Fast, Cheap & Accurate Methods for Ototoxicity Monitoring

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Outline

- Background
- ASHA and AAA guidelines
- Strategies for behavioral and objective monitoring and support for their use
- Determining and validating objective monitoring techniques

BACKGROUND

Ototoxicity

- Commonly prescribed ototoxins are:
  - Platinum-based chemotherapies and aminoglycoside antibiotics
- Symptoms are:
  - Hearing loss
    - Permanent, high frequency, progressive
  - Tinnitus
  - Dizziness
    - Dysequilibrium, oscillopsia, vertigo

Pathophys: Platinum-based Drugs

- Oxidative Damage (Evans & Halliwell, 1999; Gratton & Smith, 2004; Rybak & Kelly, 2003)
  - Hair cell damage/death
  - Damage to stria vascularis and sprial ganglion cells (Tsukassaki et al., 2000)
- Hair cell damage begins at base, progresses toward apex, first row of OHCs followed by second / third rows, and then the IHCs (Gratton & Smyth, 2004)

Effects of HL

- HL impacts emotional well-being (Kochkin & Rogin, 2000)
- For patients with pre-exposure HL, even small hearing shifts can be handicapping (Laurell & Jungnelius, 1990)
- HL often overlooked by the sufferer and under-treated by health professionals, particularly when it coincides with a disease that threatens general health (Durrant et al., 2005)

Potential Benefit of Monitoring

- "[Monitoring] before every treatment course can frequently, but not always, identify patients at risk of sustaining hearing loss leading to social handicap during the next course." pp 733

Laurell G, Jungnelius U, High-dose cisplatin treatment: Hearing loss and plasma concentrations. *Laryngoscope*, 100:724-734, 1990.

ASHA 1994 & AAA 2009 POSITION STATEMENTS & CLINICAL GUIDELINES

- American Speech-Language-Hearing Association. (1994). Guidelines for the audiologic management of individuals receiving cochleotoxic drug therapy. ASHA, 36, 11-19.
- American Academy of Audiology. (2009). Ototoxicity monitoring: Position Statement and Clinical Guidelines. AAA, in press.

ASHA Threshold Shift Criteria

- Threshold shifts at adjacent test frequencies indicate more systematic change (Atherly, 1963; Dobie, 1983)
  - Notion of examining threshold shift across adjacent frequencies
  - Notion of *any* frequency or set of frequencies, as opposed to a *fixed* frequency, e.g., 8 kHz
- Threshold shifts on repeated tests are also a stronger indication of a true threshold change (Royster & Royster, 1982)

ASHA Threshold Shift Criteria

- ≥20 dB change at any 1 test frequency
- ≥10 dB change at any 2 adjacent test frequencies
- Loss of responses at 3 consecutive frequencies, where responses were previously obtained
- Changes confirmed by repeat testing

AAA Goals of Monitoring

1. Early detection of ototoxic HL and intervention to prevent hearing handicap
2. Rehabilitation to lessen the impact of unavoidable handicapping HL
   - Provision of counseling and education, communication strategies, assistive listening devices and/or hearing aids

AAA Suggested Protocol

- Protocol selection dictated by clinical purpose and patient considerations. pp7
- Baseline should include ALL tests that may be needed in subsequent testing... to serve as a basis for comparison. pp 7
- Test battery approach (use of behavioral and objective measures) increases chances of obtaining reliable monitoring data over time. pp 15

AAA Suggested Protocol

Baseline Evaluation	If Ototoxicity Occurs
▪ AC thresholds (0.5-8.0 kHz) ▪ HFA (8-16 or 20 kHz) ▪ Tympanometry ▪ Speech audiometry ▪ OAEs	▪ ASHA criteria used to identify ototoxic hearing changes ▪ Follow up tests same as Baseline, but include other tests as appropriate e.g., BC thresholds

AAA Suggested Protocol

Monitoring Evaluation Considerations

- Conventional audiometric assessments not likely to be efficient , cost-effective and/or well-tolerated by an ailing patient, particularly when administered in the sound booth.
- Need time-efficient, cost-effective, accurate monitoring tests
- HFA?
- OAE testing?

⇐ Portable?

High Frequency Audiometry

A portable, handheld audiometer-like device that will enable ward testing of ototoxicity

High Frequency Audiometry

- The most vulnerable part of the cochlea is the basal region, which processes high frequency sounds
- Ototoxic damage due to cisplatin and aminoglycoside exposure progresses from the cochlear base to the apex

On Diagnostic Test Performance

- Examine measurements in groups of patients that are either exposed to ototoxic drugs, or not exposed, and to see how well measures reflect the exposure difference
  - Is auditory dysfunction among the exposed group large compared with normal variability?
  - Is auditory dysfunction in exposed patients is more common when using one measurement compared to another measurement?

Exposed ears with HFA Changes

- Compared with CA, HFA affected in more patients receiving ototoxic drugs
  Jacobson et al., 1969; Fausti et al., 1984,1992; Tang et al., 1985; Rappaport et al., 1985; Dreschler et al., 1989; Kopelman et al., 1988

Non-exposed ears with HFA Changes: Booth vs. Ward

	Booth		Ward		
Earphone Type	**≥ 20 dB at 1 Frequency**	**≥ 10 dB at 2 Consecutive Frequencies**	**≥ 20 dB at 1 Frequency**	**≥ 10 dB at 2 Consecutive Frequencies**	**Frequency Range**
Koss Pro/4X*	0%	0%	0%	7%	2, 5-16
ER-4B*	0%	0%	0%	0%	2, 5-16
Sennheiser HDA 200**	0%	2%	n/a	n/a	8-16

*Gordon et al., *JRR&D*, 2005.

