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Multivariate DPOAE metrics for identifying changes in hearing: Perspectives from ototoxicity monitoring

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Abstract

Distortion-product otoacoustic emissions (DPOAEs) provide a window into real-time cochlear mechanical function. Yet, relationships between the changes in DPOAE metrics and auditory sensitivity are still poorly understood. Explicating these relationships might support the use of DPOAEs in hearing conservation programs (HCPs) for detecting early damage leading to noise-induced hearing loss (NIHL) so that mitigating steps might be taken to limit any lasting damage. This report describes the development of DPOAE-based statistical models to assess the risk of hearing loss from cisplatin treatment among cancer patients. Ototoxicity risk assessment (ORA) models were constructed using a machine learning paradigm in which partial least squares and leave-one-out cross-validation were applied, yielding optimal screening algorithms from a set of known risk factors for ototoxicity and DPOAE changes from pre-exposure baseline measures. Single DPOAE metrics alone were poorer indicators of the risk of ototoxic hearing shifts than the best performing multivariate models. This finding suggests that multivariate approaches applied to the use of DPOAEs in a HCP, will improve the ability of DPOAE measures to identify ears with noise-induced mechanical damage and/or hearing loss at each monitoring interval. This prediction must be empirically assessed in noise-exposed subjects.

Keywords

Otoacoustic emission; noise-induced hearing loss; ototoxicity monitoring

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Otoacoustic emissions (OAEs) are a consequence of normal outer hair cell (OHC) mechanical function. An intact OHC system acts as an output-limiting amplifier of the basilar membrane (BM) traveling wave response to sound, providing amplification for low-intensity sounds and compression for high-intensity sounds. The amplification is frequency specific in that OHCs at a given place on the BM amplify responses to sounds that match the tonotopic frequency of that place. A given cochlear location therefore processes sounds in a manner that is highly nonlinear with respect to the level and frequency of an acoustic stimulus, and the OHC system is the basis of this nonlinearity. Normal OHC function underlies the ability of the mammalian auditory system to code a very large range of stimulus levels, discriminate small differences in the frequencies of sounds, and detect low-level sounds.

Sound-evoked OAEs arise from a combination of coherent linear reflection and nonlinear distortion sources. The contribution of each of these sources to an OAE depends in part on the stimulus parameters with which it is generated. At low stimulus levels stimulus-frequency (SF) and transient-evoked (TE) OAEs arise from coherent linear reflection of the forward traveling wave in cochlear models that incorporate realistic (broad and tall) BM traveling waves typically ascribed to OHC function (Zweig & Shera, 1995; Talmadge et al, 1998). Imperfections randomly located along the organ of Corti create backward traveling reflections, which can interact coherently with the stimulus-generated forward traveling wave if arising from reflection sites near its peak. At higher levels, SFOAEs and TEOAEs arise from linear reflection and nonlinear distortion in the BM response to the stimulus (Talmadge et al, 2000; Kalluri & Shera, 2007).

Distortion product (DP) OAEs are generated when two BM traveling wave responses, elicited by two tones at closely-spaced frequencies, f_1 and f_2 , interact and undergo intermodulation distortion. This produces distortion products in the BM vibratory response at non- f_1 and f_2 frequencies that are arithmetically related to the primary frequencies. Energy at $2f_1-f_2$, the distortion product often measured clinically, is transmitted bi-directionally. It travels backward from the BM region that undergoes intermodulation distortion toward the tympanic membrane and forward toward its own relatively apical tonotopic place, where a reflection emission may be generated (Kim et al, 1980; Talmadge et al, 1998). In experimental data, the reflection source appears to be most prominent for DPOAEs elicited using lower-level stimuli; DPOAEs elicited by higher-level stimuli tend to be dominated by the distortion source (Konrad-Martin et al, 2001; Abdala et al, 2011). Of the evoked emissions, DPOAEs and TEOAEs were historically the easiest to measure and most of the OAE literature involves responses of these two types.

For pure-tone thresholds to be in a clinically normal range, OHC function must be normal and, therefore, cochlear processing is expected to be nonlinear. Environmental exposures that damage OHCs reduce auditory sensitivity, make cochlear processing more linear (e.g. Dallos et al, 1978), and reduce or abolish DPOAEs (e.g. Avan & Bonfils, 1993; Bonfils & Avan, 1992; Gorga et al, 1993a, b, 1996; Kim et al, 1996; Martin et al, 1990; Stover et al, 1996). Because of these relationships, OAEs (typically DPOAEs and TEOAEs) are commonly used to identify impaired function in populations that are difficult to test for pure-tone threshold sensitivity. There is also increasing interest in developing OAE methods for

use in hearing conservation programs (HCPs), in order to identify real-time changes in cochlear function and pure-tone threshold sensitivity from overexposure to noise.

OAEs are an attractive test to include in a HCP in part because OHCs are among the organ of Corti structures initially damaged by noise (Davis et al, 1989; Hamernick et al, 1989; Liberman et al, 1982; Nordmann et al, 2000). Both DPOAEs and TEOAEs appear more sensitive to various cochlear insults than the audiogram based on observations that they sometimes change when pure-tone thresholds levels remain stable, at least for thresholds tested in the conventional audiometric frequency range (e.g. Engdahl et al, 1996; Marshall et al, 2009; Seixas et al, 2005). It has been suggested, based on noise damage studies in chinchilla, that up to 30% of OHCs contributing to responses at a given cochlear location can be damaged before producing a hearing shift sufficient to be detected by an audiogram (Bohne & Clark, 1982). Accordingly, several case-control studies report decreased TEOAEs in noise-exposed persons with normal hearing, with normal TEOAEs measured in hearing-matched control groups not exposed to noise (Desai et al, 1999; Hamdan et al, 2008). Other prospective trials note changes in DPOAEs and TEOAEs that mirror the time course of temporary threshold shifts (TTS) (Sutton et al, 1994; Marshall et al, 2001), a finding also established for DPOAEs in animal studies of TTS (e.g. Kujawa & Liberman, 2009). Generally, OAE changes have been found in regions outside the initial NIHL lesion (Konopka et al, 2005) as well as within the NIHL lesion (i.e. at the same frequencies as the hearing shift) (Marshall et al, 2001). Taken together, these studies suggest that OAEs may be useful not only for detecting NIHL, but also for detecting noise-induced damage to the inner ear prior to the development of a significant hearing loss. An OAE-based screening approach might therefore substantially improve the quality of auditory surveillance done in HCPs today.

The use of DPOAEs in hearing conservation programs (HCPs)

What clinical objectives of a HCP might OAEs serve?

OSHA standards explicitly define the minimum audiometric monitoring standards for businesses that are required to have a HCP (OSHA, 2004). Building on Marshall et al (2001), OAEs could be used to meet several additional clinical objectives. Proposed HCP clinical objectives, including potential applications of OAE monitoring are summarized in Table 1 and discussed in detail below.

