u> M mode LVEF – CMR LVEF: mean 5.5%, SD=6.3, SE=0.89 2D LVEF – CMR LVEF: mean 1.8%, SD=5.5, SE=0.78 3D LVEF – CMR LVEF: mean 1.9%, SD=5.3, SE=0.78 <u>Correlations CMR - echocardiography</u> M mode LVEF – CMR LVEF: 0.17, P=0.265 2D LVEF – CMR LVEF: 0.44, p=0.001 3D LVEF – CMR LVEF: 0.24, p=0.12 **Biomarkers:** <u>1 patient with elevated NT-proBNP >300 ng/L had normal LVEF on CMR (LVEF>=53%)</u> Sensitivity: 0% (95%CI 0-23) Specificity: 98% (95%CI 98-100) Positive predictive value: 0% (NA) Negative predictive value: 92% (95%CI 92-94) <u>1 other patient with elevated troponin I >0.03 ng/mL had normal LVEF on CMR (LVEF>=53%)</u> Sensitivity: 0% (95%CI 0-23) Specificity: 98% (95%CI 98-100) Positive predictive value: 0% (NA) Negative predictive value: 92% (95%CI 92-94)	radiographer was aware of previous MRI or echo reports. <u>D. Verification bias</u>: Low risk Reason: Cardiac MRI, echo and blood biomarkers were obtained on the same day <u>E. Attrition bias</u> - Low risk Reason: All of the study group received the same tests.

WG2: What surveillance modality should be used?
Ylänen et al. Cardiac biomarkers indicate a need for sensitive cardiac imaging among long-term childhood cancer survivors exposed to anthracyclines. Acta paediatrica 2015 104, pp. 313–319

Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**
Study design: cross sectional study Treatment era: not reported Examinations: February 2010 - June 2011. Follow-up: Time from end of primary therapy (years) median 7.1 (range 5.0–18.0) Time from diagnosis, median 9.0 (range 5.4-18.4) years	Type and number of Participants: 76 >5-year survivors of childhood cancer 34 males (45%) Age at diagnosis: Median 3.8 (range 0.0–13.8) years Age at follow-up: Median 14.3 (7.2–20.0) years Cancer treatment: 100% anthracyclines Cumulative anthracycline dose (mg/m2) 224 (80–454) Chest RT: 10 (13%) Cancer types Leukaemia 42 (55) Solid tumour 34 (45) Relapse 6 (8) Allogeneic stem cell transplantation 7 (9) Cardiac irradiation 10 (13)	Diagnostic test(s): -NT-proBNP (n=76), cut-off for abnormal <63 ng/L for males and <116 ng/L for females. Children: Nir 2009* -cTnT (n=76), cut-off 0.03 ng/mL -high-sensitivity cTnT (n=76), cut-off 0.014 ng/mL -cTnI (n=75), cut-off 0.0095 ng/mL -cTnAAbs (n=75), cut-off 100 counts or higher Outcome definitions -**FS <28% in 2/76 (2.6%)** -**3D LVEF <50% in 10/75 (13.3%)** -**MRI LVEF <55% or LVED or LVES volumes >2SD from normal in 49/62 (79%)**	Results Of the survivors, four (5.3%) without risk factors for cardiotoxicity were cTnAAb positive with an impaired cardiac function in MRI. Another four (5.3%) had an abnormal NT-proBNP level associated with an abnormal cardiac function and risk factors for cardiotoxicity. None showed measurable cardiac troponins, determined by the three different methods, with even the high-sensitivity cTnT-levels remaining normal. Diagnostic outcomes (sensitivity, specificity, PPV, NPV, ROC)~ **NT-proBNP to detect 3D LVEF<50% on echo** Sensitivity: 20% (95% CI 4-56) Specificity: 97% (95%CI 88-99) Positive predictive value: 50% (95%CI 9-91) Negative predictive value: 89% (95%CI 78-95) **NT-proBNP to detect LVEF<55% on MRI (in n=62)** Sensitivity: 8.2% (95%CI 3.4-8.2) Specificity: 100% (95%CI 82.1-100) Positive predictive value: 100% (95%CI 41.7-100)	4 patients on cardiac medication for anthracycline cardiotoxicity A. Selection bias: Low risk Reason: All consecutive survivors who visited the outpatient clinic were included. Underlying cohort not described B. Index test bias: Unclear Reason: Blinding of investigators not mentioned C. Reference test bias: Unclear Reason: Blinding of investigators and sonographers for biomarker measurements not mentioned D. Verification bias: Low risk Reason: Biomarkers and echo was performed at the same visit. E. Attrition bias: Low risk for echo. High risk for MRI outcomes Reason: Echo was performed in all patients MRI only in 62 patients.

			Negative predictive value: 22.4% (95%CI 18.4-22.2) **Troponins to detect 3D LVEF<50% on echo** -cTnT, hs-cTnT, troponin I were normal in all -none of 4 with abnormal autoantibodies to troponin T had 3D LVEF <50%.	

*Nir A, Lindinger A, Rauh M, et al. NT-pro-B-type natriuretic peptide in infants and children: reference values based on combined data from four studies. *Pediatr Cardiol*. 2009;30(1):3-8. doi:10.1007/s00246-008-9258-4

~Adopted from Leerink et al 2019 (3D LVEF) or calculated using https://statpages.info/ctab2x2.html.

WG2: What surveillance modality should be used?

Pourier et al. Values of high-sensitive troponin T in long-term survivors of childhood cancer treated with anthracyclines. Clinica Chimica Acta 441 (2015) 29–32

Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**
Study design: Cross sectional study Treatment era: not reported Follow-up: median 8.3 (range 4.5–34.1) years Study conducted between February 2012 and September 2012	Type and number of Participants 64 survivors without heart failure symptoms, 38 Male (59%) Age at diagnosis: median 5.8 (range 0.3–17.3) Age at follow-up: median 16.7 (range 7.2–39.8)	Diagnostic test(s): High sensitive troponin T (Hs-cTnT), cut-off for abnormal 0.0135 ng/mL N-terminal-pro-brain natriuretic peptide (NT-pro-BNP). Cut-off: above sex and age adjusted normal values (adults: Fradley et al; children: Nir et al) 2. Outcome definitions	Prevalence of LV dysfunction echo -Mean left ventricular shortening fraction (SF) was 34% (range 28 to 43%) -Mean ejection fraction (EF) was 61% (range of 48 to 74%). -Seven survivors had a mildly decreased EF between 48% and 55% (10.9%) Prevalence of abnormal biomarkers hs-cTnT: -0/64 abnormal (0%)	Patients with heart failure symptoms were excluded. Risk of bias A. Selection bias: Low risk Reason: 67/75 survivors who visited between feb 2012 and sep 2012 were included. Underlying cohort not described. B. Index test bias: Unclear risk Reason: Blinding of investigators for reference standard was not reported.

