Role of the Otolaryngologist in EHDI:
Etiologic Testing, Medical and Surgical Care, and Multidisciplinary Collaboration

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EHDI 2019 – Chicago, International D/E
2:15 – 3:15 pm, Monday, March 4, 2019

Children's MINNESOTA

UCSF Benioff Children's Hospital San Francisco

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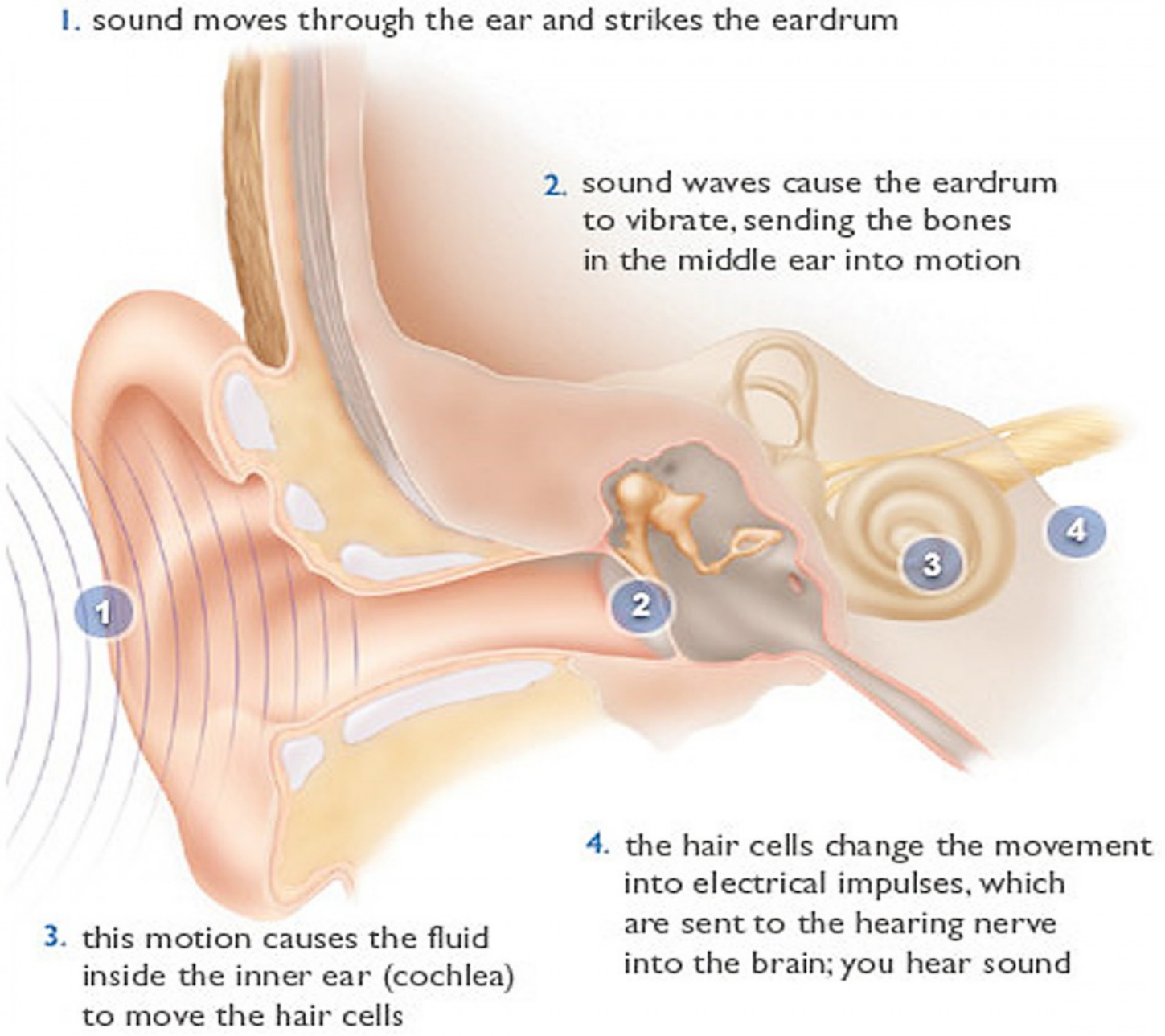
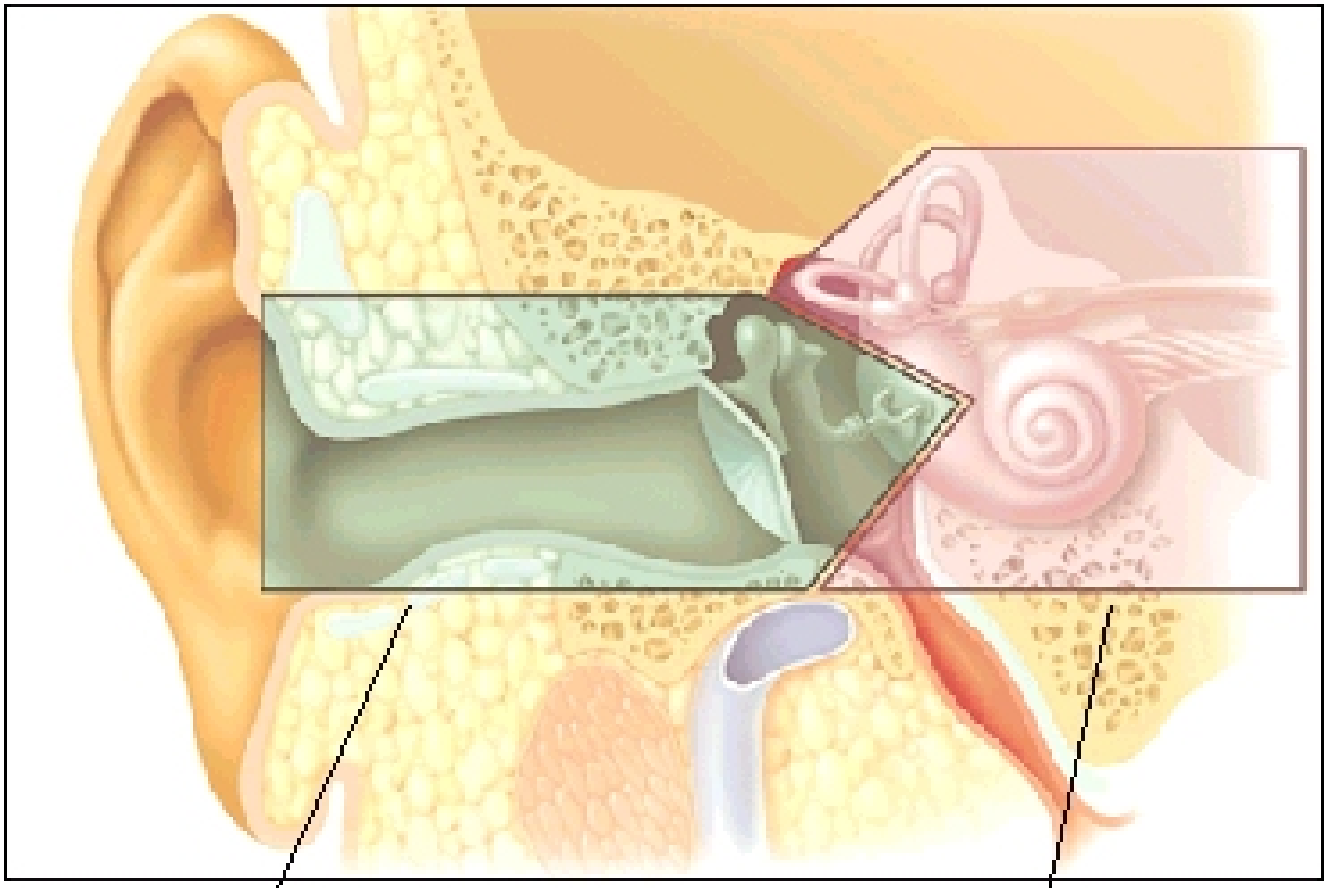
Etiologic Work Up



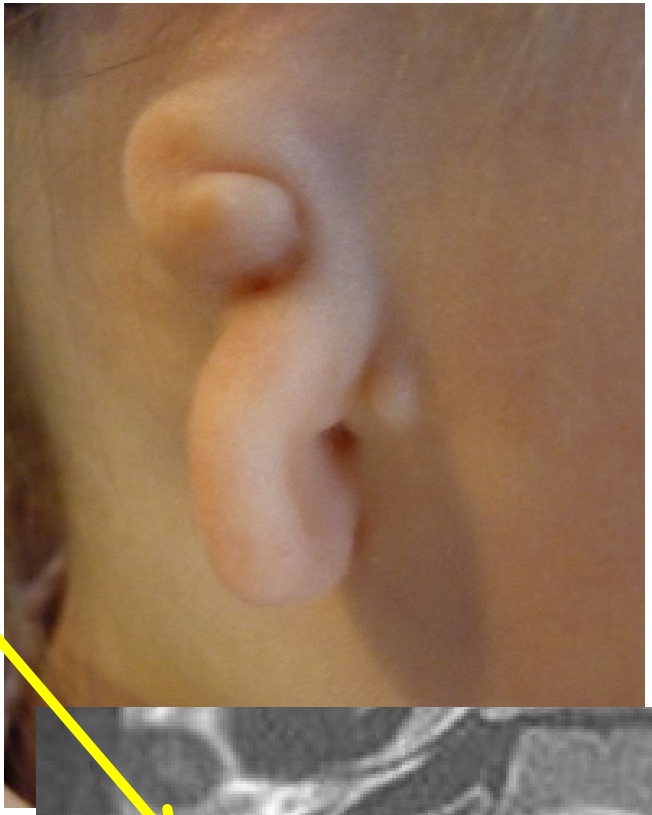
Courtesy of The University Hospital of Newark, N.J.



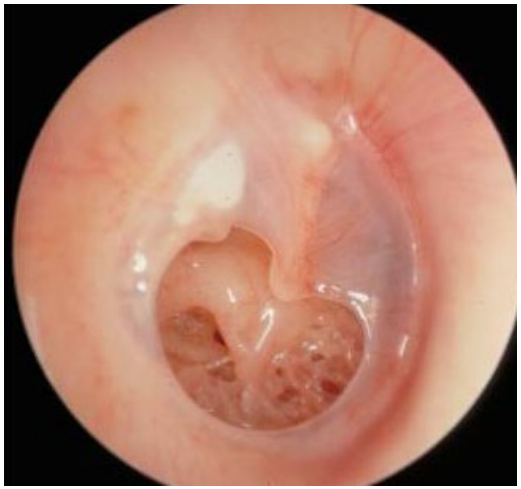
Conductive hearing loss occurs when sound waves do not reach the inner ear.

Sensorineural hearing loss occurs when sound waves are not processed correctly.

