Inno-VA-tions in Ototoxicity Management for Patients with Cancer

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NCRAR Seminar
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Potential Conflicts of Interest

Dr. Konrad-Martin is co-inventor on two patents related to ototoxicity monitoring methodology and equipment. She receives no remuneration from this intellectual property.

Author Statement

These contents are the opinions of the speaker and do not necessarily represent the views of the VA or the United States Government.

IOMG Acknowledgement

I am a member of the International Ototoxicity Management Group (IOMG).

This work is intended to align with the IOMG mission and its views for effective ototoxicity management.

Acknowledgements

- NCRAR colleagues
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- Kelly Reavis, PhD
- Hunter Stuehm, BS
- Sarah Theodoroff, PhD

Outline

- Background
- Study 1: Perspectives of VA audiologists: Valued aspects of OtoM, current practices, and barriers to care
- Study 2: VA clinical trial: OtoM effectiveness
- Study 3: Overview of ototoxicity prediction algorithms
- Conclusions, implications

Background

1 of 3 Americans diagnosed with cancer in their lifetime
1.7 million Americans *newly diagnosed* each year
17 million cancer survivors currently

https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf

This is what success looks like

Ototoxic platinum-based drugs are a mainstay of cancer treatment

- 5-year survival rate is 60-70% for all cancers depending on race
- Platinum compounds are used in 10-20% of all cancer treatment
  - solid tumors: colorectal, head & neck, lung, ovarian, testicular, and bladder
- Within VHA in 2018, 10.4K Veteran patients received a platinum-based chemotherapy
- High reported rates of ototoxic hearing loss, tinnitus and balance problems following tx with platinum-based drugs

VA Cancer Registry, 2018

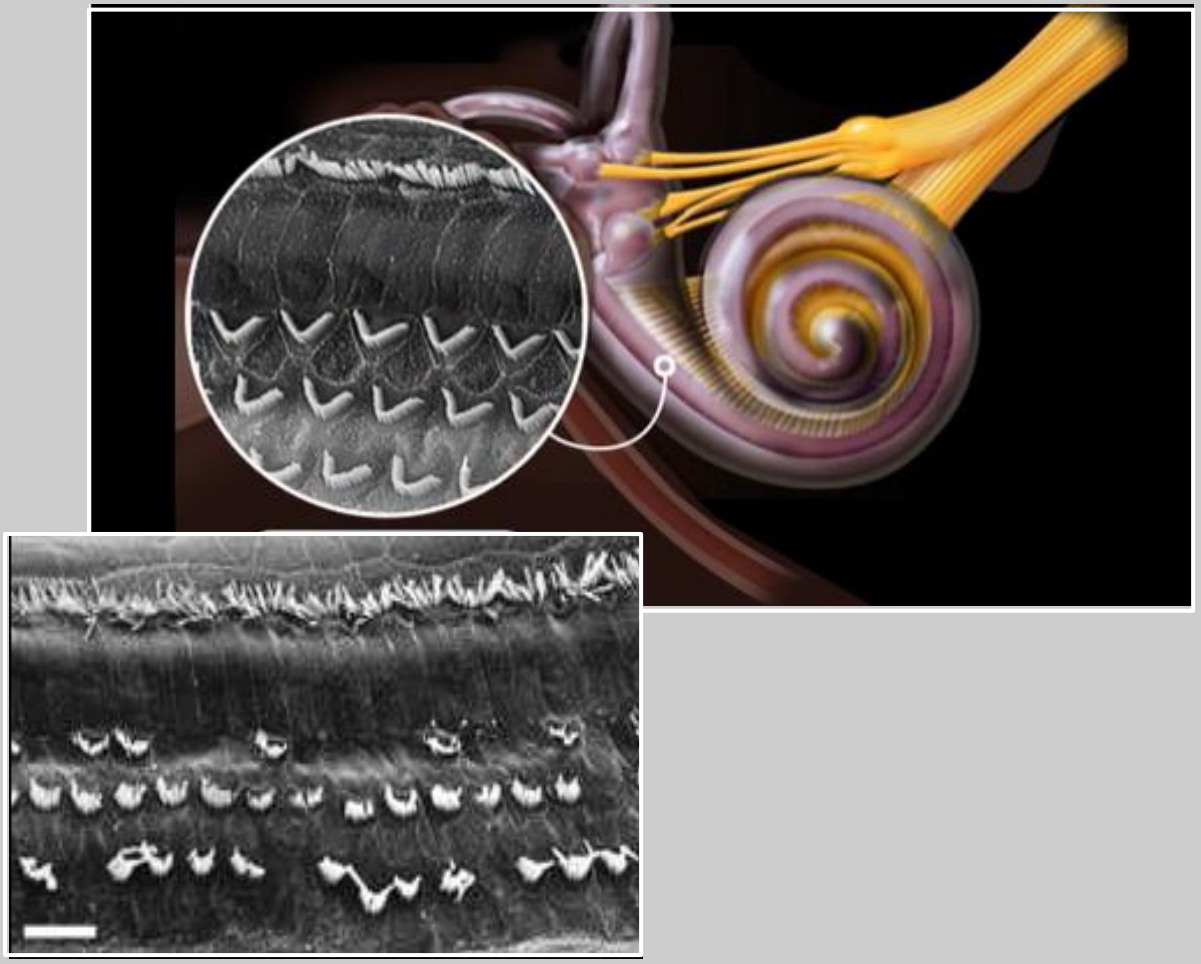
https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf

https://www.cancer.gov/research/progress/discovery/cisplatin#:~:text=Cisplatin%20is%20also%20used%20in%20the%20treatment%20of,10%20to%2020%20percent%20of%20all%20cancer%20patients.

Ototoxicity

Damage to the inner ear, targeting cochlear and vestibular structures and function, due to exposure to certain pharmaceuticals, chemicals, and/or ionizing radiation

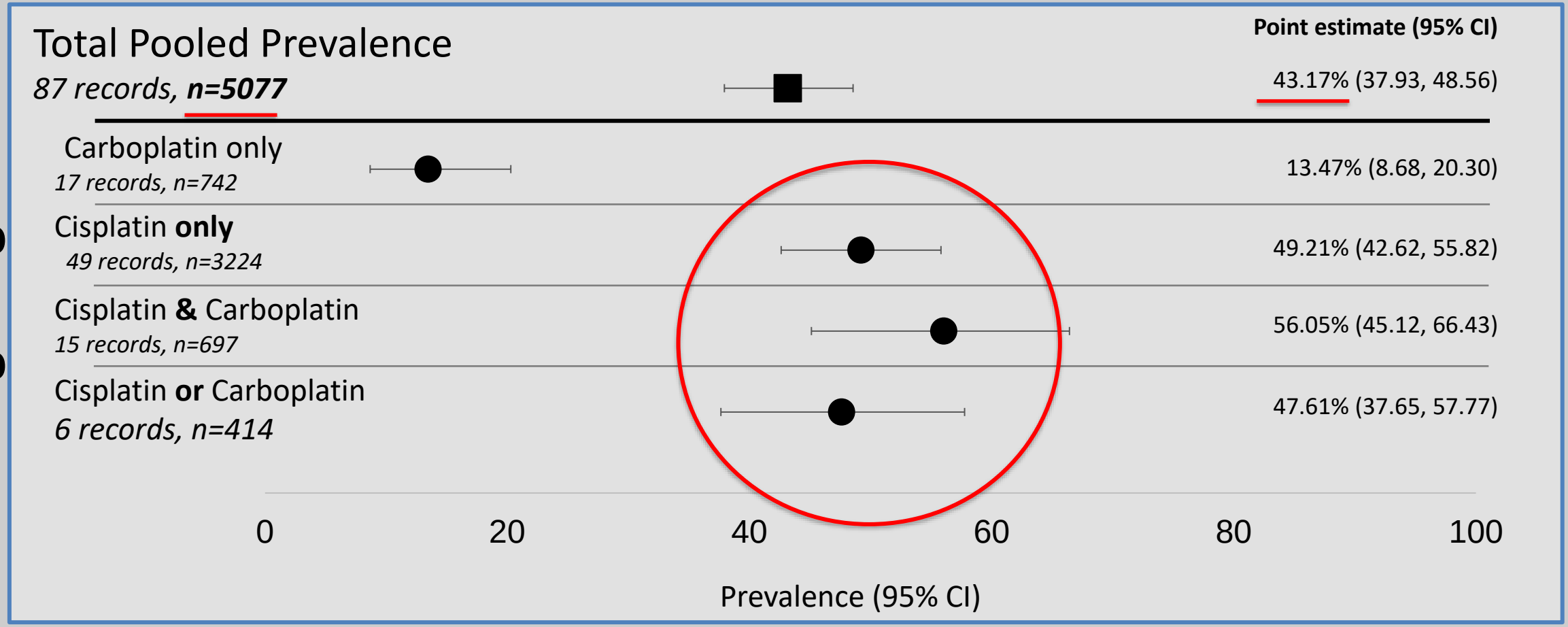
Department of Defense, HCE, PIHL Working Group, Ototoxicity Subcommittee, 2018



Photos courtesy of Dr. Marc Lenoir, from "Promenade around the cochlea" EDU website: http://www.cochlea.org, by Remy Pujol et al., INSERM and University of Montpellier