**Frank, *Ear & Hearing*, 2001.

HFA has good specificity in booth and ward

Fast High Frequency Tests

Fixed high-frequency approaches

- Pasic and Dobie, 1990
- Simpson et al., 1992

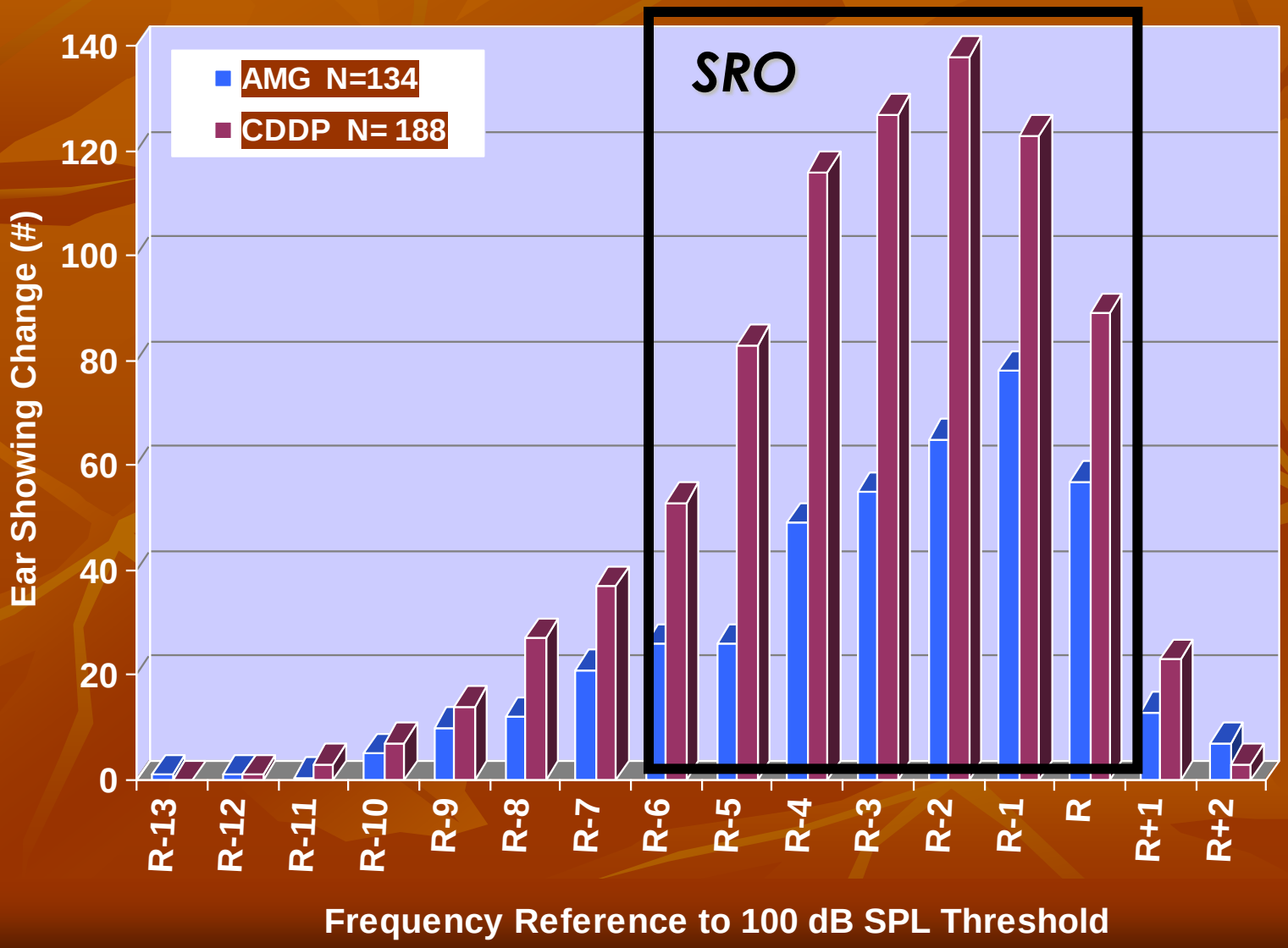
- Time-efficient
- Limited to patients with hearing at specific test frequencies

Fast High Frequency Tests

Individualized Sensitive Range for Ototoxicity (SRO)

- Fausti et al., 1992, 1999
- Time efficient
- Can be used to test most patients (even in those with substantial pre-exposure HL)

Initial Ototoxicity Detection

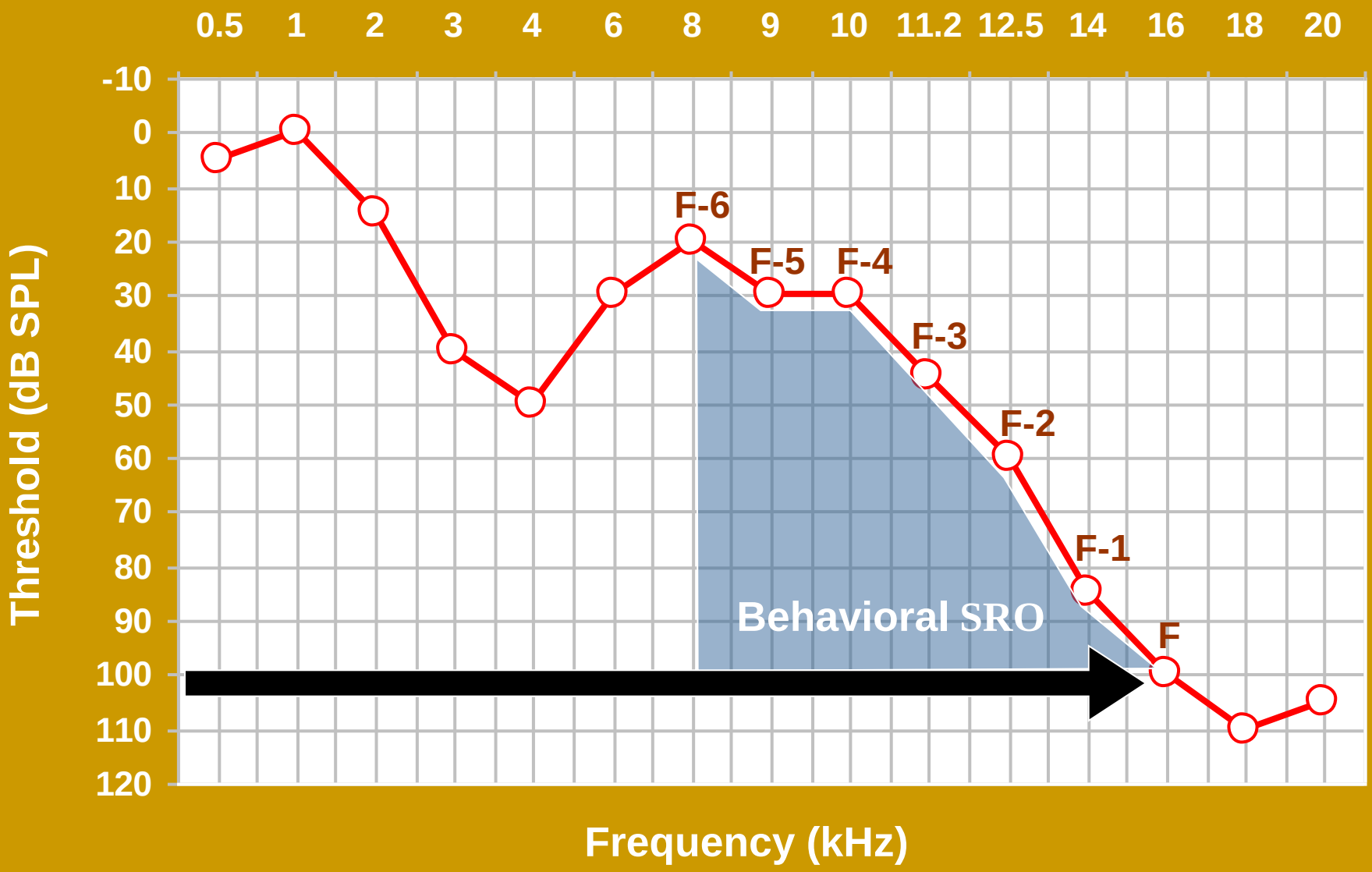


SRO Principle

- Thresholds > 100 dB SPL remain unchanged
- Early changes seen within one octave below the highest audible frequency
- Range for each individual is unique and specific to their hearing configuration

SRO is the uppermost frequency with a threshold ≤100 dB SPL and 6 lower consecutive frequencies tested in 1/6th octave steps

Example SRO


0.5
1
2
3
4
6
8
9
10
11.2
12.5
14
16
18
20
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
Threshold (dB SPL)
F-6
F-5
F-4
F-3
F-2
F-1
F
Behavioral SRO
Frequency (kHz)

Most Exposed Ears Have Hearing Shifts within SRO

	Total (Ears)	Hit	Miss	Initial Change on SRO
AMG	54	46	8	85%
Cisplatin	226	207	19	92%
Carboplatin	59	50	9	85%
Total	339	303	36	89%

Fausti SA, Helt WJ, Phillips DS, Gordon JS, Bratt GW, Sugiura KM, Noffsinger D: Early detection of ototoxicity using 1/6th-octave steps. *J Am Acad Audiol* 14(8):444-50, 2003.

