Hearing Loss and Usher Syndrome

Kathleen Sie, MD

Professor, Otolaryngology Head and Neck Surgery
University of Washington
Director, Childhood Communication Center
Seattle Children's Hospital

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Seattle Children's
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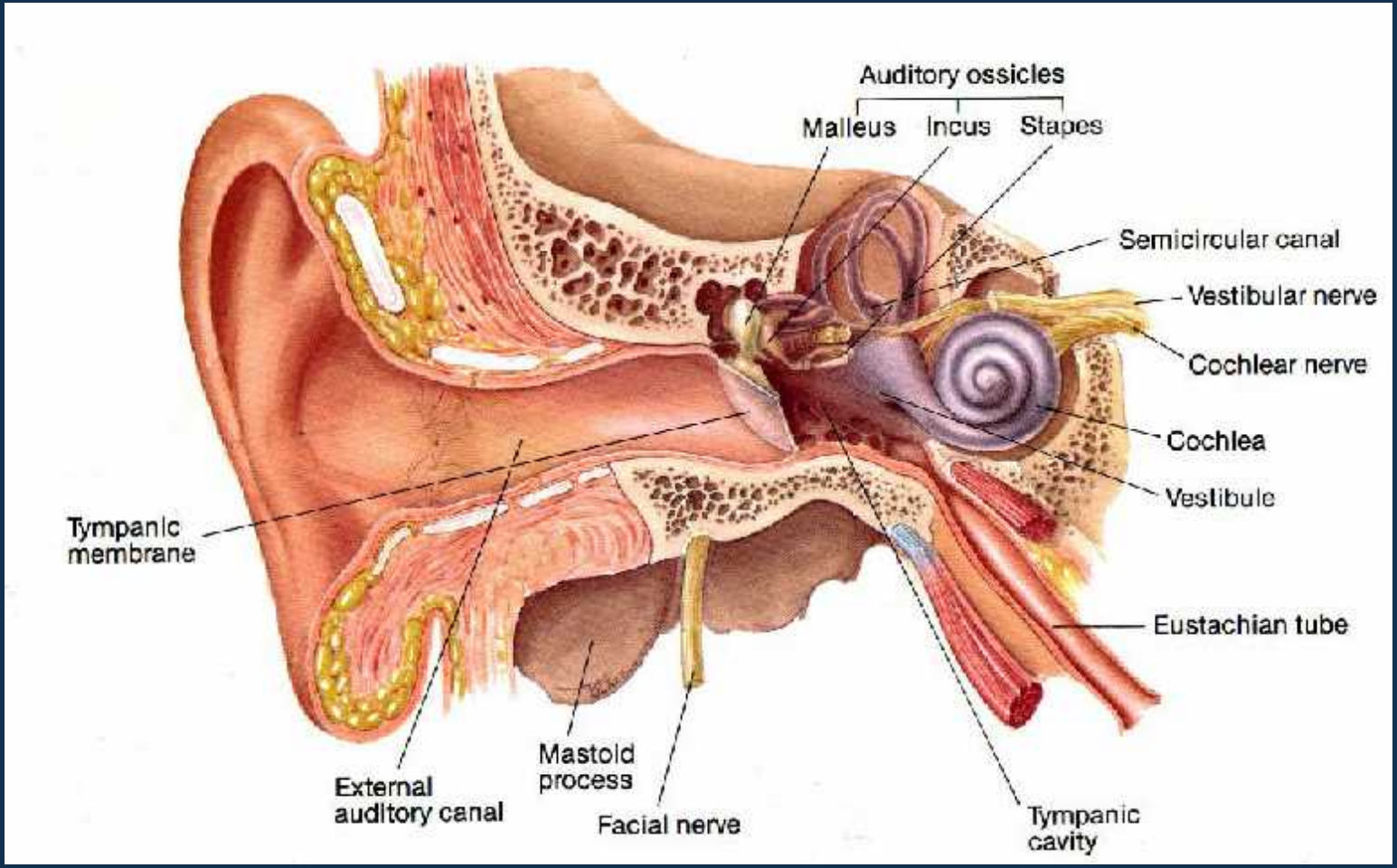
Overview

- **Childhood hearing loss**
  - Review of auditory system
  - How we measure hearing
  - Medical evaluation
- **Usher Syndrome and hearing loss**
  - **Classification**
  - **Genetic causes**
  - **Treatment**

Ears and Hearing 101



How the ear functions – microscopically

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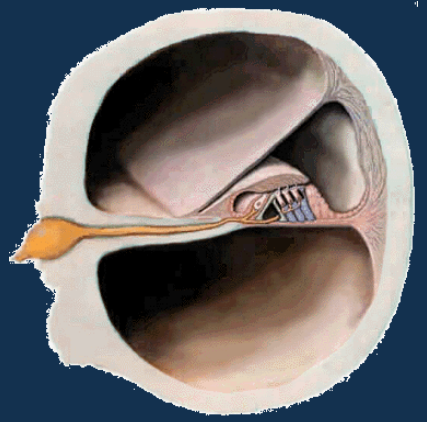

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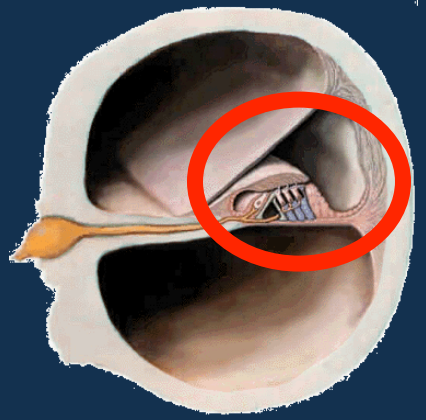

