Conclusions of evidence tables from the systematic literature search and expert opinion for ototoxicity surveillance in CAYA cancer survivors.

Who needs surveillance? – Hearing loss

What is the risk of hearing loss in CAYA cancer survivors treated with platinum agents?
What is the risk after higher doses?
What is the risk after longer duration?

Conclusion single studies	
Cisplatin	
In CAYA solid tumor survivors, **cisplatin treatment** was **significantly associated** with hearing loss according to Münster classification **compared to carboplatin** in multivariable analysis adjusted for age at diagnosis and furosemide (OR: 5.3, 95% CI: 2.9-9.5).	*Clemens, 2016*
In CAYA neuroblastoma survivors, **cisplatin treatment** was **not significantly** associated with **hearing loss** according to CTCAEv3.0 classification **compared to no cisplatin** in multivariable analysis adjusted for age at primary cancer diagnosis, sex and cumulative cisplatin dose (OR: 9.7, 95% CI: 0.9-101.6). However, only 7 patients were not treated with cisplatin.	*Laverdiere, 2005*
In CAYA solid tumor and leukemia survivors treated with cisplatin and cranial radiotherapy, **cisplatin treatment** was **significantly** associated with hearing loss according to BIAP classification **compared to no cisplatin** in multivariable analysis adjusted for cisplatin, cranial radiotherapy and age at diagnosis (OR right ear: 11.7, 95% CI: 4.2-32.1, p<0.001; OR left ear: 17.6, 95% CI: 6.0-51.4, p<0.001).	*Liberman, 2016*
Cisplatin dose	
In CAYA solid tumor survivors, a **cumulative cisplatin dose >400 mg/m^2** was **significantly associated** with **hearing loss** according to Brock classification compared to **a cumulative cisplatin dose ≤400 mg/m^2** in multivariable analysis adjusted for GSTT1 wild genotype (OR: 17.5, 95% CI: 3.1-98.6).	*Choeyprasert, 2013*
In CAYA solid tumor survivors, **higher cisplatin dose** was **significantly associated** with hearing loss according to Münster classification **compared to lower cisplatin doses** in multivariable analysis adjusted for age at diagnosis and furosemide (OR: 1.3, 95% CI: 1.2-1.5 per 100 mg/m^2 increase). In CAYA solid tumor survivors, **total cumulative dose ≥300 mg/m^2** was **significantly associated** with hearing loss according to Münster classification compared to **cisplatin dose <300 mg/m^2** in a multivariable analysis adjusted for age at diagnosis (OR: 5.0, 95% CI: 2.2-11.3).	*Clemens, 2016*
In CAYA medulloblastoma survivors, **higher cisplatin dose** was **not significantly** associated with **hearing loss** according to Brock and ASHA classifications compered to **lower cisplatin dose** in multivariable analysis adjusted for treatment protocol, presence of cerebrospinal fluid shunt, sex and age at evaluation (no effect measures reported).	*Guillaume, 2012*
In CAYA neuroblastoma survivors, **cisplatin dose ≥502 mg/m^2** was **not significantly** associated with **hearing loss** compared to **cisplatin <502 mg/m^2** in multivariable analysis adjusted for age at primary cancer diagnosis and sex (OR: 1.82, 95% CI: 0.2-15.4).	*Laverdiere, 2005*
In CAYA osteosarcoma survivors, **cisplatin 120 mg/m^2/day** was **significantly associated** with **hearing loss** according to Brock and functional loss classification compared to **cisplatin dose of 60 mg/m^2 per 2 days** in a multivariable analysis adjusted for age at diagnosis (Brock: OR: 4.67, 95% CI: 1.05-20.7; functional loss: OR: 12.03, 95% CI: 1.69-85.5). In CAYA osteosarcoma survivors, **total cisplatin dose of 480 mg/m^2** was **significantly associated** with **hearing loss** according to Brock and functional loss classification compared to **total cisplatin dose of 120 mg/m^2** in multivariable analysis adjusted for age at diagnosis (Brock: OR: 12.6, 95% CI: 2.16-73.7; functional loss: 12.76, 95% CI: 2.06-79). In CAYA osteosarcoma survivors, **total cisplatin dose of 360 mg/m^2** was **not significantly** associated with **hearing loss** according to Brock classification compared to **total cisplatin dose of 120 mg/m^2** in multivariable analysis adjusted for age at diagnosis (OR: 3.78, 95% CI: 0.82-17.5). In CAYA osteosarcoma survivors, **total cisplatin dose of 360 mg/m^2** was **significantly** associated with **hearing loss** according to functional loss classification compared to **total cisplatin dose of 120 mg/m^2** in multivariable analysis adjusted for age at diagnosis (OR: 5.14, 95% CI: 1.07-24.5).	*Lewis, 2009*
In CAYA solid tumor survivors, **cumulative cisplatin dose >400 mg/m^2** was **significantly** associated with **hearing loss** according to Brock classification compared to **cumulative cisplatin dose <400 mg/m^2** in multivariable analysis adjusted for age at treatment (OR: 3.35, 95% CI: 1.4-8.04). In CAYA solid tumor survivors, **individual cisplatin dose of >100 mg/m^2** was **not significantly** associated with **hearing loss** according to Brock classification compared to **individual cisplatin dose of <100 mg/m^2** in multivariable analysis adjusted for age at treatment (OR: 0.93, 95% CI: 0.35-2.50).	*Li, 2004*
In CAYA cancer survivors, **higher cisplatin dose** was **significantly associated** with **hearing loss** according to ASHA and Chang classification compared to **lower cisplatin dose** in multivariable analysis adjusted for sex (OR: 1.02, 95% CI: 1.01-1.03).	*Peleva, 2014*
In CAYA osteosarcoma survivors, **cisplatin dose of ≥360 mg/m^2** was **significantly** associated with **hearing loss** according to a self-developed score system compared to **cisplatin dose of ≤240 mg/m^2** in multivariable analysis adjusted for age at cancer diagnosis (OR: 17.4, 95% CI: 3.1-96.8).	*Stohr, 2005*
Overall conclusion	

Risk hearing loss after cisplatin vs. no cisplatin There is moderate quality evidence that CAYA cancer survivors treated with cisplatin have an increased risk of hearing loss as compared to survivors treated without cisplatin.	*3 studies* **Level B**
Risk hearing loss after higher vs. lower doses of cisplatin There is high quality evidence that CAYA cancer survivors treated with higher cisplatin doses have an increased risk of hearing loss as compared to lower doses of cisplatin.	*8 studies* **Level A**
Risk hearing loss after longer vs. shorter cisplatin administration duration There are no studies that reported on the risk of hearing loss after longer vs. shorter cisplatin administration duration in CAYA cancer survivors.	*0 studies* **No studies**
Risk hearing loss after carboplatin vs. no carboplatin Univariate studies showed that CAYA cancer survivors treated with carboplatin have an increased risk of hearing loss (Frappaz 1992, Macdonald 1994, Qaddoumi 2012, Landier 2014, Dahlborg 1998, Parsons 1998, Punnett 2004).	*7 studies* **Expert opinion**
Risk hearing loss after higher vs. lower doses of carboplatin There are no studies that reported on the risk of hearing loss after higher vs. lower doses of carboplatin in CAYA cancer survivors.	*0 studies* **No studies**
Risk hearing loss after longer vs. shorter carboplatin administration duration There are no studies that reported on the risk of hearing loss after longer vs. shorter carboplatin administration duration in CAYA cancer survivors.	*0 studies* **No studies**
Risk hearing loss after oxaliplatin vs. no oxaliplatin There are no studies that reported on the risk of hearing loss after oxaliplatin vs. no oxaliplatin in CAYA cancer survivors.	*0 studies* **No studies**
Risk hearing loss higher vs. lower doses of oxaliplatin There are no studies that reported on the risk of hearing loss after higher vs. lower doses of oxaliplatin in CAYA cancer survivors.	*0 studies* **No studies**
Risk hearing loss after longer vs. shorter oxaliplatin administration duration There are no studies that reported on the risk of hearing loss after longer vs. shorter oxaliplatin administration duration in CAYA cancer survivors.	*0 studies* **No studies**

Hearing loss risk after cisplatin		
Choeyprasert 2013	Cisplatin dose >400 mg/m^2 vs. ≤400 mg/m^2	**OR: 17.5 (3.1-98.6) – Brock ≥ grade 1**
Clemens 2016	Cisplatin vs. carboplatin	**OR: 5.3 (2.9-9.5)** – Münster ≥ grade 2b and Brock ≥ grade 2
	Higher cisplatin dose vs. lower cisplatin dose	**OR: 1.3 (1.2-1.5)** per 100 mg/m^2 increase – Münster ≥ grade 2b and Brock ≥ grade 2
	≥300 mg/m^2 vs <300 mg/m^2	**OR: 5.0 (2.2-11.3)** – Münster ≥ grade 2b and Brock ≥ grade 2
Guillaume 2012	Higher cisplatin dose vs. lower cisplatin dose	No effect measures reported (not significant) – Brock and ASHA
Laverdiere 2005	Cisplatin vs. no cisplatin	OR: 9.7 (0.9-101.6) – CTCAEv3.0
	Cisplatin dose ≥502 mg/m^2 vs. <502 mg/m^2	OR: 1.82 (0.2-15.4) – CTCAEv3.0
Lewis 2009	Cisplatin dose 120 mg/m^2/day vs. 60 mg/m^2/2 days	**OR: 4.67 (1.05-20.7) – Brock**
	Cisplatin dose 480 mg/m^2 vs. 120 mg/m^2	**OR: 12.6 (2.16-73.7) – Brock**
	Cisplatin dose 360 mg/m^2 vs. 120 mg/m^2	OR: 3.78 (0.82-17.5) – Brock
Li 2004	Cisplatin dose >400 mg/m^2 vs. 400 mg/m^2	**OR: 3.35 (1.4-8.04) – Brock**
	Cisplatin dose >100 mg/m^2 vs. <100 mg/m^2	OR: 0.93 (0.35-2.50) – Brock
Liberman 2016	Cisplatin vs. no cisplatin	**OR right ear: 11.7, 95% CI: 4.2-32.1, p<0.001; OR left ear: 17.6, 95% CI: 6.0-51.4, p<0.001** - BIAP
Peleva 2014	Higher cisplatin dose vs. lower cisplatin dose	**OR: 1.02 (1.01-1.03) – ASHA and Chang**
Stohr 2005	Cisplatin dose ≥360 mg/m^2 vs. ≤240 mg/m^2	**OR 17.4 (3.1-96.8) – self-developed score system**

What is the risk of hearing loss in CAYA cancer survivors treated with cranial radiotherapy? **What is the risk after higher doses?** **What is the additive effect (combination of therapy)?**	
Conclusion single studies	
Cranial radiotherapy dose	
In CAYA brain tumor survivors treated with cranial radiation, **higher cochlear radiotherapy dose** was **significantly** associated with hearing loss according to Chang classification compared to survivors with lower cochlear radiotherapy dose in multivariable analysis adjusted for age at radiotherapy, higher cochlear radiotherapy dose and cerebrospinal fluid shunt (HR: 1.1, 95% CI: 1.03-1.11, p<0.001).	*Bass, 2016*
In CAYA solid tumor survivors treated with platinum agents and cranial radiation, **cranial radiation** was **not significantly** associated with **hearing loss** according to Brock classification compared to **no cranial radiation** in multivariable analysis adjusted for age, gender, race and primary cancer diagnosis (no effect measures reported).	*Dean, 2008*
In CAYA medulloblastoma survivors treated with cisplatin and posterior fossa irradiation, **cochlear radiation dose** was **not significantly** associated with **hearing loss** according to criteria used in A9961 protocol in multivariable analysis adjusted for amifostine (no effect measures reported).	*Fouladi, 2008*
In CAYA solid tumor and leukemia survivors, **cranial radiotherapy dose** was **not significantly** associated with hearing loss according to BIAP classification compared to no cranial radiation in multivariable analysis adjusted for cisplatin, cranial radiotherapy and age at diagnosis (OR right ear ≤40 Gy: 0.9, 95% CI: 0.2-3.3, p=0.894; >40 Gy OR: 4.3, 95% CI: 0.8-24.1, p=0.196; OR left ear ≤40 Gy: 0.9, 95% CI: 0.2-3.4, p=0.912, >40 Gy OR: 3.9, 95% CI: 0.5-31.2, p=0.192).	*Liberman, 2016*
CAYA brain tumor survivors treated with **ototoxic chemotherapy, cerebrospinal fluid shunts and a cochlear radiotherapy dose >32 Gy** had significantly greater hearing loss compared to patients treated with <32 Gy (p<0.003) in longitudinal analyses (no effect measures reported).	*Merchant, 2004*
Overall conclusion	
Risk hearing loss after higher vs. lower doses of cranial radiotherapy: There is low quality evidence that CAYA cancer survivors treated with higher cranial radiotherapy doses have an increased risk of hearing loss.	*4 studies* **Level B**
Association with time of administration of platinum and cranial radiotherapy There are no studies that reported on association with time of administration of platinum and cranial radiotherapy	*0 studies* **No studies**
Risk hearing loss after combination of platinum chemotherapy and cranial radiotherapy: There is low quality evidence that CAYA cancer survivors treated with cochlear radiotherapy dose >32 Gy have an additional increased risk of hearing loss when treated with ototoxic chemotherapy and cerebrospinal fluid shunts. *Note: According to Merchant 2004 there is an additive effect after high-dose cranial radiotherapy (>32 Gy).*	*1 study* **Level C**