Konrad-Martin et al., *JAAA* 2010

1. How well does SRO monitoring detect ototoxic hearing loss using various significant threshold shift (STS) definitions?
2. Do results support use of ASHA-recommended STS definitions?
3. Does testing in 1/6- or1/3-octave steps improve the test when compared to use of 1/2-octave?

Methods

- All subjects
  - at least 3 audiograms, one audio ~1.5 months, one audio ~6.5 months after initial dose
- Cisplatin-exposed Group
  - 78 ears of 41 patients receiving cisplatin
  - cumulative dose at least 350 mg
  - mean age 59.4 years (SD 10.2)
- Control Group
  - used as the comparison group
  - 53 ears of 28 hospitalized patients receiving non-ototoxic antibiotics
  - mean age 56.0 (SD 10.5)

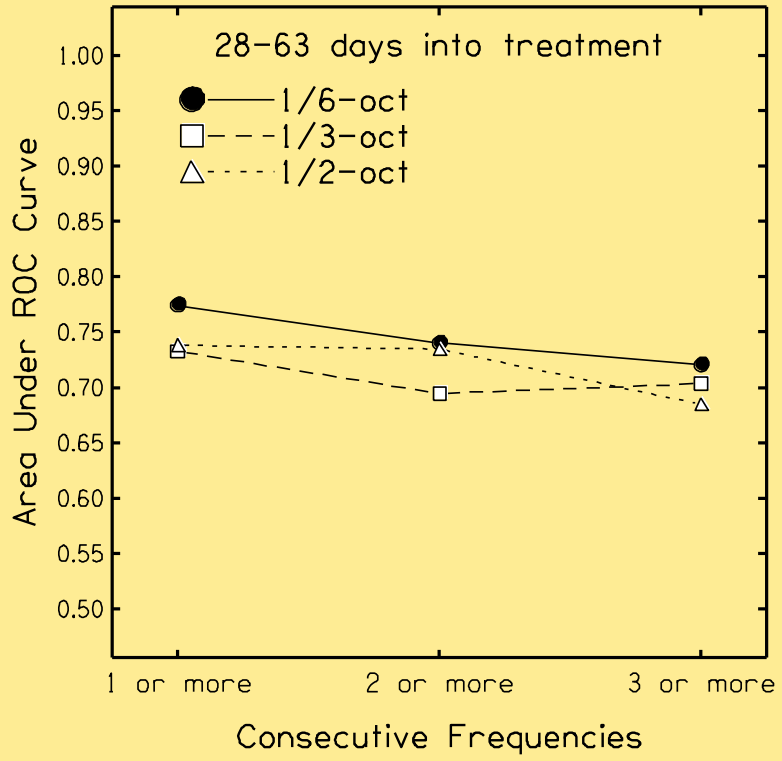
Methods

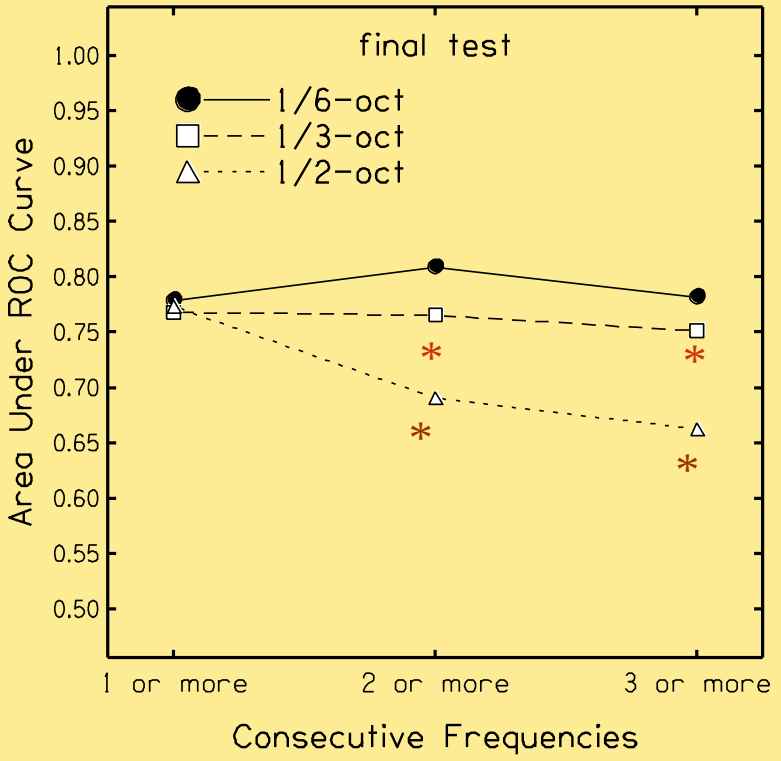
- Hearing changes calculated n SRO
- Compared initial audiogram to tests obtained 1.5 and 6.7 months later
- Determined if changes met STS criteria
  - based on positive threshold shifts (worsening by 5, 10, 15, or 20 dB)
  - and numbers of frequencies affected (shifts at a minimum of 1, 2, or 3 adjacent frequencies)

Methods

- Estimated relative performance in 2 ways
- 1. Plotted receiver operating characteristic (ROC) curves
  - Plots of hit rates in exposed ears as a function of hit rates in non-exposed ears
  - Tested whether or not confidence intervals surrounding the areas under the curves (AUCs) were statistically diferent
- 2. Determined STS definitions with highest hit rates among exposed ears for a fixed hit rate among non-exposed ears of 5%
  - Chosen to minimize the number of patients incorrectly diagnosed with ototoxic hearing loss

AUCs


28-63 days into treatment
1/6-oct
1/3-oct
1/2-oct
Area Under ROC Curve
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
1 or more
2 or more
3 or more
Consecutive Frequencies


final test
1/6-oct
1/3-oct
1/2-oct
Area Under ROC Curve
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
1 or more
2 or more
3 or more
Consecutive Frequencies