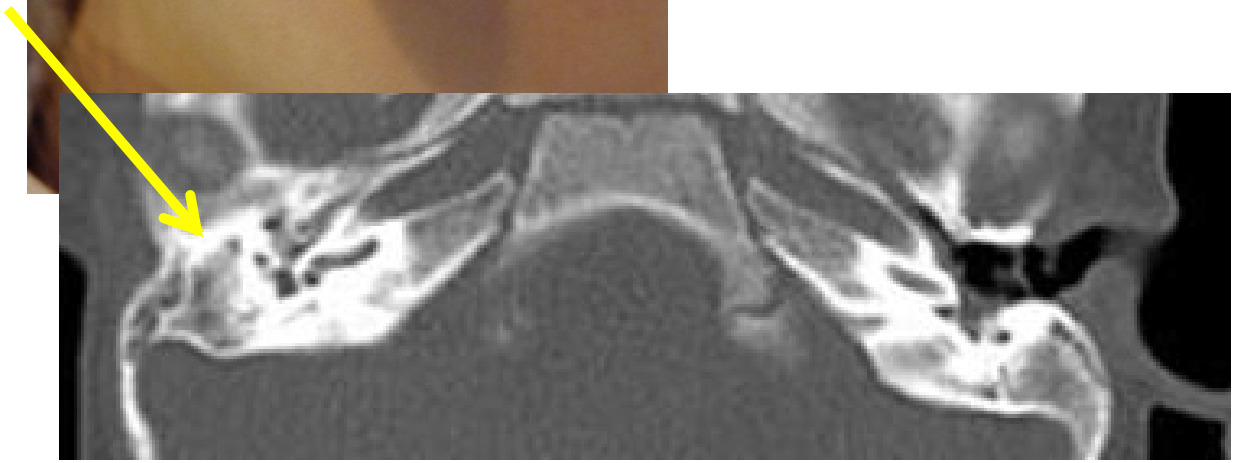
Conductive Hearing Loss

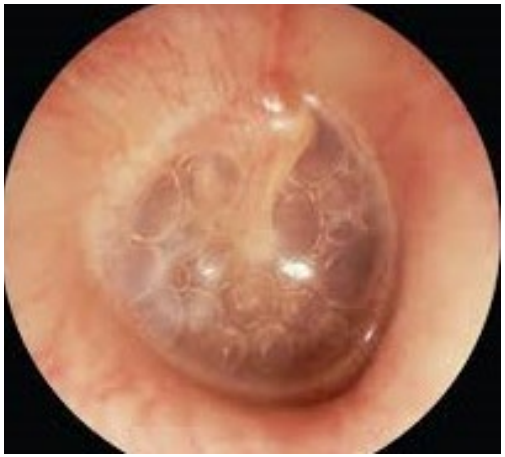


Right microtia &
aural atresia



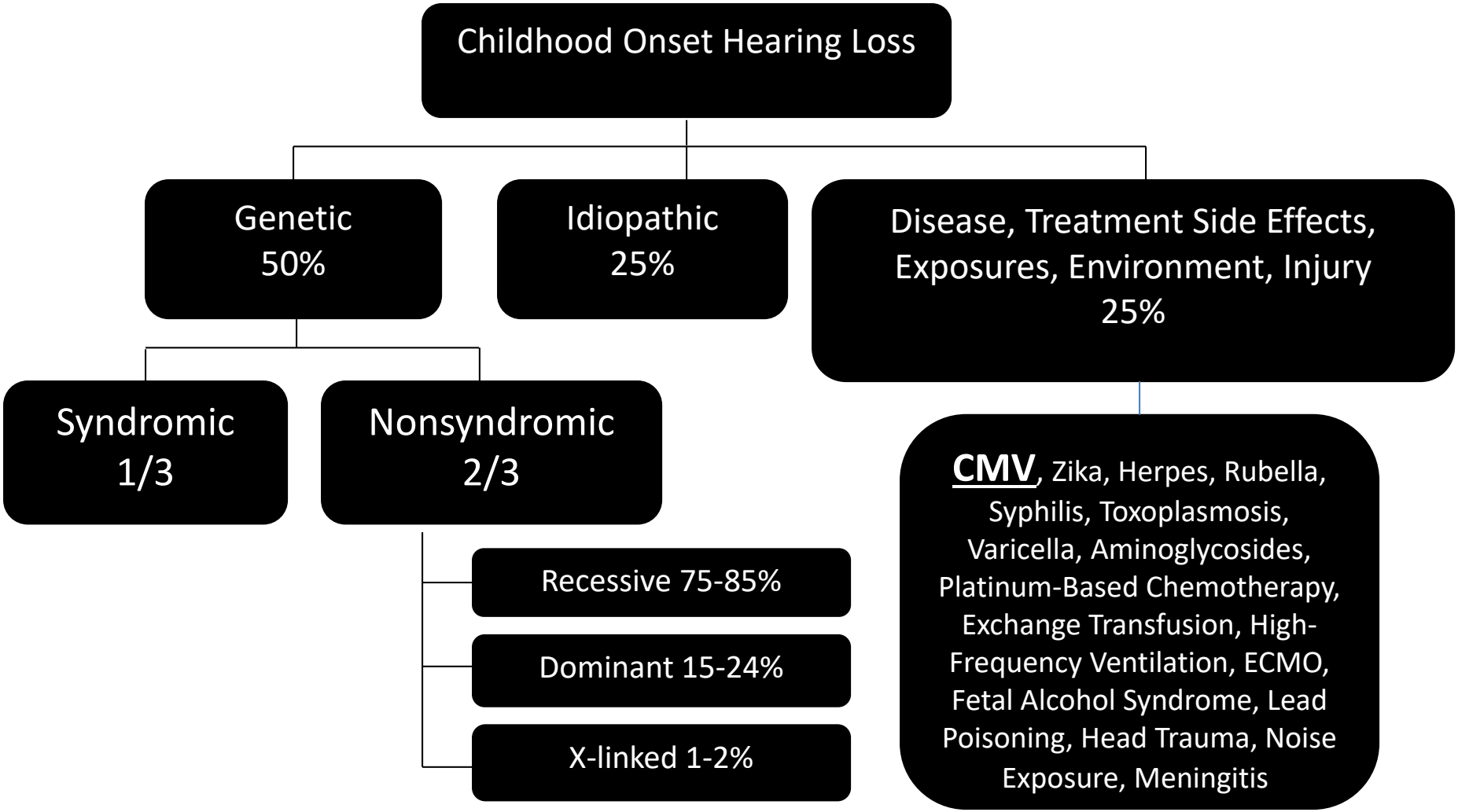
Right tympanic membrane perforation



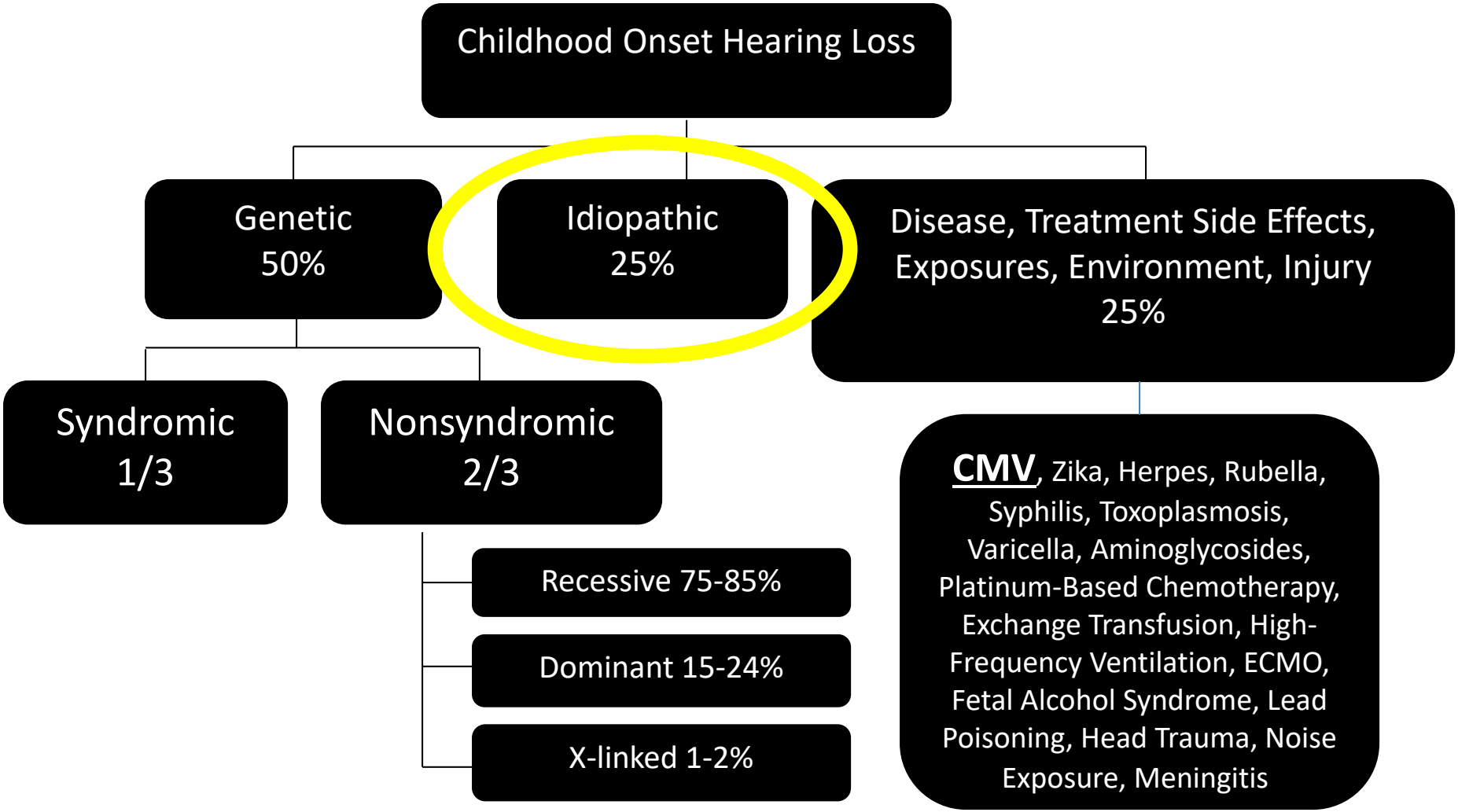


Right middle ear effusion

Etiology of Childhood Hearing Loss

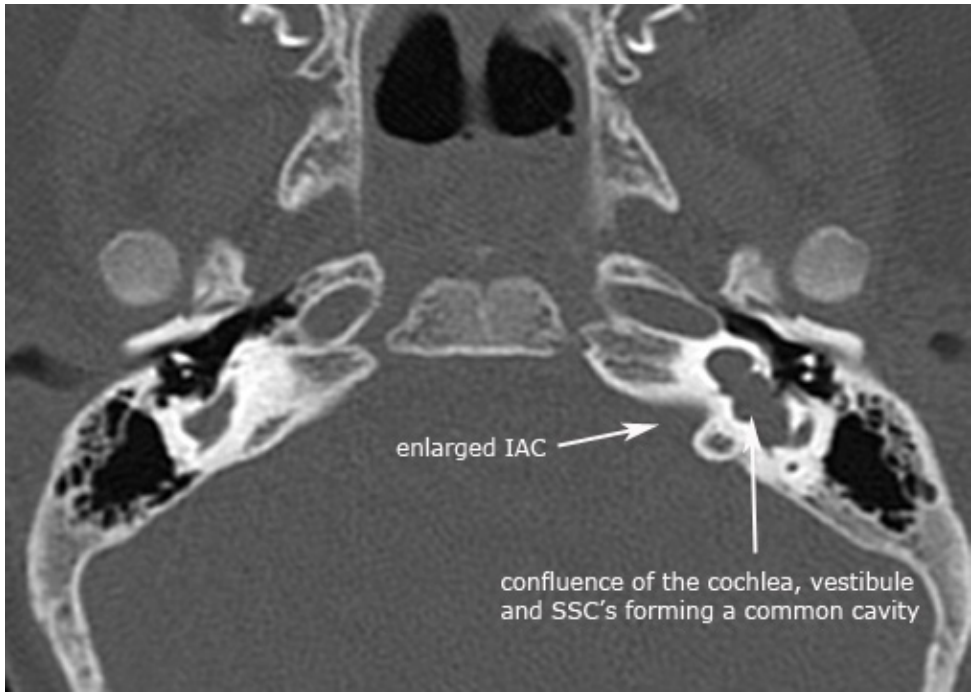


Etiology of Childhood Hearing Loss



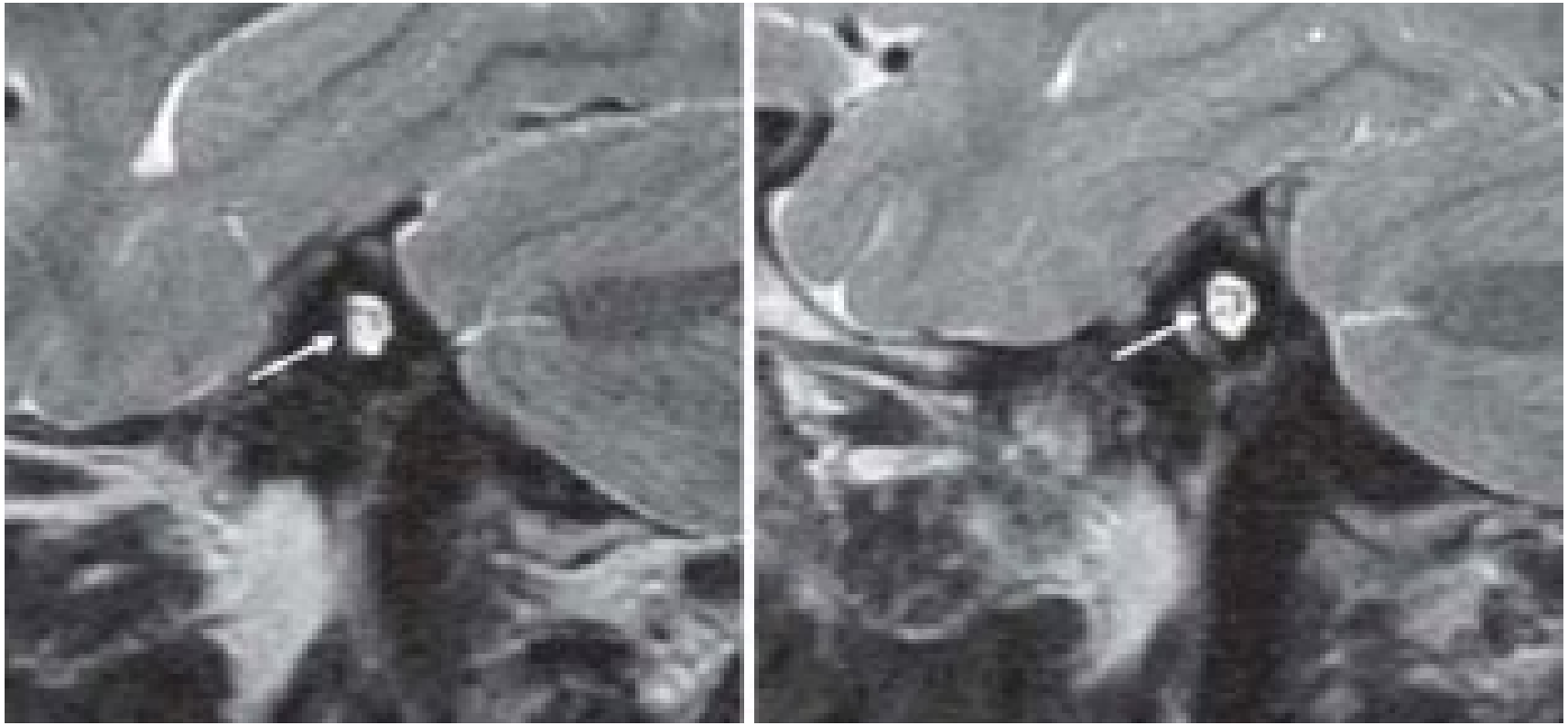
Work-up: Imaging

- CT vs. MRI debate
- Sometimes need both
- When to image?