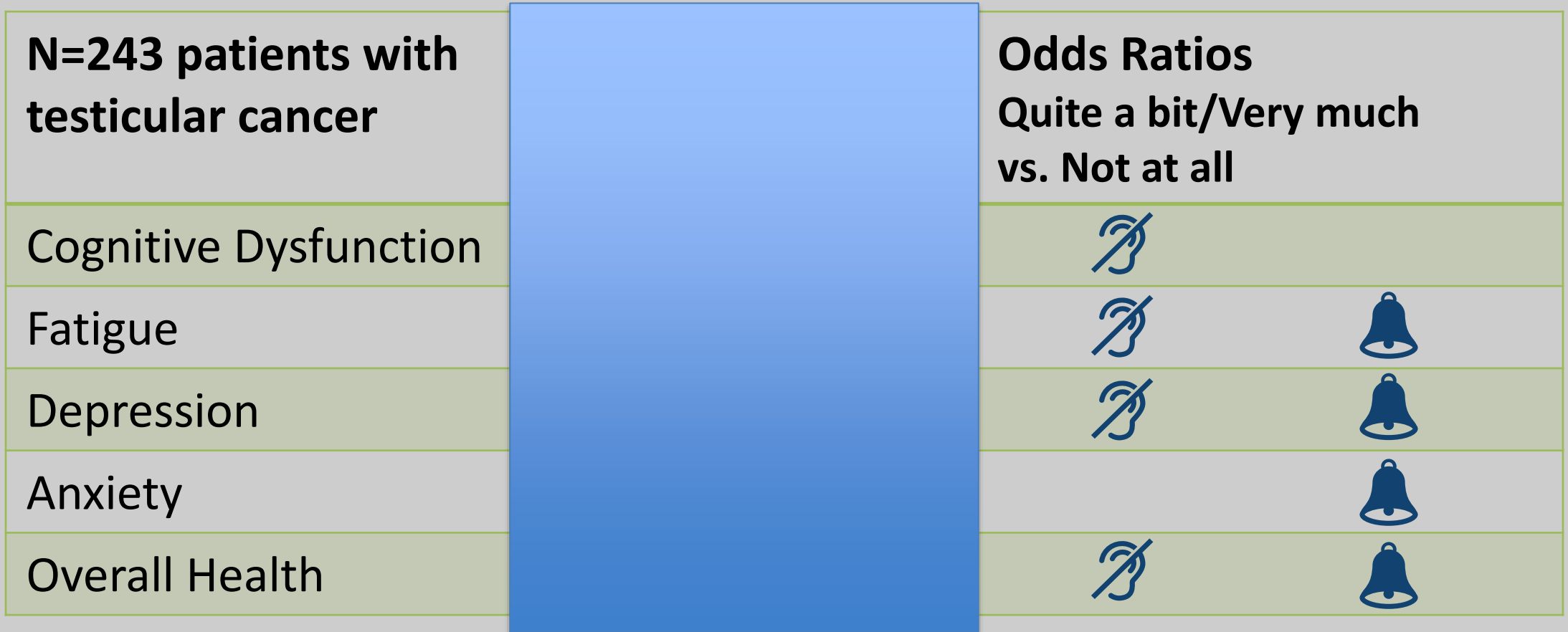
Prevalence of hearing loss after treatment for cisplatin and/or carboplatin: A systematic review and meta-analysis of literature from 2005-2008

Lauren K Dillard, Catherine M McMahon, Amanda M Fullerton, Lucero Lopez Perez, Ricardo X Martinez, Shelly Chadha, *Cancer Epidemiology*, vol 79, 2022



Hearing loss & tinnitus associated with decreased physical and psychological health after tx with cisplatin

Sanchez, Victoria A., Megan M. Shuey, Paul C. Dinh, Patrick O. Monahan, Sophie D. Fosså, Howard D. Sesso, M. Eileen Dolan, et al. "Patient-Reported Functional Impairment Due to Hearing Loss and Tinnitus After Cisplatin-Based Chemotherapy." *Journal of Clinical Oncology*, January 10, 2023, JCO.22.01456. https://doi.org/10.1200/JCO.22.01456.



Wide support for ototoxicity management from national and international groups

Association and document name	Patient Population	Helpful Content
American Academy of Audiology (AAA) Position Statement and Clinical Practice Guidelines: Ototoxicity Monitoring (2009) http://www.audiology.org	• Adults • Pediatrics	• Overview of ototoxic medications • Outline of vestibulotoxicity monitoring
American Speech-Language-Hearing Association (ASHA) Guidelines for the Audiologic Management of Individuals Receiving Cochleotoxic Drug Therapy (1994) http://asha.org	• Adults • Pediatrics • Unresponsive patients	• Suggested procedures for monitoring
Health Professions Council of South Africa (HPCSA) Audiological management of patients on treatment that includes ototoxic medications (2019) https://www.hpcsa.co.za	• General population	• Outline of ototoxicity and vestibular toxicity management programs • Ototoxic monitoring flow chart • Inclusion of vestibular point-of-care screenings • Inter-professional team collaboration chart
World Health Organization (WHO) World Report on Hearing (2021) https://www.who.int/publications/i/item/world-report-on-hearing	• General population	• Epidemiological data from different world regions • Emphasis on screening targeted to different age groups, including ototoxicity monitoring
American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) Position Statement: Ototoxicity (2015) http://www.entnet.org	• General population	• Role of Otolaryngologists in ototoxicity monitoring
American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Disease (2007) *Am J Res Crit Care Med*, 175:367-416.	• Patients with pulmonary infections	• Diagnostic criteria of Nontuberculous Mycobacterial (NTM) Lung Disease • Clinical diseases caused by NTM • Table of ototoxic drug side effects

Ototoxicity Management is An Unmet Need

- de Andrade, Khoza-Shangase, Hajat, 2009 (South Africa)
- Ehlert, Heinze, Swanepoel, 2022 (South Africa)
- Garinis, Cornell, Allada, Fennelly, Maggiore, Konrad-Martin (USA)
- Khoza-Shangase & Jina, 2013 (South Africa)
- Khoza-Shangase & Masondo, 2020 (South Africa)
- Konrad Martin, Poling, Garinis, Ortiz, Hopper, O'Connell Bennett, Dille, 2018 (USA/ 5 regional hospitals)
- Konrad-Martin, O'Connell Bennett, Garinis, McMillan, 2021 (USA)
- Kuchya, Tode, Sachdeva, Salankar, 2019 (India)
- Maru & Malky, 2018 (UK)
- Paken, Govender, Pillay, Sewram, 2020 (South Africa)
- Paken, Govender, Pillay, Sewram, 2022 (South Africa)
- Santucci, Garber, Ivory, Kuhn, Stephen, Aizenberg, 2021 (USA/UC Davis)
- Steffens, Venter, O'Beirne, Kelly-Campbell, Gibbs, Bird, (2014) (New Zealand)
- Wium & Gerber, 2016 (South Africa)

International Ototoxicity Management Group, IOMG

- Awareness pertaining to ototoxicity is generally missing from routine health and safety monitoring in occupational settings
- Few healthcare delivery models integrate auditory and vestibular health providers into the care pathways of patients receiving ototoxic treatments
- Ototoxic exposures occur in a wide variety of contexts (i.e. across work environments, clinical populations, healthcare structures, models of care, global regions, cultures) in which approaches will need to be tested and adapted
- There are no widely-used standardized objectives or theoretically grounded delivery approaches for ototoxicity management
- We lack contextually appropriate guidance on how to achieve objectives and implement approaches in specific contexts

http://www.ncrar.research.va.gov/ClinicianResources/IOMG.asp

OXFORD

JNCI J Natl Cancer Inst (2021) 113(9): djab049

doi: 10.1093/jnci/djab049
First published online March 23, 2021
Commentary

COMMENTARY

Evidence Gaps in Cancer Survivorship Care: A Report From the 2019 National Cancer Institute Cancer Survivorship Workshop

Lisa Gallicchio, PhD,[1,*] Emily Tonorezos, MD, MPH,[2] Janet S. de Moor, PhD, MPH,[3] Joanne Elena, PhD,[1] Margaret Farrell, MPH, RD,[4] Paige Green, PhD, MPH, FABMR,[5] Sandra A. Mitchell, PhD, CRNP,[6] Michelle A. Mollica, PhD, MPH, RN, OCN,[6] Frank Perna, EdD, PhD,[7] Nicole Gottlieb Saiontz, MHS,[8] Li Zhu, PhD,[9] Julia Rowland, PhD,[10] Deborah K. Mayer, PhD, RN, AOCN, FAAN[11,12]

- Treatment-survivorship continuum of care should include:
  - Surveillance for recurrence/new cancers
  - Management for physical and psychosocial consequences of cancer and its treatment
  - Care coordination between specialists and primary care providers to ensure all health needs are met
  - Health promotion/implementation science
  - Financial hardship
- Evidence needed to inform survivorship care