	Cancer treatment: Median anthracycline dose 225 (range 85–450) mg/m2 Cancer types ALL: 24, AML:1, Anaplastic T Cell lymphoma: 1, Burkitt lymphoma: 2, Cystadenofibromatosis pancreas: 1, Rhabdomyosarcoma: 2, Ewing sarcoma: 6, Hepatoblstoma: 1, Hodgkin: 8, Neuroblastoma: 4, NHL: 3, osteosarcoma: 1 PNET: 1, Wilms tumor:8, Yolk Salk tumor:1 Prevalence/risk of late effect Described under outcomes	LV dysfunction on 2D echocardiogram (biplane ejection fraction (EF) <55%)	-Values did not differ among different anthracycline dosage groups: ≤120, 120–300 and ≥300 mg/m2. NT-proBNP -5/64 (7.8%) abnormal. -Only 1 also had mild LV dysfunction (EF 51%). **Diagnostic values of NT-proBNP to detect LVEF<55% on echo (adopted from Leerink et al 2019)** Sensitivity: 14% (95%CI 1-58) Specificity: 93% (95%CI 83-98) Positive predictive value: 20% (95%CI 1-70) Negative predictive value: 90% (95%CI 79-96)	C. Reference test bias: Unclear risk Reason: Blinding of investigators for index test was not mentioned. D. Verification bias: Low risk Reason: time interval between biomarker and echo was not mentioned but the study was conducted within a one-year time period (feb 2012 – sep 2012). E. Attrition bias: Low risk Reason: All patients received the same index and reference test

WG2: What surveillance modality should be used?				
Leerink et al. Biomarkers to diagnose ventricular dysfunction in childhood cancer survivors: a systematic review. Heart, 2019				
Study design Treatment era Years of follow-up	**Participants**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**
Study design Systematic review	Type and number of Participants	Diagnostic test(s) Blood biomarkers -NT-proBNP	**NT-proBNP studies (n=5, 575 patients, 61 LV dysfunction)** Variable cut-offs for abnormal (range 63 ng/L for males/116 ng/L for females to 125 ng/L for	-3 studies did not exclude symptomatic patients and patients on heart failure medication and

Eligibility criteria -childhood cancer diagnosis <= 21 years -treated with anthracyclines ->1 year after treatment -biomarker and echo not more than 1 month apart -LV dysfunction defined by EF or FS cut-off Treatment era Not reported Follow-up since anthracyclines Median in studies ranged from 0.9-18.2 years	8 studies (691 survivors) included Age at diagnosis Median in studies 3.8-8.8 years Age at follow-up Median in studies 9.1-27.5 years Range all studies 3-48 years Cancer treatment Median anthracycline dose in studies 165-480 mg/m2 Prevalence/risk of LV dysfunction Range in studies 0-36.8%	-BNP -Troponins -Cut-off for abnormal as defined by the authors of each study Outcome definitions LV systolic dysfunction defined as an **EF <50% or <55% and/or a FS <28%, <29% or <30%** measured with echocardiography.	males and females). Other studies used age and sex specific cut-offs. Diagnostic accuracy in 4 studies (n=539) Sensitivity range 14-22% Specificity range 88-97% PPV range 13-50% NPV range 65-90% No meta-analysis due to heterogeneity in patient characteristics and biomarker/echo cut-offs **Troponins** 5 studies, 423 patients, 128 with LV dysfunction Only 1 of the 5 patients with abnormal troponin had LV dysfunction (troponin T >0.01 ng/mL) Diagnostic accuracy could be calculated for 1 study (Kismet 2004). In other studies, no patients with LV dysfunction AND abnormal troponin were present. Kismet 2004: Sensitivity 50% (95% CI 3-97%) Specificity 91% (69-98%) PPV 33.3% (2-87%) NPV 95% (74-99%) **BNP** 1 study, 63 patients. Higher BNP values were present in CCS with a FS <29% compared with CCS with a FS >29% (32.4±34.9 vs 15.6 ±	one study excluded patients with CAD <400 mg/m2 -3 studies did not report biomarker cut-offs for abnormal impairing the calculation of diagnostic accuracies **Risk of bias** A. Selection bias: Low risk Reason: study cohorts were representative of the population of interest. However, most survivors were <30 years old. B. Index test bias: Unclear Reason: blinding of investigators who performed the echo for the biomarker values was not reported in the included studies C. Reference test bias: Unclear Reason: blinding of investigators who performed the echo for the biomarker values was not reported in the included studies D. Verification bias: Low risk Reason: <1 month between biomarker and echo in all studies E. Attrition bias: Low risk Reason: within each study all patients received the same reference standard. However, between studies LV dysfunction

			12.4pg/mL, p<0.008) but no cut-off values or contingency tables were provided.	cut-offs varied (EF<50 or <55% or FS <28%, <29% or <30%)

WG2: What surveillance modality should be used?				
Corella Aznar et al. Use of speckle tracking in the evaluation of late subclinical myocardial damage in survivors of childhood acute leukaemia. The International Journal of Cardiovascular Imaging (2018) 34:1373–1381. https://doi.org/10.1007/s10554-018-1346-9				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**
Study design Cross-sectional, retrospective study Treatment era 1991-2006 Follow-up Mean 16.97 ± 4.04 years	Type and number of Participants 57 asymptomatic survivors of childhood leukaemia diagnosed > 10 yrs. ALL 52(91.2%), AML 5 (8.8%) Low tumor risk- 40 (70.2%) High tumor risk-17 (29.8%) Age at diagnosis <1 year: 2 (3.5% 1-5 yrs: 30 (54.1%) > 5 years: 25 (55.9%) Age at follow-up 22.56 ± 3.76 years Cancer treatment Anthracycline ≤ 250 mg/m2- 39 (68.4%) ≥ 250 mg/m2- 18 (3.6%)	Diagnostic test(s) -Two-dimensional echocardiography, tissue Doppler,longitudinal/ circumferential strain* -**troponin-T and NT-ProBNP, no normal values reported** Outcome definitions **Lower limits of EF<52% in males and EF< 54% in females (by M-mode and biplane Simpson's)** Lower limits of global longitudinal strain (GLS) of < 16.9% in males and < 18.5% in females	Diagnostic outcomes (sensitivity, specificity, PPV, NPV, ROC) **Biomarkers as predictors of myocardial damage** **-Troponin levels; all within the normal range (normal cut-off not reported)** **-Higher NT-Pro BNP associated with lower EF (r = –0.49, p < 0.05) and GLS (R = 0.61, p < 0.05). - -NT-proBNP: Only 2 had values above normal, with a sensitivity of 100% and specificity of 81.4% (normal biomarker cut-off not reported)** LV Function -5.2% had reduction of EF ≥ 10%, with EF ≤ 53% since diagnosis (M-mode), -7% had EF values below normal (biplane Simpson's method), -10.5% had Tei index > 0.5. -LVEF reduction since diagnosis until the evaluation was significant (from 69.26 ± 5.9% to 58.8 ± 6.8%; p = 0.00). -Abnormal GLS 21.05% -Abnormal GCS 8.8% **-Only 4 patients with altered GLS had a reduced EF.** Strain comparison with 2-D and tissue Doppler ECHO	Diagnostic values for NT-proBNP to detect LV dysfunction (LVEF<52 males or <54 females) are high but biomarker cut-off for abnormal was not mentioned **Risk of bias** Selection bias: High risk From 84 survivors, 57 eligible Index test bias: Unclear Reason: blinding of sonographers and investigators for biomarker levels was not mentioned Reference test bias: Unclear Blinding of sonographers and

