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Genetics of Pediatric Hearing Loss in the Age of Precision Medicine, in partnership with the American Academy of Audiology

Margaret Kenna, MD MPH
Sarah Fuller Chair for Hearing Loss and Hearing Restoration
Director of Clinical Research
Otolaryngology and Communication Enhancement
Boston Children's Hospital

Shelby Redfield, MS CGC
Licensed Genetic Counselor
Department of Otolaryngology
Boston Children's Hospital

Margaret Kenna, MD, MPH

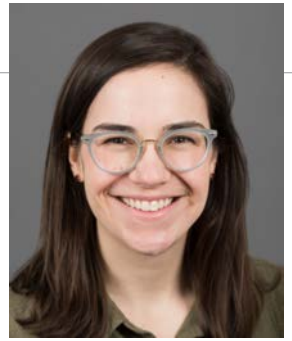
Director of Clinical Research, Department of Otolaryngology, Boston Children's Hospital

Dr. Margaret Kenna conducts research on the causes of pediatric hearing loss, including genetics, congenital cytomegalovirus, and structural anomalies of the temporal bone. Along with Shelby Redfield, MS, CGC, and Eliot Shearer, MD, PhD, her group has recently identified a new hearing loss gene, become involved in first-in-human gene therapy for hearing loss, and participates in prenatal genetic testing for hearing loss.

Dr. Kenna received her undergraduate degree from the University of Pennsylvania and her MD from Boston University School of Medicine. She completed a residency in Otolaryngology-Head and Neck Surgery at the University of Arkansas for Medical Sciences, a Pediatric Otolaryngology Fellowship at Children's Hospital of Pittsburgh, and a Master's in Public Health at the Harvard School of Public Health.

Dr. Kenna co-founded the Boston Children's Hospital Pediatric Cochlear Implant Program and was its Director from 1995-2003. Since 2003, she has been the Director of Clinical Research in the Dept. of Otolaryngology, Boston Children's Hospital, and is Director of the Hearing Loss Program.

She is a founding member of the Universal Newborn Hearing Screening Advisory Committee of the Massachusetts Department of Public Health, the Harvard Medical School Center for Hereditary Deafness, the Massachusetts Coalition for Congenital CMV, the Usher Syndrome Coalition, and the American Society for Pediatric Otolaryngology.



Shelby Redfield, MS CGC

Shelby Redfield, MS CGC, is a genetic counselor in the Department of Otolaryngology and Communication Enhancement at Boston Children's Hospital and a member of the Translational Hearing Genomics Lab. Her clinical practice brings personalized, passionate genetic counseling to patients and families with sensorineural hearing loss. She is the clinical research manager for genomics research efforts within the Department of Otolaryngology at Boston Children's. Her research interests include hearing loss gene discovery, expansion of known phenotypic spectrums of rare genetic conditions, and identification of novel variants in hearing loss genes using cutting-edge sequencing technologies. She received her Master's in Genetic Counseling from Boston University.

Disclosures

- **Presenter Disclosure**: Financial: Margaret Kenna is employed by Boston Children's Hospital and receives royalties from Up-to-Date. She received an honorarium for this presentation. Non-financial: Margaret Kenna has no relevant non-financial relationships to disclose. Financial: Shelby Redfield is employed by Boston Children's Hospital and serves as a consultant for Eli Lilly and Company and for Skylark Bio. She received an honorarium for this presentation. Non-financial: Shelby Redfield has no relevant non-financial relationships to disclose.
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Limitations/Risks

- The applicability and accuracy of the course content may vary by the clinical, geographical, and cultural context; you should evaluate the course accordingly.
- As healthcare is rapidly evolving, new findings may change the validity of the information presented in this course. Providers should always consult the latest research and guidelines from professional associations.
- The interventions discussed in this course may be limited in generalizability, requiring practitioners to consider specific individual and population factors.
- The course may not cover all possible risk factors, diagnostic methods, or treatment options, and complex cases may require additional considerations.
- Healthcare providers should apply cultural competence and sensitivity to ensure effective and respectful care based on their patients' diverse needs.
- Providers should always evaluate the limitations of diagnostic and screening tools, considering their potential for false results as well as any ethical implications.
- It is the responsibility of course participants to critically evaluate the evidence from multiple sources to guide professional practice.

Learning Outcomes

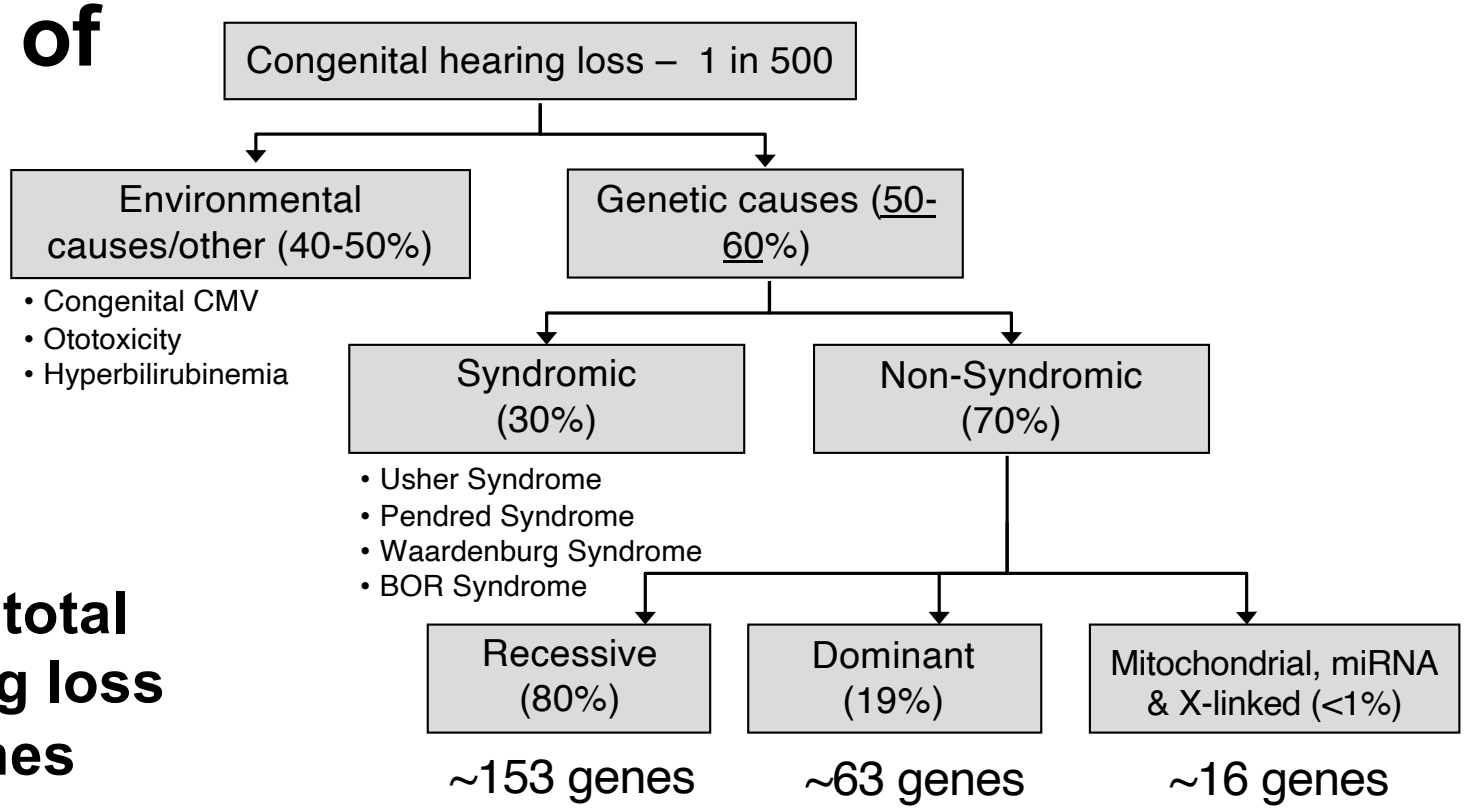
After this course, participants will be able to:

- Describe key concepts and define terms used in the genetic diagnosis, evaluation, and management of pediatric sensorineural hearing loss.
- Describe current clinical practices in the genetic evaluation and diagnosis of pediatric sensorineural hearing loss, including implications for patients.
- Identify avenues for collaboration between audiology professionals and genetic counselors at their place of employment.

Quiz Hint

Q1

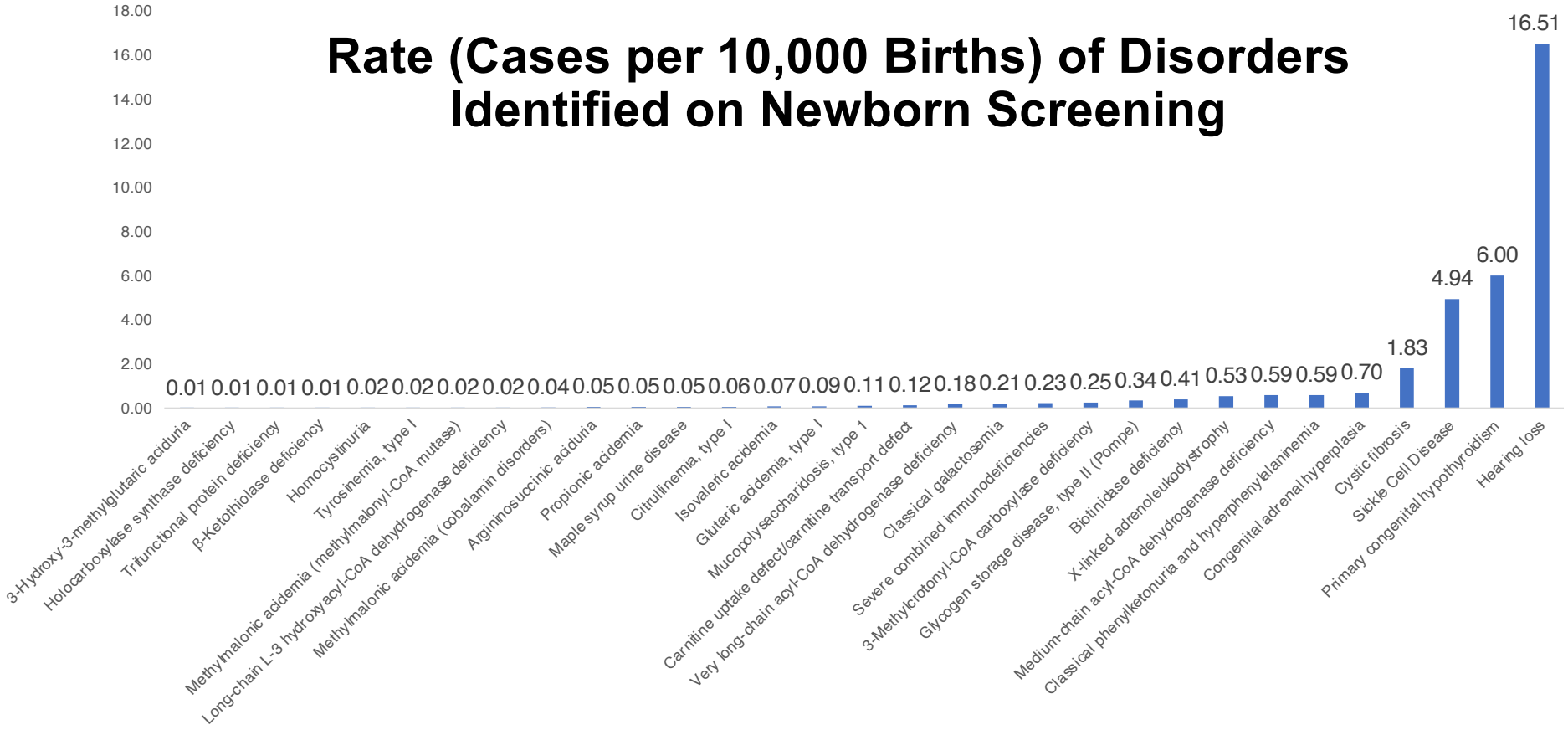
Incidence of SNHL in Children



~232 total hearing loss genes

Adapted from Shearer et al., GeneReviews (2017)