Study 1

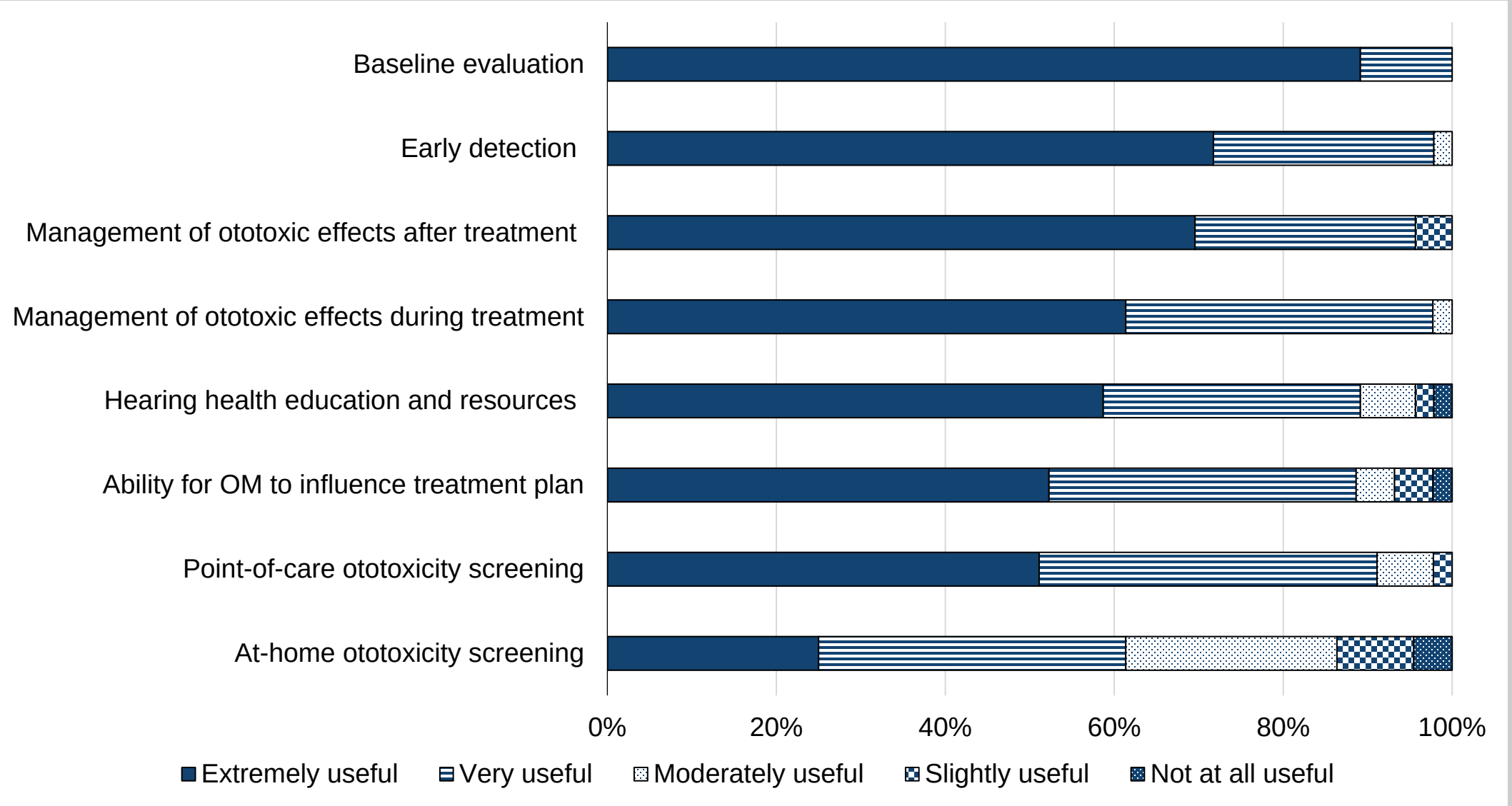
Journal of Cancer Survivorship
https://doi.org/10.1007/s11764-022-01316-7

Audiologists' perceived value of ototoxicity management and barriers to implementation for at-risk cancer patients in VA: the OtoMIC survey

Dawn Konrad-Martin[1,2] · Rachel Polaski[1] · J. Riley DeBacker[1] · Sarah M. Theodoroff[1,2] · Angela Garinis[1,2] · Cecilia Lacey[1] · Kirsten Johansson[3] · Rosemarie Mannino[3,4] · Trisha Milnes[1,5] · Michelle Hungerford[1] · Khaya D. Clark[1,6]

Received: 14 September 2022 / Accepted: 7 December 2022

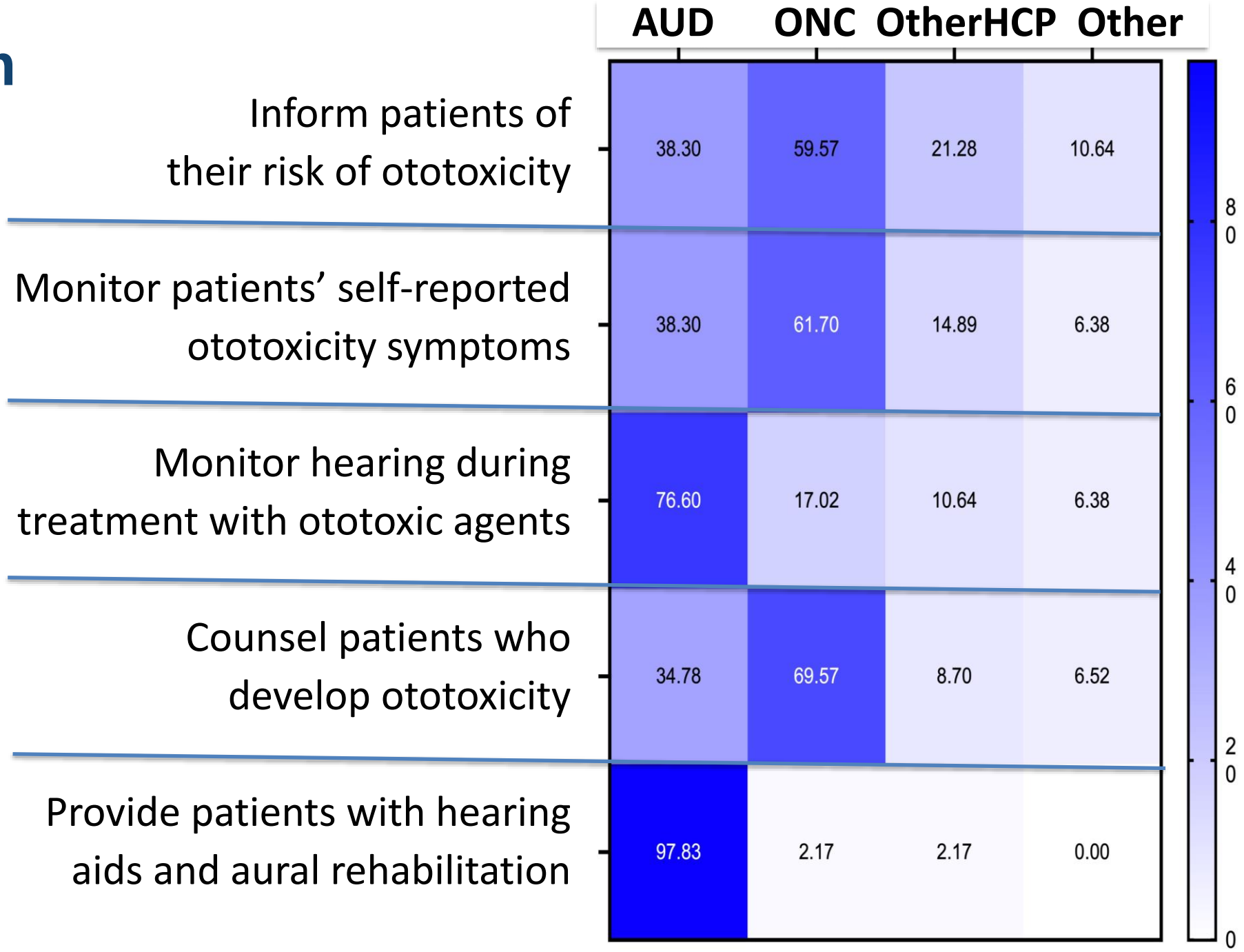
Valued objectives of ototoxicity management N=46