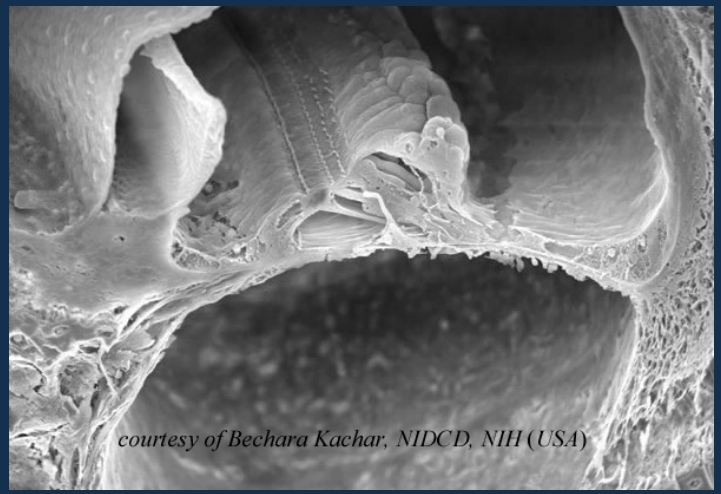

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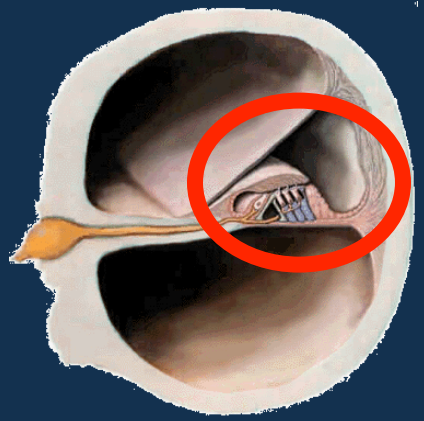
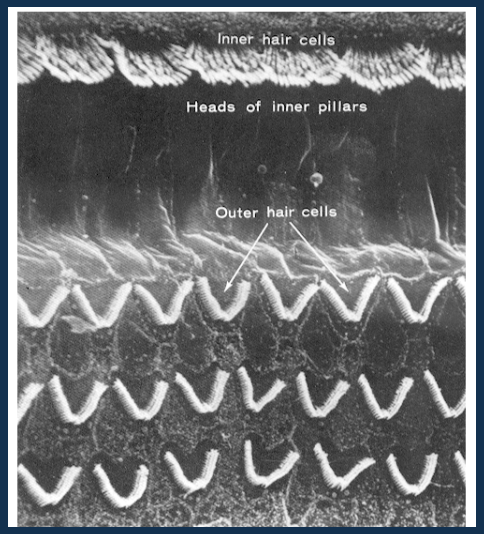
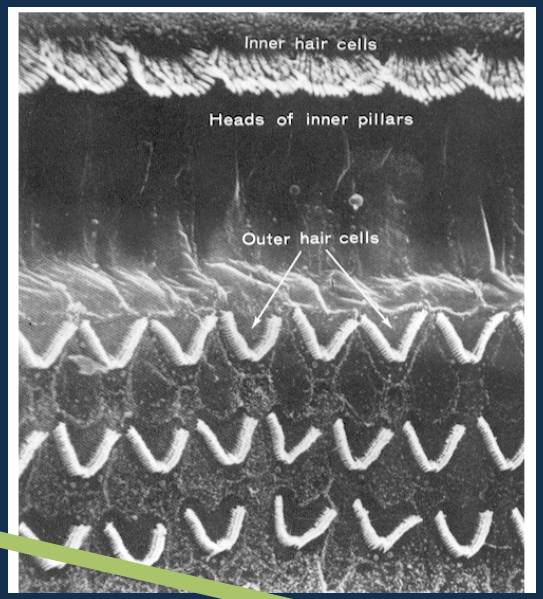
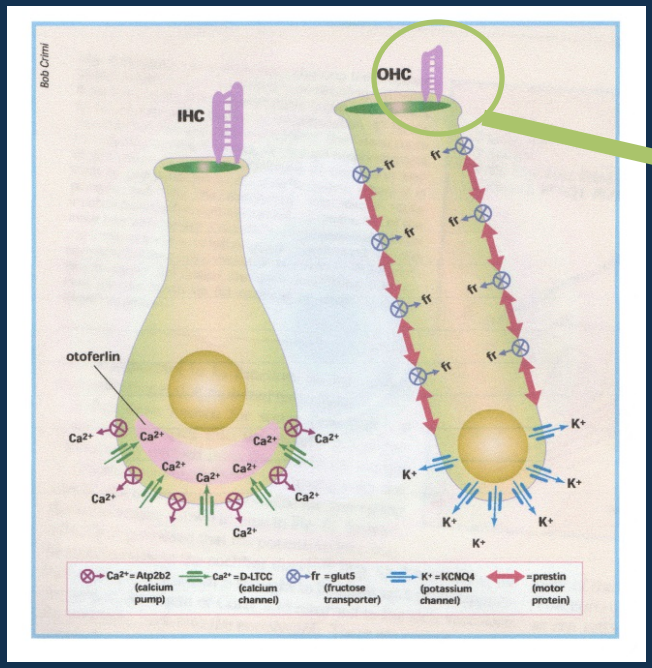
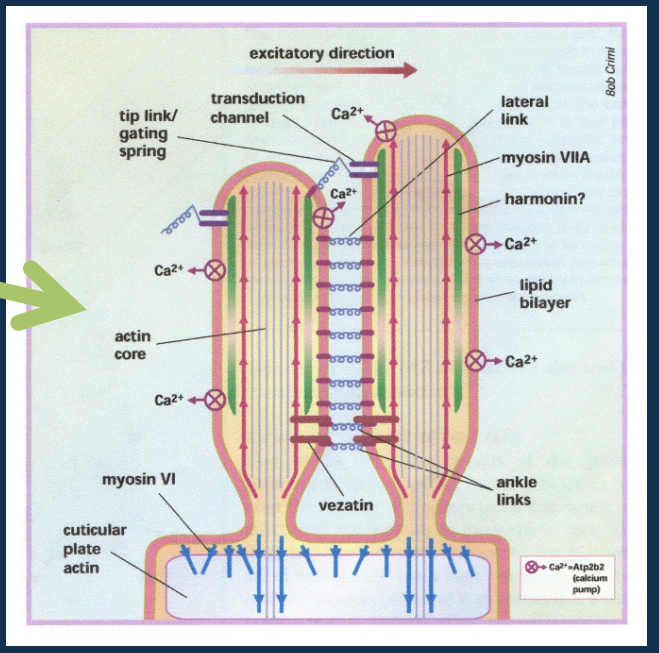