SNHL Genetics Background



Sontag, Marci K., et al. Morbidity and Mortality Weekly Report 69.36 (2020)

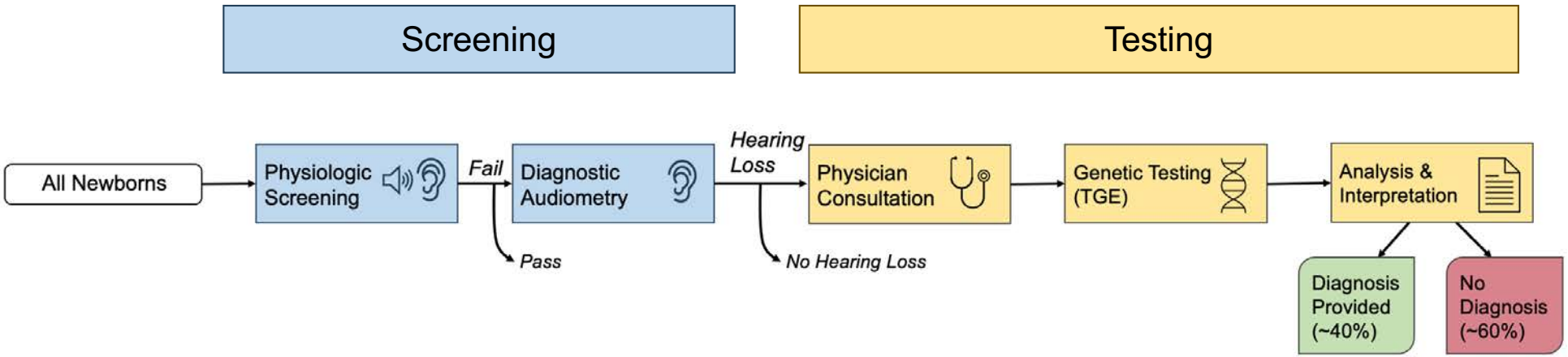
Quiz Hint

Q3

Determining an Underlying Etiology of Pediatric SNHL Has Crucial Implications for Outcomes

- Provides Prognostic information
- Guides treatment options and surgical planning
  - May affect cochlear implant outcomes
- Increases familial uptake of treatment
- Determines if SNHL is part of a syndrome and facilitates appropriate follow-up
- Determines targeted therapeutic eligibility

Clinical Evaluation of Children with Hearing Loss at Our Center

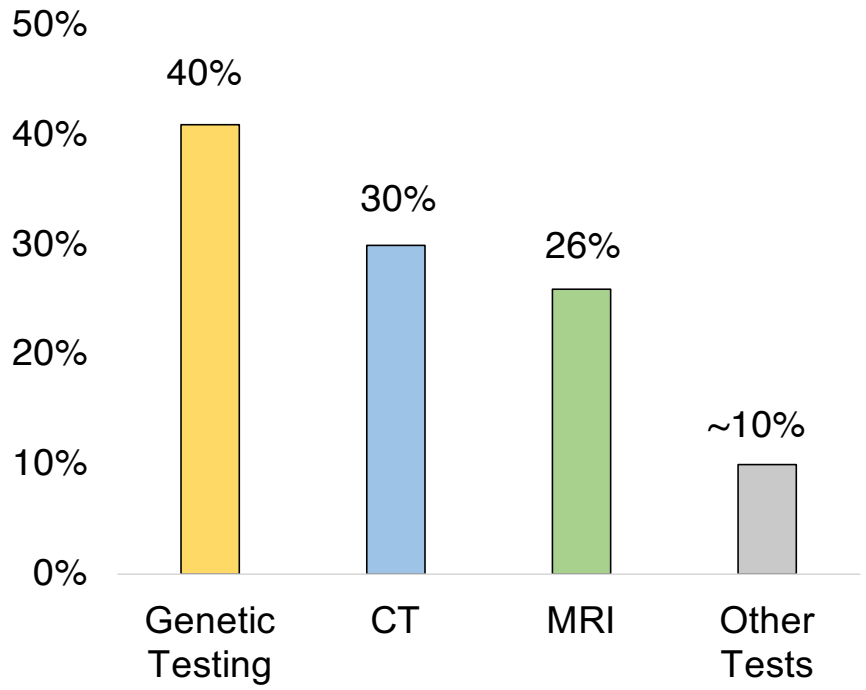


Average age @ BCH: 9.3 months

Quiz Hint

Q5

The Single Most Effective Test



Shearer & Smith 2015; Chen et al 2014; Kachniarz et al 2014

Information for Families

- ✓ Prognostic information for patients/families
- ✓ Chance of recurrence for patients/families
- ✓ Evaluation for syndromic causes of hearing loss – **~20% of diagnoses**

Monogenetic (Mendel
Causes of Hearing Lo
by far, The Most Com
Pediatric SNHL

SNHL etiology of 637 patients who underwent evaluation at Boston Children's from 2019-2024

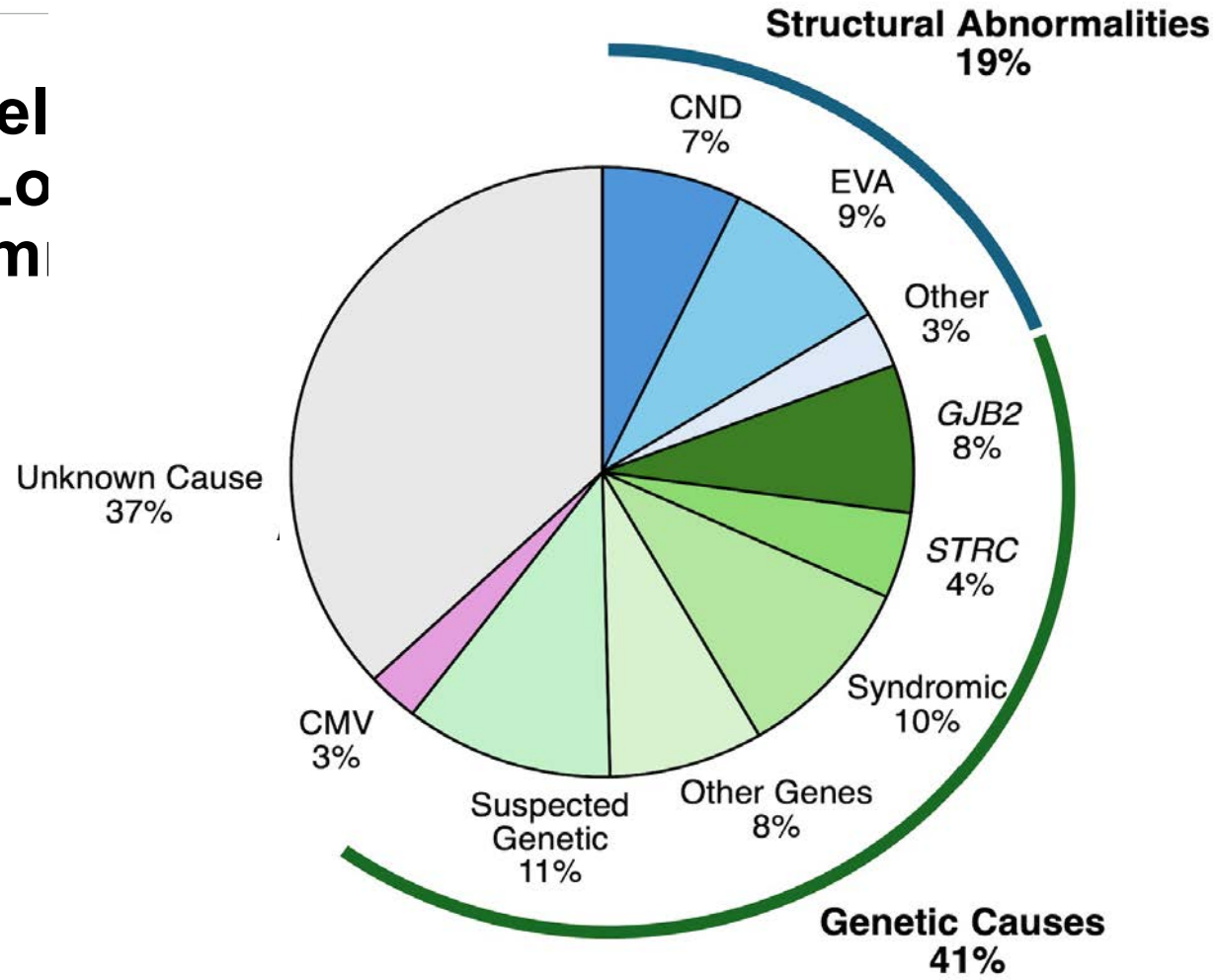


Image courtesy of A.E. Shearer; internal data

Professional Societies Endorse Genetic Testing for Pediatric SNHL

American College of Medical Genetics

- Practice guideline (2014) and practice resource (2022) recommend genetic testing for all deaf and hard of hearing children

Joint Committee on Infant Hearing (JCIH)

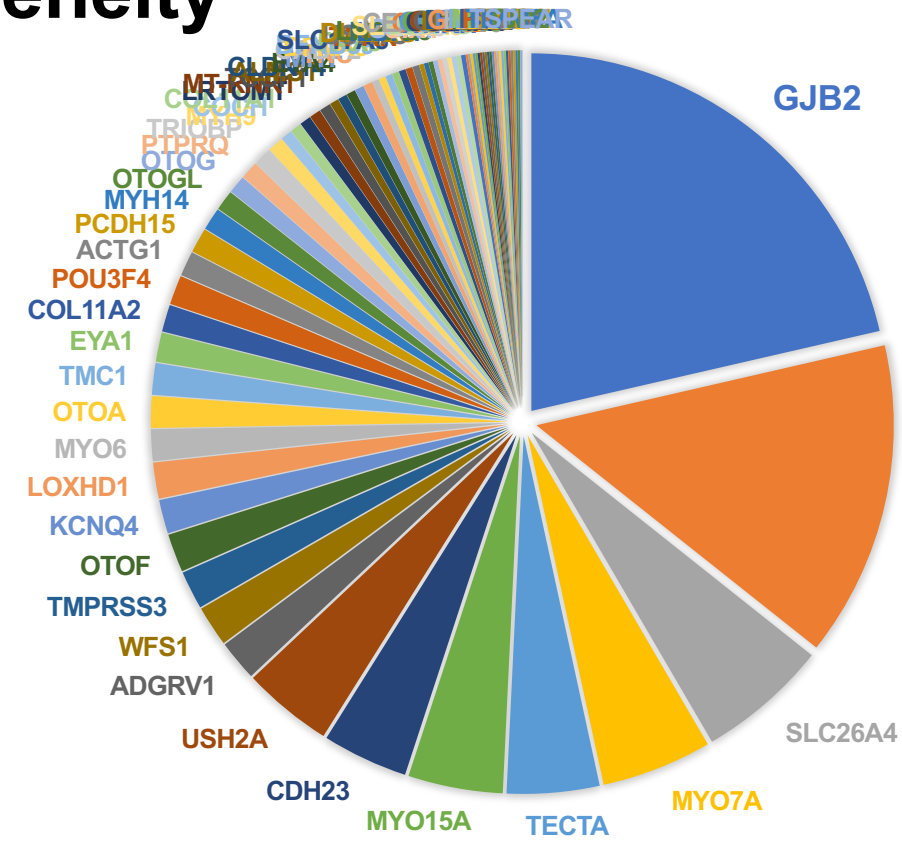
- Year 2019 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs endorses importance of genetic testing/counseling

Quiz Hint

The Genetic Heterogeneity of Hearing Loss

Comprehensive Genetic Testing for Hearing Loss Recommended:

- **Gene panels** targeted 150-300 SNHL genes at once (massively parallel sequencing)
- Panels should include most nonsyndromic hearing loss genes and many syndromes

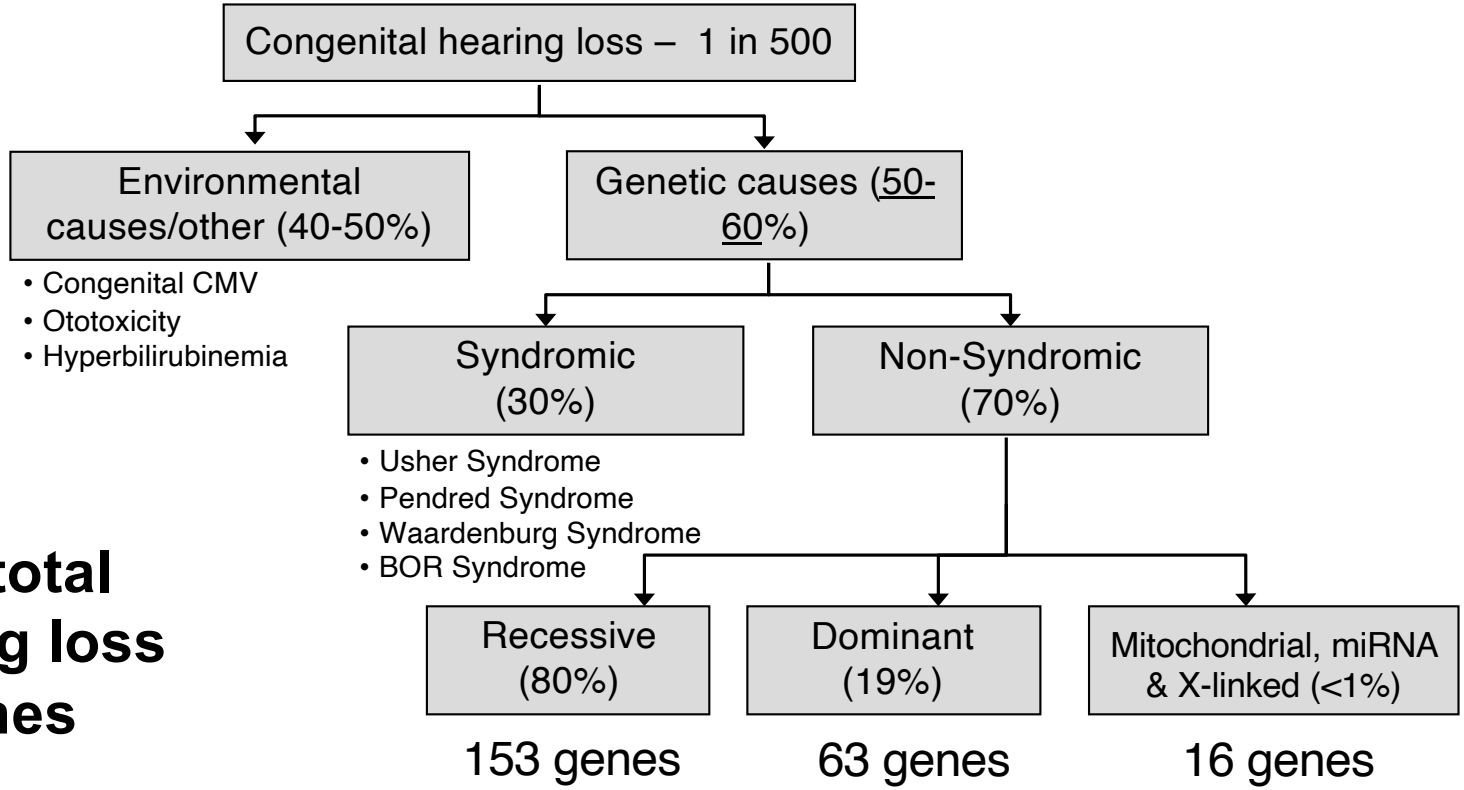


2,460 Patients with Hearing Loss

Shearer et al Genet in Med 2019

Nonsyndromic Genetic Sensorineural Hearing Loss

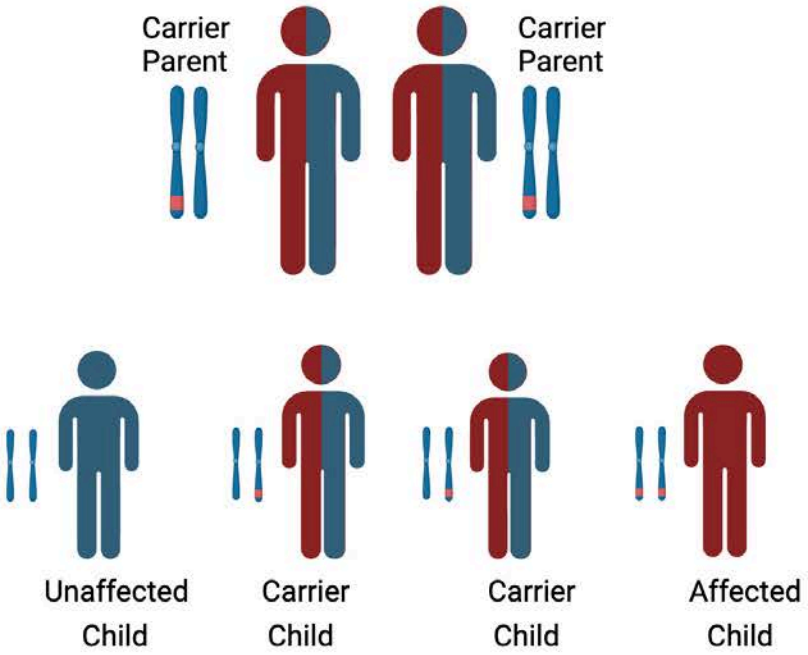
Nonsyndromic SNHL makes up 70% of genetic diagnoses and involves 232+ genes



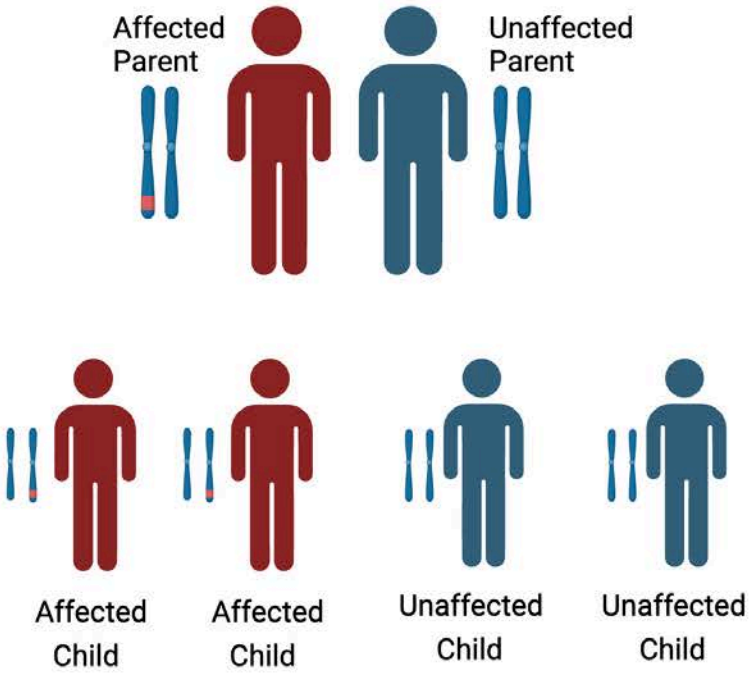
232 total hearing loss genes

Adapted from Shearer et al., GeneReviews (2017)

Autosomal Recessive Inheritance



Autosomal Dominant Inheritance



made with BioRender

Quiz Hint

Q2

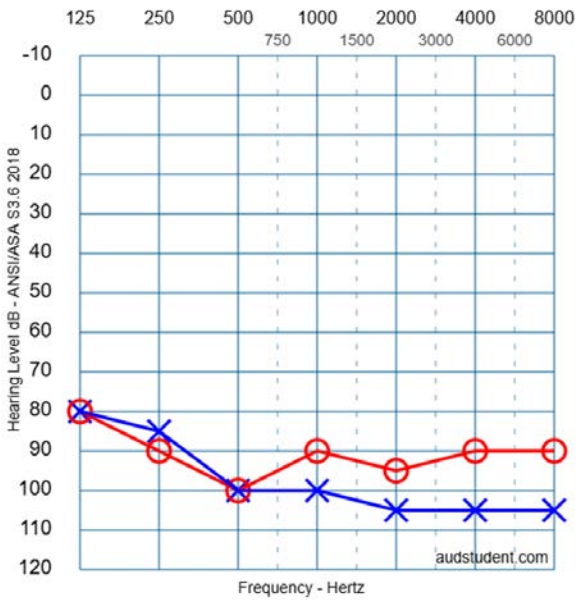
GJB2 (Connexin 26)

- Autosomal recessive nonsyndromic hearing loss type 1a (DFNB1)
  - First discovered and described in 1997
- Connexin 26: important gap junction protein that contributes to potassium homeostasis in the cochlea
- Most common cause of genetic hearing loss
  - Between 25% and 50% of all diagnoses, depending on the population
- There are population-specific mutations in GJB2 that are very common
  - Example: 35delG or V37I

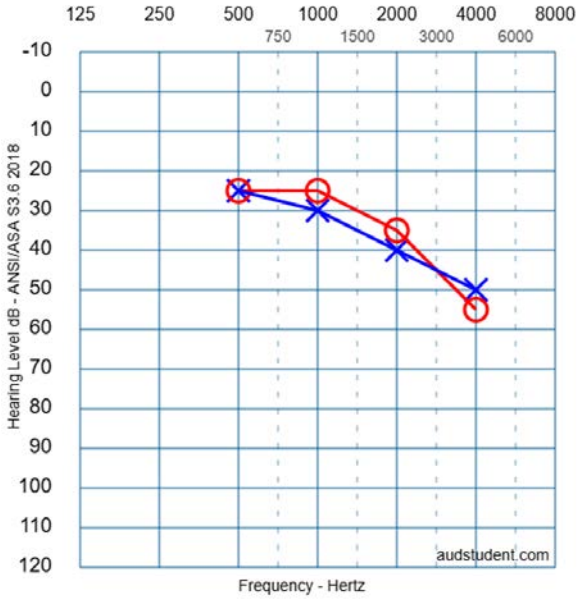
GJB2 (Connexin 26)

- Degree of hearing loss depends on the severity of the genetic mutation
  - Severe mutations cause severe SNHL
  - Mild (i.e., missense) mutations cause milder SNHL
  - Combination of mild and severe mutations = somewhere in the middle
- Notoriously variable – siblings with the same genetic result can have very different audiograms
- Progression of SNHL seen for ~50%

Two Siblings, Same Gene: GJB2, 35delG Variant (Homozygous)