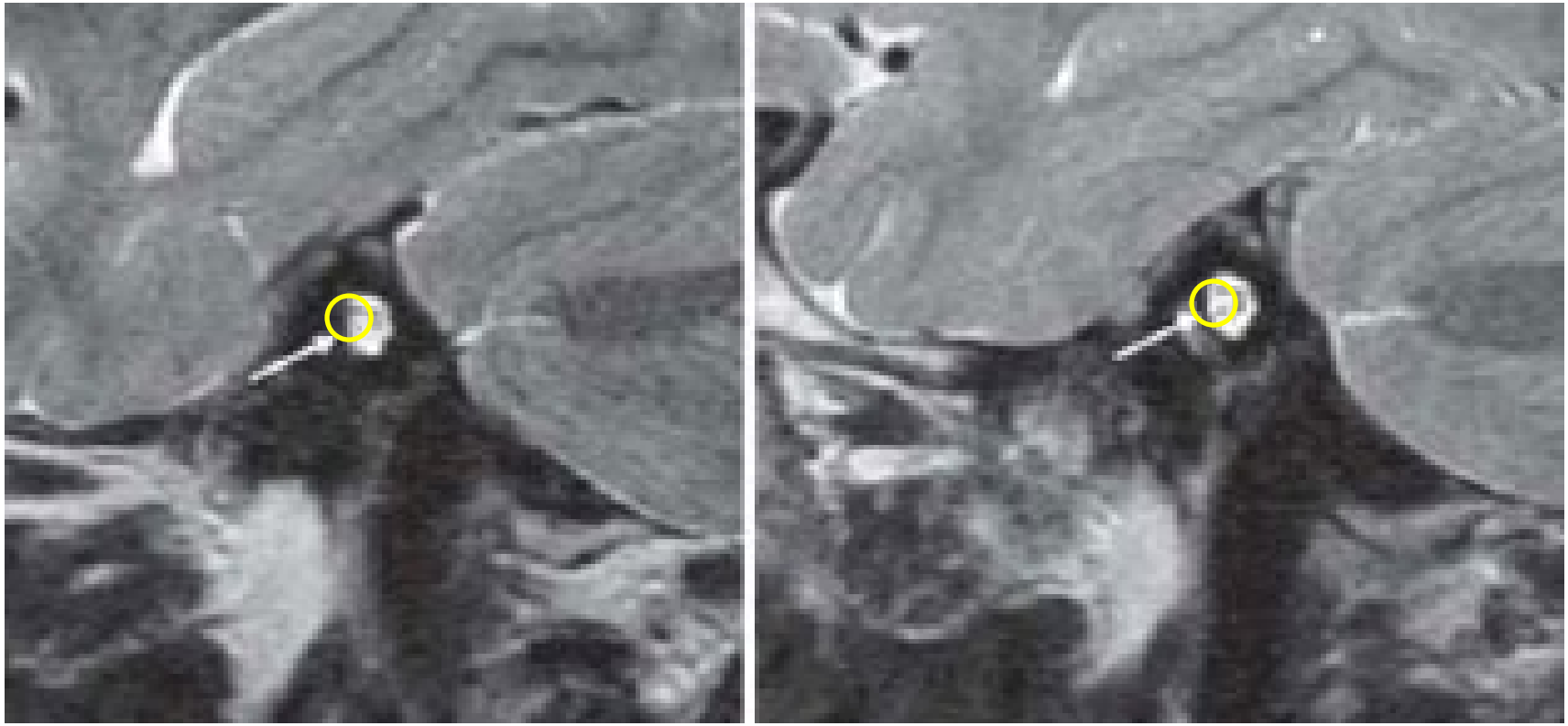


uwmsk.org/temporalbone/congenital.html

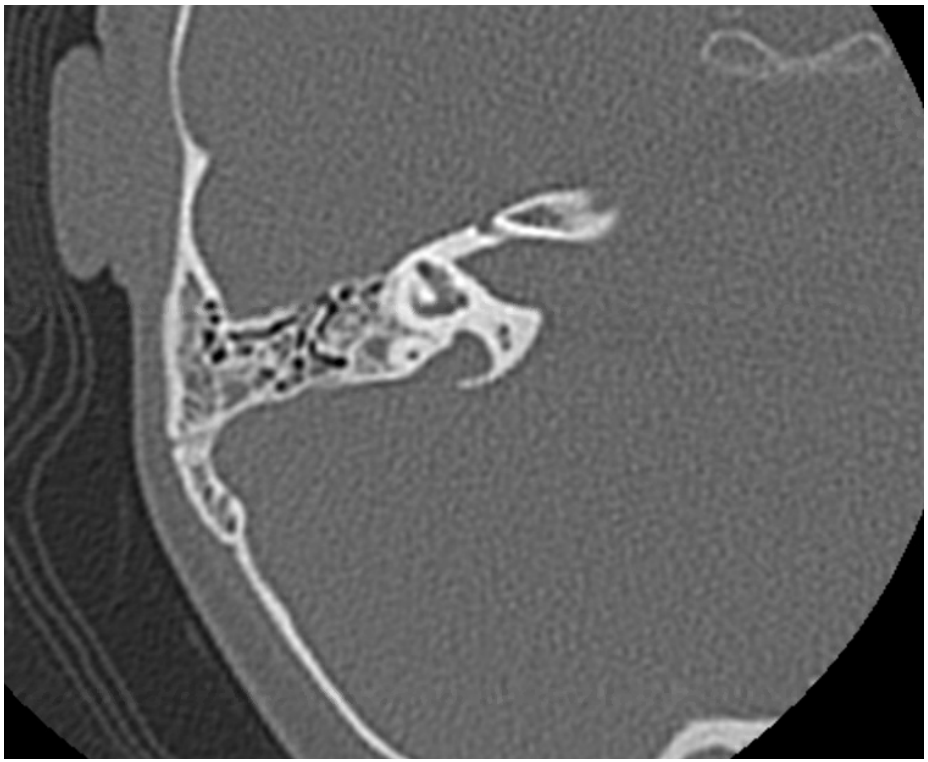
Work-up: Imaging



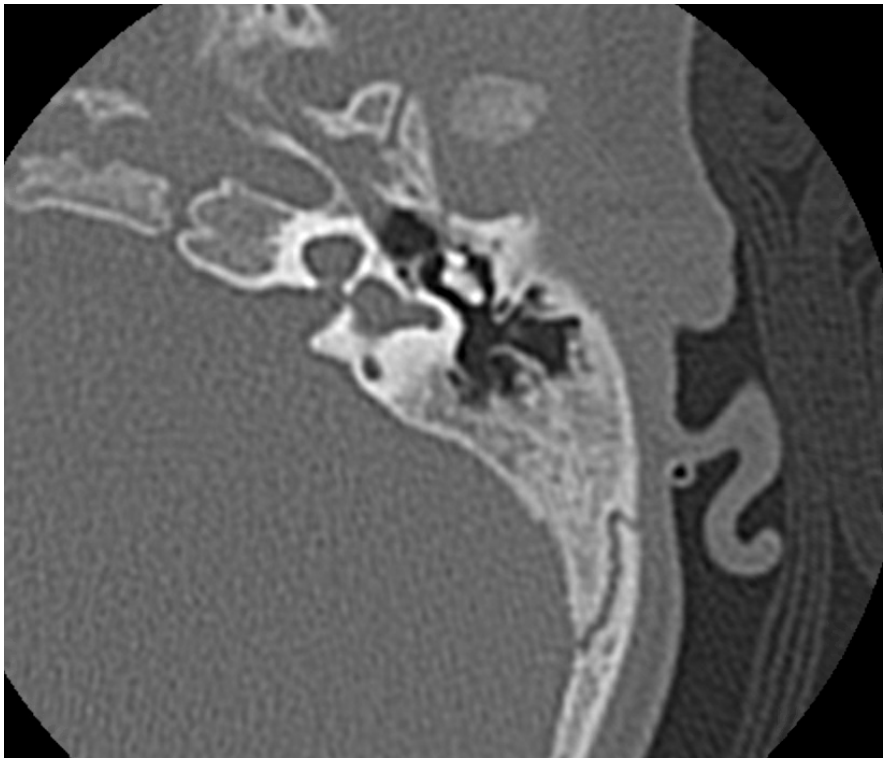
Work-up: Imaging



Work-up: Imaging

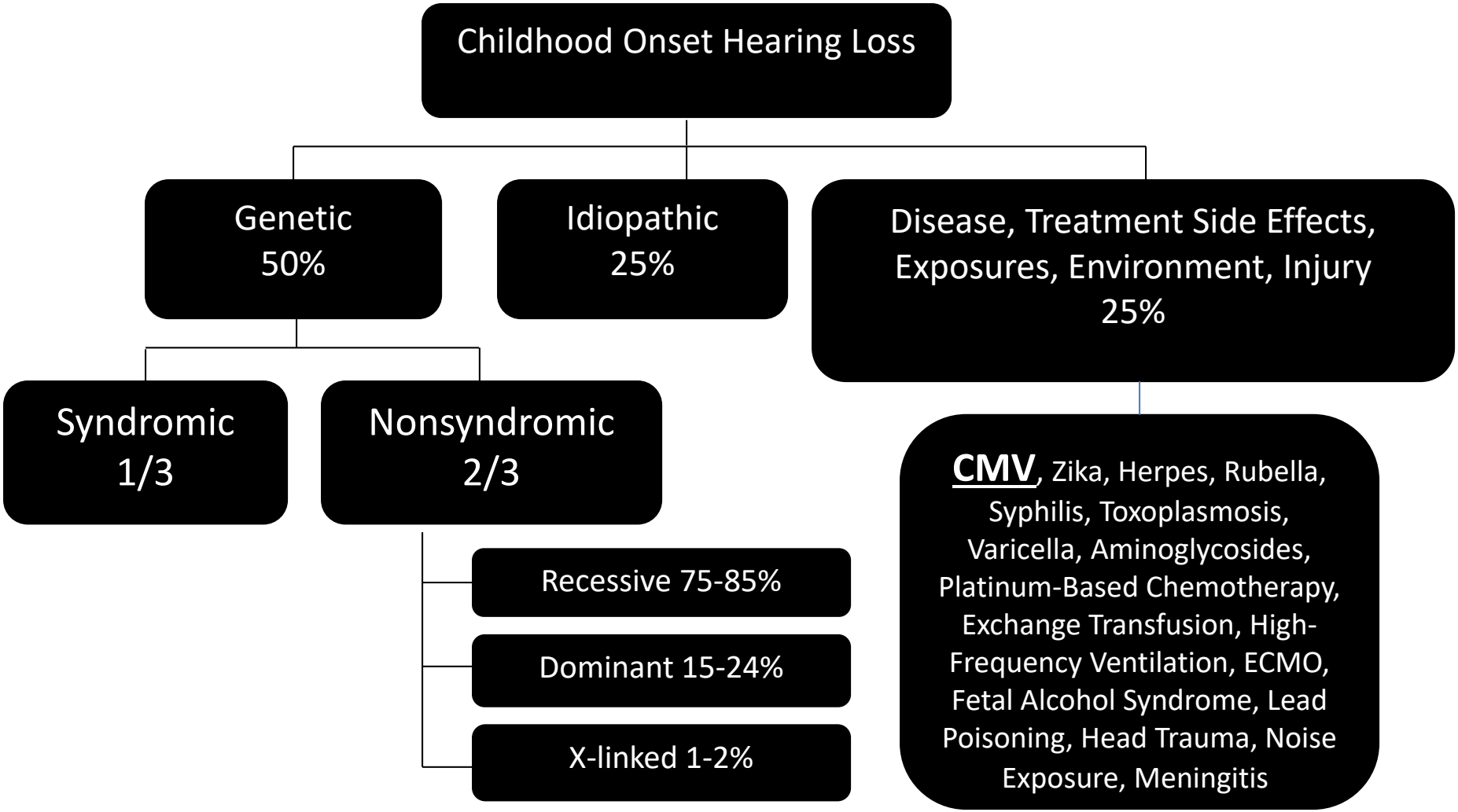


Right enlarged vestibular aqueduct (EVA)

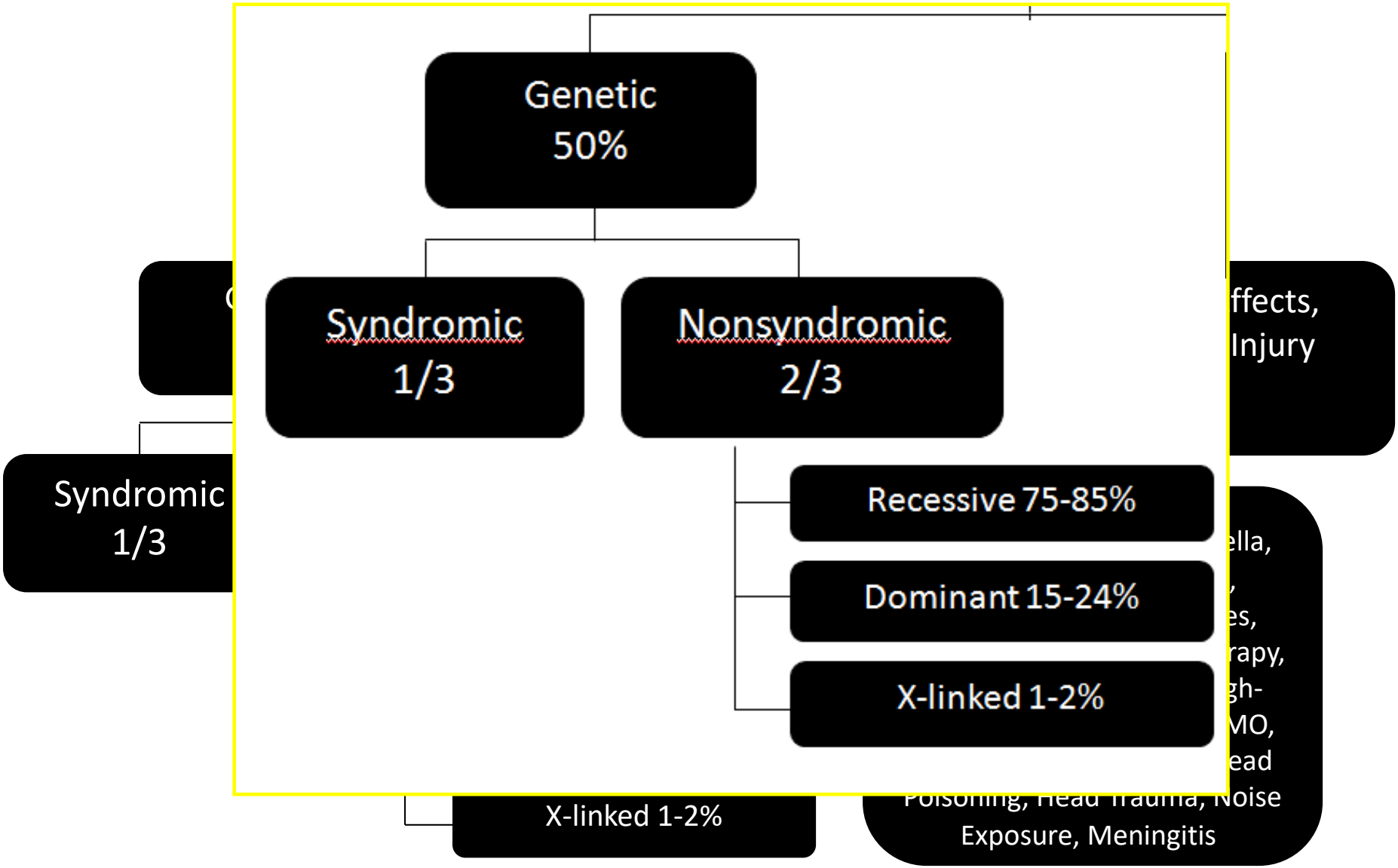


Left cochlear incomplete partition (Mondini)

Work-up: Genetics Consultation



Work-up: Genetics Consultation



Work-up: Genetics Consultation

ACMG PRACTICE GUIDELINES | Genetics inMedicine

American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss

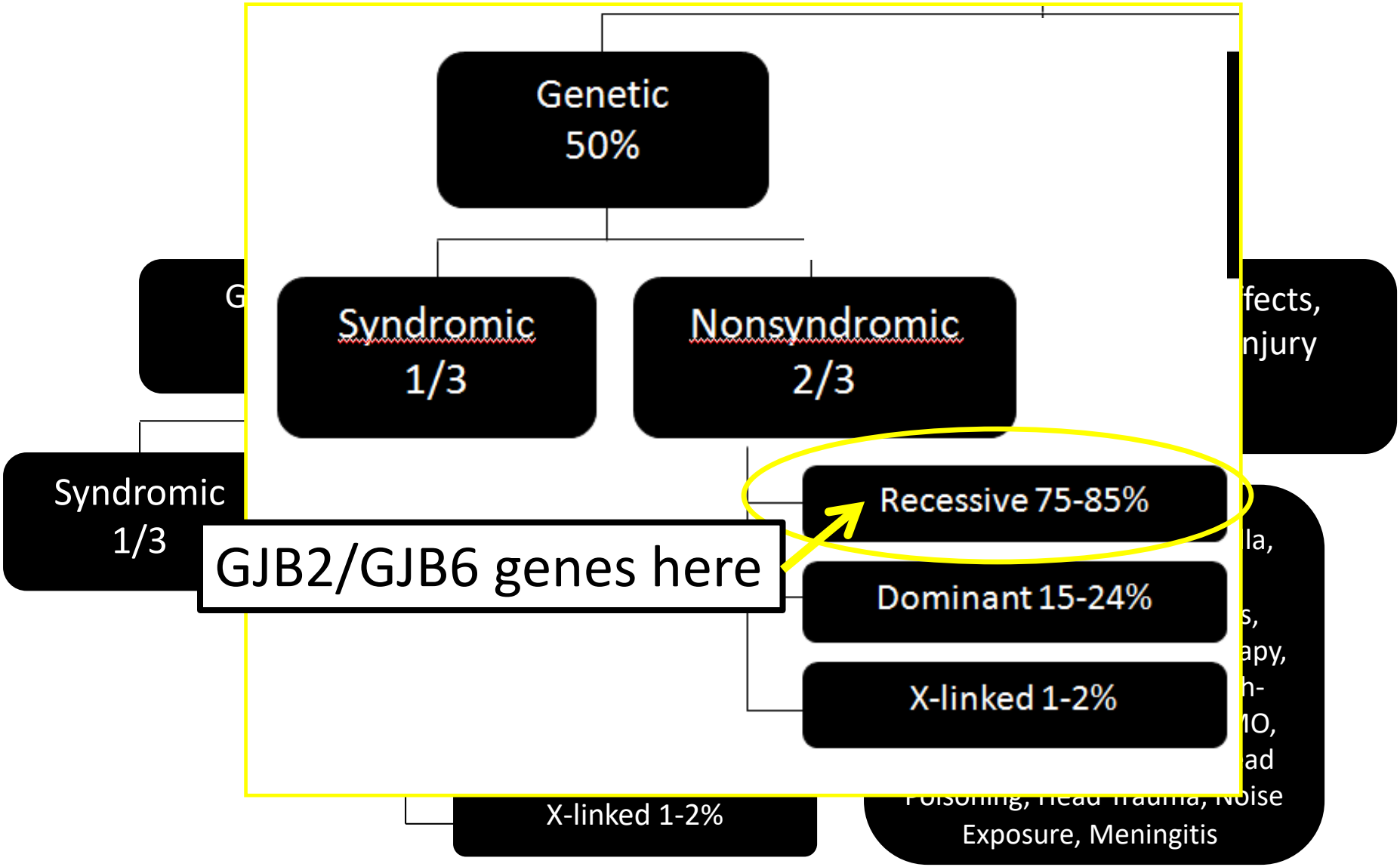
Raye L. Alford, PhD, FACMG[1], Kathleen S. Arnos, PhD, FACMG[2], Michelle Fox, MS, CGC[3,4], Jerry W. Lin, MD, PhD[1], Christina G. Palmer, PhD, FACMG[5,6], Arti Pandya, MD, FACMG[7], Heidi L. Rehm, PhD, FACMG[8], Nathaniel H. Robin, MD, FACMG[9], Daryl A. Scott, MD, PhD[10,11] and Christine Yoshinaga-Itano, PhD[12]; ACMG Working Group on Update of Genetics Evaluation Guidelines for the Etiologic Diagnosis of Congenital Hearing Loss; for the Professional Practice and Guidelines Committee

GENETICS in MEDICINE | Volume 16 | Number 4 | April 2014

Work-up: Genetics Consultation

- Having a consultation does not mean genetic testing has to be pursued by the family
- Careful, detailed history (including family history) and physical to help determine the recommended approach to testing
- Extensive genetic counseling by Genetic Counselors

Work-up: Genetics Consultation



Work-up: Genetics Consultation

- Provide pre-test genetic counseling and genetic testing as clinically indicated:
  - If syndromic hearing loss is suspected, consider targeted gene testing based on suspected diagnosis;
  - If nonsyndromic hearing loss is suspected, consider single-gene tests such as *GJB2* and *GJB6*, gene panel tests, or NGS testing based on history and findings
- Provide imaging or other testing as appropriate for suspected diagnosis

ACMG PRACTICE GUIDELINES | Genetics inMedicine

American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss

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GENETICS in MEDICINE | Volume 16 | Number 4 | April 2014

Enlarged Vestibular Aqueduct (EVA)