Hearing loss risk after cranial radiation		
Bass 2016	Higher cochlear radiotherapy dose	**HR: 1.07 (1.04-1.11, p=0.002)** – Chang ≥ grade 2a
Dean 2008	Cranial radiotherapy vs. no cranial radiotherapy All patients treated with platinum agents	Not significant (no effect measures reported) – Brock ≥ grade 1
Fouladi 2008	Cochlear radiotherapy vs. no cochlear radiotherapy All patients treated with platinum agents	Not significant (no effect measures reported) – criteria A9961 protocol ≥ grade 3
Liberman 2016	Cranial radiotherapy vs no cranial radiotherapy	OR right ear ≤40 Gy: 0.9, 95% CI: 0.2-3.3, p=0.894; >40 Gy OR: 4.3, 95% CI: 0.8-24.1, p=0.196; OR left ear ≤40 Gy: 0.9, 95% CI: 0.2-3.4, p=0.912, >40 Gy OR: 3.9, 95% CI: 0.5-31.2, p=0.192.
Merchant 2004	Hearing thresholds over time in longitudinal analyses	Cranial radiotherapy alone was not significantly associated with hearing loss (no effect measures reported) **Ototoxic chemotherapy, CSF shunts and cochlear radiotherapy dose >32 Gy significantly greater hearing loss compared to patients treated with <32 Gy (p<0.003) (no effect measures reported)**

What is the risk of hearing loss in CAYA cancer survivors after concomitant treatment with ototoxicity inducing co-medication?	
Conclusion single studies	
In CAYA solid tumor survivors treated with platinum agents, **co-treatment with furosemide** was **significantly associated** with hearing loss according to Münster classification compared to no co-treatment with furosemide in multivariable analysis adjusted for age at diagnosis, furosemide and platinum compound (OR: 1.9, 95% CI: 1.2-3.0). In CAYA solid tumor survivors treated with cisplatin alone, **co-treatment with furosemide** was **not significantly** associated with hearing loss according to Münster classification compared to no co-treatment with furosemide in multivariable analysis adjusted for age at diagnosis, furosemide and total cumulative cisplatin dose (OR: 1.6, 95% CI: 0.9-3.0). In CAYA solid tumor survivors treated with cisplatin or carboplatin, and cranial radiotherapy, **co-treatment with aminoglycosides** was **significantly** associated with hearing loss according to Münster and Brock classification compared to no co-treatment with aminoglycosides in multivariable analysis adjusted for sex, aminoglycosides and GSTP1 rs1695 genotype (OR Münster: 3.55, 95% CI: 1.18-10.66, p=0.023; OR Brock: 3.83, 95% CI: 1.18-12.47, p=0.025).	*Clemens, 2016* *Olgun, 2016*
Overall conclusion	
Risk hearing loss after concomitant treatment with co-medication There is low quality evidence that CAYA cancer survivors co-treated with furosemide or aminoglycosides have an increased risk of hearing loss.	*2 studies* **Level C**

What is the risk of hearing loss in CAYA cancer survivors after concomitant treatment with ototoxicity inducing co-medication?	
Conclusion single studies	
Amifostine	
In an RCT with CAYA hepatoblastoma survivors, co-treatment with **amifostine** was **not significantly** associated with **reduced hearing loss** according to modified Brock classification compared to **no co-treatment with amifostine** in multivariable analysis adjusted for disease stage and treatment with cisplatin and carboplatin (p=0.68, no effect measures reported).	*Katzenstein, 2009*
In CAYA medulloblastoma survivors treated with cisplatin and cranial radiotherapy, the **absence of amifostine** was **significantly** associated with **hearing loss** according to criteria used in A9961 protocol compared to **treatment with amifostine** in multivariate analysis adjusted for cochlear dose (p=0.047, no effect measures reported).	*Fouladi, 2008*
Sodium thiosulfate	
In an RCT with CAYA solid tumor survivors treated with cisplatin and cranial radiotherapy, **co-treatment with sodium thiosulfate** was **significantly** associated with **less hearing loss** according to ASHA classification compared to no co-treatment with sodium thiosulfate in multivariable analysis adjusted for age at diagnosis and cisplatin infusion duration (OR: 0.31, 95% CI: 0.13-0.73, p=0.0036). In an RCT with CAYA solid tumor survivors treated with cisplatin, **co-treatment with sodium thiosulfate** was **significantly** associated with **less hearing loss** according to ASHA classification compared to no co-treatment with sodium thiosulfate in multivariable analysis adjusted for age at diagnosis and cisplatin infusion duration (OR: 0.32, 95% CI: 0.13-0.76, p=0.010).	*Freyer, 2017*
In an RCT with CAYA hepatoblastoma survivors treated with cisplatin, **delayed treatment with sodium thiosulfate** was **significantly** associated with **less hearing loss** according to Brock classification compared to no delayed treatment with sodium thiosulfate in multivariable analysis adjusted for age at randomization, tumor extent and country (RR: 0.52, 95% CI: 0.33-0.81, p=0.02).	*Brock, 2018*
Overall conclusion	
Risk hearing loss after concomitant treatment with amifostine There is low quality evidence that CAYA cancer survivors co-treated with amifostine may have a decreased risk of hearing loss.	*1 RCT and 1 cohort study* **Level C**
Risk hearing loss after concomitant treatment with sodium thiosulfate There is moderate quality evidence that CAYA cancer survivors co-treated with sodium thiosulfate have a decreased risk of hearing loss	*2 RCTs* **Level B**

Hearing loss risk after co-treatment		
Katzenstein 2009	Amifostine vs. no amifostine (RCT)	Not significantly associated with reduced hearing loss (p=0.68) (no effect measures reported)

Fouladi 2008	No amifostine vs. amifostine (cohort study)	**Absence significantly associated with hearing loss (p=0.047)** (no effect measures reported)
Freyer 2017	Sodium thiosulfate vs no (RCT)	**Less hearing loss** (OR: 0.31, 95% CI: 0.13-0.73, p=0.0036)
Brock 2018	Sodium thiosulfate vs no (RCT)	**Less hearing loss** (RR: 0.52, 95% CI: 0.33-0.81, p=0.002)

What is the risk of hearing loss in CAYA cancer survivors treated at a younger vs. older age?

Conclusion single studies	
Cisplatin	
In CAYA solid tumor survivors treated with cisplatin alone, **younger age** was **significantly associated** with hearing loss according to Münster classification in multivariable analysis adjusted for age at diagnosis, furosemide and total cumulative dose cisplatin (OR: 0.7, 95% CI: 0.6-0.8, per 5 years increase in age).	*Clemens, 2016*
In CAYA osteosarcoma survivors treated with cisplatin, **age at primary cancer** diagnosis was **significantly** associated with **hearing loss** according to functional loss classification in multivariable analysis adjusted for cumulative cisplatin dose (OR for each 1-year unit increase in age: 0.82, 95% CI: 0.69-0.97).	*Lewis, 2009*
In CAYA solid tumor survivors treated with cisplatin, **younger age at primary cancer treatment (<5 years and 5-14 years)** was **significantly** associated with **hearing loss** according to Brock classification compared to **older age at primary cancer treatment (15-20 years)** in multivariable analysis adjusted for cisplatin dose (OR <5 yr vs. 15-20 yr: 21.17, 95% CI: 2.48-180.94; OR 5-14 yr vs. 15-20 yr: 10.09, 95% CI: 1.18-86.08).	*Li, 2004*
Platinum agents	
In CAYA solid tumor survivors treated with platinum agents, **younger age** was **significantly associated** with hearing loss according to Münster classification in multivariable analysis adjusted for age at diagnosis, furosemide and platinum compound (OR: 0.6, 95% CI: 0.6-0.7, per 5 years increase in age).	*Clemens, 2016*
In CAYA osteosarcoma survivors treated with cisplatin and 1 survivors treated with carboplatin, **age at primary cancer** diagnosis was **not significantly** associated with **hearing loss** according to Brock classification in multivariable analysis adjusted for cumulative cisplatin dose (OR for each 1-year unit increase in age: 0.93, 95% CI: 0.81-1.07).	*Lewis, 2009*
In CAYA cancer survivors treated with cisplatin and/or carboplatin, **younger age at primary cancer treatment** was **significantly** associated with **hearing loss** according to ASHA and Chang classification compared to **older age at primary cancer treatment** in multivariable analysis adjusted for cisplatin dose and sex (OR for each 1-month unit increase in age: 0.994, 95% CI: 0.990-0.999).	*Peleva, 2014*
In CAYA osteosarcoma survivors treated with cisplatin and/or carboplatin, **younger age at primary cancer diagnosis (≤12 years)** was **significantly** associated with **hearing loss** according to a self-developed score system compared to **older age at primary cancer diagnosis (>15.5 years)** in multivariable analysis adjusted for cisplatin dose (OR: 6.4, 95% CI: 1.6-25.4). IN CAYA osteosarcoma survivors treated with cisplatin and/or carboplatin, **age at primary cancer diagnosis >12-15.5 years** was **not significantly** associated with **hearing loss** according to a self-developed score system compared to **age at primary cancer diagnosis >15.5 years** in multivariable analysis adjusted for cisplatin dose (OR: 2.8, 95% CI: 0.8-9.8).	*Stohr, 2005*
Cranial radiotherapy	
In CAYA brain tumor survivors treated with cranial radiation, **age <3 years at radiotherapy** was **significantly** associated with hearing loss according to Chang classification in multivariable analysis adjusted for age at radiotherapy, higher cochlear radiotherapy dose and cerebrospinal fluid shunts (HR: 2.3, 95% CI: 1.21-4.46, p=0.01).	*Bass, 2016*
Platinum agents and cranial radiotherapy	
In CAYA solid tumor survivors treated with cisplatin, carboplatin and/or cranial radiation, **age** was **not significantly** associated with **hearing loss** according to Brock classification in multivariable analysis adjusted for cranial radiotherapy, sex, race and primary cancer diagnosis (no effect measures reported).	*Dean, 2008*
In CAYA solid tumor and leukemia survivors treated with cisplatin and cranial radiotherapy, **age >6 years at diagnosis** was **significantly associated** with hearing loss in the right ear according to BIAP classification **compared to age ≤6 years at diagnosis** in multivariable analysis adjusted for cisplatin, cranial radiation and age at diagnosis (OR right ear: 2.7, 95% CI: 1.1-6.4, p=0.028, OR left ear: 2.1, 95% CI: 0.9-5.0, p=0.084).	*Liberman, 2016*
In CAYA rhabdomyosarcoma survivors treated with carboplatin and cranial radiotherapy, **age at diagnosis** was **not significantly** associated with hearing loss according to CTCAEv4.0 classification in multivariable analysis adjusted for treatment group and tumor localization (no effect measures reported).	*Schoot, 2016*
Overall conclusion	
Risk hearing loss after younger vs. older age at cancer treatment: There is moderate quality evidence that CAYA cancer survivors treated at a younger age have an increased risk of hearing loss.	*9 studies* **Level B**

Hearing loss risk at younger vs. older age		
Bass 2016	Age <3 years vs ≥3 years at RT	**HR: 2.32 (1.21-4.46) p=0.01** – Chang ≥grade 1a
Clemens 2016	Younger age vs older age	**OR: 0.7, 95% CI: 0.6-0.8, per 5 years increase in age**
Dean 2008	Age at diagnosis	Not significant (no effect measured reported) – Brock
Lewis 2009	Age at diagnosis	OR for each 1-year unit increase in age: 0.93 (0.81-1.07) – Brock
Li 2004	<5 years vs. 5-20 years at treatment 5-14 years vs. 5-20 years at treatment	**OR: 21.17 (2.48-180.94 – Brock** **OR: 10.09 (1.18-86.08) – Brock**
Liberman 2016	>6 vs. ≤6 years at diagnosis	**OR right ear: 2.7, 95% CI: 1.1-6.4, p=0.028**, OR left ear: 2.1, 95% CI: 0.9-5.0, p=0.084
Peleva 2014	Age at treatment	**OR for each 1-month unit increase in age: 0.994 (0.990-0.999) – ASHA and Chang**
Pogany 2006	1-4 years vs. <1 year at diagnosis 5-9 years vs. <1 year at diagnosis 10-14 years vs. <1 year at diagnosis 15-19 years vs. <1 year at diagnosis	OR: 0.93 (0.31-2.80) –self-reported hearing loss OR: 1.34 (0.31-5.78) –self-reported hearing loss OR: 1.37 (0.22-8.50) – self reported hearing loss OR: 1.43 (0.17-11.83) – self reported hearing loss
Schoot 2016	Age at diagnosis	Not significant (no effect measured reported)
Stohr 2005	≤12 years vs. >15.5 years at diagnosis >12-15.5 years vs. >15.5 years at diagnosis	**OR: 6.4 (1.6-25.4) – self-developed score system** OR: 2.8 (0.8-9.8) – self-developed score system

What is the risk of hearing loss in male vs. female CAYA cancer survivors?

