Nucleus® Hybrid™ L24 Implant System

Ear, Nose, and Throat Devices Panel Meeting
Cochlear Limited
November 8, 2013

Cochlear®

Introduction

Christine Menapace, MA
Vice President Clinical, Quality and Regulatory Affairs
Cochlear Americas Corporation

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Nucleus® Hybrid™ L24 System Components

Patient Components

Nucleus Hybrid
L24 Implant

Nucleus 6
Sound Processor

Electric Component

Acoustic Component

Remote
Assistant Options

Programming Component

Custom Sound Fitting
Software – Version 4.0

Intraoperative Remote Assistant
(optional use - not shown)

Indications for Use

- The Nucleus® Hybrid L24 Implant System is intended for patients aged 18 years and older who have residual low-frequency hearing sensitivity and bilateral severe to profound high frequency sensorineural hearing loss, and who obtain limited benefit from bilateral hearing aids
- Typical preoperative hearing of candidates ranges from normal to moderate hearing loss in the low frequencies (thresholds no poorer than 60 dB HL up to and including 500 Hz), with severe to profound hearing loss at frequencies above 1500 Hz (threshold average of 2000, 3000, and 4000 Hz ≥ 75 dB HL)
- The CNC word recognition score will be between 10% and 60%, inclusively, in the ear to be implanted in the preoperative aided condition and in the contralateral ear will be equal to or better than that of the ear to be implanted but not more than 80% correct

Cochlear Panel Attendees

J. Thomas Roland, Jr., MD
Lead Investigator, New York University Langone Medical Center
Mendik Foundation Chairman, Department of Otolaryngology-Head and Neck Surgery
Professor of Otolaryngology and Neurosurgery
Co-Director, NYU Cochlear Implant Center

Bruce J. Gantz, MD
Principal Investigator, University of Iowa Carver College of Medicine
Head, Department of Otolaryngology—Head and Neck Surgery
Brian F. McCabe Distinguished Chair in Otolaryngology—Head and Neck Surgery
Professor of Otolaryngology and Neurosurgery

René Gifford, PhD
Assistant Professor, Vanderbilt University
Director, Cochlear Implant Program
Associate Director, Pediatric Audiology Services
Vanderbilt Bill Wilkerson Center
Department of Hearing and Speech Sciences

Christine Menapace, MA
Vice President Clinical, Quality and Regulatory Affairs
Cochlear Limited

Aaron J. Parkinson, PhD
Principal Clinical Studies Manager
Cochlear Limited

Sean Bundy
Director, Regulatory Affairs
Cochlear Limited

Additional Cochlear Representatives

Chris Mullin, MS
Director of Consulting Services, Statistician NAMSA

William H. Shapiro, AuD
Director of Audiology, New York University Langone Medical Center

Christopher W. Turner, PhD
Professor, University of Iowa

Kristien Verhoeven, PhD
Medical Device Biologist, Cochlear Limited

Agenda and Presenters

Introductions	Christine Menapace, MA
Clinical Background & Rationale	Rene Gifford, PhD
Development of the Hybrid L24	Bruce J. Gantz, MD
Overview of the Pivotal Study	Aaron J. Parkinson, PhD
Effectiveness Results	Bruce J. Gantz, MD
Safety & Hearing Sensitivity Results	J. Thomas Roland, Jr., MD
Labeling & Post Approval Summary	Sean Bundy
Risk Benefit & Conclusions	J. Thomas Roland, Jr., MD

Clinical Background and Rationale

René Gifford, PhD

Assistant Professor, Director of Cochlear Implant Program

Director, Cochlear Implant Research Laboratory

Vanderbilt University

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An Unmet Need

- High frequency hearing loss (“Ski-slope”) loss is common
  - Normal to moderate low frequency hearing loss, but severe to profound sensorineural hearing loss in the high frequencies
- Individuals experience significant hearing difficulty and fail in their social and work environments
  - Poor speech intelligibility, talking on the phone, difficulty in noise
  - Frustration is high

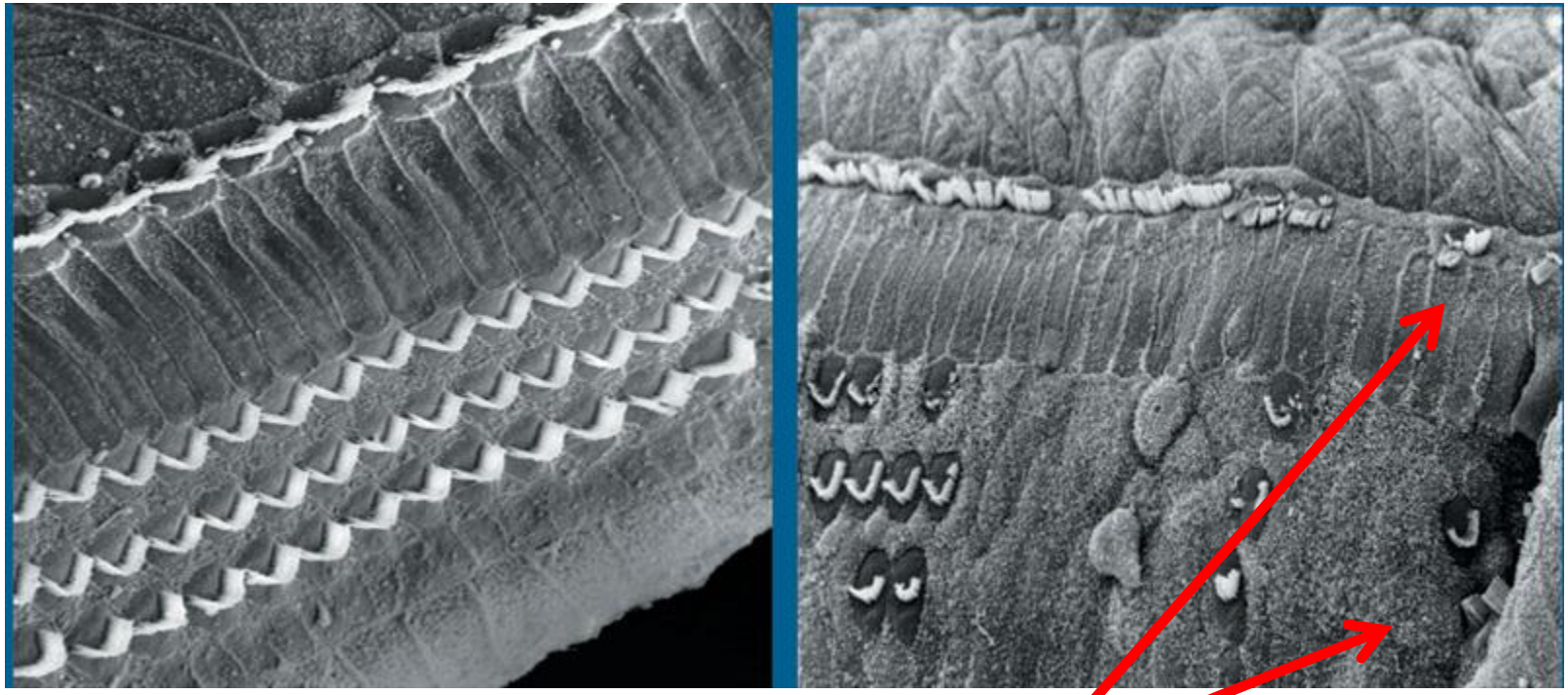
Current Therapy Options

Current technologies are inadequate

Amplification Alone	• High frequency loss is not effectively addressed • Frequency lowering technologies (FLT) are limited • Dissatisfaction is high
Standard Cochlear Implantation	• Destroys remaining low frequency acoustic hearing – Which improves hearing in noise and aid localization – Electric hearing does not provide these important cues • Beyond the scope of current indications
Do Nothing	• Individuals are highly frustrated, having exhausted many options - constant struggle to listen effectively, interact and remain independent

Physiological Limitations: Cochlear Dead Regions

Cochlear dead regions are prevalent when thresholds ≥ 70 dB HL (~60%) Vinay & Moore (2007)



Severe to profound hearing loss associated with OHC *and* IHC damage

Limits of Amplification in High Frequencies

- Numerous studies have suggested limited benefit for amplification in the presence of high frequency hearing loss
  - Thresholds greater than 60 to 70 dB HL
- Limitations of amplification (beyond dead regions)
  - Difficulty in achieving adequate audibility
  - High presentation levels resulting from high gain
  - Poor spectral resolution in basal cochlea
- Excessive high-frequency gain requires occluding ear molds
  - Rejection of hearing aids due to occlusion effect
  - Open-fit or open-canal fittings are not indicated for profound HF losses

Hogan C, Turner, CW. (1998). J Acoust Soc Am, 104:432-41.
Turner CW, Cummings KJ (1999). Am J Audiol, 8: 47-56. Turner, CW. (2006). Audiol Neurotol, 11(Suppl 1): 2-5.
Hornsby BW, Ricketts TA. (2006). J Acoust Soc Am, 119:1752-63.

Frequency Lowering Technologies (FLT)

- Over 30 years of research with FLT
  - Multiple variations of FLT
- Little to no benefit (< 10-percentage points) for:
  - Phonemes
  - Consonants
  - Plurals
  - Vowels
- Few reported significance at the group level
- Did not use same measures as CI studies
  - Does not allow for across-technology comparison

Glista et al., (2009). Int J Audiol., 48:632-644. Simpson et al., (2005) Int J Audiol., 44:632-644.
Robinson et al.,(2007). Int J Audiol, 46: 293-308. Kuk et al., (2009). Jnl Am Acad Aud, 20:465-479

Recent Research into Frequency Lowering Technologies

Gifford et al. (2007). Effect of Digital Frequency Compression (DFC) on Speech Recognition in Candidates for Combined Electric and Acoustic Stimulation (EAS). *J Speech Lang Hear Res*, 50: 1194–1202.

Subjects in Study were Audiometric Candidates for Hybrid

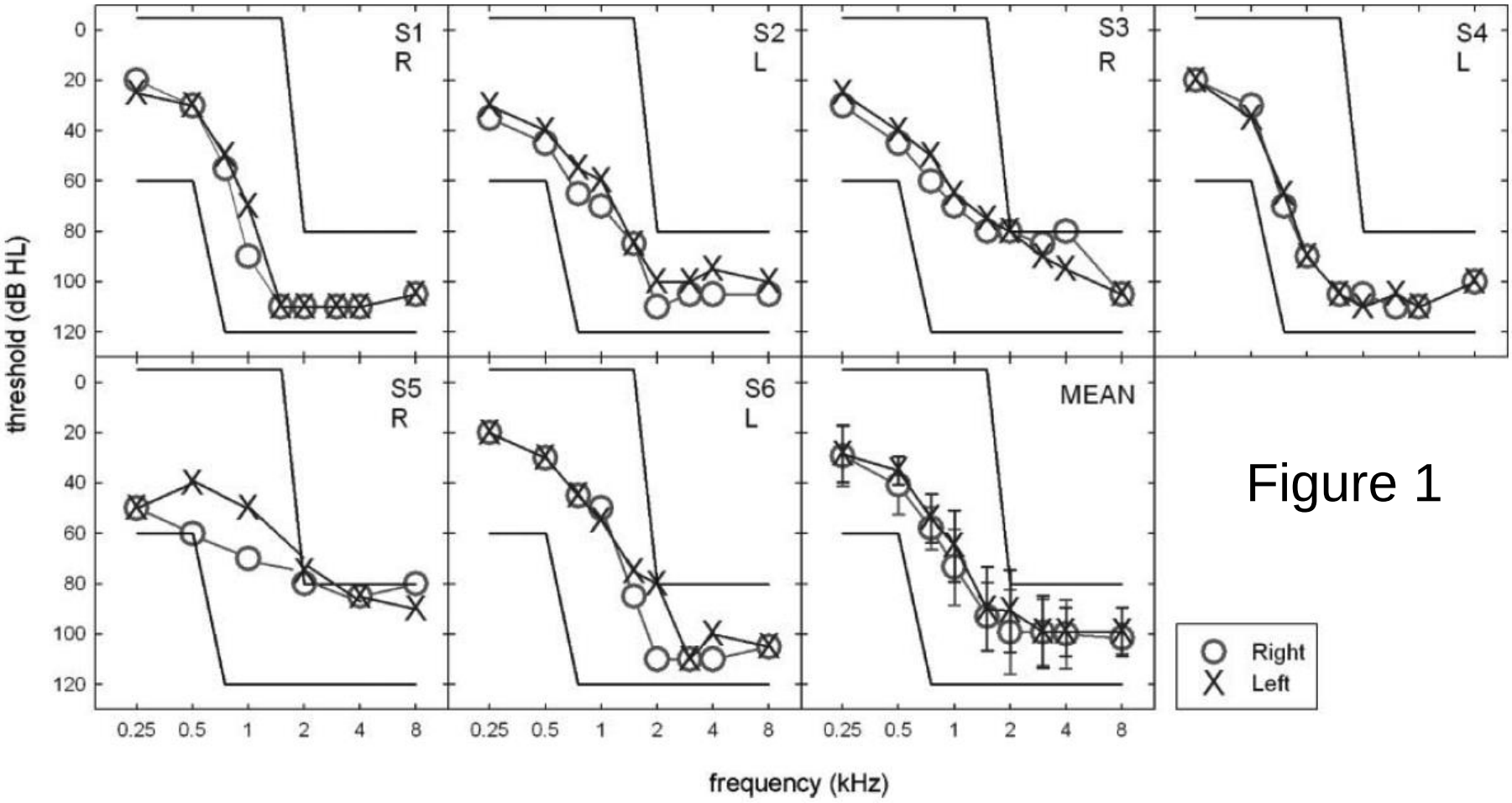
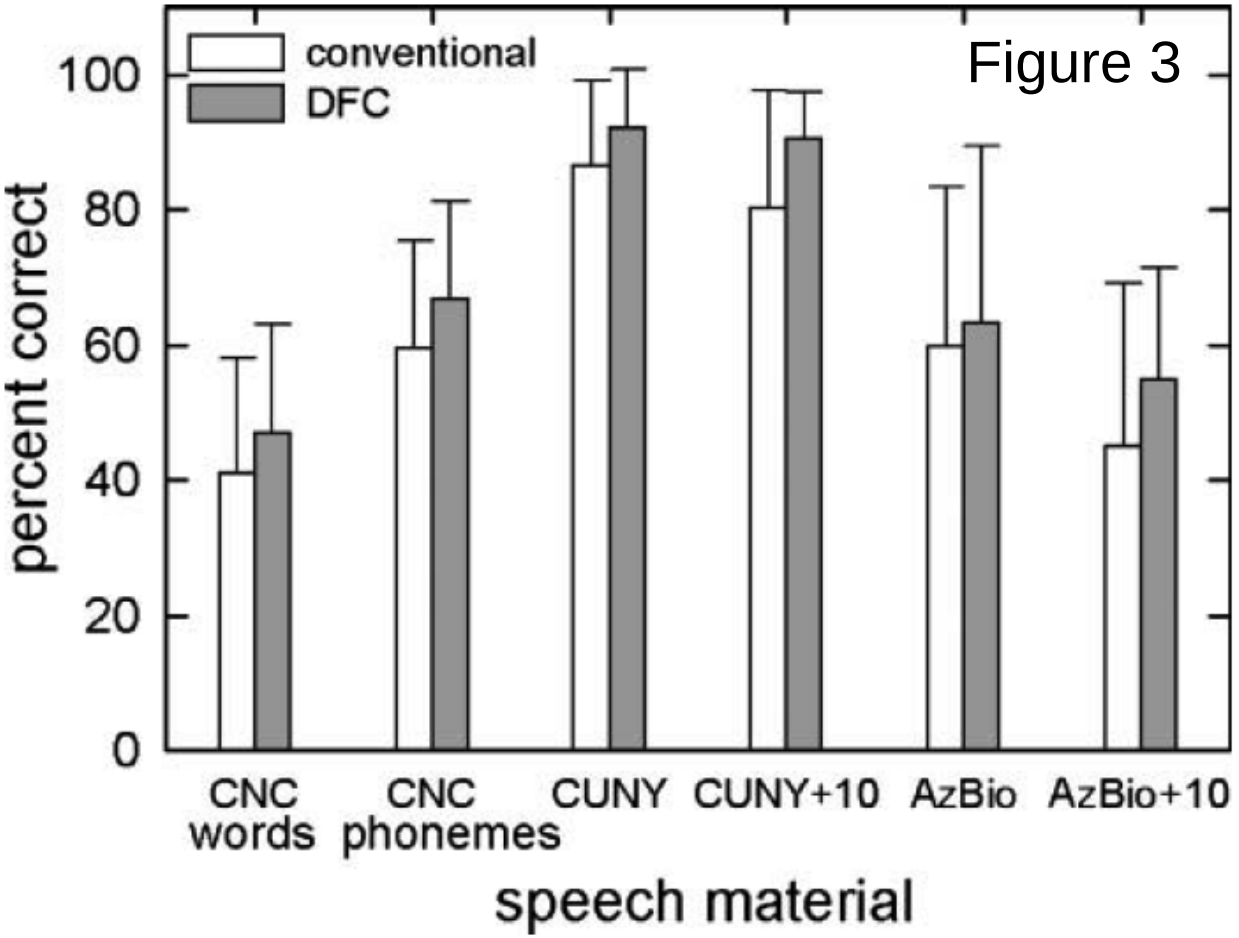
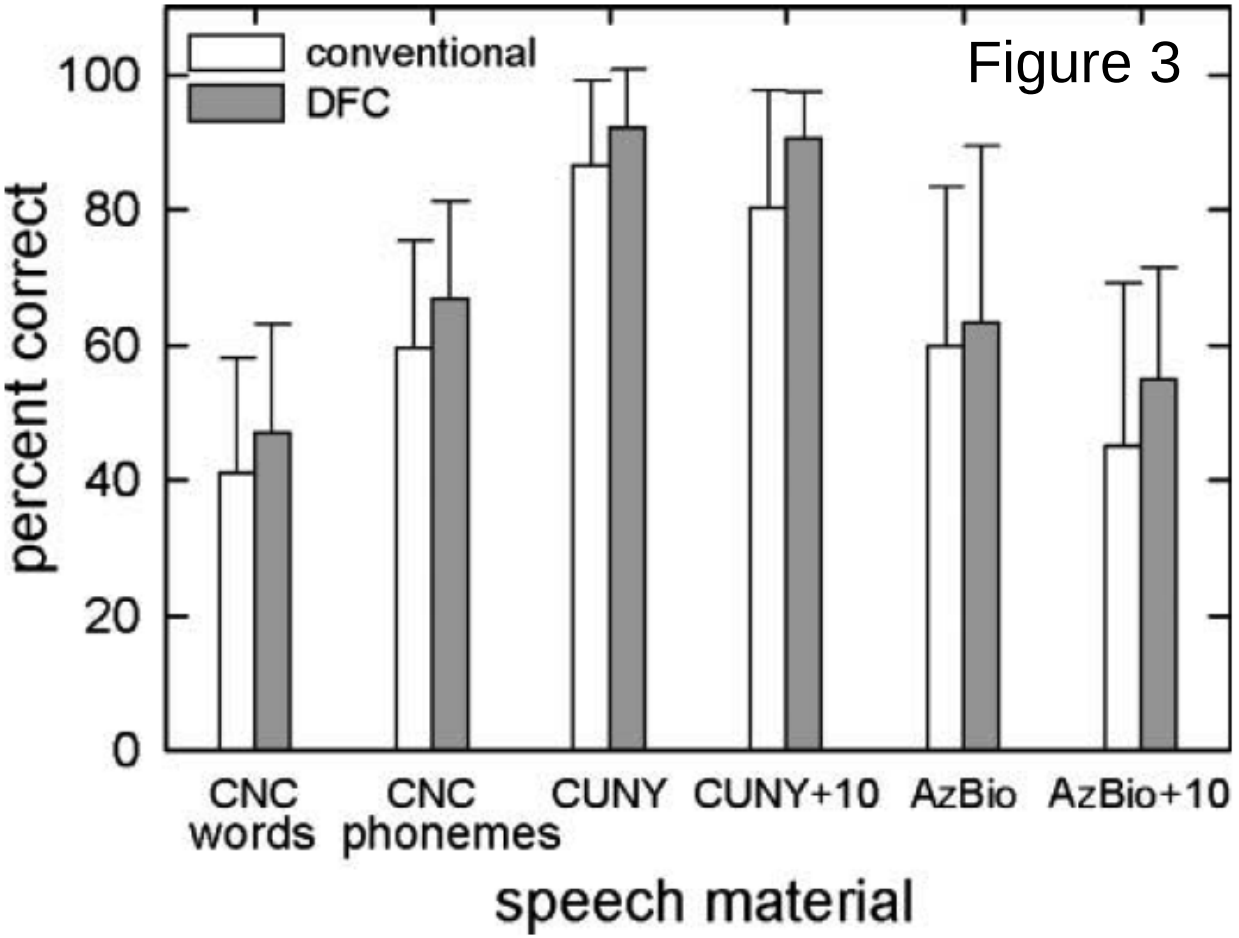