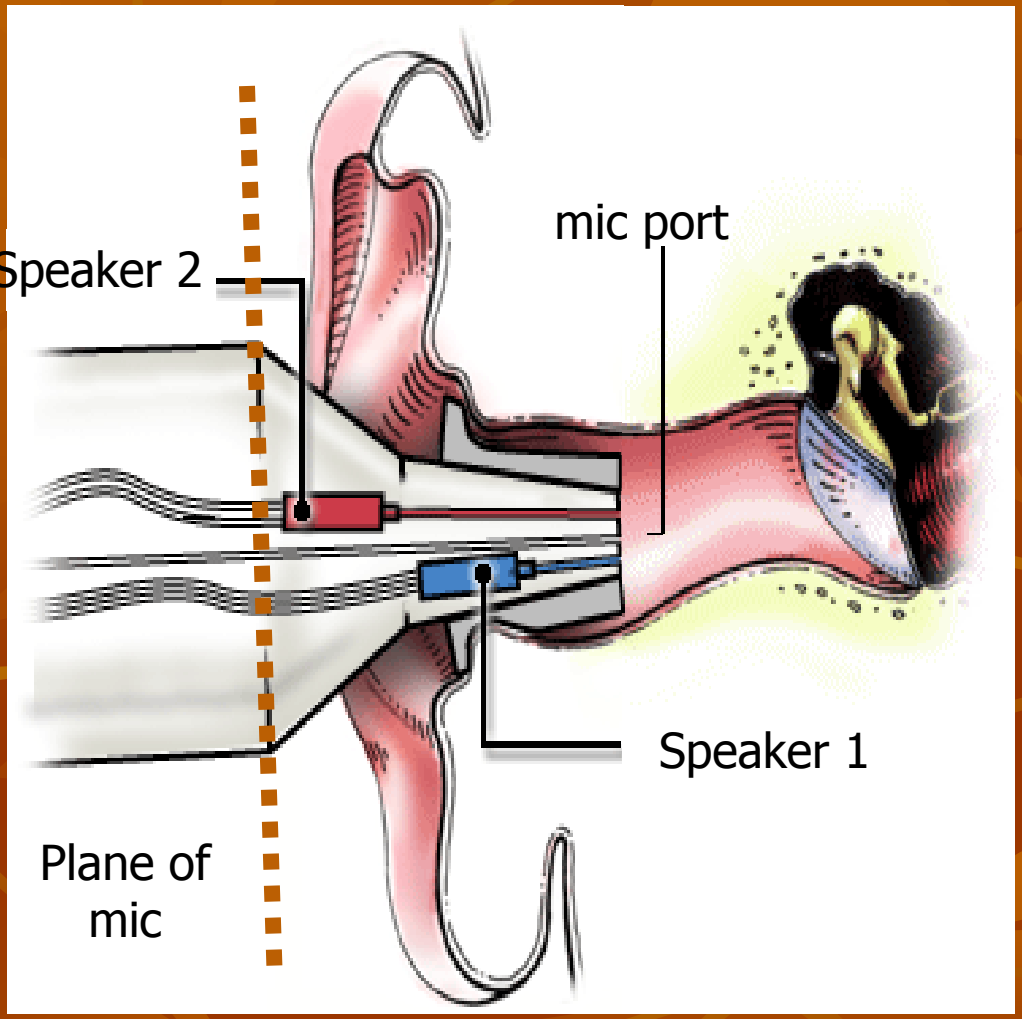
Results

- Best AUCs were for 1/6th octave step size
- Use of 1/6 and 1/3rd octave step sizes increased relative performance significantly compared to 1/2 octave step sizes for shifts at 2 or 3 adjacent frequencies

Results

- Certain ASHA-recommended criteria performed well
  - threshold shifts ≥ 20 dB at 1 frequency
  - ≥ 10-dB at 2 or more adjacent frequencies
- Loss of response at three frequencies should be changes ≥10 dB because 5 dB changes had high FP rates

Distortion-product OAEs



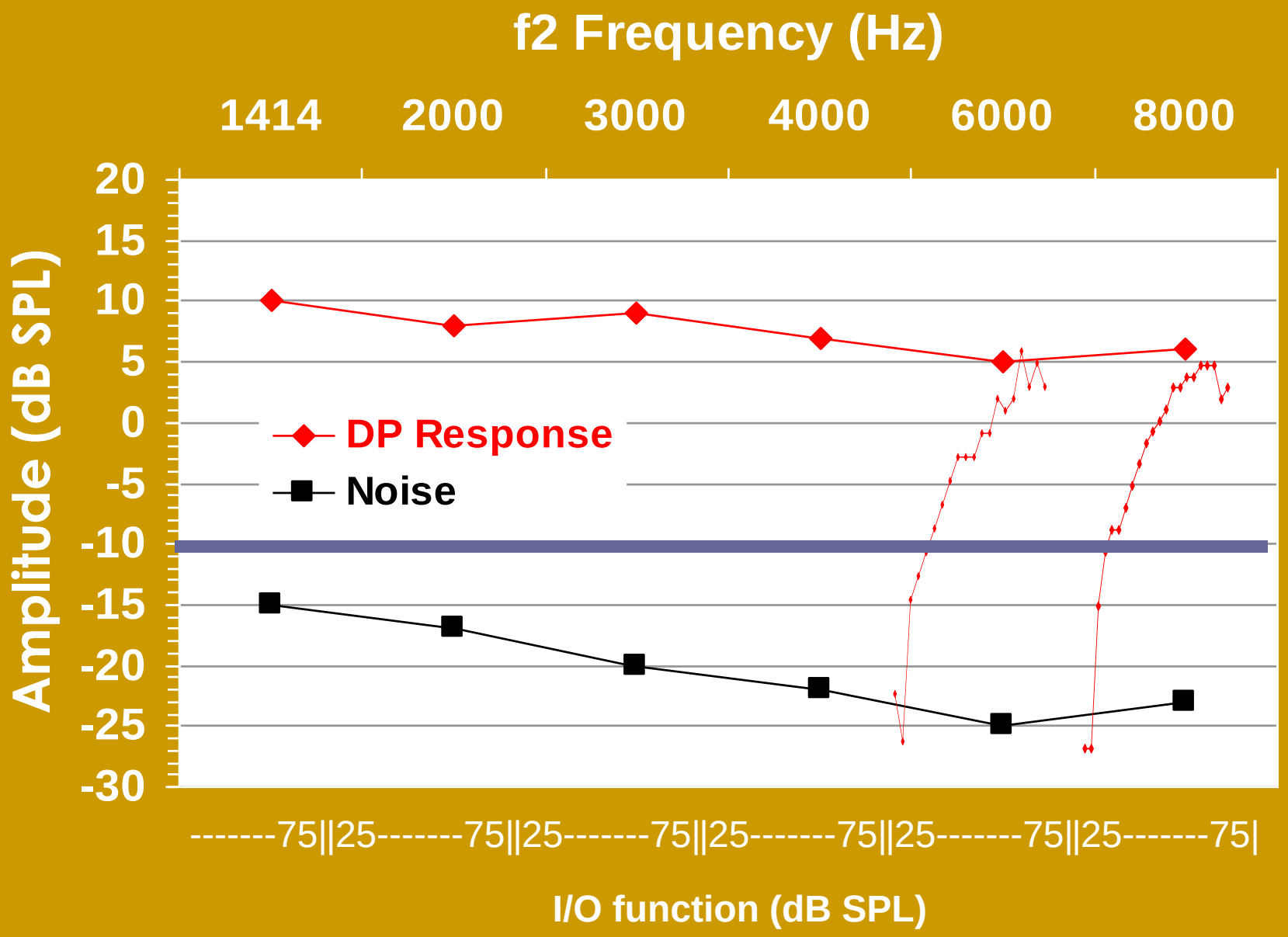
Drawing by S. Blatrix from "promenade around the cochlea" EDU website www.cochlea.org by Rémy Pujol et al., INSERM and University Montpellier 1