Conclusion single studies	
Platinum agents	
In CAYA brain tumor survivors treated with cisplatin and/or carboplatin, **sex** was **not significantly** associated with **hearing loss** according to Brock and CTCAEv3.0 in multivariable analysis adjusted for time of hearing test and age at primary cancer diagnosis (p=0.063; no effect measures reported).	*Orgel, 2012*
In CAYA cancer survivors treated with cisplatin and/or carboplatin, **sex** was **not significantly** associated with **hearing loss** according to ASHA and Chang classifications in multivariable analysis adjusted for cisplatin dose and age at primary cancer treatment (OR: 0.958, 95% CI: 0.551-1.668).	*Peleva, 2014*
Platinum agents and cranial radiotherapy	
In CAYA solid tumor survivors treated with cisplatin, carboplatin and/or cranial radiation, **sex** was **not significantly** associated with **hearing loss** according to Brock classification in multivariable analysis adjusted for cranial radiotherapy, age, race and primary cancer diagnosis (no effect measures reported).	*Dean, 2008*
In CAYA medulloblastoma survivors treated with posterior fossa surgery, platinum agents, and/or cranial radiotherapy, **sex** was **not significantly** associated with **hearing loss** according to Brock and ASHA classifications in multivariable analysis adjusted for treatment protocol, cisplatin dose, presence of cerebrospinal fluid shunt, and age at evaluation (no effect measures reported).	*Guillaume, 2012*
In CAYA solid tumor survivors treated with cisplatin or carboplatin, and cranial radiotherapy, **male sex** was **significantly associated** with hearing loss according to Münster and Brock classification in multivariable analysis adjusted for sex, aminoglycosides and GSTP1 rs1695 genotype (OR Münster: 3.42, 95% CI: 1.12-10.4, p=0.03, OR Brock: 6.32, 95% CI: 1.77-22.49, p=0.04).	*Olgun, 2016*
Overall conclusion	
Risk hearing loss in males vs. females There is moderate quality evidence that sex is not significantly associated with an increased risk of hearing loss in CAYA cancer survivors.	*5 studies* **Level B**

Hearing loss in male vs. female		
Dean 2008	Sex	Not significant (no effect measures reported)
Guillaume 2012	Sex	Not significant (no effect measures reported)
Olgun 2016	Male vs female	OR Münster: 3.42 (1.12-10.4) and OR Brock: 6.32 (1.77-22.49)
Orgel 2012	Sex	p=0.063 (no effect measured reported)

Peleva, 2014	Sex (unclear if male vs. female or the other way around)	OR: 0.958 (0.551-1.668)

What is the association between timing of administration of platinum and cranial radiation in CAYA cancer survivors?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of hearing loss after posterior fossa tumor surgery in CAYA cancer survivors?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of hearing loss after surgery involving the ear or cranial nerve VIII in CAYA cancer survivors?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of hearing loss in brain tumor CCS with hydrocephalus at diagnosis and/or cerebrospinal fluid shunts independent of cranial radiation?

Conclusion single studies	
Childhood cancer survivors	
In CAYA brain tumor survivors, **presence of a cerebrospinal fluid shunt** was **significantly associated** with hearing loss compared to no shunt in multivariable analysis adjusted for age at radiotherapy, higher cochlear radiotherapy dose and cerebrospinal fluid shunt (HR: 2.0, 95% CI: 1.07-3.78, p=0.03).	*Bass, 2016*
In CAYA medulloblastoma survivors, presence of a **cerebrospinal fluid shunt** was **not significantly** associated with **hearing loss** according to Brock and ASHA classifications compared to **no shunt** in multivariable analysis adjusted for treatment protocol, cisplatin dose, sex, and age at evaluation (no effect measures reported).	*Guillaume, 2012*
In brain tumor CAYA cancer survivors, **cerebrospinal fluid shunts** were **significantly associated** with hearing loss compared to no shunt in longitudinal analyses (p<0.0005, no effect measures reported).	*Merchant, 2004*
Overall conclusion	
Risk hearing loss after cerebrospinal fluid shunts: There is moderate quality evidence that CAYA cancer survivors treated with cerebrospinal fluid shunts have an increased risk of hearing loss.	*3 studies* **Level B**

Hearing loss risk after CSF shunts		
Bass 2016	CSF Shunt vs. no shunt	**HR: 2.0, 95% CI: 1.07-3.78, p=0.03**
Guillaume 2012	CSF Shunt vs. no shunt	Not significant (no effect measures reported)
Merchant 2004	CSF Shunt vs. no shunt	**Significant effect on hearing loss (no effect measures reported)**

Who needs surveillance? – Tinnitus

What is the risk of tinnitus in CAYA cancer survivors treated with platinum agents? **What is the risk after higher doses?** **What is the risk after longer duration?**	
Conclusion single studies	
Platinum agents as a group	
In CAYA cancer survivors, **platinum-based chemotherapy** was **significantly** associated with **self-reported tinnitus** compared to **non-platinum based chemotherapy** in multivariable analysis adjusted for age at diagnosis, sex, maximum radiation dose to posterior fossa or temporal lobe and ventriculoperitonal shunt placement (RR: 2.8, 95% CI: 1.9-4.2). In CAYA cancer survivors, **platinum agent doses of 1-349 mg/m^2 and ≥350 mg/m^2** were **significantly** associated with **self-reported tinnitus** compared to **non-platinum based chemotherapy** in multivariable analysis adjusted for age at diagnosis, sex, maximum radiation dose to posterior fossa or temporal lobe and ventriculoperitonal shunt placement (RR 1-349 mg/m^2: 3.8, 95% CI: 2.2-6.8; RR ≥350 mg/m^2: 2.1, 95% CI: 1.1-4.2).	*Whelan, 2011*
Overall conclusion	
Risk tinnitus after platinum agents as a group vs. no platinum agents There is low quality evidence that CAYA cancer survivors treated with platinum agents have an increased risk of tinnitus.	*1 study* **Level C**
Risk tinnitus after higher vs. lower doses of platinum agents as a group There are no studies that reported on the risk of tinnitus after higher vs. lower doses of platinum agents. *Note: Whelan 2011 only compared higher doses to no platinum agents, so we are unable to conclude if higher doses are associated with an increased risk as compared to lower doses.*	*0 studies* **No studies**
Risk tinnitus after longer vs. shorter platinum agent administration duration There are no studies that reported on the risk of tinnitus after longer vs. shorter platinum agent administration duration in CAYA cancer survivors.	*0 studies* **No studies**

Tinnitus risk after platinum agents		
Whelan 2011	Platinum agents vs. no platinum agents	**RR: 2.8 (1.9-4.2) – self-reported tinnitus**
	1-349 mg/m^2 vs. no platinum agents	**RR: 3.8 (2.2-6.8) – self-reported tinnitus**
	≥350 mg/m^2 vs. no platinum agents	**RR: 2.1 (1.1-4.2) – self-reported tinnitus**

What is the risk of tinnitus in CAYA cancer survivors treated with cranial radiotherapy? **What is the risk after higher doses?** **What is the additive effect (combination of therapy)?**	
Conclusion single studies	
In CAYA cancer survivors, **radiation to the posterior fossa or temporal lobe** was **not significantly** associated with **self-reported tinnitus** compared to **no radiotherapy** in multivariable analysis adjusted age at diagnosis, sex, any platinum drug use and ventriculoperitonal shunts (RR: 1.2, 95% CI: 0.9-1.6). In CAYA cancer survivors, **radiation doses of 1-29.9 Gy to the temporal lobe or posterior fossa** were **not significantly** associated with **self-reported tinnitus** compared to **0 Gy radiation** in multivariable analysis adjusted for age at diagnosis, sex, any platinum drug use and ventriculoperitonal shunts (RR temporal lobe: 1.2, 95% CI: 0.9-1.70; RR posterior fossa: 1.2, 95% CI: 0.9-1.7). In CAYA cancer survivors, **radiation doses of 30-49.9 Gy and ≥50 Gy to the temporal lobe** were **significantly** associated with **self-reported tinnitus** compared to **0 Gy radiation** on multivariable analysis adjusted for age at diagnosis, sex, any platinum drug use and ventriculoperitonal shunts (RR 30-49.9 Gy: 2.4, 95% CI: 1.6-3.6; RR ≥50 Gy: 2.6, 95% CI: 1.7-4.1). In CAYA cancer survivors, **radiation doses of 30-49.9 Gy and ≥50 Gy to the posterior fossa** were **significantly** associated with **self-reported tinnitus** compared to **0 Gy radiation** on multivariable analysis adjusted for age at diagnosis, sex, any platinum drug use and ventriculoperitonal shunts (RR 30-49.9 Gy: 2.6, 95% CI: 1.7-4.1; RR ≥50 Gy: 2.9, 95% CI: 1.8-4.6). In CAYA cancer survivors, **temporal lobe and posterior fossa high scatter or low scatter** were not significantly associated with **self-reported tinnitus** compared to **0 Gy radiation** on multivariable analysis adjusted for age at diagnosis, sex, any platinum drug use and ventriculoperitonal shunts (RR high scatter temporal lobe: 1.3, 95% CI: 0.7-2.2; RR high scatter posterior fossa: 1.4, 95% CI: 0.9-2.1; RR low scatter temporal lobe: 0.8, 95% CI: 0.6-1.1, RR low scatter posterior fossa: 0.8, 95% CI: 0.6-1.1).	*Whelan, 2011*
Overall conclusion	
Risk tinnitus after cranial radiotherapy vs. no cranial radiotherapy There is low quality evidence that CAYA cancer survivors treated with high-dose cranial radiotherapy (≥30 Gy) have an increased risk of tinnitus.	*1 study* **Level C**
Risk tinnitus after higher vs. lower doses of cranial radiotherapy: There are no studies that reported on the risk of tinnitus after higher vs. lower doses of cranial radiotherapy in CAYA cancer survivors.. *Note: Whelan 2011 only compared higher doses to no radiotherapy, so we are unable to conclude if higher doses are associated with an increased risk as compared to lower doses.*	*0 studies* **No studies**
Risk tinnitus after combination of ototoxic chemotherapy and cranial radiotherapy: There are no studies that reported on the risk of tinnitus after combinations of therapy in CAYA cancer survivors.	*0 studies* **No studies**

Tinnitus risk after cranial radiation		
Whelan 2011	Radiation to posterior fossa or temporal lobe vs. no radiotherapy	RR: 1.2 (0.9-1.6) – self-reported tinnitus
	1-29.9 Gy radiation temporal lobe vs. 0 Gy	RR: 1.2 (0.9-1.70) – self-reported tinnitus
	30-49.9 Gy radiation temporal lobe vs. 0 Gy	**RR: 2.4 (1.6-3.6) – self-reported tinnitus**
	≥50 Gy radiation temporal lobe vs. 0 Gy	**RR: 2.6 (1.7-4.1) – self-reported tinnitus**
	High scatter temporal lobe vs. 0 Gy	RR: 1.3 (0.7-2.2) – self-reported tinnitus
	Low scatter temporal lobe vs. 0 Gy	RR: 0.8 (0.6-1.1) – self-reported tinnitus
	1-29.9 Gy radiation posterior fossa vs. 0 Gy	RR: 1.2 (0.9-1.70) – self-reported tinnitus
	30-49.9 Gy radiation posterior fossa vs. 0 Gy	**RR: 2.6 (1.7-4.1) – self-reported tinnitus**
	≥50 Gy radiation posterior fossa vs. 0 Gy	**RR: 2.9 (1.8-4.6) – self-reported tinnitus**
	High scatter posterior fossa vs. 0 Gy	RR: 1.4 (0.9-2.1) – self-reported tinnitus
	Low scatter posterior fossa vs. 0 Gy	RR: 0.8 (0.6-1.1) – self-reported tinnitus

What is the risk of tinnitus in CAYA cancer survivors after concomitant treatment with ototoxic increasing or reducing co-medication?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of tinnitus in CAYA cancer survivors treated at a younger vs. older age?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of tinnitus in male vs. female CAYA cancer survivors?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of hearing loss in brain tumor CCS with hydrocephalus at diagnosis and/or cerebrospinal fluid shunts independent of cranial radiation?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of tinnitus after posterior fossa tumor surgery in CAYA cancer survivors?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of tinnitus after surgery involving the ear or cranial nerve VIII in CAYA cancer survivors?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of tinnitus after concomitant treatment with ototoxic co-medication?
No studies identified in childhood, adolescent and young adult cancer survivors.

