# Monitoring Ototoxicity with DPOAEs

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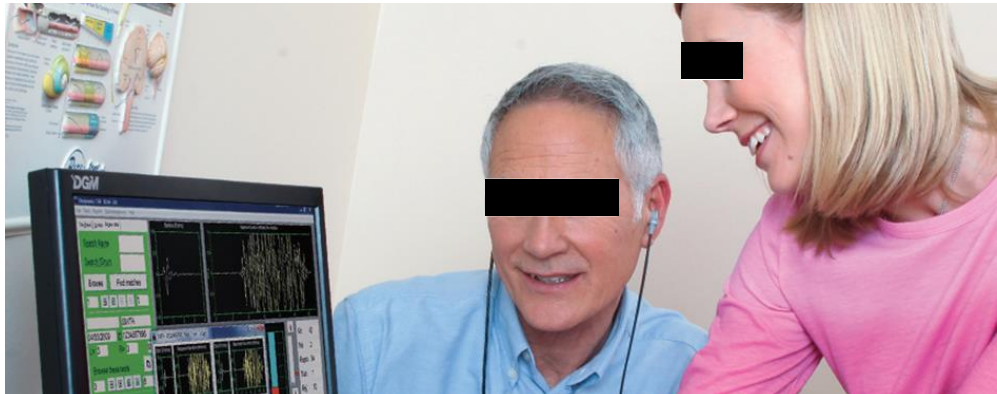


# History

1662
- **Descartes**
- Sound amplitude->neural reflex (time coding of freqs.)

1863-'85
- **Helmoholtz**
- Fourier Analysis in the cochlea

1900
- **ter Kuile**
- Tone freq. determined from BM length activated

Georg Von Békésy

1928-'47
- **Von Békésy**
- Travelling wave theory

Thomas Gold

1948
- **Thomas Gold**
- Active mechanical amplifier

1977-78
- **David Kemp**
- Recorded OAEs reflecting the mechanical amplifier & travelling wave

1988
- The first commercial OAE system available

David Kemp

# Initiation of newborn screening in the US in 1999 – endorsed by the Joint Committee on Infant Hearing (JCIH)

HEALTH CARE

## Hospitals to screen newborns' hearing

**Detection and treatment of hearing loss could defuse problems later in life that are grounded in early years.**

By Kendra Rosencrans
*News-Tribune staff writer*

Erika Joy Chelf arrived at 11:14 a.m. Friday with 10 fingers, 10 toes, and — her parents hope — perfect hearing.

Next month, St. Mary's Medical Center and St. Luke's Hospital in Duluth will begin screening all newborns for hearing loss before sending them home.

Although Erika must come back to the doctor for her test, her parents, Stacey and Kevin Chelf, think the new hospital-based screening program is a good idea.

"I think it would be a real service," said Stacey Chelf, 28, of Duluth. "It would be one less thing to worry about."

About six in 1,000 babies are born with hearing loss significant enough to interfere with their speech and language development during the critical first six months of life.

The Duluth hospitals' decision to start screening is part of state and national movements to implement hearing tests for newborns in all hospitals.

Last year, the Minnesota Legislature appointed a committee to study whether hospitals in the state would voluntarily implement the testing. That committee returned a report to the governor on Thursday.

"If we can identify infants with hearing problems soon after they are born and provide the necessary treatment and care, we can prevent many of the problems that may occur later with learning, socialization and self-concept development," said Michelle Foss, chief audiologist for St.

*Please see* HEARING, back page

DAVE BALLARD / NEWS-TRIBUNE

**Stacey Chelf** of Duluth kisses her daughter, Erika Joy, who was born Friday morning at St. Mary's Medical Center in Duluth. Next month, St. Mary's will start giving newborns like Erika a hearing test before they leave the hospital. Although Erika must have her test a little later, Chelf thinks the new program is a good idea.

Early Hearing Detection & Intervention (EHDI) programs:

Advantages: Recordable at birth, Reliable, Quick, Non-invasive, Easily interpreted
Cost effective, Objective, Specifically assesses cochlear function,
Provides ear specific information, high sensitivity and specificity

# UK Newborn Hearing Screening Programmes

- North Wales - NBHSW: started in March 2003, and in October 2004 became the first fully implemented national newborn hearing screening programme in the UK.
  (http://www.wales.nhs.uk/sitesplus/980/home)

- Scotland – UNHSScotland: The roll out across the country was completed in December 2005. 15 local programs (~60 000/annum).
  (http://www.nsd.scot.nhs.uk)

- NHSP-England: introduced in a phased and nationally organized process between 2002 and 2006- fully implemented in March 2006. 113 local programs covering all births in England (~660 000/annum).
  (Wood et al., 2015)

- Ireland -Newborn Hearing Screening Programme: 2011- rolled out in 19 hospitals

# Clinical applications of OAEs

1. Hearing Screening
   a. Newborn hearing screening
   b. Pre/school aged children screening
   c. Occupational noise exposure screening
2. Monitoring of cochlear function
   a. Ototoxicity monitoring,
   b. NIHL and hearing conservation programmes
3. Diagnostic assessment of cochlear function
   a. Sensory vs. Neural HL (ANSD, APD, AN, Autism)
   b. NOHL (non-organic hearing loss)
   c. Non-cooperative subjects
4. Assessment of Inhibitory Efferent Olivocochlear Pathway

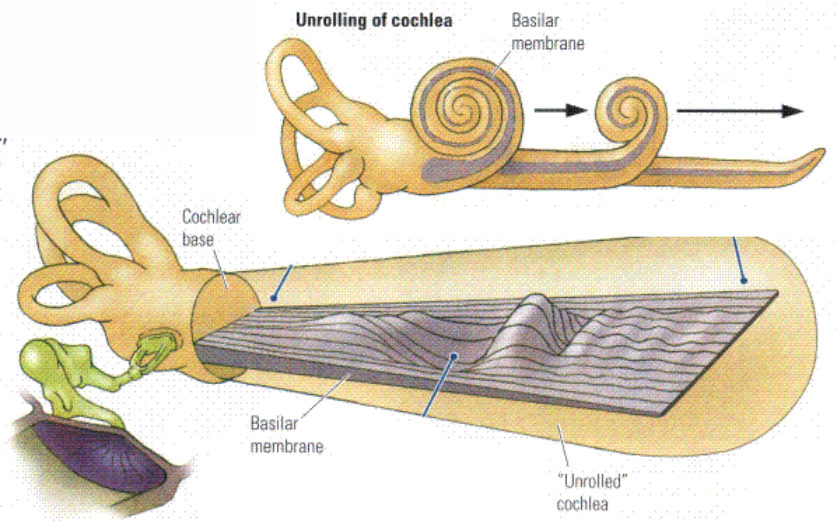
# Ototoxicity

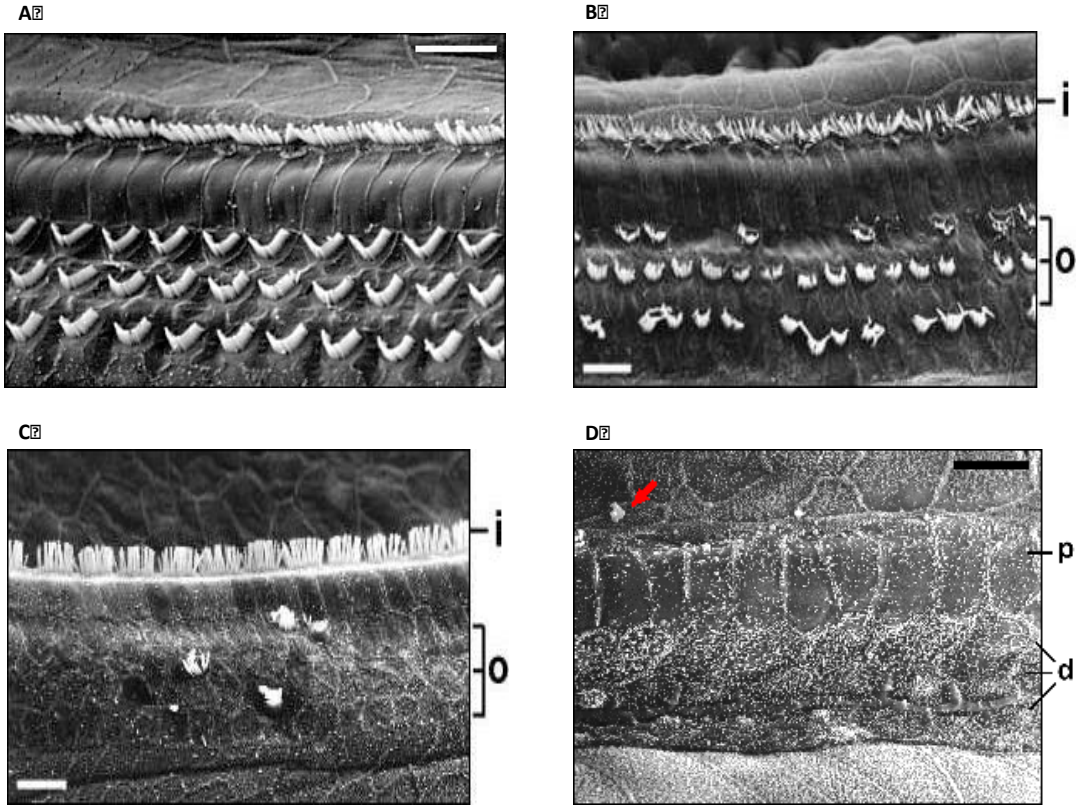
- Damage to hearing and/or balance function following exposure to certain drugs or solvents