Sibling 1, age 10 years



Sibling 2, age 15 months

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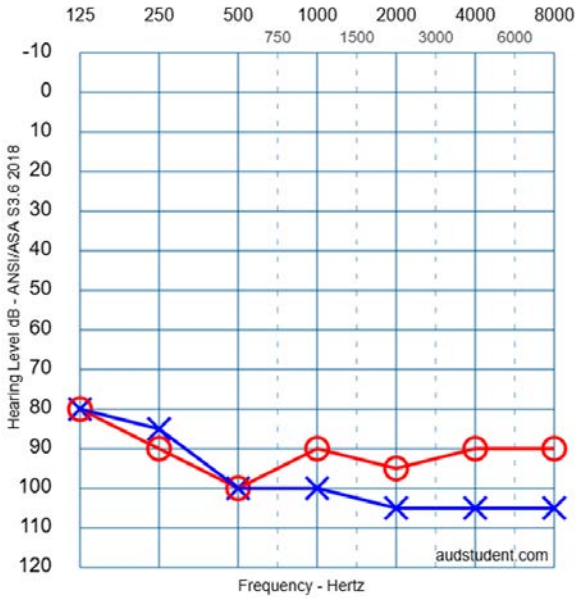
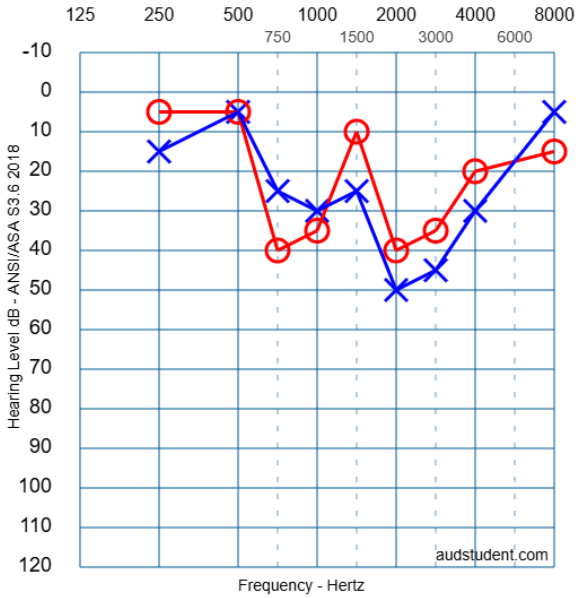
GJB2

Same Gene, Different Mutations: GJB2, 35delG vs M34T



Age 10y, 35del/35del



Age 3y, M34T/M34T

Images generated on AudStudent.com

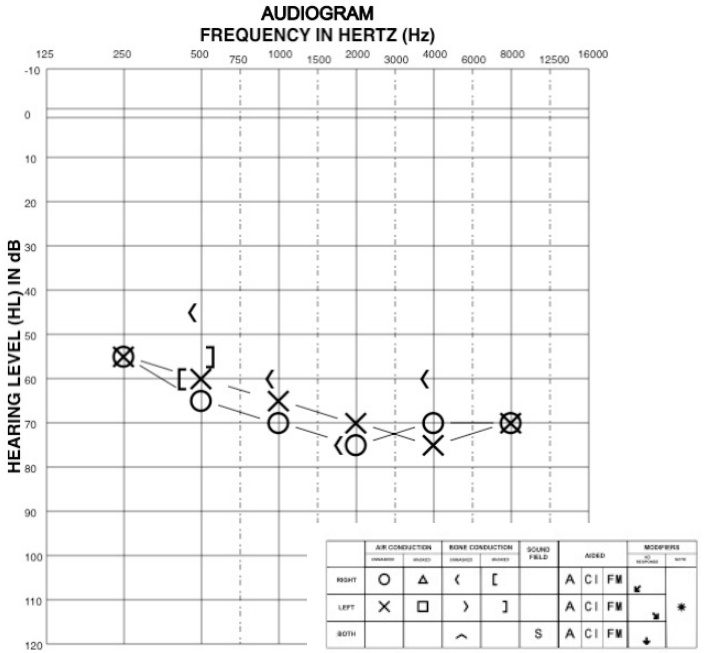
Case Example: Common Diagnoses Present Along a Clinical Spectrum

- 3 y.o. female presenting with concerns for hearing
- Passed a newborn hearing screen and subsequent OAE screens
- Speech and language were developing normally until age 2.5 y.o. at which time she experienced a significant regression; parents developed significant concerns for her hearing
- Behavioral audiology testing was inconclusive at first evaluation
  - Sedated ABR at age 3 y.o. revealed a bilateral moderate to severe SNHL

Case Example: Common Diagnoses Present Along a Clinical Spectrum

Hearing loss gene panel testing was performed:

- Positive for **GJB2**
- Homozygous variant 35delG
  - Typically causes congenital severe-profound SNHL
- Indicated risk for further progression – family is considering cochlear implantation



Speech Perception

	Test	Level (dB)	Masking (dB)	Score (%)
Right Ear	WIPI	90	65	68
Left Ear	WIPI	90	65	48

Quiz Hint

Q9

STRC/CATSPER2 AR Nonsyndromic SNHL and Decreased Male Fertility

- Autosomal recessive
- Formerly called “deafness infertility syndrome”
  - Actually, two separate conditions – can have one without the other, but usually both together
- 2nd most common cause of genetic hearing loss – most common cause of mild/moderate SNHL
- ***STRC****:* mild to moderate nonsyndromic sensorineural hearing that is generally quite stable; occasionally very slow progression
- ***CATSPER2:*** asthenoteratozoospermia (sperm immobility)
- STRC and CATSPER2 genes sit right next to each other on the chromosome
  - They are often both deleted together as a contiguous gene deletion
- *STRC hearing loss is probably underdiagnosed because genetic testing for it is complicated*
  - *There is a copy-cat gene with no function right next door on the chromosome, called a pseudogene, that makes accurate testing tricky*

Syndromic Genetic Sensorineural Hearing Loss

Overview Of Common Hearing Loss Syndromes: ~20-25% of All Diagnoses

Multi-systemic Involvement Including:

- Renal
- Craniofacial
- Neurologic
- Ophthalmologic
- Pulmonary
- Pigmentary
- Genitourinary
- Thyroid
- Cardiac

Quiz Hint

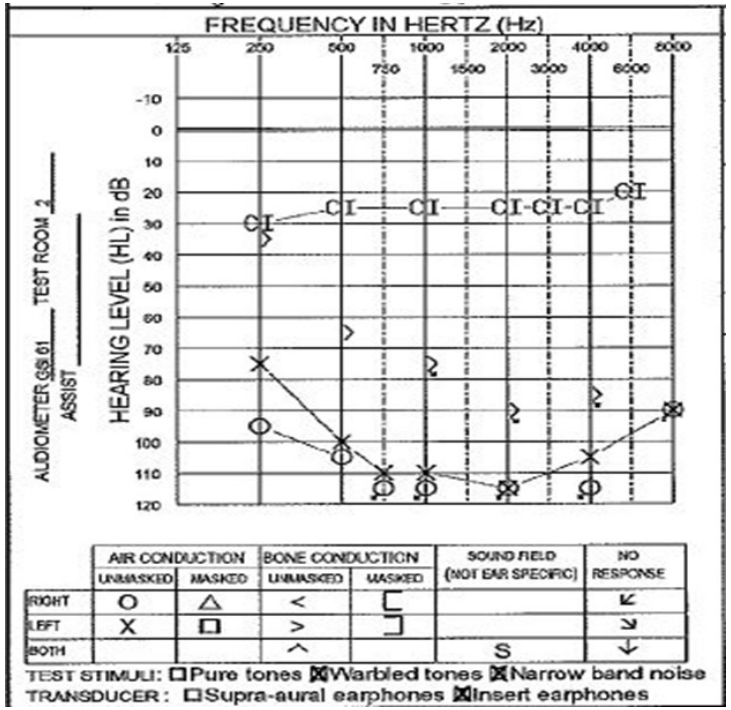
Q4

Common Forms of Syndromic Hearing Loss Which Present as Mimics

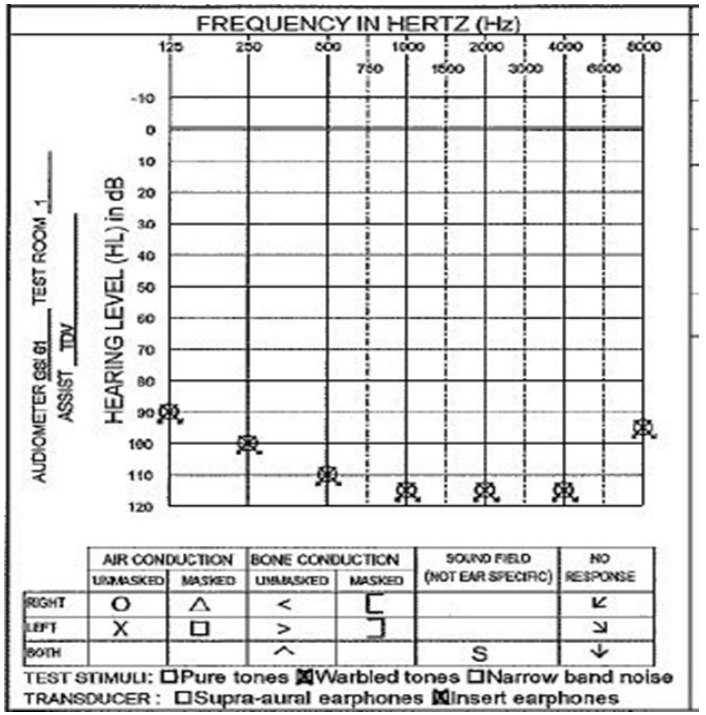
- Usher syndrome: mimics nonsyndromic hearing loss
  - Progressive loss of vision (retinitis pigmentosa in childhood or adolescence)
  - Variable vestibular dysfunction
  - Relatively common: three main subtypes and many genes involved
  - Autosomal recessive inheritance pattern
  - Crucial management implications

Which Gene?

GJB2
(nonsyndromic)



MYO7A (Usher
syndrome)



Common Forms of Syndromic Hearing Loss Mimics

Jervell and Lange-Nielsen syndrome: mimics non-syndromic hearing loss

- Profound hearing loss from birth
- Also causes life-threatening heart condition (Long QT syndrome)
- Many otolaryngologists will order an EKG for all babies with profound SNHL to quickly assess

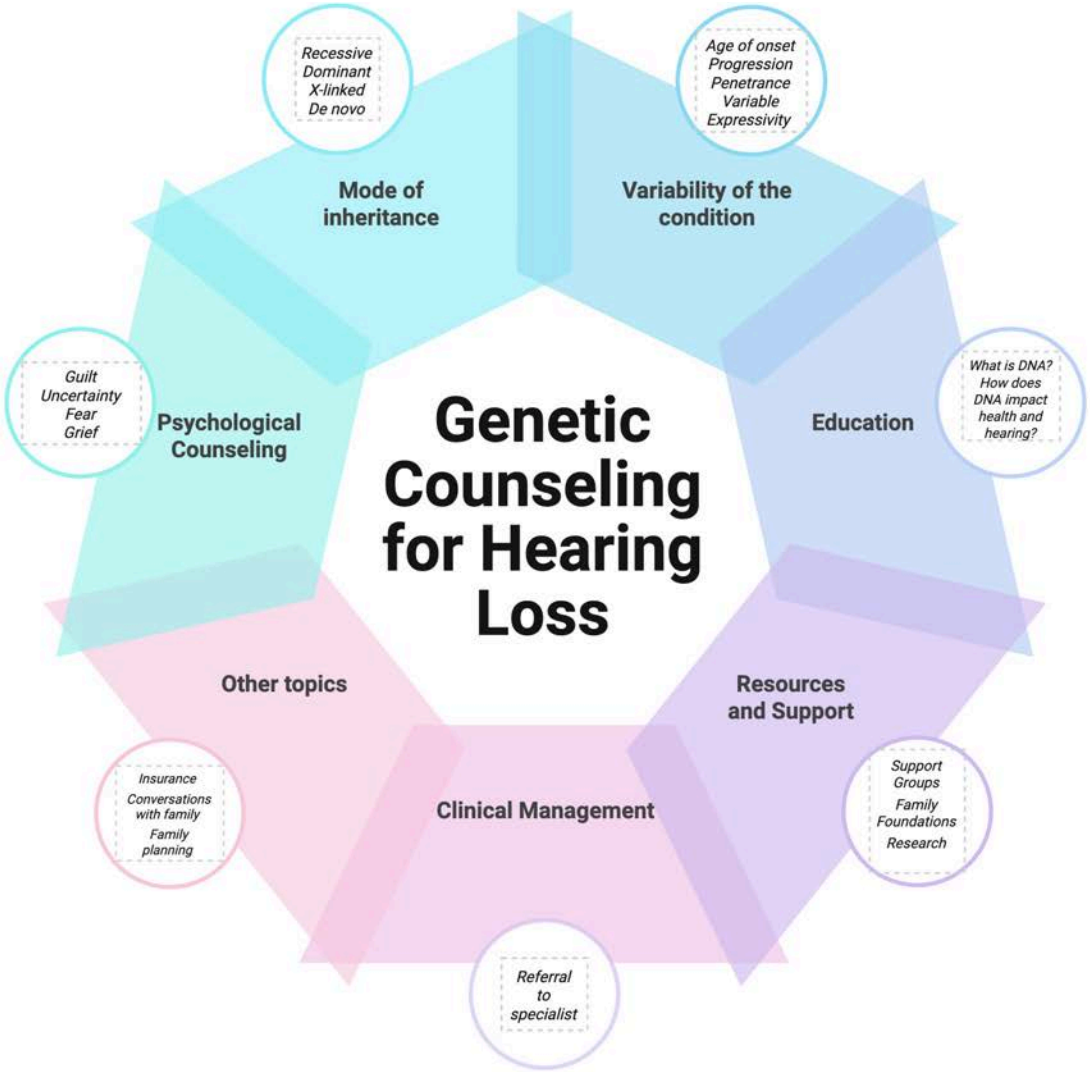
Many Others!