	RT: 14 (24.6%) No RT: 43 (75.4%) HSCT: 10 (17.5%) <u>Prevalence/risk of late effect</u> Abdominal obesity- 11 (20.3%) Hypertriglyceridemia- 6 (11.1%) Low HDL- 10 (18.5%) Hypertension- 9 (16.7%) Hypergycemia- 1 (1.8%)	Lower limits of global circumferential strain (GCS) of <15.4% Biochemical markers: Myocardial function: Troponin-T, NT-pro-BNP. Cardiovascular risk factors: glucose, total cholesterol, HDL-c, LDL-c and triglycerides.	The decrease in myocardial longitudinal deformation was correlated with lower values of LV systolic function: EF (r = 0.82; R2 = 0.68), M-mode EF (r = 0.54; R2 = 0.34) and fractional shortening (FS) (r = 0.58; R2 = 0.41), excursion of the mitral annulus (r = 0.46; R2 = 0.3), S-wave velocity (r = 0.62; R2 = 0.53), and increase in the Tei index (r = − 0.71; R2 = 0.6). The decrease in the GCS was correlated with lower E-wave velocity (r = 0.51), higher Tei index (r = − 0.62), and isovolumetric relaxation time (r = − 0.46) and with decreased EF and FS ($p < 0.05$). <u>Risk factors associated with subclinical myocardial dysfunction by 2-D strain</u> Patients with high-risk leukaemia treated with RT or high doses of anthracyclines (≥ 250 mg/m2) had a higher risk of GLS alteration (OR 13.8, 7.6, and 7.19, $p < 0.05$) There was a linear correlation between doses of anthracyclines and the decrease of GLS (r = 0.68; $p < 0.05$). The strain and overall longitudinal strain rate were lower in those exposed to high doses than those receiving doses < 250 mg/m2 (|16.43 ± 1.9| vs. |22.23 ± 4.14|, $p < 0.05$ and |1.09 ± 0.3| vs. |1.33 ± 0.41|, $p < 0.05$). Prevalence of higher altered GLS in those receiving high doses of anthracyclines (43.7 vs. 12.9%, $p < 0.05$). No differences were found in strain and GCS rate (|20.73 ± 6.38| vs. |23.55 ± 4|, $p > 0.05$). There was no age difference between survivors with abnormal GLS and those who not (23.1 ± 4.5 vs. 22.6 ± 3.6 years, $p > 0.005$).	investigators for biomarker levels was not mentioned <u>Verification bias</u>: Unclear Not mentioned if biomarker and echo was performed at the same time. <u>Attrition bias</u>: Low risk All patients received the same tests

			Survivors with metabolic syndrome (14.8%) had increased risk of abnormal GLS (RR 3.28; 95% IC 1.24–8.68); obese (RR 3.26; 95% IC 1.21–8.7), with reduced HDL (RR 3.67; 95% IC 1.35–9.65) and hypertriglyceridemia (RR 4.57; 95% IC 1.88–11.1). In multivariable logistic regression, the risk of presenting altered GLS was increased in those treated with cumulative anthracyclines doses ≥ 250 mg/m2 (ORa 10.6; 95% CI 1.64–100.1; p = 0.017).	
*Normal values according to ASE: Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernade L et al (2015) Recommendations for cardiac chamber quantification by echocardiography and the european Association of Cardiovasular Imaging. Eur Heart J Cardiovasc Imaging 16:233–271				

WG2: What surveillance modality should be used?				
Hayakawa et al. Plasma levels of natriuretic peptides in relation to doxorubicin-induced cardiotoxicity and cardiac function in children with cancer. Med Pediatr Oncol. 2001 Jul;37(1):4-9. doi: 10.1002/mpo.1155. PMID: 11466716.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic tests**	**Main outcomes~**	**Additional remarks**
Study design Single-center cohort study/cross-sectional study at time of first echocardiogram after treatment (Japan). Treatment era January 1994 to January 1999. Years of follow-up after last	Type and number of Participants 34 childhood cancer patients (no further information on diagnoses provided) treated with anthracyclines who continued to be in complete remission. 18 males/ 16 females. Age at diagnosis Not reported	Diagnostic test(s) ANP and BNP; an abnormal test result was defined as **ANP > 26 pg/ml and BNP > 13 pg/ml** (i.e. > mean + 2 SD of 19 healthy controls) **(n=6; prevalence 17.6%*).** Outcome definitions Pulsed wave doppler and M-mode echocardiography (number of observers nm); an abnormal test	Diagnostic outcomes (sensitivity, specificity, PPV, NPV, ROC) When the echocardiographic result is used as the reference standard*^: Sensitivity: 62.5% (95% CI 30.6 to 74.3) Specificity: 96.2% (95% CI 86.3 to 99.8) Positive predictive value: 83.3% (95% CI 40.8 to 99.1)	Patients who received mediastinal radiotherapy, developed congestive heart failure or had other illness such as infection were excluded. **Risk of bias** A. Selection bias: low risk Reason: all 34 eligible patients were included. B. Index test bias: unclear Reason: nm if outcome assessors were blinded.

anthracycline dose: at least 1 month.	Mean age at study 11.5 years (range 0.7 to 21.7). Treatment Mean cumulative doxorubicin dose 315 mg/m²; median 314 mg/m² (range 42 to 696).	result was defined as **LVEF <60% or LVSF <30% and if abnormal regional wall motion such as dyskinesis, hypokynesis or akinesis was detected (n=8; prevalence 23.5%).** Time between tests All tests were performed at the same time.	Negative predictive value: 89.3% (95% CI 80.2 to 92.7) Agreement between tests (i.e. either both abnormal or both normal): 30/34 (88.2%).	C. Reference test bias unclear Reason: nm if outcome assessors were blinded. D. Verification bias: low risk Reason: tests performed at the same time E. Attrition bias low risk Reason: all 34 patients had both tests
^ Since echocardiography is most often used to assess cardiac function in clinical practice, we have chosen the echocardiographic results as reference standard ~ Calculated by the guideline developers based on information provided in the article (for the main outcomes we used the calculator on http://statpages.org/ctab2x2.html)				