How the ear functions – hair cells





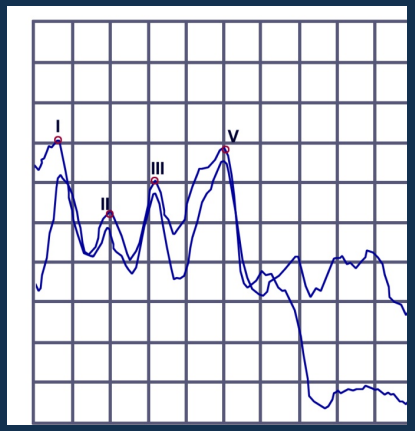


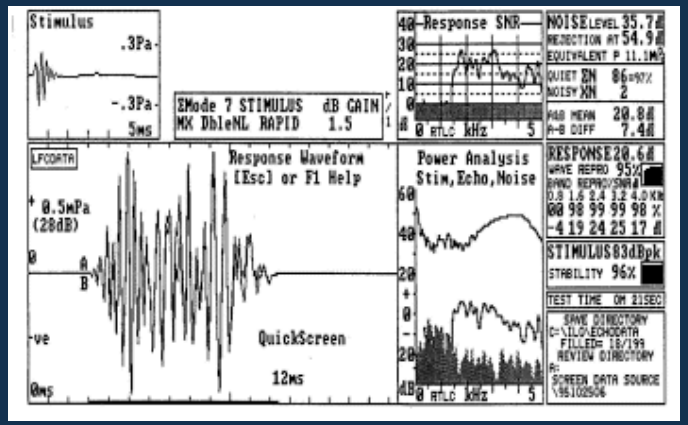
Milestones in diagnosis of childhood hearing loss

- **1960's** Auditory brainstem response testing
- **1980s** Automated auditory testing
  - ABR and EOAE
- **1999** Walsh Bill
- **2000's** Early Hearing loss Detection and Intervention (EHDI)
  - Screening by 1 month
  - Diagnosis by 3 months
  - Intervention by 6 months

How we measure hearing

Type of test	Requirements	Advantages	Disadvantages
Physiologic tests **ABR, BSER, BAER** **EOAE**	Sleep or quiet	-Ear specific responses -Does not require patient cooperation -Correlates well with behavioral responses	-Requires sedation over 6 months of age -Physiologic response





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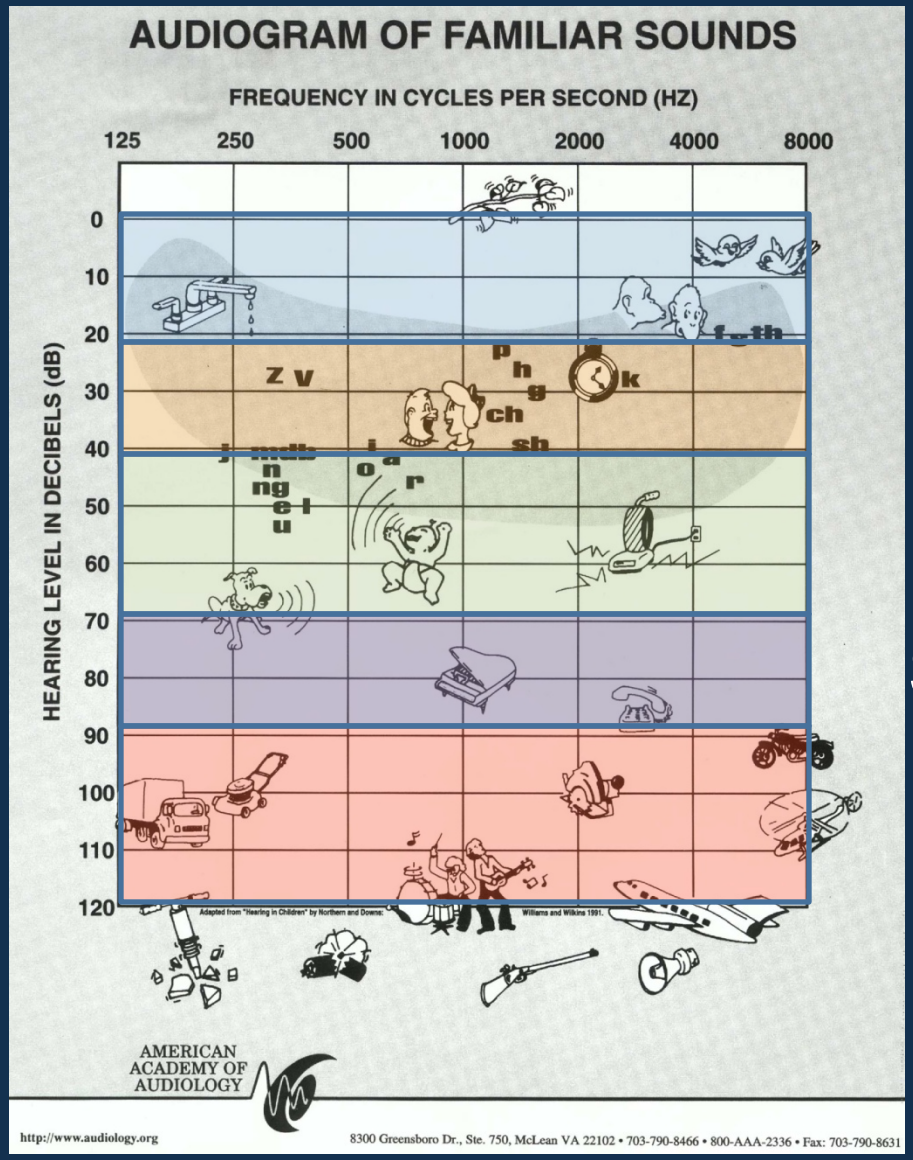
Behavioral • **VRA-**visual reinforced • **CPA-** conditioned play • **CA-** conventional	>6 months old Cooperative	Gold standard for assessment of hearing	Patient must be developmentally ready