- Waardenburg Syndrome
- CHARGE Syndrome
- Stickler Syndrome
- Alport Syndrome
- Pendred Syndrome
- Perrault Syndrome
- Branchiootorenal Syndrome
- Alstrom Syndrome
- 400+

Genetic Counseling for Hearing Loss

And how audiologists can support the genetic counseling and testing process

Ger



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Quiz Hint

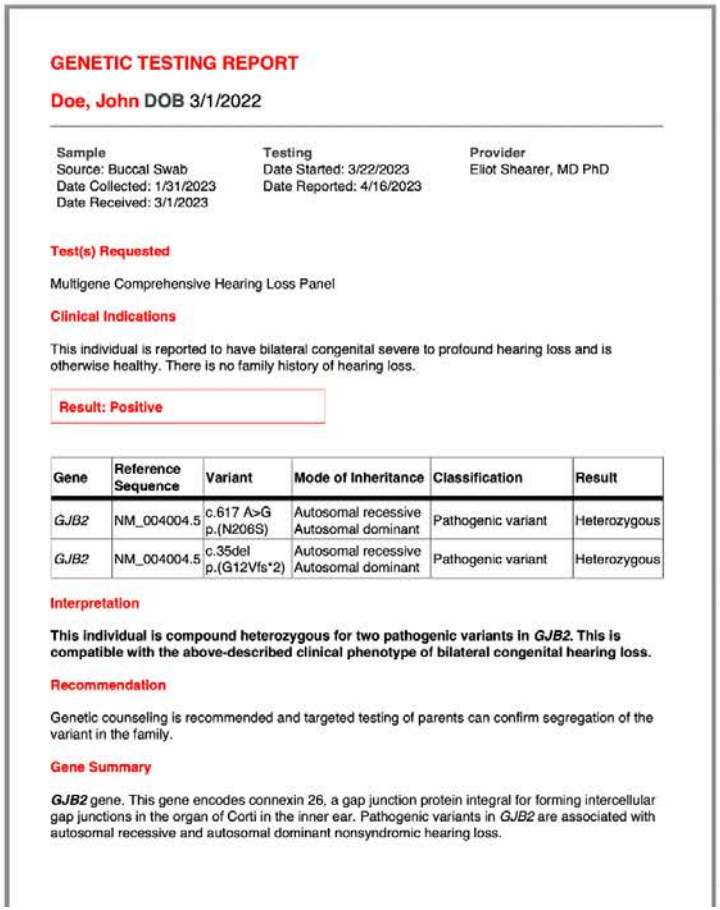
Q10

Genetic Counseling:

Pre-test	Testing	Post-test
• Education • Risks/Benefits • Possible results • Written informed consent	• Cost, insurance, logistics • Biospecimen (saliva, buccal, blood) • Sequencing/testing • Interpretation	• Disclose to family • Counsel and educate • Make appropriate referrals • Educate other HCPs

Core Tenets: knowing your patient and meeting them where they're at

Interpretating Genetic Testing Results is Nuanced (but not impossible!)



GENETIC TESTING REPORT

Doe, John DOB 3/1/2022

Sample	Testing	Provider
Source: Buccal Swab	Date Started: 3/22/2023	Eliot Shearer, MD PhD
Date Collected: 1/31/2023	Date Reported: 4/16/2023	
Date Received: 3/1/2023		

Test(s) Requested

Multigene Comprehensive Hearing Loss Panel

Clinical Indications

This individual is reported to have bilateral congenital severe to profound hearing loss and is otherwise healthy. There is no family history of hearing loss.

Result: Positive

Gene	Reference Sequence	Variant	Mode of Inheritance	Classification	Result
GJB2	NM_004004.5	c.617 A>G p.(N206S)	Autosomal recessive Autosomal dominant	Pathogenic variant	Heterozygous
GJB2	NM_004004.5	c.35del p.(G12Vfs*2)	Autosomal recessive Autosomal dominant	Pathogenic variant	Heterozygous

Interpretation

This individual is compound heterozygous for two pathogenic variants in *GJB2*. This is compatible with the above-described clinical phenotype of bilateral congenital hearing loss.

Recommendation

Genetic counseling is recommended and targeted testing of parents can confirm segregation of the variant in the family.

Gene Summary

GJB2 gene. This gene encodes connexin 26, a gap junction protein integral for forming intercellular gap junctions in the organ of Corti in the inner ear. Pathogenic variants in *GJB2* are associated with autosomal recessive and autosomal dominant nonsyndromic hearing loss.

Patient Identifying Information

Sample Collection and Test Information

Test Result

Variant Summary Table

Test Interpretation, Clinical Recommendations, and Summary

Any Child with Sensorineural Hearing Loss

↓

Order Gene Panel Testing

↓

Provide Result in Clinic

⇣

Refer to Genetics
if Indicated/Required

Genetic Counseling: Results

Three possible results

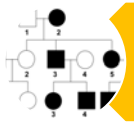
Positive (Pathogenic)

Variant of uncertain significance

Negative

Gene and clinical information
- Syndromic vs. nonsyndromic

Prognosis
- Progression
- Onset of other clinical features



Inheritance
- Dominant vs. Recessive
- Recurrence

Follow-up testing
- Parents? Siblings?

Referral to other specialists
- For syndromic diagnosis

Provision of Resources
- Additional reading
- Support groups, research organizations

Quiz Hint

Q6

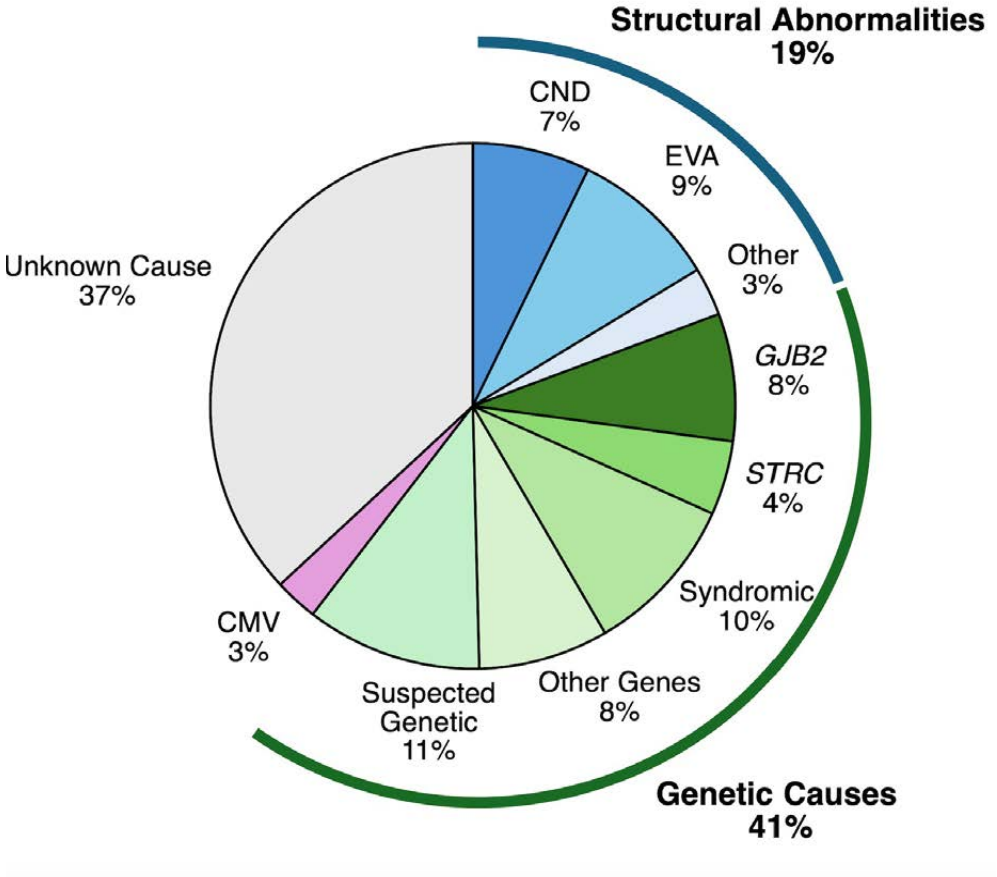
How Can Audiologists Work With Genetics Professionals Families?

- Educate families and lay groundwork for a successful genetic counseling experience by introducing some basic benefits of testing
- Refer to genetics professionals when able
- Get familiar with local resources
  - If lacking, what else is out there?
- Invest time to understand each patient's diagnosis, in particular the audiological manifestations (prognosis)

What Do We Do If We Don’t Find The Answer With Standard Testing?

Genetic Research and Innovation for Pediatric Hearing Loss

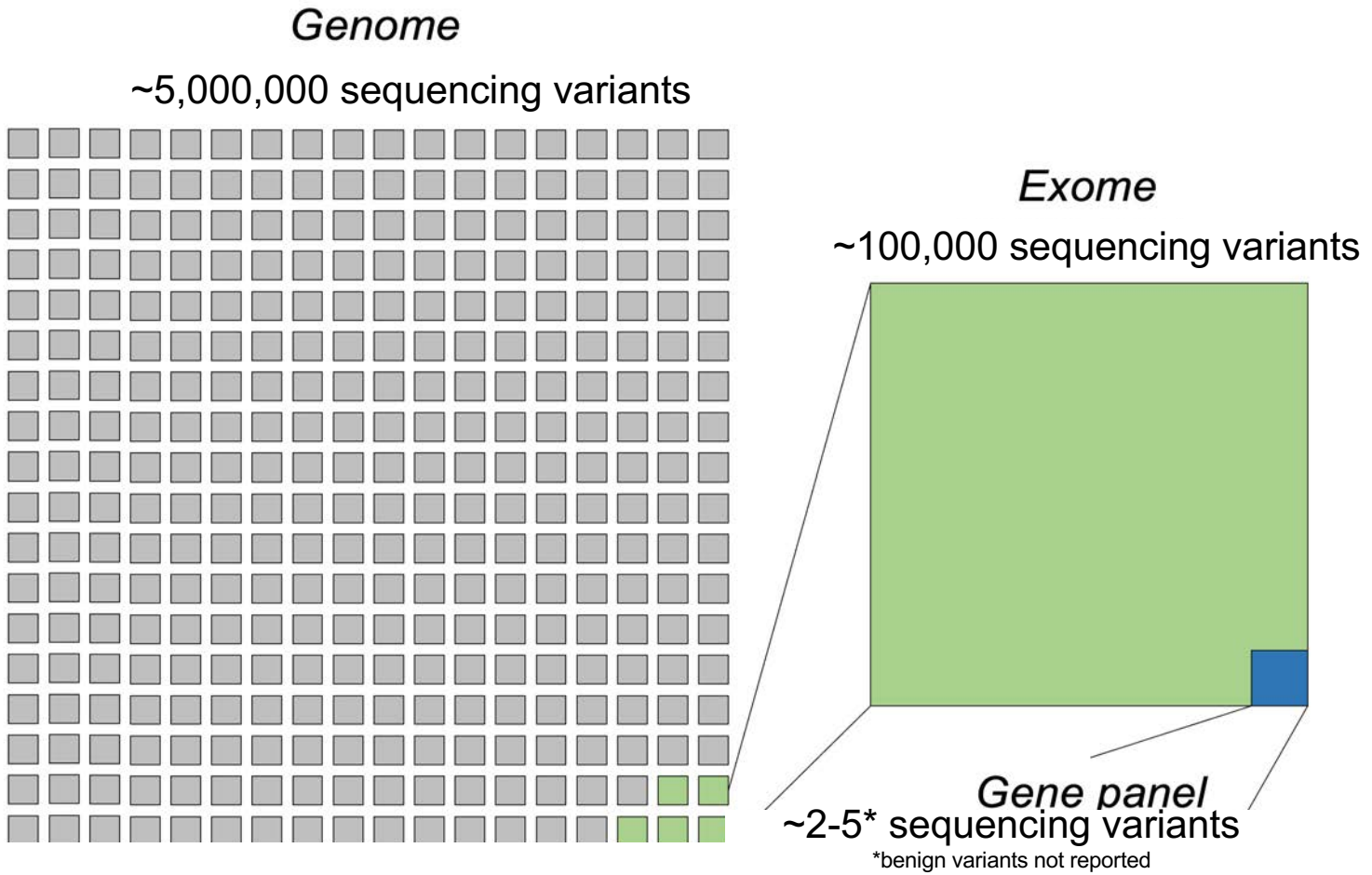
Many Children Will Not Receive an Etiological Diagnosis After Full Clinical Evaluation, Even When a Genetic Cause is Strongly Suspected