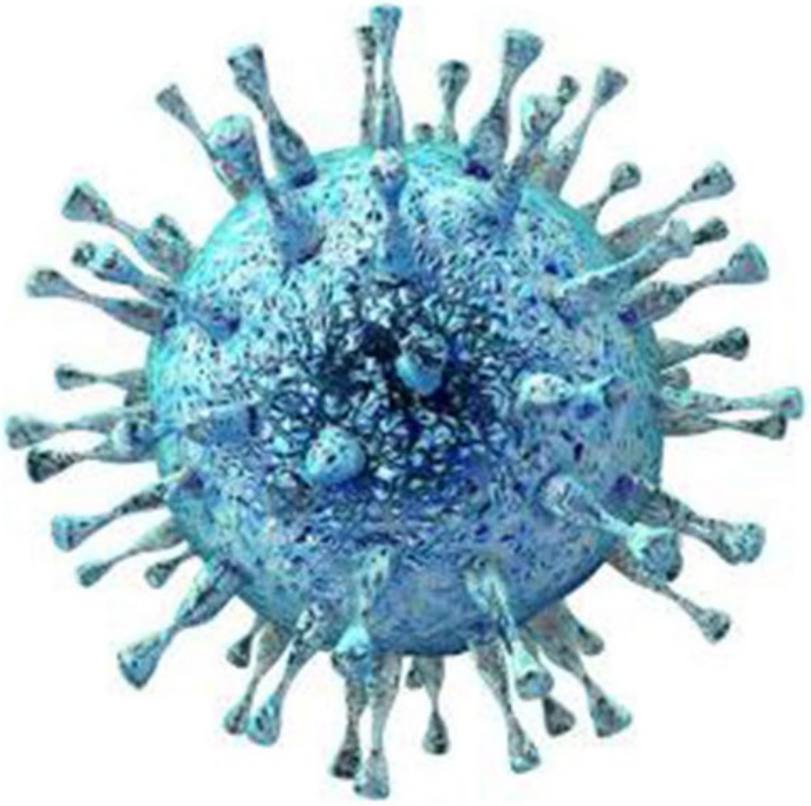
- Can be isolated or seen with other imaging abnormalities such as incomplete partition
- Can be seen in nonsyndromic or syndromic causes of hearing differences
- Can be unilateral or bilateral
- Can be associated with conductive hearing loss, sensorineural hearing loss, or mixed hearing loss
- Can be associated with fluctuating hearing levels
- Can be associated with stable hearing but is one finding that is more associated with progressive hearing loss
- Progression can be sudden or slow over many years

Work-up: Congenital CMV

- Most common cause of nongenetic congenital hearing difference (estimate is ~20% of all childhood SNHL)
- 30-40% risk of transmission with primary infection, up to 2% risk with reactivation or reinfection
- Incidence of cCMV is 1%
- 90% have no detectable clinical abnormalities at birth, yet 10–15% of these asymptomatic infants will develop sensorineural hearing loss

Work-up: Congenital CMV

- CMV is a member of the Herpesviridae family of DNA viruses
- The pathophysiology of how the virus causes hearing loss is not completely understood: Different studies have shown different effects of the virus within different locations within the cochlea

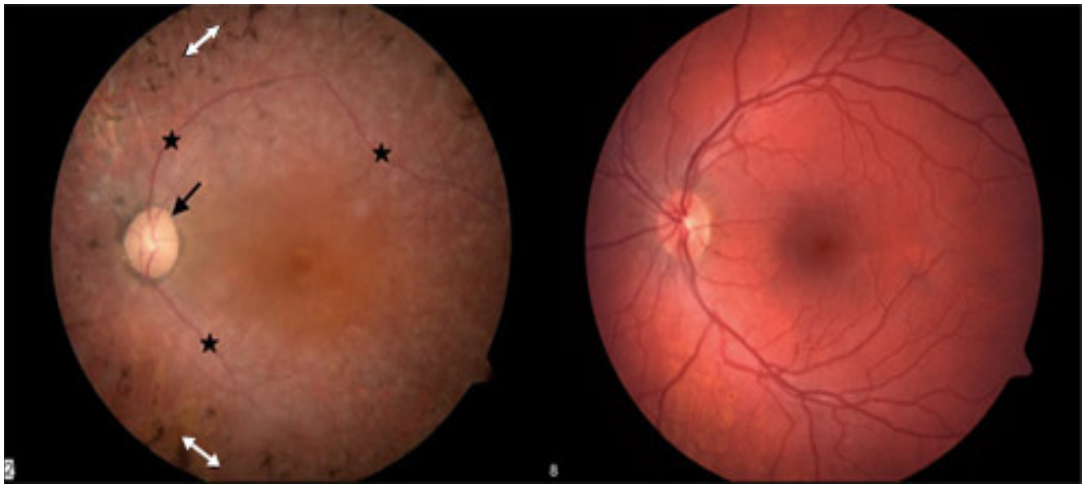


Work-up: Congenital CMV

- Urine CMV PCR by 21 days of life is considered current gold standard
- A negative result most likely excludes cCMV as the cause of the hearing loss
- A positive result does not confirm it is cCMV, especially if obtained in infant >21 days old
- Dried blood spot PCR testing can be done to confirm cCMV when urine or saliva testing is positive in an infant who is >21 days old

Work-up: Ophthalmology Consultation

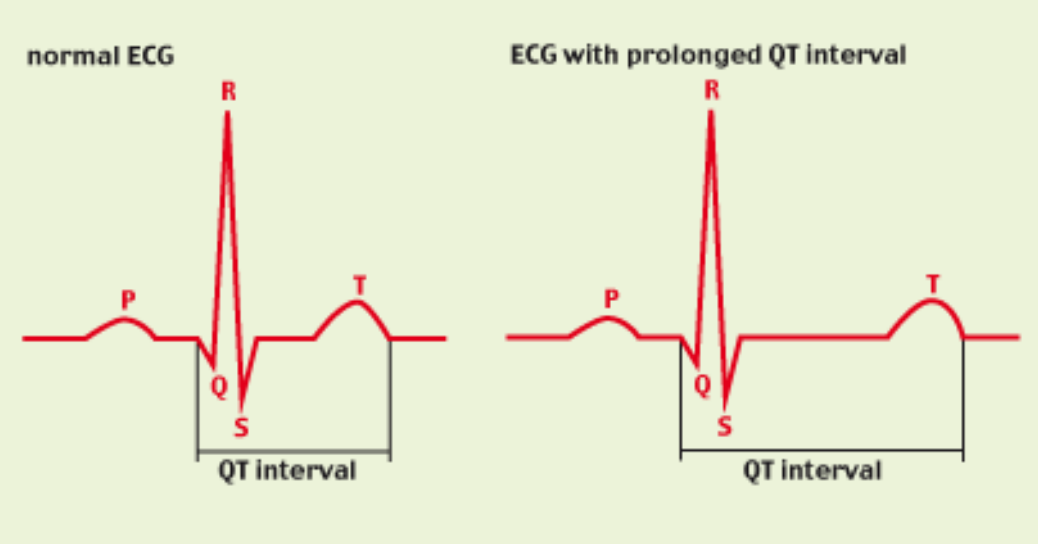
- One of my strongest recommendations
  - May be vision-related differences that are important for the multidisciplinary care team to know and understand, some of which may require intervention or treatment to optimize vision and communication
  - May give clues to etiology (Usher, CHARGE, Waardenburg, Stickler)
  - Review by Nikolopoulos et al in 2006 showed ~40-60% of deaf children have ophthalmologic findings, which is higher than in typical hearing children
  - Timing: Ideally within 6 months of when child is identified as DHH



www.ushersyndrome.nih.gov/whatis/

Work-up: EKG

- EKG
  - Also known as ECG, or electrocardiogram
  - Jervell and Lange-Nielsen Syndrome---very rare but important not to miss
  - History of sudden cardiac death in family



http://www.socialstyrelsen.se/rarediseases/jervellandlange-nielsensyndrome

Work-up: Why do it?

- Identify other conditions that could co-exist with a hearing difference and may necessitate the expansion of the multidisciplinary team to other specialists/providers
- Help family make informed decisions for their child
- Have as much information as possible to help the multidisciplinary care team meet the individual needs of the child, both now and those that may be anticipated in the future
- May have a better ability to prognosticate—chances of hearing changing, involving the other ear if unilateral, etc
- Understand what technology may or may not be an option in the management of the hearing difference
- Genetic counseling for families and for the child as they become an adult

Medical and Surgical Care

Management of the D/HH Child

School

Early Interventionalist

Teacher of the Deaf (TOD)

Speech-language pathologist

Parents

Pediatrician

Audiologist

Otolaryngologist

Medical geneticist

Educational

Medical

Otolaryngology Management of the D/HH Child

Goals of medical/surgical management

- Improve access to sound
- Reversing acquired hearing loss
- Not “curing” or “fixing” deafness

Otolaryngology Management of the D/HH Child

Surgical management
- Bone-conduction hearing aids
- Cochlear implantation

Medical management
- CMV
- Cisplatin ototoxicity
- Noise-induced hearing loss
- Gene therapy

Otolaryngology Management of the D/HH Child

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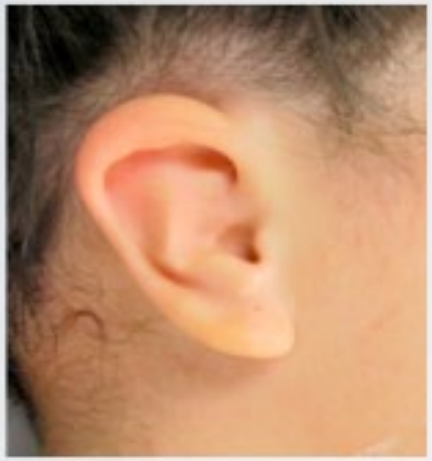
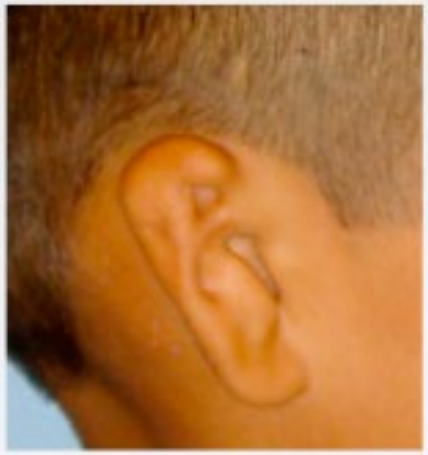
Conductive Hearing Loss Atresia



Grade 1

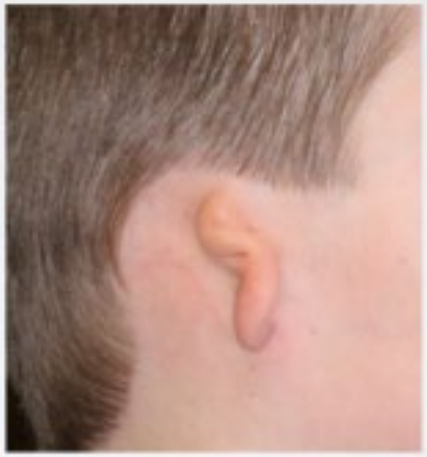
Smaller than normal, but the ear has mostly normal anatomy



Grade 2

Part of the ear looks normal, usually the lower half

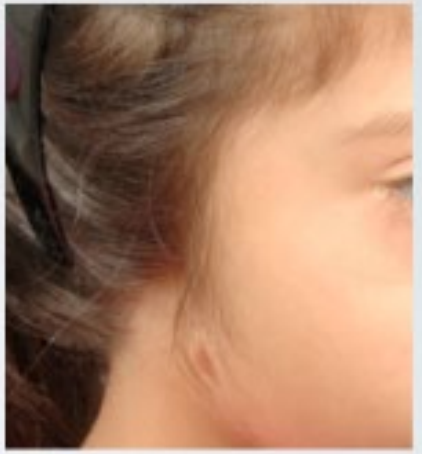
The canal may be normal, small or completely closed



Grade 3

Just a small remnant of "peanut-shaped" skin and cartilage

There is no canal, which is called aural atresia



Grade 4

Complete absence of both the external ear and the ear canal, also called "anotia"

Bone conduction devices Non-surgical

BAHA softband

Med-El AdHear

Cochlear SoundArc

Bone conduction devices Surgical

Percutaneous
Abutment
+
Osseointegrated
Passive Implant

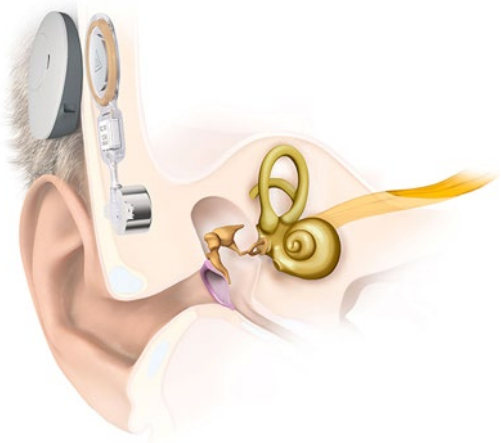
Cochlear BAHA Connect

Oticon Ponto

Transcutaneous
Magnet
+
Osseointegrated
Passive Implant

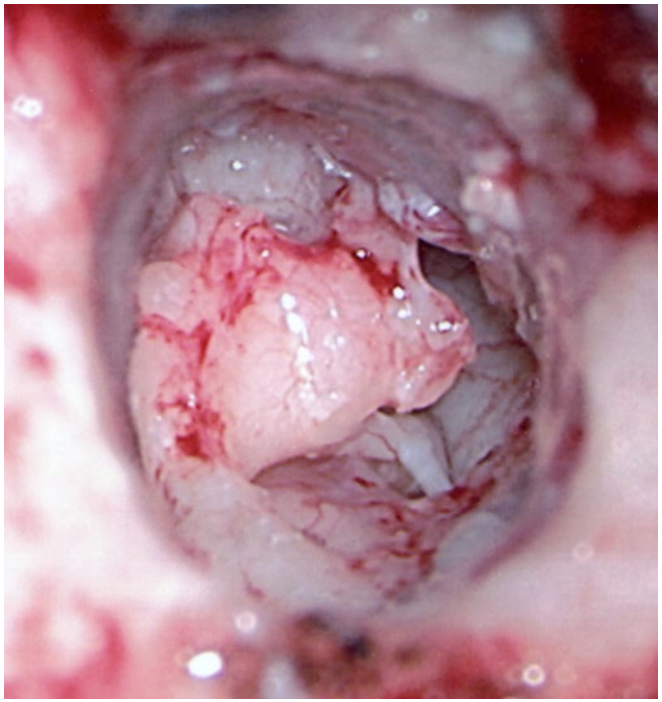
Cochlear BAHA Attract

Transcutaneous
Magnet
+
Active Implant



Med-El BoneBridge

Aural atresia Surgery



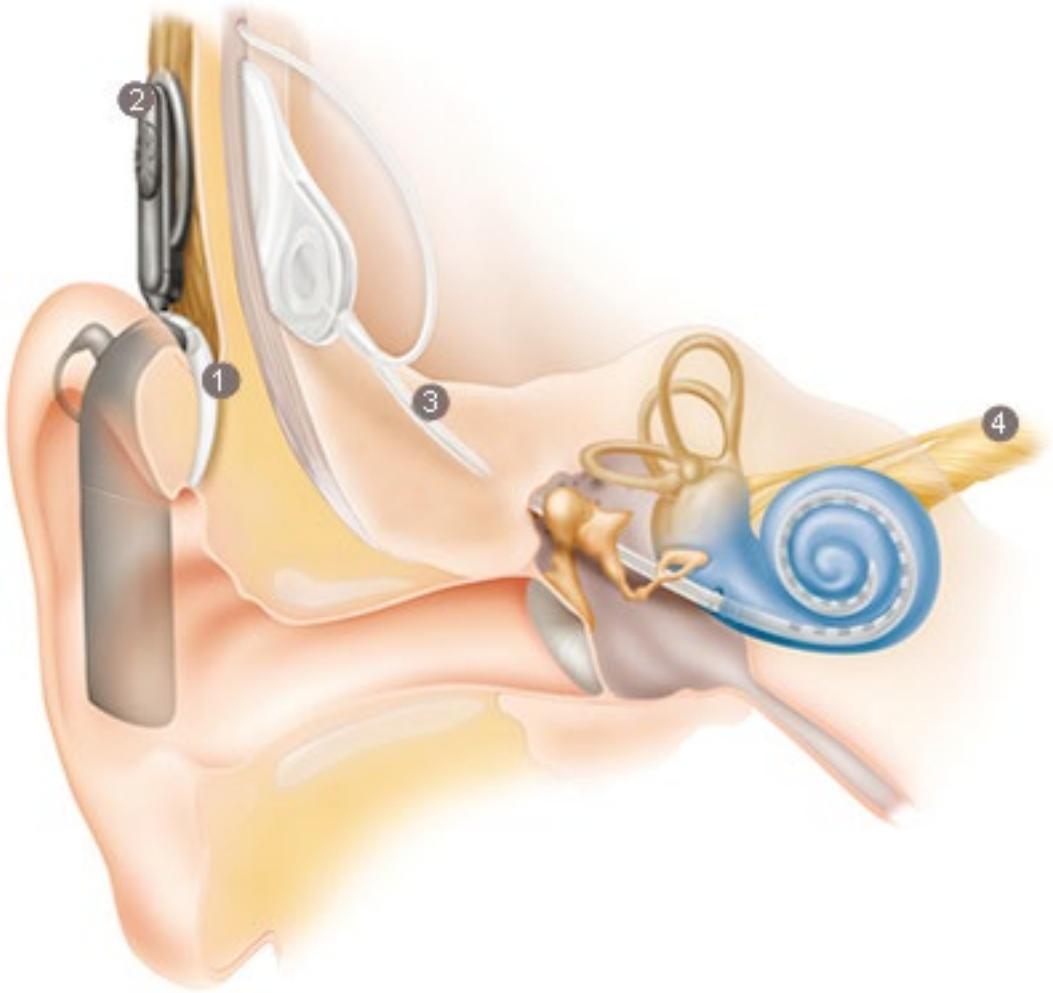
Indications

1) Cholesteatoma
2) Severe canal stenosis
3) Bilateral atresia
4) Inability to tolerate BAHA (softband or surgery)
5) Patient preference