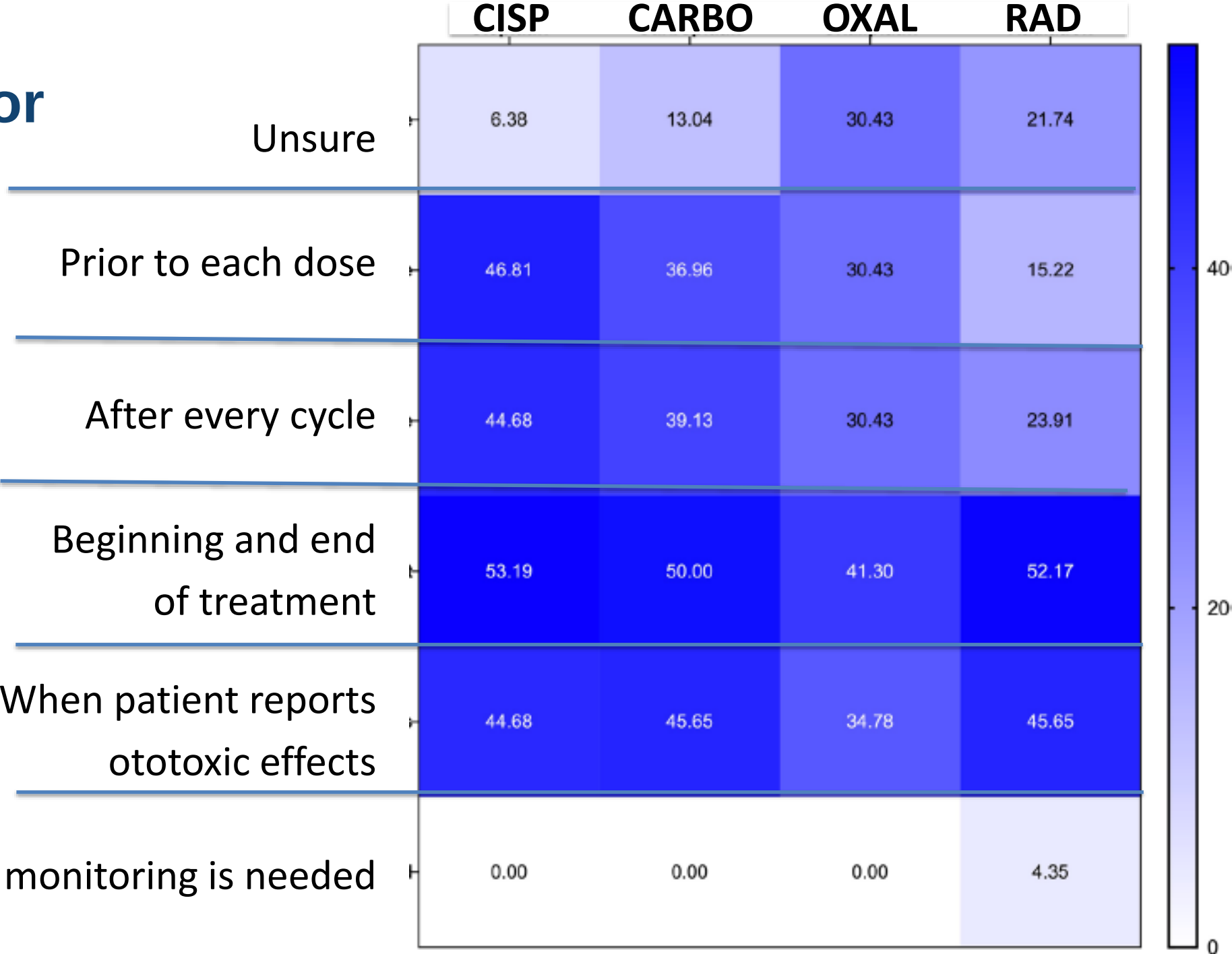
Highest Value

Lowest Value

Perceived team member roles N=46

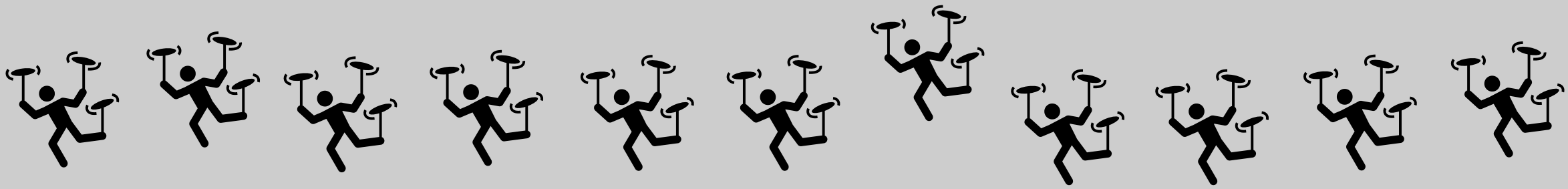


When to monitor
N=47



Barriers to ototoxicity management in VA N=63

Theme	CFIR domain	Example quotations
Interdisciplinary communication and identifying patients	Inner setting	• Without an oncologist on site, it has been difficult to generate referrals or know which patients are receiving any of these ototoxic medications • Lack of communication between oncology and audiology • [Audiology] services not integrated as part of the treatment team with oncology
Resources	Inner setting	• Time and space to get patients seen before, after treatments, and after complaints of changes • Do not have ototoxic[ity] program specialist position • Perhaps if someone was on-call when ototoxic patients are identified
Lack of protocol	Outer setting	• A national standardized protocol would be helpful to encourage good communication between [audiology and oncology] departments • Scope of practice • No known protocol that both [audiology and oncology] departments follow



Proportion of respondents who felt they implement key OtoM objectives

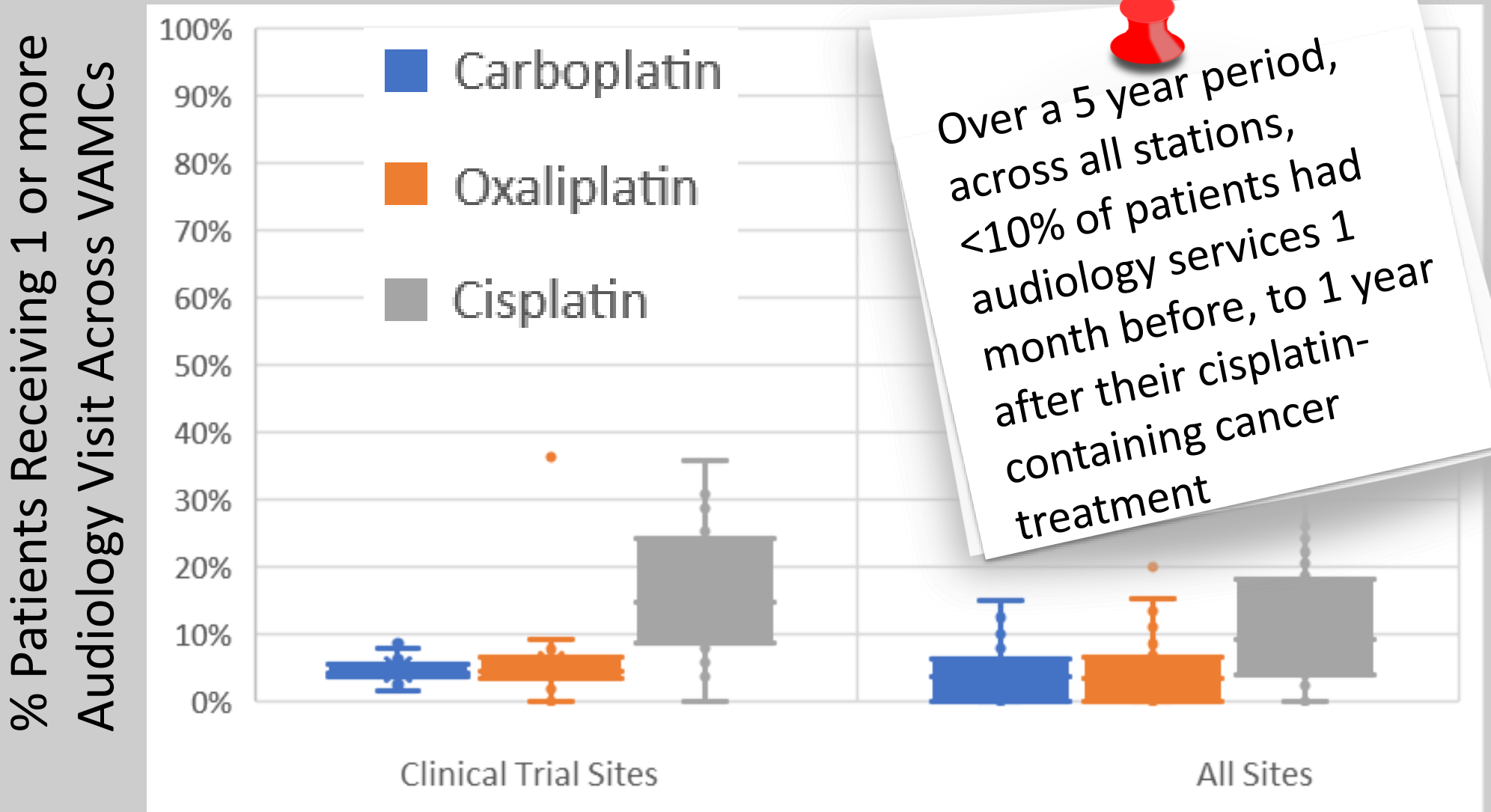
44%-64% reported having implemented

- baseline,
- monitoring,
- and follow up

for patients receiving cisplatin and carboplatin

		Fully implemented (Yes)
Perform a Baseline Evaluation		
Agent	Cisplatin	**53%**
	Carboplatin	**45%**
	Oxaliplatin	33%
	Radiation	20%
Monitor for Hearing Changes		
Agent	Cisplatin	**64%**
	Carboplatin	**50%**
	Oxaliplatin	32%
	Radiation	32%
Perform a Follow-up Evaluation		
Agent	Cisplatin	**51%**
	Carboplatin	**44%**
	Oxaliplatin	28%
	Radiation	21%

VA audiology service use for patients on a platinum-containing chemotherapy (based on medical record)



Study 2

AJA

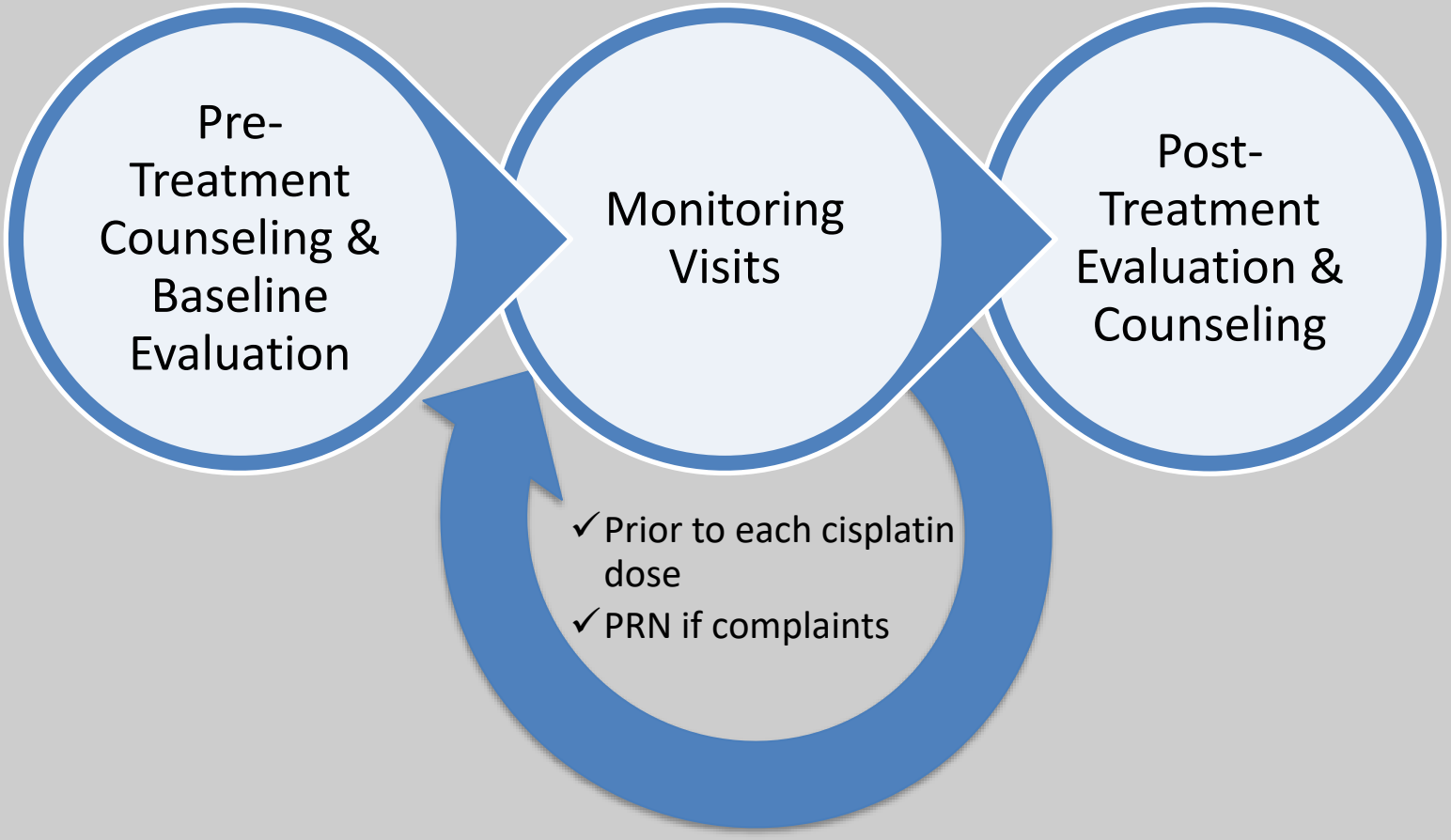
Research Article

A Randomized Controlled Trial Using Automated Technology for Improving Ototoxicity Monitoring in VA Oncology Patients

