The Importance of Early Intervention
or
To Diagnose or Not to Diagnose: That is the Question

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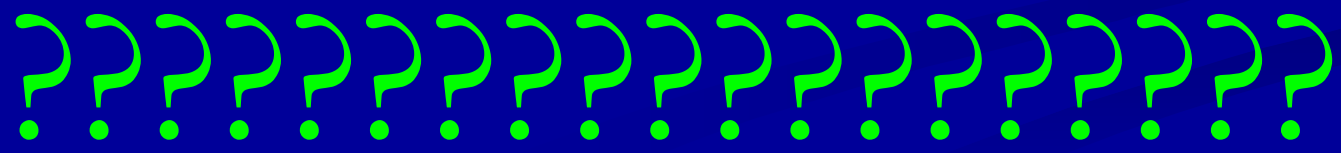


Seven steps to treatment for an Inherited Disease (Bill Kimberling)

- Find the disease gene
- Correlate genotype with phenotype
- Find or develop animal models
- Elucidate the disease mechanism
- Find or develop and effective treatment in the animal model
- Screen the human population to identify people who might benefit
- Test the treatment in these people
  - Orphan diseases, small numbers

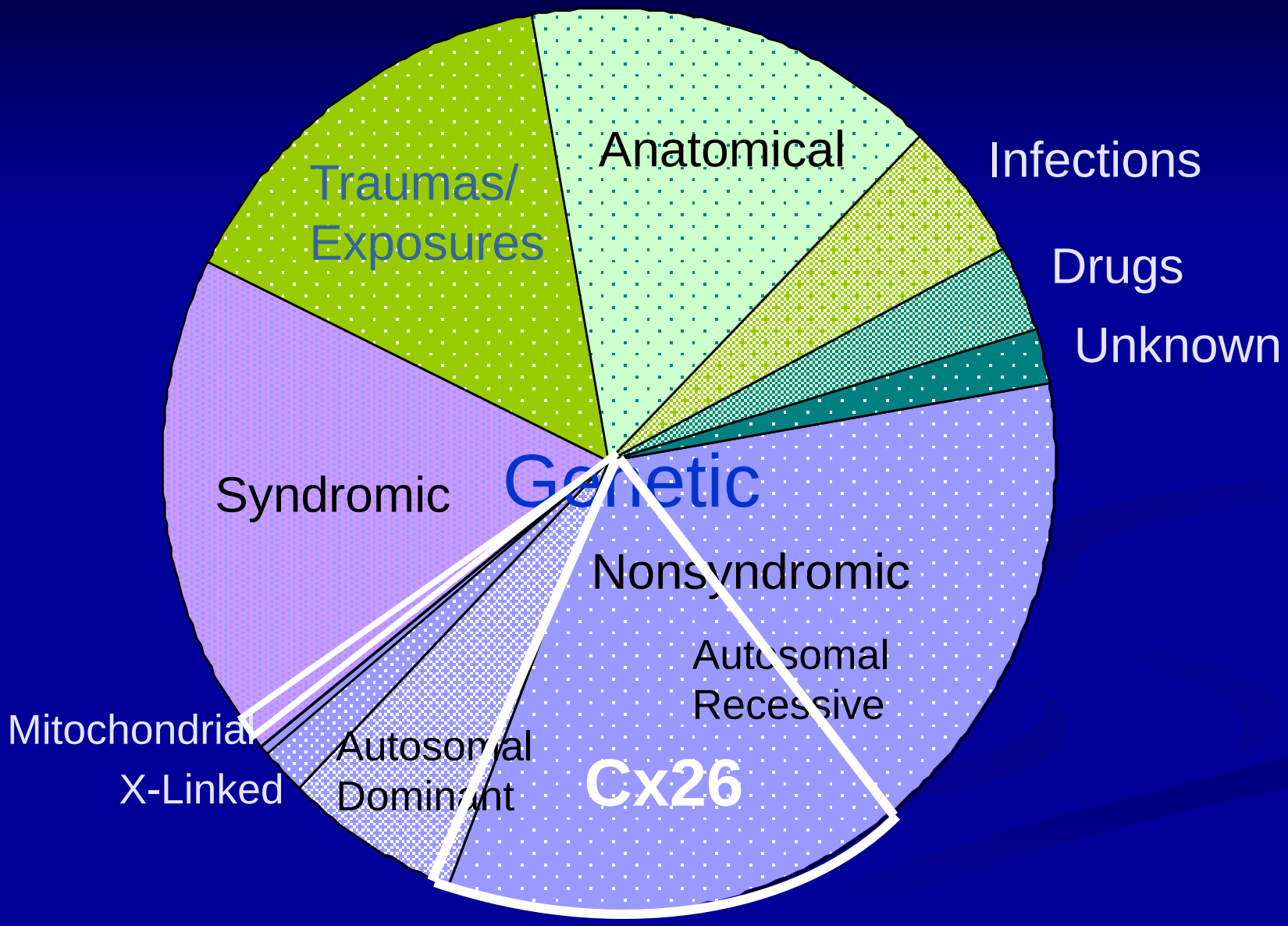
How Common Is Permanent Hearing Loss?