Contraindications

1) Only hearing ear
2) Significant sensorineural component
3) Significant anterior displacement of facial nerve
4) Severe middle/inner-ear dysmorphism

Sensorineural Hearing Loss Cochlear implant



Cochlear.com

Sensorineural Hearing Loss Cochlear implant

Cochlear implants can:

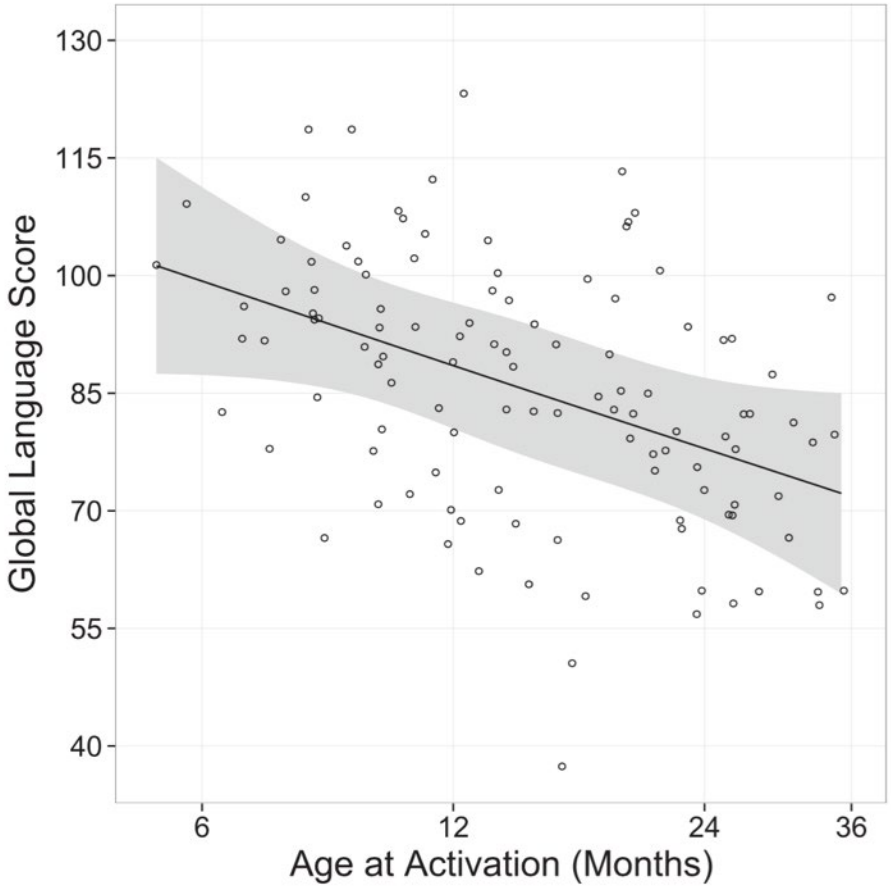
Support development of spoken language
Provide enviromental awareness of sound

Cochlear implants are traditionally for:

Severe-to-profound hearing loss
Failed hearing aids
Complete cochlear implant evaluation
Appropriate expectations
Appropriate support
Over age 1

blog.lib.umn.edu

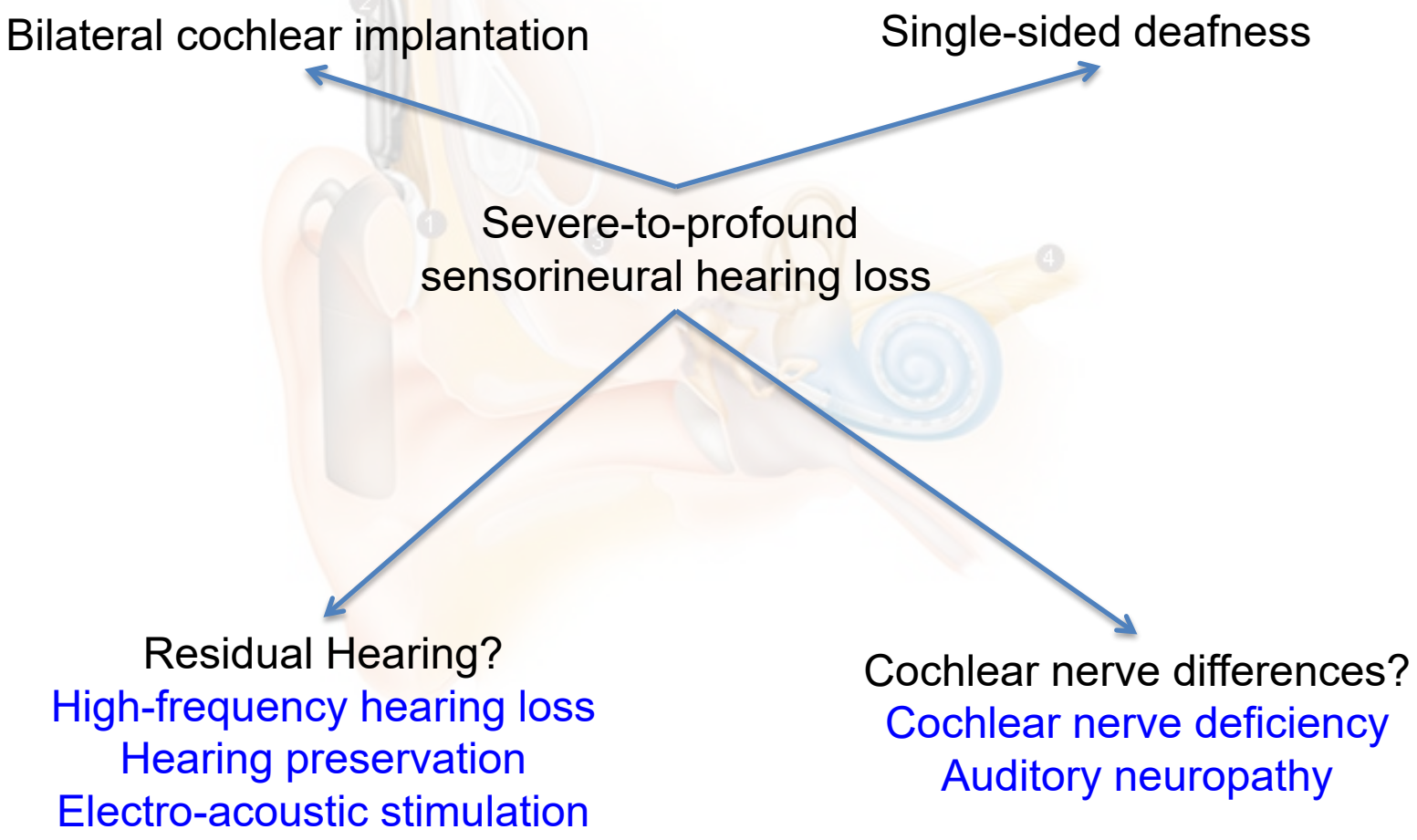
Cochlear implant Timing Matters



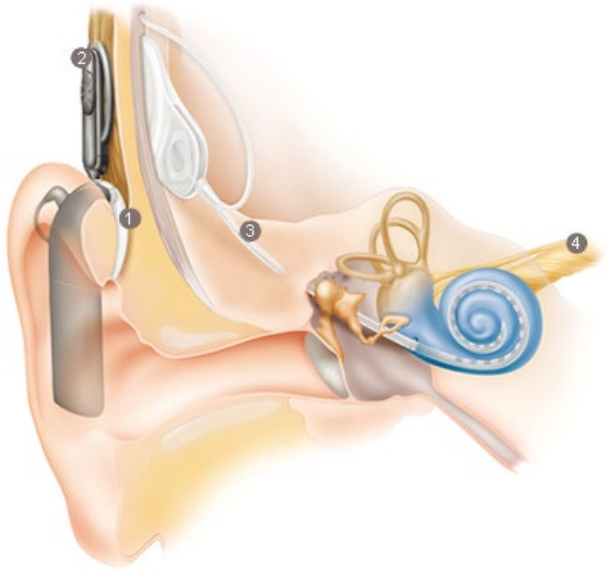
"Childhood hearing loss is a developmental emergency"

Ching, 2017

Cochlear implantation Expanded indications



Cochlear implantation Medical considerations



How does etiologic testing affect cochlear implant decision-making?

Anatomy
- Cochlea
- Auditory nerve

Prognosis for hearing
- Progression
- Contralateral hearing

Other affected systems
- Vision
- Motor

Otolaryngology Management of the D/HH Child

Surgical management
- Bone-conduction hearing aids
- Cochlear implantation

Medical management
- CMV
- Cisplatin ototoxicity
- Noise-induced hearing loss
- Gene therapy

Hearing loss Medical Treatment

There are no medications
to reverse or prevent sensorineural hearing loss

Hearing loss Medical Treatment

There are no medications
to reverse or prevent sensorineural hearing loss

But are we getting close?

Hearing loss Medical Treatment

ORIGINAL ARTICLE

Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss

P.R. Brock, R. Maibach, M. Childs, K. Rajput, D. Roebuck, M.J. Sullivan, V. Laithier, M. Ronghe, P. Dall'Igna, E. Hiyama, B. Bri
A.A. Rangaswami, M. Ansari, C. Rechnitz
G. Perilongo, P. Czauderna, B.

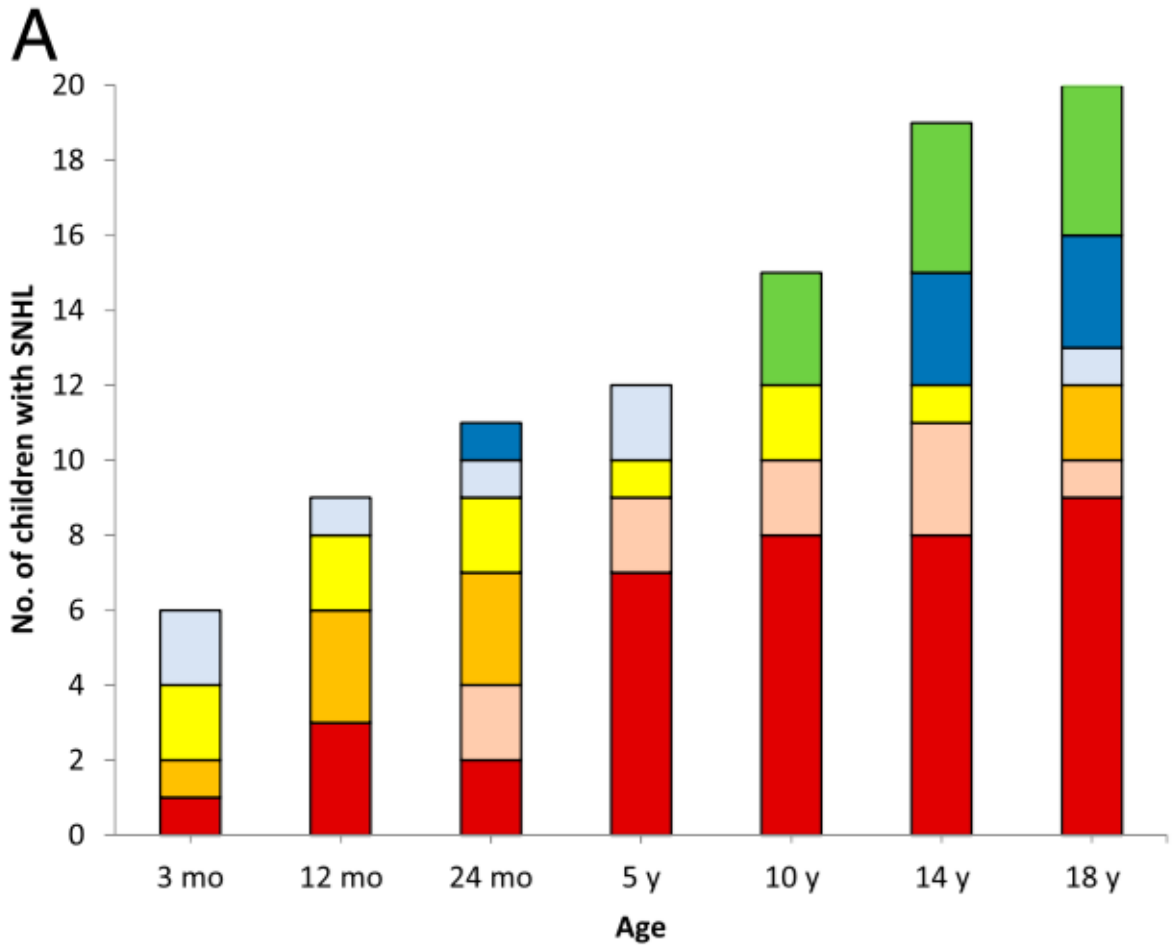
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease

D.W. Kimberlin, P.M. Jester, P.J. Sánchez, A. Ahmed, R. Arav-Boger, M.G. Michaels, N. Ashouri, J.A. Englund, B. Estrada, R.F. Jacobs, J.R. Romero, S.K. Sood, M.S. Whitworth, M.J. Abzug, M.T. Caserta, S. Fowler, J. Lujan-Zilbermann, G.A. Storch, R.L. DeBiasi, J.-Y. Han, A. Palmer, L.B. Weiner, J.A. Bocchini, P.H. Dennehy, A. Finn, P.D. Griffiths, S. Luck, K. Gutierrez, N. Halasa, J. Homans, A.L. Shane, M. Sharland, K. Simonsen, J.A. Vanchiere, C.R. Woods, D.L. Sabo, I. Aban, H. Kuo, S.H. James, M.N. Prichard, J. Griffin, D. Giles, E.P. Acosta, and R.J. Whitley, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group

CMV Hearing loss Long-term Outcomes

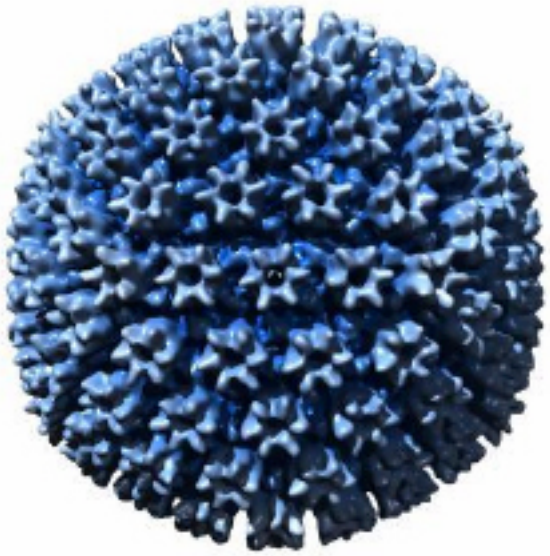


- Progressive hearing loss in 60-70% up to age 18
- Progression to profound in 89% of unilateral HL
- New hearing loss in other ear in 75% of SSD