Audiograms 101



NORMAL

MILD

MODERATE

SEVERE

PROFOUND

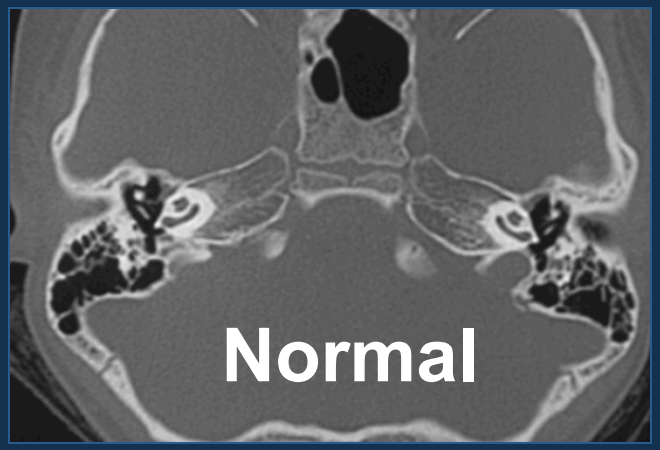
Medical evaluation of childhood hearing loss

- **History**
- **Physical examination**
- **Characterization of hearing loss**
- **Imaging studies**
  - CT and/or MRI scans
- **Tests for causes of hearing loss**
  - CMV testing
  - Genetic tests

Medical evaluation of childhood hearing loss

- **Tests to look for associated problems**
  - Balance testing
  - Ophthalmologic evaluation
  - Electrocardiogram
  - Renal ultrasound
  - Thyroid function studies
  - Electroretinogram
  - Others

CT scans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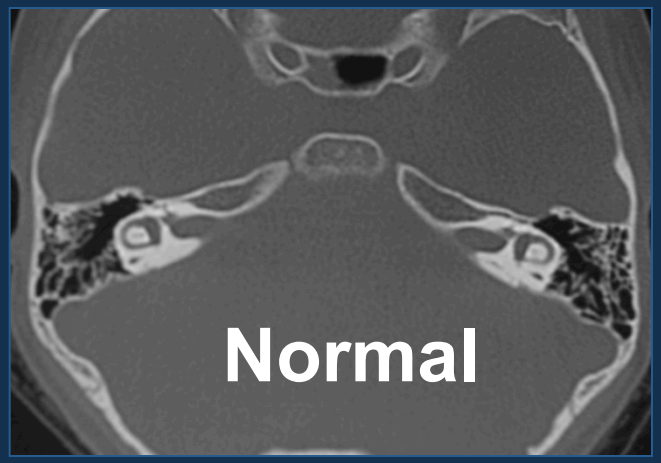
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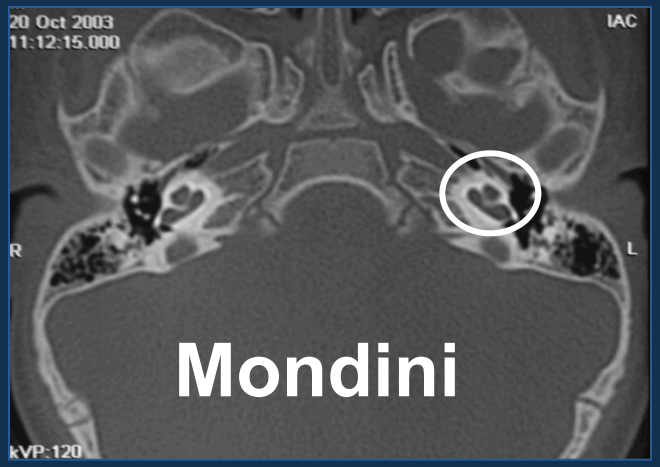
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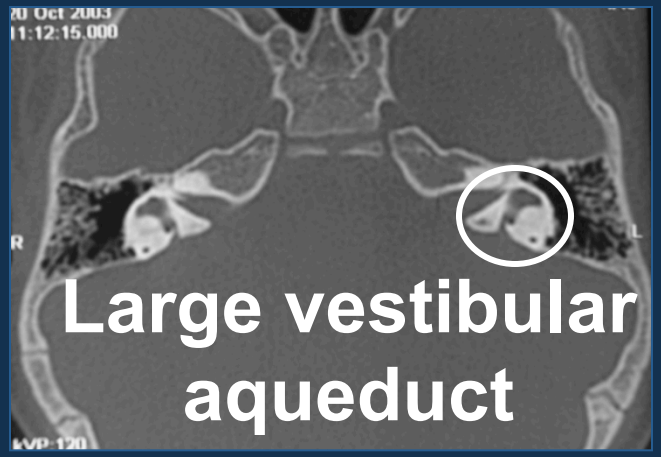