What surveillance modality and classification system should be used?

What tests are available to measure clinically relevant hearing loss and what is the indication of the tests in CAYA cancer survivors?	
Conclusion guidelines	
Children	
Neonates and infants at birth – 6 months: 1. **Case history** 2. **Otoscopy** 3. **Otoacoustic emission** 4. **Auditory brainstem response** **Children 6 months – 5 years:** 1. **Case history** 2. **Otoscopy** 3. **Visual reinforcement audiometry** (air and bone conduction with masking) OR **conditioned play audiometry** (air and bone conduction with masking) 4. **Tympanometry** 5. **Otoacoustic emission** 6. **Auditory brainstem response** **Children 5 years – adult:** 1. **Case history** 2. **Otoscopy** 3. **Pure tone audiometry** with appropriate masking (air and bone conduction) 4. **Speech audiometry** with appropriate masking 5. **Tympanometry** 6. **Otoacoustic emission** 7. **High-frequency audiometry**	*American Academy of Audiology, 2000*
Children 5 – 24 months of age: 1. **Case history:** the audiologist may want to include evaluation of the high-frequency region of the cochlea (>4 kHz) for a young child with a history of ototoxic drug exposure. 2. **Otoscopy:** visual inspection of the outer ear canal to verify that there is no contraindication to placing a probe in the ear canal (e.g. drainage, foreign objects, occluding cerumen). 3. **Behavioral assessment:** visual reinforcement is the test of choice 4. **Physiological assessment:** tympanogram, otoacoustic emissions (OAEs) and auditory brainstem responses (ABRs). ABR using frequency-specific stimuli are used to estimate the audiogram; ABR using click stimuli is used to assess VIIIth nerve integrity. OAEs and acoustic immittance measures are used to supplement and corroborate the evoked-potential findings. **Children 25 – 60 months of age:** 1. **Case history:** the audiologist may want to include evaluation of the high-frequency region of the cochlea (>4 kHz) for a young child with a history of ototoxic drug exposure. 2. **Otoscopy:** visual inspection of the outer ear canal to verify that there is no contraindication to placing a probe in the ear canal (e.g. drainage, foreign objects, occluding cerumen). 3. **Behavioral assessment:** method that is used is dependent to a large extent on the developmental level of the child (visual reinforcement audiometry, conditioned play audiometry, pure tone conventional audiometry). 4. **Physiological assessment:** tympanogram, OAEs and ABRs.	*American-Speech-Language-Hearing Association, 2004*

Children birth – 6 months of age: 1. **Auditory brainstem response**: when permanent hearing loss is detected, frequency-specific ABR is needed to determine the degree and configuration of hearing loss in each ear for fitting amplification devices. 2. **Otoacoustic emission** (distortion product or transient evoked) 3. **Tympanometry** Children 6 – 36 months of age: 1. **Behavioral pure-tone audiometry** (visual reinforcement or conditioned play): depending on the child's developmental age 2. **Otoacoustic emission** 3. **Tympanometry** 4. **Auditory brainstem response:** if responses to behavioral audiometry are not reliable or if ABR testing has not been performed in the past.	*American Academy of Pediatrics, 2007*
Children from birth – 7 months of age: 1. **Auditory brainstem response** 2. **Behavioral observation audiometry** 3. **Tympanometry** **Older children** 1. **Visual reinforcement audiometry** 2. **Tympanometry** (children aged ≥7 months) 3. **Pure tone audiometry** (children aged ≥2.5 years) 4. **Speech discrimination tests**	*Australia, 2010*
Children 6 months – 15 years: 1. **Pure-tone audiometry**: children age 3 years and older. 2. **Tympanometry**: as a second-stage screening method following failure of pure-tone audiometry or otoacoustic emissions screening. 3. **Otoacoustic emission**: below 3 years of age.	*American Academy of Audiology, 2011*
1. **Auditory brainstem assessment:** for infants <6 months of age; or for older infants who are unsuitable for behavioral assessment. 2. **Behavior assessment:** visual reinforcement audiometry (for infants >6 months of age) or conditioned play audiometry (for infants >24 months of age). 3. **Tympanometry** 4. **Otoacoustic emission**	*British Columbia, 2012*
Children 18 months – 5 years: 1. **Otoacoustic emission (transient evoked or distortion product)**: very young children who are unable to cooperate with conventional testing. 2. **Tympanometry**: not specified.	*Canadian Agency for Drugs and Technologies in Health, 2012*
1. **Visual reinforcement audiometry**: infants between 5-24 months developmental age. 2. **Conditioned play audiometry:** children between 2-5 years developmental age. 3. **Speech audiometry**: above 6 months developmental age. 4. **Tympanometry**: not specified. 5: **Otoacoustic emission**: in neonates and infants: cross-check verification of behavioral testing (no age limitation). 6. **Auditory brainstem response**: not specified.	*American Academy of Audiology, 2012*
1. **Otoscopy** 2. **Tympanometry** 3. **Audiometry**: visual reinforcement, play tone, pure-tone (with air and bone conduction and masking where required) 4. **Speech perception** 5. **Otoacoustic emission**	*Audiology Australia, 2013*
Preschool – adults: 1. **Tympanometry**: not specified 2. **Otoacoustic emission (distortion product or transient evoked)**: not specified 3. **Pure-tone audiometry**: not specified 4. **Conditioned play audiometry**: between 3-5 years chronological or developmental age.	*Alberta College of Speech-Language Pathologists and Audiologists, 2015*
Adults	
1. **Pure-tone audiometry**: not specified	*American-Speech-Language-Hearing*

2. **Otoacoustic emission**: for populations who may be difficult to test 3. **Self-report questionnaires**	*Association, 1997*
1. **Otoscopy** 2. **Tympanometry** 3. **Audiometry**: (with air and bone conduction and masking where required) 4. **Speech audiometry** (masking if required) 5. **Otoacoustic emission**	*Audiology Australia, 2013*
1. **Pure-tone audiometry**: not specified 2. **Otoacoustic emissions**: not specified 3. **Tympanometry**: not specified	*American Academy of Audiology, 2015*
Conclusions recommendations in existing guidelines	
Children	*10 guidelines*
1. Behavioural testing • Pure tone conventional audiometry: able to reliable respond to stimuli, age 5 years and older. • Visual reinforcement audiometry: infants between 5-24 months developmental age. • Conditioned play audiometry: children between 2-5 years developmental age. • Speech audiometry: above 6 months developmental age. **2. Non-behavioural testing** • Auditory brainstem response: for those unable to do behavioural testing or for those with unreliable results. **3. Otoacoustic emission**: children who are difficult to test using pure tone audiometry, cross-check verification of behavioural testing **4. Tympanometry**: second-stage screening method added to pure tone audiometry or otoacoustic emission testing. There is no knowledge about the gold standard.	**Existing guidelines**
Adults	*3 guidelines*
1. Pure tone conventional audiometry **2. Otoacoustic emissions** **3. Tympanometry** **4. Speech audiometry**	**Existing guidelines**

What is the prevalence of hearing abnormalities according to distortion product otoacoustic emission (DPOAE) and behavioral testing methods and what is the agreement between the results of distortion product otoacoustic emission and behavioral testing methods in CAYA cancer survivors?

Conclusion single studies	
Childhood cancer survivors	
In CAYA solid tumor survivors with a median age of 14.5 years at testing (range: 4-37), the **prevalence** of hearing loss after pure tone audiometry (>25 dB hearing loss at all frequencies) and DPOAE was **57%** and **64%,** respectively. The **agreement** between either normal or altered pure tone audiometry and DPOAE was **significant** (K:0.553, p<0.001).	*Abujamra, 2013*
In CAYA solid tumor survivors with a median age of 12.3 years at diagnosis (range: 10.4-16.1), the **prevalence** of hearing loss after pure tone audiometry (>20 dB hearing loss) and DPOAE (signal/noise ratio below 6 dB in each frequency) was **52% and 71%,** respectively. The **concordance** between abnormal pure tone audiometry and DPOAE at **2 kHz, 4 kHz, 6 kHz and 8 kHz** was **significant** (4 kHz: kappa 0.70, p<0.01; 3 kHz: kappa: 0.54, p<0.01; 4 kHz: kappa: 0.69, p<0.01; 6 kHz: kappa: 0.55, p<0.01; 8 kHz: kappa: 0.42, p=0.04).	*Coradini, 2007*
In CAYA survivors with a median age of 9.6 years at testing (range: 2.3-26), the **correlation** between pure tone audiometry and DPOAE (based on categorization of DP-grams according to Brock grade of hearing loss seen on the pure tone audiogram) was **significant** (r: 0.82, p<0.01).	*Dhooge, 2006*
In CAYA survivors with a median age of 5.7 years at diagnosis (range: 0.6-16.2), the **agreement** between abnormal pure tone audiometry and normal DPOAE was 68% and the **agreement** between normal pure tone audiometry and abnormal DPOAE was 95%.	*Punnett, 2004*
Overall conclusion	
There is moderate quality evidence that there is agreement between pure tone audiometry and DPOAE in detecting abnormalities, but there is also evidence that DPOAE detects more abnormalities than audiometry.	*4 studies* **Level B**

What is the prevalence of hearing abnormalities according to extended high frequency audiometry and behavioral testing methods and what is the agreement between the results of extended high frequency audiometry and behavioral testing methods in CAYA cancer survivors?

Conclusion single studies	
Childhood cancer survivors	
In CAYA solid tumor survivors with a median age of 14.5 years at testing (range: 4-37), the **prevalence** of hearing loss after pure tone audiometry (>25 dB hearing loss at all frequencies) and high frequency audiometry was **57%** and **86%,** respectively.	*Abujamra, 2013*
Overall conclusion	
There is low quality evidence that high frequency audiometry detects more abnormalities than pure tone audiometry.	*1 study* **Level C**

What is the prevalence of hearing abnormalities according to speech audiometry in noise and behavioral testing methods and what is the agreement between the results of speech audiometry in noise and behavioral testing methods in CAYA cancer survivors?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the prevalence of hearing abnormalities according to frequency-specific auditory brainstem response and what is the agreement between the results of frequency-specific auditory brainstem response and behavioral testing methods in CAYA cancer survivors?

Conclusion single studies	
Childhood cancer survivors	
In CAYA cancer survivors with ages between 3 months and 4.3 years at diagnosis, the **prevalence** of hearing loss after ABR (blunted response by 10 dB) and pure tone audiometry (10 dB threshold shift in both ears) was **34%** and **66%**, respectively.	*Weatherly, 1991*
Overall conclusion	
Behavioral testing vs. auditory brainstem response There is low quality evidence that pure tone audiometry detects more abnormalities than auditory brainstem response.	*1 study* **Level C**

What is the prevalence of hearing abnormalities according to distortion product otoacoustic emission and frequency-specific auditory brainstem response and what is the agreement between the results of distortion product otoacoustic emission and frequency-specific auditory brainstem response testing methods in CAYA cancer survivors??