One objective of a HCP may be to obtain a measure of an individual's susceptibility to (or conversely, their tolerance for) NIHL prior to an exposure. Having such information in advance could help identify workers who require hearing protection devices at lower exposure levels than stipulated for an 8-hour day in the current OSHA standard (OSHA, 2004). This standard requires hearing monitoring and available hearing protection devices if the exposure is 85 dBA time-weighted average (TWA) or greater; hearing protection device use only is required for 85 dBA, if there has been a significant hearing shift, or if there has been no baseline hearing test yet, and; hearing protection must be used if the exposure is 90 dBA TWA or greater. Those who are more susceptible to damage from noise could also be monitored more frequently than the annual screening stipulated by OSHA based on the

expectation that measurable changes in auditory function accrue more rapidly in these more vulnerable workers.

The OSHA standard also establishes criteria for a significant hearing shift following exposure to noise that once confirmed by retest, requires workers to be notified. It is not always possible to obtain precise behavioral threshold measures for a variety of reasons (e.g. due to methodological issues, time constraints, malingering, or the lack of well-trained staff). Therefore, a procedure that provided an ability to more accurately, rapidly, and objectively identify hearing loss (that may require reporting per OSHA regulations) would be an important new tool for HCPs. It may also be useful to detect incipient NIHL (not yet meeting OSHA reporting requirements) with OAE testing, using a criterion hearing shift that is smaller than an OSHA-significant shift. Because a small shift could become a future OSHA-significant NIHL with continued exposure, making the decision to improve hearing conservation methods when thresholds are just beginning to increase might prevent a larger shift from happening later.

Based on evidence that OAEs may be more sensitive to noise insults compared with audiometric thresholds, it may also be useful in a HCP to identify changes in OAEs as a screening measure of OHC dysfunction irrespective of changes in auditory sensitivity. Finally, education to prevent NIHL and remediation to lessen the impacts of any NIHL through rehabilitation and/or counseling are also important HCP goals.

Useful attributes of an objective hearing shift assessment tool

The overarching clinical objectives given in Table 1 require methods that are theoretically sound based on known patterns of damage, involve minimal time, cost and discomfort, are suitable for inattentive or non-cooperative individuals, and generate valid results in the majority of individuals tested.

There is theoretical and empirical support for the use of OAEs to detect damage from noise (see above), and, OAEs require only minimal compliance from the test subject, with the ability to quickly collect large data sets. OAEs can be used to test individuals with varying degrees of attentiveness to the task. OAEs are also relatively easy and inexpensive to measure, which would enable testing to be done by trained technical staff using affordable equipment. Assuming OAEs can be shown to accurately estimate probability of NIHL or provide additional information about pre-NIHL OHC damage, they are well suited for use in a large scale HCP.

Determining test accuracy using a gold standard—Interpreting results of a clinical test requires an understanding of its accuracy. Strictly speaking, an accurate clinical test is one that correctly identifies whether or not a ‘gold standard’ measure of disease/damage has occurred. A gold standard is a well-accepted proxy measure of the damage, such as a significant pure-tone threshold shift as defined by OSHA. A blind comparison of the new test and the gold standard test of the damage in an exposed population of individuals (some of whom have the damage, some of whom do not) is required. This comparison determines if the new test identifies those with damage as indicated by results of the gold standard test. An OAE test developed in this manner might provide a score that quantifies the likelihood of

NIHL. A score can be a simple 'Pass/ Fail' or can be expressed on an arbitrary numerical scale. In this case, an accurate test is one that often identifies a threshold shift when one actually occurs and rarely identifies a threshold shift when such a shift does not actually occur. These measures of test performance are sometimes called, respectively, the true positive rate (or sensitivity) and the false positive rate; together they completely describe the accuracy of a new clinical test and establish the test's clinical utility.

Determining test accuracy without a gold standard—OAEs will likely prove useful for a HCP beyond their ability to predict hearing shifts because they may be an effective screening measure for identifying OHC damage. This requires a different approach to determine test accuracy because there is no commonly accepted gold standard of OHC damage in humans. One approach is to estimate the range of normal measurements (i.e. group variability) in a non-exposed control group. A positive screen result is diagnosed in any new case (i.e. patient with noise exposure) with a measured OAE outcome outside the range of normal variability. The accuracy of this case-control group comparison is difficult to quantify, however. Estimates of the true positive rate are impossible, so test performance can never be completely described. The false positive rate can perhaps be estimated by the number of positive screens in an independent sample of control subjects who are not exposed to damage-inducing noise levels (but are otherwise similar to the exposed 'cases') but, finding such a sample may be difficult. The concept of determining what is a clinically meaningful OAE change based on normal test-retest variability has already received some attention in the literature (Beattie et al, 2003; Franklin et al, 1992; Roede et al, 1993). If this approach continues to be successful, this type of OAE test information would almost certainly be valuable in a HCP to counsel individual workers and their managers in order to motivate more rigorous hearing conservation practices. Motivating hearing conservation interventions that workers or managers perceive as being inconvenient or costly, however, may require the use of OAE test information verified against a gold standard (such as a hearing test) simply because the gold-standard approach yields a higher degree of certainty about how the test will perform in a clinical setting.

It is important to point out that the same OAE data could be used not only to identify OAE changes with respect to normal test-retest variability, but also to determine if a significant hearing shift has occurred. These are two very different approaches to the use of OAEs in HCPs, which provide important and complimentary information.

Beyond test accuracy—Even if an OAE test is highly accurate at identifying cochlear damage or hearing shifts, it is not very useful if valid test results are frequently unable to be obtained. This is unlikely to be an issue with DPOAE tests; among Veterans enrolled in two separate prospective trials investigating DPOAE test-performance for detecting ototoxicity, only 10% of ears had to be excluded for a lack of DPOAEs at baseline (Reavis et al, 2008, 2011). DPOAEs sometimes could not be recorded at test frequencies with substantial pure-tone threshold deficits, and there were cases in which drug-induced pure-tone threshold shifts were restricted to those (DPOAE 'no response') frequencies. However, DPOAEs obtained at comparatively lower f2 frequencies in such cases were still useful for predicting the drug-induced hearing shifts, either because DPOAEs are sensitive to pre-clinical damage

or are influenced by threshold loss at comparatively higher frequencies than the eliciting primaries (Arnold et al, 1999; Dreisbach et al, 2008; Konrad-Martin et al, 2002; Martin et al, 2009). Overall, these results suggest that OAE measurements could be used for functional monitoring in the majority of ears.