Figure 1

Frequency Lowering Technologies (FLT)

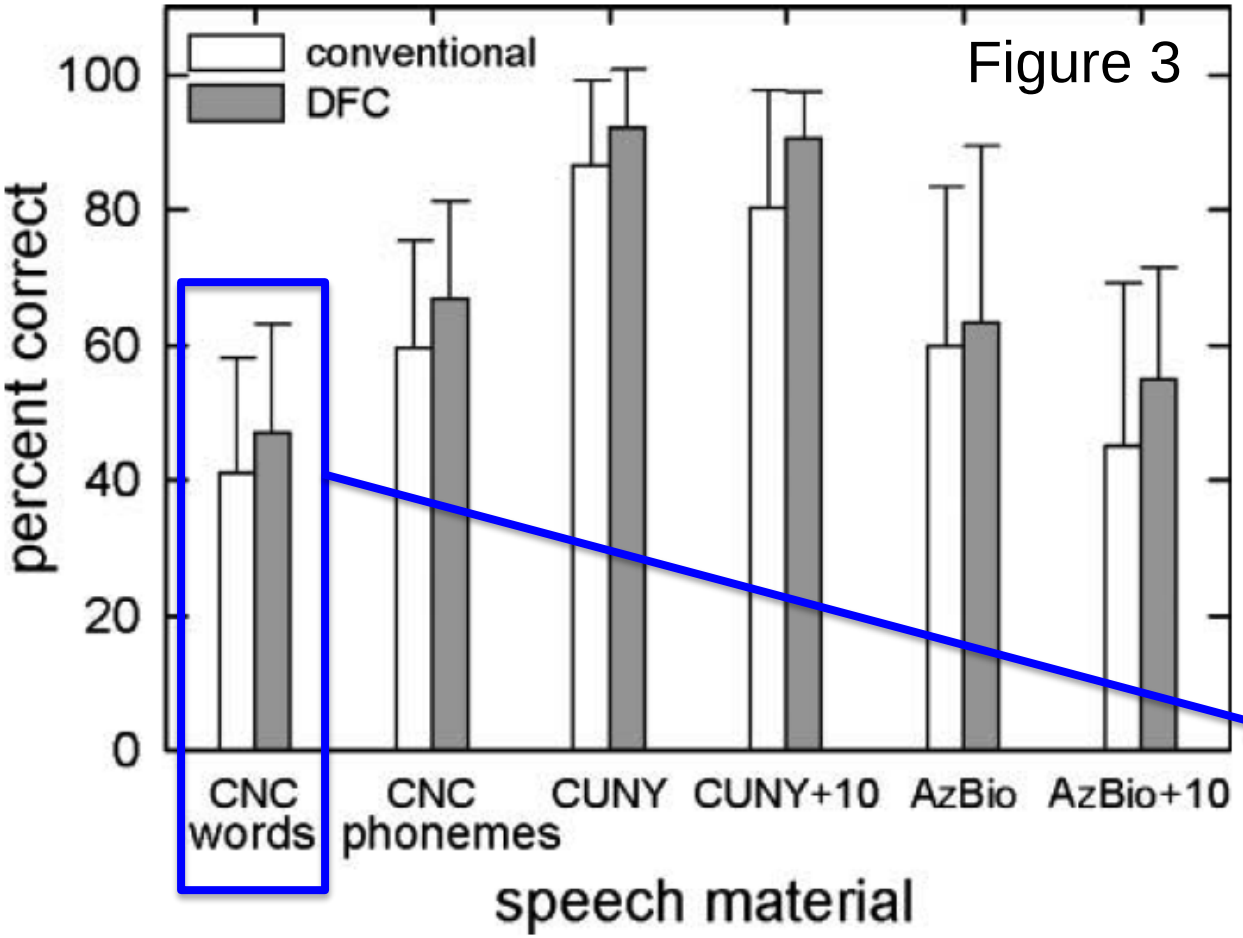


Frequency Lowering Technologies (FLT)



"There were no statistically significant differences between conventional amplification (CA) and DFC for any of the measures tested."

Frequency Lowering Technologies (FLT)



"There were no statistically significant differences between conventional amplification (CA) and DFC for any of the measures tested."

6-percentage points not significant

Frequency Lowering Technologies (FLT)

Summary of Results:

- No significant benefit for speech understanding in quiet or noise for patients with Hybrid-qualifying audiograms
  - Same metrics used in the Hybrid-L trial
    - CNC and AzBio
- No improvement in subjective benefit with FLT

Cochlear Implantation

Benefits

- CI provides access to high frequencies with preserved spectral contrasts
  - Required for high levels of speech understanding

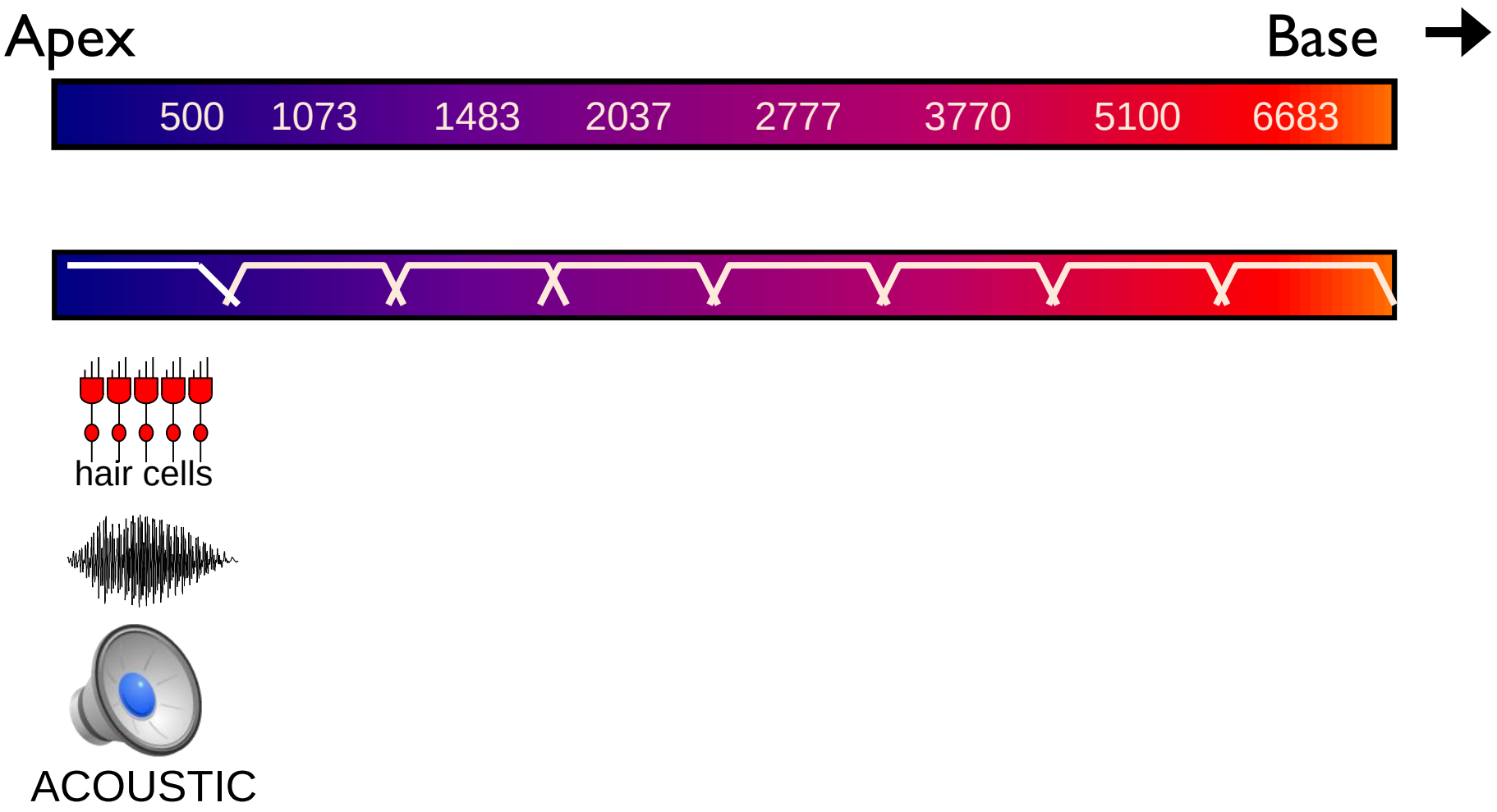
Limitations

- Fine Structure Cues
  - Rapid fluctuations in sound are not well transmitted by CI
  - Fluctuations are well preserved in LF acoustic hearing
- Current labeling indicates that all residual hearing will be lost.
  → Loss of fine structure in LF acoustic hearing
- Candidates for the Hybrid L24 Implant are not candidates for a traditional cochlear implant.

Benefits of Low Frequency Acoustic Hearing

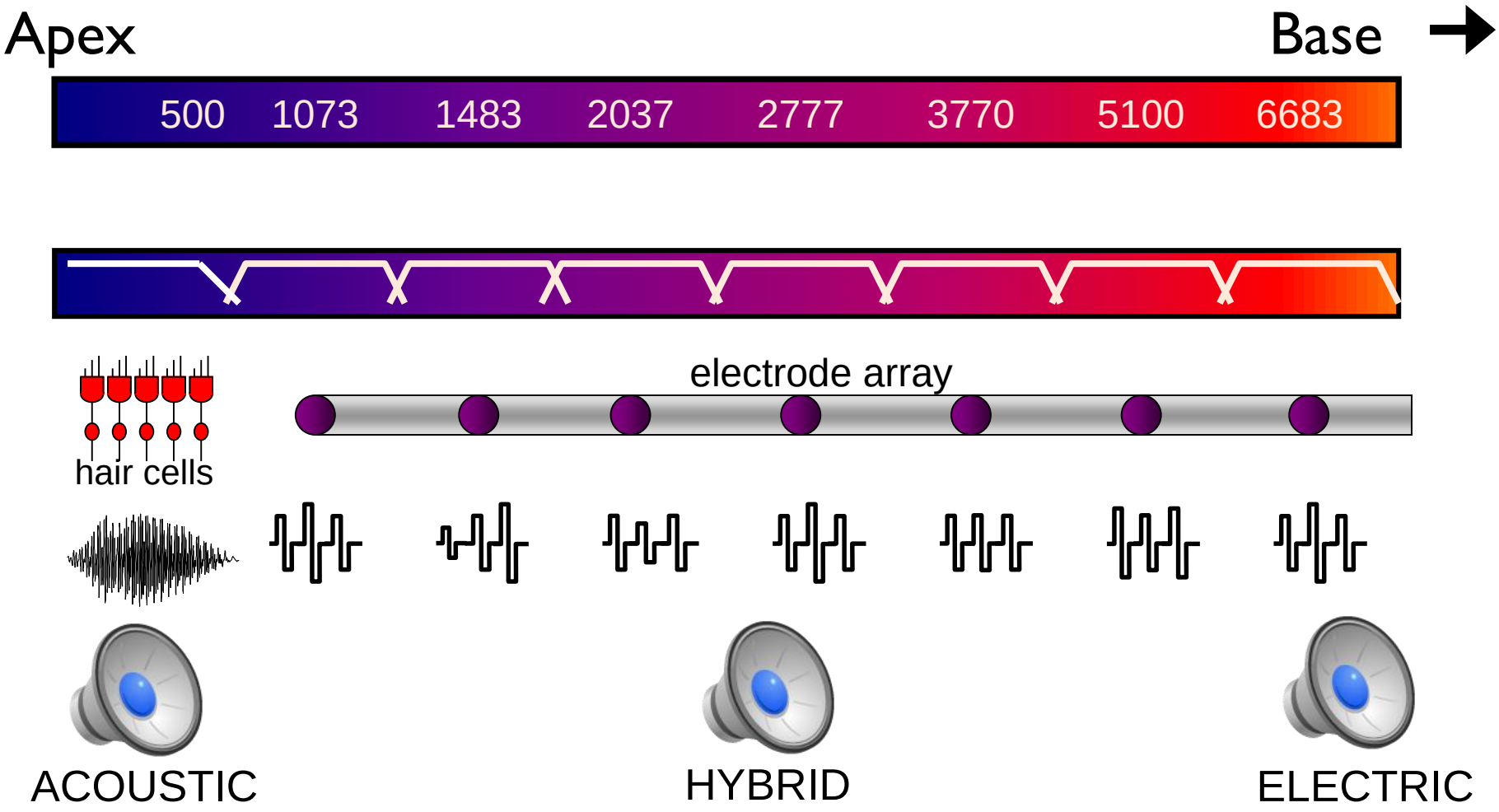
- Access to low frequency acoustic hearing is associated with better:
  - **Localization** (Dunn et al., 2010; Gifford et al., submitted)
  - **Pitch Recognition** (Kang et al., 2009; Wright and Uchanski, 2012)
  - **Hearing in Noise** (Dunn et al., 2005; Gifford et al., 2007; Dorman et al., 2009)
  - **Melody Recognition** (Dorman et al., 2009; Gfeller et al.,2006, 2007, 2012; Wright and Uchanski, 2012)
  - **Interaural timing cues** (Gifford et al., 2013)
- LIMITATION: LF hearing alone is not sufficient for high levels of speech understanding

Electric and Acoustic Stimulation with Hybrid L24



Simulations courtesy of Mario Svirsky, Ph.D. NYU Medical Center

Electric and Acoustic Stimulation with Hybrid L24



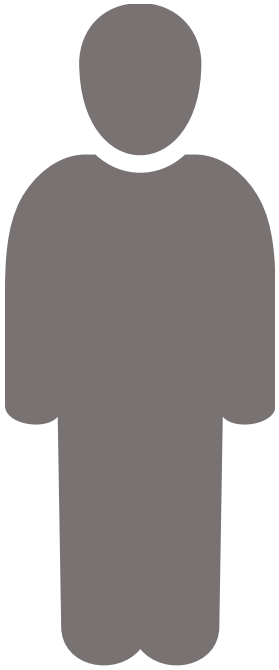
Simulations courtesy of Mario Svirsky, Ph.D. NYU Medical Center

Hybrid L24

Hybrid L24: Viable option for the “in-between” patient

Conventional, FLT, & implantable HAs

Hybrid L24



Cochlear Implantation

Development of the Hybrid L24 Implant

Bruce Gantz, MD
Principal Investigator
University of Iowa

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Hybrid History

- 1988: Research into cochlear implantation in severely hearing impaired subjects began
- Early 1990's: Began to recognize many CI patients perform better than those with amplification
- Based on inadequate treatment options and clear patient need the following questions arose:
  - Can we expand electrical speech processing to more of the hearing impaired population?
  - Is there a downside to implanting those with more residual hearing?
  - What are the advantages of preserving residual auditory function?

Hybrid History

1996

Development Began (University Iowa/Cochlear Corp)

1999

IDE Approval

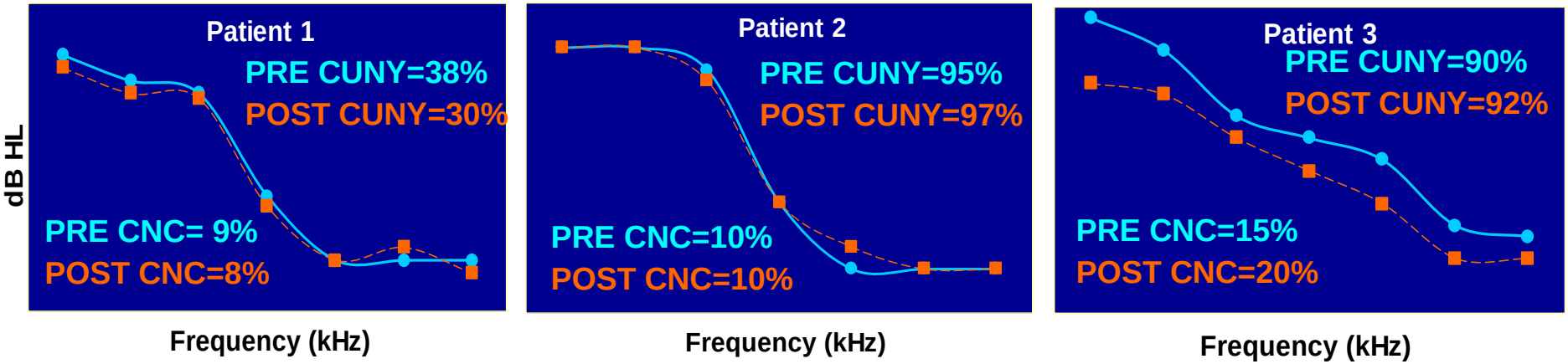
3 Subjects,

(6mm/6 electrode), Hearing Preserved

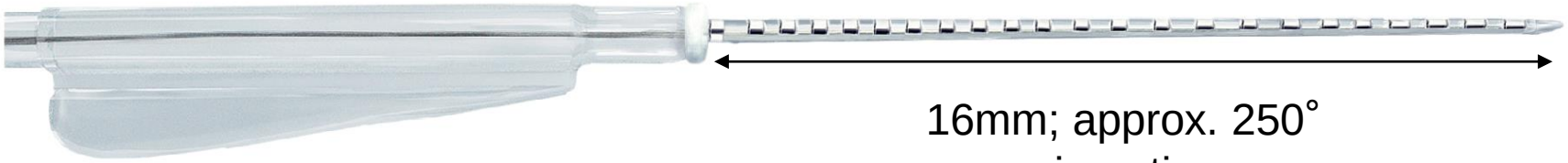
2000

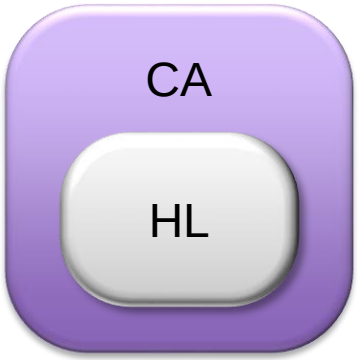
Gantz & Turner Report, 3 pts; 6th International CI Conference, Miami Florida

PRE AND POST OPERATIVE AUDIOGRAMS (1999)