Larger, genomic sequencing may help find additional answers

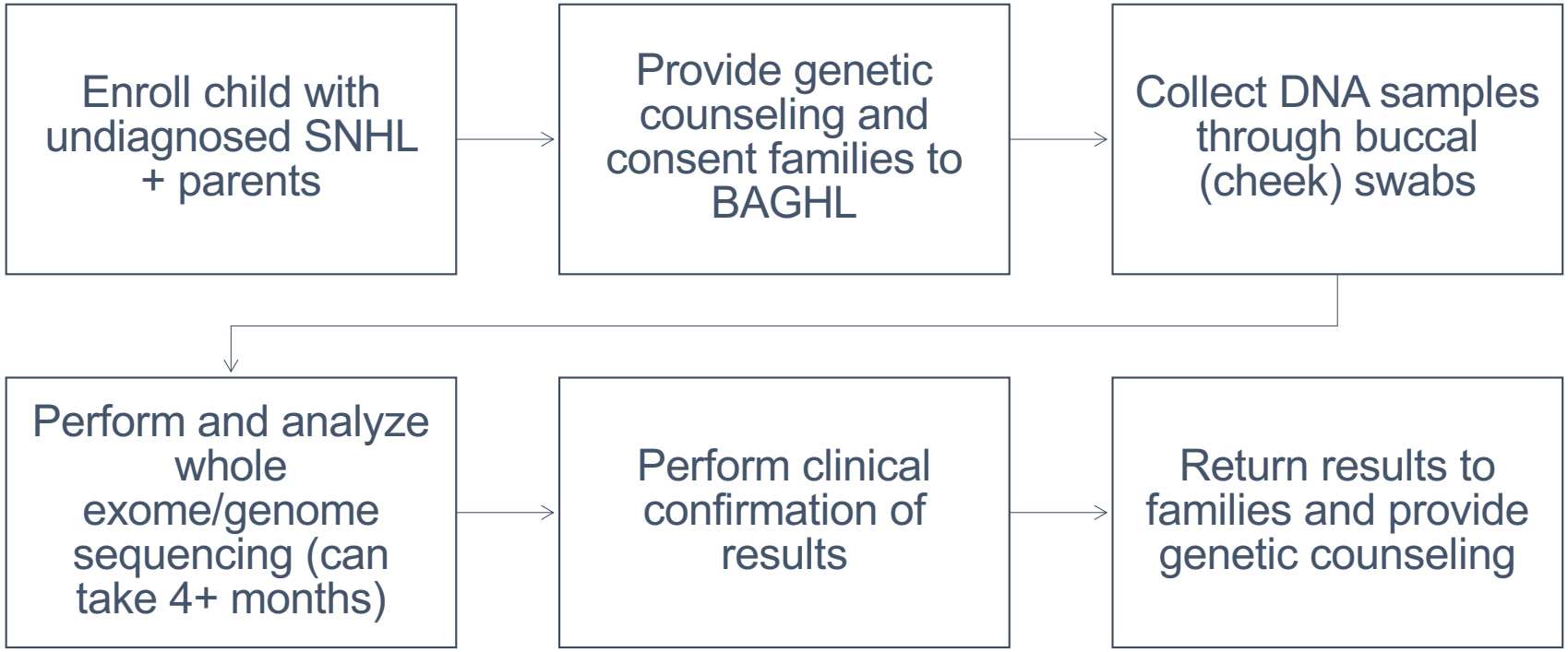
Genetic Research and Innovation

Gene Panel vs. Exome vs. Genome: Genetic Variants Identified

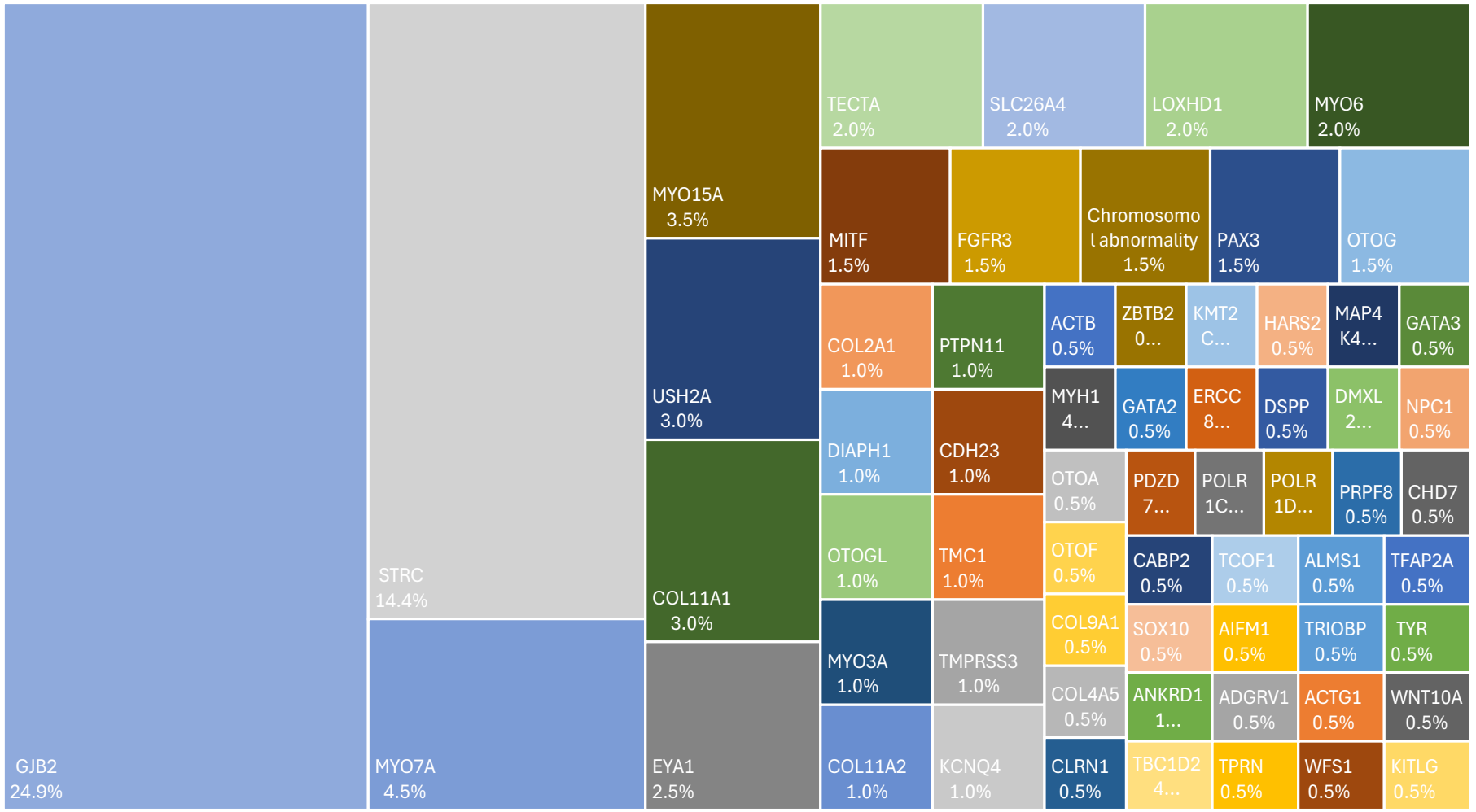


Genetic Research and Innovation

The Bilateral and Unilateral Genetic Hearing Loss Study (BAGHL)



More genes tested, more genes found…



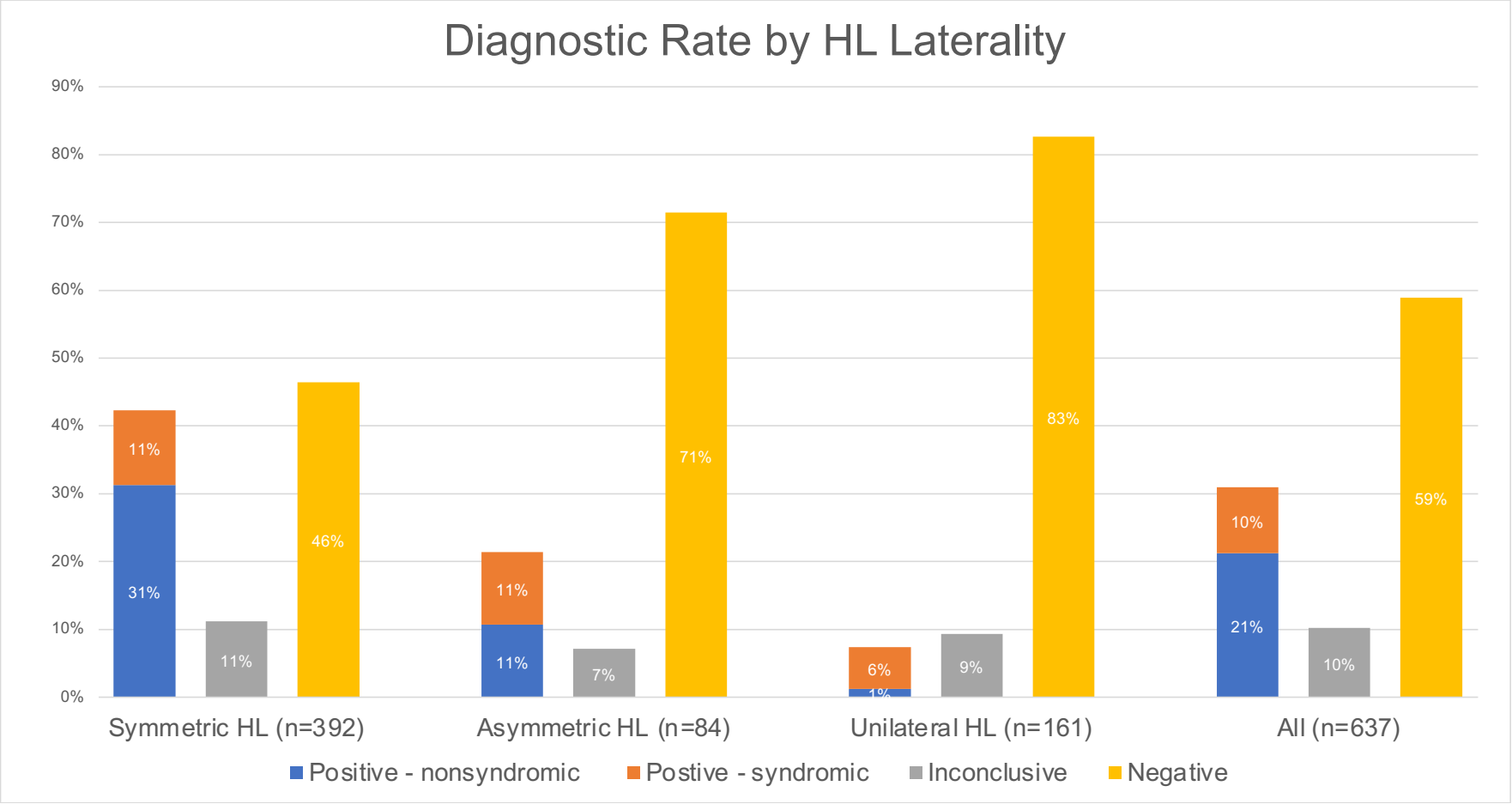
Case Example:
Rare Syndrome Impacts Surgical Plan