- Hearing loss most common sensory impairment
- Of every 1000 babies screened
  - 1-3 will have permanent SNHL/CHL
    - 33 babies born every day with significant permanent hearing loss
    - >12,000 babies per year in the U.S. with HL
    - By age 80 >70% with hearing loss
- Increasing evidence that mild and unilateral hearing loss affects communication, speech and language, and learning

Early Hearing Detection Intervention (EHDI) Programs

- 1993 NIH Consensus Development
- 1999 AAP Task Force
- 2000, 2007 JCIH statement
  - Recommends eye exam and genetics evaluation
- Goals of UNHS programs 1-3-6
  - Screening by 1 MONTH
  - Audiological diagnosis by 3 MONTHS
  - Early intervention by 6 MONTHS

Major Causes of Sensorineural Hearing Loss



Diagnosis of Hearing Loss: Olden Days

- Infrequent newborn hearing screening
  - Few legal mandates to test hearing in the newborn period
  - Testing techniques not well worked out
  - ABR restricted to Neurology and academic centers
  - Otoacoustic emissions were a research tool
- Poor imaging
  - Mainly computed tomography
    - Slices so far apart the inner ear was occasionally missed
  - Polytomes
  - Plain films
- Genetics
  - Clinical exam by dysmorphologists
  - No routine genetic testing for HL
- Despite TORCH titers, little awareness of CMV, toxoplasmosis
  - Testing almost never done, or not done in a timely fashion
- No cochlear implants
- Less advanced hearing aids

What Used to Cause Hearing Loss
(that we could figure out)

- Bacterial meningitis
- Congenital Rubella
- Measles
- Mumps
- Family history
- Prematurity
- CT scans usually “normal”
- Usually we had no idea

Hearing Loss: "Modern Times"

- Nearly universal NHS in US and many other countries
- Cochlear implants FDA approved for adults in 1984 and for children in 1990
- High resolution MRI and CT
- Hearing aids that are small, actually work, and connect to phones, MP3 players, FM systems

What Causes Hearing Loss Now (that we can figure out better)

- Congenital rubella almost completely gone
- Mumps almost completely gone
- HIB and Prevnar® have reduced meningitis

- More premature babies survive but not much smarter about what causes the hearing loss
- But new causes of SNHL identified
  - NICU, ECMO and other medical interventions
  - Noise (MP3, etc)
  - HIV, Lyme

What Causes Hearing Loss Now (big advances in diagnosis)

- CMV most common viral cause of congenital SNHL
- Better imaging
  - CT
  - MRI
- Available genetics: A1555G, Cx26, PDS, Usher

Why Pursue a Hearing Loss Diagnosis?