Nucleus Hybrid L24 Electrode Array

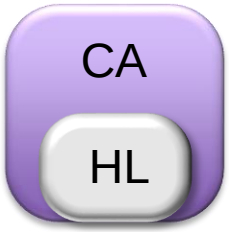




Base

HL: 0.40x0.55mm

CA: 0.80x0.80mm



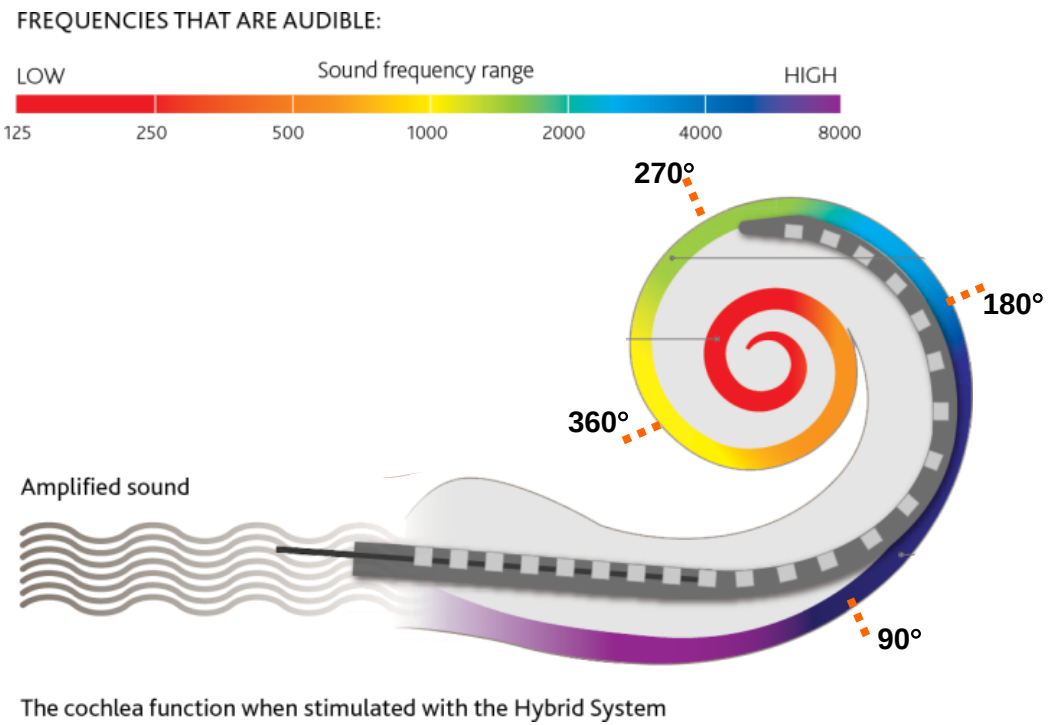
Apex

HL: 0.25x0.35mm

CA: 0.50x0.50mm

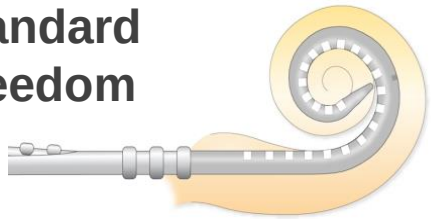
How the Hybrid L24 Electrode Works

Hybrid L24

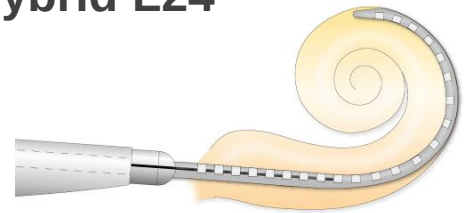


The cochlea function when stimulated with the Hybrid System

Standard Freedom

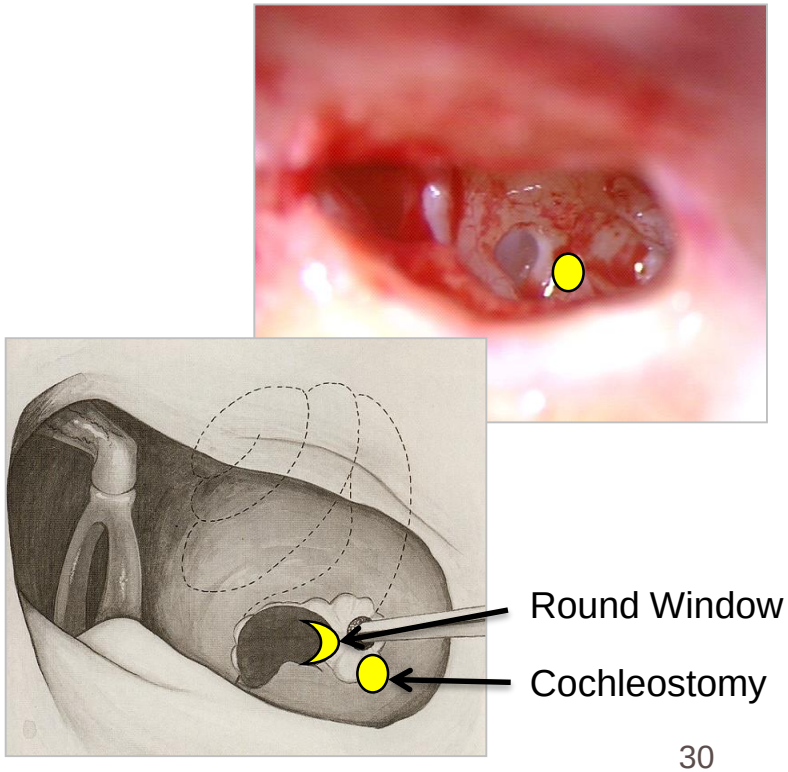


Hybrid L24



Hybrid Surgical Technique

- Same basic approach as cochlear implant surgery
- Specific care taken to protect hearing
  - Similar approach to drill-out stapedectomy
  - Diamond burr, slow speed, no suction of perilymph
  - Slow insertion of the array
- Cochleostomy (0.75mm – smaller than CI)
  - Anterior to floor of round window membrane
- Round window
  - Used in European study with good results



Round Window Surgical Approach

- Data are available from outside the US demonstrating that the round window approach is appropriate
  - Results of the study are published; it is important for surgeons to have access to surgical instructions for this alternate approach[1]
- Both approaches are approved for the Nucleus CI422 Cochlear Implant, electrode placement inside the cochlea is similar for both approaches
- Cochlear believes the decision should be based on the surgeon's judgment regarding the anatomical circumstances for each patient

1 Publication not provided to FDA as it was unavailable at the time of PMA submission. Lenarz et al. 2013. European multi-centre study of the Nucleus Hybrid L24 cochlear implant. International Journal of Audiology, early online 1-11. Meta-analysis Otol. Neurot. 2013 June; 34(4):667-74.

Pivotal Study Overview

Aaron J. Parkinson, PhD
Principal Clinical Studies Manager
Cochlear Americas

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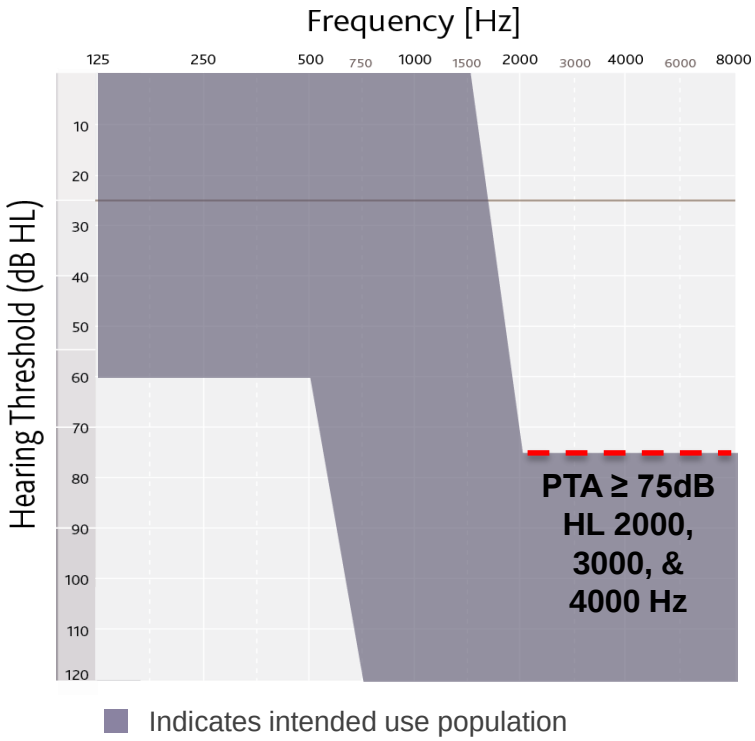
Study Design

- The study was conducted as a multicenter repeated-measures, single-subject design, where each subject served as his or her own control
  - Design appropriate since it accommodates the heterogeneity that characterizes hearing-impaired populations, including cochlear implant recipients
  - This study design has been implemented for many years in cochlear implant clinical trials and research studies
- Blinding or masking procedures were not possible to conceal the presence or absence of a cochlear implant from device recipients and/or clinical investigators

Key Inclusion and Exclusion Criteria

INCLUSION

- 18 years-of-age or older at the time of implantation
- Monosyllabic word scores between 10% and 60% in ear to be implanted (worse ear)
- Word scores equal to or better than ear to be implanted, but no better than 80%, in the better ear



EXCLUSION

- Duration of severe to profound high-frequency hearing loss greater than 30 years
- Congenital hearing loss (for this study, onset prior to 2 years of age)

Hearing Aid Fitting Guidelines

- All hearing aids were **verified** to be appropriately fit based on the widely accepted **NAL** prescriptive rule, consistent with ASHA practice policy
- A majority, 49/50, were hearing aid users at study entry[1] with an average of 18 years use
- In the event that amplification was not used, a minimum 14-day hearing aid trial was required prior to assessing candidacy

Make and model was documented for each ear[1]

- 92% of cases used current digital technology
- 31% had tried ipsilateral Frequency Lowering Technology (FLT) prior to enrollment in the Hybrid study (all digital technology)

1 This information was not provided to FDA in original PMA submission.

Test Conditions

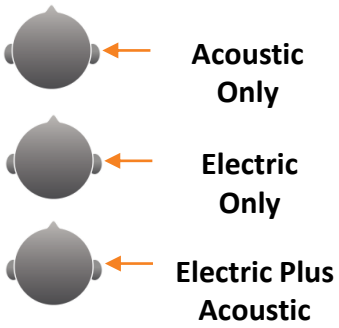
5 pre and post listening conditions tested

Implant Ear

Acoustic Alone

Electric Alone

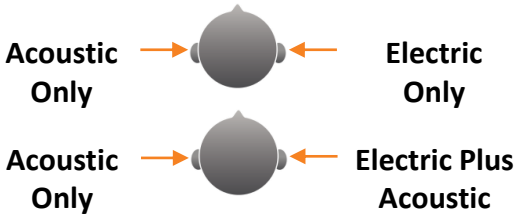
Hybrid Mode (Study Endpoint)



Both Ears (Everyday Use)

Bimodal Mode

Combined Mode



Evaluation Intervals

Preoperative: All Measures

Postactivation: Initial activation, 3, 6, 12 months and semiannually thereafter

Endpoint: 6 Months postactivation

Study Measures

PRIMARY

- CNC Monosyllabic Word Recognition Test

- AzBio Sentence Test in Noise (+5 dB SNR)

Efficacy Endpoints - Implant Ear

Co-Primary

Use of the Nucleus® Hybrid™ L24 Implant System will improve speech perception, as measured at the 6-month endpoint by:

- CNC Monosyllabic Word Recognition
- AzBio Sentences in Noise

Secondary

Most subjects (> 75%) will score equal to or better at 6 months than the preoperative unilateral condition:

- CNC Monosyllabic Word
- CNC Phoneme Recognition
- AzBio Sentences in Noise

Safety Measures

Adverse Events (AEs)

- Any surgical and/or device related event
- Reported as the number and proportion of individuals

Hearing Sensitivity

- Subjects' levels examined to assess any changes and to characterize impact on low frequency hearing sensitivity

Speech, Spatial, & Qualities of Hearing (SSQ) Questionnaire

- A Self-Assessment Questionnaire
  - Validated metric
  - Commonly used in CI and HA research
- Measures listening ability in a large number of listening situations
- Assesses 3 overall domains:
  1. Speech hearing in quiet and noise
  2. Spatial hearing - where sounds are coming from, and from what direction and distance
  3. Qualities of hearing - music, naturalness of speech & music, sound segregation, ease of listening/listening effort,
- 49 questions, self administered

Device Use Questionnaire (DUQ)

- An “in-house” designed device usability metric, complementary to the SSQ
  - Adapted from questionnaire previously used in FDA approved implantable middle ear studies
- Administered to determine subjective preferences with regards to device use in various listening environments
- It was administered preoperatively, 6 months postactivation, and 12 months postactivation
  - The preoperative questionnaire contained 93 questions
  - The postoperative questionnaire contained 95 questions
  - The majority of the questions were multiple choice

Evaluation Matrix

	Baseline Evaluation	Initial Activation	3 Months	6 Months	12 Months‡
Consent Medical & Hearing History	X				
Hearing Aid Verification	X		X¥	X¥	X¥
Unaided Hearing Thresholds & Tympanometry	X	X	X	X	X
Aided Audiometric Thresholds	X	X	X¥	X¥	X¥
CNC test in quiet	X	X	X	X	X
AzBio sentences-in-noise test	X		X	X	X
Adaptive SRT in noise	X			X	
UW-CAMP music perception	X			X	
Questionnaires (SSQ, DUQ, MBQ)	X			X	X
Psychophysical Ts, Cs & electrical impedance		X	X	X	X
Adverse Events	X	X	X	X	X

¥ In the event that a change in hearing > 10 dB at two or more frequencies occurred since previous visit.

‡Subjects were followed up semiannually thereafter

Study Sites and Principal Investigators

Study Site	Principal Investigator
NYU	J. Thomas Roland, M.D. **(Lead)**
University of Iowa	Bruce J. Gantz, M.D.
Center for Hearing & Balance	Jacques Herzog, M.D.
Hearts for Hearing	R. Stanley Baker, M.D.
Mayo Clinic, Rochester	Colin Driscoll, M.D.
Midwest Ear Institute	Charles Luetje, M.D.
Northwestern University	Andrew Fishman, M.D.
Ohio State University	Brad Welling, M.D., Ph.D.
Rocky Mtn. Ear Center	David Kelsall, M.D.
University of Cincinnati	Ravi Samy, M.D.

Enrollment & Accountability of PMA Cohort

Primary Endpoint

Enrolled & Implanted	1 month Initial Activation	3 month Evaluation	6 month Evaluation	12 month Evaluation
50 subjects at 10 sites	50 subjects	50 subjects	49 subjects	46 subjects

- One subject reimplanted with a cochlear implant; did not complete 6 month test interval

- Two subjects withdrew prior to 12 month test interval due to medical conditions unrelated to the device or procedure
- Two subjects reimplanted with a cochlear implant; did not complete 12 month test interval

Effectiveness Results

Bruce J. Gantz, MD
Principal Investigator
University of Iowa

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Topics

- Speech Perception Outcomes
  - Co- primary and secondary endpoints
  - Performance in the Combined Condition (Everyday)
  - Performance over time
  - Performance in different listening conditions

- Other efficacy outcomes
  - Music Perception
  - Self Assessment Questionnaires

Study Demographics (N=50)

Characteristic	Average (S.D.)
Age at Implantation	64.1 years (±14.7)
Gender	50% males, 50% females
Ear Implanted	24 left, 26 right
Duration of High Frequency Hearing Loss	28.1 years (±14.9)
Duration of Severe to Profound High Frequency Hearing Loss	13.7 years (±7.2)
Preoperative Aided CNC Score – Implant Ear	28.4% (±14.7%)
Preoperative Aided AzBio Sentence Score (+ 5dB SNR) – Implant Ear	16.3% (±14.4%)

Co-Primary and Secondary Study Endpoints: 6 Months

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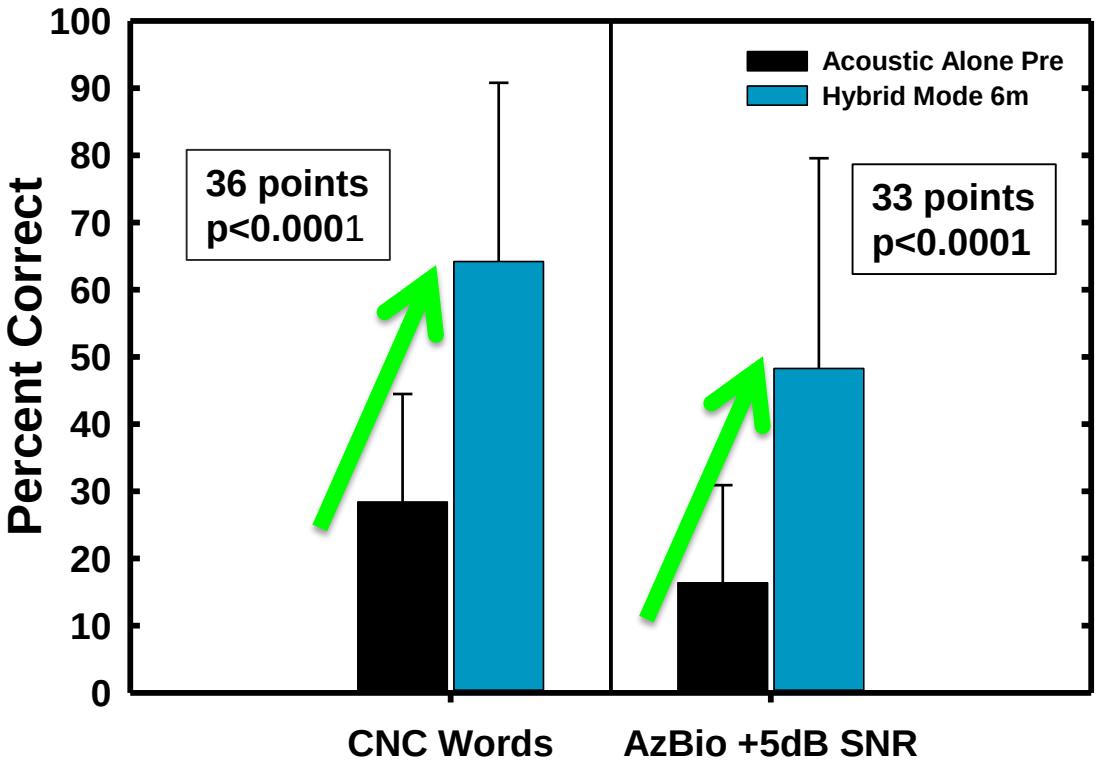
Co-Primary Endpoints: Implant Ear 6 Months (N=50[1])

Study Endpoints met – more than doubled mean scores

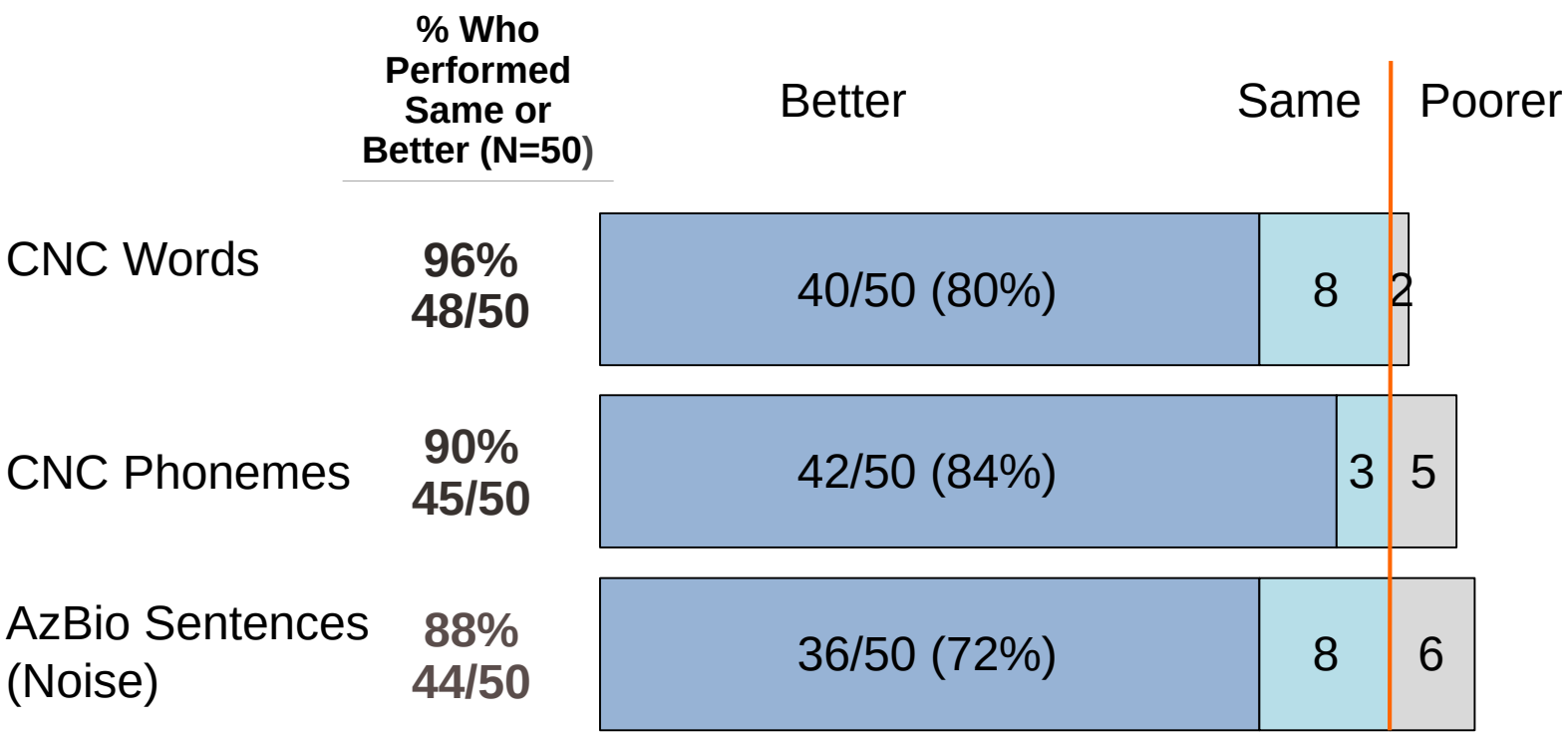


Electric Plus Acoustic

[1]Data reported here are based on the data using LOCF (N=50);