Large vestibular aqueduct

Evaluation of children with hearing loss

- CMV testing
  - Infants
  - Need to get specimen from first 3 wks of life
- Genetic testing
  - Single mutation analysis
  - Next Gen Sequencing

Management of children with hearing loss

Exposure to language

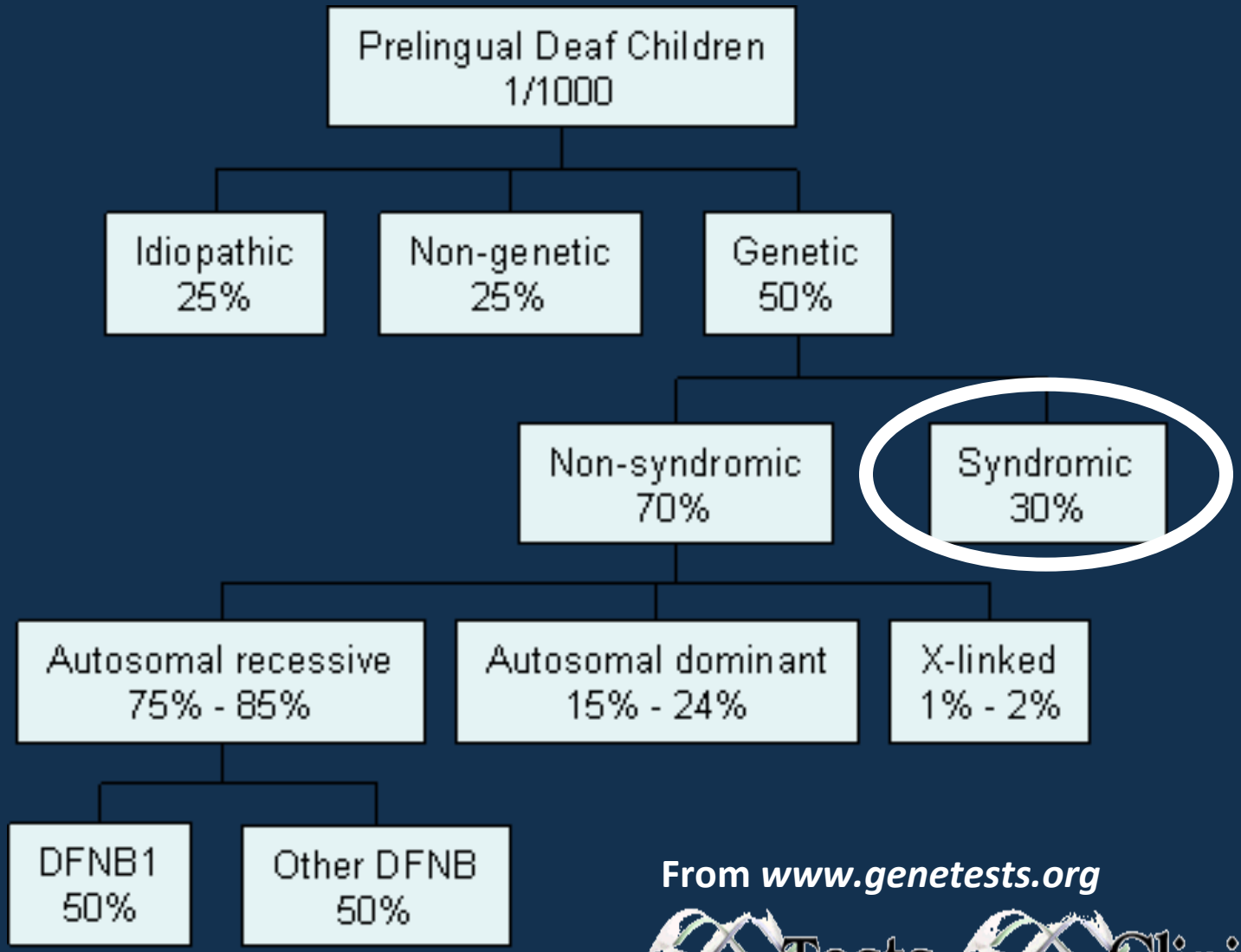
Early intervention

Amplification

- Hearing aids
- Cochlear implants
- FM systems

School accommodations

Childhood Hearing Loss



From *www.genetests.org*

GENETests · GENEClinics

Hearing loss and Usher syndrome

- **CHILDHOOD HEARING LOSS IN USA**
  - 1-3/1000 newborns have severe to profound HL
  - 2-5/1000 newborns have milder degrees of HL
  - Over 95% of children with hearing loss have parents with normal hearing.