No studies identified in childhood, adolescent and young adult cancer survivors.

What are the ototoxicity classifications systems used in audiometric testing for research in CAYA cancer survivors?	
Conclusion expert opinion	
Children	
1. **Brock.** Description: 5-point scale; designed to grade hearing loss progression from high to low frequencies in the configuration commonly associated with ototoxic cancer therapy. Features: widely used. Limitation: does not capture hearing loss <40 dB; misses significant functional deficits. 2. **American Speech-Language-Hearing Association (ASHA).** Description: presence/absence of hearing loss in comparison with baseline. Features: designed for early detection of hearing loss. Limitation: does not classify severity of hearing loss. 3. **Münster.** Description: 8-point scale for minimal hearing loss (>10-20 dB), subgroups with major classifications, and tinnitus. Features: designed for early detection of hearing loss. Limitation: complexity of use 4. **Chang.** Description: 7-point scale; modification of Brock scale; grades hearing loss >20 dB and measures interval frequencies. Features: addresses functional deficits. Limitation: complexity of use. 5. **Common Terminology Criteria for Adverse Events version 4 (CTCAEv4).** Description: 4-point scale includes both objective and subjective criteria; grades are assigned based on threshold shift from baseline. Features: familiar to oncologists. Limitation: no configures for high- to low-frequency hearing loss commonly associated with cancer treatments. 6. **International Society of Pediatric Oncology (SIOP) Boston (2012).** Description: 5-point scale; designed to grade hearing loss progression from high to frequencies until 2 kHz; grades hearing loss >20 dB and uses absolute hearing levels. Features: potential application across clinical trials worldwide. Limitation: limited reliability and validity testing to date	*Landier, 2016*
1. **Common Terminology Criteria for Adverse Events (CTCAE).** Description: to report on adverse events during chemotherapy (adult and pediatric grades) Features: widely used for grading all chemotherapy-related toxicities Limitation: frequencies not specified; grades 2 and 3 are too coarsely defined. 2. **Brock.** Description: designed specifically for the assessment of platinum-induced hearing loss in children. Features: practical and easy to apply; no baseline required. Limitation: failure to indicate whether there has been a change in hearing due specifically to chemotherapy; does not capture hearing loss <40 dB; does not include frequencies >8 kHz; low sensitivity. 3. **American Speech-Language-Hearing Association (ASHA).** Description: measures threshold change from baseline. Features: evaluates hearing loss during or after treatment; sensitive. Limitation: does not classify severity of hearing loss; the lack of differentiation between affected frequencies; hard to interpret clinical impact. 4. **World Health Organization (WHO).** Description: based on the average of the thresholds at 0.5, 1, 2 and 4 kHz in the better ear. Features: outline the usual auditory performance at each grade and give recommendations for intervention. Limitation: failure to include frequencies above 4 kHz.	*Waissbluth, 2017*

5. **Pediatric Oncology Group Toxicity (POGT).** Description: developed for children treated with chemotherapy. Features: developed for children treated with chemotherapy. Limitation: low sensitivity (losses <4 kHz not included); high frequencies not specified. 6. **Münster.** Description: designed for early detection of cisplatin-induced hearing loss; also classifies tinnitus. Features: designed for early detection of cisplatin-induced hearing loss; also classifies tinnitus. Limitation: losses <4 kHz are assigned higher grades than losses at higher frequencies; classification does not specify which higher frequencies to test. 7. **Chang.** Description: a modified version of the Brock criteria. Features: takes into consideration that hearing loss affects children and adults differently and makes recommendation for children <10 years and for older children and adults; lower cutoff to 20 dB. Limitation: does not indicate whether there has been a change in hearing due to chemotherapy specifically; validation in process. 8. **Functional Hearing Loss (FHL).** Description: developed at the Children's Hospital in Boston and focuses on hearing loss affecting function. Features: sensitive; loss at lower frequencies assigned higher grade. Limitation: >8 kHz not specifically included. 9. **Hirntumor Studie (HIT).** Description: used in the European multicenter HIT-SIOP PNET4 trial. Features: based in thresholds at 2 kHz; no baseline required. Limitation: does not include frequencies >2 kHz; considers grading based on the worst ear; has not been used in any other chemotherapy trial or article. 10. **International Society of Pediatric Oncology (SIOP) Boston.** Description: a new scale combining the best features of previous criteria; a modification of the FHL scale. Features: sensitive; specific for children; loss at lower frequencies assigned higher grade. Limitation: certain concerns still need to be addressed, such as cranial irradiation, conductive hearing loss, and reporting of asymmetrical hearing loss; validation in process.	
Adults	
1. **TUNE (2014).** Description: 7-point scale; designed to provide insight into the effect of hearing loss on specific daily life situations. Features: includes subjective symptoms and threshold shifts at higher frequencies (up to 12.5 kHz); designed to represent the auditory system's real-world functionality. Limitation: time-consuming to use; needs external validation.	*Landier, 2016*
Conclusions expert opinion	
Children • ASHA • Brock • Chang • CTCAE • FHL • HIT • Münster • POGT • SIOP Boston • WHO	*2 studies* **Expert opinion**
Adults • TUNE	*1 study* **Expert opinion**

How often and for how long should surveillance be performed?

What is the likelihood of change (improvement or deterioration) of ototoxicity in CAYA cancer survivors treated with platinum agents? What is the time of such change?	
Conclusion single studies	
In 4 longitudinally followed CAYA solid tumor survivors treated with platinum agents with hearing loss, **hearing function deteriorated in 50%** (2/4) of the right ears **and in 50%** (2/4) of the left ears during a median follow-up period of 1.9 years after therapy (range: 0.9-3.1 years) according to ASHA criteria. Average worsening of the right ear was 10 dB, resulting in an average loss of 85 dB at 4 kHz. Average worsening of the left ear was 15 dB, resulting in an average loss of 85 dB at 4 kHz. In 4 longitudinally followed CAYA solid tumor survivors treated with platinum agents with hearing loss, **hearing function improved in 25%** (1/4) of the right ears and **in 25%** (1/4) of the left ears during a median follow-up period of 1.9 years after therapy (range: 0.9-3.1 years) according to ASHA criteria. Improvement of the right ear was 10 dB, resulting in a loss of 60 dB at 4 kHz. Improvement of the left ear was 10 dB, resulting in a loss of 60 dB 4 kHz. In 4 longitudinally followed CAYA solid tumor survivors treated with platinum agents with hearing loss, **hearing function was stable in 25%** (1/4) of the right ears **and in 25%** (1/4) of the left ears during a median follow-up period of 1.9 years (range: 0.9-3.1 years) according to ASHA criteria. Loss of the right ear was 80 dB at 4 kHz and loss of the left ear was 70 dB at 4 kHz. In 17 longitudinally followed CAYA solid tumor survivors treated with platinum agents (and some with cranial radiotherapy) without hearing loss, **hearing function deteriorated in 18%** (3/17) of the right ears **and in 31%** (5/16) of the left ears during a median follow-up period of 2 years (range: 1.1-5 years) according to ASHA criteria. Average worsening of the right ear was 20 dB, resulting in average function of 20 dB at 4 kHz. Average worsening of the left ear was 18 dB, resulting in average function of 26 dB at 4 kHz. In 17 longitudinally followed CAYA solid tumor survivors treated with platinum agents (and some with cranial radiotherapy) without hearing loss, **hearing function improved in 35%** (6/17) of the right ears **and in 13%** (2/16) of the left ears during a median follow-up period of 2 years (range: 1.1-5 years) according to ASHA criteria. Average improvement of the right ear was 11.6 dB, resulting in average function of 13.3 dB at 4 kHz. Average improvement of the left ear was 20 dB, resulting in average function of 15 dB at 4 kHz. In 17 longitudinally followed CAYA solid tumor survivors treated with platinum agents (and some with cranial radiotherapy) without hearing loss, **hearing function was stable in in 47%** (8/17) of the right ears **and in 56%** (9/16) of the left ears during a median follow-up period of 2 years (range: 1.1-5 years) according to ASHA criteria. Average function of 7.5 dB at 4 kHz of the right ear and average function of 11.1 dB at 4 kHz of the left ear.	*Al-Khatib, 2010*
In 36 longitudinally followed CAYA solid tumor survivors treated with platinum agents with hearing loss at the end of treatment, **hearing function was stable in 14%** (5/36) from <2 years post-therapy to a median of 7 years (range: 2-14 years) after end of treatment according to Brock criteria. Brock grade ≥2 after treatment and Brock grade ≥2 at follow-up. In 36 longitudinally followed CAYA solid tumor survivors treated with platinum agents without hearing loss at the end of treatment, **hearing function deteriorated in 25%** (9/36) from <2 years post-therapy to a median of 7 years (range: 2-14 years) after end of treatment according to Brock criteria. Brock grade 0 or 1 after treatment and Brock grade ≥2 at follow-up. In 36 longitudinally followed CAYA solid tumor survivors treated with platinum agents without hearing loss at the end of treatment, **hearing function was stable in 61%** (22/36) from <2 years post-therapy to a median of 7 years (range: 2-14 years) after end of treatment according to Brock criteria. Brock grade 0 or 1 after treatment and Brock grade 0 or 1 at follow-up.	*Bertolini, 2004*
In 61 longitudinally followed CAYA solid tumor survivors treated with platinum agents with hearing loss at the end of treatment, **hearing function was stable in 53%** during a median follow-up of 5.1 years after end of platinum treatment (range: 1.1-21.3) according to Münster criteria; **hearing function was stable in 89%** during a median follow-up of 9 years after end of platinum treatment (range: 1.1-21.3) according to SIOP Boston criteria. In 61 longitudinally followed CAYA solid tumor survivors treated with platinum agents with hearing loss at the end of treatment, **hearing function deteriorated in 47.5%** after end of platinum treatment according to Münster criteria; **hearing function deteriorated in 11%** after end of platinum treatment according to SIOP Boston criteria.	*Clemens, 2017*
In 6 longitudinally CAYA solid tumor survivors treated with platinum agents with hearing loss, **hearing function deteriorated in 100%** (6/6) from immediate post-chemotherapy to a median of 16 years (range 12.3-21.5 years) after the end of treatment according to Brock (no p-value reported). Average worsening was 20 dB at 4 kHz, resulting in an average loss of 70 dB. Average worsening was 20 dB at 8 kHz, resulting in an average loss of 80 dB. In 9 longitudinally followed CAYA solid tumor survivors treated with platinum agents without hearing loss, **hearing function was stable in 100%** (9/9) from immediate post-chemotherapy to a median of 10.4 years (range 6.2-22.3 years) after the end of treatment according to Brock (no p-value reported). Average loss of 10 dB at 4 kHz and 15 dB at 8 kHz.	*Einarsson, 2010*
In 204 longitudinally followed CAYA cancer survivors treated with platinum agents, the **prevalence of hearing loss increased** from **34%** (70/204) post-chemotherapy to **38%** (78/204) at a median of 39 months (range: 6-125 months) post-treatment according to Chang criteria. In 204 longitudinally followed CAYA cancer survivors treated with platinum agents, **hearing function deteriorated in 48%** (97/204) from a median of 4 months post-therapy (range: 0-42 months) to a median of 39 months (range: 6-125 months) post-treatment according to ASHA criteria.	*Peleva, 2014*
In 20 longitudinally followed CAYA osteosarcoma survivors treated with platinum agents with hearing loss, **hearing function improved in 10%** (2/20) 1 year after the first post-treatment audiogram according to a self-developed score system (no p-value reported). In 20 longitudinally followed CAYA osteosarcoma survivors treated with platinum agents with hearing loss, **hearing function deteriorated in 10%** (2/20) 1 year after the first post-treatment audiogram according to a self-developed sore system (no p-value reported).	*Stohr, 2005*

In 20 longitudinally followed CAYA osteosarcoma survivors treated with platinum agents with hearing loss, **hearing function was stable in 80%** (16/20) 1 year after the first post-treatment audiogram according to a self-developed score system (no p-value reported).	
Overall conclusion	
Likelihood of change of ototoxicity after platinum agents: There is low quality evidence in longitudinal studies with two measurements that hearing function may deteriorate in CAYA cancer survivors treated with platinum agents. However, there is also low quality of evidence that hearing function may improve. None of the studies reported the predictors for change. In one longitudinal study with more measurements, the proportion of CAYA cancer survivors with decreasing hearing function was stable between 10 and 25 months after initiation of treatment	*6 studies* **Level C**

Abbreviation: ASHA=American Speech-Language-Hearing Association

What is the likelihood of change (improvement or deterioration) of ototoxicity in CAYA cancer survivors treated with cranial radiation? What is the time of such change?