Secondary Endpoints – Implant Ear

Secondary Endpoint thresholds greatly exceeded for quiet and noise



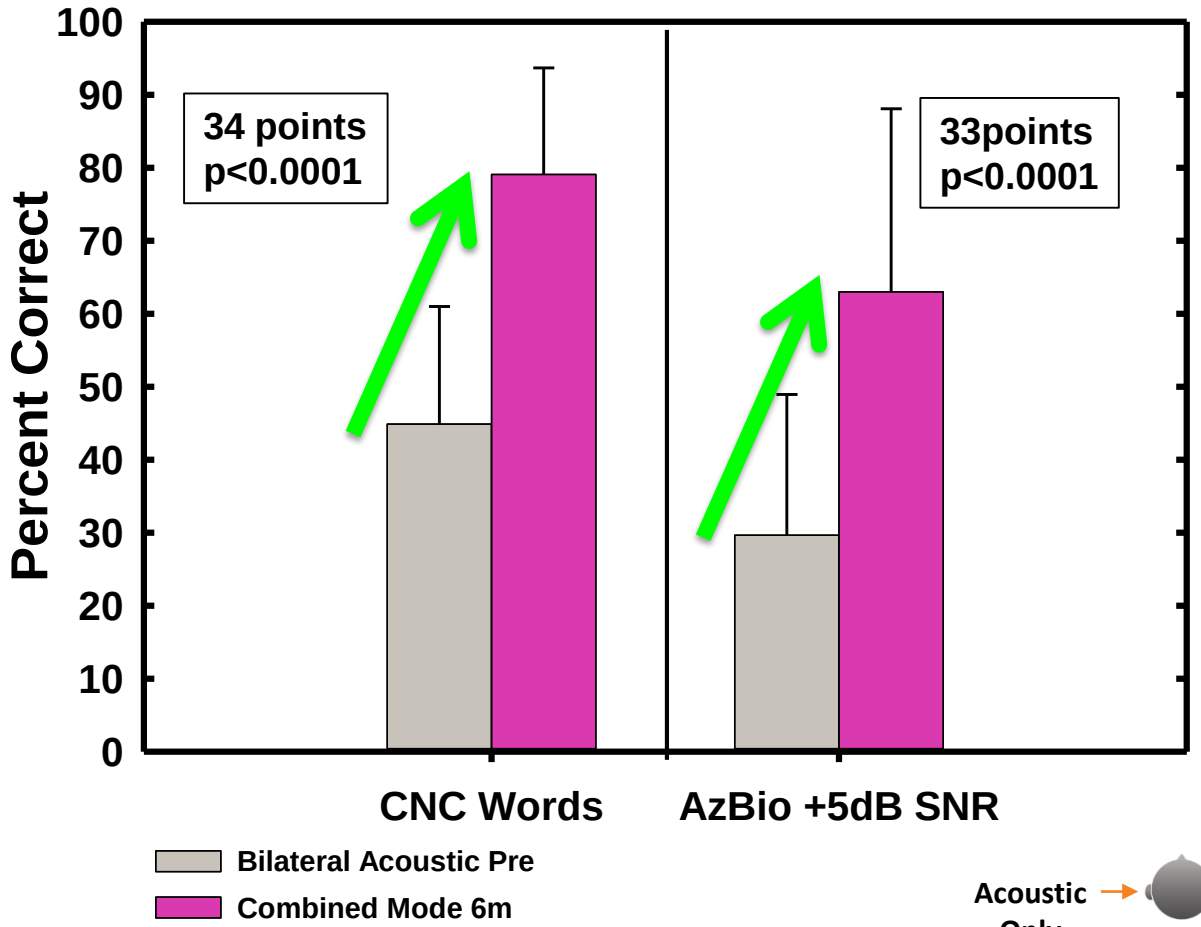
[1]Data reported here are based on the data using LOCF (N=50); [redacted] counted as "poorer"

Electric Plus Acoustic

Everyday Use Results: (Combined Mode) Both Ears

Everyday Use Results - Both Ears (N=50[1])

Speech perception significantly improved in both and quiet and noise

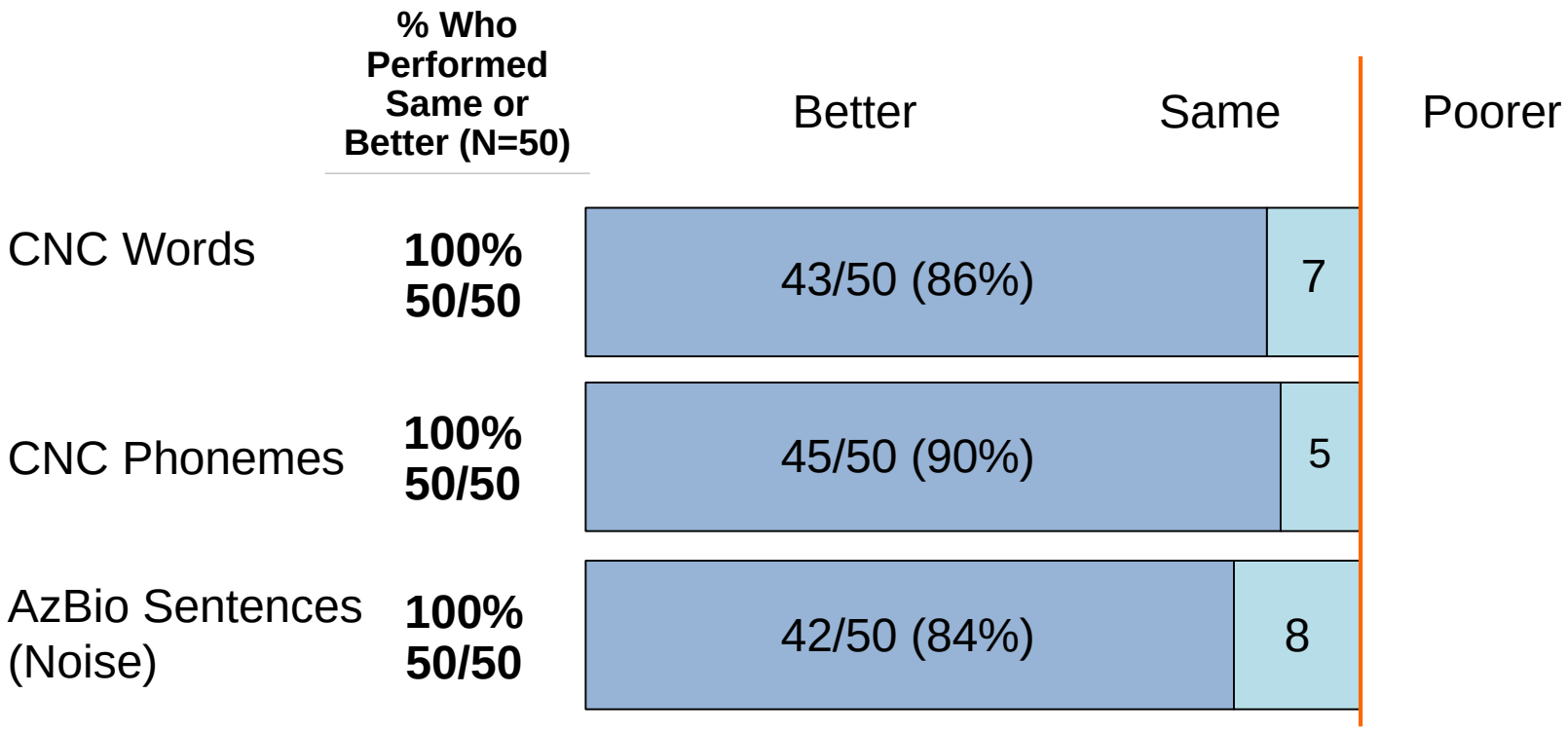


[1]Data reported here are based on the data using LOCF (N=50);

Acoustic Only ← → Electric Plus Acoustic

Everyday Use Results - Both Ears

100% of subjects performed the same or better postoperatively

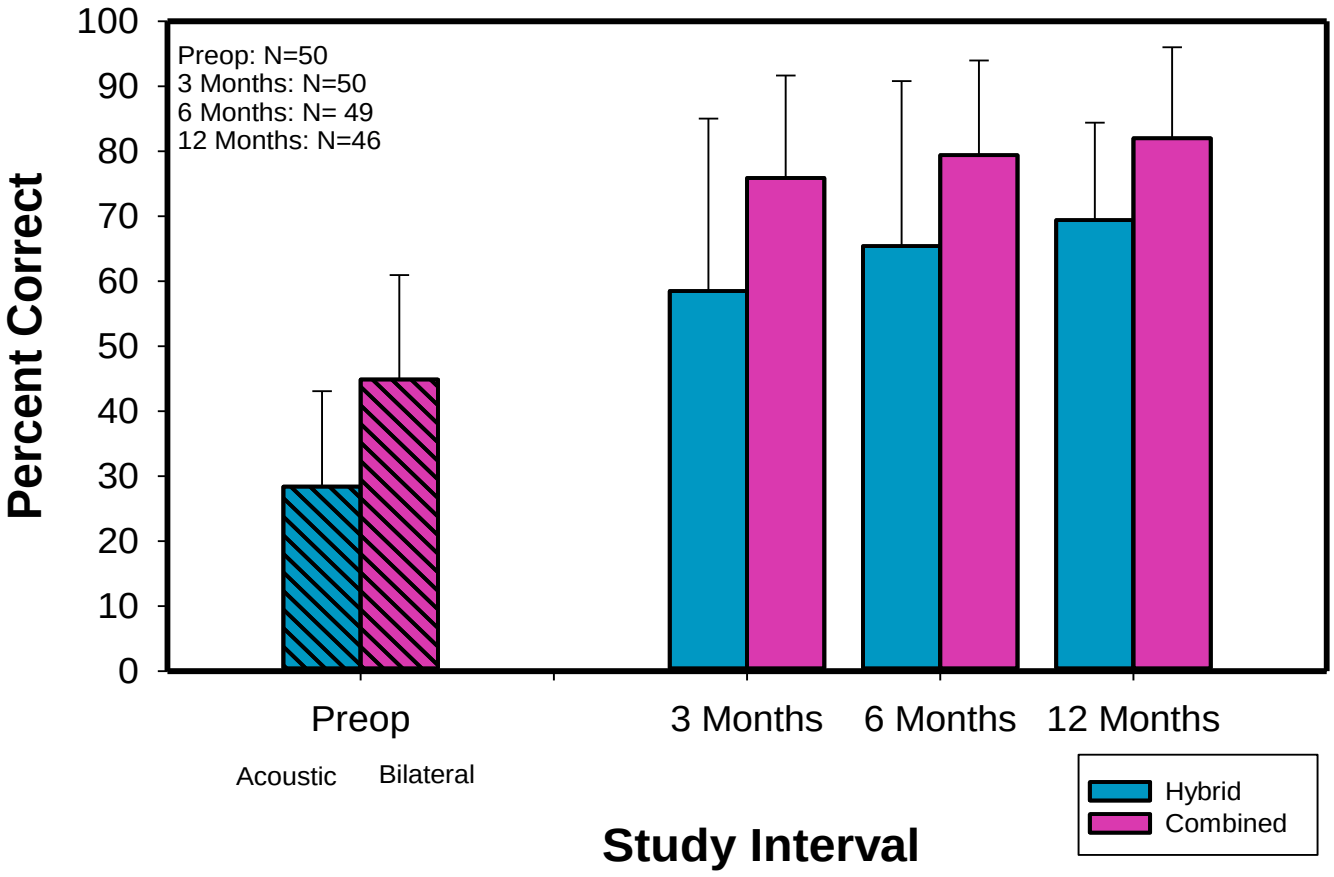


[1]Data reported here are based on the data using LOCF (N=50); [redacted] counted as "poorer"

Acoustic Only ← → Electric Plus Acoustic

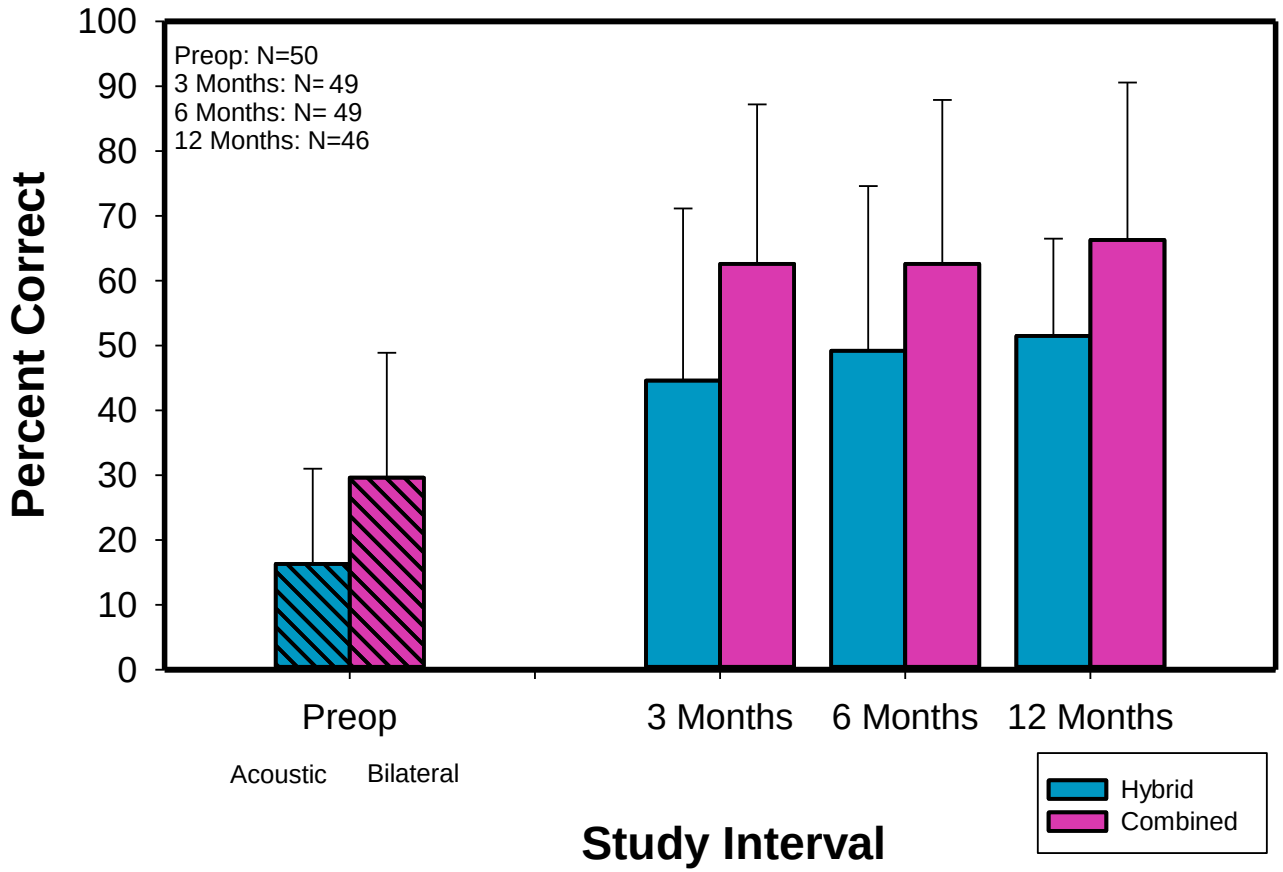
Performance Over Time

CNC Word Recognition Overtime
(Implant Ear & Both Ears)



In both the Hybrid and combined conditions; Significant improvement pre to 3, 6 &12 months; $p<0.0001$

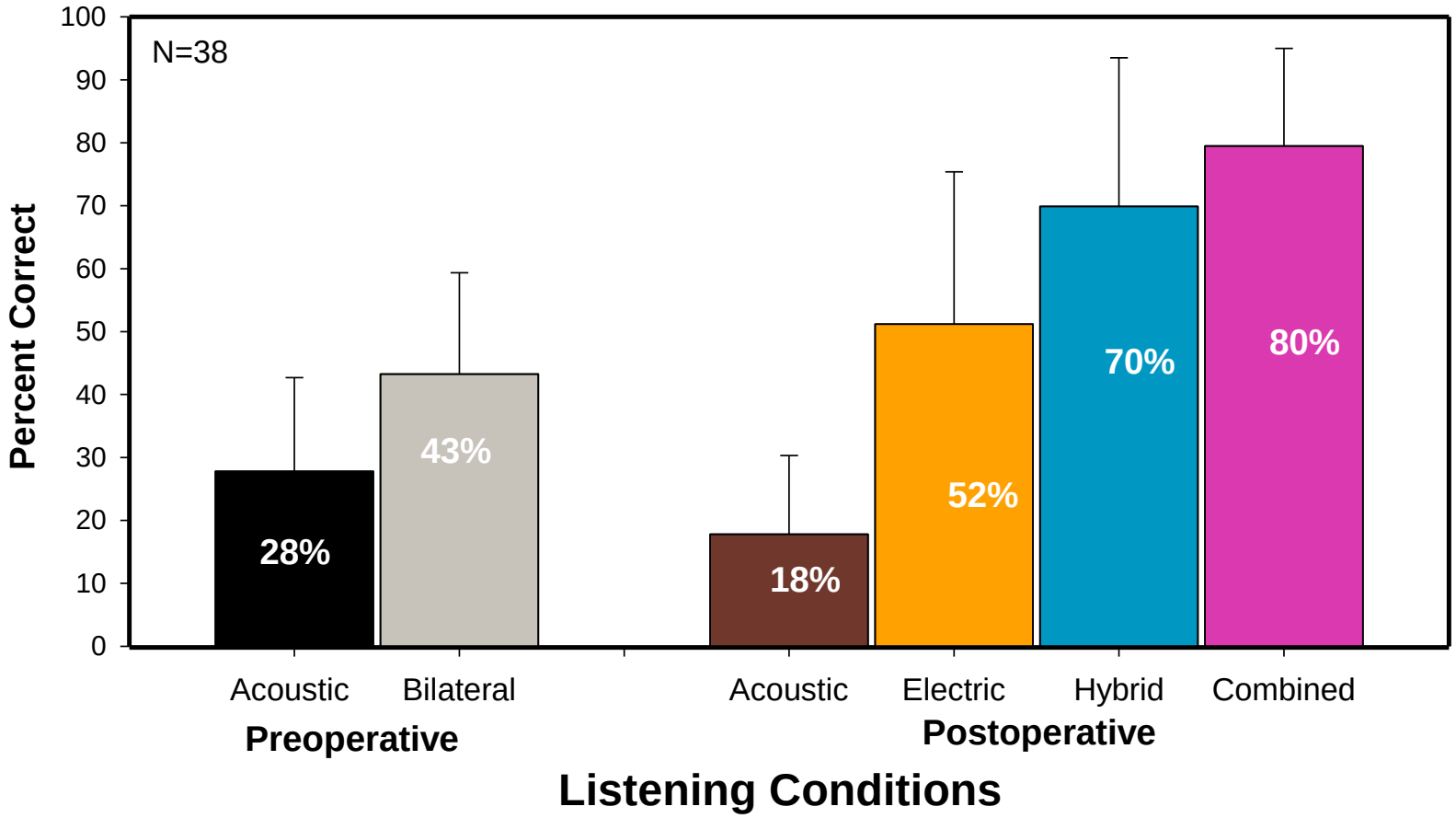
AzBio Sentences in Noise at + 5 dB SNR Over time (Implant Ear & Both Ears)



In both the Hybrid and Combined conditions; Significant improvement pre to 3, 6 &12 months; $p<0.0001$