Obstacles to the use of OAEs as an objective hearing shift assessment tool

Although we have argued that functional monitoring could be achieved in the majority of ears, we do acknowledge the challenges associated with monitoring low-level OAEs such as might be recorded from impaired ears. Namely, measurement noise contaminates the OAE signal for levels near the noise floor, and there is little room for the OAE measurement to decline (i.e. a floor effect). This means that subject and system noise (system distortion) need to be low to effectively monitor OAEs in impaired ears.

Another challenge is that early effects of noise exposure may be small relative to inherent variability of the OAE measurement, which limits OAE interpretation in both case-control and gold standard comparisons. If the magnitude of a true noise-induced OAE change is smaller than measurement variability among control subjects, it will be difficult to define an OAE-change cut point that distinguishes ears with change versus non-change. Similarly, if true noise-induced OAE changes among individuals with a gold standard diagnosis of NIHL are comparable to OAE changes among individuals with a gold standard diagnosis of stable hearing, it will be difficult to define an OAE-change cut point to distinguish ears with changed versus stable hearing. Better OAE metrics could improve the problem. For example, while no single DPOAE metric (DPOAE level or signal-to-noise ratio, termed SNR) has been capable of completely separating those with normal hearing from those with impaired hearing (Gorga et al, 1993b, 1997; Kim et al, 1996), multivariate DPOAE models which include both amplitude and SNR at multiple DPOAE frequencies and/or a multiple-frequency pure-tone threshold gold-standard have shown increased test accuracy (Dorn et al, 1999; Gorga et al, 1999). The remainder of this paper focuses on approaches for auditory surveillance developed for ototoxicity monitoring and the potential application of such approaches to an HCP.

Possible improvements in DPOAE tests for detecting NIHL based on cisplatin ototoxicity studies

We have developed DPOAE-based statistical models to assess the risk of hearing loss from cisplatin treatment among cancer patients. Our approach linking changes in various DPOAE metrics to changes in auditory sensitivity may provide insights into the use of OAEs in a HCP where the goal is to distinguish between ears with stable and changed function at each monitoring interval.

Employing a gold standard measure for NIHL

In our ototoxicity experiments, shifts in pure-tone threshold sensitivity relative to a pre-exposure audiogram served as the gold standard indicator of ototoxic damage (Dille et al, 2010; Reavis et al, 2011). Damage from cisplatin generally follows a base to apex progression in the cochlea, with high frequency coding regions affected first. For an

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ototoxicity monitoring program (OMP), Fausti and colleagues proposed using a behavioral protocol that monitors the highest seven frequencies (tested in 1/6-octave steps) heard by each individual patient (Fausti et al, 1999, 1993, 1994). The highest frequency that can be heard, as defined by a pure-tone threshold no higher than 100 dB SPL, is specifically identified as 'FB'. This 'sensitive range for ototoxicity' (SRO) varies across patients depending on their pre-exposure hearing ability. It is not a set frequency range that is tested on everyone and can include conventional or extended-high frequencies, or both. Each patient's SRO can be monitored for signs of progressive hearing change over multiple visits by expanding the SRO frequency range when thresholds can no longer be obtained at a limit of 100 dB SPL. The rationale is that this approach will sometimes allow a decision to be considered to alter treatment before a handicapping hearing loss occurs, which is generally considered one that affects frequencies below about 4 kHz. Past reports suggest that this individualized SRO approach is fast, yet captures those frequencies at which ototoxic hearing shifts are first detected audio-metrically. This makes it especially useful as a gold standard when testing the efficacy of DPOAE metrics.

A gold standard for NIHL monitoring will depend on the pattern of damage associated with a particular form of noise exposure and its relationship to measures of auditory function. It is compelling to develop a DPOAE test for NIHL monitoring using pure-tone threshold shift as a comparison test, given that pure-tone threshold shift is the current legal standard for detecting NIHL in a HCP. However, DPOAE test results could also be compared against measures that are not part of a typical audiometric test battery.

Primary damage with high frequency noise is generally described as occurring in the mid-frequency coding region of the cochlea (Bohne & Harding, 2000), consistent with the audiometric 'noise notch' at 3–6 kHz in humans. Some permanent changes in hearing may not be detected by measuring pure-tone thresholds solely within the conventional frequency range however. Evidence both in animals and humans suggests that cochlear locations coding the extended high frequencies may also be especially vulnerable to damage from noise (animals: Hamernik et al, 1989; humans: Ahmed et al, 2001; Fausti et al, 1981; Somma et al, 2008). Thus, there may be both mid-and high-frequency 'sensitive ranges' to monitor for noise damage.

There are important limitations to the use of pure-tone threshold measures as a gold standard when establishing the efficacy of OAE metrics. First, clinically feasible gold standards such as the modified Hughson-Westlake procedure sacrifice threshold accuracy for reduced test time. Thresholds obtained in this procedure using relatively coarse (5-dB) steps and fewer reversals compared with more time-consuming classical psychophysical procedures could result in misclassification of an ear as having stable (unchanged) hearing when in truth, hearing changed following an exposure. Using smaller dB-step sizes, more reversals, and/or 'catch trials' in which no stimulus is presented would likely generate more precise comparison data.

The second and more vexing problem is the fact that OAEs may change prior to hearing thresholds. An unknown portion of these changes are likely false positives, while others could be misclassified as false positives when they are in fact preclinical changes that

artificially drive down OAE test performance. This limitation might be alleviated to some extent by identifying small NIHL shifts in the behavioral protocol, for example, by using a pure-tone threshold criterion shift that is smaller relative to an OSHA-significant shift.

A third limitation relates to recent findings that shifts in auditory sensitivity and DPOAE levels that return to normal after a noise exposure can be associated with progressive deterioration of the auditory nerve, at least for large TTS exposures (Kujawa & Liberman, 2009; Lin et al, 2011). This deafferentation and related changes in the central auditory system may have important effects for the processing of complex stimuli, such as speech (Wang et al, 2009; Zeng et al, 2005). This limitation highlights the need for development of HCP methods that include a quick and sensitive measure of auditory nerve activity.

Choosing the ‘best’ DPOAE features to measure in an HCP

In both noise-exposed and ototoxin-exposed study populations post-exposure changes in DPOAE level evoked with moderate f1 and f2 tone levels have been routinely assessed. However, various DPOAE recording parameters have been used with most showing promise. In a comparison of DPOAE levels, input-output functions, and group delays in a population of adults exposed to an ototoxin, the thresholds from input-output functions and group delays identified changes more often than did DPOAE level obtained using moderate-level stimuli (Katbamna et al, 1999). Similarly, in a noise-exposed population, a comparison of DPOAE primary levels (Delb et al, 1999; Engdahl & Kemp, 1996; Sutton et al, 1994) and DPOAE step-size (Engdahl & Kemp, 1996) demonstrated that lower overall primary levels (L1 and L2) with greater L1-L2 separation done in fine frequency step-sizes increased the sensitivity of DPOAEs to detect post-exposure changes. Low (stimulus) level DPOAEs, fine-resolution f2 step-sizes and phase may be important to include in future studies of DPOAEs in HCP and OMP applications, since these DPOAE measurements may be more sensitive than others.