Conclusion single studies	
Cranial radiotherapy	
In 33 longitudinally followed CAYA brain tumor survivors treated with cranial radiotherapy with hearing loss, 19/33 (65.5%) experienced **continued decline** in hearing sensitivity at a median time of 1 year after hearing loss onset (range: 0.4-5.6 years).	*Bass, 2016*
In 62 longitudinally followed CAYA brain tumor survivors treated with cranial radiotherapy, **hearing function improved over time** at 0.25, 0.5 and 1 kHz (no p-value reported). In 22 longitudinally followed CAYA brain tumor survivors with infratentorial tumors treated with cranial radiotherapy, hearing function **improved over time** at 2 and 3 kHz ($p<0.0135$) compared to 50 survivors without infratentorial tumors.	*Merchant, 2004*
Cranial radiotherapy dose	
In 11 longitudinally followed CAYA brain tumor survivors treated with >38 Gy cranial radiotherapy (mean: 54.9 Gy, range: 38.2-61.1 Gy), **hearing function deteriorated** in 100% (11/11) after a median follow-up of 5 years (range: 4-6 years) post-radiotherapy.	*Hua, 2008*
In 16 longitudinally followed CAYA brain tumor survivors treated with >32 Gy cranial radiotherapy and cerebrospinal fluid shunts, hearing function had a **significantly greater rate of decline** at 0.25, 0.5 and 1 kHz ($p<0.003$) and 2 and 3 kHz ($p<0.0001$) compared to 5 survivors with a cochlear dose of <32 Gy ($p<0.0001$).	*Merchant, 2004*
Cranial radiotherapy and platinum	
In 379 longitudinally followed CAYA medulloblastoma survivors treated with cranial radiotherapy and platinum agents, the **proportion of survivors with hearing impairment increased shortly after treatment and plateaued** between 10 and 25 months after initiation of treatment (5 months: 5% hearing loss, 10 months: 30% hearing loss, 15 months: 32% hearing loss, 20 months: 33% hearing loss, 25 months: 33% hearing loss; no p-value reported).	*Gurney, 2014*
In 45 longitudinally followed CAYA medulloblastoma and pineoblastoma survivors treated with cranial radiation and cisplatin, **hearing function deteriorated** (CI hearing loss at 3 years: 12%, 95% CI: 4-25; CI hearing loss at 5 years: 16%, 95% CI: 6-29; CI hearing loss at 7 years: 16%, 95% CI: 6-29).	*Yock, 2016*
Cranial radiotherapy and platinum and cerebrospinal fluid shunts	
In 4 longitudinally followed CAYA brain tumor survivors treated with cranial radiotherapy, platinum agents and cerebrospinal fluid shunts, **hearing function declined** at 2 and 3 kHz (no p-value reported). In 3 longitudinally followed CAYA brain tumor survivors treated with >32 Gy cranial radiotherapy, platinum agents and cerebrospinal fluid shunts, there was a **significantly greater rate of decline** of hearing function at 2 and 3 kHz ($p<0.0001$) and at 4, 6 and 8 kHz ($p<0.0005$) compared to 2 survivors without shunts. In 4 longitudinally followed CAYA brain tumor survivors with central tumors, treated with cranial radiotherapy, and cerebrospinal fluid shunts, there was a **significantly greater rate of decline** of hearing function at 2 and 3 kHz compared to 22 central tumor survivors with cranial radiotherapy, but without shunts ($p<0.03$).	*Merchant, 2004*
Overall conclusion	
Likelihood of change of ototoxicity after cranial radiotherapy: There is low quality evidence in longitudinal studies that hearing function may deteriorate or improve in CAYA cancer survivors treated with cranial radiotherapy. None of the studies reported the predictors for change.	*2 studies* **Level C**
Likelihood of change of ototoxicity after cranial radiotherapy dose: There is high quality evidence in longitudinal studies that hearing function may deteriorate in CAYA cancer survivors treated with high dose cranial >32 or >38 Gy radiotherapy. None of the studies reported the predictors for change.	*2 studies* **Level C**

Likelihood of change of ototoxicity after cranial radiotherapy and platinum: There is low quality evidence in longitudinal studies that hearing function may deteriorate in CAYA cancer survivors treated with cranial radiotherapy and platinum agents. None of the studies reported the predictors for change. In one longitudinal study with more measurements, the proportion of CAYA cancer survivors with decreasing hearing function was stable between 10 and 25 months after initiation of treatment	*2 studies* **Level C**
Likelihood of change of ototoxicity after cranial radiotherapy, platinum and cerebrospinal fluid shunts: There is low quality evidence in longitudinal studies that hearing function may deteriorate in CAYA cancer survivors treated with cranial radiotherapy, platinum agents and cerebrospinal fluid shunts. The study did not report the predictors for change.	*1 study* **Level C**

What is the likelihood of change (improvement or deterioration) of ototoxicity in CAYA cancer survivors treated with cerebrospinal fluid shunts? What is the time of such change?

Conclusion single studies	
Cerebral spinal fluid shunts, cranial radiotherapy and platinum	
In 4 longitudinally followed CAYA brain tumor survivors treated with cranial radiotherapy, platinum agents and cerebrospinal fluid shunts, **hearing function declined** at 2 and 3 kHz (no p-value reported). In 3 longitudinally followed CAYA brain tumor survivors treated with >32 Gy cranial radiotherapy, platinum agents and cerebrospinal fluid shunts, there was a **significantly greater rate of decline** of hearing function at 2 and 3 kHz ($p<0.0001$) and at 4, 6 and 8 kHz ($p<0.0005$) compared to 2 survivors without shunts. In 4 longitudinally followed CAYA brain tumor survivors with central tumors, treated with cranial radiotherapy, and cerebrospinal fluid shunts, there was a **significantly greater rate of decline** of hearing function at 2 and 3 kHz compared to 22 central tumor survivors with cranial radiotherapy, but without shunts ($p<0.03$).	*Merchant, 2004*
Overall conclusion	
Likelihood of change of ototoxicity after cerebrospinal fluid shunts: There is low quality evidence in longitudinal studies that hearing function may deteriorate in CAYA cancer survivors treated with cranial radiotherapy, platinum agents and cerebrospinal fluid shunts. The study did not report the predictors for change.	*1 study* **Level C**

What is the likelihood of change (improvement or deterioration) of ototoxicity in CAYA cancer survivors after surgery involving the ear or cranial nerve VIII? What is the time of such change?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the likelihood of change (improvement or deterioration) of ototoxicity in CAYA cancer survivors after noise exposure? What is the time of such change?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the likelihood of change (improvement or deterioration) of tinnitus in CAYA cancer survivors treated with platinum agents? What is the time of such change?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the likelihood of change (improvement or deterioration) of tinnitus in CAYA cancer survivors treated with cranial radiotherapy? What is the timing of such change?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the likelihood of change (improvement or deterioration) of tinnitus in CAYA cancer survivors treated with cranial radiotherapy? What is the timing of such change?

No studies identified in childhood, adolescent and young adult cancer survivors.

What should be done when abnormalities are identified?

What is the effect of wearable technology in CAYA cancer survivors with hearing loss?

Conclusion single studies	
Childhood cancer survivors	
In solid tumor CAYA survivors with **hearing aids**, the total score on the Hearing Measurement Scale (HMS) was on average 61.7% lower than before hearing aid use. **Disability** was on average 26.6% **lower** than before hearing aid use on the HMS. **Difficulty with hearing speech** was on average 32.3% **lower** than before hearing aid use on the HMS. **Difficulty with spatial location** was on average 11.6% **lower** than before hearing aid use on the HMS. **Difficulty with speech distortion** was on average 15% **lower** than before hearing aid use on the HMS. **Word recognition** at ─8 S/N ratio **improved** with 21.5% (9-40%) and word recognition at ─5 dB S/N ratio improved with 33% (16-46%).	*Einarsson, 2011*
Overall conclusion There is low quality evidence that hearing aids decrease disability, difficulties with hearing speech, spatial location and speech distortion, and improving word recognition in CAYA cancer survivors with hearing loss.	*1 study* **Level C**

What is the effect of implantable technology in CAYA cancer survivors with hearing loss?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of tinnitus masker in CAYA cancer survivors with hearing loss?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of cochlear implant in CAYA cancer survivors with hearing loss?

Conclusion single studies	
Childhood cancer survivors	
In a patient with nephroblastoma and cerebellar metastasis, the **pure tone audiometry thresholds** at 6 and 12 months post cochlear implantation (120 dB at 4 kHz) were **similar** to preoperative levels (110 dB at 4 kHz). Monosyllable discrimination in quiet conditions was 50% preoperative, 65% at 6 months and 72% at both 12 and 18 months post cochlear implantation. Monosyllable discrimination in noisy conditions was 40% preoperative, 63% at 6 months and 68% at both 12 and 18 months post cochlear implantation. Sentence recognition in quiet conditions was 58% preoperative, 75% at 6 months and 82% at both 12 and 18 months post cochlear implantation. Sentence recognition in noisy conditions was 56% preoperative, 72% at 6 months at 78% at both 12 and 18 months post cochlear implantation.	*Kuthubutheen, 2012*
Overall conclusion There is low quality evidence that cochlear implantation improves hearing function in CAYA cancer survivors with hearing loss (preserving low frequency hearing, monosyllable discrimination and sentence recognition).	*1 study* **Level C**

What is the effect of upfront communication management strategies in CAYA cancer survivors with hearing loss?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of provision of educational changes/school support in CAYA cancer survivors with hearing loss?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of counseling in CAYA cancer survivors with hearing loss?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of social/emotional guidance in CAYA cancer survivors with hearing loss?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of speech and language therapy in CAYA cancer survivors with hearing loss?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of aural rehabilitation in CAYA cancer survivors with hearing loss?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of hearing conservation in CAYA cancer survivors with hearing loss?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of assistive listening devices/hearing assistive technology in CAYA cancer survivors with hearing loss?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of educational/vocational accommodations in CAYA cancer survivors with hearing loss?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of improvement of classroom acoustics in CAYA cancer survivors with hearing loss?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of tinnitus management strategies in CAYA cancer survivors with tinnitus?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of counseling in CAYA cancer survivors with tinnitus?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of social/emotional guidance in CAYA cancer survivors with tinnitus?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of tinnitus-retraining therapy in CAYA cancer survivors with tinnitus?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of educational/vocational accommodations in CAYA cancer survivors with tinnitus?

No studies identified in childhood, adolescent and young adult cancer survivors.