Performance on Word Recognition: Different Listening Conditions

CNC Word Recognition in different listening conditions at 6 months

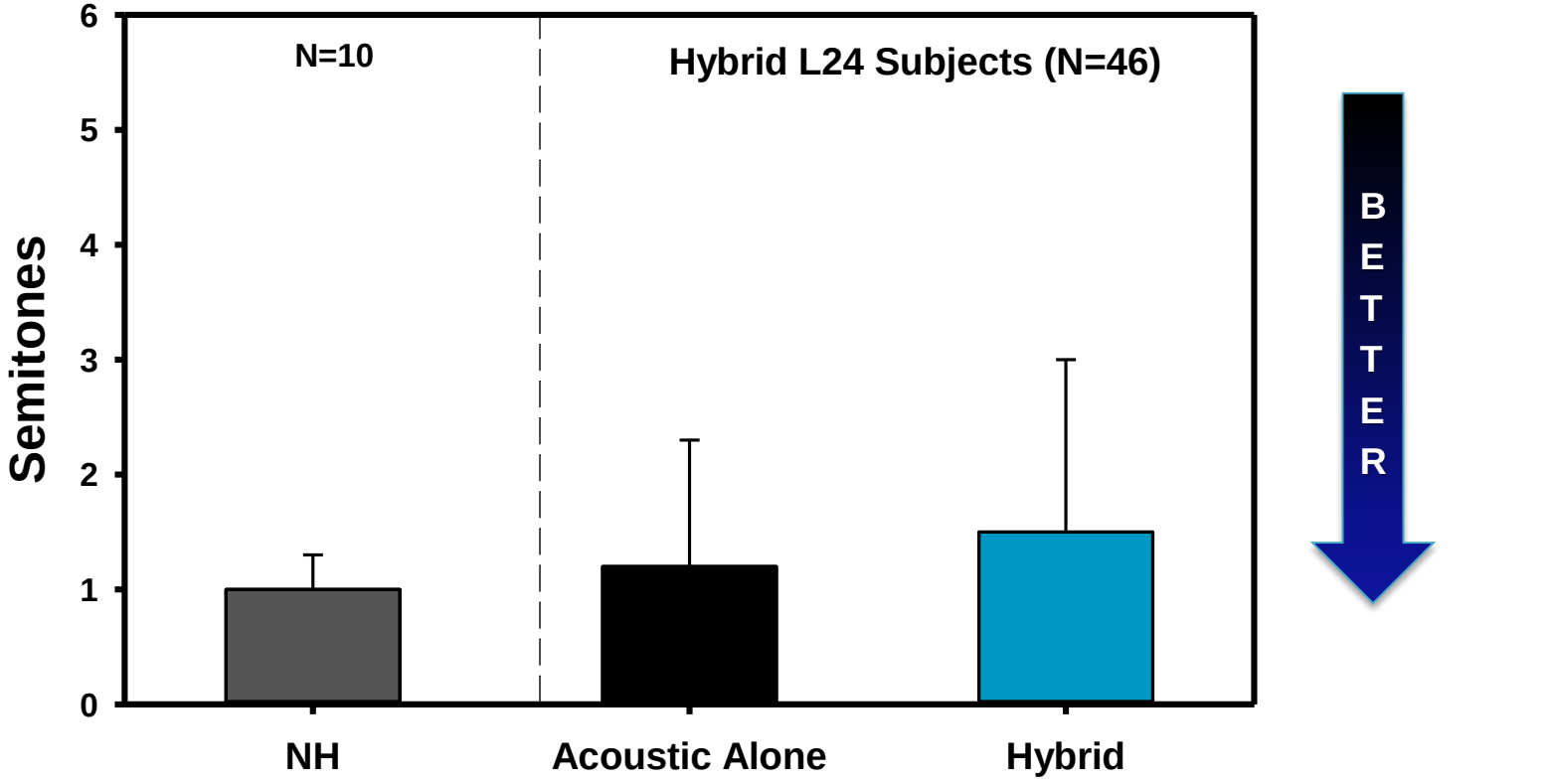


Other Efficacy Assessments

Pitch Perception
Self Assessment Questionnaires

UW-CAMP: Pitch Direction Discrimination

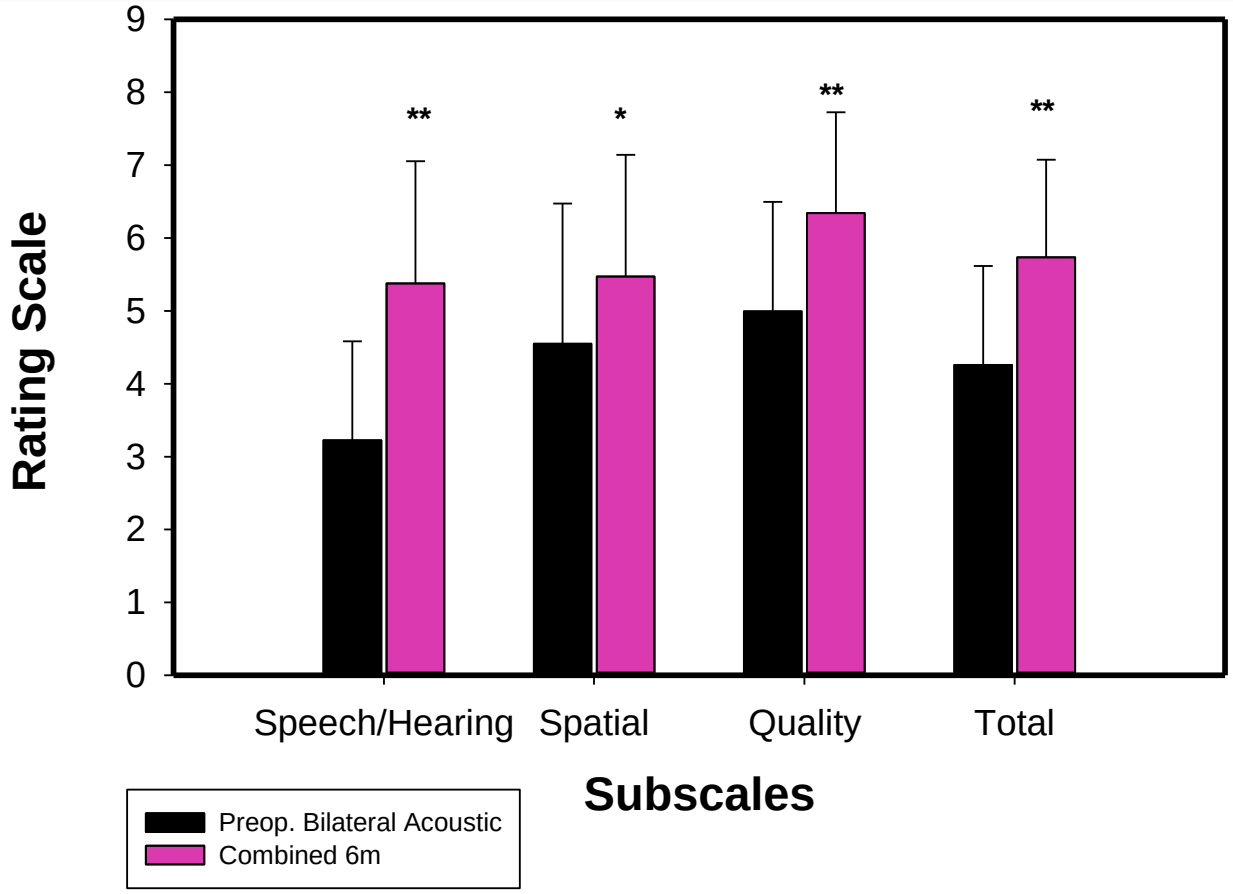
Pitch perception capabilities not impacted



Normally Hearing (NH) score from (Kang et al., 2009)

Speech Spatial and Quality of Sound Scale 6 Months

Significant benefit across all subscales



**Significant different from preoperative at p<0.0001

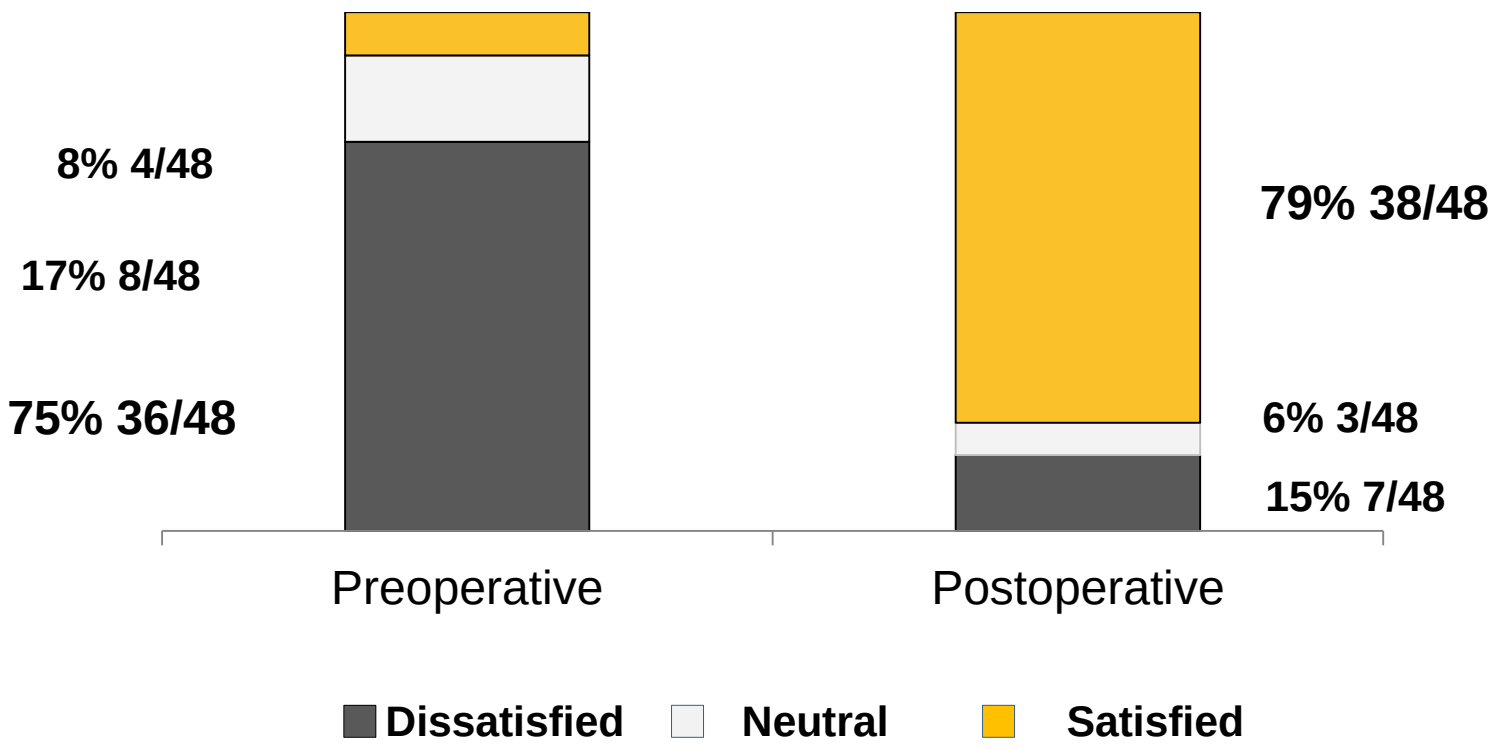
*Significant different from preoperative at p<0.01

Acoustic Only → ← Electric Plus Acoustic

(Noble et al., 2009)

Device Use Questionnaire: Satisfaction

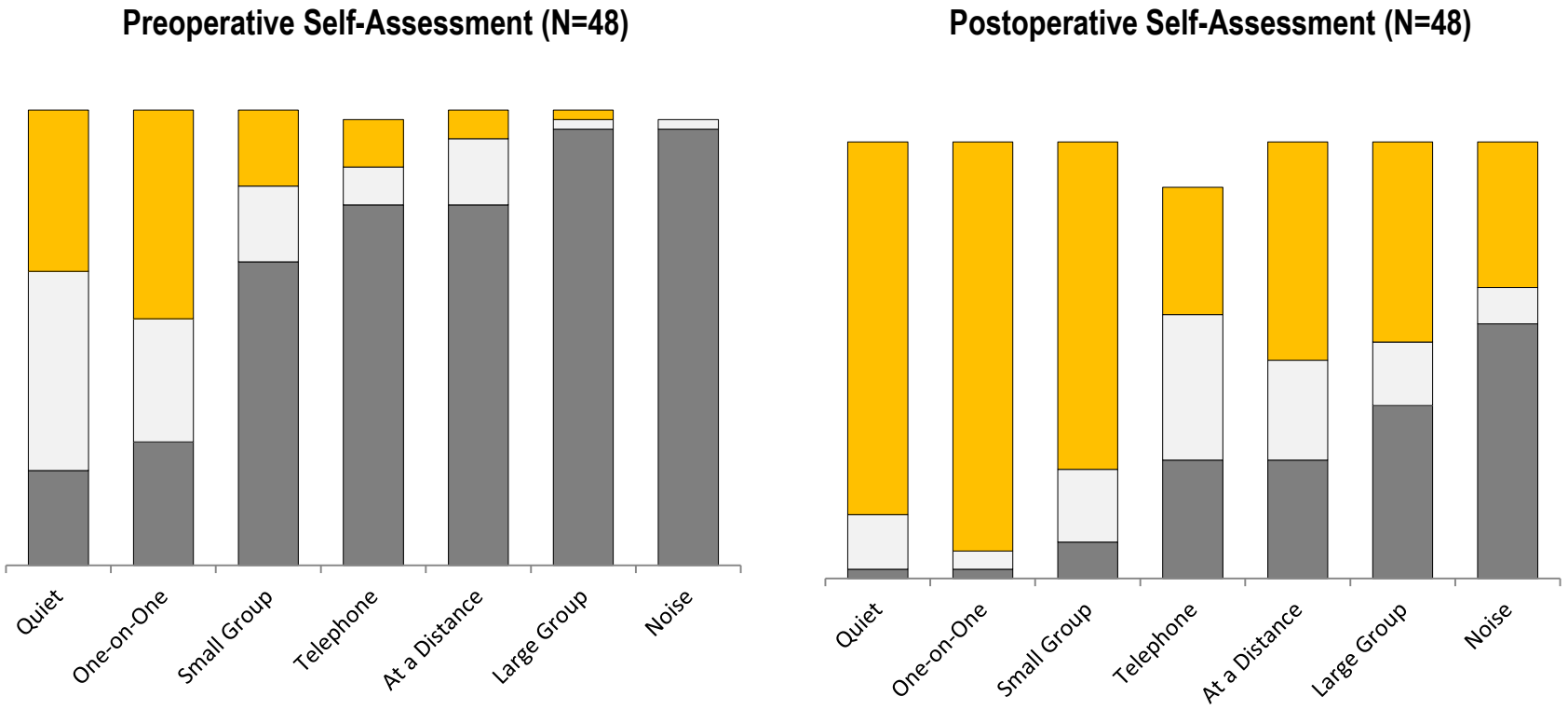
Subjects reported higher satisfaction levels postoperatively



Acoustic Only → ← Electric Plus Acoustic

Pre- vs. Postoperative Satisfaction in Various Listening Situations

Subjects reported higher levels of satisfaction across various situations



Summary

- The primary and secondary study endpoints were met
  - In the implant ear; 80% and 72% of subjects demonstrated significant improvements in quiet and noise
- SSQ results corroborate speech perception results
- 79% of the subjects reported being satisfied/very satisfied with hearing performance in their postoperative condition
- 100% of subjects showed equal or greater speech perception performance when listening in the Everyday Condition

Safety Results

J. Thomas Roland, Jr., MD
Lead Investigator
NYU Medical Center

Cochlear®

Primary Safety Measures

- Medical/Surgical and/or device-related events were recorded as AEs for any subject at any time during the course of the entire study
- Data reported as the number and proportion of individuals experiencing the AE
- Medical/surgical events included instances of hearing loss, increased tinnitus, vertigo, and other symptoms
- Many of the AEs are typical of those seen in any ear surgery

Adverse Events

- 65 adverse events were reported involving 34 of 50 subjects over the course of the study
  - 43 events were very consistent in the type and proportion of events seen in other cochlear implant studies. All but 2 AE's resolved.
  - 22 cases of Profound/Total hearing loss - categorized as an AE for the first time in industry history

Adverse Events > 5% Incidence

Event	# of Events	% Resolved
Increased tinnitus	14	100%
Open/Short circuited electrodes	11	100%
Dizziness type symptoms	9	100%
All Other*	9	78%
Profound/Total loss	22	0%
All Events	65	--

* Sound quality issues, decreased performance, skin irritation, overstimulation, pain with effusion, local stitch infection

Unresolved Adverse Events

Unresolved Events Observed					
Event	# of Events	% of Events	# of Subjects with Event	% of Subjects with Event	% Resolved
Profound/Total Loss	22	34%	22	44%	0%
Sound Quality	2	3%	2	4%	50%
Decreased Performance	1	2%	1	2%	0%

TWO CASES

- One sound quality issue unresolved despite programming changes
- One decrease in performance possibly unrelated to prior total loss of hearing

Summary

- No Unanticipated Adverse Device Effects have been reported
- Hybrid L24 AEs consistent in terms of severity, type and number of events as observed in the Nucleus Freedom clinical trial
- AEs regarding loss of residual hearing not previously reported in CI studies as total loss was assumed

Hearing Sensitivity

Hearing Sensitivity Outcomes

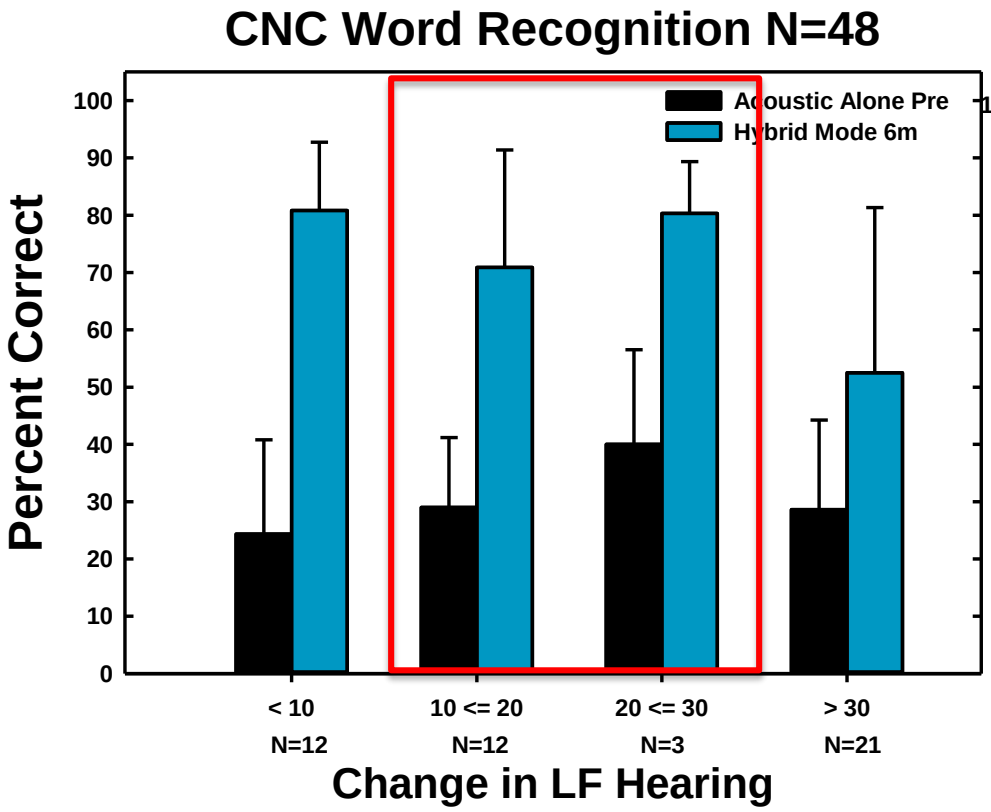
- There are 2 ways to assess hearing sensitivity over time:
  - The amount of low frequency hearing loss induced by implantation
  - The degree of residual low frequency hearing
- It is important to convey both the amount of hearing lost and the functional impact of that loss on the ability to combine electric and acoustic hearing in the implanted ear
  - Hearing sensitivity is one of many measures used to assess outcomes in the Hybrid population

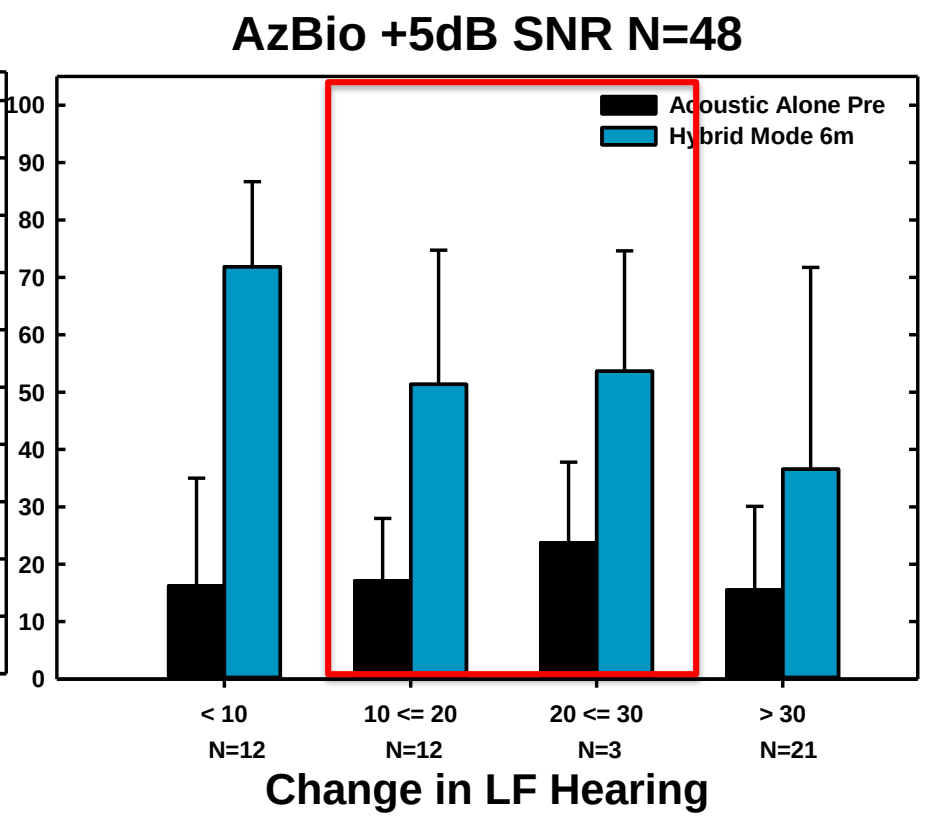
Amount of hearing loss: 6 and 12 months

At 6 months, subjects experienced on average a 33 dB change in low frequency pure tone average

Change in LF PTA (125-1k Hz)	Number of Subjects		Subgroups		
	6 months (N=50)	12 months (N=46)	dB Loss	6 months (N=50)	12 months (N=46)
≤ 30 dB	27 (54%)	27 (59%)	≤ 10 dB	12 (24%)	9 (20%)
			>10 ≤ 20 dB	12 (24%)	12 (26%)
			>20 ≤ 30 dB	3 (6%)	6 (13%)
> 30 dB	23 (46%)	19 (41%)	> 30 ≤ 40 dB	6 (12%)	6 (13%)
			> 40 ≤ 50 dB	6 (12%)	1 (2%)
			> 50 dB	11 (22%)	12 (26%)