Using multivariate methods to improve DPOAE test performance

Few studies have used gold standard comparison-based methods to obtain estimates of DPOAE test performance. Most of these are studies aimed at developing non-behavioral methods to classify ears as having normal or impaired hearing to inform universal newborn hearing screening programs. Univariate methods for estimating DPOAE test performance typically compare a single DPOAE measure to a single audiometric threshold at the same frequency. Multivariate comparisons typically use multiple DPOAE measures to predict a single audiometric frequency or multiple DPOAE measures to predict a composite of audiometric frequencies. Multivariate DPOAE solutions, which emphasize across-frequency performance, have frequently been found to be more accurate than univariate methods that place the importance on a single frequency.

Dorn et al (1999) compared single variables with multivariate logistic regression and discriminant analysis for categorizing ears as normal or impaired. They found that diagnostic accuracy was improved when DPOAE level and SNR at multiple frequencies were considered. In most cases, the best multivariate analysis strategies included DPOAE tones at frequencies near the audiometric frequency for which they were attempting to make

functional predictions. Improvements in test performance, for predicting normal vs. impaired hearing, were seen across all frequencies; however, the greatest improvements were seen in the low and high frequencies. Gorga et al (1999) similarly investigated the role of multivariate analysis in predicting normal or impaired hearing. Gorga et al (1999) also included a multi-frequency threshold average as the gold standard rather than a single audiometric frequency. Findings were similar to Dorn et al (1999) in that test performance improved at the low and high frequencies, and test performance especially improved when discriminating mildly impaired ears from normal-hearing ears. Additionally, with increasing hearing loss, test performance from multivariate solutions increased, nearing 100% for more severe hearing impairments. Gorga et al (2005) validated these findings and noted that multivariate methods, which improve test performance, require no additional test time.

Two cisplatin studies using multivariate methods to identify ototoxicity

We have applied a multivariate clinical decision theory approach in two separate studies of ototoxicity among veterans receiving cisplatin as part of their chemotherapy treatment at participating VA Medical Centers. In these studies, we model the probability of behavioral hearing shift within the SRO as a binomial (yes, no) outcome variable. Some of the models incorporate DPOAE-based predictor variables, while others offer hearing shift risk assessment for a hypothetical future ototoxicity exposure and do not include DPOAEs or require serial monitoring data of any sort. These two studies are summarized below. Detailed information about data collection and statistical analysis methods is described in detail elsewhere (Dille et al, 2010; Reavis et al, 2011) and is only briefly reviewed here. Aspects of this approach, adapted to use noise-tolerance and noise-dose variables, may be applicable in a HCP.

Common methods—Participants in the two cisplatin monitoring studies underwent otoscopy, tympanometry, behavioral pure-tone threshold testing, and DPOAE testing. They also completed questionnaires to assess tinnitus and noise exposure history prior to cisplatin exposure at baseline, and during chemotherapy infusion at each monitoring visit.

The baseline visit was done within the week prior to or up to 24 hours after the initial treatment with cisplatin. Subsequent monitoring visits were completed typically within 24–48 hours of each chemotherapy treatment. Chemotherapy schedule was variable across subjects, as is typical in studies like these. Additionally, when possible, monitoring visits were completed immediately after treatment had been discontinued.

Pure-tone threshold testing included frequencies up to 8 kHz in 1/2-octave steps. Frequencies from 9 to 20 kHz, and within the individualized SRO, were tested in 1/6th-octave steps. At and above 2 kHz, all thresholds were measured using a Virtual Corporation, Model V320 audiometer and modified Koss Pro/4X Plus earphones. Frequencies below 2 kHz were tested using TDH-50P earphones in MX-41/AR cushions in Reavis et al (2011) and were not tested in Dille et al (2010).

Presence or absence of behavioral hearing change was based on published clinical guidelines (ASHA, 1994) and includes: (1) 20 dB change at any one test frequency; (2) 10 dB change at any two consecutive test frequencies; or (3) loss of response at three consecutive

test frequencies at which responses were previously obtained. Using these criteria, a binary indicator for presence/absence of hearing change was established for each post-baseline (monitoring) appointment, for each ear in the samples.

DPOAE data were collected and stored electronically using custom software from Boys Town National Research Hospital (Neely & Liu, 1993). A Card Deluxe digital signal processing board (Digital Audio Labs) was used to generate stimuli and record responses. The two DPOAE primary frequencies (f_1 and f_2 , where $f_1 < f_2$) were separately digitized, converted to analog voltages, and passed through locally developed custom headphone buffers to two Etymotic Research (ER-2) tube phones. Stimuli were delivered to the occluded ear canal through separate ports in a probe assembly fitted with a foam ear tip. The probe housed an ER-10B+ microphone to record the DPOAE signals. Signals were amplified (20 dB) by the ER-10B+ preamplifier, digitized, and stored in two interleaved buffers, which were averaged in the time domain. The DPOAE level at $2f_1-f_2$ was estimated using fast Fourier transform of the grand average of the two response buffers and the noise level was estimated at the DPOAE frequency from the difference of the A and B buffers.

All DPOAEs were collected using a constant f_2/f_1 ratio of 1.22. The DPOAE protocol for both studies included an initial 'DP-gram' in which level was held constant at $L_1 = L_2 = 65$ dB SPL and f_2 was swept (from 1–14 kHz for Dille et al, 2010; from 1–10 kHz for Reavis et al, 2011). The DP-gram was used to determine 'FD', which was specifically defined as the highest f_2 that elicited a valid DPOAE response (i.e. a DPOAE response level that was high relative to the noise floor and system distortion). Just as the behavioral SRO (sensitive range for ototoxicity) is defined based on the highest threshold that can be detected during behavioral testing, a DPOAE SRO is defined using FD as an upper limit. From there, the DPOAE protocols differed for the two studies. Reavis and colleagues (Reavis et al 2011) measured DPOAEs near FD in the form of input-output or 'growth' functions whereas Dille et al 2010 measured DPOAEs near FD in frequency sweeps done in 1/48th-octave steps.

In those studies, DPOAE changes measured during monitoring visits were the input data used in models designed to predict the likelihood of a hearing shift occurring within SRO frequencies at that same visit. Hearing shift within SRO frequencies was measured, and those data were used to validate model performance. Using marginal regression techniques for serial monitoring data, a dose-ototoxicity risk curve relating risk factors for ototoxicity to the likelihood of a hearing shift from a given accumulated cisplatin dose was developed. Next, the dose-ototoxicity model was combined with DPOAE test-retest data to provide a means to detect hearing shifts in those patients who become unable to provide reliable behavioral data during treatment because of health issues. This 'ototoxicity risk assessment' (ORA) was constructed using logistic regression in a machine-learning paradigm in which leave-one-out cross-validation was applied to find an optimal ototoxicity screening algorithm. Predictor variables were either DPOAE metrics alone or DPOAE metrics combined with the ototoxicity risk factors. For one ORA, the DPOAE change metrics included in the model were developed using partial least squares analysis (Dille et al, 2010). A second ORA method used simple summary metrics rather than statistically derived metrics (Reavis et al, 2011). Models were reduced by backward elimination so that the final models incorporated only significant predictor variables.