Interventions in patients with tinnitus

Conclusion guidelines	
Adults	
1. Recommendation: **targeted history and physical examination**. Benefit: identify patients with primary tinnitus 2. Recommendation: **audiologic examination** in patients with unilateral tinnitus. Benefit: prioritize the need for otolaryngologic evaluation and identify hearing loss which is frequently associated with tinnitus. 3. Recommendation: **audiologic examination** in patients with tinnitus Benefit: detect a hearing loss not perceived by patient, identify patients who may be candidate for **sound therapy**, identity opportunities for patient **counseling/education**. 4. Recommendation: distinguish patients with bothersome tinnitus from patients with non-bothersome tinnitus. Benefit: Identify patients for further **counseling and/or intervention/management**; identify patients with bothersome tinnitus who may benefit from additional assessment for anxiety and depression. 5. Recommendation: **educate patients** with persistent, bothersome tinnitus about management strategies. Benefit: improved QOL, increased ability to cope with tinnitus; improved outcomes and patient satisfaction; less health care utilization. 6. Recommendation: a **hearing aid** for patients with hearing loss and persistent, bothersome tinnitus. Benefit: access to technologies/devices that may relieve tinnitus; improve QOL, sleep and concentration. 9. Recommendation: **cognitive behavioral therapy** to patients with persistent, bothersome tinnitus. Benefit: treatment of depression and anxiety; improved QOL; tinnitus coping skills.	*International guideline clearinghouse, 2013*
Conclusions recommendations in existing guidelines	
Possible interventions for adults with tinnitus are: • Sound therapy • Counseling/education	*1 guideline* **Existing guidelines**

• Intervention/management • Education about management strategies • Hearing aid • Cognitive behavioral therapy	

Interventions in patients with hearing loss

Conclusion single guidelines	
Adults	
1. Recommendation: exclusion of conductive hearing loss. Benefit: guide choice of appropriate diagnostic test. 2. Recommendation: assess patients with presumptive sudden sensorineural hearing loss Benefit: identification of those who required specialized assessment and management. 3. Recommendation: evaluate patients with sudden sensorineural hearing loss for retrocochlear pathology by MRI, auditory brainstem response or audiometric follow-up. Benefit: identify brain tumor patients; identify conditions that might benefit from early treatment. 4. Recommendation: **educate** patients with sudden sensorineural hearing loss about history of condition, benefits and risk of medical interventions, and limitation of existing evidence regarding efficacy. Benefit: increase patient adherence to proposed therapy. 5. Recommendation: counsel patients with incomplete recovery of hearing about benefits of **amplification** and **hearing-assistive technology** and **other supportive measures.** Benefit: improved QOL; improved functionality; emotional support; improved hearing	*International guideline clearinghouse, 2011*
Children	
1. Recommendation: **unilateral cochlear implantation** Benefit: benefits in auditory, speech perception and speech production outcomes. 2. Recommendation: **bilateral cochlear implantation** Benefit: improvement in the ability to identify the direction from which a sound is coming and improvement in speech perception in noisy conditions with bilateral cochlear implants.	*National Institute for Health and Care Excellence, 2009*
1. **Hearing aids** (behind the ear; in the ear; body style; bone conduction) 2. **Tactile aids** 3. **FM systems** 4. **Cochlear implant** (children 12 months-2 years: profound deafness in both ears, lack in the progress in the development of auditory skills; children 2-17 years: severe-to-profound sensorineural hearing loss in both ears, receiving little or no useful benefit from hearing aids; 5. **Communication approaches**: auditory approaches, sign language, parental involvement. 6. **Intervention programs**: family education and participation; family support; language development; auditory skill training (speech-language therapy); opportunities for the family to interact with deaf or hard of hearing child; techniques to facilitate listening and speech).	*New York State Department of Health, 2007*
1. Air conduction and bone conduction **hearing aids**: for sensorineural hearing loss. 2. **Cochlear implants**: for children with severe to profound sensorineural hearing loss. 3. Referral for **educational services**: individualized education plans, performing periodic assessments of the child's listening situation and needs to determine candidacy for hearing assistance technology).	*American Academy of Audiology, 2013*
Conclusions recommendations in existing guidelines	
Possible interventions for adults with hearing loss are: • Education • Amplification • Hearing-assistive technology • Other supportive measures	*1 guideline* **Existing guidelines**
Possible interventions for children with hearing loss are: • Cochlear implantation (unilateral or bilateral) • Hearing aids	*3 guidelines* **Existing guidelines**

• Tactile aids • FM system • Communication approaches • Intervention programs	

"What surveillance modality system should be used?"

Behavioral testing:

Behavioral testing, including pure tone conventional audiometry, visual reinforcement audiometry, conditioned play audiometry, and speech audiometry is dependent on developmental age and cooperation of the patient[34-38].

Extended high frequency audiometry

Extended high frequency (EHF) audiometry or speech audiometry can be used in addition to traditional behavioral pure tone audiometry in detecting hearing loss. EHF audiometry can detect ototoxic damage to hearing before the conventional frequency range is impacted. This testing identifies early signs of ototoxicity. Patients must be old enough to understand behavioural threshold testing in order for EHF audiometry to be measured.

Speech audiometry

Speech audiometry provides a functional evaluation on the patient's ability to perceive and discriminate speech at various intensity levels, both in quiet and in noise. Many different speech tests are available dependent upon age and language development. Phoneme discrimination tests (like speech reception thresholds, word recognition, or speech testing in noise) in addition to abnormal visual reinforcement audiometry provides information on phoneme discrimination abilities. This, in turn, informs audiological counselling about options for addressing the person's hearing status.

Non-behavioral testing:

Auditory brainstem response

Auditory brainstem response (ABR) is a non-behavioral testing method that does not require an active response of the patient. In addition to determination of site(s) of lesion of hearing loss, ABR can be helpful in estimating hearing thresholds and is generally used in a test battery including distortion product otoacoustic emission and acoustic immittance tests to provide a more comprehensive profile of hearing status than is available by using a single objective test procedure. ABR is used to estimate hearing thresholds when reliable behavioral testing is not possible due to age, equipment, or medical condition. ABRs can also be recommended for older children/adolescents/adult survivors who are cognitively impaired and unable to participate in conventional pure tone audiometry. It provides an estimate of hearing sensitivity and is, therefore, more appropriate in determining hearing status compared to distortion product otoacoustic emissions in difficult-to-test patients.

Distortion product otoacoustic emission

As an established alternative for children who are difficult to test, distortion product otoacoustic emission (DPOAE) testing is used as a cross-check for verification of behavioral testing[18,39-41]. In the presence of normal outer and middle ears, DPOAEs provide an indication of cochlear function at the level of the outer hair cells. This serves as a helpful crosscheck in determining the site of lesion of the hearing loss. Essentially, DPOAEs are extremely sensitive to detecting outer hair cell deterioration and has the ability to measure subclinical signs of ototoxicity before hearing loss occurs. DPOAEs are standard part of the ototoxicity monitoring test battery for all patients, regardless of ability to cooperate for pure tone hearing threshold testing.

Acoustic immittance tests

Acoustic immittance includes tympanometry as well as other measures such as ear canal volume, static compliance, acoustic reflexes, which audiologists will employ as needed for the individual case. Tympanometry is an assessment that can be added to behavioral testing or otoacoustic emission testing. Tympanometry assesses middle ear pressure, tympanic membrane mobility, and ear canal volume. While a useful indicator, tympanometry alone may be insufficient in determining some middle ear pathologies; thus, bone conduction audiometry is warranted to rule out a conductive component to hearing loss. The components of adequate audiological testing will vary with the purpose of any given assessment.

While the focus of the test battery for long term follow up patients may differ from the focus during treatment; the essential principles of determining nature, degree, stability and implications of hearing status remain the same.

Test method	Testing procedures	Testing result	Strengths	Limitations
Behavioral testing				
Pure tone conventional audiometry	Tones between 125 and 8,000 Hz are delivered through headphones, bone conductors or speakers*. When the patient hears a tone he/she pushes a button or raises a hand – survivors ≥5 years of age	Audiogram showing the amount of hearing loss per frequency in dB (HL)**	• Provides information about type, degree and configuration of hearing loss	• Not useful for patients who are unable to cooperate
Conditioned play audiometry	Tones are delivered through headphones, bone conductors or speakers. Patient is taught to perform an action in response to a sounds, such as placing a block in a basket – survivors aged 2-5 years	Audiogram showing the amount of hearing loss per frequency in dB (HL)**	• Provides information about type, degree and configuration of hearing loss	• Not useful for patients who are unable to cooperate
Visual reinforcement audiometry	Tones are delivered through headphones, bone conductors or speakers. Patient is trained to look toward the direction of the sound, giving him/her rewards like video animation or lighted toys – infants between 5-24 months developmental age	Reactogram indicating the level at which a head turn as a reaction to sound is observed in dB (HL) or dB (DL)***	• Provides information about type, degree and configuration of hearing loss	• Not useful for patients who are unable to cooperate
Extended high frequency audiometry	Tones ≥8,000 Hz are delivered through headphones. When the patient hears a tone he/she pushes a button or raises a hand – survivors ≥5 years of age	Audiogram showing the amount of hearing loss per frequency in dB (SPL)****	• Can detect ototoxic damage to hearing before the conventional frequency range is impacted • Can be used in addition to pure tone audiometry	• Not useful for patients who are unable to cooperate
Speech audiometry	A variety of test procedures using speech stimuli ranging from phoneme detection to speech understanding in background noise. Tests are selected as suitable for patient's developmental level	Ability to detect and/or understand speech	• Provides indication of the functional effect of hearing loss on communication	• Not useful for patients who are unable to cooperate
Non-behavioral testing				
Auditory brainstem response	Electrical activity from the auditory pathway is generated by a click or tone pip via earphones. The response is measured by electrodes placed on the scalp that is analyzed by a computer and produces a waveform.	Cranial nerve VIII and brainstem brain wave activity in response to sound. Provides an estimate of hearing sensitivity in dB $(nHL)^{+}$ or dB $(eHL)^{\S}$. Aides in determining site of lesion.	• Requires no active response from the patient • Provides an estimate of hearing sensitivity in patients unable to respond due to young age, delayed development, or impaired cognition	• Detects fewer patients with hearing loss than with behavioral testing • Less sensitive than behavioral audiometry • Requires patient should be very still, asleep, or under sedation to ensure accurate test results
Distortion product otoacoustic emission	Ear probe that produces paired tones and includes a microphone to measure the response of functioning outer hair cells to acoustic stimuli	An indication of cochlear function at the level of outer hair cells	• Crosscheck in determining the site of lesion of the hearing loss • Extremely sensitive to detecting outer hair cell deterioration and has the ability to measure subclinical signs of ototoxicity before hearing loss occurs.	• Measurement affected by outer and middle ear pathologies • Does not provide information on hearing loss severity • Does not provide information on the auditory pathway past the level of the cochlear outer hair cell
Tympanometry	Hand-held probe is inserted into the ear, producing a tone and changing the pressure. Microphone on the probe measures the amount of sound that is reflected back from eardrum	Assesses middle ear pressure, tympanic membrane mobility, and ear canal volume	• Needed for valid interpretation of otoacoustic emissions • Provides information about middle ear function	• Tympanometry alone may be insufficient in determining some middle ear pathologies; thus, bone conduction audiometry is warranted to rule out a conductive component to hearing loss

*125 Hz is not very relevant. Speakers can be calibrated to the frequency range 250-6000 Hz (frequency range depends on type of loudspeaker. For higher frequencies the sound level at the ear may vary due to shorter wavelength of standing wave pattern in rooms)

** dB(HL) is dB Hearing Level according to ISO 1975 and 0 dB(HL) corresponds to the threshold of hearing for young adults with normal hearing.

*** dB(DL) is dB Dial Level. The smaller size of the ear canal of young children affects the actually sound level at the eardrum. Hence, without correction using Real-Ear-to-Coupler-Difference (RECD) the sound level read from the audiometer [dB(DL)] does not necessarily correspond to the sound level that would have been presented at the ear drum of an adult with pure tone audiometry [dB(HL)]. Furthermore, thresholds of 20-25 dB(DL) are considered normal for presentation with a loudspeaker and 10-15 dB(DL) are considered normal for presentation with earphones.

**** dB(SPL) is dB Sound Pressure Level. There is debate about standards for normal hearing for frequencies above 8 kHz. The reason is that the sound level of pure tone may vary at the ear drum by as much as 20 dB, depending on earphone placement. This is due to standing wave patterns in the ear canal that can occur at frequencies above 10 kHz.

+ dB(nHL) is dB Above Normal Adult Hearing Level. This is the lowest sound level at which neural response can be observed.

§ dB(eHL) is dB Equivalent Hearing Level. This is the sound level that would have been found in an adult with the same hearing loss but measured with pure tone audiometry. The correction factor needed to obtain dB(eHL) from dB(nHL) is a function of transducer type, stimulus type and subject age.

Classification systems for research and clinical trials

Grading systems are most often used to report hearing loss or hearing outcomes in groups of patients in clinical trials and for clinical research. There are many classification systems in use to describe audiological outcomes. The widely used 5-point Brock scale is designed to grade hearing loss progression from high to low frequencies until 1 kHz.[16,42] The American Speech-Language-Hearing Association (ASHA) scale is designed for early detection of hearing loss and indicates a hearing threshold shift (or decrease in hearing threshold level) in comparison with baseline testing.[16,43] The Münster scale is an 8-point scale to detect minimal hearing loss (>10-20 dB), considers tinnitus and is also designed for early detection of hearing loss.[16,44] The 7-point Chang scale is a modification of the Brock scale and captures hearing loss >20 dB, but <40 dB.[16,45] The Common Terminology for Adverse Events (CTCAE) classification system is widely used in the field of oncology to grade several adverse events, including hearing loss.[16,46] The CTCAEv4 ototoxicity grading system is based on threshold shift from baseline and therefore requires baseline testing. Furthermore, some scales are designed for use in the pediatric population, whereas others are designed for use in adults.
Because of the need for harmonization of grading sales, a consensus meeting was held at SIOP Boston in 2010 producing the International Society of Pediatric Oncology (SIOP) Boston scale. This is a 5-point scale designed to grade hearing loss progression from high to low frequencies until 2 kHz.[16,47] However, when grading hearing loss according to Brock, Chang or the SIOP Boston scale in patients treated with cranial radiotherapy, the lower frequencies which may be affected, technically cannot be graded using these scales. The scale of the hearing loss depends on which classification is chosen and the cut-off points within each system are not the same, hence the SIOP Boston consensus grading for clinical trials developed in 2010. There is *low* quality evidence that there is strong concordance and agreement between the Brock, Chang, CTCAE version 3, SIOP, ASHA, CCG and POGT classification systems (level C evidence).[15,16,48-51] It is clear that these grading systems are essential for comparative clinical trial research. It is not clear that they are useful for assessing hearing at follow-up unless a particular follow-up research study is being carried out.