Hearing loss and Usher syndrome

- **USHER SYNDROME ACCOUNTS FOR**
  - About 1:25,000 in USA
  - 3-6% of children with hearing loss in USA*
  - 50% of people with deaf-blindness in USA
  - Most common recessively inherited form of syndromic hearing loss

Diagnosis of Usher syndrome

- Family history
- Congenital bilateral profound hearing loss and bilateral vestibular areflexia (US 1) *
- Retinitis pigmentosa **
- Clinical presentation

Diagnosis of Usher Syndrome

- Genetic testing (11 loci on 9 different genes)
  - Otochip
  - Otoscope
- Other tests: vestibular testing and ERG

Hearing loss and Usher Syndrome

US Type	Hearing	Balance	Vision	Genes*
Type I B,C,D,E,F,G,H,J,K	Congenital Bilateral Profound	Congenital Bilateral Areflexia	RP Progressive loss	*MYO7A, CDH23, PCDH15, USH1C, USH1G*
Type II	Congenital Bilateral Moderate to severe	Normal	RP Adolescent to adult onset	*USH2A, GPR98, DFNB31*
Type III	Postlingual Bilateral Progressive	Variable Progressive	RP Late onset	*CLRN1*

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* All these genes have also been described with nonsyndromic HL

The John and Marcia Carver Nonprofit Genetic Testing Laboratory, U of Iowa

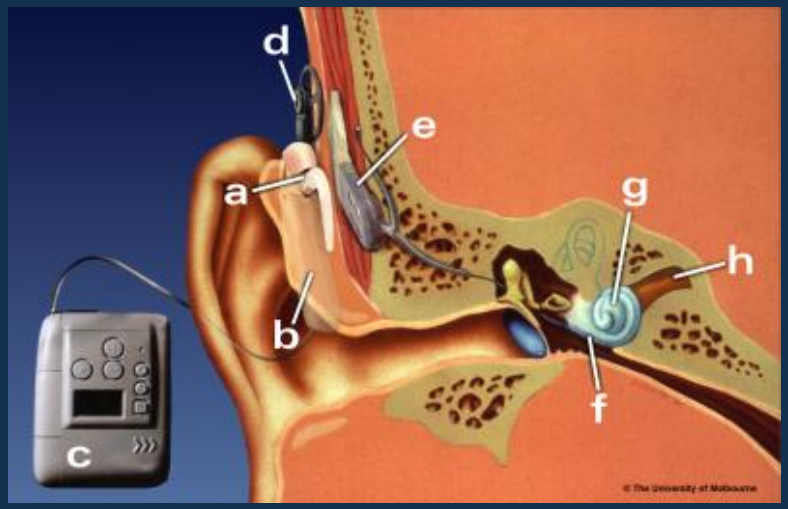
Disorder	Mode of Inheritance	Gene(s)	Cost	Estimated Turnaround	Methodology	CPT Codes
Usher Syndrome	Autosomal Recessive	CDH23, CLRN1, MYO7A, PCDH15, USH1C, USH1G & USH2A	First Tier Testing $575	8-10 weeks	Allele-Specific Testing Followed by Conventional Sequencing	81400, 81407, 81408, 81479
			Second Allele Testing $575-$1,626	10-12 weeks	Conventional Sequencing	81400, 81407, 81408, 81479
		ABHD12, CDH23, CIB2, CLRN1, DFNB31, GPR98, HARS, MYO7A, PCDH15, USH1C, USH1G & USH2A	Exome Testing $2200	14-16 weeks	Allele-Specific Testing Followed by Conventional Sequencing and Next Generation Sequencing	81400, 81407, 81408, 81479

Treatment for Usher syndrome

- **EXPOSURE TO LANGUAGE**
- Early intervention
- Support for vision impairment
- Psychosocial support
- Exposure to spoken language
  - Amplification
  - Cochlear implantation

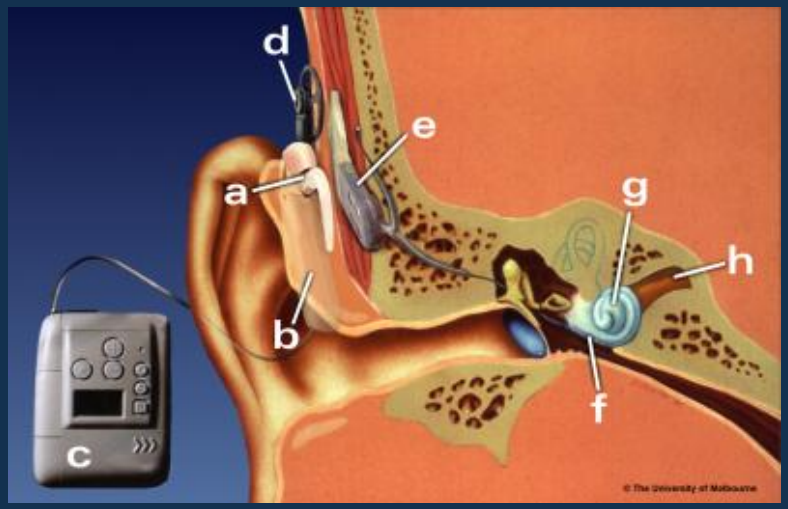
Cochlear implantation

- Indications/guidelines
  - No significant speech benefit from appropriately fit hearing aids
  - 12 months of age
  - Absence of medical contraindications