WG2: What surveillance modality should be used?				
Dixon et al. Cardiac biomarkers and association with subsequent cardiomyopathy and mortality among adult survivors of childhood cancer: A report from the St. Jude Lifetime Cohort. Cancer 2020				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**
Study design: Prospective cohort study with cross sectional biomarker assessment and follow-up for cardiac events/mortality Treatment era: 1962-2007	Type and number of Participants 1213 adults >10 year from childhood cancer. Excluded: congenital heart disease, chronic kidney disease (eGFR <60). **Previous cardiomyopathy (CTCAE grade >=2) in 8.6%**	Diagnostic test(s): NT-proBNP: sex and age normal values* (n=273, 22.5%) -Troponin T (cTnT) >0.01 ng/mL (n=5, 0.4%) Outcome definitions -Echo 3D LVEF<53% (n=171, 16.4%)	Diagnostic values -Patients with grade 3-4 (symptomatic) cardiomyopathy were excluded for calculation of diagnostic values **Troponin T** 2/5 with abnormal cTNT had echo LVEF<53% **NT-proBNP to detect 3D LVEF <53% on echo** Sensitivity: 23% (95%CI 17-29)	Patients with heart failure symptoms were excluded. Risk of bias A. Selection bias: Low risk Reason: 88.6% of original cohort was included

Follow-up: At biomarker evaluation 26.4 (IQR 19.9-33.8) years	**Coronary artery disease in 6.9%** Age at diagnosis: 8.7 (IQR 3.7-14.3) years CV risk factors Diabetes 9.9%, Hypertension 28.5%, Dyslipidemia 14.8% Age at follow-up: At biomarker assessment median 35.5 (IQR 29.8-42.5) Cancer treatment: 786 exposed to anthracyclines/chest RT Anthracycline median dose 204 mg/m2 (IQR 152-342) Chest RT dose 1-19.9 Gray 5.4%, 20-29.9 17.1%, 30+ 12% Cancer types ALL 21.2%, AML 3.1%, other leukemia 0.9%, Hodgkin 19.6%, Non-Hodgkin 4.8%, CNS 14.6%, Wilms 7.5%, Retinoblastoma 3.7%, Soft tiss sarc 5.3%, Neuroblastoma 4.9%,	-Echo GLS >2SD above sex, age and vendor specific means***(n=425, 39.8%) -Diastolic dysfunction according to ASE** (n=222, 22.1%) -Cardiac events: (CTCAE 2-4). -Cardiac mortality: ICD 9-10 or review of death certificates	Specificity: 82% (95%CI 80-85) Positive predictive value: 20% (15-26%) Negative predictive value: 85% (82-87%) **NT-proBNP to detect abnormal GLS on echo** Sensitivity: 22% (95%CI 18-26) Specificity: 83% (95%CI 80-86) Positive predictive value: 47% (95%CI 40-54) Negative predictive value: 62% (95%CI 59-65) **NT-proBNP to detect diastolic dysfunction on echo** Sensitivity: 26% (95%CI 20-32) Specificity: 84% (95%CI 81-86) Positive predictive value: 31% (95%CI 24-38) Negative predictive value: 80% (95%CI 77-83) -Comparable results in an analysis limited to survivors exposed to cardiotoxic treatments Association of treatment exposures with abnormal NT-proBNP in multivariable model -Age at diagnosis <5 years vs 15-20.9 RR 1.56 (1.14-2.14) -Attained age >40 vs 18-30 RR 1.10 (0.84-1.42) -Non-hispanic white vs other RR 1.18 (0.88-1.58) -Male vs female RR 1.28 (1.05-1.57) -Anthracycline dose (0mg/m2=ref) 1-200 RR 1.39 (1.01-1.91) 201-350 RR 2.28 (1.74-2.99) >350 RR 2.99 (2.27-3.95) -Chest RT dose (0 Gray=ref) 1-19.9 RR 1.62 (1.07-2.46)	B. Index test bias: Low risk Reason: Echocardiograms were obtained in blinded manner C. Reference test bias: Low risk Reason: Echocardiograms were obtained in blinded manner D. Verification bias: Low risk Reason: Biomarkers and echo were performed at the same baseline evaluation E. Attrition bias: Low risk Reason: Outcomes were assessed in all participants.

	Osteosarc 5.0%, Ewing sarcoma 4.1%, other 5.4%.		20-29.9 RR 1.68 (1.23-2.30) >=30 RR 3.66 (2.89-4.64) <u>Association of CV risk factors and previous CMP with abnormal NT-proBNP in multivariable model</u> Adjusted for Sex, race, Age at diagnosis, current age -Diabetes yes/no RR 1.04 (0.73-1.41) -Hypertension yes/no RR 1.06 (0.82-1.36) -Dyslipidemia yes/no RR 1.02 (0.76-1.36) -BMI (18.5-24.9=reference) <18.5 RR 1.43 (1.02-2.00) 25-29.9 RR 0.61 (0.48-0.78) >=30 RR 0.57 (0.44-0.75) -Cardiomyopathy (no=ref) Grade 2 RR 1.41 (1.02-1.94) Grade 3 RR 2.59 (1.93-3.47) Grade 4 RR 3.05 (1.94-4.80) -Coronary artery disease (no=ref) Grade 2-3 RR 1.54 (1.13-2.09) <u>Predictive value of NT-proBNP among survivors without cardiomyopathy and normal LVEF at baseline using poisson regression.</u> 132 (24.7%) had abnormal NT-proBNP Median FU 5.4 years, 72 cardiac events, 52 CMP, 15 deaths (4 cardiac) Cardiac mortality higher in abnormal NT-proBNP group (rate/1000 person years 2.93 vs 0.96, p<0.0001) Any cardiac event rate 35.76 vs 24.56, p<0.0001 Cardiomyopathy rate 32.10 vs 15.98, P<0.0001	

			Adjusted HR of abnormal NT-proBNP for cardiac events using Cox regression adjusted for age at diagnosis, attained age, sex, race, BMI and CV risk factors **Any cardiac event HR 1.75 (1.04-2.94)** **Cardiomyopathy HR 2.28 (1.28-4.08)** Cardiac mortality HR 3.31 (0.32-34.59) ns	

*Fradley MG, Larson MG, Cheng S, et al. Reference limits for N-terminal-pro-B-type natriuretic peptide in healthy individuals (from the Framingham Heart Study). *Am J Cardiol*. 2011

**Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:1321-1360.

***Takigiku K, Takeuchi M, Izumi C, et al. Normal range of left ventricular 2-dimensional strain: Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) study. *Circ J*. 2012;76:2623-2632.

WG2: What surveillance modality should be used?