| Antineoplastic Drugs | Aminoglycosides | Other Antibiotics | Loop Diuretics | Salicylates & NSAIs | Antimalarial Drugs | Industrial solvents |
|---|---|---|---|---|---|---|
| **Cisplatin**<br>**Carboplatin**<br>**Oxaliplatin**<br>Nitrogen mustard<br>Methotrexate*<br>Vincristine<br>Dactinomycin<br>Bleomycin | **Gentamicin***<br>**Neomycin***<br>**Kanamycin**<br>**Amikacin**<br>**Streptomycin***<br>**Tobramycin***<br>**Netilmicin** | Vancomycin<br>Erythromycin | Furosemide*<br>Ethacrynic acid*<br>Bumetanide* | Aspirin | Quinine | Toluene<br>Benzene<br>Lead<br>Mercury<br>Carbon monoxide<br>Nicotine |

** also vestibulotoxic*

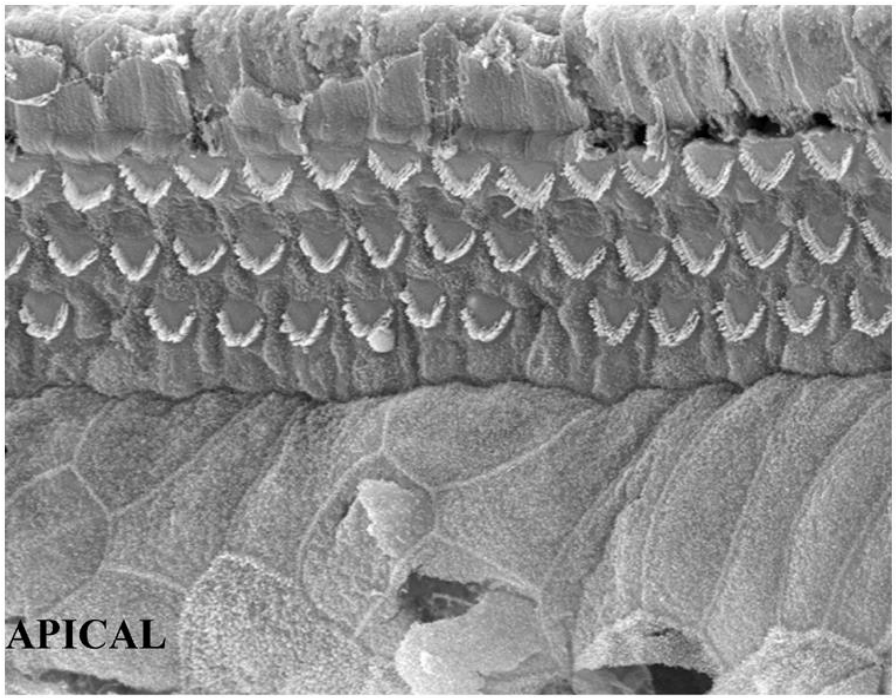
# Selective damage of AGs & Cisplatin on the cochlea

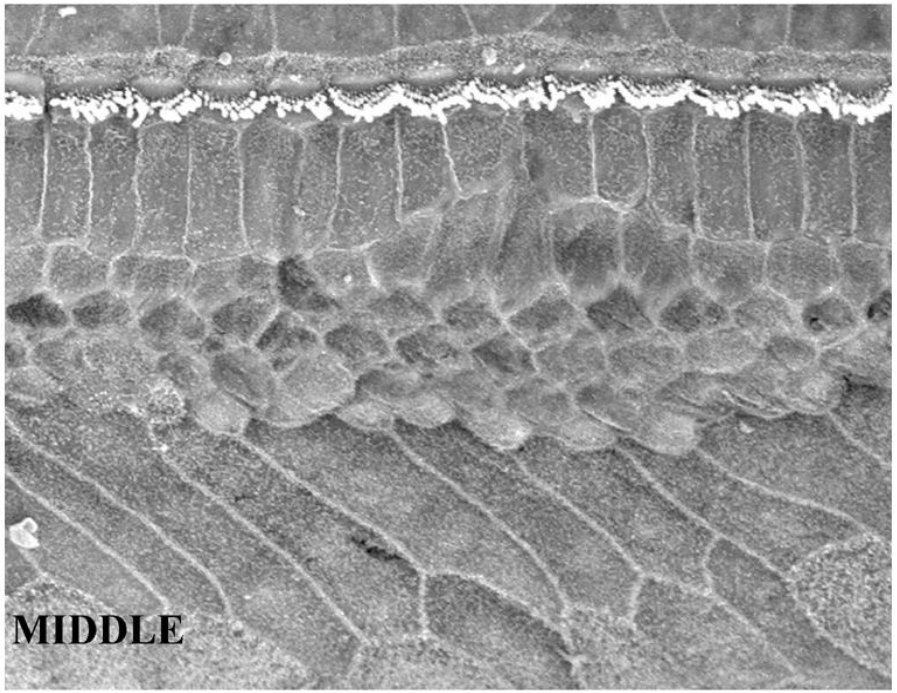


# Base-to-Apex gradient of damage due to differential vulnerability

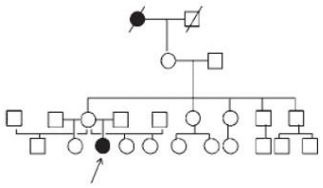
Brummett 1980; Komune et al. 1981; Nakai et al.1982; Konishi et al. 1983; Schweitzer et al. 1984



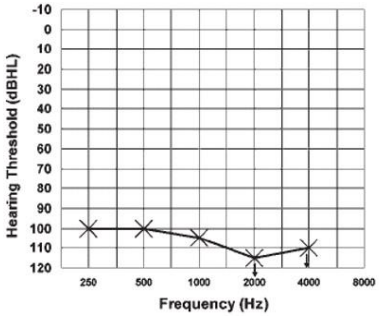




Courtesy of Dr. Ruth Taylor & Prof. Andy Forge (Ear Institute, UCL)

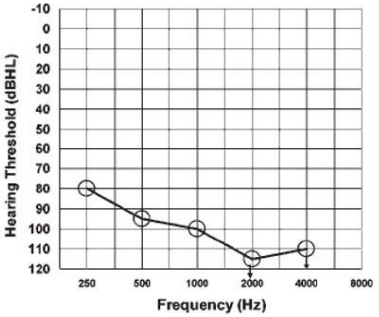
# Genetic susceptibility to Aminoglycoside ototoxicity – mtDNA A1555G mutation



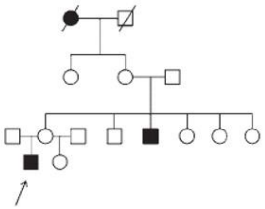
a) Family tree of case 1



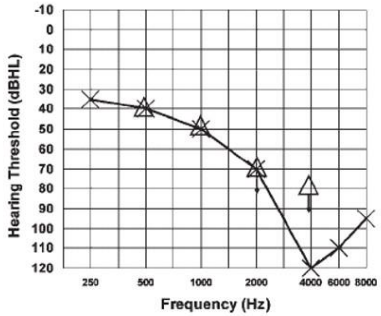

b) Case 1 left ear



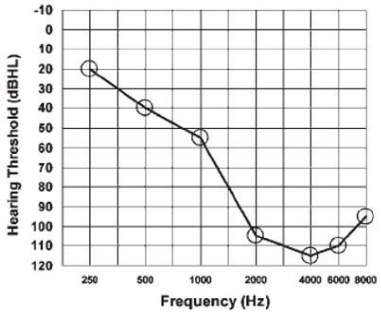

c) Case 1 right ear



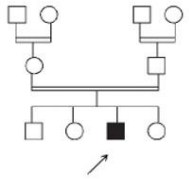
d) Family tree of case 2



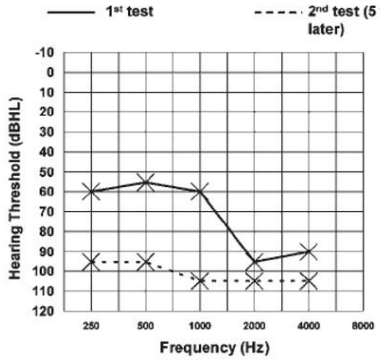

e) Case 2 left ear



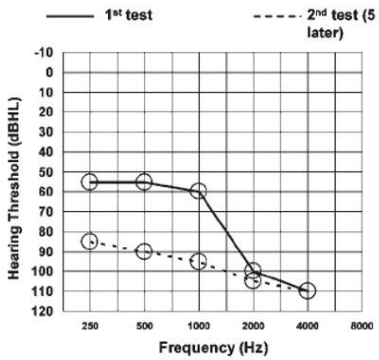

f) Case 2 right ear



g) Family tree of case 3




h) Case 3 left ear




i) Case 3 right ear

Bitner-Glindzicz M et al. Arch Dis Child 2010;95:153-155

# Rationale for Ototoxicity Monitoring

- **Early detection of hearing loss --> Potential Treatment modification --> Prevention of further loss**
- **Enable clinicians to make informed choices:**
  - Limit the dose of the drug
  - Change to an alternative drug
  - Alter treatment regimen
  - Improve counselling
    - Pre- and post treatment counselling offered to the patient
  - Provide realistic expectations
  - Allow appropriate treatment planning
  - Facilitate early introduction of hearing assistance
  - Provide important information for post treatment planning in order to ensure an acceptable quality of life