Distortion-product OAEs

- Objective measure that tests functional integrity of outer hair cell (OHC) system
- OHC system must be normal for hearing thresholds to be normal
- Initial damage from cisplatin and aminoglycosides located in the OHCs of the basal turn
- DPOAE changes may signal hearing changes, or more subtle ototoxic effects

DPOAE Measurement

- DP-gram
  - Plot DPOAE level as a function of f2 frequency, while primary levels are held constant
  - Uses moderate level, e.g., L1, L2 in dB SPL= 65, 65 or 65,59
  - f2 is varied in small frequency steps
- Input/output (I/O) function
  - Plot DPOAE level as a function of primary level, while primary frequency held constant


f2 Frequency (Hz)
1414
2000
3000
4000
6000
8000
20
15
10
5
0
-5
-10
-15
-20
-25
-30
Amplitude (dB SPL)
DP Response
Noise
-------75||25-------75||25-------75||25-------75||25-------75||25-------75|
I/O function (dB SPL)

Non-exposed ears with DPOAE Changes

- *~5% of control ears have DPOAE level changes of ~6 dB*
- Standard error of measurement difference (SEM) Typically 2 X SEM is about 5 dB for f2 from 1-4 kHz (Franklin et al. 1992)
- Average amplitude difference plus 2 SD 6 dB for most frequencies 1-6 kHz (Roede et al., 1993)
- Cumulative distributions
  - Our preliminary data typically show > 95% of ears had test-retest change of 6 dB or less for frequencies from 1 -10 kHz

Exposed ears with Ototoxic Changes:

OAE vs. Behavioral Testing

- DPOAEs were affected in more ears than conventional audiometry (CA)

  Aminoglycosides: Katbamna et al., 1999; Stavroulaki et al., 2002; Mulheran & Degg, 1997; Cisplatin: Stavroulaki et al., 2001

- DPOAEs were affected in more ears than CA, but in a similar number of ears compared with HFA

  Cisplatin: Ress et al., 1999

- DPOAEs were affected in fewer ears and later than HFA

  Cisplatin, Carboplatin or both: Knight et al., 2007

Ress, Sridhar, Balkany, Waxman, Stagner, Lonsbury- Martin, *Otolaryngology-Head and Neck Surg, 1999*

- Adult cancer patients treated with cisplatin
  - hearing in CA range <=70 dB HL
- DP-grams, f2= 0.8-8 kHz, L1=L2=75 dB SPL
- DP change >=5 dB at 2 consecutive frequencies

	CA	HFA	DPOAE
Ears at baseline	52/65 (80%)	35/65 (54%)	53/65 (82%)
Ears changed	34/52 (65%)	26/35 (74%)	40/53 (75%)

Knight, Kraemer, Winter and Neuwelt, *J ClinicalOncology, 2007*

- Pediatric (age 8 months to 20 years) cancer patients treated with cisplatin, carboplatin or both
- DP-grams, f2=1.5-8.4 kHz, L1=65, L2=55 dB SPL
- DP change >=8 dB that persisted or worsened

	CA	HFA	DPOAE
Patients at baseline	32/32 (100%)	n/a	32/32 (100%)
Patients with bilateral changes	20/32 (63%)	16/17 (94%)	26/32 (81%)

Reavis et al., *Ear Hear* 2008

1) For subjects with ASHA-significant hearing changes in the SRO, how well do DPOAEs detect the change?
2) What variables are associated with DPOAE sensitivity?

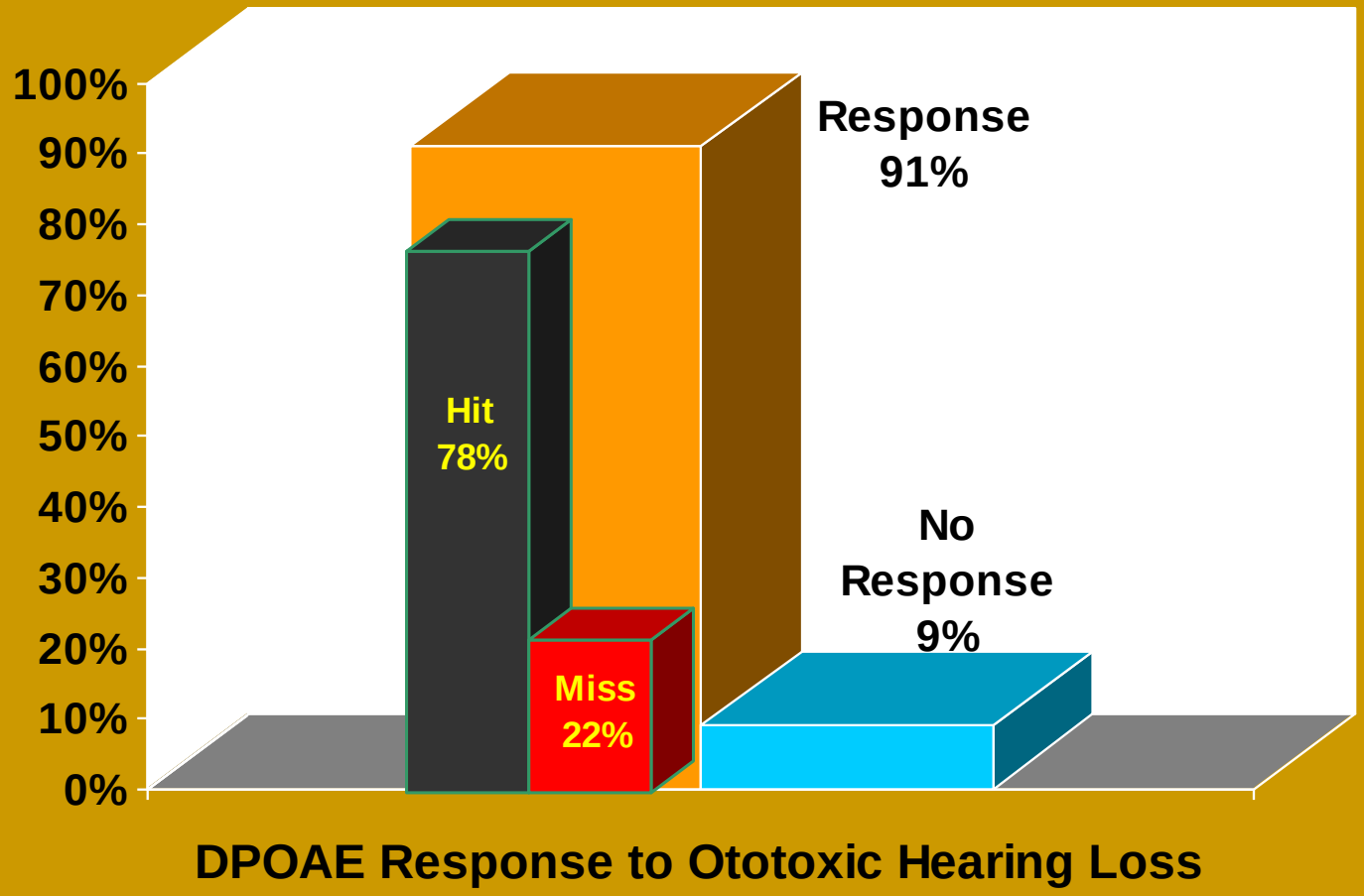
Methods

- Drug-exposed Subjects:
  - 53 exposed subjects (90 ears) with demonstrated ototoxic hearing change based on ASHA changes within SRO
  - Mean age 59 years (range 46 – 82 years)
  - Could have any degree of hearing loss
- Received at least one chemotherapy (cisplatin or carboplatin)
- Received more than 3 days of ototoxic antibiotic