To determine the test performance of these models in clinical patients, model-based risk scores were compared to a gold standard (the observed hearing changes) at each monitoring interval using receiver operating characteristic (ROC) curve analysis (Pepe, 2003). A 95% confidence interval for the area under the ROC curve (AUC) was estimated using the non-parametric standard error estimator proposed by Obuchowski (1997) for correlated measurements, since most subjects were observed during several monitoring visits.

Leave-one-out cross-validation was used to obtain a nearly unbiased estimate of the accuracy of the models in a clinical population (Simon, 2005). This is an approach whereby each subject is successively excluded from the data set used to develop a 'training model', thus partitioning the data into a test sample, which includes the omitted subject's data, and a training sample composed of all remaining data. The risk score weights for all model predictors are determined from the training sample and then used to predict the excluded subject's risk of hearing change at each monitoring visit. The procedure is iterated by leaving out a different subject at each step until all visits are assigned a risk score according to each of the training algorithms so developed. Cross-validated ROC curves, AUCs, and standard error of the AUC are then calculated from the risk scores as described and illustrated in our previously published work.

Sample descriptions—The Reavis et al (2011) study described data from 36 ears of 24 study participants treated with cisplatin. Participants' mean age was 58.5 years (range = 28–75). On average, they each took part in 3.4 monitoring visits and received approximately 400 mg of cisplatin over 42 days. Half the participants experienced hearing shifts defined per the ASHA (1994) criteria described above, in at least one ear within the SRO frequencies. The highest audible frequency in the pre-treatment SRO (FB) provides an estimate of the severity of high frequency hearing loss; the average FB was 12.5 kHz (range = 5–16 kHz).

Dille et al (2010) described data from 19 ears of 19 subjects who were followed over a total of 56 monitor visits across the 19 subjects (average number of monitor visits per subject = 2.9, range = 1–12). Participants' mean age was 62.6 years (range = 51–79). A hearing change within the SRO was measured during 23 of the 56 monitoring visits (41%). The SRO FB was 11.6 kHz on average (range = 5.7–16 kHz). Taken together, both the average patient age and the degree of high-frequency hearing loss (defined using FB) were similar for the two population samples assessed by Reavis et al (2011) and Dille et al (2010).

Characterizing the behavioral SRO hearing shift—Figure 1 shows post-exposure pure-tone threshold shifts observed in the Reavis et al (2011) study for subjects with and without ASHA-significant hearing changes. The amount of hearing shift in dB from baseline to the final treatment visit is plotted at each of the seven SRO frequencies for the groups of ears. SRO frequencies are listed in rank order of the lowest frequency, FB-6, to highest frequency, FB. FB-1 is 1/6th-octave below FB, FB-2 is 1/6th octave below FB-1, and so on. Average threshold shifts across all of the ears with ASHA-significant hearing changes were between 15 and 18 dB at the five highest frequencies (FB-4 through FB). Although each patient's specific SRO frequencies are different, the strength of the SRO is that it includes those frequencies most likely to be first affected by ototoxicity for each individual patient (Fausti et al, 1999, 2003). In our experience, monitoring based on SRO frequencies captures

over 90% of all initial ototoxic threshold shifts due to cisplatin exposure. Initial shifts are rarely below the SRO; if they do occur, most quickly progress to include the SRO frequencies.

Development of ‘dose-ototoxicity risk curves’ to identify hearing shifts—The hearing shift data at SRO frequencies were used to model effects of various risk factors on ototoxicity, including radiation treatment, prior cochlear damage, and the patient’s pre-drug-exposure hearing thresholds within the SRO. Dose was also explicitly considered since the probability of observing a hearing shift during an ototoxicity monitoring visit depends on the dose administered prior to that visit. Dose (mg/m^2) across treatments from which dose given (in mg) at a single treatment was calculated, and cumulative dose (in mg) were also included in the model. Pre-exposure hearing and cisplatin cumulative dose were the only two statistically significant predictors of whether or not hearing shifted after cisplatin.

The best fitting dose-ototoxicity model from Reavis et al (2011) is shown in Figure 2 (left panel) to illustrate how the risk of hearing shift from cisplatin depends on the total accumulated dose at test time (with the risk of hearing loss increasing based on increasing cisplatin dose). In addition, baseline hearing modifies this dose-ototoxicity relationship (with the risk of hearing loss increasing in patients with better baseline thresholds). Similar results were obtained in a separate sample of subjects by Dille et al (2011; see Figure 2, right panel). Both samples comprised middle-aged and older veterans, some of whom had poor hearing to begin with. The three risk curves in each panel represent model predictions obtained for different pre-exposure hearing levels (55, 65, or 75 dB SPL mean threshold across the seven SRO frequencies). As a point of reference, the mean baseline SRO threshold level for the sample was 70.9 (range = 48.6–97.5) in Reavis et al (2011) and 69.9 (range = 43.6–86.7) in Dille et al (2010). At an exposure level (cisplatin dose) of 400 mg, the risk of incurring a hearing shift is predicted to be at least 60% for those with mean SRO threshold of 65 dB SPL; the risk of hearing shift increases to over 90% if hearing at baseline is comparatively better (55 dB SPL), and decreases if hearing at baseline is comparatively worse (75 dB SPL). Although the risk of cisplatin-induced hearing loss varied across studies, both models clearly indicate that there is a significant contribution of baseline hearing to the risk of a hearing shift during treatment, and an interaction between the baseline hearing effect and cumulative dose on the risk of a hearing shift.

Developing univariate DPOAE-based models of SRO hearing shift—In the Reavis et al (2011) study, DPOAE input-output functions were obtained at four frequencies. These frequencies included the highest f_2 frequency (up to 10 kHz) that produced a valid response at baseline at $L_1 = L_2 = 65$ dB SPL (termed FD), and the next three lower adjacent frequencies in 1/3-octave frequency steps. DPOAE stimulus input levels were optimized based on a covaried paradigm ($L_1 = 0.4L_2 + 39$) following Kummer et al (1998) to obtain measurements at six intensity levels: L_1/L_2 in dB SPL = 63/60, 61/55, 59/50, 57/45, 55/40, and 53/35. FD varied across subjects depending on pre-cisplatin exposure emission levels. In the population of older adults investigated in Reavis et al (2011), FD ranged from 1.5 to 8 kHz and the median was 4 kHz.