Natural history of congenital CMV infection:
Ongoing SNHL
Progression to profound SNHL

Lanzieri, 2017

Treatment Valganciclovir for CMV hearing loss



The NEW ENGLAND JOURNAL of MEDICINE

NIAID Collaborative Antiviral Study Group
Kimberlin *et al.,* (2015) *NEJM* 372(10):933-43

Multinational 31-institution Phase III randomized, controlled clinical trial

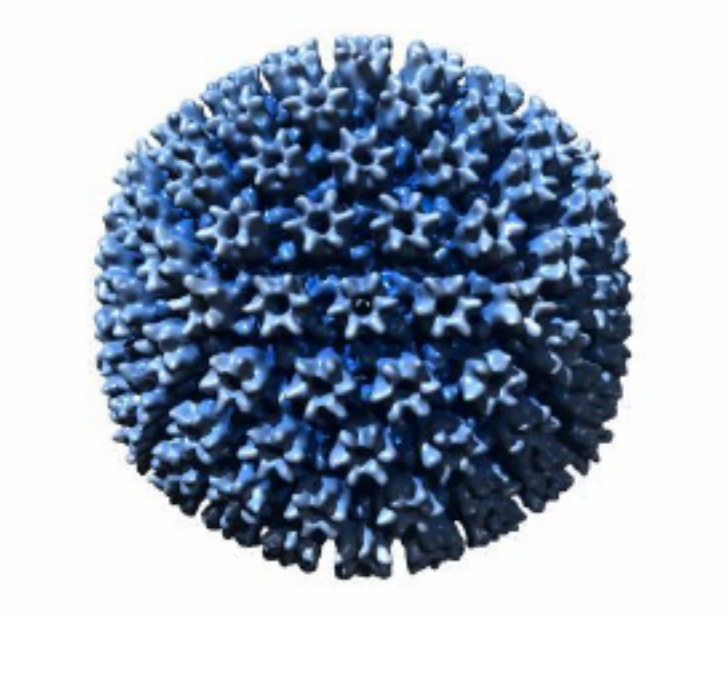
109 infants < 30 days old
Symptomatic congenital CMV
43% with baseline hearing loss

6 wks vs. 6 mos PO valganciclovir
24-month follow up

Significantly increased odds of hearing improvement or stabilization of normal hearing with 6-month course (OR (1.02-6.91) at 24 months)

77% vs 64% maintenance of normal, or improved, hearing at 24 months

CMV-associated SNHL Valgan Toddler Study

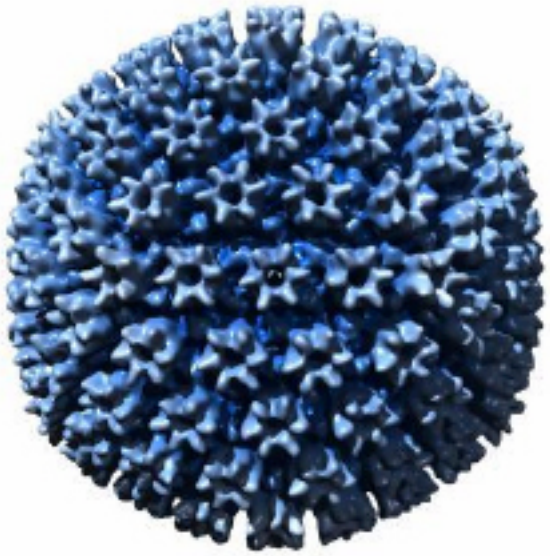


NCT01649869 (Valgan Toddler Study) - Kimberlin

Multi-institution Phase II randomized, controlled clinical trial

6 wks PO valganciclovir vs. placebo
Age 1 month – 4 years with sensorineural hearing loss

Congenital CMV by neonatal urine CMV or dried blood spot CMV



CMV-associated SNHL ValEar Trial

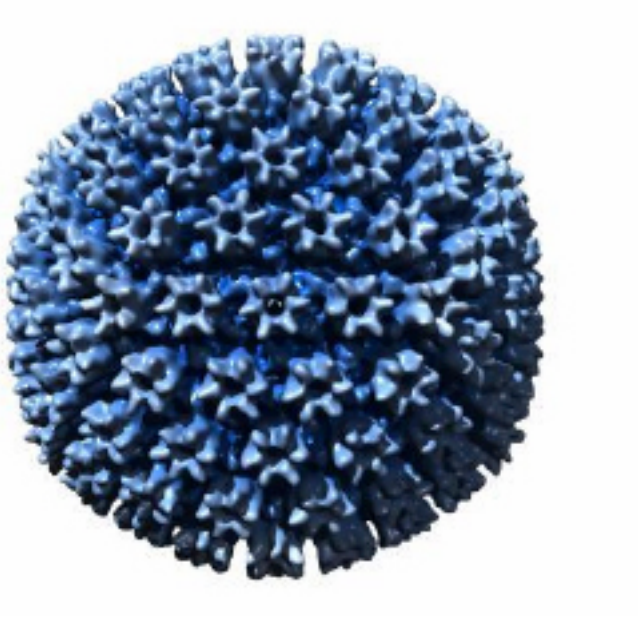
NCT03107871 (ValEar Trial) - Park

Multi-institution Phase II randomized, controlled clinical trial

Age 1 month – 6 months with congenital CMV-associated isolated SNHL

6 mos PO valganciclovir vs. placebo

Auditory, speech, language, developmental outcomes



CMV-associated SNHL ValEar Trial

NCT03107871 (ValEar Trial) - Park

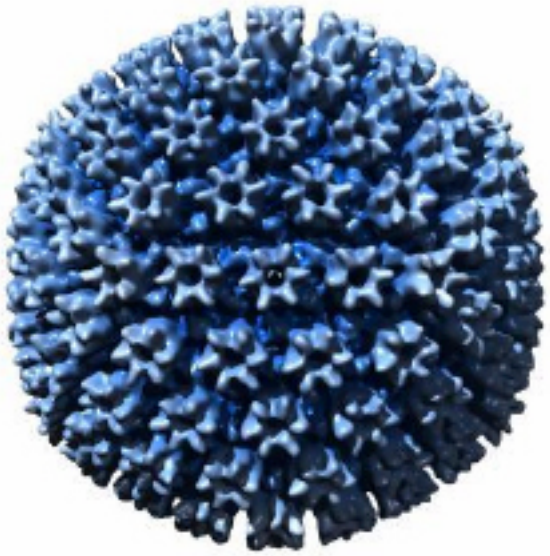
Inclusion criteria:

1) Age 1-6 months
2) > 37 weeks gestational age at birth
3) Positive congenital CMV by urine culture or PCR by 21 days' age, OR Positive congenital CMV by urine culture/PCR AND positive newborn dried blood spot PCR
4) Confirmed SNHL by auditory brainstem response (ABR)

Exclusion criteria:

1) Symptomatic CMV
2) Parent/guardian does not speak English or Spanish

CMV Treatment Summary



CMV treatment (6 months valganciclovir):

- Can prevent progression of hearing loss
- Unknown benefit in kids with isolated CMV-associated hearing loss AND in older kids
- Risks (neutropenia, fertility)
- Not currently officially recommended by AAP Red Book
- Is being discussed with parents in collaboration with ID/OHNS
- Is being evaluated in two clinical trials

CMV-associated SNHL Current Practice

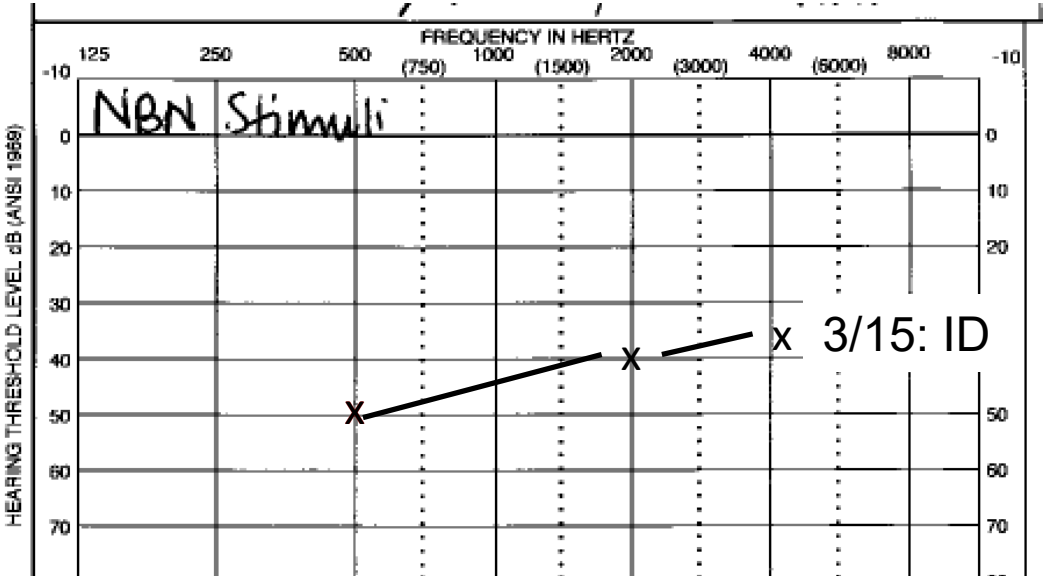
Babies under 3 weeks of age with referred NHS
- CMV testing (urine/saliva PCR or culture)
- Diagnostic audiologic testing

Babies over 3 weeks of age with referred NHS
- Diagnostic audiologic testing

Babies and children 3 weeks - 6 months of age with confirmed SNHL
- CMV urine culture/PCR
- If positive, CMV DBS testing
- If confirmed congenital CMV and SNHL, consider ValEAR trial

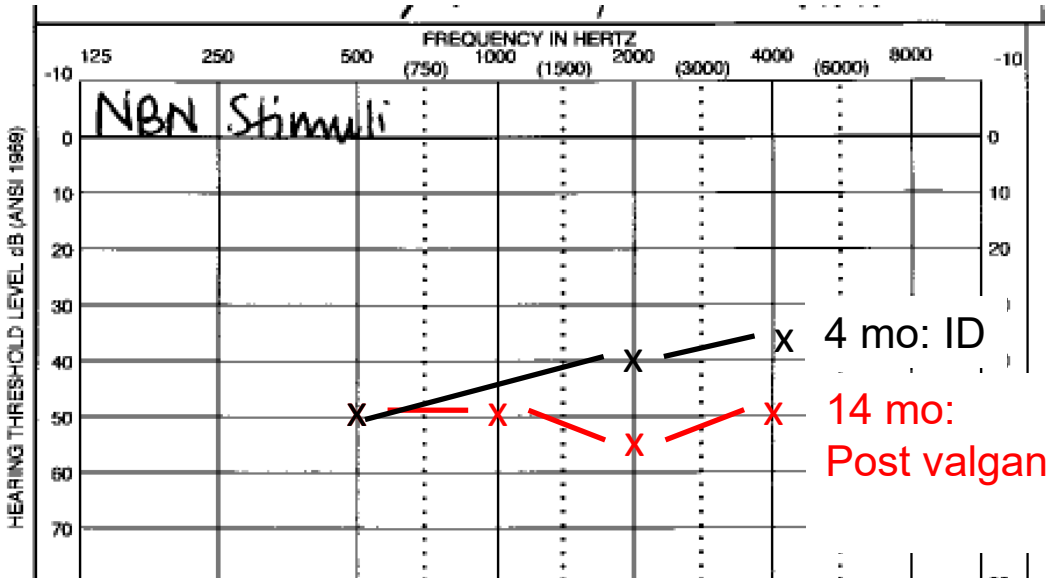
Children over 6 months of age with confirmed SNHL
- Consider CMV DBS testing (for etiologic workup for SNHL)
- If positive, consider prognosis in management decision-making

Case SR



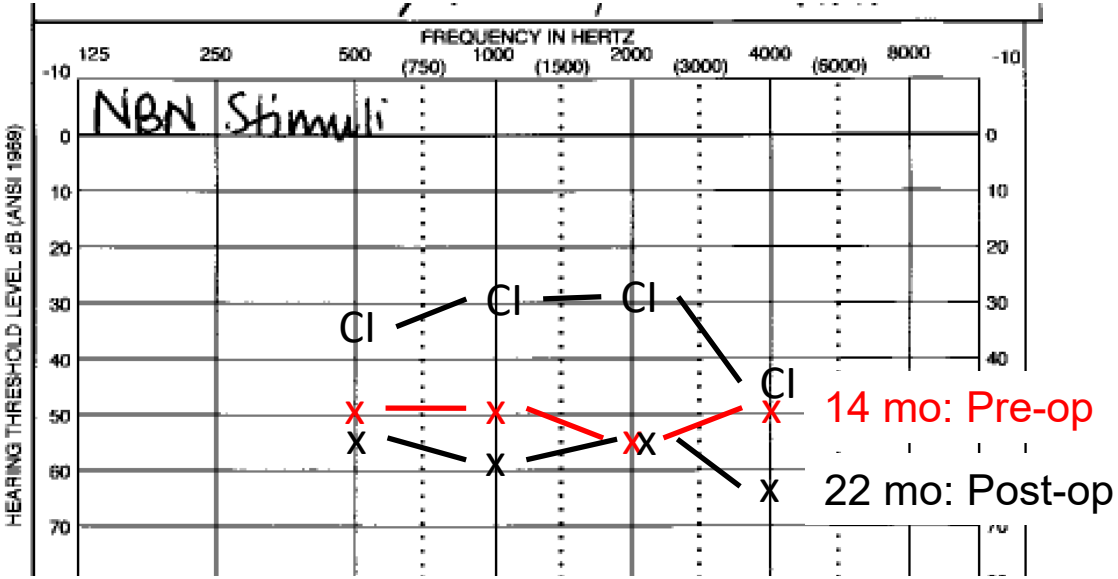
- 4 mo girl with congenital R profound, L mild-moderate SNHL
- CMV DBS positive

Case SR



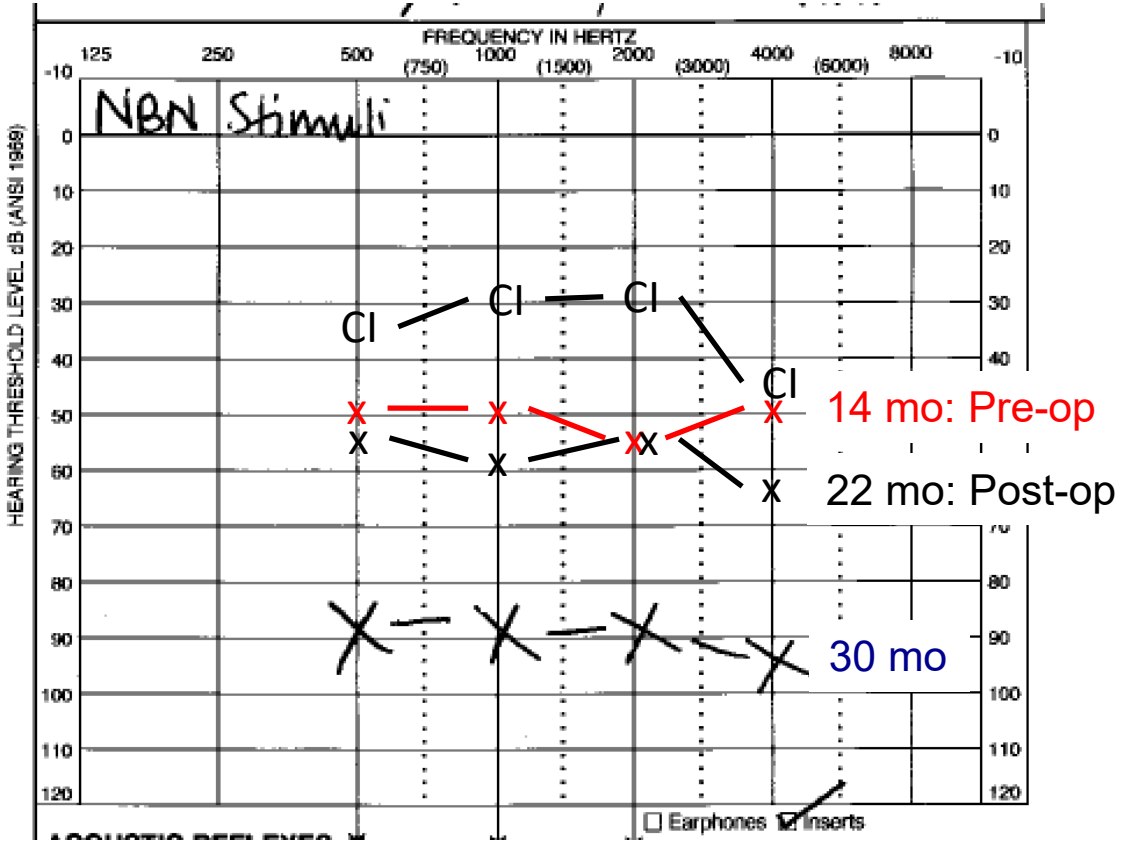
- 4 mo girl with congenital R profound, L mild-moderate SNHL
- CMV DBS positive
- 6 mo valganciclovir treatment (completed at 10 mos of age)