Methods

- DPOAE testing
  - F2= 0.8-8 kHz; f2/f1=1.22; L1, L2=65, 59
- Criteria for inclusion of DPOAE data
  - Level $\geq$ -10dB SPL; SNR $\geq$ 6 dB
- Criteria for Change in DPOAE level
  - 4 dB amplitude change or loss of response at *two* consecutive frequencies
  - Changes could be outside the region of frequencies showing behavioral changes
  - Changes could occur before, together with, or after behavioral changes

DPOAE Sensitivity re: Behavioral Gold Standard



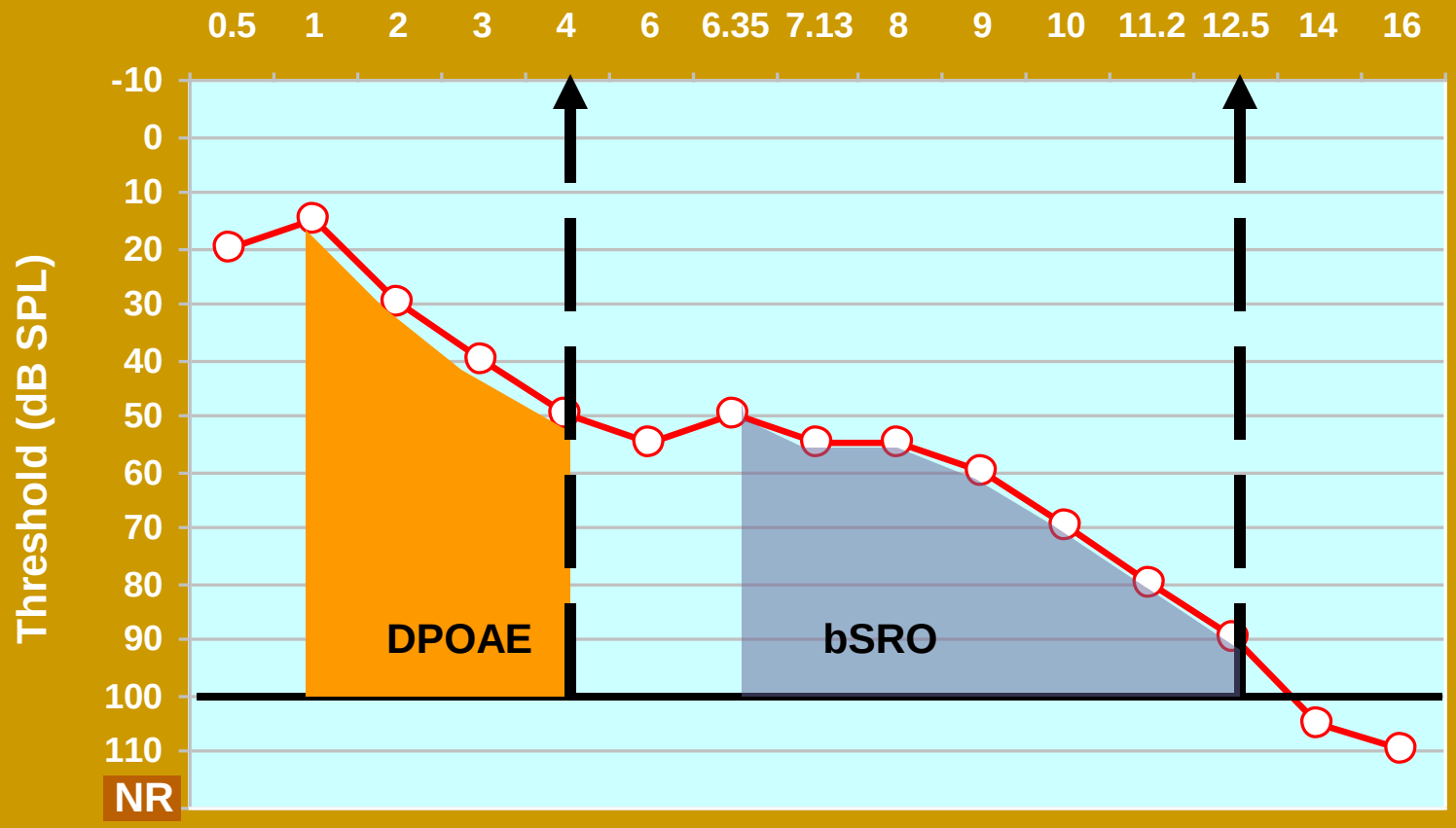
Hit: N = 64 Miss: N = 18 No Response: N = 8