Dawn Konrad-Martin,[a,b] Keri O'Connell Bennett,[a] Angela Garinis,[a,b,c] and Garnett P. McMillan[a,b]

American Journal of Audiology • Vol. 30 • 870–886 • October 2021 • In the Public Domain

Ototoxicity management recommended practices



American Speech-Language Hearing Association, 1994;
American Academy of Audiology, 2009

Clinical trial randomization arms

Automated-OtoM Arm (N=24)

- ✓ A-OtoM with the Oto-ID mobile audiometer allowed patients to test own hearing in the chemo infusion unit
- ✓ Follow up and care coordination provided by study team

The Oto-ID was previously validated for use in VA cancer patients. It meets or exceeds ANSI specifications for audiometers (Dille et al. 2013; Brungart et al. 2018)

Usual Care Arm (N=22)

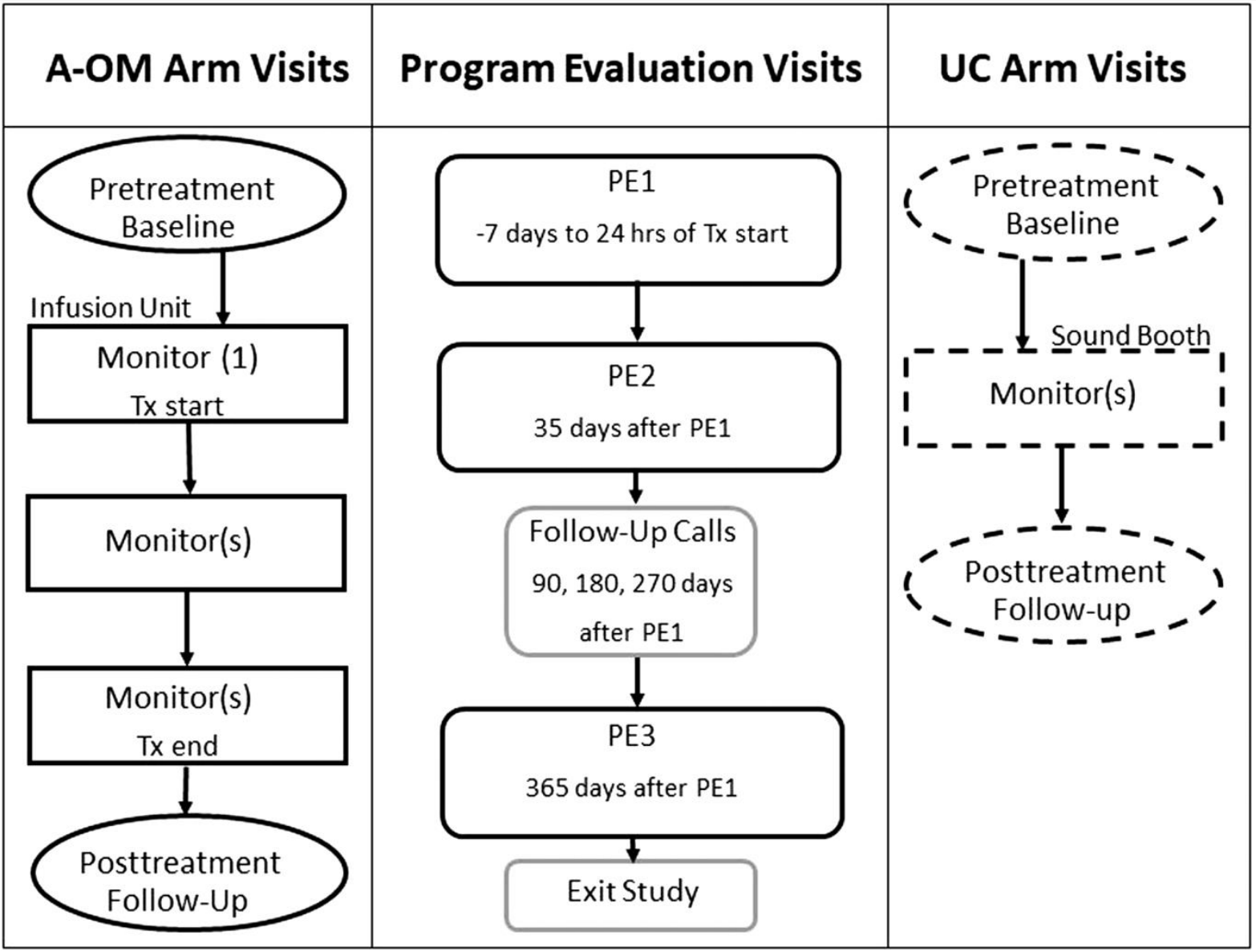
- ✓ Study team provided a referral to the audiology clinic
- ✓ The clinic has a protocol for OtoM that is consistent with ASHA and AAA
- ✓ The clinic and patient had to coordinate to set up any audiology visit(s)
- ✓ Visits conducted in the audiology clinic

Patient demographics, aspects of cancer by arm

Treatment arm	A-OM	UC	All
Participants, no.	24	22	46
Age, mean (range), *y*	64.5 (51–78)	64.8 (30–77)	64.7 (30–78)
Primary tumor location, no. (%)			
Bladder	0	2 (9)	2 (4)
Head and neck	4 (17)	5 (23)	9 (20)
Kidney	1 (4)	0	1 (2)
Lung	6 (25)	7 (32)	13 (28)
[1]Oropharyngeal	13 (54)	7 (32)	20 (43)
Testicular	0	1 (5)	1 (2)
Treatment characteristics			
Cisplatin initial dose, *M* (range), mg/m^2	49.4 (30–80)	48.9 (20–75)	49.1 (20–80)
Cisplatin cumulative dose, at last program evaluation, *M* (range), mg/m^2	206 (0–320)	224 (0–450)	214 (0–450)
Concurrent radiation, No. (%)	17 (70.8)	16 (72.7)	33 (71.7)
Radiation dose, *M* (range), Gy	69.2 (63–70)	66.3 (45–70)	67.8 (45–70)

Note. [1]Oropharyngeal cancer includes tonsil, base of tongue, uvula, and soft palate. A-OM = automated ototoxicity monitoring; UC = usual care; Gy = gray (absorbed energy per unit mass of tissue).

Study design and participant flow



Randomization arms:

- A-OM = automated ototoxicity monitoring
- UC = usual care

Program evaluations

- PE = program evaluation data used to assess outcomes (other than # visits)
- Provided basic information about ototoxicity and hearing including appropriate referrals based on findings
- Ethically important, but could limit arm differences

Usual Care audiology services fails to adhere to recommended practices

Number of pre-exposure Chemotherapy doses,

Table 3. Chemotherapy doses and baseline and hearing monitor tests during treatment by study arm.

Arm	Baseline (*N*)	Doses of drug (*N*)	Doses per pt (*M*, range)	Total monitors (*N*)	Monitors per pt (*M*, range)	Best practice provided (%)
A-OM (*N* = 24)	24	128*	5.3¥, 2–8	117+	4.8, 2–7	83.3%
UC (*N* = 22)	10	128	5.8, 2–20	14	0.6, 0–3	4.5%

Preferred Practice would have meant a lot of testing (too much?)

UC did not come close to preferred Practice

UC fails to provide audiology case management for most patients

These data correspond to testing conducted for clinical purposes in the A-OtoM and UC arms of the study.