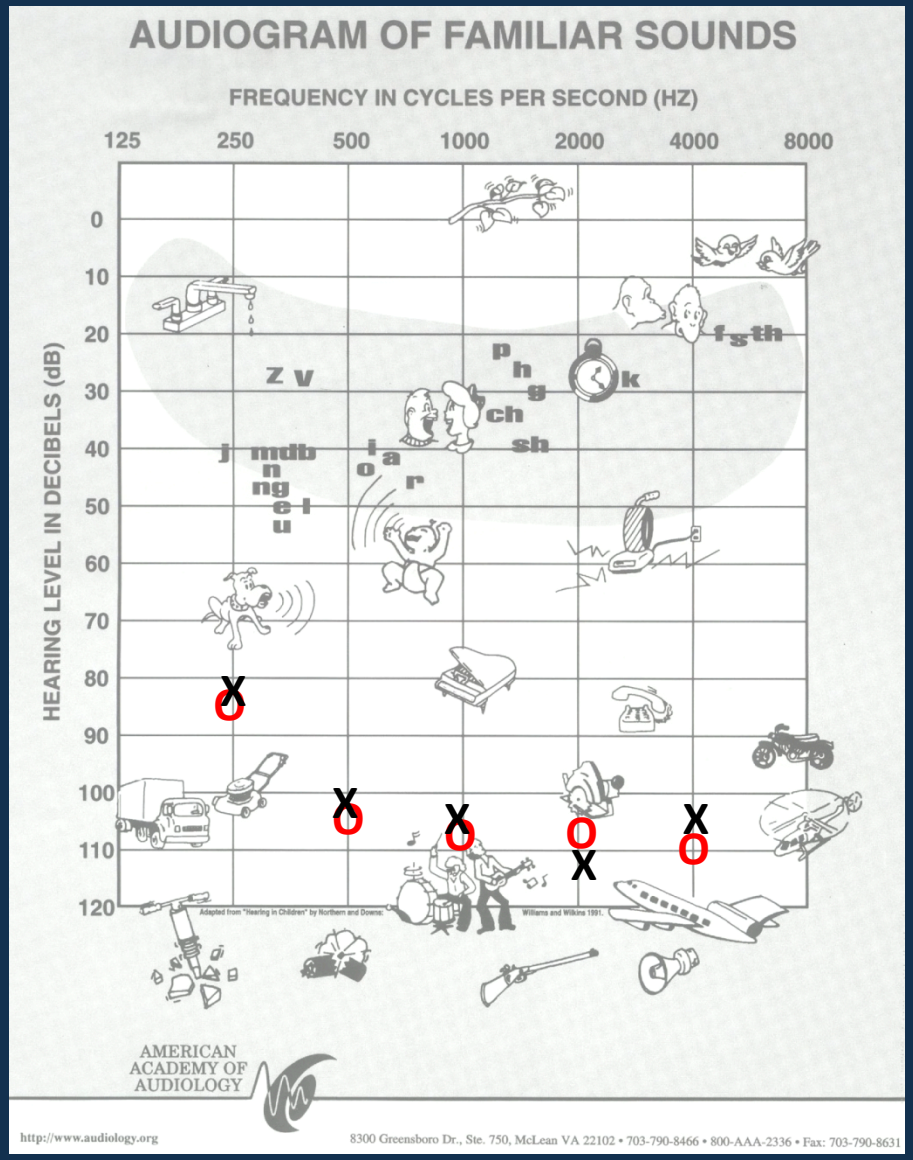


Cochlear implantation

- Emerging trends in CI
  - Earlier age
  - Lesser degrees of HL
  - Hearing preservation surgery