Case SR



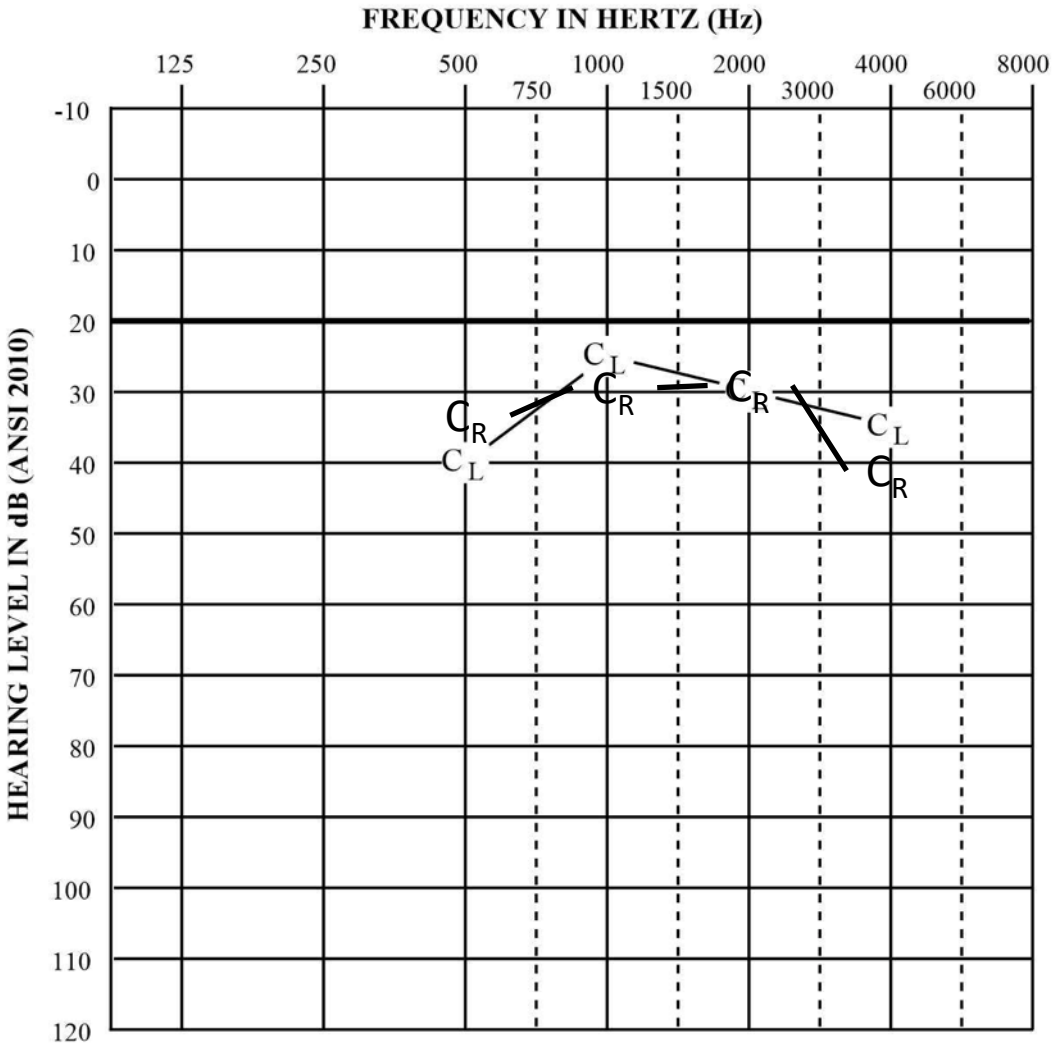
- 4 mo girl with congenital R profound, L mild-moderate SNHL
- CMV DBS positive
- 6 mo valganciclovir treatment (completed at 10 mos of age)
- 16 mo: R cochlear implant
- Continued aiding L ear

Case SR



- 4 mo girl with congenital R profound, L mild-moderate SNHL
- CMV DBS positive
- 6 mo valganciclovir treatment (completed at 10 mos of age)
- 16 mo: R cochlear implant
- Continued aiding L ear
- 30 mo: – drop in L hearing; Underwent L cochlear implant

Case SR



- 4 mo girl with congenital R profound, L mild-moderate SNHL
- CMV DBS positive
- 6 mo valganciclovir treatment (completed at 10 mos of age)
- 16 mo: R cochlear implant
- Continued aiding L ear
- 30 mo: – drop in L hearing; Underwent L cochlear implant
- 42 mo: Age-appropriate speech, language, auditory skills (PLS, GFTA, LittlEars)

Otolaryngology Management of the D/HH Child

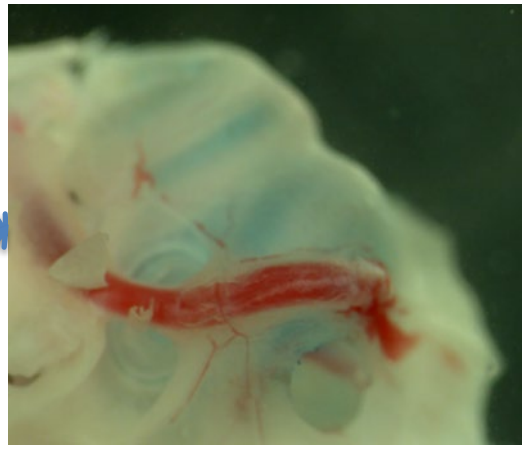
Surgical management
- Bone-conduction hearing aids
- Cochlear implantation

Medical management
- CMV
- Cisplatin ototoxicity
- Noise-induced hearing loss
- Gene therapy