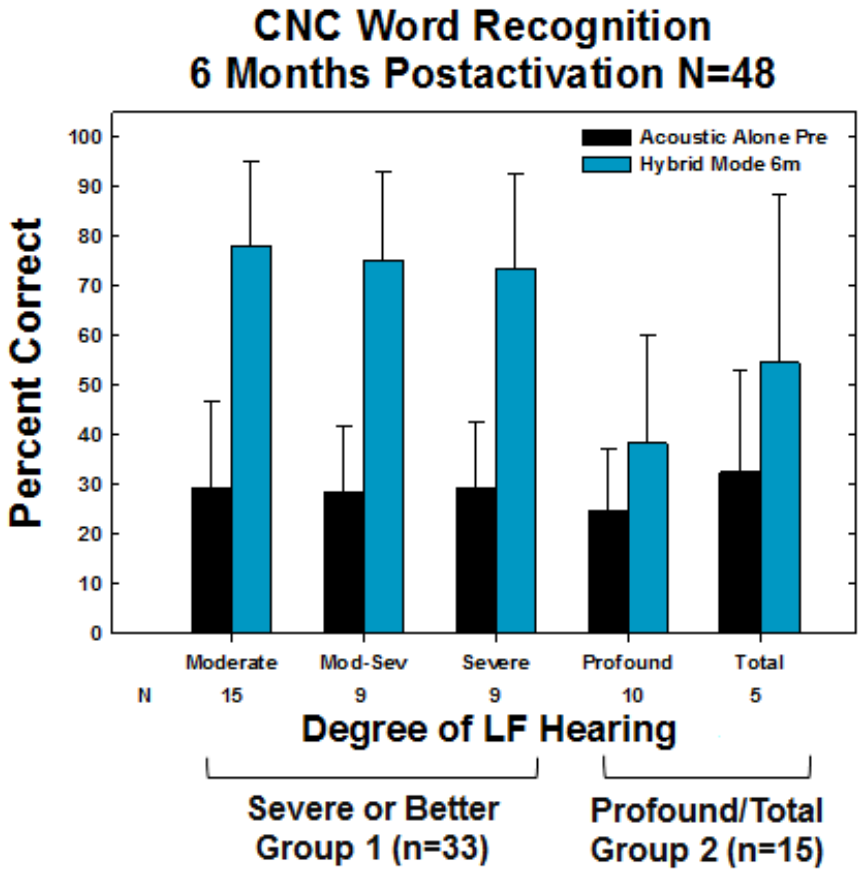
Outcomes by Hearing Loss

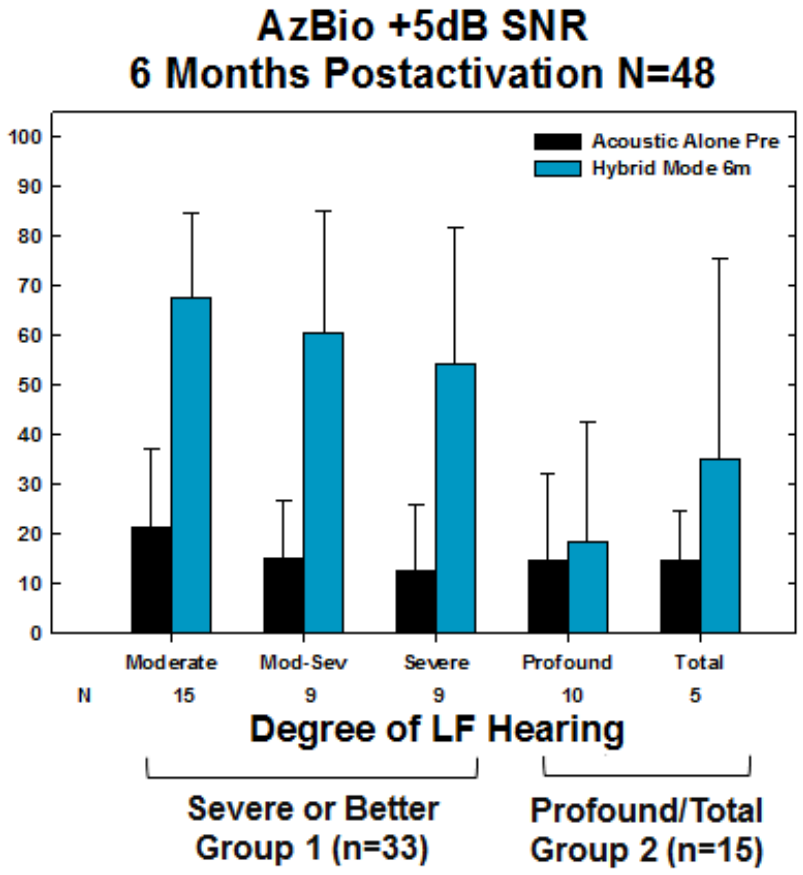




Electric Plus Acoustic

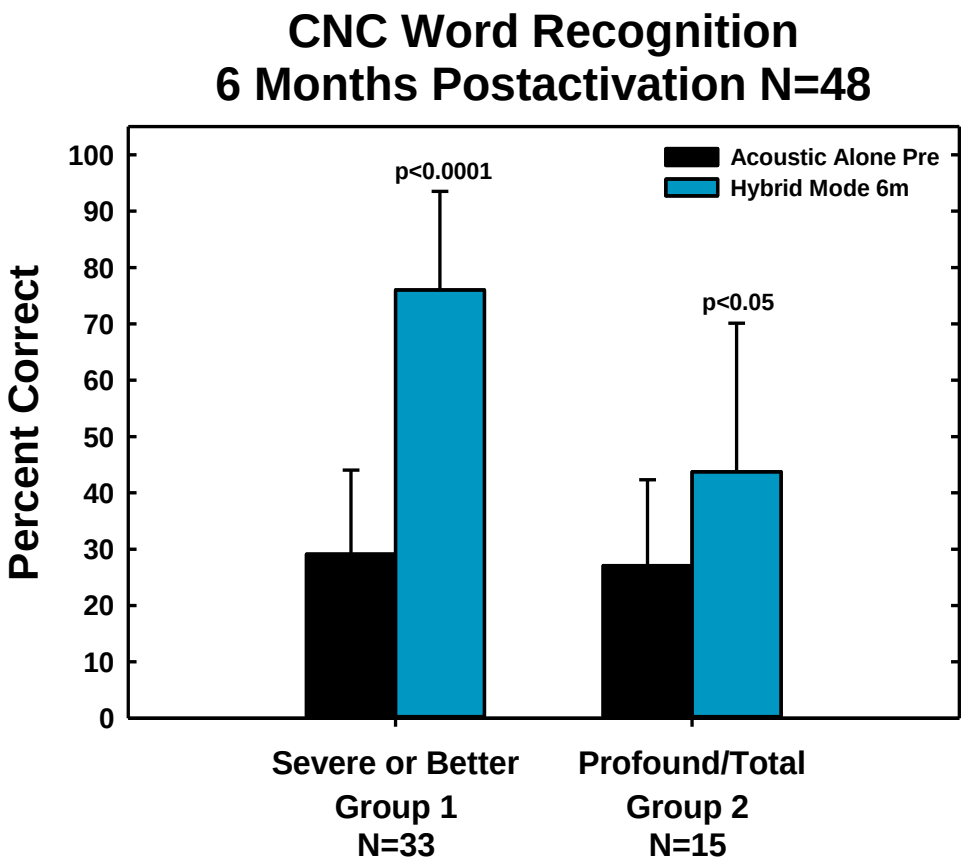
Clinical Significance of Groups 1 and 2

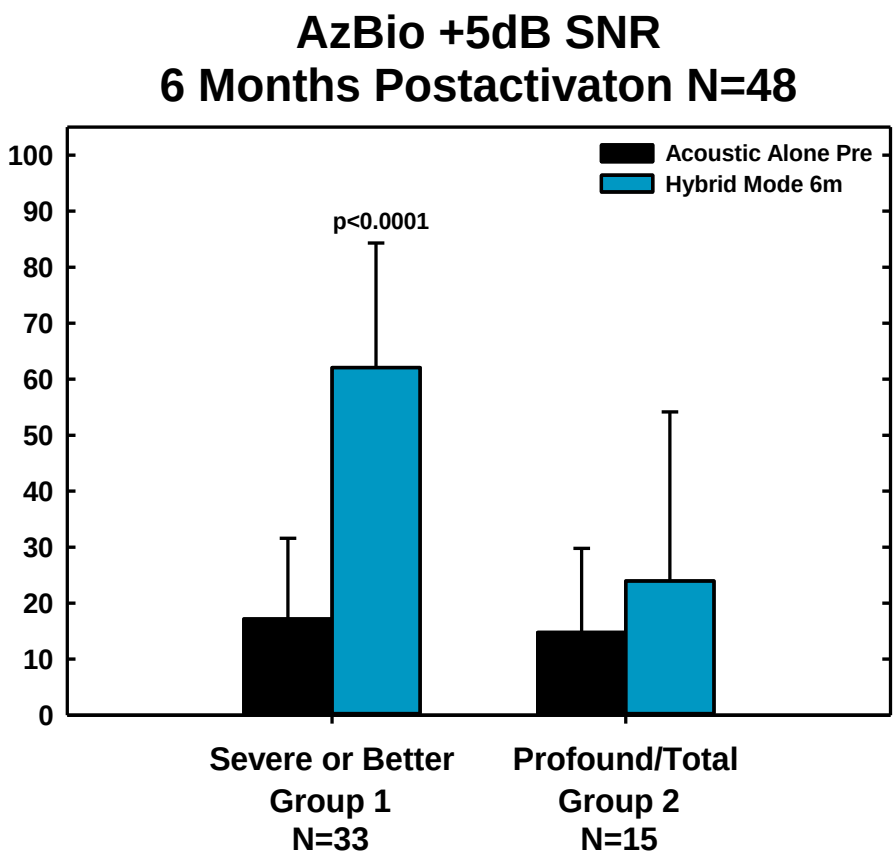




Electric Plus Acoustic

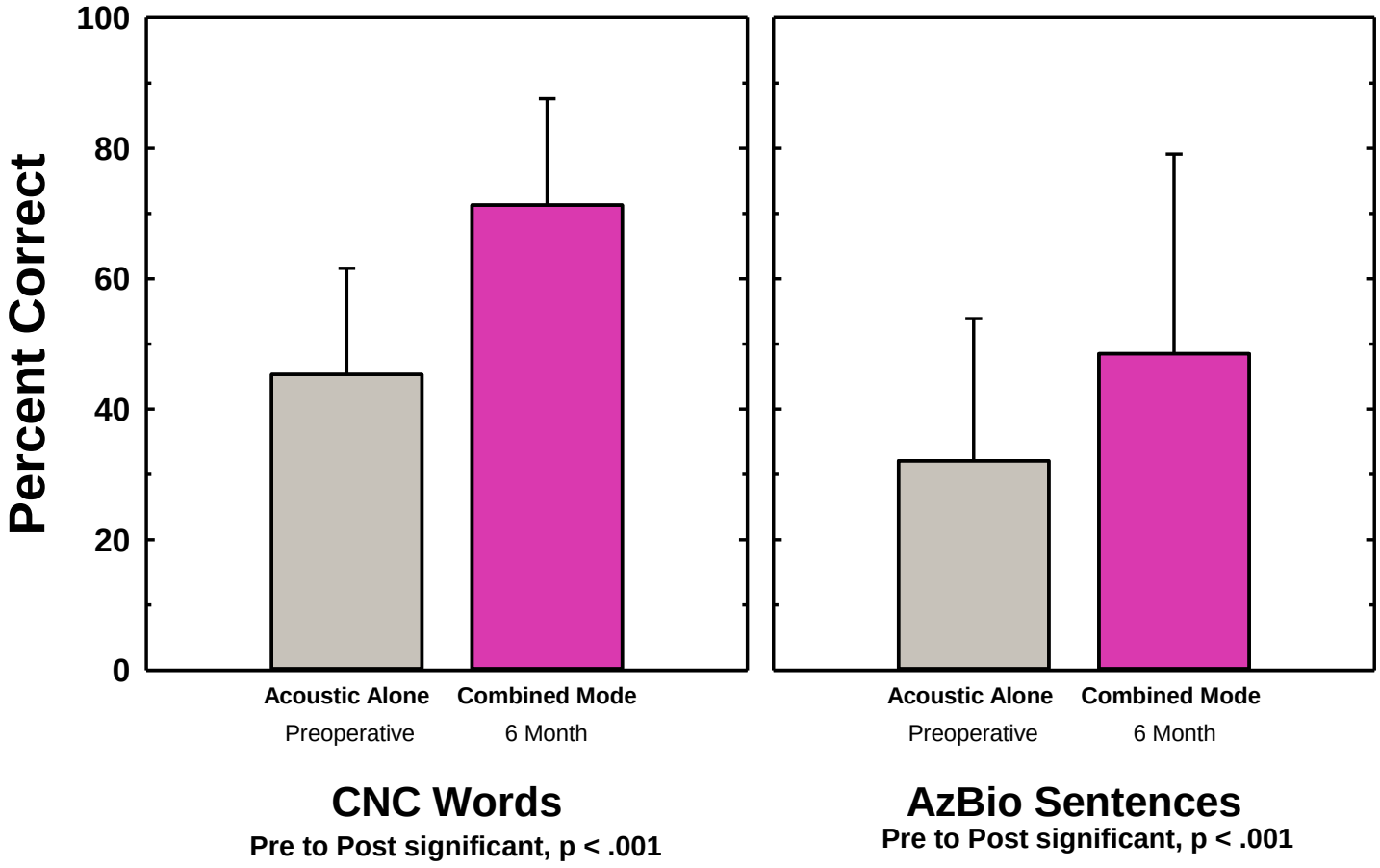
Clinical Significance of Groups 1 and 2



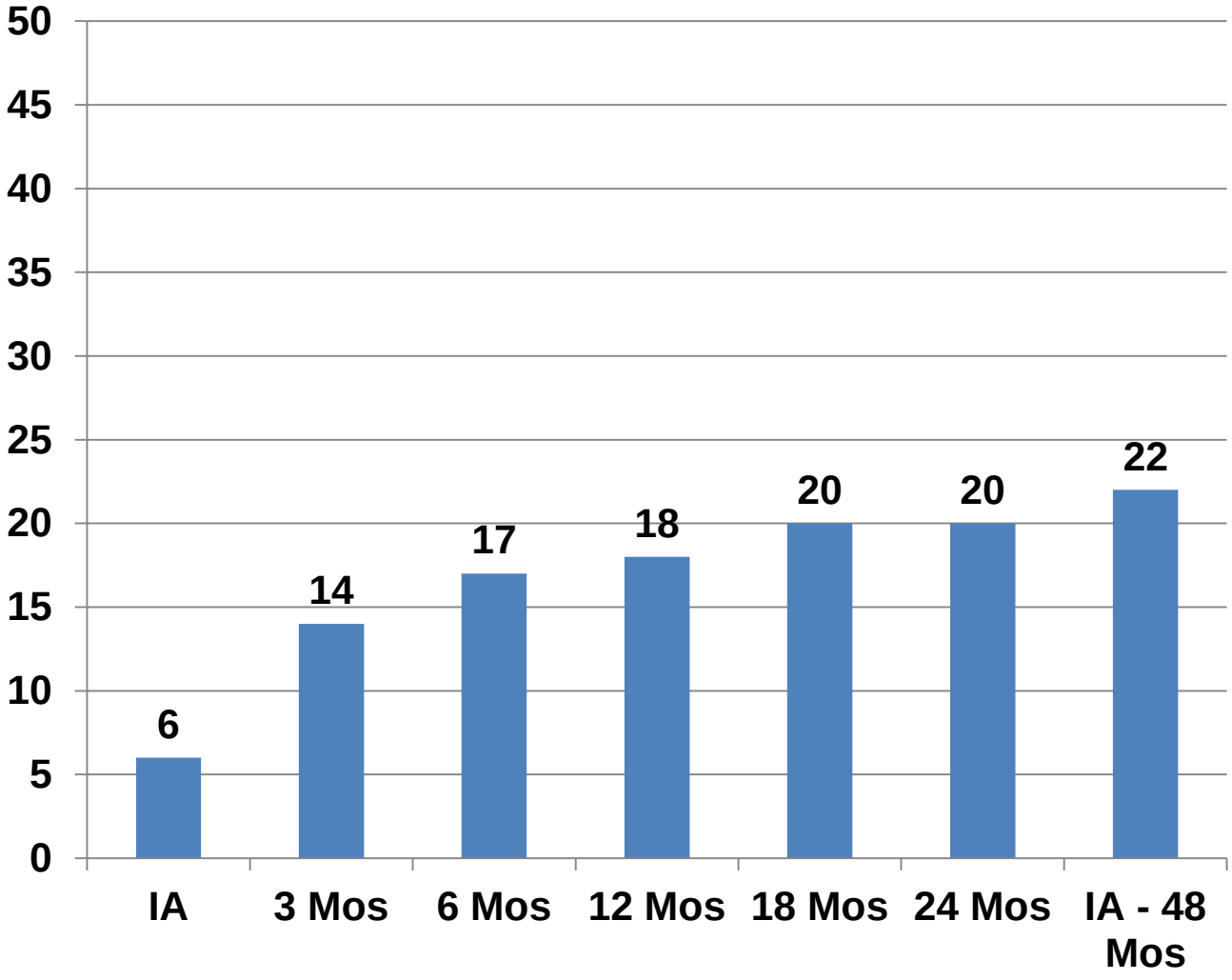


Electric Plus Acoustic

Everyday Use Outcomes:
Both Ears – Group 2 - Profound/Total Loss



Number of Subjects with Total/Profound



- 44% Profound/ Total Losses
- 17/22 at 6 months
- 5 additional post 6 months

Revision Cases

- 6 Subjects have undergone revision surgery as of today
  - 4 subjects were explanted and reimplanted with a cochlear implant (full array) as of the May 31 database closure
    - All 4 cases experienced profound/total low frequency hearing loss, dissatisfaction, and poor performance in the implanted ear
    - Straight-forward revision procedure
      - Not impacted by prior Hybrid implantation
    - Post-revision data for these four subjects demonstrates improved performance when compared to the subjects' preoperative and pre-revision scores
  - 2 additional subjects have been reimplanted after database closure

FDA was not provided data regarding two subjects reimplanted after database closure as part of the original PMA submission as data was not available until October 2013.

Potential Predictive Factors – Hearing Sensitivity

Outcome Measure	Gender P-value*	Age P-value*	Duration of Loss P-value*	Duration of Severe to Profound Loss P-value*	Etiology P-value*	Baseline CNC Score P-value*	Baseline AzBio Score P-value*
Change LFHL	**0.010**	0.160	0.722	0.275	0.970	0.450	0.900
Degree LFHL	**0.016**	0.088	0.536	0.581	0.949	0.910	0.264

*ANOVA p-value.