- Find out what caused the hearing loss
- Find out what did not cause the hearing loss
- Finding out the cause can help in several areas
  - Prognosis of the hearing loss
  - Check out other organ systems
    - E.g.: Usher, if know that vision may become impaired, really work hard on the audition and language early on
  - If genetic, may help with family planning

Why not pursue a hearing loss diagnosis

- Expensive
  - Time
  - $$$
  - Insurance hassles
  - Otochip: $3800
  - Interpretation
  - Which test to chose?
- Fear of the unknown
- Embarrassment/culturally difficult
- Frustration
  - That a definite cause won't be identified
  - That the cause won't help with the management
  - That there is nothing we can do about the cause, even if found

Genetic Testing

- Have the symptoms and then pick a gene, or pick a gene and look for the symptoms
- Expensive
  - Money
  - Insurance
    - Will it pay for the testing?
    - Will I be denied insurance?
    - Will I be denied a job?
  - Time
- Emotional Expense
  - My genes, “my fault”
    - Your genes, your fault
  - Non-paternity
  - Will the other children have it
  - Cultural
    - We don’t believe in testing
    - It is God’s will

New Era of Genetic Diagnosis in SNHL

- 1993: 1555A→G Mitochondrial gene for aminoglycoside ototoxicity.
- 1997: Identified Connexin 26 (GJB2) as the first non-syndromic autosomal recessive deafness gene, DFNB1
- 1998: Presence of large vestibular aqueducts in Pendrin syndrome (SLC26A4 [PDS] gene)
- **Myosin VII gene described in 1995 in by Weil et al, including Dr. Kimberling**

Why pursue genetic testing for Usher Syndrome?

- Find out what caused the hearing loss
  - Symptoms alone cannot exclude the diagnosis
    - Balance, age at walking
    - Vision, “normal” eye exam
    - Degree of hearing loss
- Find out what did not cause the hearing loss
- Plan for the future
- Plan for other children
- If find a definite genetic cause
  - Can apply current therapy
  - May qualify for future therapy/research

Why not pursue genetic testing for Usher Syndrome

- Usher diagnosis seems unlikely
- Normal balance and vision so must not be Usher
- No one in the family has it
- We aren't planning to have any more children
- By the time the test results come back it will be too late or the results will be inconclusive
- Fear
  - Fear of the unknown
  - Fear of the known
  - Not smart enough to understand it

Incidence of Usher Syndrome

- 3-6.2/100,000 general population
  - 45,000 Americans with a form of Usher Syndrome
- 0.6-28% HOH, deaf population
  - 1:6500 general population have genotype
- Still late diagnosis
  - Much later than Connexin 26
- Limited availability of genetic testing
- Heterogeneous presentation
- Later onset of visual loss than hearing loss
- Retinal findings difficult to determine
- Prevalence of balance abnormalities has been poorly studied

Usher Syndrome

(3-6% of childhood deafness)

Traditional classification

	Hearing Loss	Vestibular System	Retinitis Pigmentosa
Type I	Congenital profound	Congenital balance problems; absent responses	Onset pre-puberty
Type II	Congenital mild-severe sloping	Normal	Onset in teens-20s
Type III	Progressive later onset	Variable, often progressive balance problems	Variable onset

Audiologic Features

- USH 1 - bilateral congenital profound SNHL
- USH 2 - bilateral moderate SNHL; may progress
- USH 3 – May be of later onset, may progress
- **All patients initially appear non-syndromic except for the hearing loss**
- **Not all patients with mutations in the same Usher gene have the same presentation**

Locus name	Genome Location	Gene name	Gene Protein Product
USH1B	11q13.5	MYO7A	Myosin 7A
USH1C	11p15.1-p14	USH1C	Harmonin
USH1D	10q22-q22	CDH23	Cadherin 23
USH1E	21q21.1	Unknown	Unknown
USH1F	10q21.1	PCDH15	Protocadherin 15
USH1G	17q25.1	USH1G	Usher Syndrome Type 1G protein
USH1H	15q22-23	USH1H	Unknown
USH2A	1q41	USH2A	Usherin
USH2C	5q13	GRP98	G protein-coupled Receptor 98
USH2D	9q32-34	DFNB31	Cask-interacting protein
USH3	3q21-q25	CLRN1	Clarin-1
USH2A modifier	10q24.31	PDZD7	PDZD7

Routine Eye Exams in Children with SNHL: Can you diagnose Usher Syndrome?