# Methods of auditory monitoring

- Standard pure-tone audiometry (0.25-8 kHz)

(Riethmueller et al., 2009, Mulherin et al., 1991, Mulheran et al., 2001).

- High-frequency audiometry (9-20 kHz)

(Knight et al. 2007)

  - Sensitive Range for Ototoxicity (SRO) (Fausti et al., 2005)

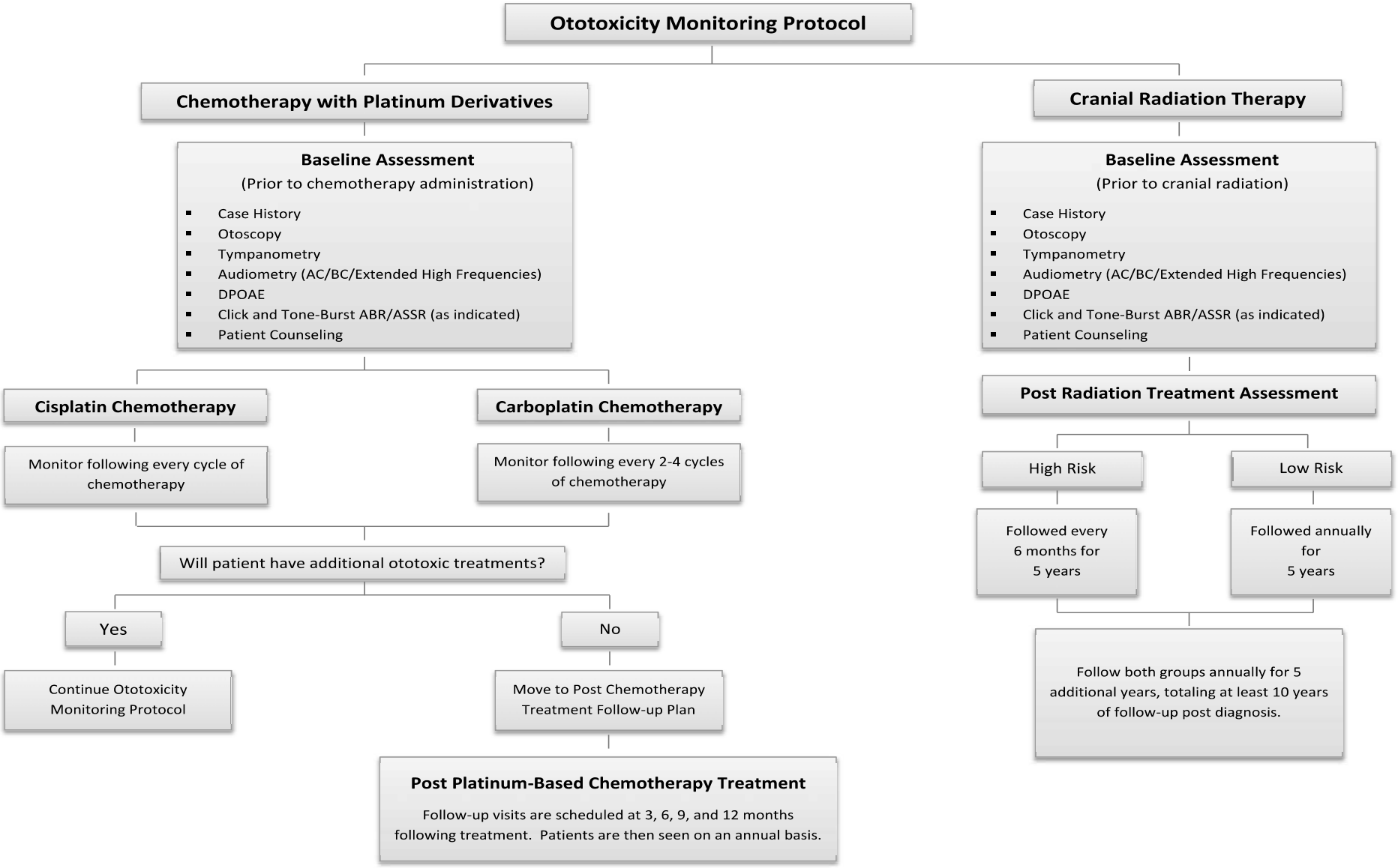
- Distortion-product otoacoustic emissions (DPOAEs)

(Rybak et al., 2009,Lonsbury-Martin and Martin, 2003, Fausti et al., 1992, Stavroulaki et al. 2001, 2002, Campbell et al., 2003,)

  - Ototoxicity Risk Assessment (ORA) model (Dille et al., 2010)

- Others: Speech Audiometry, ABR, ASSR

# How often to repeat the testing?




The ASHA recommended ototoxicity monitoring protocol for oncology patients (*ASHA, 2013*)

# Why use OAEs in monitoring ototoxicity?

| Pros | Cons |
|---|---|
| Both TE and DP OAEs are highly sensitive to OHC cochlear dysfunction | OAEs can be affected/stopped by ME changes e.g. otitis media |
| Most ototoxic drugs affect the **OHCs first** | Changes in ME pressure can affect repeatability of recordings |
| OAEs allow for **earlier identification** of cochlear damage before it is evident through audiometry | **Repeatability** can be affected by probe fitting, time difference from baseline, and changes in middle ear condition |
| DPOAEs can detect basal cochlear HF damage before PTA speech frequencies (0.5-8kHz) | OAE Equipment may not be readily available in all healthcare settings (cost implications) |
| **OAEs are objective – can be performed in young /very ill patients** | **Absence of agreed pass/fail or significant change criteria** |
| **Test time is brief- usually only 1-2 mins needed** | |
| Only **quiet** testing environment needed | |
| **Hand-held / Portable equipment - go to patient** | |
| High degree of **detailed** (8-16 points/octave) **frequency selective** information can be provided. | |

# Use of different tools & criteria

| Author | Study method | Criteria for ototoxicity (HL) | Results | Frequency |
|---|---|---|---|---|
| Pendersen et al, 1987 | Standard PTA (0.25-8kHz)<br>EHF PTA (4-20 kHz) | ≥ 15dB | 2/42 (5%) | Only at high freq ≥ 8 kHz |
| Scheenstra et al, 2006 | Standard PTA (0.25-8kHz)<br>EHF PTA (8-20 kHz) | ≥ 20 dB (1 freq) | 13/27 (48.1%) | Only 7/27 (25.1%) with standard PTA |
| Mulheran et al, 2001 | Standard PTA (0.25-8kHz)<br>EHF PTA (10-16 kHz) | ≥ 20 dB (≥ 2 Freq) or<br>≥ 25 (1 freq) | 17% - mainly adults | |
| Conrad et al, 2008 | Standard PTA (1-8kHz)<br>DPOAE (841-7996Hz) | ≥ 25dB or Abnormal DPOAE | 50.8% | |