Pourier MS et al. Myocardial 2D Strain During Long-Term (> 5 Years) Follow-up of Childhood Survivors of Acute Lymphoblastic Leukemia Treated with Anthracyclines. Am J Cardiol 2020;127:163-168

Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**
1. Study design Longitudinal study during anthracycline upto >=5 years after treatment **T0=before anthracyclines** **T1=after 120mg/m2** **T2=1 year after end treatment** **T3= >=5 years after end treatment** 2. Treatment era	1. Type and number of participants ALL-suvivors ≥ 5 years after completion of anthracycline treatment (n=41) Standard risk n=16 Medium risk n=23 High risk n=2 Exclusion: clinical heart failure, known cardiovascular disease or chronic kidney failure Healthy controls n=70, age matched	1. Diagnostic test(s) NT-pro-BNP (age and sex specific normal values according to Fradley et al)* cTNT >0.01 ng/mL echocardiography at rest - conventional parameters - strain (rate) parameters 2. Outcome definitions Subclinical cancer therapeutics related cardiac dysfunction (CTRCD): - Adults:	1. Diagnostic outcomes (sensitivity, specificity, PPV, NPV, ROC) -No diagnostic values reported -cTNT abnormal in 1 patient (3.0%) at 1 year after treatment (T2) **-normal cTNT at >=5 follow-up in all survivors** **-2/33 (6.1%) survivors with abnormal NT-proBNP at >=5 years follow-up (T3), LVEF not reported for these pts.** -No further decrease in LVSF and LVEF at 1-year after end of treatment (T2) through >5 years (T3) **-T3 vs T0: Relative reduction of 10% in GLS over total time in 54% (≥ 15%**	No diagnostic values of biomarkers reported. Troponins were not abnormal >=5 years from anthracyclines. No correlations between echo and biomarkers are shown. All echocardiographic parameters over time are shown in table 3. Risk of bias A. Selection bias: Unclear Reason: unclear how many of original cohort were included.

not indicated, presumably 2010-2012. Included were survivors who visited late effects outpatient clinic between march 2016 and June 2018 3. Follow-up Median 9.7 (range 7.9-12.6) after diagnosis	2. Age at diagnosis Median 5.1 (range 2.2 – 16.9) years 3. Age at follow-up Median 15.1 (range 11.1 – 28.2.) years 4. Cancer treatment 100% anthracyclines Median cumulative dose 300 (range 120-300) mg/m2 0% radiotherapy 5. Prevalence/risk of late effect LVSF < 30% in 1/41 survivors	Relative reduction of 15% in GLS (global longitudinal strain) compared with baseline Children: Relative reduction of 10% in GLS (global longitudinal strain) compared with baseline, - Reduction of > 10% in LVEF	**reduction in 40%) despite preserved LVEF (<=10% LVEF decrease).** -All myocardial strain parameters decreased during anthracycline treatment and at late follow-up (T3 vs T2) (global longitudinal strain rate and global circumferential strain rate p < 0.001) -T3: Lower FS, GLS and GLS rate values in survivors compared to healthy controls (GLS p < 0.001 and GLSR p=0.008). LVEF and GCS were not different.	Only survivors who visited outpatient clinic were included. B. Index test bias: Unclear Reason: blinding not mentioned C. Reference test bias: Unclear Reason: blinding not mentioned D. Verification bias: Unclear Reason: time between echo and biomarkers not reported E. Attrition bias - Low risk Reason: all patients received the same tests *Additional items for change in EF* F. Detection bias – unclear, blinding not reported G. Confounding – unclear, no multivariable adjustment for EF change but it is unclear if this biased the results.
*Fradley MG, Larson MG, Cheng S, McCabe E, Coglianese E, Shah RV, Levy D, Vasan RS, Wang TJ. Reference limits for N-terminal- pro-B-type natriuretic peptide in healthy individuals (from the Framingham Heart Study). Am J Cardiol 2011;108:1341–1345.				

WG2: What surveillance modality should be used? WG3: At what frequency should surveillance be performed?
Ehrhardt et al. Cost-effectiveness of the International Late Effects of Childhood Cancer Guideline Harmonization Group screening guidelines to prevent heart failure in survivors of childhood cancer. J Clin Oncol 2020.

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Study design Simulation model Treatment era Not stated, but includes all of CCSS, which is 1970-1999, and SJLIFE which includes 1962-2012 Follow-up, median (range) CCSS 21.1 (5-39.3) SJLIFE 27.2 (11-53.2)	Type and number of participants 24,297 CCSS and 3,010 SJLIFE survivors used to inform risk for simulation model Diagnoses All childhood cancer survivors in CCSS and SJLIFE Age at diagnosis, median (range) CCSS 7 (0-20.9) yrs SJLIFE 7.3 (0-24.8) yrs Age at follow-up, median (range) CCSS 28.6 (5.6-58.9) SJLIFE 35.1 (18.9-68.3) Cardiac symptoms Not reported Cardiac medications Not reported Controls (if applicable)	Anthracyclines CCSS and SJLIFE None: 49.6% and 41.7% >0 to <100: 14.6% and 21.3% 100 to <250: 20.4% and 23.6% ≥250: 15.4% and 13.4% Mean heart RT dose CCSS and SJLIFE None: 48.4% and 44.6% >0 to <15: 37.4% and 36.5% 15 to <35: 9.9% and 15.4% ≥35: 4.4% and 3.4% IGHG Risk Group CCSS and SJLIFE High: 27.4% and 26.4% Mod: 32.7% and 32.0% Low: 43.6% and 41.6% Surgery Not reported HSCT Not reported	Outcome definitions IGHG High: (250+ mg/m^2; OR 35+ Gy; OR both 100+ mg/m^2 and 15+ Gy) IGHG Mod: (100 to < 250 mg/m^2; OR 15 to < 35 Gy) IGHG Low: (> 0 to < 100 mg/m^2 AND/OR > 0 to < 15 Gy) Preferred screening strategy had ICER <$100,000/QALY gained Results 40 year and lifetime HF risk -IGHG High: 9.9% and 36.7% -IGHG Mod: 4.5 and 24.7% -IGHG Low: 2.2% and 16.9% Preferred screening strategy -IGHG High: 2-year ($77,880/QALY gained) -IGHG Mod: 5-year ($94,580/QALY gained) -IGHG Low: none (all >$175,000/QALY gained) Delay in HF onset and reduction in HF deaths and for preferred strategy compared to no screening -IGHG High: 1.7 years and 196 -IGHG Mod: 0.9 years and 70 -IGHG Low: -	This is a simulation study, which has inherent limitations (i.e., assumptions for model inputs). Risk of bias A. Selection bias: Unclear Reason: It's not stated how many of the eligible source population participated. B. Attrition bias: Unclear Reason: Not reported for source cohorts C. Detection bias: High Reason: Outcomes in CCSS and SJLIFE (cardiomyopathy) are not blinded D. Confounding: Low risk Reason: unclear how this applies to a simulation study such as this. Effect measures from CCSS and SJLIFE were adjusted in MV analyses.

	NA		Sensitivity analyses showed stability of results for high- and low-risk across several model parameters (e.g. treatment efficacy), but much variability for the moderate-risk group.	