- 16 children
- All have two pathogenic USH mutations
- “Routine” eye exams did not pick up USH in any patients who were pre-symptomatic (i.e. not night blind)
- 9/16 had diagnosis made by genetic testing; youngest was 8 months
- Age of walking not entirely predictive of USH 1 patients, and was normal in USH 2 and USH 3

Kenna, Fulton, Hansen, Rehm, et al, 2010

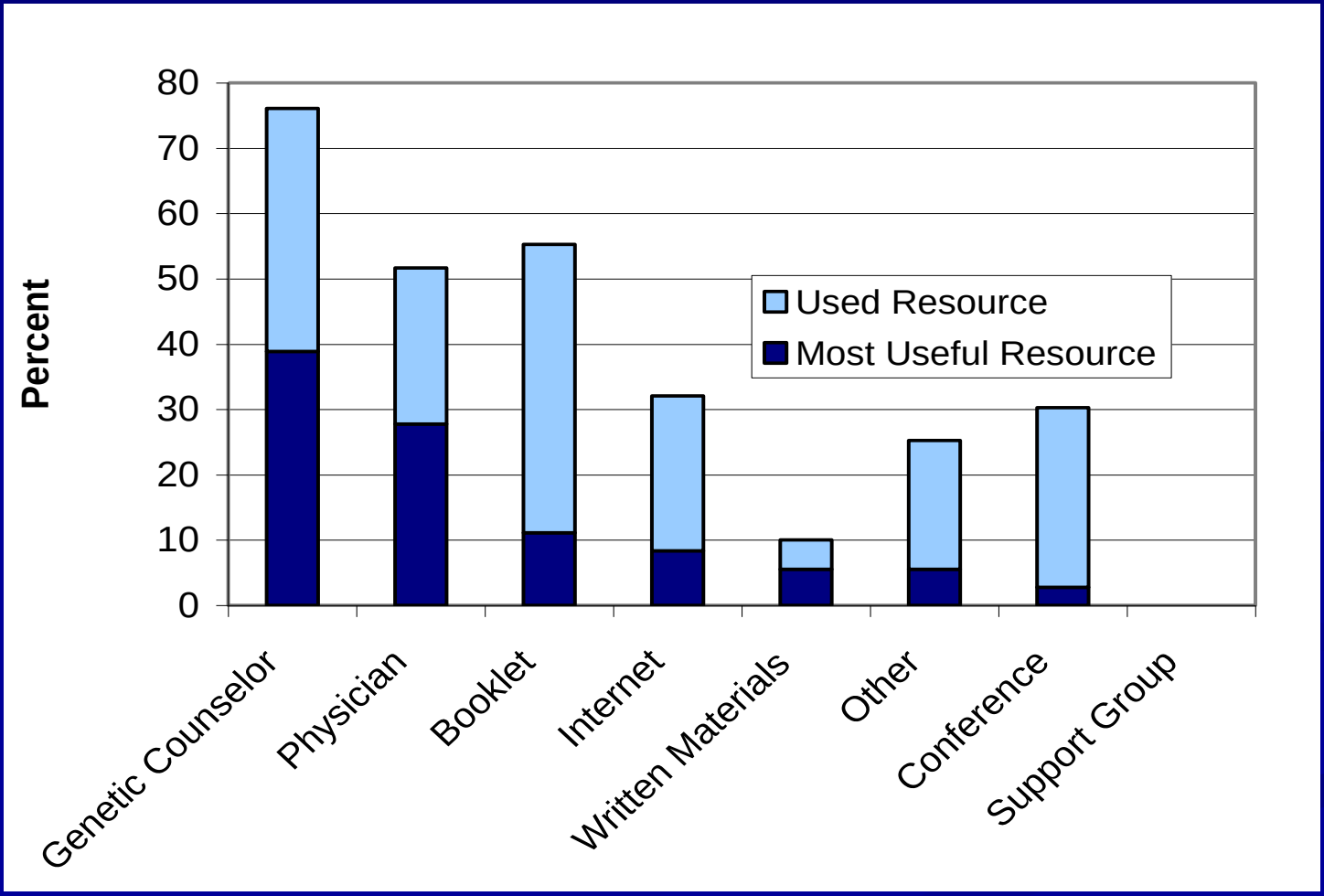
Importance of Genetic Counseling

With expanding genetic testing, counseling more important than ever

We examined:

1. The extent to which families are receiving genetic counseling for hearing loss
2. How well they understand the genetics of hearing loss
3. Which information sources are most useful (or most used)

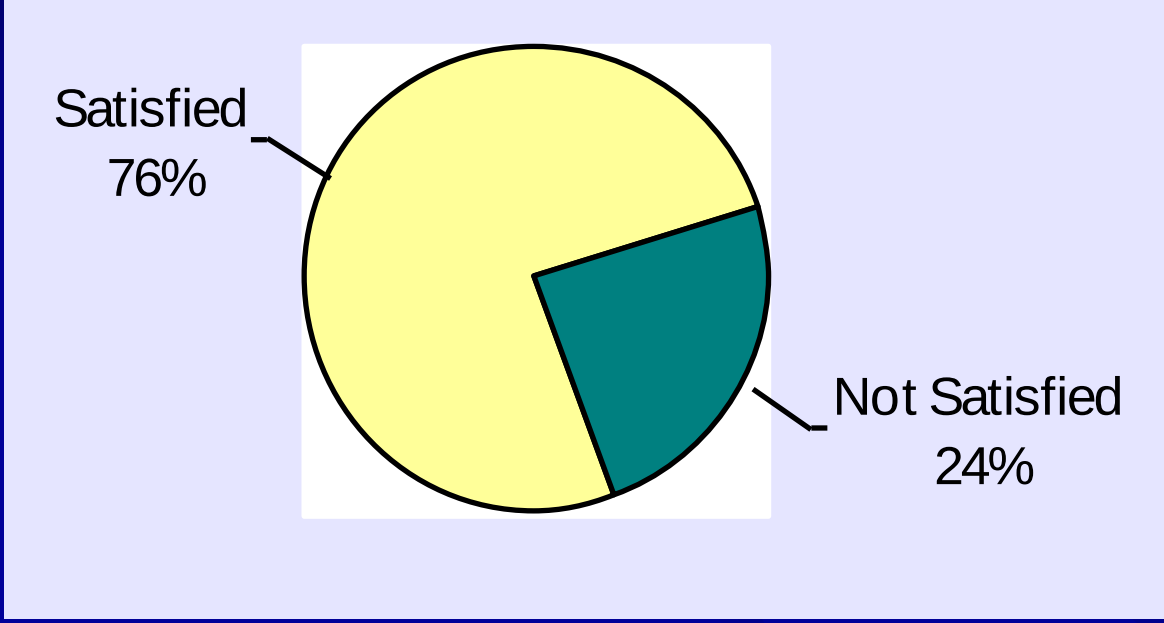
Sources of Genetic Information Cited by Parents



Results of genetic counseling studies

- Parents who had post-test genetic counseling with a genetic professional were more likely to understand their genetic test results
- Results suggests that there may be a greater need for genetic counseling when test results are negative
- Of Physicians who provided information geneticist>ENT>primary care

Satisfaction with the Level of Understanding of their Child's Genetic Test Results (despite what they actually knew)



79% did not intend to pursue genetic counseling in the near future

"Ignorance is Bliss"

Getting results of testing

- Telephone
- Internet
- Mail
- In person
- Support people
- What if results are negative or inconclusive?


SPINACH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To Diagnose or Not to Diagnose? That is the question

- Get good information
- Feel (more or less) comfortable with decision to go forward with testing
- Get results when you have time to digest them (i.e. not by cell phone during rush hour on the Mass Pike)
- If results negative or inconclusive
- Reach out to others no matter what


THANKS