# Grading Systems/Criteria For Defining Ototoxicity

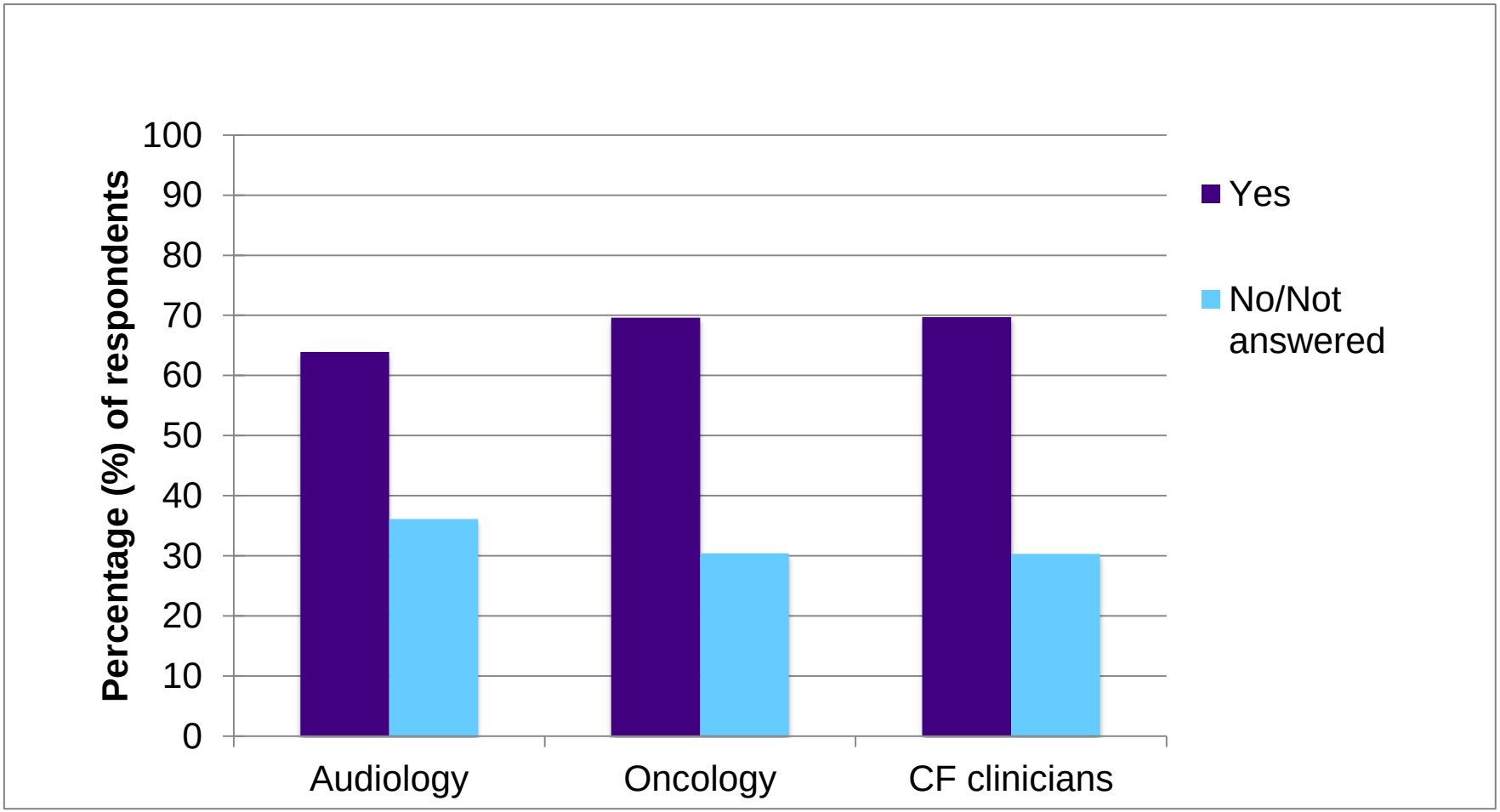
| ASHA criteria for ototoxicity (1994) |
|---|
| (A) 20 dB or greater increase (worsening) in pure tone threshold at one test frequency<br>OR |
| (A) 10 dB or greater increase at two adjacent test frequencies<br>OR |
| (C) Loss of response at 3 consecutive test frequencies where baseline responses were previously obtained, signifying a decrease in hearing following treatment |

| Brock's grading criteria for ototoxicity (1991) | |
|---|---|
| **Grade** | **Thresholds** |
| 0 | < 40 dB at 500 - 8,000 Hz |
| 1 | ≥ 40 dB at 8,000 Hz |
| 2 | ≥ 40 dB at 4,000-8,000 Hz |
| 3 | ≥ 40 dB at 2,000-8,000 Hz |
| 4 | ≥ 40 dB at 1,000-8,000 Hz |

# Grading Systems/Criteria For Defining Ototoxicity

| SIOP Boston Ototoxicity Scale (2012) | |
|---|---|
| Grade | Parameters |
| 0 | ≤ 20 dB HL at all frequencies |
| 1 | > 20 dB HL (i.e. 25 dB HL or greater) SNHL above 4,000 Hz (i.e. 6 or 8 kHz) |
| 2 | > 20 dB HL SNHL at 4,000 Hz and above |
| 3 | > 20 dB HL SNHL at 2,000 Hz or 3,000 Hz and above |
| 4 | > 40 dB HL (i.e. 45 dB HL or more) SNHL at 2,000 Hz and above |

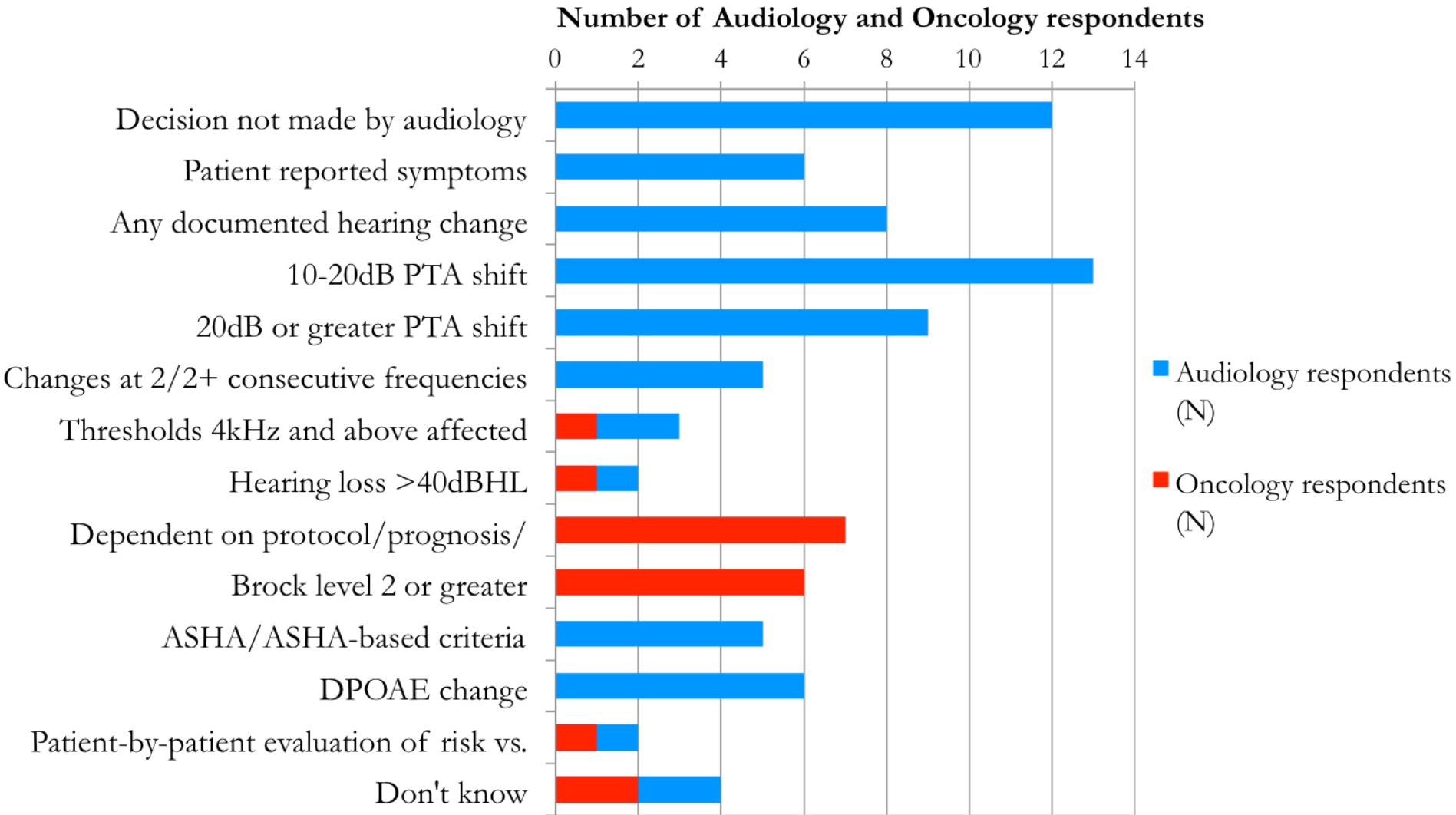
# Responses to: *Do you monitor your patients' hearing for signs of ototoxicity?*