A-OtoM = automated ototoxicity monitoring

UC = usual care

High rates of ototoxicity in VA cancer patients treated with cisplatin

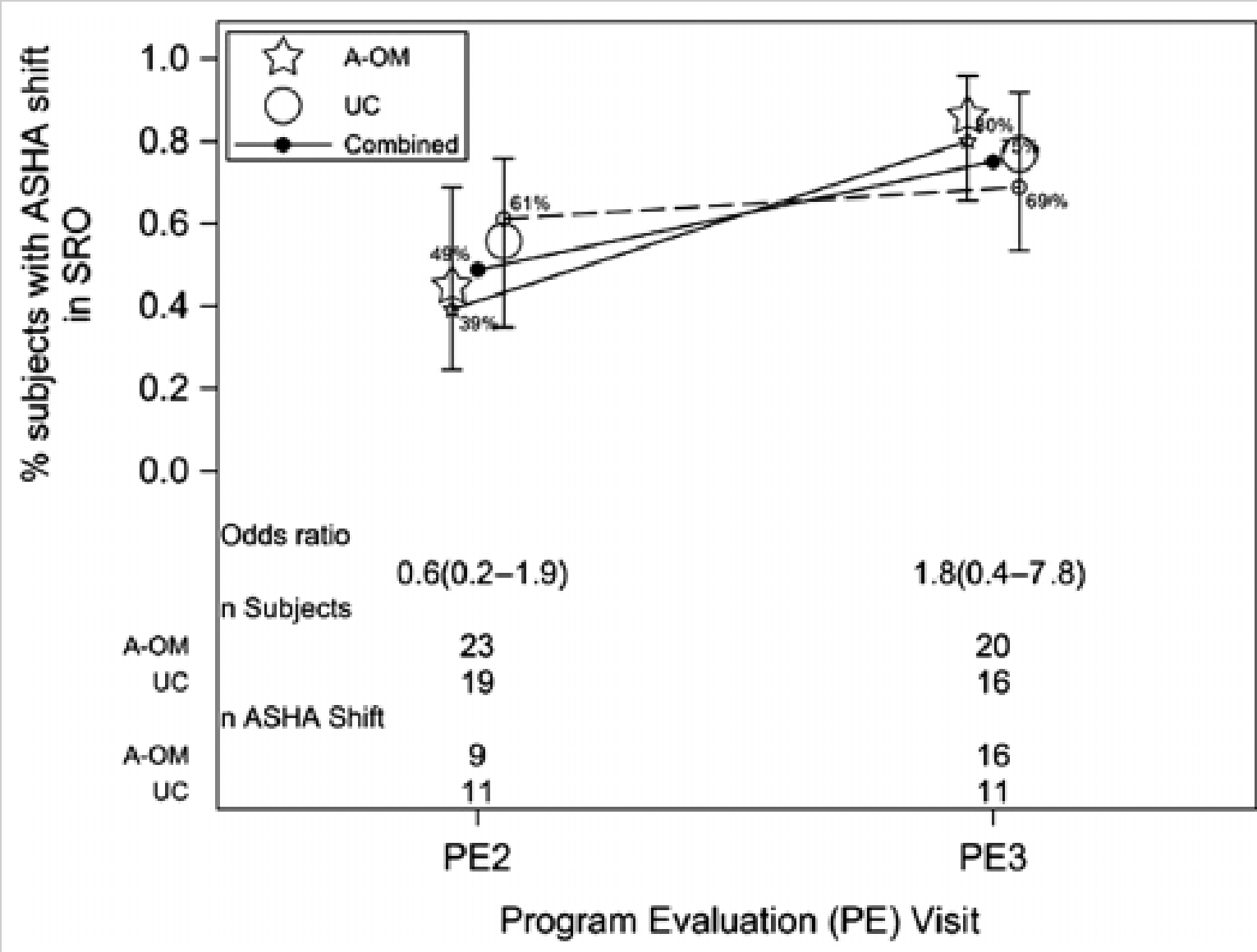
Stars: Automated monitoring using OtoID

Open circles: Usual care

Filled circles: Combined across randomization arms

No differences across arms

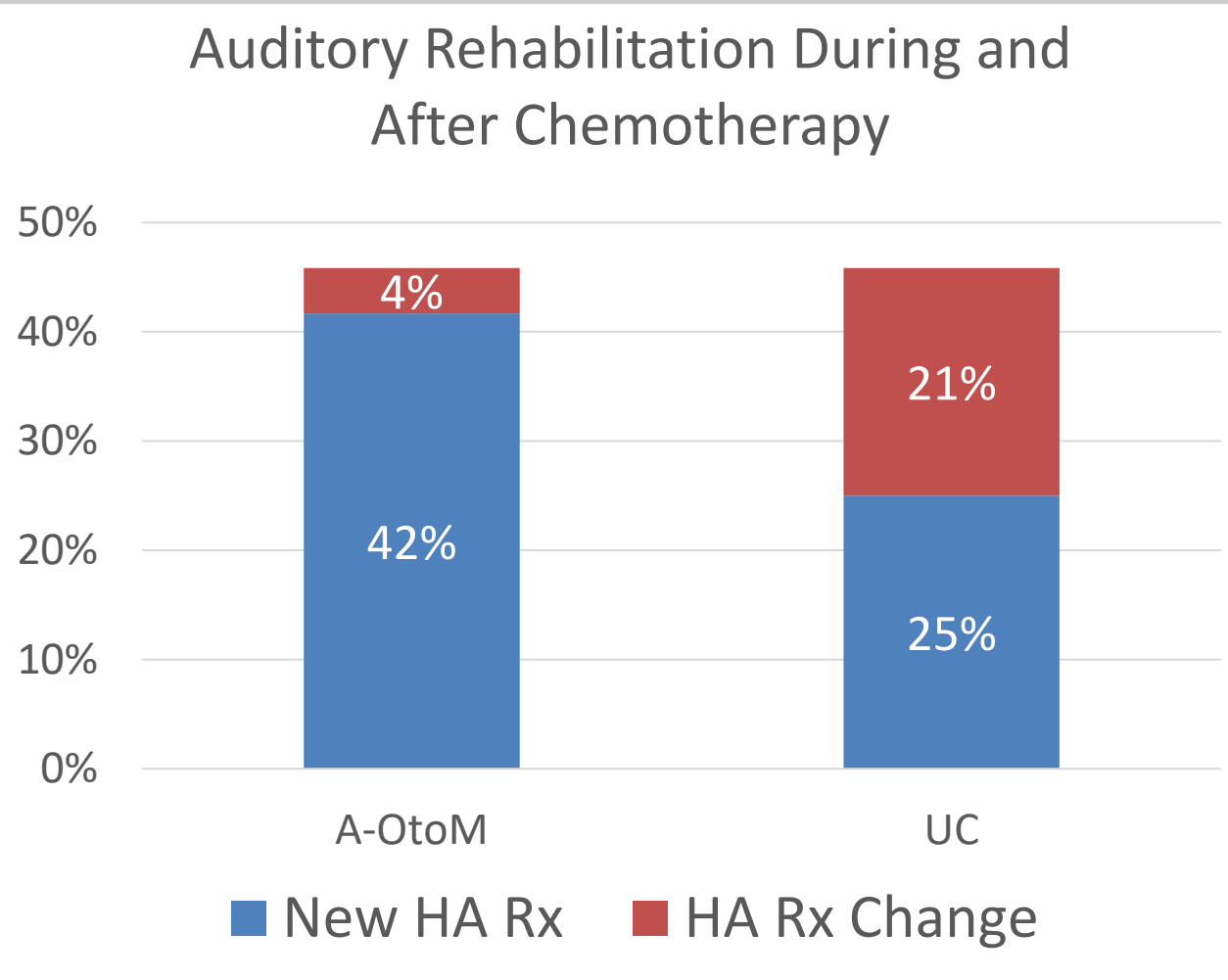
Risk of hearing shift **46 - 75%** depending on PE time point

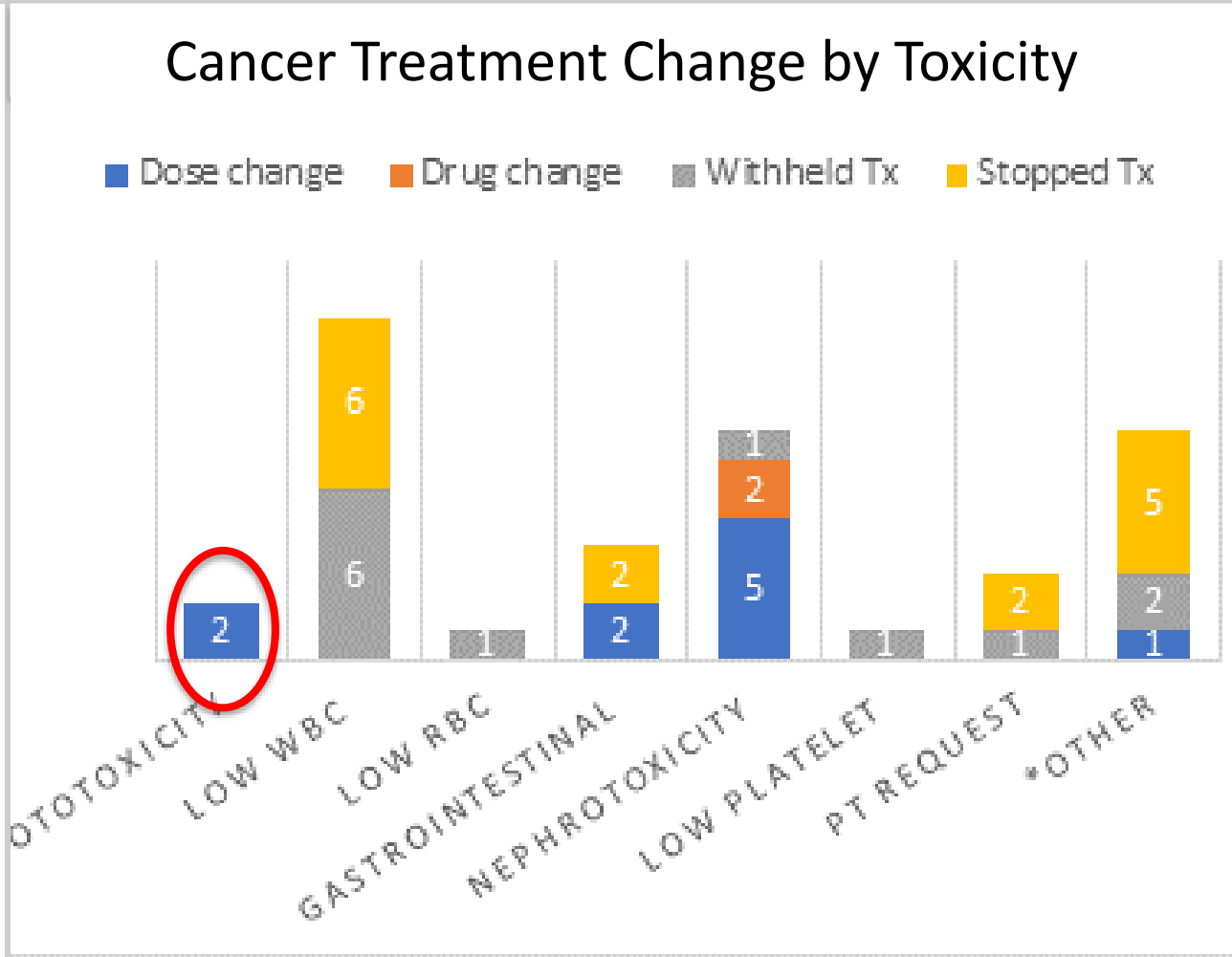


Cancer patients and their oncologists act on ototoxic hearing loss

No difference by randomization arm;