- 9-month-old male
- Referred on NBHS bilaterally
- ABR suggested severe to profound hearing loss; absent DPOAEs
- History and physical exam were otherwise totally unremarkable
- Underwent genetic testing targeted to hearing loss (150 gene panel) = negative
- Scheduled for bilateral cochlear implantation

Case Example:
Rare Syndrome Impacts Surgical Plan

- In the meantime, enrolled in a research study to have exome sequencing
- Diagnosed with Noonan syndrome (*PTPN11* gene)
  - Not included on hearing loss panels
- This had crucial implications for surgery because he needed:
  - Cardiac evaluation
  - Hematology evaluation

Research Programs Allow Us to Diagnose Children With Unilateral and Asymmetric SNHL



Genetic Research and Innovation

We Can Identify Novel Hearing Loss Genes

Human Genetics (2024) 143:311–329
https://doi.org/10.1007/s00439-024-02649-2

ORIGINAL INVESTIGATION

PKHD1L1, a gene involved in the stereocilia coat, causes autosomal recessive nonsyndromic hearing loss

Shelby E. Redfield[1] · Pedro De-la-Torre[2,3] · Mina Zamani[4,5] · Hanjun Wang[6] · Hina Khan[7] · Tyler Morris[2] · Gholamreza Shariati[5,8] · Majid Karimi[9] · Margaret A. Kenna[1,2] · Go Hun Seo[10] · Hongen Xu[6] · Wei Lu[11] · Sadaf Naz[7] · Hamid Galehdari[4] · Artur A. Indzhykulian[2,3] · A. Eliot Shearer[1,3] · Barbara Vona[12,13]

Received: 9 October 2023 / Accepted: 21 January 2024 / Published online: 9 March 2024

International collaboration led to assertion that PKHD1L1 is a nonsyndromic hearing loss gene

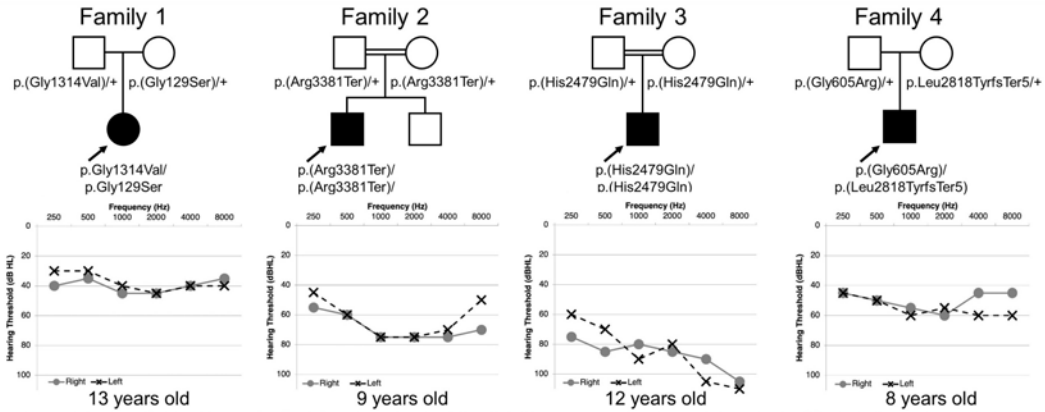
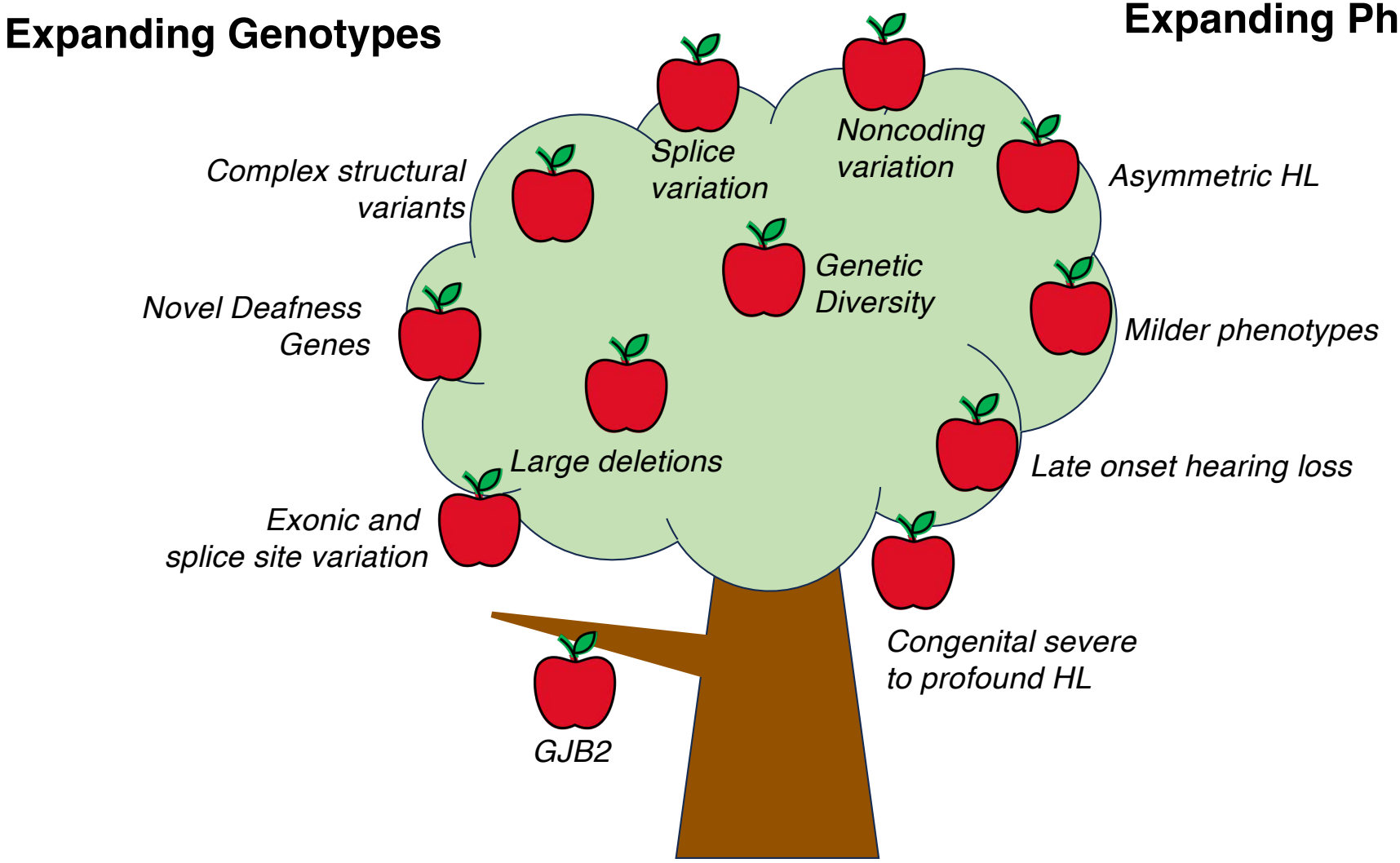
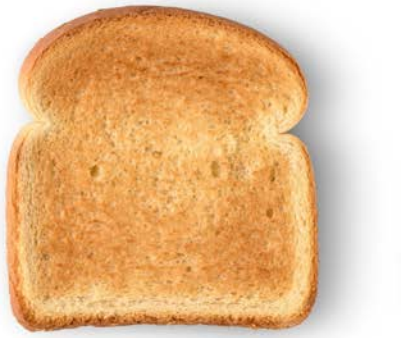


Fig. 1. Pedigrees & audiograms for four families with biallelic *PKHD1L1* variants. Upper panel: Pedigrees of families 1-4. Probands have congenital, progressive, non-syndromic hearing loss without prior family history. Lower panel: Pure tone audiometry for probands 1-4.


Expanding Genotypes
Expanding Phenotypes
Complex structural variants
Splice variation
Noncoding variation
Asymmetric HL
Genetic Diversity
Novel Deafness Genes
Milder phenotypes
Large deletions
Late onset hearing loss
Exonic and splice site variation
Congenital severe to profound HL
GJB2