WG3: At what frequency should cardiomyopathy surveillance be performed?				
Border et al. Longitudinal changes in echocardiographic parameters of cardiac function in pediatric cancer survivors. JACC: CardioOncology 2020				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design</u> Retrospective multicenter case-control study <u>Treatment era</u> 1991-2015 <u>Follow-up from cancer to last echocardiogram</u> Cases: <10 years 46%, 10+ years 54%. Mean 5.4±5.0. Controls: <10 years 58%, 10+ years 42%. Mean 6.2±4.4 years. <u>Follow-up from cancer to first abnormal echo</u>	<u>Type and number of participants</u> Childhood cancer survivors treated below age 21 and surviving for at least 1 year. Cases (n=50): FS<=28% or EF<=50% at two occasions with one measurement obtained after cancer treatment. Or at one occasion after cancer treatment when cardiac medications were initiated. Controls (n=50): individually matched to controls on 1) anthracycline dose and type, 2) chest RT dose, 3) follow-up duration, 4) age at cancer diagnosis and 5) sex. FS>=30 and EF>=55% at the same follow-up interval as the matched case. No cardiac medication.	<u>Anthracyclines</u> Cases: median dose 280 mg/m2 (IQR 200-450) Controls: median dose 300 (IQR 200-450) <u>Chest RT</u> Cases: 44% Controls: 42% <u>Surgery</u> Not reported <u>HSCT</u> Not reported	<u>Outcome definitions</u> Longitudinal changes in echocardiographic measurements before cardiomyopathy onset. 412 echocardiograms in total. -LV systolic function: FS, LVEF, mitral S' TDI, Septal S' TDI -LV diastolic function: Mitral E/A ratio, mitral E', mitral E/E' ratio, septal E', septal E/E' ratio. -LV combined: PW doppler derived MPI, TDI derived MPI -LV size and geometry: Posterior wall thickness Z score, LVEDD z score, thickness to dimension ratio <u>Mixed models modeling time as a categorical variable</u> Parameters that showed a significant difference between cases and controls at >2 years prior to cardiomyopathy onset -FS significant difference from 4-5.9 years prior, 3.1% difference (95%CI 0.7-5.5)	-Absolute values of echo parameters aswell as their slope of change over time are different already >2 years prior to cardiomyopathy onset compared to those who will not develop cardiomyopathy **Risk of bias** A. Selection bias: High risk Reason: case control study with no mention whether all cases from a specified cohort were included

Cases: <2 years 34%, 2-9 years 34%, 10+ years 32% Mean 6.4±5.3 years	<u>Diagnoses</u> Cases/controls Leukemia 28%/28% Lymphoma 22%/30% Sarcoma 28%/36% Other solid 22%/6% <u>Age at diagnosis</u> Cases: Mean 8.0±5.5 years Controls: Mean 7.2±4.6 years <u>Age at follow-up (last echo)</u> Cases: Mean 18.3±5.2 years Controls: Mean 17.2±4.4 years <u>Treated for cardiomyopathy</u> Cases 54%, controls 0%		-LVEF significant from 2-3.9 years, 4.8% difference (95% CI 1.5-8.1) -mitral E/A ratio, significant from 2-3.9 years prior -LVEDD significant difference from 4-5.9 years prior <u>Mixed model: Differences in slope of change with time modeled as a continuous variable and a case*time interaction (to estimate the slope differences) upto 2-years prior to cardiomyopathy</u> -biplane EF showed a significant difference in slope of change over time between cases and controls -also significant differences in slope of septal E', septal E/E' -other showed no significant differences in slope over time	B. Attrition bias: Low risk Reason: outcome was assessed in all patients C. Detection bias: low risk Reason: echo core lab was blinded for patient characteristics D. Confounding: Low risk Reason: well matched controls

WG3: At what frequency should cardiomyopathy surveillance be performed?				
Leerink et al. Refining the 10-year prediction of left ventricular systolic dysfunction in long-term survivors of childhood cancer. JACC: CardioOncology 2021				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design</u> Retrospective longitudinal follow-up of	<u>Type and number of participants</u>	<u>Anthracyclines</u>	<u>Outcome definitions</u> Left ventricular systolic dysfunction with an ejection fraction <40% during echocardiographic follow-up.	-results from echo during long-term follow-up improve

2 cohorts in the Netherlands Derivation: Amsterdam, Emma Childrens Hospital Validation: Nijmegen, RadboudUMC. <u>Treatment era</u> Derivation: 1966-1997 Validation: visited outpatient clinic between 2006 and 2012 <u>Follow-up years</u> At first echocardiogram (prediction time point) Derivation: median 16.74 (IQR 11.83-23.15) Validation: 16.95 (IQR 12.99-21.70) <u>Follow-up from first echocardiogram to the outcome or last echocardiogram</u> Derivation: median 10.90 (IQR 8.19-13.05) Validation: 8.86 (IQR 5.22-10.86)	Childhood cancer survivors without heart failure or LVEF<40% before or at first echocardiogram Derivation: n=299 Validation: n=218 <u>Diagnoses</u> Derivation/validation ALL 18.4%/32.6% AML 4.7%/6.9% Hodgkin 7.7/13.8% Non-Hodgkin 20.4/17.0% Nephroblastoma 15.4/6.4% Soft-tiss sarcoma 9.4/3.2% Ewing sarc 6.0/6.4% Osteosarcoma 8/0/6.0% CNS tumor 5.7/1.8% Germ cell tumor 1.3%/0.5% Neuroblastoma 0.7/4.1% Other 2.3%/0.9% <u>Age at diagnosis</u> Derivation: median 7.22 (IQR 4.01-11.72) years Validation: median 7.02 (IQR 4.00-12.46) years <u>Age at follow-up (first echo)</u> Derivation: median 24.06 (IQR 19.60-30.71) years Validation: median 22.63 (IQR 20.05-28.06) years	Derivation: 79.9%, median dose 280 (IQR 180-400) mg/m2 Validation: 98.2%, median dose 180 (IQR 150-301) <u>Chest RT</u> Derivation: 35.1%, median dose 25.00 (IQR 18.00-33.25) Gray Validation: 27.1%, median dose 20.00 (IQR 18.00-30.00) Gray <u>Surgery</u> Not reported <u>HSCT</u> Not reported	<u>Cumulative incidence at 10-years follow-up with death as a competing risk</u> Derivation cohort: overall 3.7% (95% CI 1.4%-5.9%) EF>=50% at first echocardiogram: 2.6% vs. EF 40-49%: 11.0% (Gray's test p=0.012) Validation cohort: overall 3.6% (0.7-6.4%) <u>Multivariable Cox proportional hazard models</u> *Model 1: anthracycline dose+chest RT dose (reference)* *Model 2: anthracycline dose+chest RT dose+LVEF at first echocardiogram (as continuous variable)* EF per 10% decrease HR 9.62 (2.84-32.57) Anthracycline dose per 100 mg/m2 HR 1.43 (1.04-1.98) Chest RT dose per 10 Gray HR 1.67 (1.21-2.30) *Model 3: anthracycline dose+chest RT dose+LVEF at first echocardiogram (2 categories: EF 40-49 vs EF>=50)* EF 40-49 vs EF>=50 HR 7.81 (2.07-29.50) Anthracycline dose per 100 mg/m2 HR 1.70 (1.22-2.36) Chest RT dose per 10 Gray HR 1.91 (1.34-2.72) <u>Discrimination, reclassification and predictive values</u> *Derivation* Model 1 integrated AUC=0.74 (95%CI 0.55-0.84) Model 2 integrated AUC=0.87 (95% 0.71-0.98) Model 2 vs model 1 likelihood ratio test p<0.001 Net reclassification of cases: not significant	prediction of subsequent CMP -identification of low-risk survivors in whom surveillance frequency can be decreased -low number of events +validation in independent cohort <u>Risk of bias</u> A. Selection bias: Low risk Reason: survivors included were treated with higher anthracycline doses. However, inverse probability weighted sensitivity analysis showed comparable results B. Attrition bias: High risk Reason: survivors with <2 echocardiograms were excluded during follow-up and were treated with lower anthracycline doses. However, IPW adjusted analysis