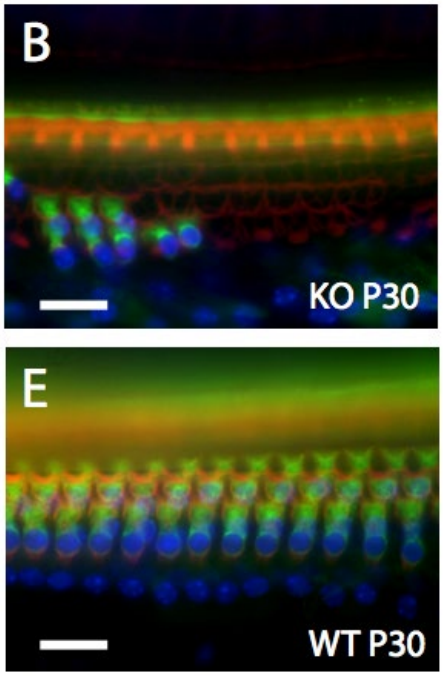
Medical Therapy Principle

Noise

Drugs



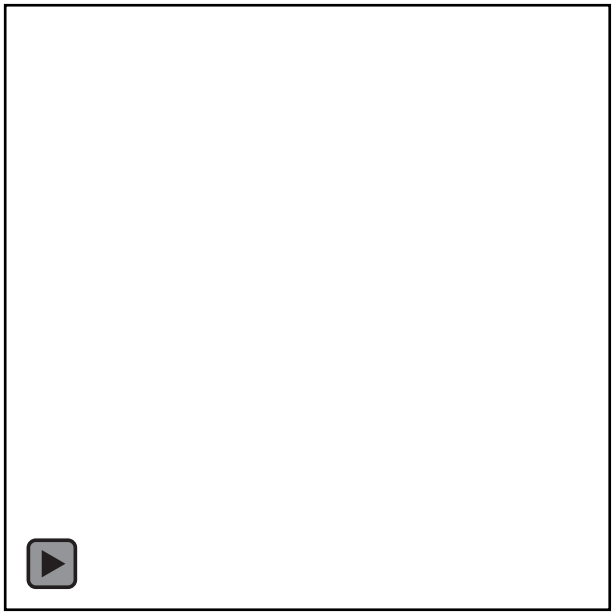
Cochlea



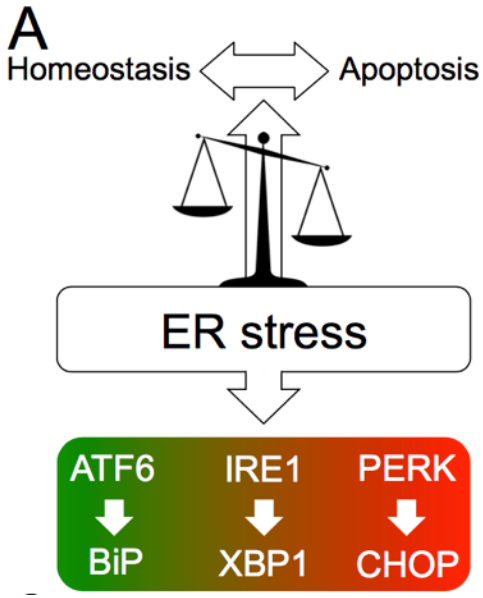
Inner-ear damage

Calcium Signaling/UPR Cochlea

Noise/Cisplatin



Calcium signalling in the cochlea

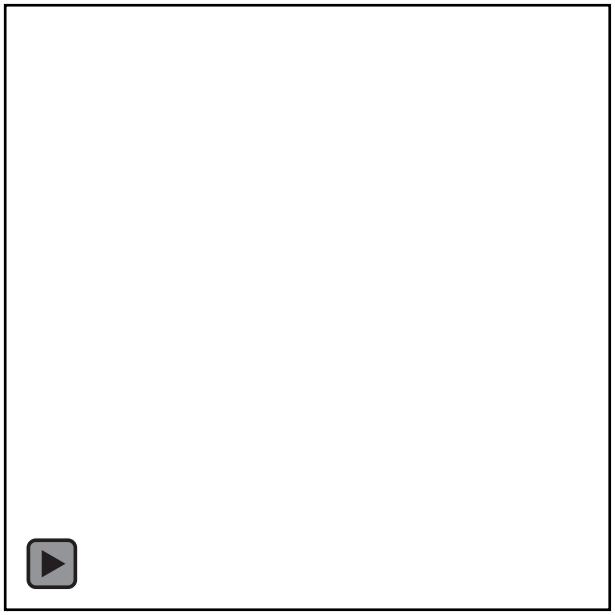


Unfolded Protein Response

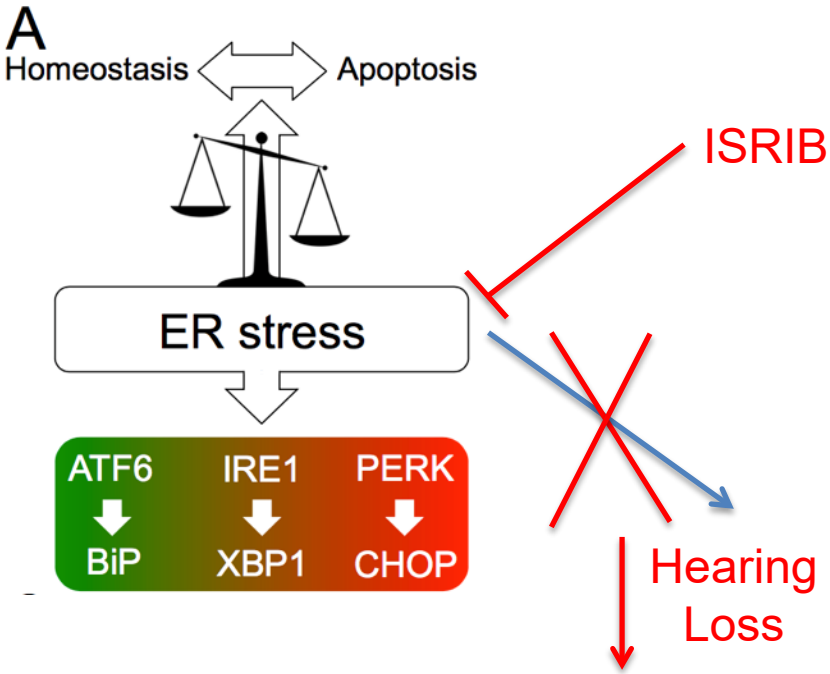
Hearing Loss

Calcium Signaling/UPR Cochlea

Noise/Cisplatin



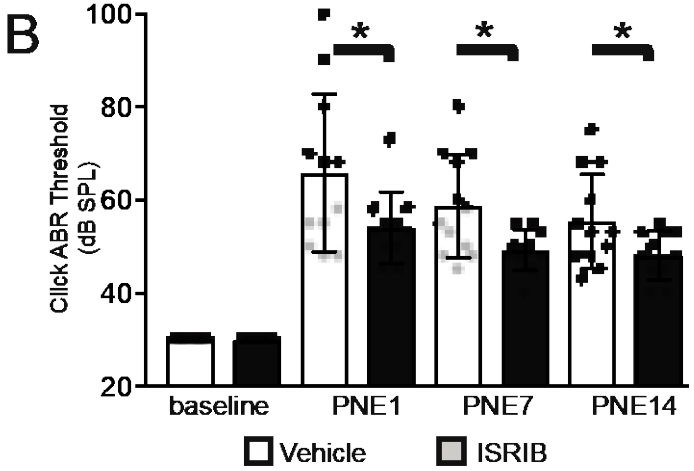
Calcium signalling in the cochlea

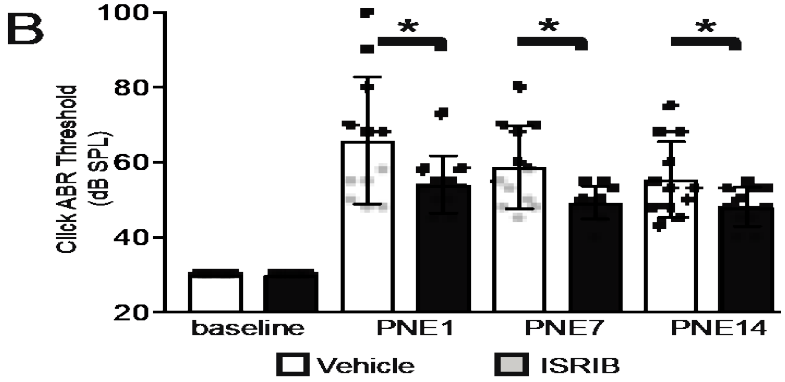


Unfolded Protein Response

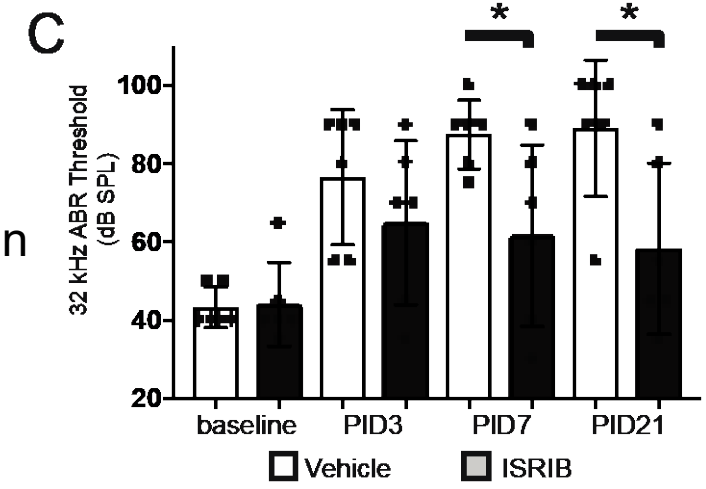
Medical therapy ISRIB

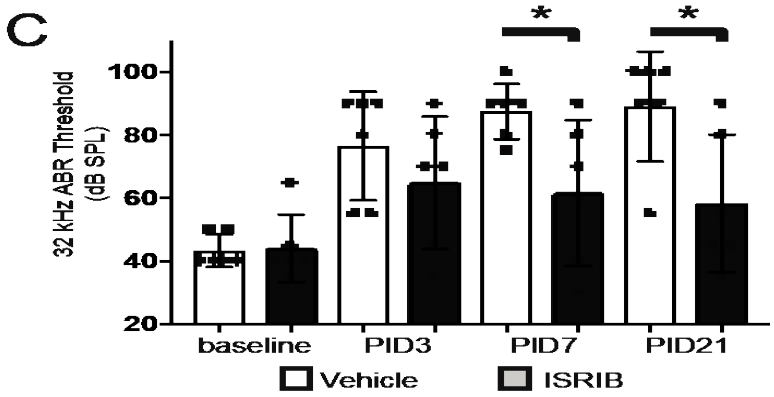
Noise



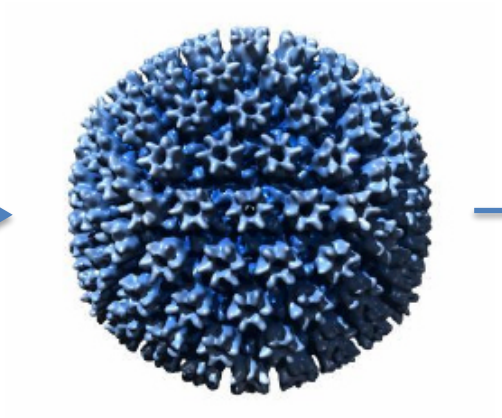


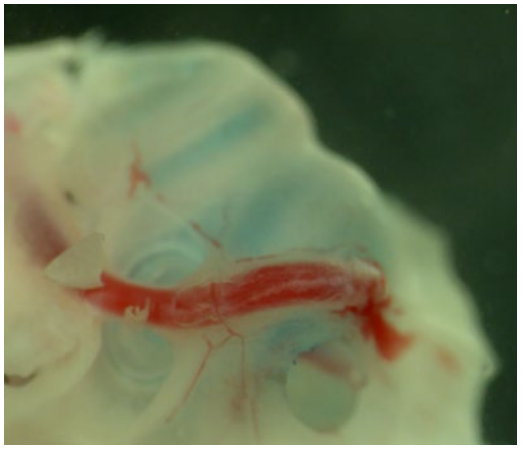
Cisplatin





Gene therapy Principle





Gene

Viral vector

Cochlea

Gene therapy Potential uses

Inherited congenital hearing loss

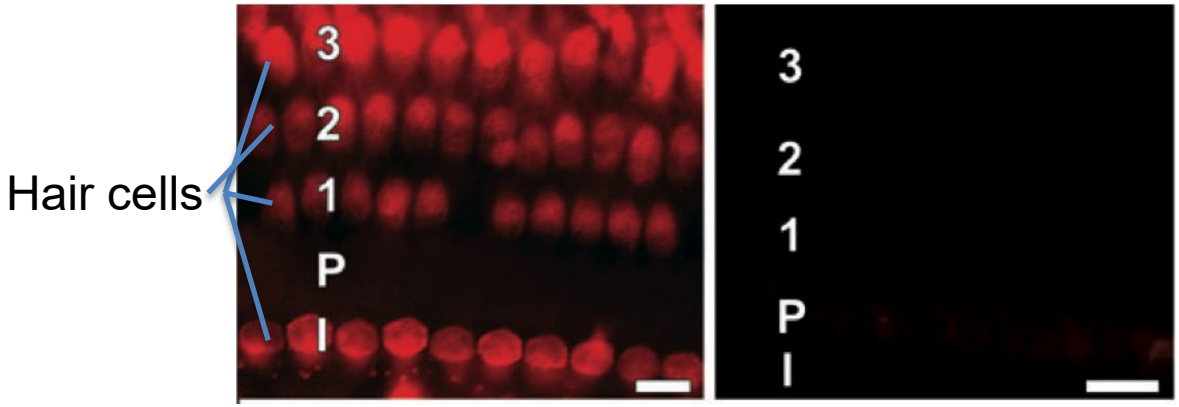
Hair-cell regeneration

Neuronal maintenance/growth

Ototoxicity prevention

Acquired hearing loss Gene therapy

Guinea pig deafened with ototoxic drugs



Atoh 1-treated untreated

Izumikawa, 2005

Congenital deafness Gene therapy

Gene Therapy (2013), 1–10

www.nature.com/gt

ORIGINAL ARTICLE

Virally expressed connexin26 restores gap junction function in the cochlea of conditional Gjb2 knockout mice

Q Yu[1,2,4], Y Wang[3,4], Q Chang[2], J Wang[2], S Gong[1], H Li[3] and X Lin[2]

ORIGINAL ARTICLE

Perinatal *Gjb2* gene transfer rescues hearing in a mouse model of hereditary deafness

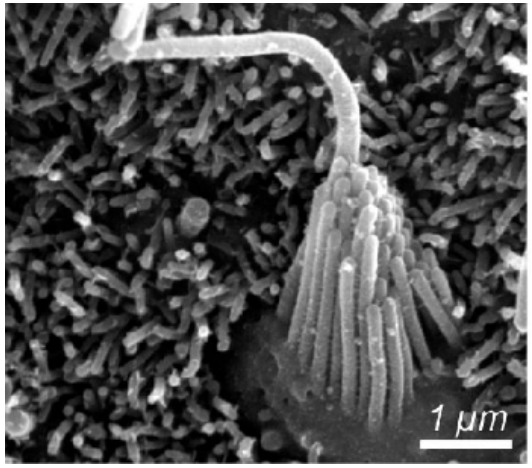
Takashi Iizuka[1], Kazusaku Kamiya[1], Satoru Gotoh[2], Yoshinobu Sugitani[2], Masaaki Suzuki[3], Tetsuo Noda[2,4], Osamu Minowa[2,4] and Katsuhisa Ikeda[1,*]

Stem cells Hair cell regeneration

Mechanosensitive Hair Cell-Like Cells from Embryonic and Induced Pluripotent Stem Cells

Kazuo Oshima[1], **Kunyoo Shin**[1], **Marc Diensthuber**[1,2], **Anthony W. Peng**[1], **Anthony J. Ricci**[1], and **Stefan Heller**[1]

[1]Departments of Otolaryngology – Head & Neck Surgery and Molecular & Cellular Physiology, Stanford University School of Medicine, Stanford, CA 94305

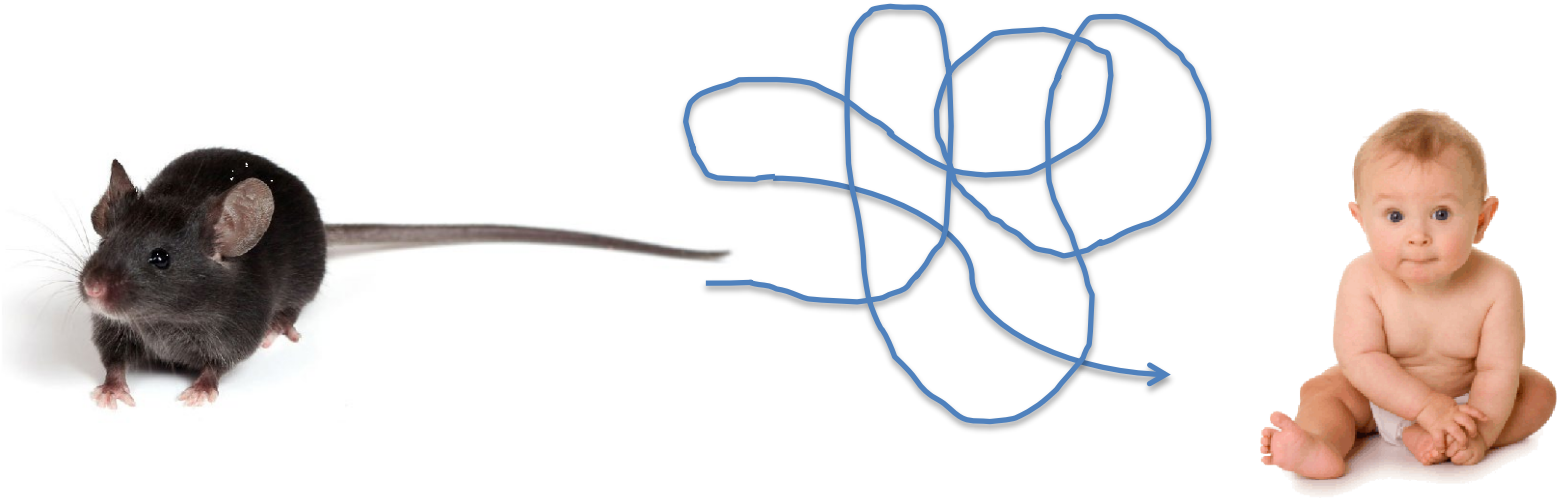


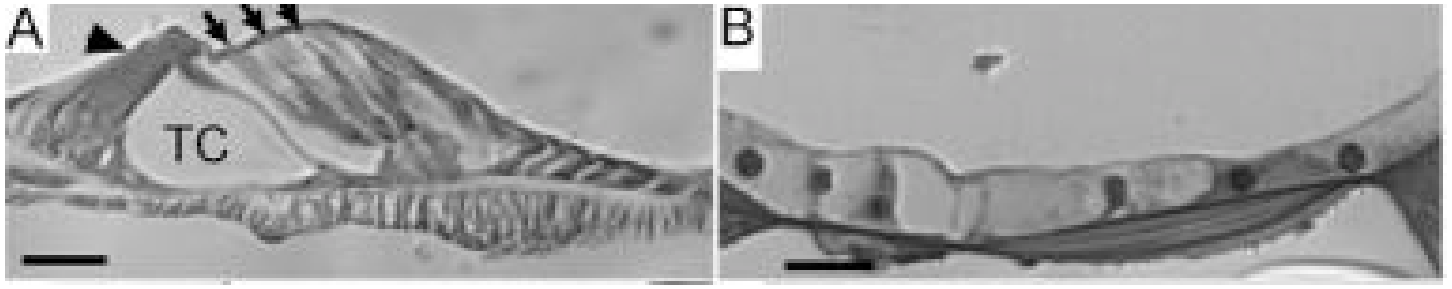
Future directions Present decisions

Cochlear implantation vs hearing restoration

“Should I get a cochlear implant or save the ear for future treatments?”

Future directions Present decisions

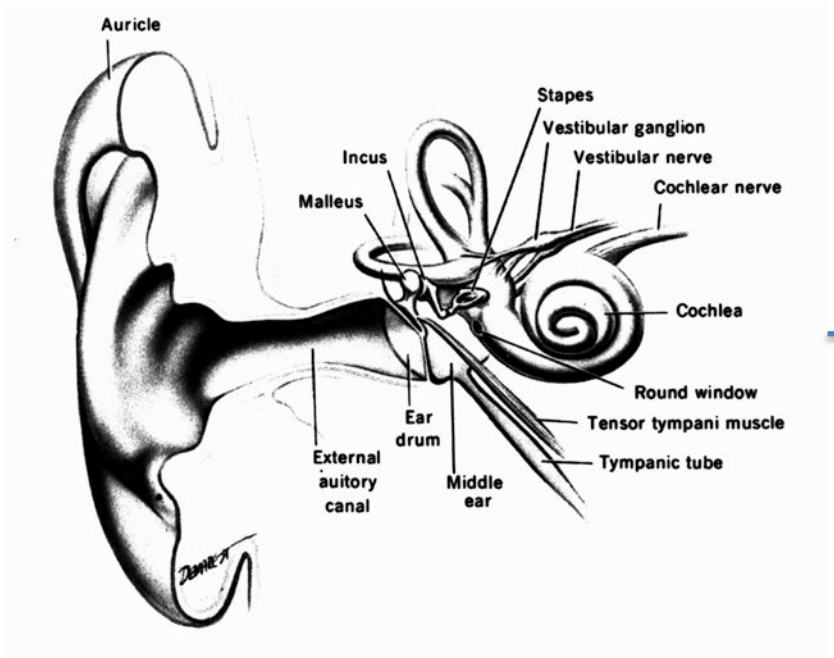




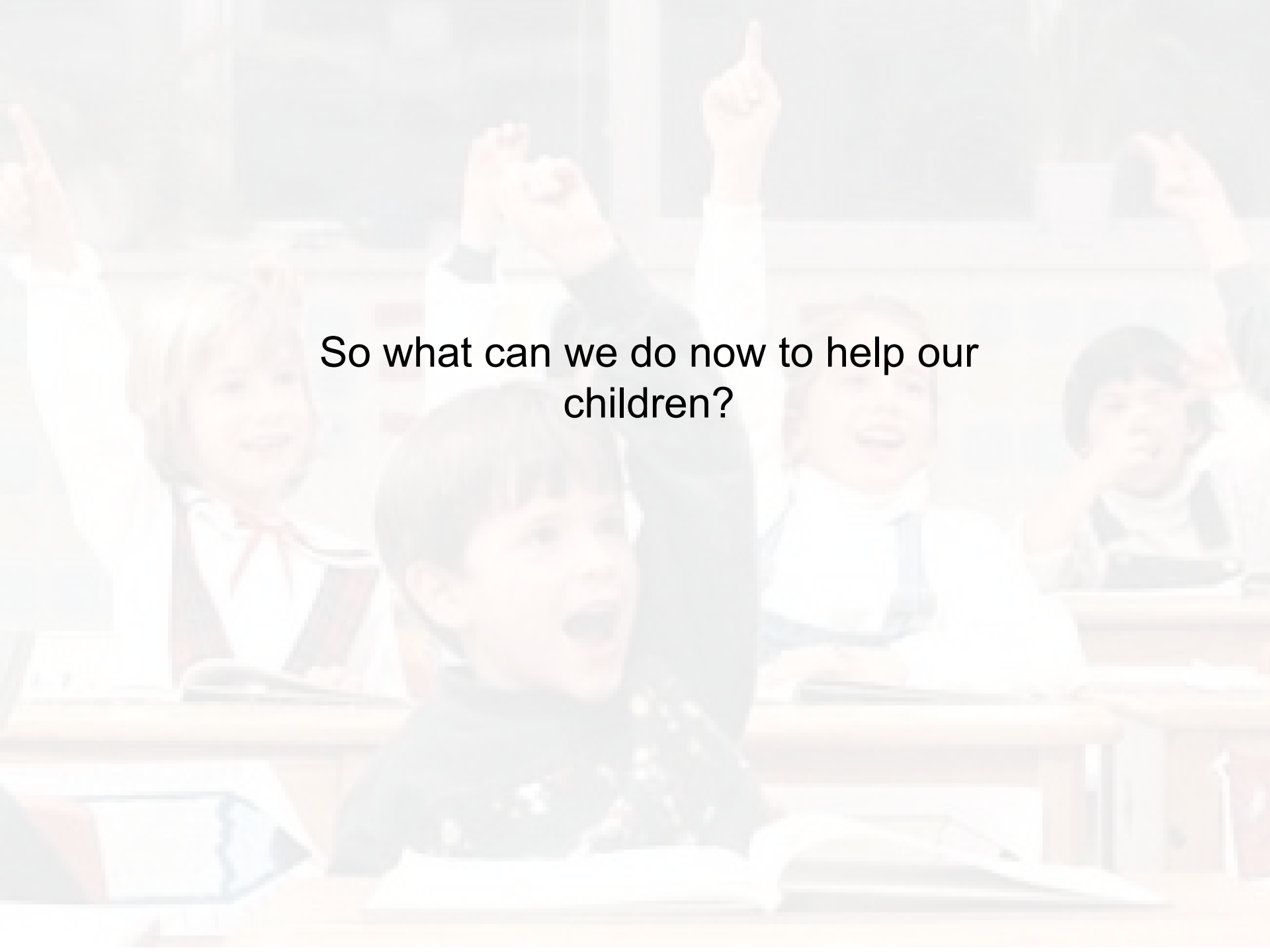
Normal cochlea

Long-deafened cochlea

Future directions Present decisions



Use it or lose it!



So what can we do now to help our children?

So what can we do now to help our children?

Work together to give our children the best access to sound, language, and education that we can right now!