Uptake of recommended hearing aid services is unusually high





Conclusions, implications for cancer survivors and research

- A-OM arm had many, many monitoring visits
  - No negative impacts of monitoring frequently on survival
  - No positive impacts of monitoring frequently on hearing, patient utilization of recommended audiology services, or on oncologists' documentation of ototoxicity as a reason for treatment change
- Trial did provide benchmark measures of all of these outcomes
- Revealed that usual care generally fails to provide preferred OtoM practice
- Documented that auditory impairment is a concern for cancer patients during their oncology treatment
- An active surveillance program using the automated screening protocols improved adherence to OtoM recommendations

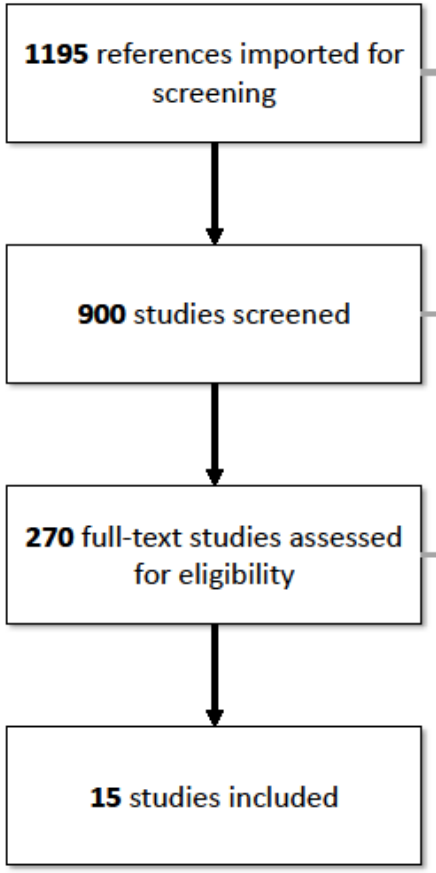
Study 3

Journal of Cancer Survivorship
https://doi.org/10.1007/s11764-022-01315-8

REVIEW

Ototoxicity prognostic models in adult and pediatric cancer patients: a rapid review

J. R. DeBacker[1,2] · G. P. McMillan[1,2] · N. Martchenke[1,2] · C. M. Lacey[1,3] · H. R. Stuehm[1,2] · M. E. Hungerford[1,2] · D. Konrad-Martin[1,2]



Common methods for model development

- Measured hearing multiple times per patient
- Used multiple regression model to predict ototoxicity
  - Outcome variable usually an abstraction of the audiogram, e.g. probability of hearing shift [yes,no]
  - Predictors usually patient and treatment characteristics that are known ototoxicity risk factors
- Built risk curve model using sequentially for several classes of predictors
- And/or reduced by backward elimination so that the final model incorporates only significant predictors
- Validated the model

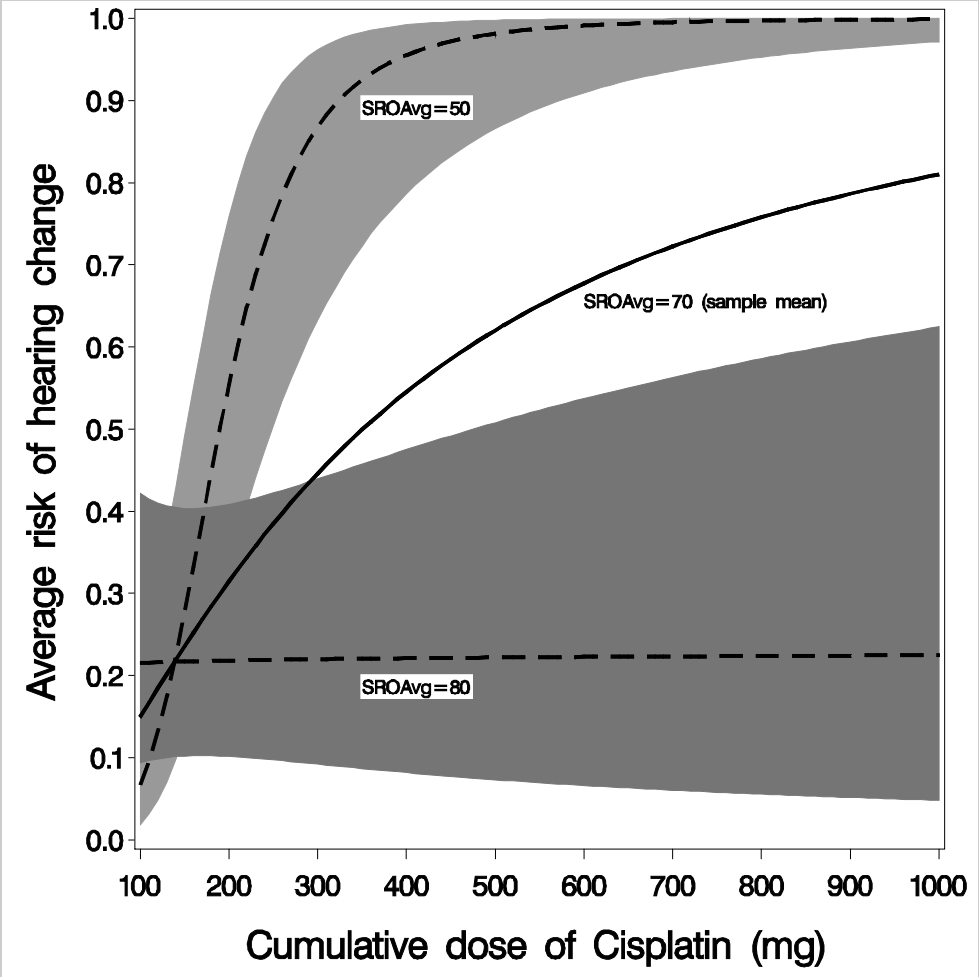


Fig from Dille, Wilmington, McMillan, Helt, Fausti, Konrad-Martin J Am Acad Audiol 23:510-521 (2012)

Conclusions, implications for cancer survivors and cancer research

- Models came from several disciplines
- All but 1 study modeled an abstraction of the audiogram
- Frequently used predictors were age, baseline hearing, cumulative cisplatin dose, and radiation dose to the cochlea
- Future modeling efforts should:
  - Adopt a transdisciplinary approach to define a unified set of clinical, treatment and/or genetic risk factors
  - Model the audiogram itself so abstractions can be developed as needed for different end users (patients, audiologists, medical oncologists, geneticists)
  - Minimize bias by following statistical best practices