	<u>Modifiable cardiovascular risk factors</u> Derivation chort Hypertension 15 (5.0%) Dyslipidemia 4 (1.34%) Diabetes 2 (0.7%) Heart failure medication use at first echocardiogram Derivation: 4 (1.3) Validation: 3 (1.4%)		Net reclassification of non-cases: 0.50 (0.40-0.60) Predicted probability <=3% in 76.3% of survivors had a negative predictive value of 99.5% (98.6-100%) *Validation* Model 1 integrated AUC=0.72 (95%CI 0.70-0.77) Model 2 integrated AUC=0.86 (95% 0.83-0.89) Net reclassification of cases: not significant Predicted probability <=3% in 74.8% of survivors had a negative predictive value of 99.3% (97.9%-100%) Sensitivity analysis to adjust for selection bias: inverse probability weighted analysis of having received echocardiographic follow-up showed comparable results. Cardiac medication use and modifiable CV risk factors (hypertension, diabetes, dyslipidemia) were not associated with the outcome and did not attenuate the association of LVEF with the outcome.	showed comparable results C. Detection bias: High risk Reason: Investigators were not blinded D. Confounding: Low risk Reason: multivariable adjusted analysis

WG3: At what frequency should cardiomyopathy surveillance be performed?				
Getz KD et al. Occurrence of treatment-related cardiotoxicity and its impact on outcomes among children treated in the AAML0531 clinical trial: A report from the Children's Oncology Group. J Clin Oncol 2018;37:12-21.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks** **e.g. risk of bias**
<u>Study design</u> Prospective study	<u>Type and number of participants</u> n=1022 Patients	<u>Chemotherapy</u> Daunorubicin and Mitoxantrone	<u>Outcome definitions</u> *Primary outcomes included incident cardiotoxicity, Event Free Survival (EFS), and Overal Survival (OS).*	**<u>Limitations:</u>** Enrolment did not include baseline EF or SF cutoffs

Treatment era Aug 2006-June 2010 Follow-up from entrance Median (range) 6.6y (0-9.8) for patients alive at last contact.	<30y with AML (female 50.3%) starting course Diagnoses AML Age at diagnosis 0-1y: n=207 (20.2%) 2-10y: n=354 (34.6%) ≥ 11: n=461 (45.1%) Age at follow-up Not reported.	Radiotherapy - Surgery - HSCT: n=158	-Cardiotoxicity (LVSD)= ≥ grade 2 systolic dysfunction on echo (resting SF<24% or EF<50%). -EFS= time from study enrollment until death, induction failure, secondary malignancy, or relapse. -OS=time to death. Secondary outcomes included compliance with echo monitoring, relapse risk (RR), and non-relapse or non-induction failure–related mortality (NRM). Results 12% of patients experienced cardiotoxicity over a 5-year follow-up, with more than 70% of incident events occurring during on-protocol therapy (on protocol= 8%). Median time to cardiotoxicity was 4.3 months (IQR 3.1-5.9). -Compliance with echo monitoring was modest: highest during induction I and intensification, only 54% with completed echo. Mutivariable risk factor analysis for off-protocol (=long-term) cardiotoxicity - 622 patients completed protocol-planned therapy. - 4.8% (n=30) had cardiotoxicity -Of those, 46.7% (n = 14) had cardiotoxicity first documented during on- protocol therapy. **-LVSD on-protocol therapy HR 12.1 (4.22 to 34.8)** **-Underweight HR 5.26 (1.23 to 22.5)** -Female sex HR 2.66 (0.91 to 7.83) -Age at diagnosis (2-10 years as reference); 0-1 years HR 0.41 (0.05 to 3.61); >=11 years HR 1.37 (0.47 to 3.97) -Black vs white race HR 0.67 (0.13 to 3.51) -Hispanic/latino HR 0.78 (0.16 to 3.70)	Moderate noncompliance with cardiac monitoring over time, suggesting underestimation of true cardiotoxicity. Detailed information on treatment modifications (e.g., timing, specific agents, and dose), cardiovascular management after LVSD, and salvage therapies on relapse were not collected. Thus, we were unable to evaluate how cumulative anthracycline exposure, cardiac directed medications, and relapse regimens may mediate the association between LVSD and EFS/OS. Dexrazoxane use was not captured but was likely used in 10% of Patients. **Risk of bias** A. Selection bias: Low risk Reason: AML trial with entry based on AML diagnosis

			-Cytogenetic risk group (intermediate vs low) HR 1.90 (0.56 to 6.44); high vs low not estimable. -Treatment arm: not significant <u>Multivariable risk factor analysis for overall cardiotoxicity (on and off-protocol)</u> Overall, the incidence of LVSD was higher among noninfants (thus older age at diagnosis) and black patients, and in the setting of a bloodstream infection. ***Both EFS*** (hazard ratio [HR], 1.6; 95% CI, 1.2 to 2.1; P = .004) ***and OS*** (HR, 1.6; 95% CI, 1.2 to 2.2, P = .005) ***were significantly worse in patients with documented early treatment related cardiotoxicity*.** Impacts on EFS were equivalent whether the incident cardiotoxicity event occurred in the absence (HR, 1.6; 95% CI, 1.1 to 2.2; P = .017) or presence of infection (HR, 1.6; 95% CI, 1.0 to 2.7; P = .069) compared with patients without documented cardiotoxicity. However, the reduction in OS was more pronounced for cardiotoxicity not associated with infection (HR, 1.7; 95% CI, 1.2 to 2.5; P = .004) than for infection-associated cardiotoxicity (HR, 1.3; 95% CI, 0.7 to 2.4; P = .387).	<u>B. Attrition bias:</u> High risk Reason: 643 of 1022 patients reached 5 years follow-up <u>C. Detection bias:</u> unclear Reason: blinding not reported <u>D. Confounding:</u> Low risk Reason: multivariable models