Summary – Hearing Sensitivity

- Hearing sensitivity is one of many measures used to assess outcomes in the Hybrid clinical study
- Assessment of residual hearing by:
  - Amount of hearing lost (pre to post change)
  - Degree of residual low-frequency hearing
- Those who maintain functional hearing (Group 1) are able to use A + E in the implant ear
- While 6 subjects underwent revision surgery due to poor performance/dissatisfaction, post-revision performance improved over hearing aids in the 5 subjects with data available
- Longitudinal low frequency PTA data supports stability beyond 6 months

Labeling and Post-Approval Summary

Sean Bundy

Director, Regulatory Affairs

Cochlear®

Labeling for Unilateral Use

- Current Cochlear Implant labeling is silent on bilateral vs. unilateral use
- Proposed Hybrid labeling is implicitly unilateral:
  - "The CNC word recognition score… in the contralateral ear will be equal to or better than that of the ear to be implanted"
- Explicit contraindication may unnecessarily constrain physicians' options when medically appropriate

Necessity for Hearing Aid Trial

- Subjects in trial had significant history of hearing aid use (average of 18+ years)
- Most subjects presented with hearing aids that were adequately fit and required no adjustment
- No subject was removed from candidacy through the hearing aid trial
  - Three subjects elected to continue with amplification and not pursue implantation

Access to Patients Under Age 22

- Historically, ‘adult’ cochlear implant indications have used 18 years of age
- There are no anatomical differences between an 18-year old and 22 year-old cochlea that support limiting the age
- Results in both standard length arrays and with the Hybrid L24 indicate good outcomes at younger ages
- No compelling reason to deny access to 18-21 year olds
- Only candidates who met the hearing loss profile would be candidates for the device
- Cochlear does not believe limiting use of the device to individuals 22 years or older is clinically necessary

Hybrid Post Approval Study Synopsis

Extended Duration

- Subjects from the original IDE study invited to participate
- Observation to 5 years
- Safety: Continue safety monitoring pre protocol
- Effectiveness: speech perception, hearing sensitivity and self assessments
- Data gathered at annual intervals

Newly Implanted

- 50 subjects, 18 years and up from up to 25 centers
- Observation to 3 years
- Safety: monitoring consistent with IDE protocol
- Effectiveness: speech perception, hearing sensitivity and self assessments
- Data gathered at initial activation, 6,12, 24 and 36 months postactivation

Post-Approval Study Questions

- Extended Duration
  - Impact of new CP900 features expected to be negligible
    - Will be deactivated during PAS testing
  - CNC and AzBio measures will be gathered at all intervening time points, primary endpoint will be 5 years
  - Historically, 5 years is longest time point for CI Study
- Newly Implanted
  - CNC and AzBio allow comparison to existing data; exhaustive additional measures can harm recruitment and retention
  - Modified DUQ allows for comparison to pivotal study – HUI included to assist in reimbursement decisions
  - Long-term retention studying commercial device can be problematic; 3 years is manageable, while still yielding long term data

Risk Benefit Assessment

J. Thomas Roland, Jr., MD
Lead Investigator
NYU Medical Center

Cochlear®

Risk Benefit Assessment

- Success in primary and secondary endpoints demonstrate objective improvement in perception:
  - Clinically significant improvement in mean CNC and AzBio scores in the implant ear
  - More than 75% of subjects experienced a significant improvement in speech understanding in both quiet and noise in the implant ear
- When evaluated in the everyday use condition (both ears), all subjects were equivalent or better with respect to speech performance

Risk Benefit Assessment

Subjective Benefits

- Significant benefit perceived by subjects across domains of hearing related to speech perception, spatial hearing, and sound quality domains
- Postoperatively, 79% of subjects reported being very satisfied or satisfied
  - Only 8% of subjects reported being satisfied or very satisfied preoperatively

Risk Benefit Assessment

Well-Characterized, Acceptable Risks

- Adverse events associated with surgery were consistent with those observed in comparable ear surgeries
- 44% of subjects experienced profound/total loss of hearing at some point during the study (IA-48 months)
- At the 6 month interval subjects with profound total loss demonstrated the following outcomes:
  - In the implanted ear, 15/17 (88%) scored the same or better on CNC Words, and 11/17 (65%) scored the same or better on AzBio Sentences
  - In the implanted ear, 8/50 subjects did not show improvement in speech perception and tended to be dissatisfied
  - In Everyday Use, all subjects scored the same or better on both CNC words and AzBio sentences

Risk Benefit Assessment

Analysis

- The Hybrid L24 Implant provides a better treatment option than amplification alone for suitable candidates with high frequency hearing loss
- The majority of subjects were able to combine high frequency information provided by the Hybrid L24, not available via acoustic hearing aids alone, with low frequency acoustic information from one or both ears
- Benefits of implantation with the Hybrid Cochlear Implant System outweigh associated risks
- Appropriate labeling will allow counseling regarding the risks and benefits of the treatment

Conclusions

- The study met all primary and secondary efficacy endpoints with no Unanticipated Adverse Device Effects
- The Hybrid L24 Implant System is an integrated electric-acoustic (EAS) solution, a new option for a patient population that currently has few therapeutic alternatives
  - Improved speech perception in quiet and in noise was observed beyond that seen historically with CI, particularly when functional hearing was maintained in the implant ear and both ears
- Most subjects reported being very satisfied or satisfied with the hybrid implant

Conclusions

- The data in this application demonstrate a reasonable assurance of safety and effectiveness for individuals meeting indications for the device
- Results support the conclusion that the benefits of the Hybrid L24 Implant System outweigh the risks for individuals meeting indications for the device

Backup Slides Shown

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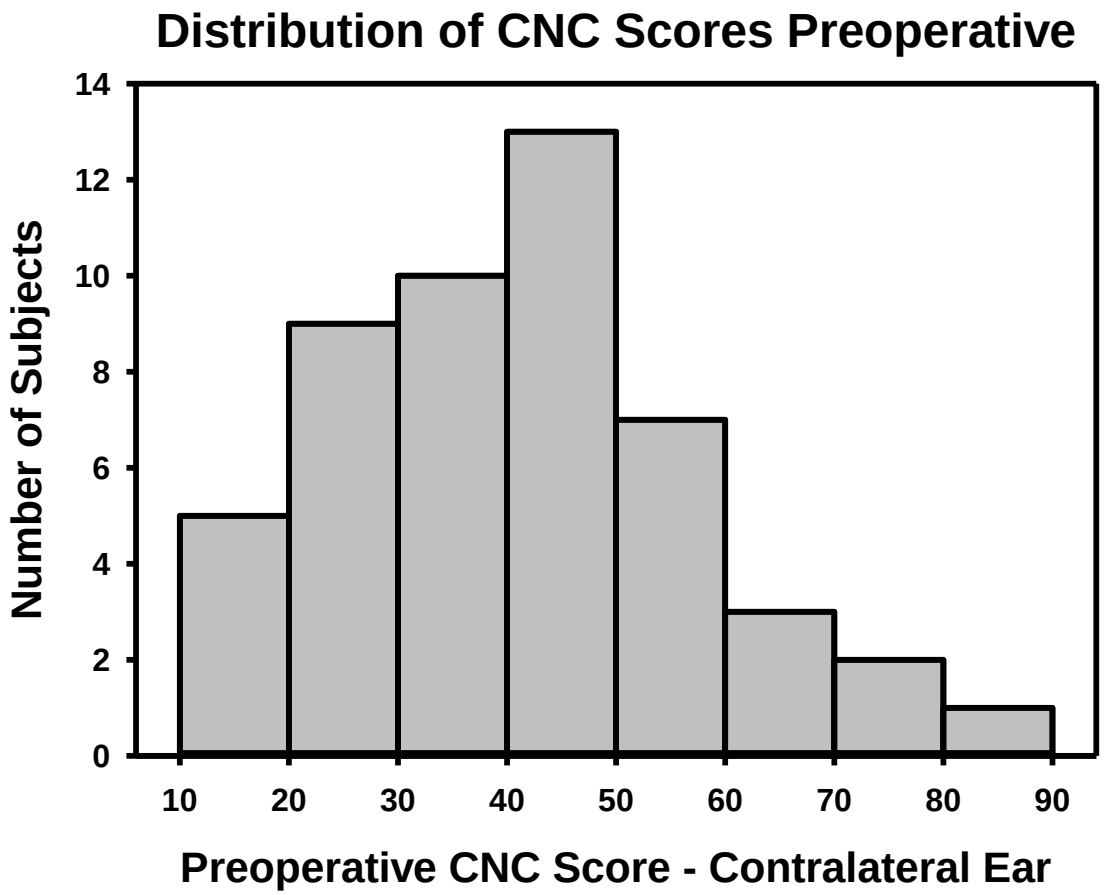
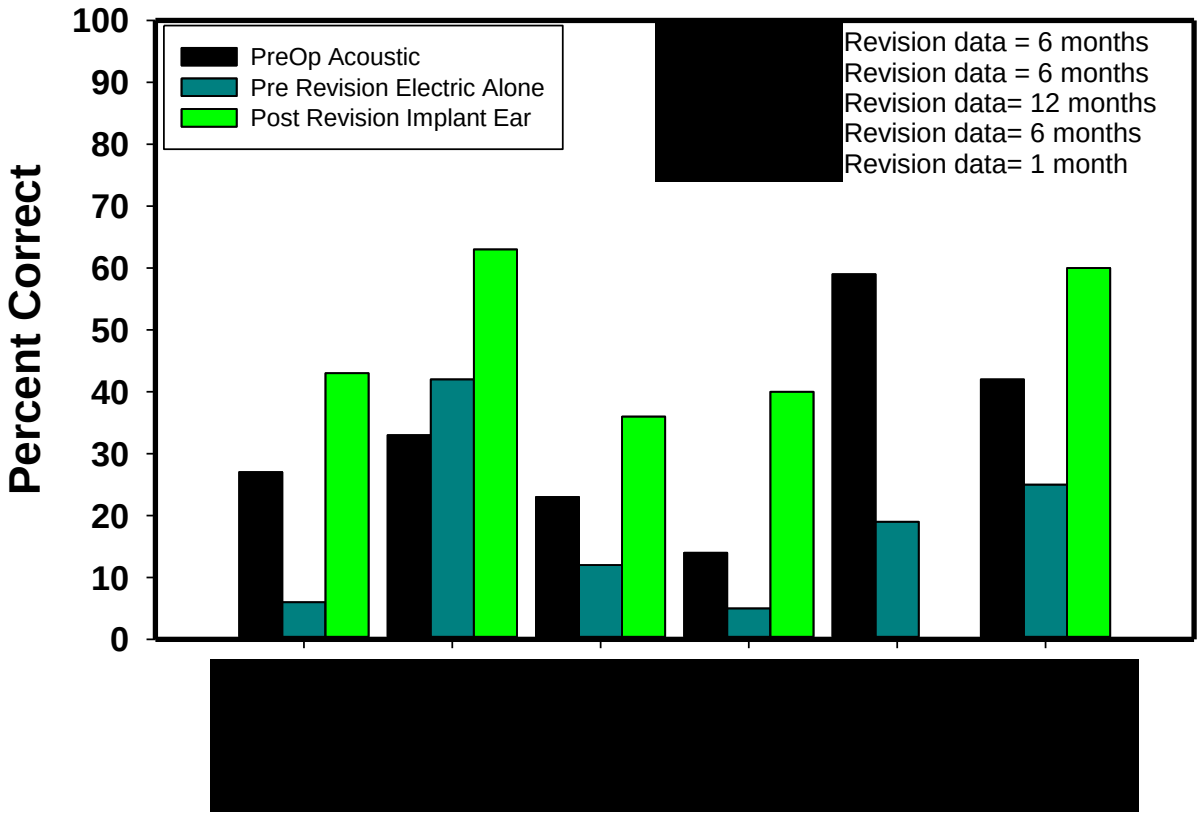
Distribution of CNC Scores Contralateral Ear

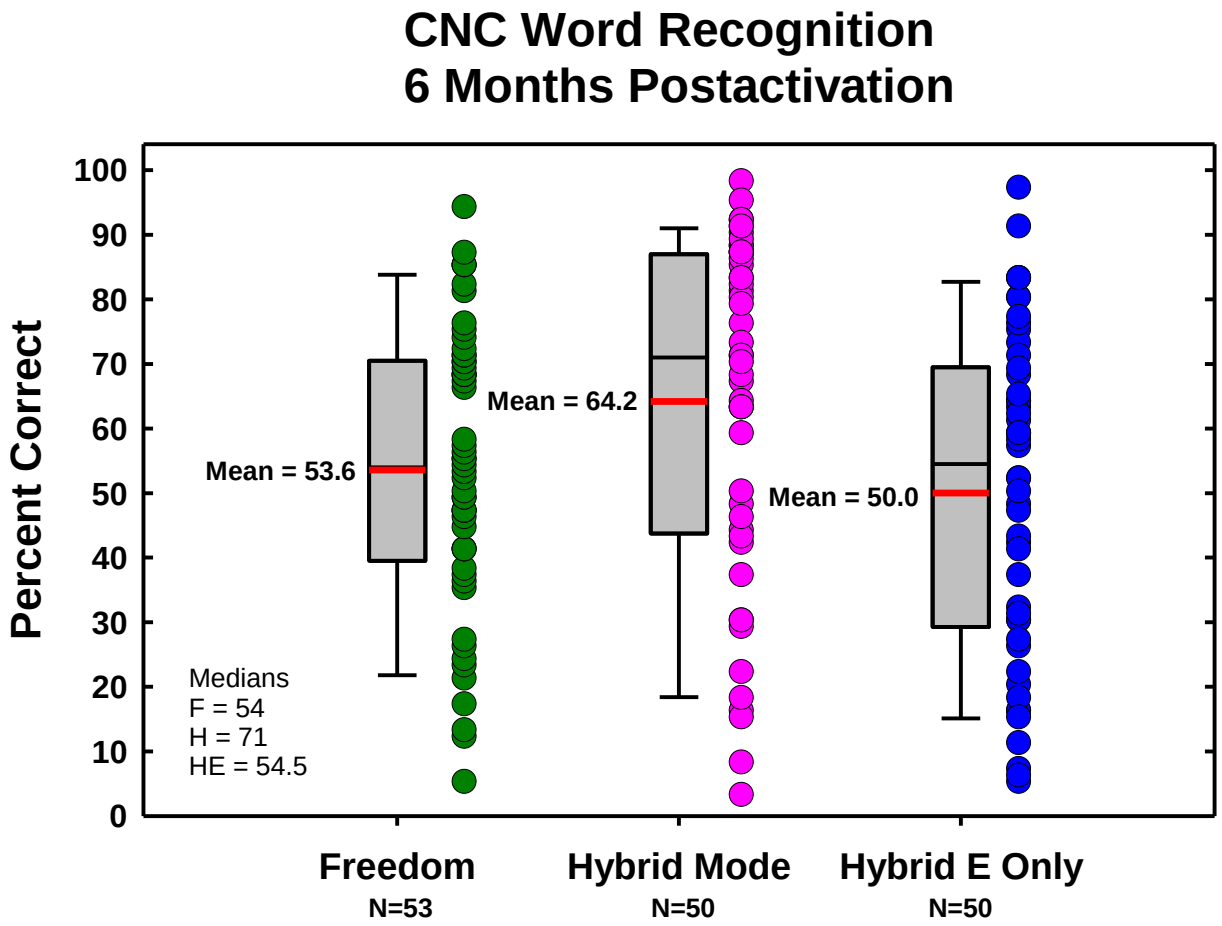


Post Revision Results: CNC Words Implant Ear



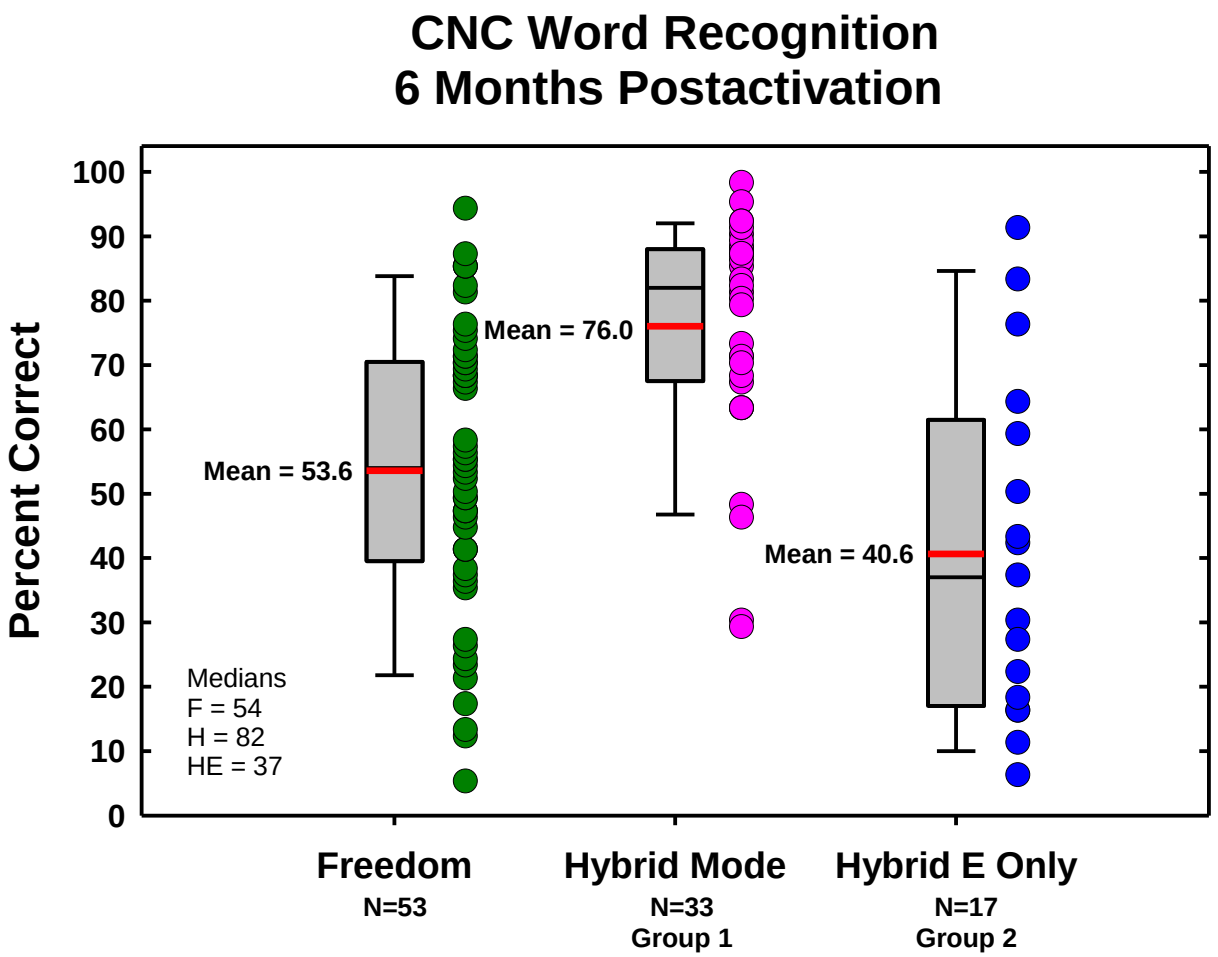
S: Significant improvement post revision CI Alone compared to both preop. Acoustic alone and pre-revision Hybrid score

Freedom vs. Hybrid CNCs



Hybrid Mode > Freedom p = 0.01
Hybrid Mode > Hybrid E Only p < 0.001
Freedom vs Hybrid E NS

Freedom vs. Hybrid CNCs – Gp 1 & 2

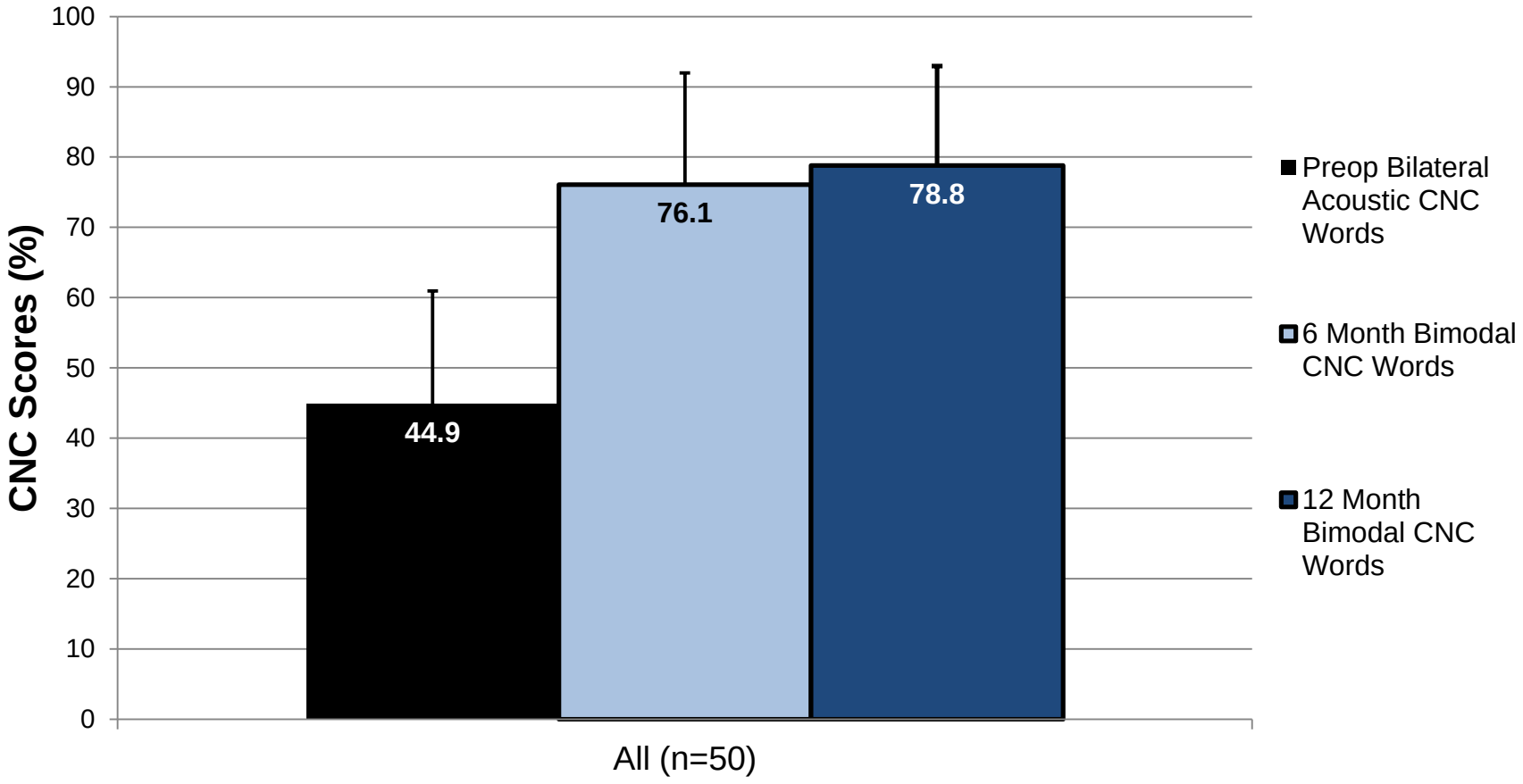


Hybrid Mode > both CI conditions ($p < 0.001$)
Freedom vs Group 2 NS

Subjects Preoperatively Satisfied with Hearing Aids

Subject ID	Preop Acoustic Alone CNC Words	6 Month Hybrid CNC Words	12 Month Hybrid CNC Words	Preop Satisfaction	6 Month Device Satisfaction	12 Month Device Satisfaction
[redacted]	40.0	70.0	66.0	Satisfied	Dissatisfied	Very Dissatisfied
	59.0	18.0	16.0	Very Satisfied	Dissatisfied	Neutral
	33.0	76.0	61.0	Satisfied	Very Satisfied	Very Satisfied
	48.0	80.0	80.0	Very Satisfied	Very Satisfied	Very Satisfied