Development of a flexible ototoxicity forecasting model

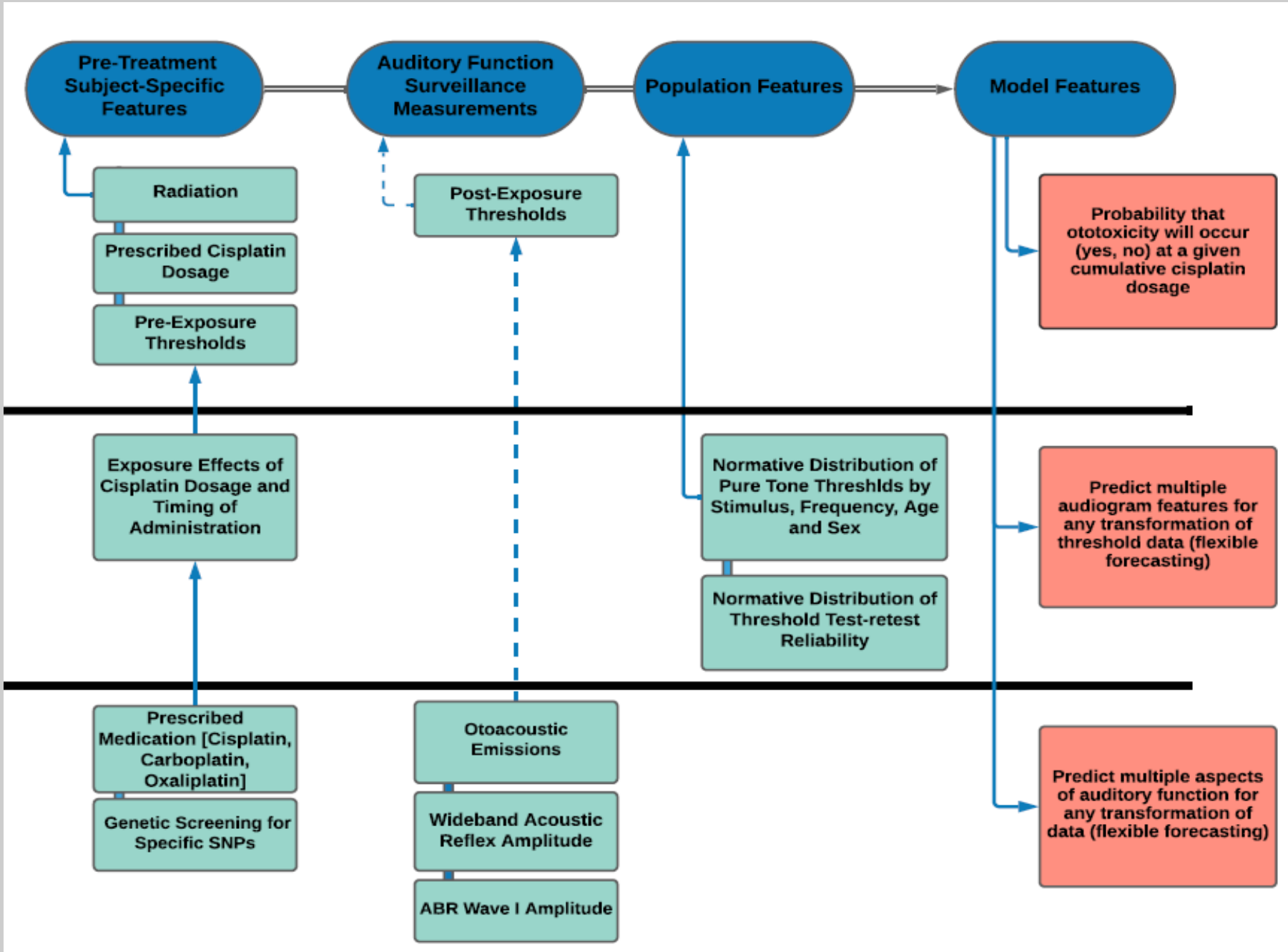
Previously Published

e.g., Dille et al., 2010; Reavis et al., 2011; Dille et al. 2012

In Progress

McMillan et al. in preparation

Planned



New Flexible Model

Treatment, Health, Hearing & Genetic Factors

Results

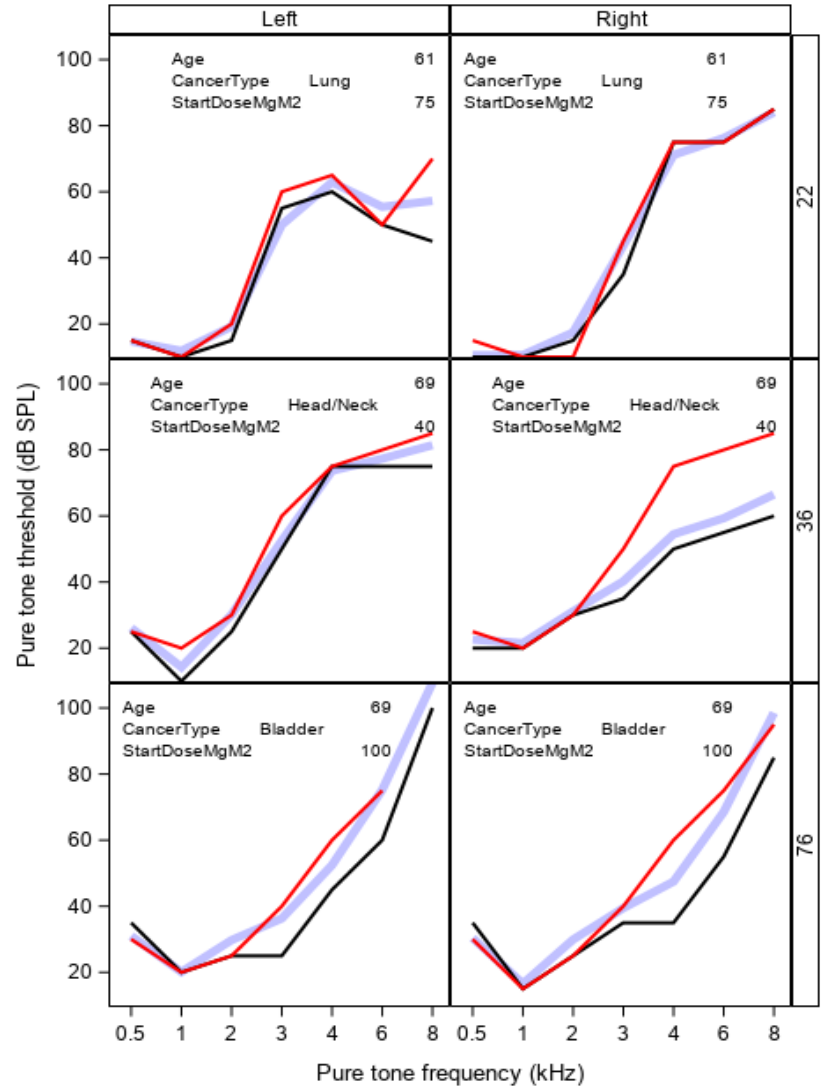
High risk for ototoxic hearing loss

- Active hearing-health surveillance program
- Discuss treatment/dose changes
- Aural rehab prep

Low risk for ototoxic hearing loss

Periodic monitoring schedule

Results



Black = baseline

Blue = predicted follow-up

Red = observed follow-up

FDA approves sodium thiosulfate to reduce the risk of ototoxicity associated with cisplatin in pediatric patients with localized, non-metastatic solid tumors

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On September 20, 2022, the Food and Drug Administration approved sodium thiosulfate (Pedmark, Fennec Pharmaceuticals Inc.) to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month and older with localized, non-metastatic solid tumors.

Efficacy was evaluated in two multicenter open-label, randomized controlled trials in pediatric patients undergoing treatment with cisplatin-based chemotherapy for cancer: SIOPEL 6 (NCT00652132) and COG ACCL0431 (NCT00716976).

SIOPEL 6 enrolled 114 patients with standard risk hepatoblastoma undergoing 6 cycles of perioperative cisplatin-based chemotherapy. Patients were randomized (1:1) to receive cisplatin-based chemotherapy with or without sodium thiosulfate administered at various doses of 10 g/m2, 15 g/m2, or 20 g/m2 based on actual body weight. The primary outcome was the percentage of patients with Brock Grade ≥1 hearing loss, assessed using pure tone audiometry after treatment or at an age of at least 3.5 years, whichever was later. The incidence of hearing loss was lower in the sodium thiosulfate and cisplatin arm (39%) compared with the cisplatin alone arm (68%); unadjusted relative risk 0.58 (95% CI: 0.40,

- One FDA approved otoprotectant
- More on the horizon
- Ototoxicity forecasting could be used to design efficient trials by including those who would benefit

Proposed Solution:

Target at risk patients for efficient, cost-effective ototoxicity management (OtoM)

Deliver OtoM when, where and with metrics that can support the goals and clinical decision-making of patients and their oncology teams

Utilizing 3 Approaches:

Computational modeling

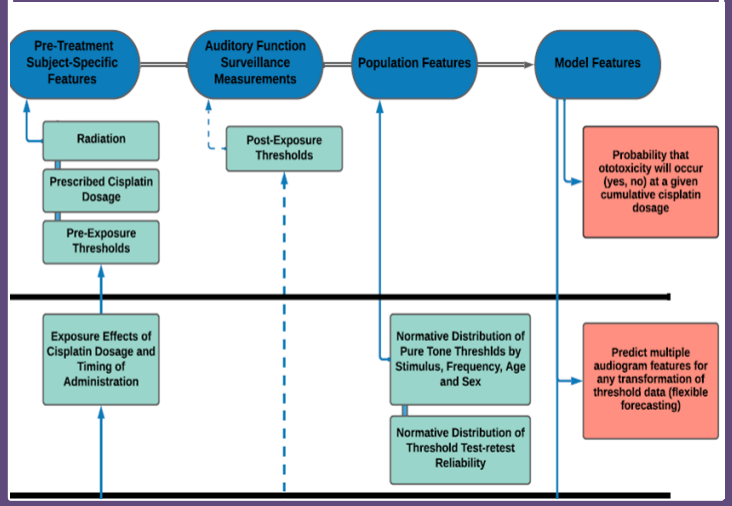
Public Health & Implementation Frameworks

Physiological & Behavioral measures

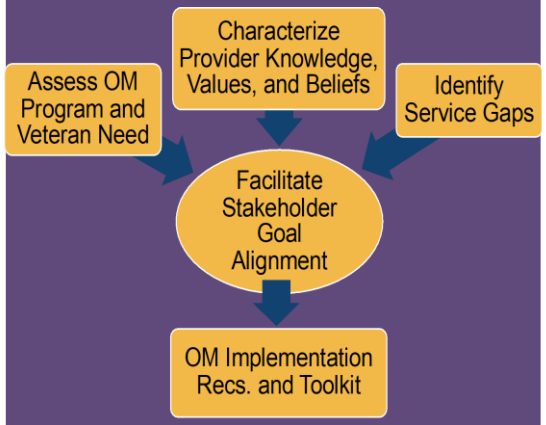
injury --> symptom development for cisplatin, carboplatin, oxaliplatin

Addressing These Aims:

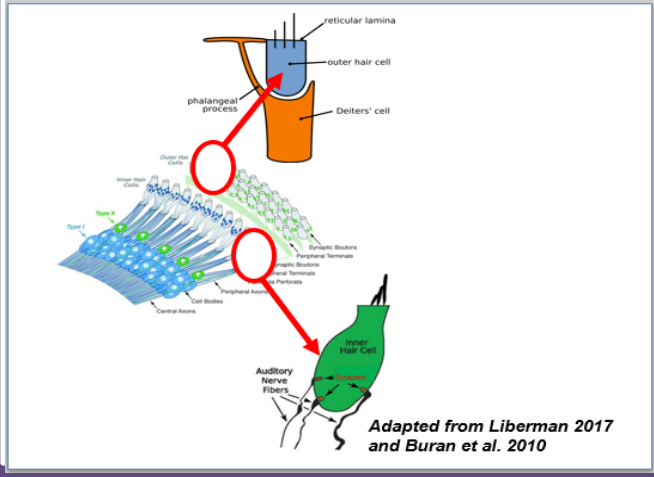
Build flexible ototoxicity risk-forecasting models



Survey VA audiologists, Oncologists & Patients



Test theories of impaired speech-in-noise perception & tinnitus



Thank You

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Thank you

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From all of us

International Ototoxicity Management Working Group (IOMG)

- 109 participants
- 19 countries
- 24 US states /territories