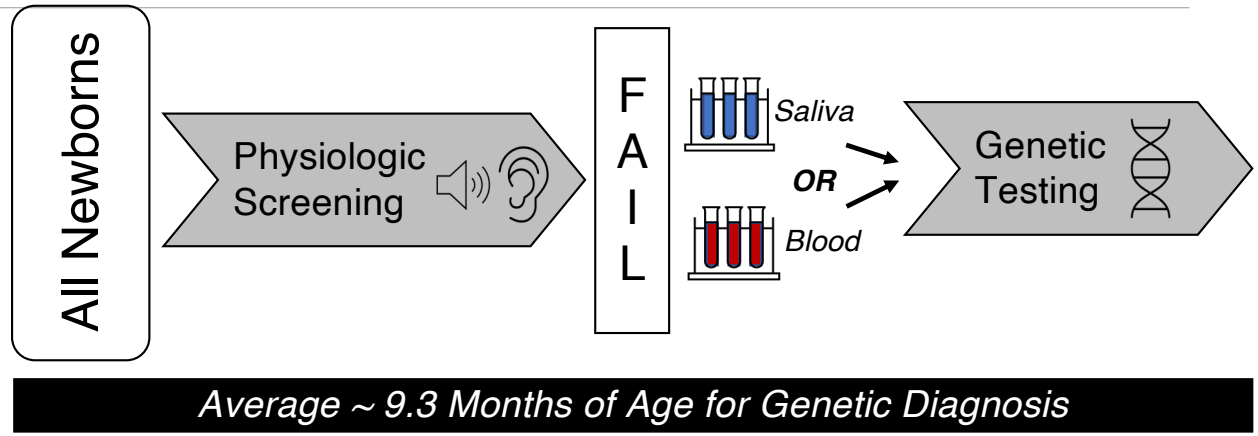
Genetic Research and Innovation

Goal: Try to Find Diagnoses Much Faster



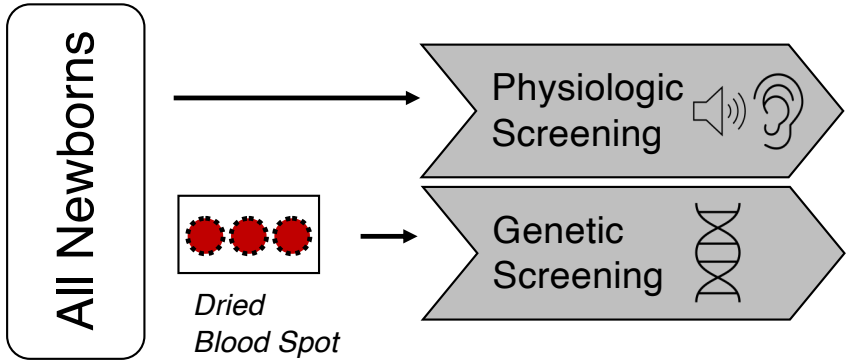
TOAST
fasT genOmic heAring loSs Testing

A) Current Standard of Care Newborn Hearing Screening



Average ~ 9.3 Months of Age for Genetic Diagnosis

B) Proposed Rapid Comprehensive Newborn Hearing Screening

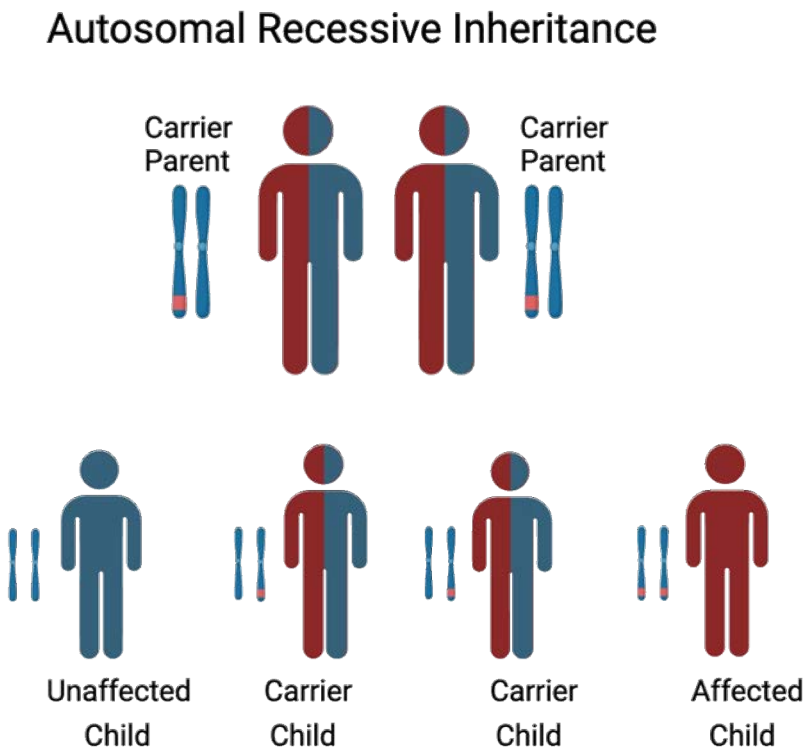


Goal: < 3 Months of Age for Genetic Diagnosis

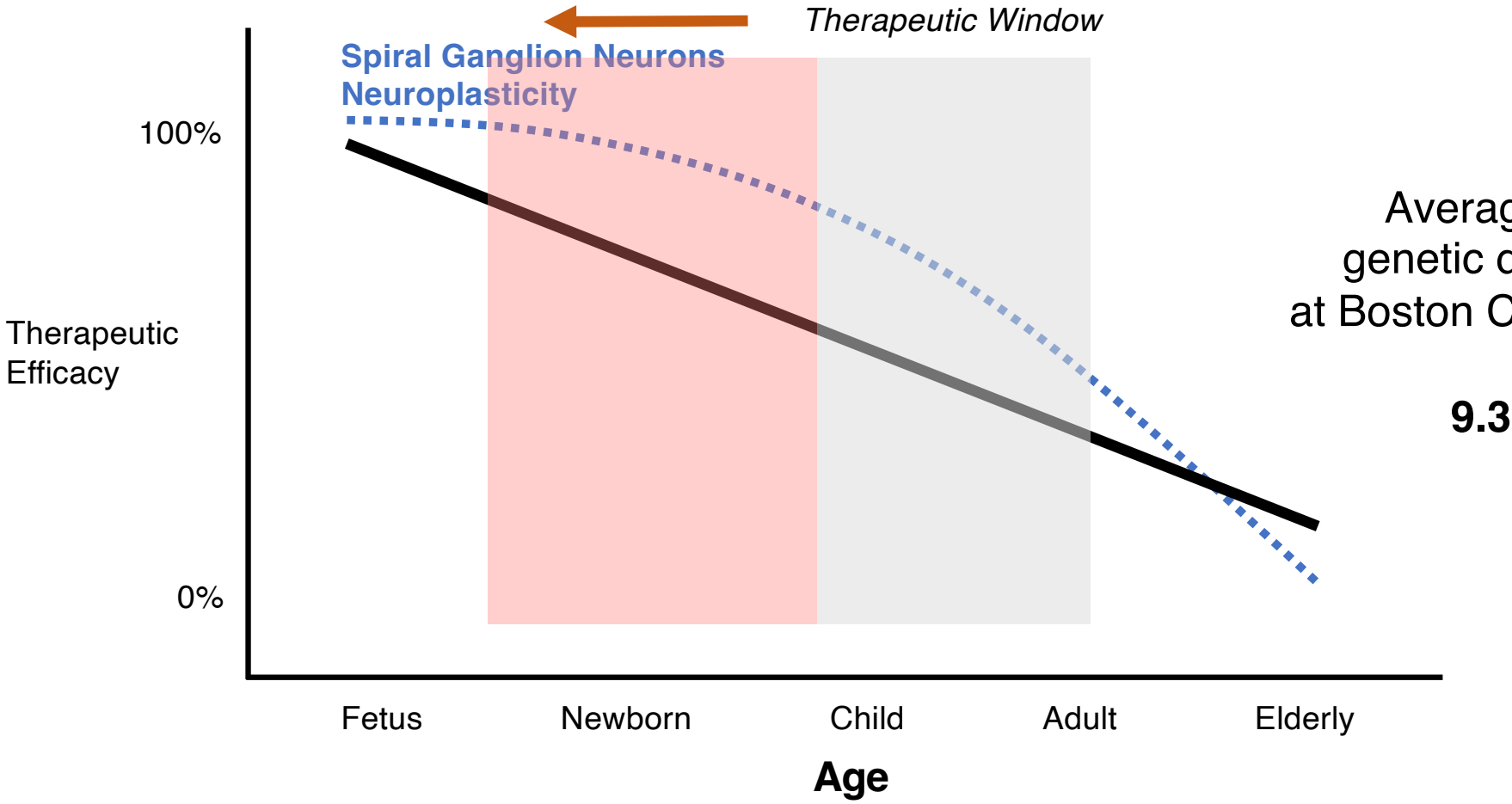
Quiz Hint

We Can Also Diagnose Genetic SNHL Prenatally Using Genetic Carrier Screening

Couple can undergo broad genetic carriers screening (for many different conditions, before a pregnancy.



Next Steps/Big Picture: Early and Accurate Genetic Diagnosis for Hearing Loss may Enable Gene Therapy



Average age of genetic diagnosis at Boston Children's Hospital:
9.3 months

Strategies for Gene Therapy

- Correct
- Replace
- Modify
- Silence
- Restore absent genetic function
- Override abnormal function
- Inhibit abnormal gene function

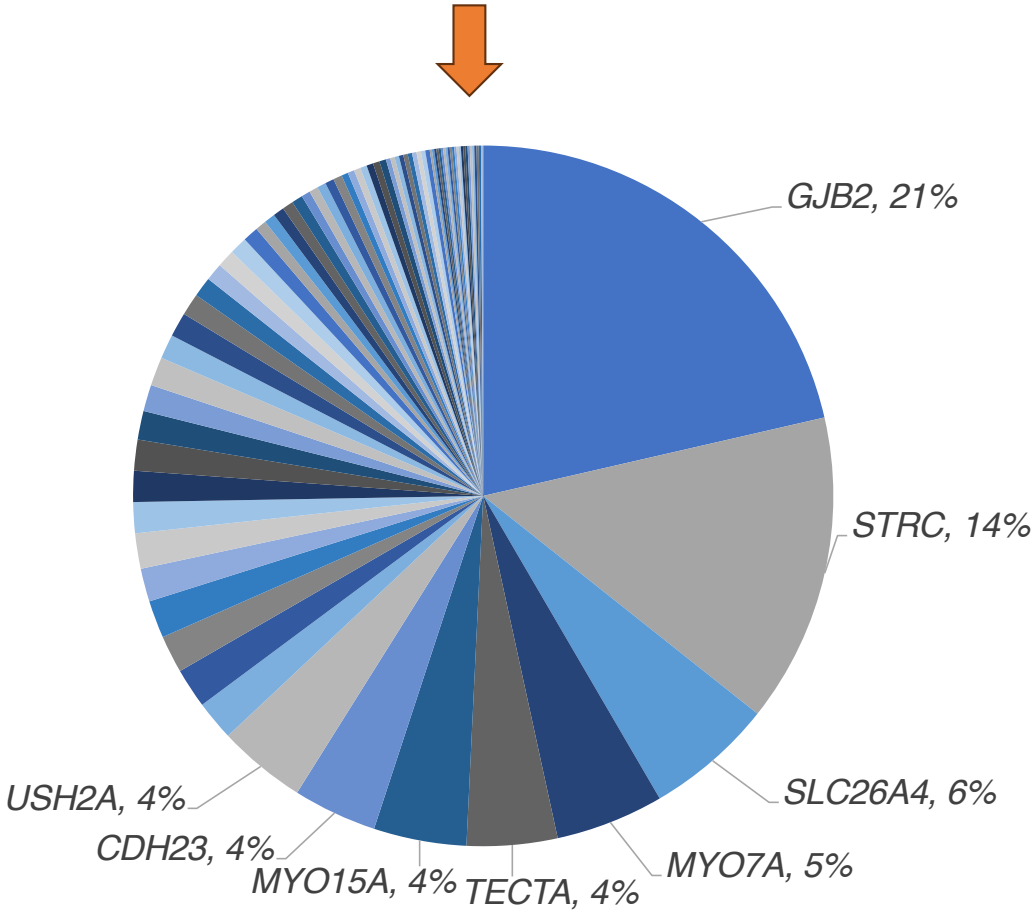
Techniques for Gene Therapy

- Gene editing: CRISPR-Cas9, etc.
  - CASGEVY® for sickle cell disease (BCL11A)
- Replacement genes attached to viral vectors
  - Luxturna® for Leber's congenital amaurosis (RPE65 retinal degeneration)
- Exon skipping; Oligosense nucleotides
  - E.g. Spinraza® for Spinal muscular atrophy (SMN2)
- Stem cells
- Nanoparticles
- Small molecules
- Exosomes
- Change cells *in vivo* or *ex vivo*

Genetic Research and Innovation

Otoferlin hiding someplace in here; trials going on actively

2,460 DHH Individuals



Shearer et al. Genet in Med 2019

Drug Delivery

- Try to preserve residual hearing
- Avoid extensive surgery
- Middle ear, with contact of the RW membrane
  - Gelatin sponge
  - Thermosensitive gels
  - Partial digestion of the RWM with collagenase
  - Microperforations in RWM
  - Co-treatment with hyaluronic acid
- Use of cochlear implant electrode

Challenges to Gene Therapy

- Multiple types of mutations
  - Point mutations
  - Expansion of exons
  - Deletions
- Not all hearing loss genes have been identified
- Multiple protein expressions
  - For example, there are three isoforms of harmonin. *Harmonin b* is localized to the stereocilia; *Harmonin a* is localized at hair cell synapses
- Off-target effects
- Durability
- Very expensive

Ethics of Gene Therapy

- Should we do this? Deafness is not life threatening
- Who will have access?
- When to diagnose? Who can access testing?
- The genetics of many populations are understudied, including Hispanics, African Americans, native Americans, smaller populations and more isolated populations.
- When to do therapy?
  - Preimplantation
  - In-utero
  - In the delivery room
  - In the clinic

In Summary

- Genetic diagnosis of pediatric SNHL enables precision medicine and informs care
- Audiologists can support patient families by understanding the audiologic implications of a condition
- New technologies and testing strategies, such as carrier screening, genome/exome sequencing, and gene therapy are brining innovation in the are of pediatric SNHL

Summary

Boston Children's Hospital | Children's Rare Disease Cohorts Initiative

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Thank You!

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