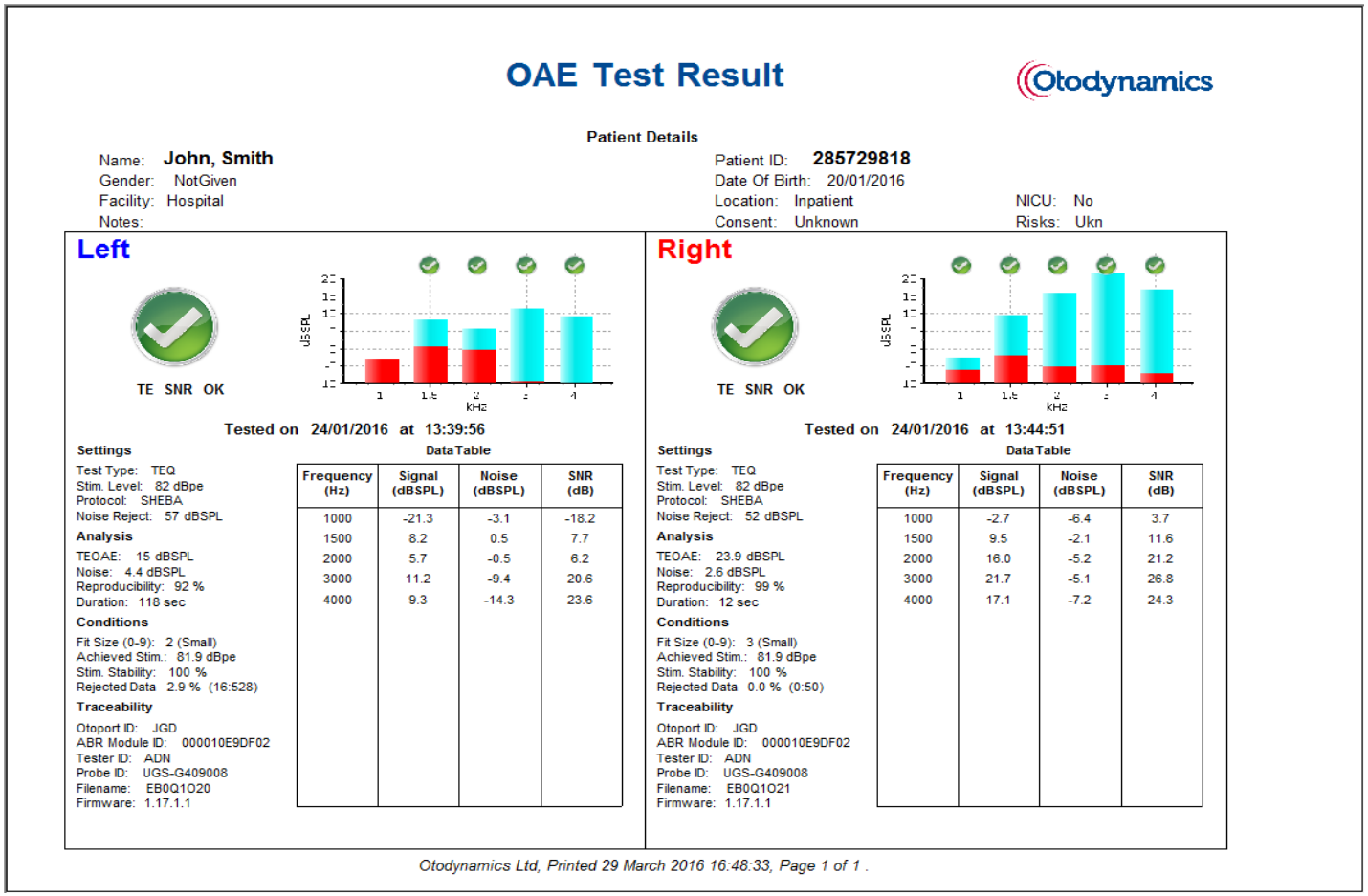
# Responses to: *What audiological testing is conducted for ototoxicity monitoring?*

| | Audiology (N=85), n (%) | Oncology (n=51), n (%) | CF clinicians (N=22), n (%) |
|---|---|---|---|
| PTA (250Hz-8kHz) | 64 (75.3%) | 15 (29.4%) | 19 (86.4%) |
| EHFA (above 8kHz) | 15 (17.7%) | 6 (11.8%) | 5 (22.7%) |
| TEOAEs | 21 (24.7%) | 2 (3.9%) | 3 (13.6%) |
| DPOAEs | 20 (23.5%) | 1 (2.0%) | 3 (13.6%) |
| Tympanometry | 46 (54.1%) | 4 (28.2%) | 1 (4.5%) |
| ART | 8 (9.4%) | 1 (2.0%) | N/A |
| ABR; neurological | 1 (1.2%) | 1 (2.0%) | N/A |
| ABR; threshold | 8 (9.4%) | 1 (2.0%) | N/A |
| Speech audiometry | 5 (5.9%) | 4 (7.8%) | N/A |
| I'm not sure which audiological tests are conducted | | 34 (66.7%) | |

# Comments to: *What changes in audiological results should prompt change in medical management?*



# Pass Criteria for Newborn screening



## OAE Test Result

Otodynamics

**Patient Details**

Name: **John, Smith**
Gender: NotGiven
Facility: Hospital
Notes:

Patient ID: **285729818**
Date Of Birth: 20/01/2016
Location: Inpatient
Consent: Unknown

NICU: No
Risks: Ukn

### Left

TE SNR OK




Tested on 24/01/2016 at 13:39:56

**Settings**
Test Type: TEQ
Stim. Level: 82 dBpe
Protocol: SHEBA
Noise Reject: 57 dBSPL

**Analysis**
TEOAE: 15 dBSPL
Noise: 4.4 dBSPL
Reproducibility: 92 %
Duration: 118 sec

**Conditions**
Fit Size (0-9): 2 (Small)
Achieved Stim.: 81.9 dBpe
Stim. Stability: 100 %
Rejected Data 2.9 % (16:528)

**Traceability**
Otoport ID: JGD
ABR Module ID: 000010E9DF02
Tester ID: ADN
Probe ID: UGS-G409008
Filename: EB0Q1O20
Firmware: 1.17.1.1

**Data Table**

| Frequency (Hz) | Signal (dBSPL) | Noise (dBSPL) | SNR (dB) |
|---|---|---|---|
| 1000 | -21.3 | -3.1 | -18.2 |
| 1500 | 8.2 | 0.5 | 7.7 |
| 2000 | 5.7 | -0.5 | 6.2 |
| 3000 | 11.2 | -9.4 | 20.6 |
| 4000 | 9.3 | -14.3 | 23.6 |

### Right

TE SNR OK




Tested on 24/01/2016 at 13:44:51

**Settings**
Test Type: TEQ
Stim. Level: 82 dBpe
Protocol: SHEBA
Noise Reject: 52 dBSPL

**Analysis**
TEOAE: 23.9 dBSPL
Noise: 2.6 dBSPL
Reproducibility: 99 %
Duration: 12 sec

**Conditions**
Fit Size (0-9): 3 (Small)
Achieved Stim.: 81.9 dBpe
Stim. Stability: 100 %
Rejected Data 0.0 % (0:50)

**Traceability**
Otoport ID: JGD
ABR Module ID: 000010E9DF02
Tester ID: ADN
Probe ID: UGS-G409008
Filename: EB0Q1O21
Firmware: 1.17.1.1

**Data Table**

| Frequency (Hz) | Signal (dBSPL) | Noise (dBSPL) | SNR (dB) |
|---|---|---|---|
| 1000 | -2.7 | -6.4 | 3.7 |
| 1500 | 9.5 | -2.1 | 11.6 |
| 2000 | 16.0 | -5.2 | 21.2 |
| 3000 | 21.7 | -5.1 | 26.8 |
| 4000 | 17.1 | -7.2 | 24.3 |

*Otodynamics Ltd, Printed 29 March 2016 16:48:33, Page 1 of 1 .*

PASS Criteria:

- 2 out of 4 frequency bands (e.g. 1,**1.5, 2, 3, 4kHz**) reach a signal-to-noise ratio (SNR) of at least 6dB
- Total TEOAE of 0dBspl (across all frequencies)
- OAE in each pass band of at least -5dBspl.

http://www.otodynamics.com/screening8.asp

# How to do it – use agreed parameters

| DPOAE Test parameters for a Diagnostic monitoring protocol | | |
|---|---|---|
| L1/L2 intensity (dB SPL) | 65/55* | |
| F2/F1 ratio | 1.22 | |
| F2 range (kHz) | 2-10 kHz | |
| Start frequency | 2000 Hz | |
| End frequency | 10,000 Hz | |
| Points/octave | 8 (4-16) | |
| **Stopping criteria** | | |
| Min DP Amplitude (dB) | -5 | (as specified by manufacturer/protocol) |
| Noise Floor (dB) | -20 | (as specified by manufacturer/protocol) |
| S/N Ratio (dB) | 6 | (as specified by manufacturer/protocol) |
| Point time limit (sec) | 20 | |
| L1/L2 intensity (dB SPL) | ± 3dB | (within Target levels) |
| Sample size | 1024 | (as specified by manufacturer/protocol) |
| Number of tests | 1 | |
| Minimum ♯Samples | 50 | (as specified by manufacturer/protocol) |