DPOAE summary metrics were derived from input-output functions collected at FD, FD-1 (i.e. 1/3 octave below FD), FD-2 (2/3 octave below FD), and FD-3 (1 octave below FD). Each of these three input-output functions was reduced by summing: (1) the stimulus (L2) input levels generating valid responses (DPOAE inputs); (2) the amplitudes of the valid emissions (DPOAE outputs); and (3) the SNRs of valid emissions (DPOAE SNRs). This resulted in 12 DPOAE summary measures (four frequencies by three metrics) used to calculate differences in DPOAEs collected at a monitoring visit from those collected at baseline. These 12 difference measures were then used in univariate models of the likelihood of hearing shift at each monitoring visit. No information about patient risk factors (i.e. the dose-ototoxicity model) is included in these models. Results of each of the 12 models were then used to calculate a ROC, and, specifically, the area under the ROC curve (AUC). The ROC is a plot of the true positive rate (in this case for predicting a hearing shift using a given DPOAE-based model) against the false positive rate (incorrectly identifying non-shifts using that same model). The curve itself is constructed by incrementally increasing the output value of the model (i.e. the risk score) used as a cut point or decision threshold for identifying an ear as having stable or shifted hearing. By comparing the model prediction at each cut point with the gold standard measure of hearing loss for each ear, we can completely describe the test performance of the model. The AUC is a measure of test sensitivity averaged over all possible false positive rates and provides an indication of overall test performance. An AUC of 0.5 indicates chance performance. An AUC of 1.0 indicates perfect test performance (i.e. the model predictions always agree with the gold standard test results).

Figure 3 shows AUCs for the 12 univariate DPOAE models. Curves are constructed by plotting the AUC for each of the three DPOAE summary metrics as a function of the four DPOAE input-output function test frequencies, with f2 normalized to FD, the highest f2 able to elicit a valid DPOAE in the baseline DP-gram. Circled are the models that could significantly (p values < 0.05) discriminate ears with and without ASHA-significant hearing shifts.

For all three metrics (i.e. sum of DPOAE inputs, sum of DPOAE outputs, and sum of DPOAE SNRs), the largest AUCs occurred at FD. This pattern of results is consistent with the high-to-low frequency progression of cisplatin-related OHC damage and behavioral threshold loss. Further, the behavioral SRO and the frequency region able to be tested using DPOAEs diverges in some patients, as indicated by the difference between the average SRO FB (12.5 kHz) and the median FD (4 kHz) in the Reavis et al (2011) sample. The best performing univariate DPOAE metrics were sum of DPOAE outputs and sum of DPOAE SNRs. Both achieved about 80% average sensitivity at FD. Results imply that DPOAEs alone provide an indication of whether or not hearing has shifted, but of the DPOAE SRO frequencies, only the highest one or two (tested in 1/3 octave steps) accurately detects SRO changes following cisplatin exposure.

Developing multivariate models using dose-ototoxicity information and DPOAE input-output function changes—In Figure 4, separate ROCs are shown for the best-performing univariate DPOAE model, which incorporates the sum of DPOAE outputs metric (dashed line), and the optimal multivariate ORA model (solid line)

investigated in the Reavis et al (2011) study. This ORA incorporates the dose-ototoxicity model described earlier in this report, which in turn includes cumulative cisplatin dose and a measure of pre-exposure hearing (the average threshold of the seven-frequency SRO). Added to this was test-retest data for each of the DPOAE metrics. Even though the sum of DPOAE outputs achieved the best performance in a univariate model, only the sum of DPOAE inputs metric improved the multivariate model fit and was retained in the final ORA model shown in Figure 4. This illustrates how a variable's univariate performance does not always predict performance within a multivariate model.

An indication of the relative test performance of the sum of DPOAE outputs model and the multivariate (dose-ototoxicity and sum of DPOAE inputs) ORA can be obtained by looking at how closely each curve in Figure 4 hugs the upper left corner of the ROC space indicating a large AUC and good test performance. Results indicate that the ORA, with an AUC of >90%, is a more accurate predictor of SRO hearing shift among patients treated with cisplatin compared with even the best-performing DPOAE metric alone.

More importantly, ROC curves allow us estimation of test performance for specific cut-point criteria. Here, if we pick a low false positive rate of 10%, the ORA sensitivity is 80%, indicating a sensitive clinical test. For the same false positive rate of 10%, the sensitivity of the best performing DPOAE model is comparatively poor at 50%, indicating that about 50% of ototoxic hearing shifts will be missed at that decision threshold.

Developing multivariate models comprised of dose-ototoxicity information and fine-frequency-resolution DPOAE Level Changes—For the Dille et al (2010) study, a DP-gram (up to 14 kHz) at $L1 = L2 = 65$ dB SPL was used to determine the highest frequency with a valid DPOAE response. Next, DPOAE level was tested in 1/48th octave frequency steps over the highest 1/4 octave and 1/2 octave range of measureable DPOAEs. A partial least squares (PLS) statistical algorithm generated a reduced set of uncorrelated components from the fine-frequency resolution DPOAE level data. The components were then used in a series of linear models to predict the presence or absence of ASHA-significant SRO hearing changes. This differs from the Reavis et al (2011) study in which DPOAE summary metrics were chosen a priori from data collected as input-output functions. The goal was to find the simplest algorithm for predicting ototoxic hearing shifts that was highly accurate and required the least test time.

Figure 5 compares the cross-validated AUC for the dose-ototoxicity model described earlier (filled black circle), and a series of candidate ORA models investigated in the Dille et al (2010) study. Each ORA model incorporates the dose-ototoxicity model with various PLS 'components', essentially summary DPOAE metrics derived from the fine-resolution DP-gram data. Black triangles show results using the 1/4 octave span of data, whereas, gray squares show results for the larger, 1/2 octave range of data. The vertical bars at each symbol indicate one standard error around the AUC estimate. Also shown is an AUC obtained using a '6-dB DPOAE rule', or rather a 6-dB or greater shift within the 1/4- or 1/2-octave of measurements as an indication of change. To allow better comparison with models incorporating DPOAE metrics derived using PLS analysis, the 6-dB DOAE rule model includes the dose-ototoxicity model.

Comparing all model possibilities in Figure 5, it is apparent that the DPOAE 6-dB change rule metric offers little to no improvement over a model that includes cisplatin cumulative dose and pre-exposure hearing levels; both models achieve some success in identifying pure-tone threshold shifts with test accuracy varying around 70%. However, multivariate models that include the dose-ototoxicity model and certain DPOAE PLS components considerably increase the success of identifying pure-tone threshold shifts. The model that achieved the highest accuracy is indicated as 'a' in Figure 5. This model includes the dose-ototoxicity model and six DPOAE PLS components collected over a 1/4-octave range. The horizontal dashed line is the lower bound of the standard error around the AUC estimate of this model. The simplest model with the greatest success of identifying pure tone shifts is indicated as 'b' in Figure 5 and includes the dose-ototoxicity model and three PLS components derived from the highest 1/4-octave of measurable DPOAEs. This ORA yielded test performance near 80%. More complex models including up to ten PLS components (not shown) did not improve test performance.