Results

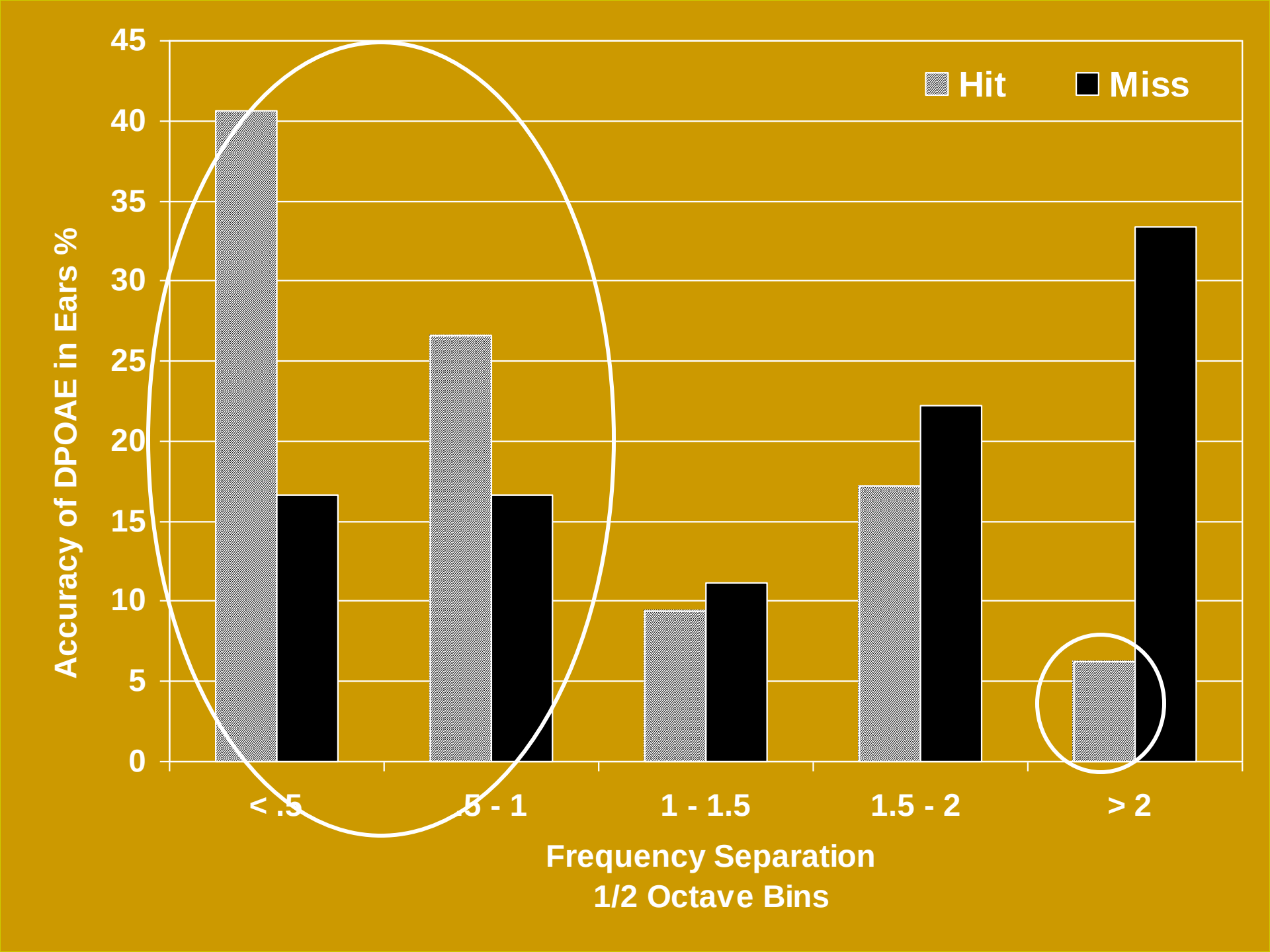
How well do DPOAEs predict ototoxic hearing changes near each subjects' high-frequency hearing limit?

- Less well than in studies in children and young adults with normal hearing
- Hit rate (78%) was comparable to hit rate found by Ress et al., 1999 (75%) in adults with some pre-exposure hearing loss
- DPOAEs were measurable in a greater number of subjects in our study (91%) compared with Ress study (82%)

Example SRO Below 8 kHz



bSRO Test Frequencies: 6.3 - 12.5 kHz


45
40
35
30
25
20
15
10
5
0
Hit
Miss
Accuracy of DPOAE in Ears %
< .5
.5 - 1
1 - 1.5
1.5 - 2
> 2
Frequency Separation
1/2 Octave Bins

Results

1. Factors affecting DPOAE sensitivity were:
   1. magnitude of post-exposure HL
   2. degree & configuration of pre-exposure HL
   3. frequency separation between DPOAEs & bSRO
   4. high-frequency limit of DPOAEs measurable at baseline
2. Highest frequency DPOAEs were most sensitive

AAA Guidelines

- A variety of significant change criteria have been proposed for interpretation of OAEs, but none yet enjoy universal acceptance. Thus, the sensitivity and specificity of these criteria need to be documented on large-scale patient populations pp14

DETERMINING & VALIDATING (*USING A GOLD STANDARD*) OBJECTIVE MONITORING TECHNIQUES

Reavis et al., *Ear Hear* 2011

1. Build a logistic regression model to separate ears with ototoxic HL from ears with stable hearing, using DPOAE measures and other risk factors.
2. Evaluate the accuracy of the model using ROC analysis

Methods

- 36 ears of 24 patients treated with cisplatin
- Mean age 58.5 years
- 3.4 monitoring visits on average
- Received approximately 400 mg of cispltin over 42 days
- Half the subjects experienced hearing change according to ASHA 1994 criteria in at least 1 ear

Methods

- Measured behavioral SRO and DPOAEs before and during chemotherapy
- Changes in both of these measures were relative to the pre-exposure test
- Used as “training set” of data in which the behavioral SRO is the outcome measure we hoped to predict, and the DPOAEs were used for making the prediction
- DPOAEs predicted HL at SAME visit using logistic regression

Methods

DP-gram search for highest frequency DP

- F2= 1-8 kHz; f2/f1=1.22; L1, L2=65, 59

Then DP I/O's at four highest frequencies tested in 1/3rd octave steps

- f2=35-60 dB SPL, L1 optimized using co-varied paradigm (Kummer et al., 1998)

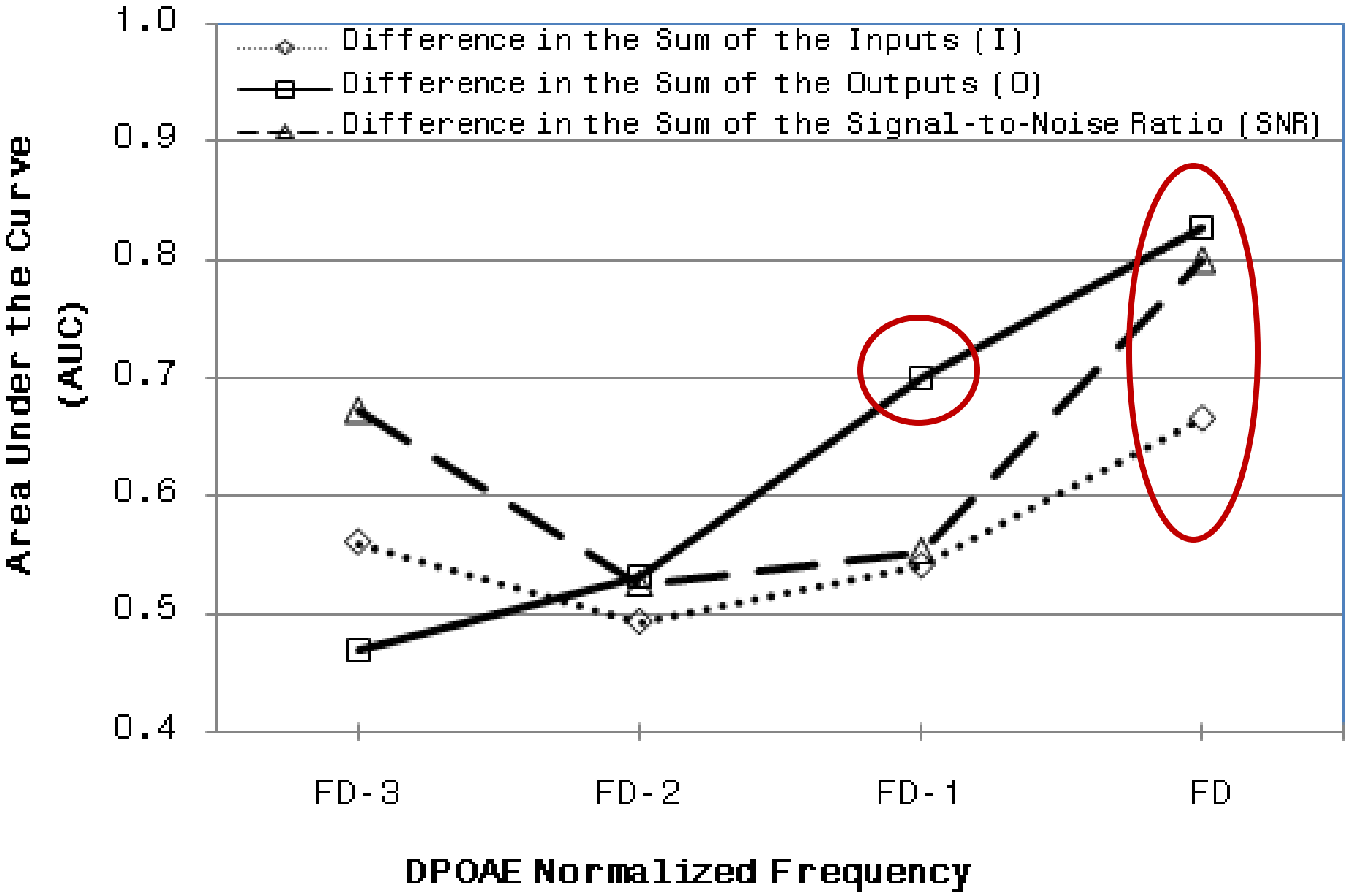
3 summary measures taken from I/O functions were used as the predictors