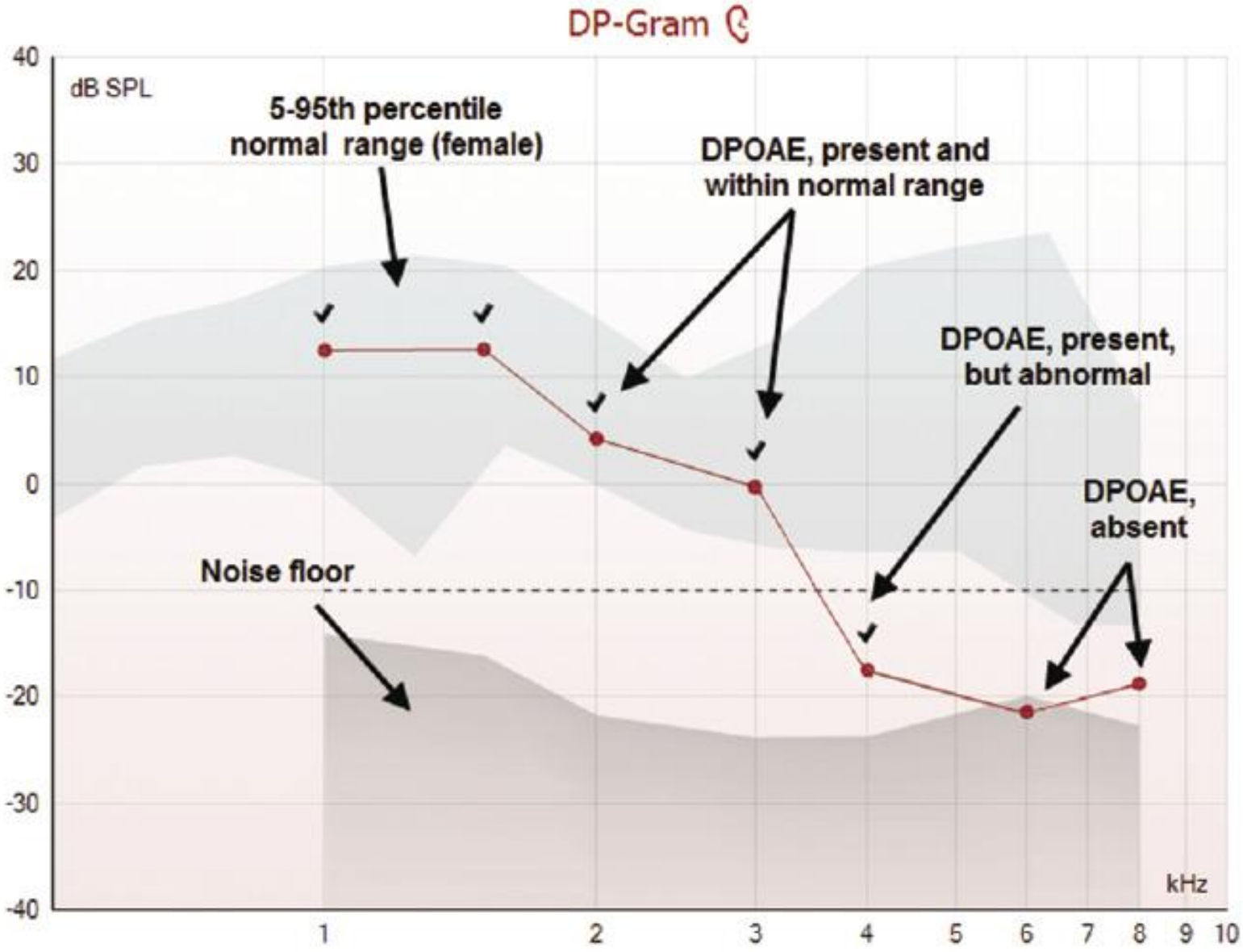
**Example of a DPOAE test parameters protocol for ototoxicity monitoring. *(Decrease intensity to increase sensitivity)***

# Prerequisites for recording DPOAEs

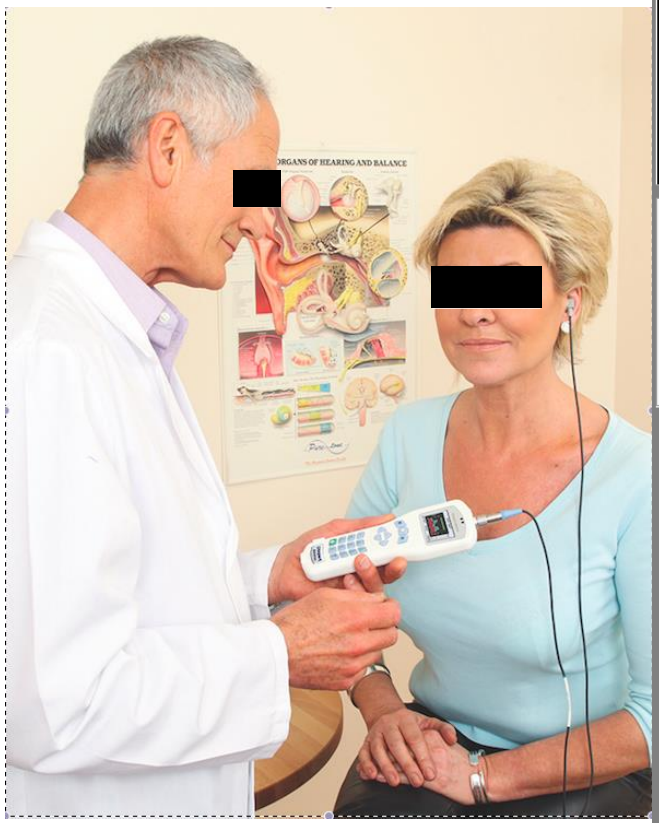
- Unobstructed external ear canal
- Optimal positioning of the OAE probe
- Ability to seal the ear canal with the probe
- Absence of middle ear pathology
- Functioning cochlear OHCs
- Relatively quiet conditions:
  - A quiescent patient to avoid internal noises such as vocalization, breathing or crying
  - A quiet recording environment –yet a sound-proof room is not required