Importance of validating ototoxicity risk assessment tools

An important limitation to the cisplatin-ototoxicity studies summarized herein is that they were conducted using small samples (19 or 36 ears), which is a common problem in prospective studies of clinical populations in general, and in ototoxicity studies in particular. This could impact analyses of diagnostic test performance due to idiosyncracies in the sample. The potential impact is that the results are not as easily generalized to another sample of clinical patients, and may be an overly optimistic estimate of test performance. This was mitigated to an extent by the use of leave-one-out cross-validation techniques. However, ORA (and dose-ototoxicity) models fitted in these two studies will need to be validated in a new sample of clinical patients to better estimate test performance in a real world clinical setting, a necessary step in the development of a clinical test.

Concluding remarks

DPOAE methods for identifying hearing shifts: Lessons from our ototoxicity studies

Several studies have shown that compared to univariate approaches, multivariate approaches improve the predictive value of DPOAEs used to determine whether or not hearing status is normal (Dorn et al, 1999; Gorga et al, 1999, 2005). Our results further show that DPOAE-based multivariate approaches provide an accurate indication of whether or not hearing within the SRO has shifted as a result of cisplatin administration (Dille et al, 2010; Reavis et al, 2011). DPOAEs alone can provide an indication of ototoxic hearing shift when measured near the highest DPOAE test frequencies that yield a robust response, but test accuracy is significantly poorer than that obtained with the best performing multivariate models. The risk factors of accumulated cisplatin dose and pre-exposure hearing together can also be used to predict risk of hearing shift, but, these factors are also less accurate than multivariate models that include serial DPOAE measurements. These findings suggest the potential to develop similar multivariate approaches for detecting noise-induced damage to the inner ear (preceding, or concurrent with, the onset of NIHL).

For the purposes of assessing the test performance of our various ototoxicity risk assessment models, we considered only changes in hearing and DPOAEs between each monitoring visit and the pre-exposure baseline test. If this approach is to be used to both identify and monitor progression of ototoxicity in a clinical setting, the model will need to be modified to incorporate comparisons among serial visits to determine the presence of visit-to-visit change. This could be done by establishing new baseline measures following each significant hearing shift that is confirmed on a repeat test; that method is already well established within the OSHA monitoring paradigm. If an OSHA-significant threshold shift is detected during annual monitoring, the new audiogram serves as the baseline against which future changes are measured.

Regarding test performance, we have specifically found that the cross-validated dose-ototoxicity risk curves showed an average sensitivity of 72% for predicting SRO hearing shifts. In other words, it is possible to make predictions about a given patient's risk of hearing shift as a side effect of their upcoming cisplatin chemotherapy. Baseline risk assessments should prove helpful for pre-chemotherapy treatment counseling and treatment planning. Multivariate DPOAE-based monitoring methods for SRO shifts during cisplatin treatment have an average sensitivity of about 80% and 90%, depending on whether input-output functions or fine-resolution DPOAE level measurements are used. Since the two DPOAE methods were not tested on the same sample, it is not clear whether they would differ statistically. Regardless, the results clearly support an emerging potential (and specific protocols) for identifying patients at risk of cisplatin-induced hearing loss using non-behavioral, DPOAE test methods.

Toward developing multivariate NIHL risk assessment tools for an HCP

To construct variables associated with risk for ototoxicity, we borrowed the concepts of 'individual tolerance' and 'exposure dose' used in bioassay and dose-response methodology. If an individual has a high tolerance for an exposure, then he or she can withstand a relatively large exposure dose before suffering ill effects. Conversely, an individual with low tolerance will likely suffer hearing threshold shifts at lower exposure doses. For ototoxicity monitoring, tolerance is a patient's resistance to the damaging effects of cisplatin, which we captured using information about known risk factors for ototoxicity. Cisplatin dose was extracted from medical treatment records.

Concepts of tolerance and dose can similarly be used to develop a monitoring protocol for NIHL in an HCP. For example, there is a well-known negative correlation between TTS magnitude and pre-noise-exposure hearing ability (e.g. Pirilä, 1991). This is consistent with our finding that ototoxicity occurs more readily in ears with good than poor hearing. The common thread between the two exposures (noise over-exposure and cisplatin) is OHC damage, which is known to affect CF-specific amplification of the BM in a manner that is inversely proportional to the level of the stimulus, meaning that OHC damage removes the portion of the dynamic range that codes low-level stimuli (e.g. Ruggero & Rich, 1991). This suggests that the extent to which thresholds are vulnerable to changes in OHC-system function depends on how low they are prior to an exposure; good pre-exposure hearing may be a risk factor for NIHL, as it is for ototoxicity.

Unlike cisplatin, noise is not administered intravenously in known quantities; noise dose is difficult to precisely define for a given individual. However, there is likely to be some record for many characteristics of the exposure, such as level and/or spectrum of the noise (based on docimetry or task-based monitoring), duration (number of hours per day), and years of exposure (based on individual work history), and whether or not hearing protection was consistently used (based on worker report).

The application of a multivariate DPOAE technique for detecting NIHL is lacking in the literature, however, Lapsley Miller and colleagues have laid the groundwork for such an approach (Lapsley Miller et al, 2006). They suggested that baseline OAE measures may offer important information about the status of the cochlear hair cells, which can be used to assess susceptibility to hearing loss after future noise exposures. In their study, low-level baseline TEOAEs were correlated with increased hearing loss following noise exposure. Studies in rodents have also shown subjects with low-level DPOAEs and normal hearing to be more likely to experience change in hearing sensitivity following noise exposure than those with low-level OAEs and hearing loss (Perez et al, 2004). Reduced OAE findings suggest some loss of OHCs was present before the exposure, although there was inadequate loss to induce a change in behavioral thresholds. Hair cell loss in ears with less than a full population of OHCs results in hearing loss more readily than would have been the case had the OHC population been normal (as evidenced by robust OAEs) prior to exposure (Lapsley Miller et al, 2009). Other investigators have shown that the magnitude of DPOAE onset adaptation (the rapid change in the amplitude of the DPOAE in the first 200 ms of the response) is inversely related to the amount of hearing loss following a noise insult (Maison & Liberman, 2000). DPOAE onset adaptation is mediated by sound-evoked feedback to the inner ear via the olivocochlear efferent pathway. A relationship between DPOAE onset adaptation or olivocochlear reflex strength and vulnerability to noise has not yet been confirmed in human subjects.