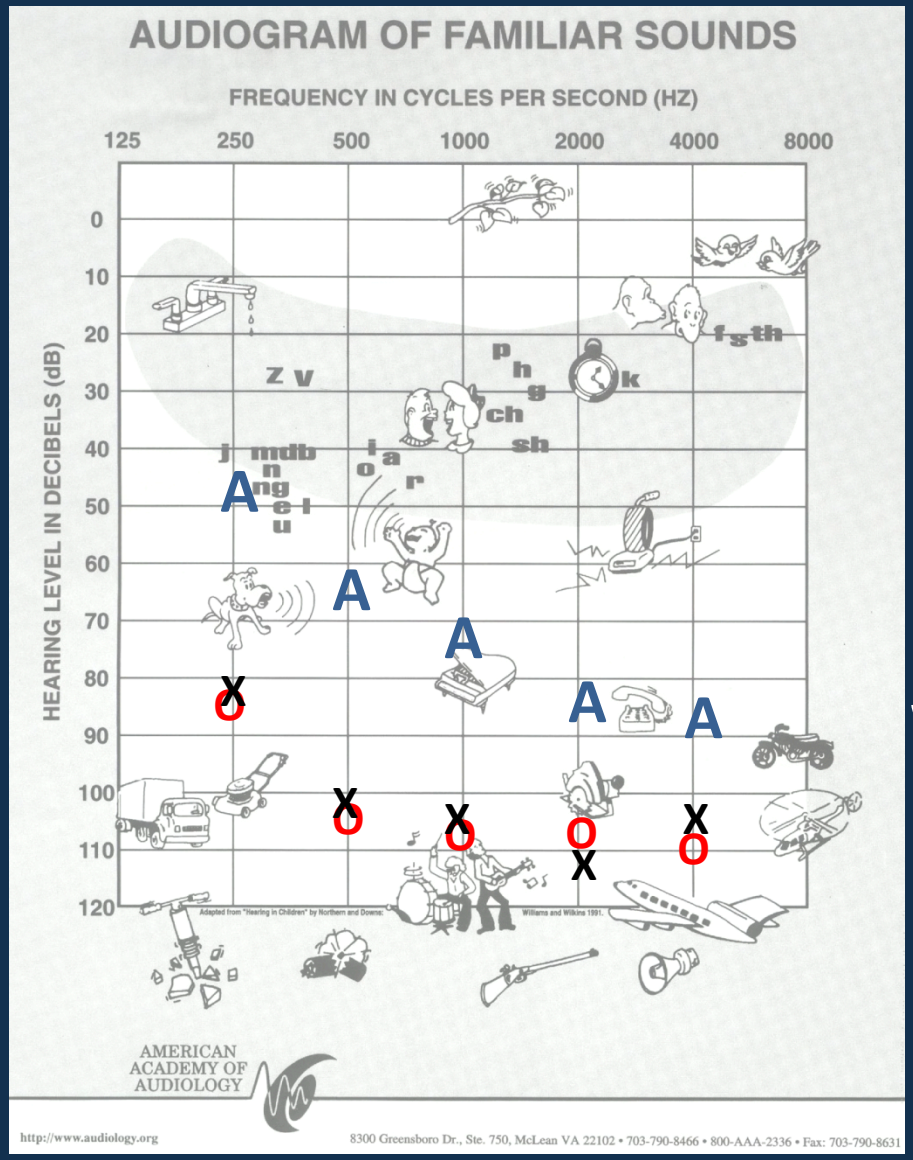


Hearing loss and US1



PROFOUND

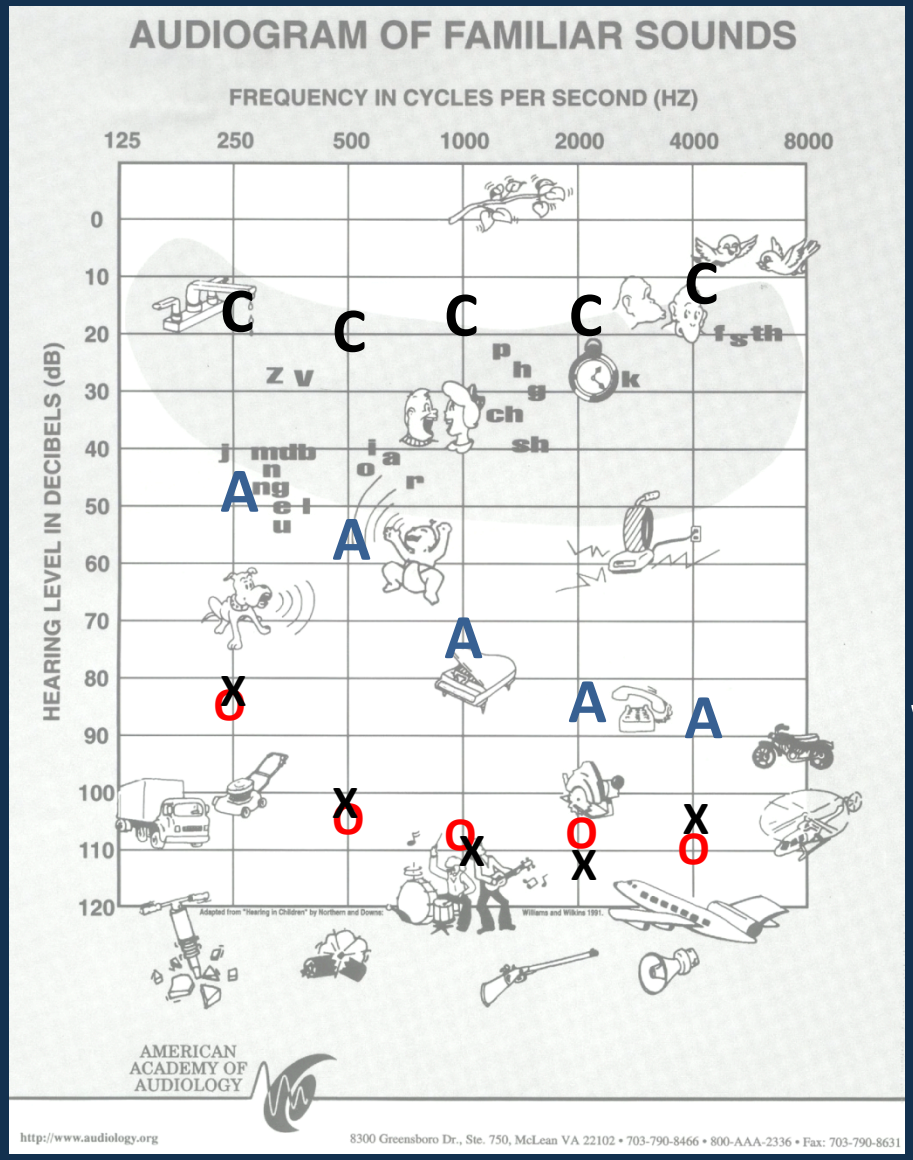
Aided hearing and US1



SEVERE

PROFOUND

CI responses and US 1



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Usher syndrome and hearing loss

- Genetic therapies for US hearing loss are not yet available for humans.

- Understanding the molecular mechanisms of hearing loss will pave the way for biologic interventions.

On the horizon…

- Usher Type 3
  - Mutation affects production of clarin-1
  - Abnormal protein does not reach cell membrane
  - Abnormal protein degraded
  - Research group aimed to stabilize clarin-1
  - Compound BF844

Alagramam, et al. A small molecule mitigates hearing loss in a mouse model of Usher 3. Nat Chem Biol 2016: 12 (6):444-451.

Summary

- Identification of Usher Syndrome in children with hearing loss:
  - Diagnosis is based upon clinical findings.
  - Genetic testing has an important role.
  - Work with hearing health care team.
  - Early diagnosis will be important.

- Treatment options will improve with our understanding of molecular mechanisms of hearing loss.

Questions?

kathysie@uw.edu