*= Avoids artifacts*

# Change in DPOAEs with repeated testing

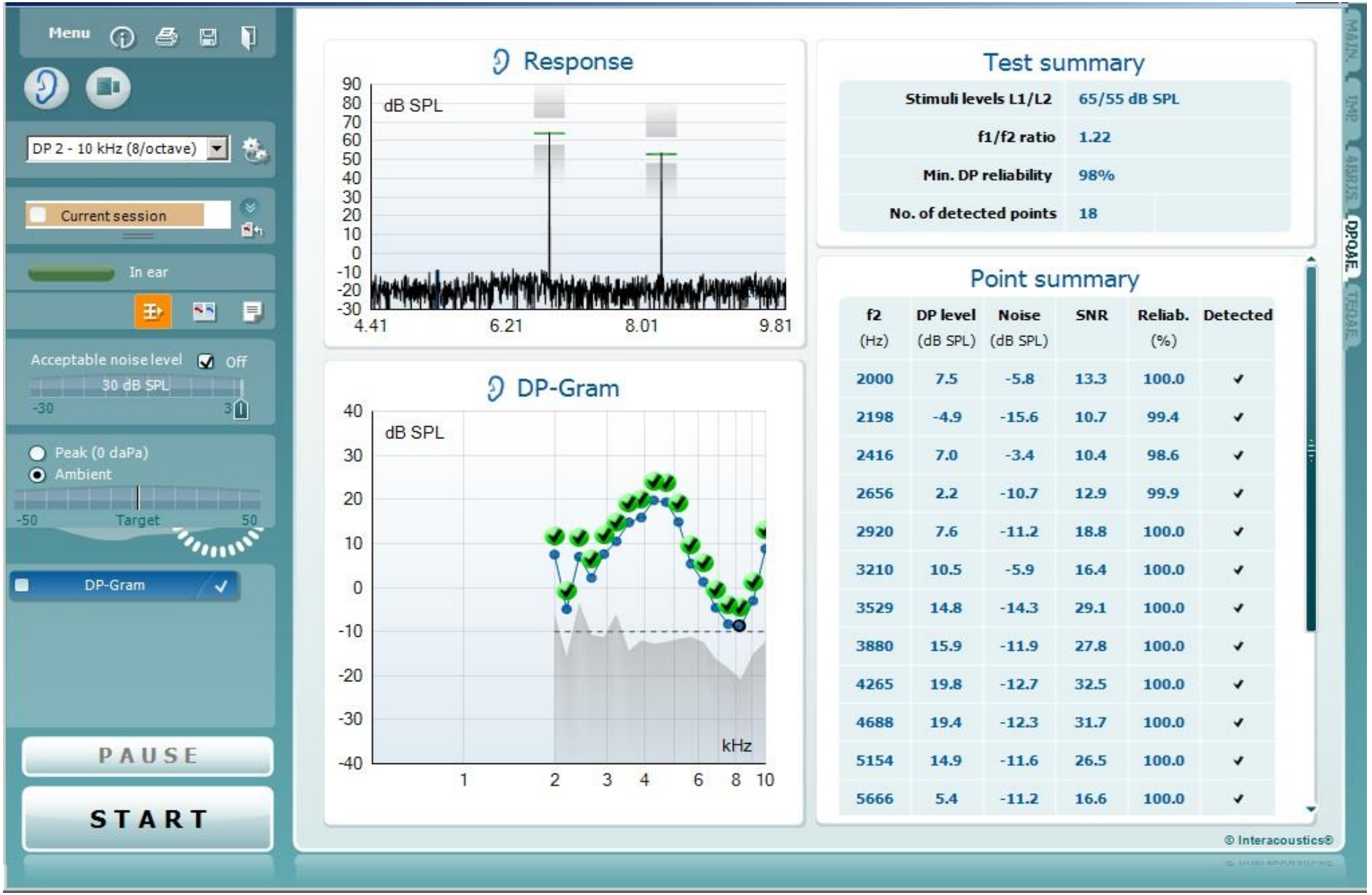



http://www.hearingreview.com/2013/10/an-overview-of-oaes-and-normative-data-for-dpoaes/



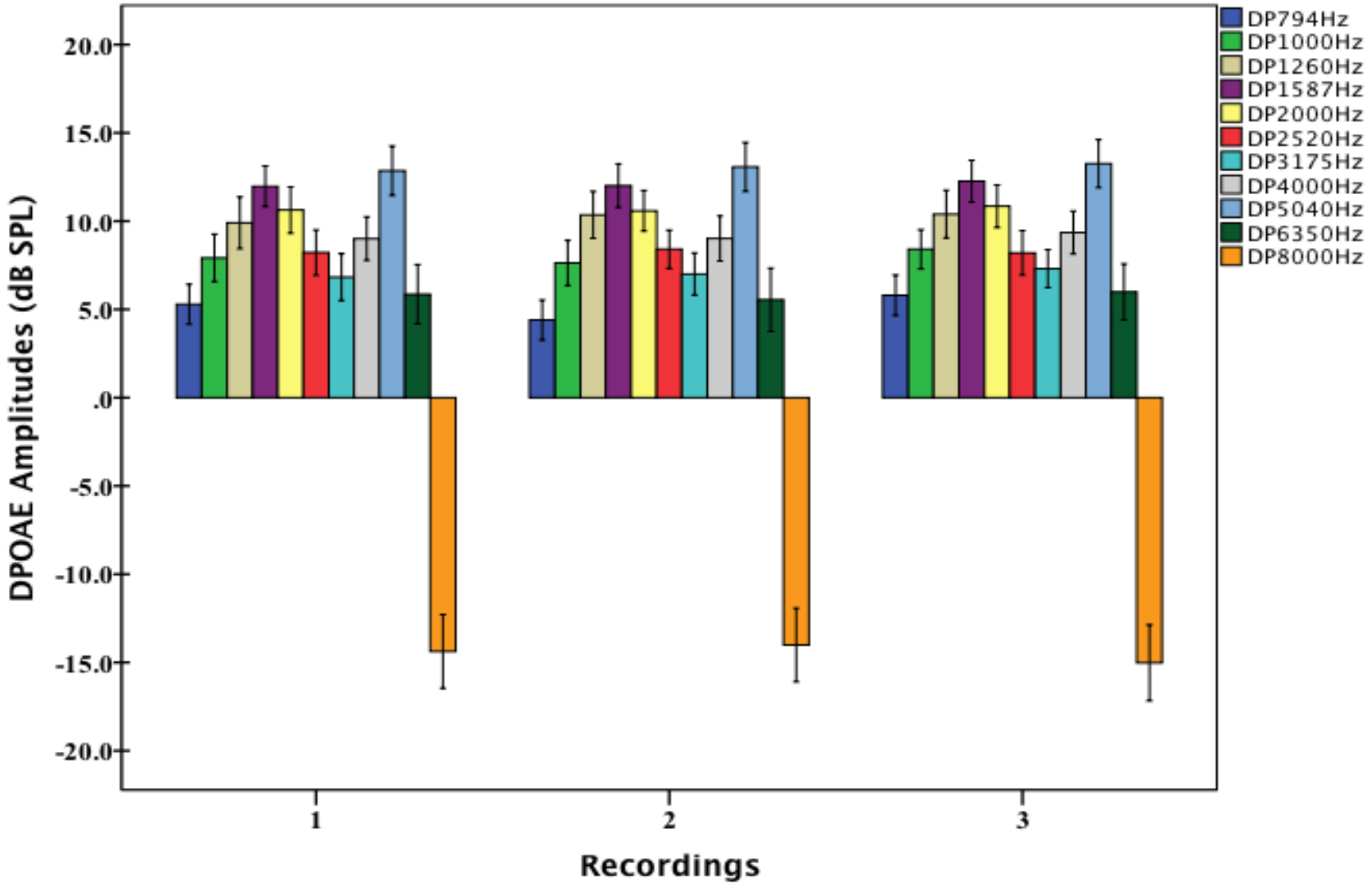

*Pictures courtesy of Otodynamics Ltd.*

# Example of DPOAE output




DPOAE recording for high frequency (2-10kHz) responses at 8 points/octave. *(Picture courtesy of Interacoustics Ltd.)*

# Repeatability of DPOAE testing




Mean ±SE DPOAE f2 amplitudes for each of three within session recordings with probe refitting – similar findings with *Roede et al.,1993; Beattie and Bleech, 2000; Beattie et al., 2003; Dreisback et al., 2006*

# What constitutes a significant change?

| Days From Baseline | DPOAE f2 Frequency | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1000 Hz | | 2000 Hz | | 4000 Hz | | 6000 Hz | |
| | SEM | 90% Reference Limits | SEM | 90% Reference Limits | SEM | 90% Reference Limits | SEM | 90% Reference Limits |
| **1** | 1.7 | ±3.95 | 1.7 | ±3.98 | 1.8 | ±4.16 | 1.6 | ±3.76 |
| **10** | 1.8 | ±4.24 | 1.9 | ±4.35 | 2.1 | ±4.85 | 2.0 | ±4.55 |
| **15** | 1.9 | ±4.41 | 2.0 | ±4.56 | 2.3 | ±5.24 | 2.1 | ±4.99 |
| **20** | 2.0 | ±4.57 | 2.0 | ±4.76 | 2.4 | ±5.63 | 2.3 | ±5.43 |

***Reavis et al, 2015:*** *Meta-Analysis of DPOAE Retest Variability for Serial Monitoring of Cochlear Function in Adults*

**Metanalysis of results of 10 studies assessing significant change criteria**

(±6dB change is considered significant with a 10% possible false positive (referral) rate).

# *Dreisback et al., 2006:* (Repeatability of HF (>8kHz) DPOAEs)

- *The average DPOAE level differences-between-trials for the higher and lower frequencies was 5.15 (SD ± 4.40 dB) and 2.80 (SD ± 2.70 dB) dB, respectively.*
- *Individual subject analysis revealed that high-frequency DPOAE levels varied no more than 10 dB for 87.5 and 83.1% of young adult subjects for the 70/55 and 60/50 dB SPL stimulus level conditions, respectively.*
- *For low frequencies, repeated DPOAE level variations were within 10 dB for 98.4 and 96%.*
- *when monitoring high-frequency DPOAEs if a change of 10 dB or more is noted at adjacent frequencies, that trial should be retested to determine if the change was due to artifact or a true change in the auditory system*

# Limitations & Cautions when using specific change criteria

- Patient population tested may affect variability
- Stimulus frequency/level used for monitoring
- Multiple test frequencies vary in test-retest variability
- Clinician test-retest variability
- Follow-up for significant DPOAE change should be followed up by a more detailed test battery
- Consider Risk Factors/ Predictors of ototoxicity
  - Pre-exposure hearing status (prior cochlear damage)
  - Radiation treatment
  - Concomitant noise / ototoxic drug exposure
  - Cumulative exposure to ototoxic drug

# How to record/report results

Great Ormond Street Hospital for Children NHS Trust

***Audiology Report for Ototoxicity monitoring of CF patients***

**DEPARTMENT**
**Audiovestibular Medicine & Cystic Fibrosis Unit, Great Ormond Street Hospital, London**

**Hearing Assessment Report:**
**Ototoxicity Monitoring Service for CF Unit**

**Please affix patient ID label:**
MRN Number: .....
Surname: .....
Name: .....
DOB: .....
Sex: .....

Date: .....
Audiologist: .....
Contact Number/Bleep: .....
New patient assessment: ☐
Existing patient monitoring: ☐