What are the concordances between different classification systems?

Conclusion single studies	
Chang vs. CTCAEv3	
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the Chang scale is **highe**r than the sensitivity of the CTCAEv3 scale in predicting the need for hearing support at the end of treatment (Chang: 83%; CTCAEv3: 43%). The **specificity** of the Chang scale is **lowe**r than the specificity of the CTCAEv3 scale (Chang: 36%; CTCAEv3: 100%). The **negative predictive value** of the Chang and CTCAEv3 scale is **equal** (Chang: 82%; CTCAEv3: 80%). The **positive predictive value** of the Chang is **lower** than the positive predictive value of the CTCAEv3 scale (Chang: 38%; CTCAEv3: 100%).	*Lafay-Cousin, 2013*
In neuroblastoma CAYA survivors, there is a **strong concordance** between the Chang and CTCAEv3 dichotomous yes/no ototoxicity (100%, p<0.05).	*Landier, 2014*
Chang vs. SIOP	
In medulloblastoma CAYA survivors, there is a **strong concordance** between the Chang and SIOP ototoxicity scales (Stuart tau-c statistics: 0.89 (95% CI: 0.86-0.91)).	*Bass, 2014*
Chang vs. ASHA	
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the Chang and ASHA scale is **equal** in predicting the need for hearing support at the end of treatment (Chang: 83%; ASHA: 71%). The **specificity** of the Chang scale is **lowe**r than the specificity of the ASHA (Chang: 36%; ASHA: 53%). The **negative predictive value** of the Chang and ASHA scale is **equal** (Chang: 82%; ASHA: 80%). The **positive predictive value** of the Chang and ASHA scale is **equal** (Chang: 38%; ASHA: 41%).	*Lafay-Cousin, 2013*
In neuroblastoma CAYA survivors, there is a **strong concordance** between the Chang and ASHA dichotomous yes/no ototoxicity (99.3%, p<0.05).	*Landier, 2014*
Chang vs. Münster	
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the Chang scale is **highe**r than the sensitivity of the Münster scale in predicting the need for hearing support at the end of treatment (Chang: 83%; Münster: 67%). The **specificity** of the Chang scale is **lowe**r than the specificity of the Münster scale (Chang: 36%; Münster: 87%).	*Lafay-Cousin, 2013*

The **negative predictive value** of the Chang and Münster scale is **equal** (Chang: 82%; Münster: 80%). The **positive predictive value** of the Chang is **lower** than the positive predictive value of the Münster scale (Chang: 38%; Münster: 64%).	
CTCAEv3 vs. SIOP	
SIOP detects significantly more survivors with any ototoxicity than CTCAEv3.0 (**p=0004**). SIOP detects significantly more survivors with severe ototoxicity than SIOP (**p=0.02**).	*Knight, 2017*
In osteosarcoma CAYA survivors, there is a **strong concordance** between the CTCAEv3 and SIOP ototoxicity scale (94%, p-value not given) There was discordance in 6%: four patients with SIOP grade 1 had CTCAE grade 2. Three patients with SIOP grade 2 had CTCAEv3 grade 3.	*Hagleitner, 2014*
CTCAEv3 vs. ASHA	
CTCAEv3 grade ≥1 vs ASHA **(K:1.0)**, CTCAEv3 grade ≥2 vs ASHA **(K: 0.82)**, CTCAEv3 grade ≥3 vs ASHA **(K:0.35).**	*Knight, 2005*
ASHA detects significantly more survivors with any ototoxicity than CTCAEv3.0 (**p=0.0002**).	*Knight, 2017*
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the CTCAEv3 scale is **lower** than the ASHA scale in predicting the need for hearing support at the end of treatment (CTCAEv3: 43%; ASHA: 71%). The **specificity** of the CTCAEv3 scale is **higher** than the ASHA scale (CTCAEv3:100%; ASHA: 53%). The **negative predictive value** of the CTCAEv3 and the ASHA scale is **equal** (80%). The **positive predictive value** of the CTCAEv3 scale is **higher** than the ASHA scale (CTCAE3v: 100%; ASHA: 41%).	*Lafay-Cousin, 2013*
In neuroblastoma CAYA survivors, there is a **strong concordance** between the CTCAEv3 and ASHA dichotomous yes/no ototoxicity **(100%, P<0.05)**.	*Landier, 2014*
CTCAEv3 vs. Münster	
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the CTCAEv3 scale is **lower** than the Münster scale in predicting the need for hearing support at the end of treatment (CTCAEv3: 43%; Münster 67%). The **specificity** of the CTCAEv3 scale is **higher** than the Münster scale (CTCAEv3:100%; Münster: 87%). The **negative predictive value** of the CTCAEv3 and the Münster scale is **equal** (80%). The **positive predictive value** of the CTCAEv3 scale is **higher** than the Münster scale (CTCAE3v: 100%; Münster: 64%).	*Lafay-Cousin, 2013*
CTCAE v3 vs. Children Cancer Group grade (CCG)	
In retinoblastoma CAYA survivors, there is a **strong agreement** between CTCAEv3 and CCG **(83.3%)**.	*Qaddoumi, 2012*
Brock vs. ASHA	
In CAYA cancer survivors, the Brock grade **does not agree** well with the ASHA criteria (Brock grade ≥1 vs ASHA (K:0.63), Brock grade ≥2 vs ASHA (K: 0.33), Brock grade ≥3 vs ASHA (K:0.06)).	*Knight, 2005*
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the Brock scale is **lower** than the ASHA scale in predicting the need for hearing support at the end of treatment (Brock: 57%; ASHA: 71%). The **specificity** of the Brock scale is **higher** than the ASHA scale (Brock: 80%; ASHA: 53%). The **negative predictive value** of the Brock and ASHA scale is **equal** (80%). The **positive predictive value** of the Brock scale is **higher** than the ASHA scale (Brock: 57%; ASHA: 41%).	*Lafay-Cousin, 2013*
In neuroblastoma CAYA survivors, there is a **strong concordance** between the Brock and ASHA dichotomous yes/no ototoxicity **(99.3%, p<0.05)**.	*Landier, 2014*
Brock vs. CTCAv3	
CTCAEv3 ≥3 vs Brock **(K:0.65)**, Brock ≥2 vs CTCAEv3 **(K:0.88)**.	*Knight, 2005*
Brock detects significantly fewer survivors with any ototoxicity than CTCAEv3 (**p<0.001**). Brock detects significantly fewer survivors with severe ototoxicity than CTCAEv3 (**p<0.001**).	*Knight, 2017*
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the Brock scale is **higher** than the CTCAEv3 scale in predicting the need for hearing support at the end of treatment (Brock: 57%; CTCAEv3: 43%). The **specificity** of the Brock scale is **lower** than the CTCAEv3 scale (Brock: 80%; CTCAEv3: 100%). The **negative predictive value** of the Brock and CTCAEv3 scale is **equal** (80%). The **positive predictive value** of the Brock scale is **lower** than the CTCAEv3 scale (Brock: 57%; CTCAEv3: 100%).	*Lafay-Cousin, 2013*
In neuroblastoma CAYA survivors, there is a **strong concordance** between the Brock and CTCAEv3 dichotomous yes/no ototoxicity **(100%, p<0.05)**. There is **less concordance** between the Brock and CTCAEv3 ototoxicity scales **(48.4%, p<0.001)**.	*Landier, 2014*
In retinoblastoma CAYA survivors, there is a **strong agreement** between Brock and CTCAEv3 grades **(86.7%)**.	*Qaddoumi, 2012*
Brock vs. Münster	
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the Brock and the Münster scale are **equal** in predicting the need for hearing support at the end of treatment (Brock: 57%; Münster: 67%). The **specificity** of the Brock and Münster scale is equal (Brock: 80%; Münster 87%).	*Lafay-Cousin, 2013*

The **negative predictive value** of the Brock and Münster scale is **equal** (80%). The **positive predictive value** of the Brock and Münster scale is equal (Brock: 57%; Münster 64%).	
Brock vs. Chang	
In neuroblastoma CAYA survivors, there is a **strong concordance** between the Brock and Chang dichotomous yes/no ototoxicity **(99.6%, p<0.05)**. There is a **less strong concordance** between the Brock and Chang ototoxicity scales **(52.8%< p<0.001)**.	*Landier, 2014*
Münster vs. ASHA	
In medulloblastoma survivors, during treatment the **sensitivity** of the Münster and ASHA scale is **equal** in predicting the need for hearing support at the end of treatment (Münster: 67%; ASHA: 71%). The **specificity** of the Münster scale is **higher** than the ASHA scale (Münster: 87%; ASHA: 53%). The **negative predictive value** of the Münster and ASHA scale is **equal** (80%). The **positive predictive value** Münster scale is **higher** than the ASHA scale (Münster: 64%; ASHA: 41%).	*Lafay-Cousin, 2013*
Brock vs. Children Cancer Group grade (CCG)	
In retinoblastoma CAYA survivors, there is a **strong agreement** between Brock and CCG **(93.3%)**.	*Qaddoumi, 2012*
ASHA vs. Bilateral Hearing Loss grade (BHL)	
In CAYA cancer survivors, there is a **weak concordance** between the ASHA and BHL ototoxicity scales **(Kappa: 0.33).** The **prevalence** of hearing loss according to the ASHA and BHL grades were **42.5% and 12.8%.**	*Da Silva, 2007*
ASHA vs. Pediatric Oncology Group Toxicity grade (POGT)	
In CAYA cancer survivors, there is a **strong concordance** between the ASHA and POGT ototoxicity scales **(Kappa: 0.96).** The **prevalence** of hearing loss according to the ASHA and POGT grades were **42.5% and 40.4%.**	*Da Silva, 2007*
BHL vs. POGT	
In CAYA cancer survivors, there is a **weak concordance** between the POGT and BHL ototoxicity scales **(Kappa: 0.36)** The **prevalence** of hearing loss according to the POGT and BHL grades were **40.4% and 12.8%.**	*Da Silva, 2007*
Overall conclusion	
There is strong concordance/agreement between the different classification systems. **Chang vs. CTCAEv3** (dichotomous scale, 100% concordance, p<0.05) **Chang vs. SIOP** (continuous scale, Stuart tau-c statistics: 0.89, 95% CI: 0.86-0.91) **Chang vs. ASHA** (dichotomous scale, 99.3% concordance, p<0.05) **CTCAEv3 vs. SIOP** (continuous scale, 94% concordance, p-value not given) **CTCAEv3 vs. ASHA** (continuous scale, K:1.0. Dichotomous scale, 100%, p<0.05) **CTCAEv3 vs. CCG** (continuous scale, 83.3%, p-value not given) **Brock vs. ASHA** (dichotomous scale, 99.3%, p<0.05) **Brock vs. CTCAEv3** (continuous scale, K: 0.88 and 0.65, 86.7%, p-values not given. Dichotomous scale, 100%, P<0.05) **Brock vs. Chang** (dichotomous scale, 99.6%, p<0.05) **Brock vs. CCG** (continuous scale, 93.3%) **ASHA vs. POGT** (continuous scale, K: 0.96) There is a low agreement between some classification systems **Brock vs. ASHA** (continuous scale, ≥grade 3 K:0.06, ≥grade 2 K:0.33) **Brock vs. CTCAEv3** (continuous scale, 48.4%, p<0.001) **ASHA vs. BHL** (continuous scale, K: 0.33) **BHL vs. POGT** (continuous scale, K: 0.36)	*6 studies* **Level C**

What is the value of different classification systems in research vs. clinical practice?

No studies identified in childhood, adolescent and young adult cancer survivors.

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