- I=difference in the sum of the inputs, O=difference in the sum of the OAE levels, SNR difference in the sum of the SNR

Methods

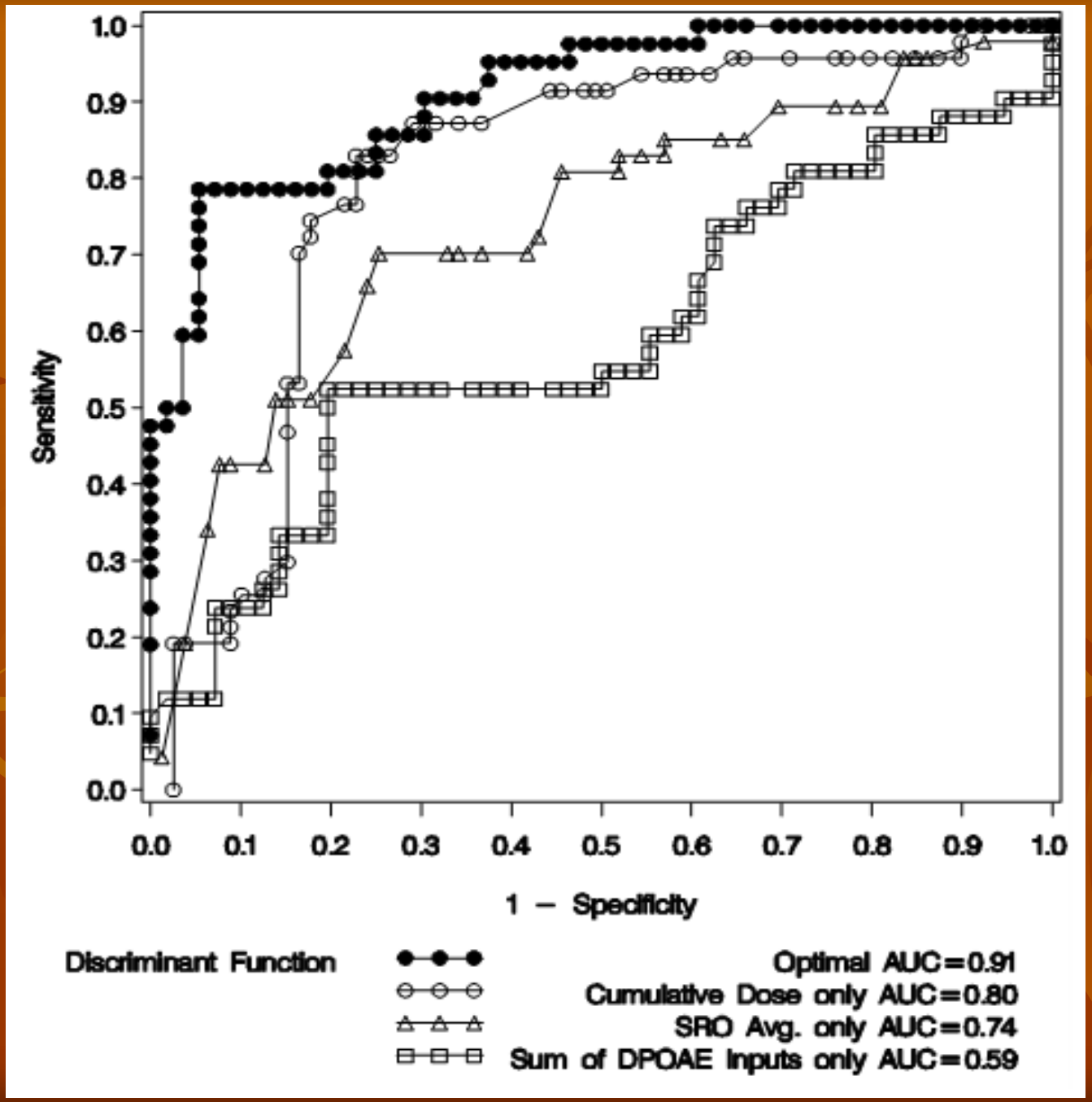
- We also evaluated whether patients had other potential risk factors for ototoxic hearing loss
- Total dose of cisplatin and pre-exposure SRO threshold average were significantly associated with whether a patient's hearing changed
- These were included in the logistic regression with DPOAEs, and evaluated separately

Figure 3.


1.0
0.9
0.8
0.7
0.6
0.5
0.4
Area Under the Curve (AUC)
Difference in the Sum of the Inputs (I)
Difference in the Sum of the Outputs (O)
Difference in the Sum of the Signal-to-Noise Ratio (SNR)
FD-3
FD-2
FD-1
FD
DPOAE Normalized Frequency

So How Would This Work?

- At each monitoring visit, you would make a DPOAE measurement
- Into the formula generated by us, you would enter the DPOAE test-retest difference (data collected at today's visit compared to the values from baseline)
- Enter the baseline SRO threshold average
- Enter the total cisplatin dose today
- Formula spits out likelihood that hearing in SRO has changed at today's visit


Sensitivity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1 – Specificity
Discriminant Function
Optimal AUC=0.91
Cumulative Dose only AUC=0.80
SRO Avg. only AUC=0.74
Sum of DPOAE Inputs only AUC=0.59

Results

- The multivariate DPOAE classifier is clearly a highly accurate predictor of ototoxic hearing change
- Compared to the use of DPOAEs alone, the multivariate classifier increases the accuracy with which DPOAEs can determine whether or not hearing has changed

Questions

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http://www.ncrar.research.va.gov/