**Summary Report: (see results enclosed)**

**Otoscopy:** ☐ Clear ☐ Non-occluding wax

**Tympanometry (middle ear analysis):**

☐ Normal ☐ Otitis Media with Effusion (OME)/ Negative Pressure

**Standard Audiometry (0.5 – 8kHz): Rt: Lt: Both:**
Description: .....

☐ Normal ☐ HF Hearing Loss –Stable ☐ HF HL - Deterioration

**Extended High-Frequency (HF) Audiometry (9 – 16kHz):Rt: Lt: Both:**

☐ Normal ☐ HL – Stable ☐ HL – Deterioration (>20dB)

**Distortion-Product Otoacoustic emissions** (DPOAE-monitor inner ear OHC function)

☐ Present ☐ Absent ☐ Deterioration
(>7dBSPL decrease in DPOAE amplitudes /<6dB SNR)

**Recommendation:**

☐ Repeat assessment after 6 months

☐ Repeat assessment after intake of next aminoglycoside course

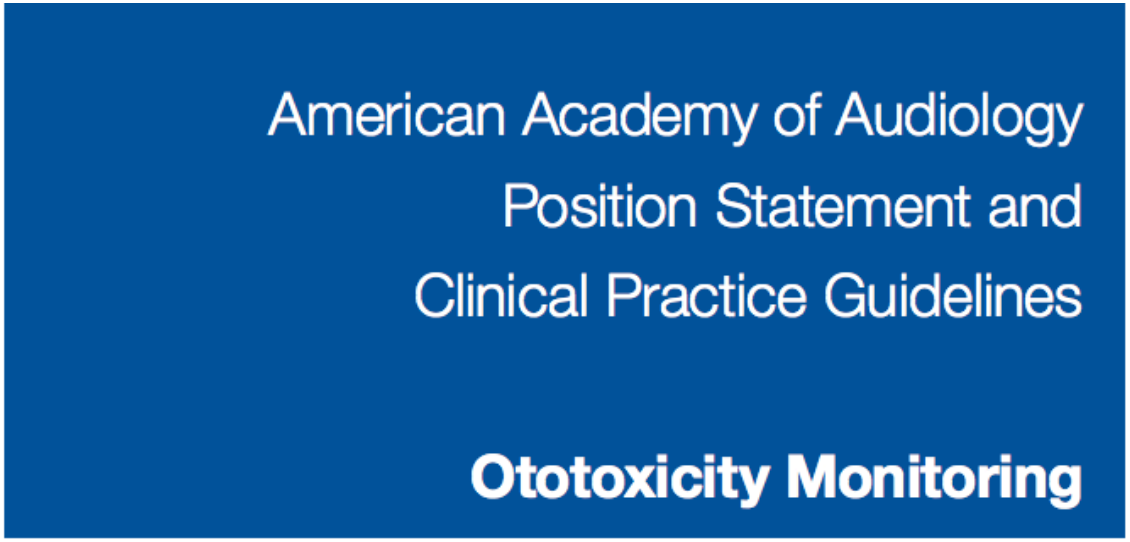
☐ Refer to Local / GOSH Audiology for hearing aids

☐ Genetic test to exclude mtDNA A1555G mutation

# Monitor/audit your service

- Your service is as strong as it's weakest link – you need to ensure that all members of the team are keen, involved, aware of their roles and responsibilities towards the monitoring program.
- Annual auditing of the service is needed until all restrictions/ obstacles are dealt with

# Audiologists as leaders - *AAA, 2009*




- Audiology professionals should take the lead in:
  - **Clinical guidelines for minimum standards of monitoring & care**
  - **Setting up this service and establishing good links and alliances with:**
    - Physicians (oncology, CF,TB, ICU, Renal)
    - Specialist Nurses, and Nurses
    - Pharmacists
  - **Professional education programmes to increase awareness and standardisation of monitoring practice.**

# Take Home Messages:

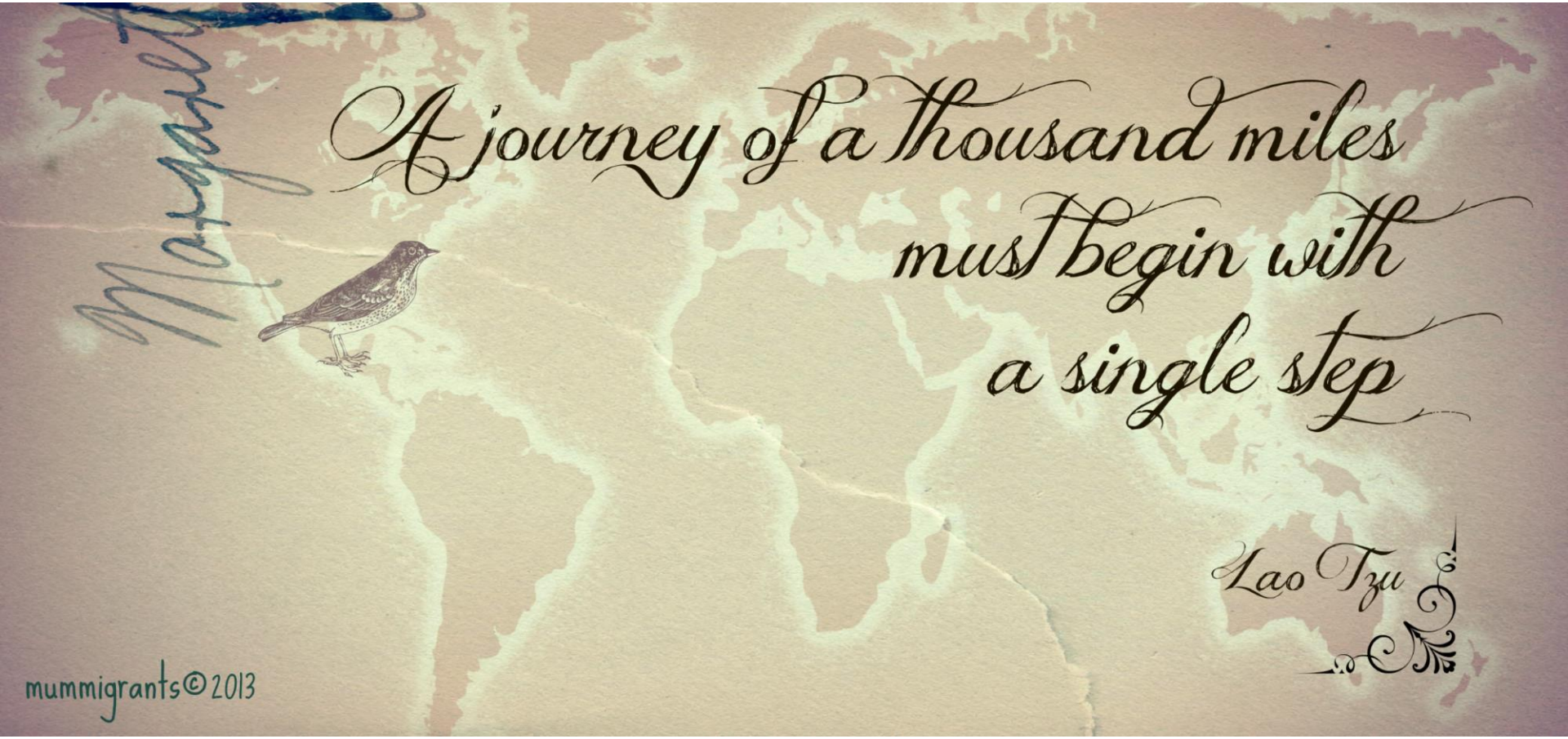
- DPOAEs can be a very useful and effective ototoxicity monitoring tool especially in unwell bedridden patients
- Repeatability and accuracy of testing can be established by consistent deep good probe fitting and testing in a quiet environment with established normative data.
- Urgent need for establishing an agreed ***National Ototoxicity Monitoring Protocol*** with set testing and outcomes parameters to confirm early evidence of ototoxicity & provide consistent minimum level of care.

# WHO Recommended roadmap for the prevention of hearing loss

Member States of the World Health Organization are required to:

- prepare national plans for the *prevention and control of major causes of avoidable hearing loss and for early detection of such loss*;
- take advantage of existing guidelines and regulations or introduce appropriate legislation for the proper management of particularly important causes of deafness and hearing impairment, such as otitis media, *use of ototoxic drugs* and harmful exposure to noise, including noise in the work environment and loud music;
- ensure appropriate *public information and education for hearing protection* and conservation in particularly vulnerable or exposed population groups.

Resolution WHA48.9. Prevention of hearing impairment. In: *Forty-eighth World Health Assembly, Geneva, 12 May 1995. Twelfth plenary meeting, Committee A* Geneva: World Health Organization; 1995. Available from: http://www.who.int/pbd/publications/wha_eb/wha48_9/en/


A journey of a thousand miles
must begin with
a single step
Lao Tzu
mummigrants©2013

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