Bimodal Results Over Time



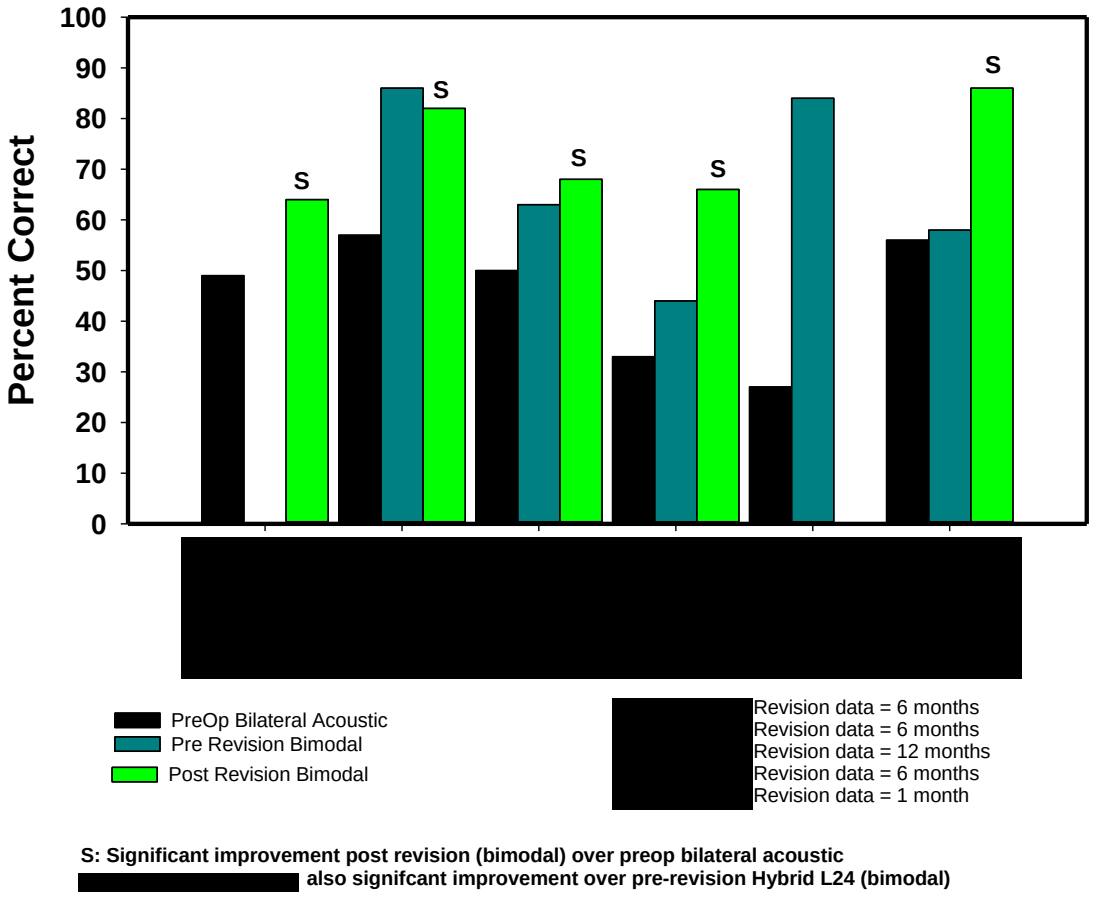
Univariable and Multivariable Models for Change in LFHL

Subject Characteristic	Univariable		Multivariable	
	Estimate	P-value	Estimate	P-value
Gender	-19.6	0.008	-15.6	0.047
Age	0.50	0.052	0.39	0.178
Duration of hearing loss	0.12	0.637	-0.19	0.522
Duration of severe hearing loss	-0.29	0.580	-0.60	0.262
CNC Words	0.29	0.266	0.48	0.093
Low-frequency hearing threshold	0.48	0.203	0.89	0.032

Analysis similar to FDA analysis for speech perception (includes LOCF imputation)

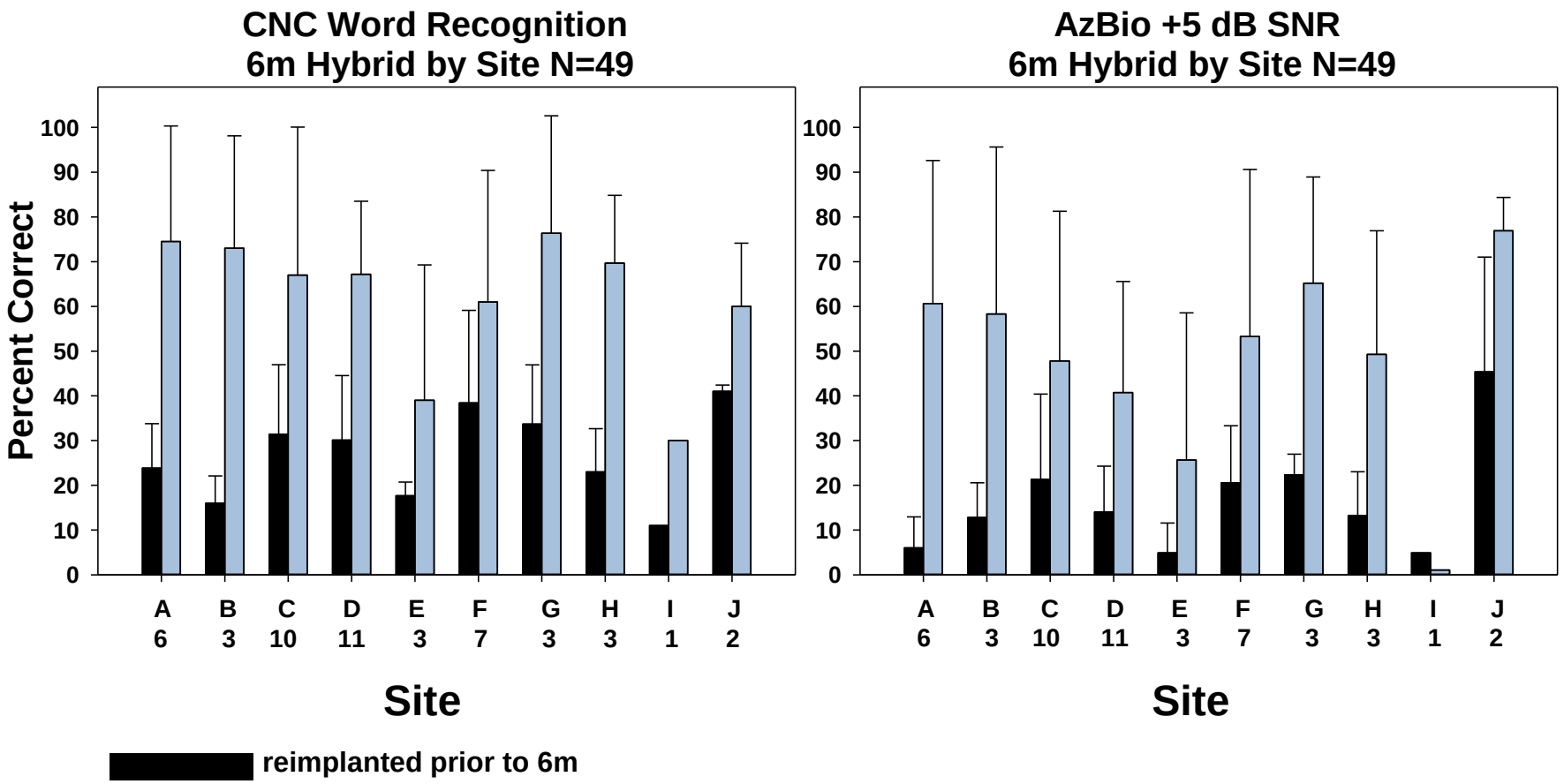
Results indicate gender most consistent predictor

Post Revision Results: CNC Words Bimodal Condition

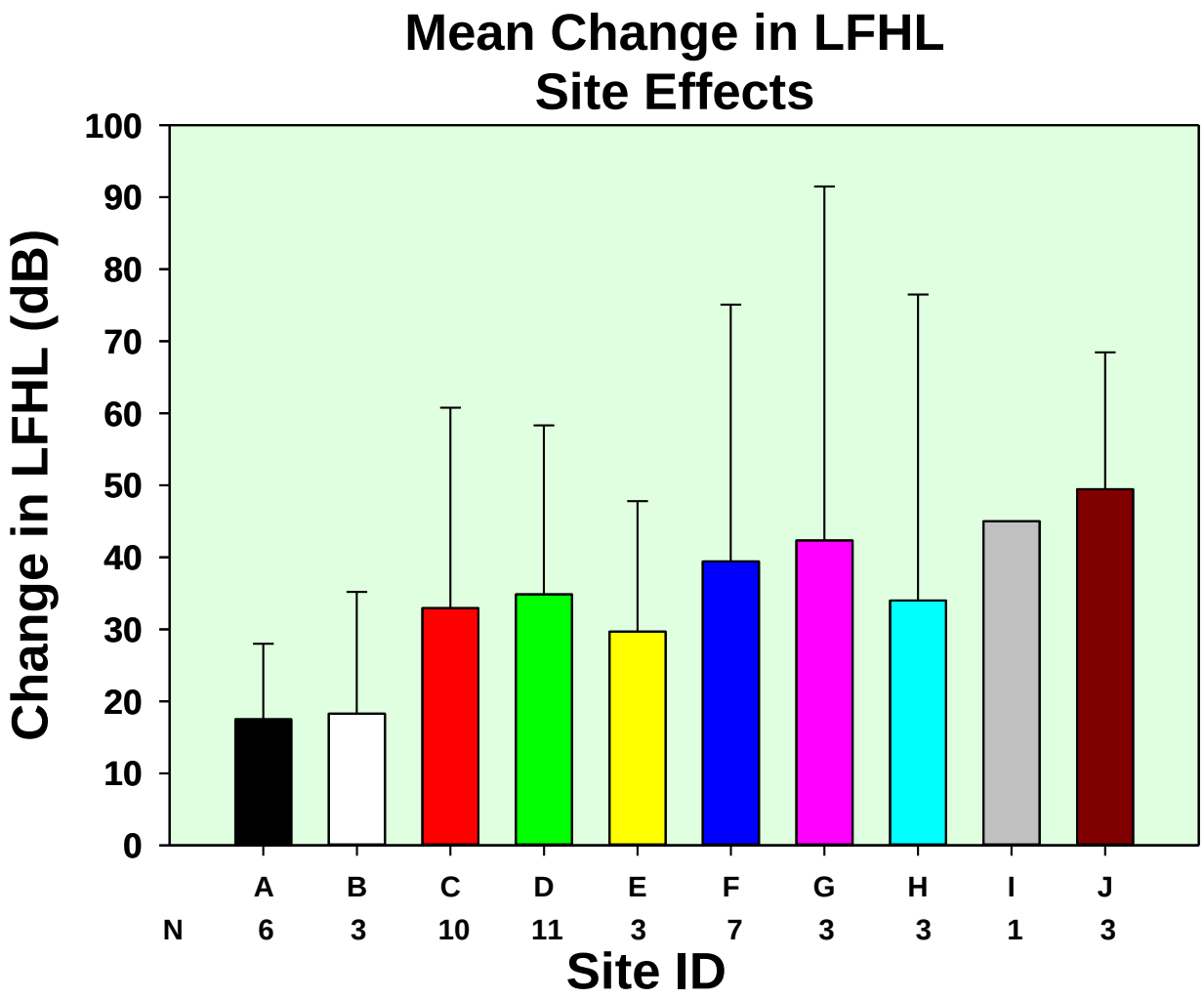


S: Significant improvement post revision (bimodal) over preop bilateral acoustic
also signifcant improvement over pre-revision Hybrid L24 (bimodal)

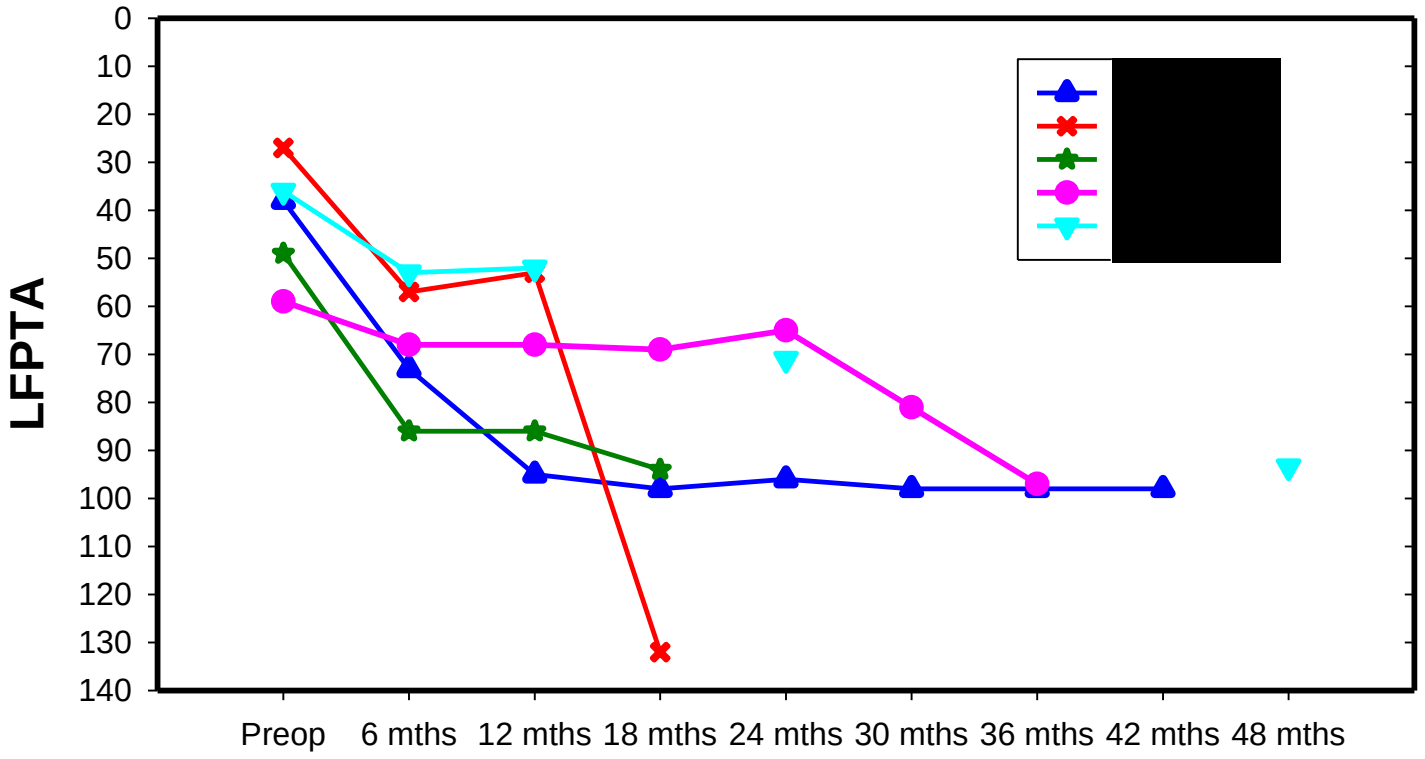
Figure 14: Mean pre- and postoperative CNC and AzBio sentences-in-noise scores for the implanted ear by site



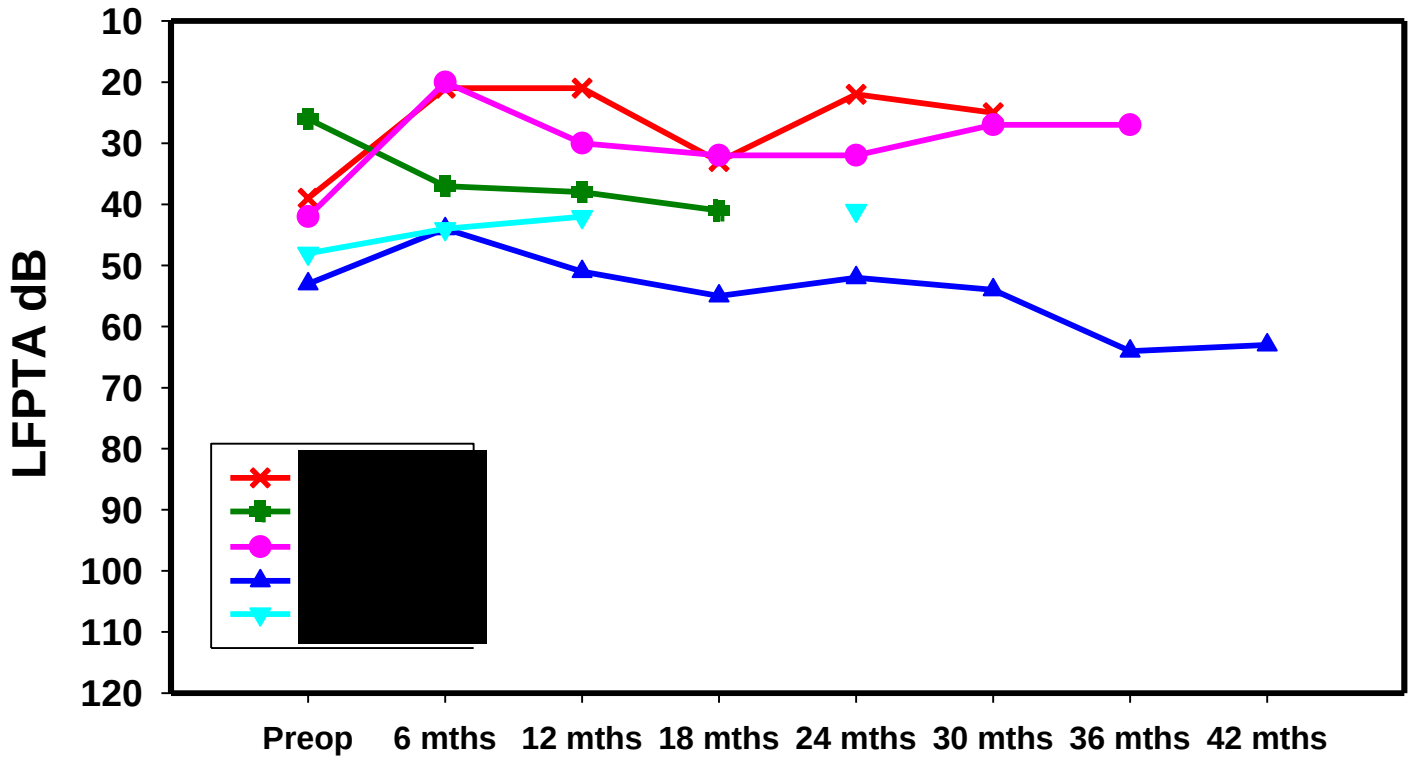
Hearing Sensitivity by Site



Hearing Profiles Implant Ear



Hearing Profile Contralateral Ear



Summation

Bruce Gantz, MD
Principal Investigator
University of Iowa

Cochlear®

Unmet Need

- Individuals experience significant hearing difficulty and fail in their social and work environments
- The Hybrid L24 Implant provides a better treatment option than amplification alone for suitable candidates with high frequency hearing loss
- Presently this population has no treatment options

Original Questions

- Based on inadequate treatment options and clear patient need the following questions arose:
  - Can we expand electrical speech processing to more of the hearing impaired population?
  - Is there a downside to implanting those with more residual hearing?
  - What are the advantages of preserving residual auditory function?
    - Spatial Hearing
    - Quality of Sound and Music
    - Hearing in Noise

Outcomes

- In the everyday (combined) condition
  - All patients are the same or better with this treatment
  - All those with functional acoustic hearing (Group 1 - <90dB PTA) receive the same benefit regardless of the magnitude of the change in hearing
  - Those without functional acoustic hearing (Group2 - >90dB PTA) are benefiting from the Hybrid Implant in the bimodal condition
- Risk benefit is a discussion between the clinician and the patient