WG3: At what frequency should cardiomyopathy surveillance be performed?				
Temming et al. Prevalence and predictors of anthracycline cardiotoxicity in children treated for acute myeloid leukaemia: retrospective cohort study in a single centre in the United Kingdom. Pediatr Blood Cancer 56:625-30, 2011				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design Retrospective cohort. Single centre study. Treatment era 1987-2004. Follow-up Median: 7.3 (0-21.7) yrs	Type and number of participants ≥ 1yr survivors N=128, AML 10 trial: 60 (48.39%) AML 12 trial: 68 (54.84%). Data on late cardiotoxicity in 86 patients. Diagnoses AML 100% Age at diagnosis Median: 2.9 (0.1–12.9) yrs Age at follow-up Not reported.	Chemotherapy Anthracyclines: Dauno and Mitox (1:5 conversion) AML 10 trial: 550 mg/m2 AML 12 trial: 610 mg/m2 Amsacrine: 100 mg/m2. Irradiation: Conditioning with total body irradiation 8 (6.45%) SCT 45(35.2%) 1st remission: autologous 7 (5.65%), allogeneic 12 (9.68%) 2nd remission: autologous 9 (7.26%), Allogeneic 17 (13.71%)	Outcome definitions Subclinical cardiotoxicity: shortening fraction (SF) <28% on 2D echocardiography. Clinical cardiomyopathy: heart failure symptoms in absence of sepsis. Not strictly by the AHA classification. **Late cardiotoxicity: > 1 year after the end of first line treatment (clinical and subclinical)** Results Prevalence of late cardiotoxicity overall, was 15/86 (17.4%; 95%CI: 10.9–26.8%) children. Non-relapse pts: 4.5% (95% CI 1.5-12%) Time to CHF: 1.75 yrs (range 0.6-8.3) Multivariate logistic regression with late cardiotoxicity as the outcome **-Early cardiotoxicity Yes vs. None OR: 9.18 (2.10–40.11)** -Female vs. Male OR: 1.36 (0.35–5.30) -Age (<4 vs. ≥4 yrs) OR: 0.76 (0.20–2.94) -Treatment intensity 2nd vs. 1st line treatment OR: 3.53 (0.86–14.48)	-Not a very wide distribution of age due to Dx. -Anthracycline dose range similar across AML 10 and 12, unable to assess dose-association -Higher cumulative dose of anthracycline compared to other studies -Echocardiograms were unavailable for 20% of the patients **Risk of bias** A. Selection bias: low risk Reason: 124/128 (78.48%) childhood survivors were eligible for the retrospective analyses of cardiotoxicity. B. Attrition bias: high risk Reason: the outcome was assessed in 86/124 (69.35%) of the study group. C. Detection bias: Unclear Reason: unclear if outcome assessors were blinded. D. Confounding: Low risk Reason: Adjusted for age (<4 vs. >4 years), gender, the role of total amount of therapy (1st line treatment alone versus 1st line treatment plus salvage therapy).

WG3: At what frequency should cardiomyopathy surveillance be performed?				
Lipshultz et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. J Clin Oncol 23:2629-36, 2005				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design Observational longitudinal cohort study Treatment era Disease/cancer free from 1989 Follow-up Median 11.8 (range 8.3-15) years off therapy	Type and number of participants 278 full cohort ALL survivors N=115 -Serial echos performed N=499 Diagnoses (%) ALL 100% Age at diagnosis Median 4.8 years (range, 1.0-19.0) Age at follow-up Not reported	Chemotherapy Median anthracycline dose: 352 mg/m2 (range 45-550) Radiotherapy None Surgery only none HSCT Not reported	Outcome definitions Longitudinal trends in echo parameters (Z-scores), stratified by anthracycline dose LV contractility (stress velocity index) LVEDD LVPW thickness LV mass LV fractional shortening LV afterload (end systolic wall stress) Thickness-dimension ratio Blood pressure trends (systolic and diastolic) Results 5 with late CHF Trends in figure 2 per anthracycline dose category (<300, 300-400, >400 mg/m2). LV contractility, LVFS significantly over time and was depressed at last f/u in those who received >300mg/m^2	No multivariate regression analysis Use of Z scores **Risk of bias** A. Selection bias: high risk Reason: 460 were eligible B. Attrition bias: low risk Reason: complete follow-up C. Detection bias: low risk Reason: sonographer was blinded for clinical data D. Confounding: high risk Reason: No multivariable analysis of anthracycline dose

WG4: What should be done when abnormalities are identified?				
Silber et al. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. J Clin Oncol 22:820-8, 2004				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Double-blinded RCT Treatment era:	-135 childhood cancer survivors (aged 8.3 to 30.6 years, 78 males, at least 4 years from diagnosis and 2	Oral enalapril once daily (n = 69) or oral placebo once daily (n = 66). Dosing of study medication was as follows: at start 0.05 mg/kg/day, escalation	Overall survival, mortality due to heart failure, development of **clinical heart failure and quality of life**: no (statistically) significant differences between treatment and control group.	**Risk of bias:** - Selection bias: low risk, blinding and random allocation - Attrition bias: unclear, low risk for clinical outcomes, unclear how many

Unknown, probable end '70-mid '90s <u>Follow-up:</u> Median (range) 2.8 years (2 weeks – 6.1 years)	years off anthracycline treatment). -asymptomatic decline of cardiac function at some time after anthracycline exposure, defined as one or more: -FS<= 29% -10% FS decrease -Gated nuclear angiography LVEF <=55% -10% decrease in LVEF with -a maximal cardiac index (MCI) of <=7.4 L/min/m2 on cycle ergometry at peak exercise -ECG QTc interval >= 440 ms <u>Primary cancer diagnosis:</u> Not described <u>Age at primary cancer diagnosis:</u> Enalapril: 7.2 (3-21.8) years Placebo: 8.2 (0.3-19.3) years <u>Age at follow-up:</u> Median (range) time since cancer diagnosis 9 (4.2 to 22.3) years in the enalapril group and 9.6 (4.3 to 25.8) years in the placebo group	after 14 days to 0.10 mg/kg/day and escalation at 3 months visit to 0.15 mg/kg/day if no side effects occurred -100% anthracyclines	**Cardiac function:** a post-hoc analysis showed a decrease (i.e. improvement) in one measure (left ventricular end systolic wall stress (LVESWS): -8.62%change) compared with placebo (+1.66% change) in the first year of treatment (P = 0.036), but not afterwards. **Adverse events:** patients treated with enalapril had a higher risk of dizziness or hypotension (RR 7.17, 95% CI 1.71 to 30.17) and fatigue (Fisher's exact test, P = 0.013).	were lost to follow-up for cardiac function outcomes - <u>Detection bias:</u> low risk, double blinded RCT - <u>Performance bias:</u> Low risk, Double blinded RCT - <u>Confounding:</u> Low risk, RCT Since the authors did not present dichotomous outcomes, we were not able to define RRs for the outcome change in cardiac function; we therefore describe the outcomes as presented in the original study. No correction for multiple echo outcomes tested. Low/mod risk of selection, performance, and detection bias. For most outcomes there was a low risk of attrition bias, but for some outcomes (the post-hoc analysis of LVESWS, other parameters of cardiac function (SF and stress-velocity index), the change in quality of life and the risk of adverse events) intention-to-treat analysis was not possible or it was unclear if follow-up was complete, leading to a possible risk of attrition bias for these other outcomes.