Multivariate methods for determining susceptibility to NIHL can be developed for use as a baseline risk assessment tool, and within a multivariate DPOAE-based (noise-induced) hearing shift assessment tool. The hearing shift assessment tool can be developed as a linear-logistic function of DPOAE changes observed at a particular monitoring session along with any available information about noise exposure from the last monitoring appointment up to that day, as well as other factors found to affect an individual's risk for NIHL or conversely their tolerance for noise. During test development, predictions of the multivariate baseline risk assessment and hearing shift assessment tools can be compared to actual threshold shifts so that the true positive rate and false positive rate of these models can be determined. Once test performance for the models has been determined and validated, the hearing shift assessment could be used in an HCP instead of direct measurements of pure tone sensitivity or compared with such measures to help interpret those outcomes, as the need arises. The baseline risk assessment could be used prior to the surveillance period, to identify those individuals who may be highly susceptible to damage from noise and require extra precautions to preserve their hearing.

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Abbreviations

BM	Basilar membrane
DPOAE	Distortion-product otoacoustic emissions
HCP	Hearing conservation program
NIHL	Noise-induced hearing loss
OHC	Outer hair cell
ORA	Ototoxicity risk assessment
ROC	Receiver operating characteristic
TEOAE	Transient-evoked otoacoustic emission
TTS	Temporary threshold shifts
TWA	Time-weighted average
SFOAE	Stimulus-frequency otoacoustic emission
SRO	Sensitive range for ototoxicity

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Figure 1.

Post-exposure pure-tone threshold differences (in dB) as a function of the seven SRO frequencies normalized to each ear's highest audible frequency (FB). FB-1 = 1/6th octave step below FB; FB-2 = 1/6th octave step below FB-1; FB-3 = 1/6th octave step below FB-2, etc. Separate bars are for those subjects with (unfilled bars) and without (filled bars) ASHA-significant hearing shift defined as 20 dB in one frequency, 10 dB in two adjacent frequencies, or loss of response at three or more frequencies (ASHA, 1994). Error bars represent 1 SD. The median FB was 12.5 kHz (range = 5 to 16 kHz). Data are from 24 subjects each providing an average of 3.4 follow-up visits across an average of 42 days. Adapted with permission from Figure 2 in Reavis et al (2011).

Figure 2.

Risk curves generated using the dose-ototoxicity model. Hearing shift risk (in %) as a function of cumulative cisplatin dose (in mg) with SRO average hearing (55, 65, & 75 dB SPL) as the parameter. The sensitive range for ototoxicity (SRO) is the seven frequency range near each ear's high frequency limit of hearing. SRO average hearing is the average of thresholds at all seven frequencies in each subject's ear. The left graph represents data from 36 subject ears (Reavis et al, 2011) while the right graph is obtained from 19 subject ears (Dille et al, 2010). The Figure is adapted with permission from Figure 4 in Reavis et al (2011).

Figure 3.

Area under the receiver operating characteristic (ROC) curve, or AUC for three DPOAE summary metrics as a function of normalized DPOAE f_2 frequency (FD to FD-3). (FD = highest f_2 frequency up to 10 kHz with a valid DPOAE; FD-1 = 1/3-octave below FD; FD-2 = 1/3-octave below FD-2; FD-3 = 1/3-octave below FD-2). DPOAE summary metrics are derived from input-output functions reduced by summing input stimulus levels (sum of DPOAE inputs, diamonds) output emission levels (sum of DPOAE outputs, squares), or signal-to-noise ratios, SNRs (sum of DPOAE SNRs, triangles) for levels associated with valid emissions. AUC of 1.0 represents perfect test consistency between gold standard measure of damage (SRO threshold testing) and DPOAE metric changes while 0.5 indicates only chance agreement between these measures. Circled metrics (included all three at FD)

could significantly ($p < .05$) discriminate ears with hearing change from those without hearing change. Adapted with permission from Figure 3 in Reavis et al. (2011).

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Figure 4.

Receiver operating characteristic (ROC) curves indicating test performance for two ototoxicity risk assessment models investigated in Reavis et al (2011). The dashed line is for the best-performing univariate DPOAE-based model (the model incorporating sum of DPOAE outputs); the solid line signifies the optimal multivariate ototoxicity risk assessment, ORA (the ORA incorporating cisplatin cumulative dose and baseline SRO hearing with sum of DPOAE inputs). Curves are constructed by determining the sensitivity (y-axis) and false positive rate (x-axis) of each model at different cut points or decision

thresholds using pure-tone threshold testing as the gold-standard for comparison. Adapted with permission from Figure 5 in Reavis et al (2011).

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Figure 5.

Test accuracy comparison for a series of ototoxicity risk assessment models investigated in Dille et al (2010). Accuracy for each predictive model (horizontal axis) is indicated using cross-validated area under the receiver operating characteristic (ROC) curves, or AUCs (vertical axis). The vertical bars represent the standard error (SE) of each measure. In order from left to right on the figure, the dose-ototoxicity (D–O) model alone is shown as a point of reference (black filled circle). All remaining models include DPOAE level measurements obtained using 1/48th octave frequency steps across the highest 1/2 octave (triangles) or 1/4 octave (squares) range of f_2 DPOAE test frequencies that yielded a valid DPOAE response. Next shown in the figure is a model that includes the D–O model and a simple ‘6 dB DPOAE change rule’ using DPOAE shifts of +6 dB or greater change within 1/2- (single

triangle) and 1/4- (single square) octave fine resolution DPOAE level measurements. Next shown are models that include the D–O model and PLS components 1–6 derived from the DPOAE level measurements using partial least squares (PLS) regression. The AUC for the most accurate model is indicated by an ‘a’ on the figure. The dashed line represents the standard error of this AUC. The AUC for the preferred model is indicated by a ‘b’ on the figure. This preferred model is the simplest model with an AUC within 1 SE of the most accurate model. It is the ORA that includes three PLS components derived from a 1/4 octave range of DPOAE data. This ORA yielded test accuracy of 80%. Figure adapted with permission from the Journal of the Acoustical Society of America. (Dille et al, 2010).

Table 1

Proposed clinical objectives of hearing conservation programs (HCPs).

1. Baseline Risk Assessment.

Determine the probability of an eventual OSHA-significant hearing shift given a hypothetical exposure.

2. Hearing Shift Assessment.

Determine whether a hearing shift has occurred during the surveillance period.

- (1) Identify OSHA-significant hearing shift directly using behavioral methods.
- (2) Identify OSHA-significant hearing shift indirectly using OAE methods.
- (3) Identify incipient (small) hearing shift indirectly using OAE methods.

3. OHC function assessment.

Identify significant OAE change from baseline as a proxy for OHC damage.

4. NIHL education, rehabilitation, counseling