1. Review Basic Concepts and Ideas

2. Review Gene Involvement in Hearing and Auditory organs development

3. Review some of the future forms of treatment involving hearing loss

4. Review the importance of recognizing that genetic testing does not equal to genetic evaluation
Used in clinical diagnostic and functional development to describe individuals who require assistance: medical, mental, or psychological.

Special needs often refers to special needs within an educational context. This is also referred to as special educational needs (SEN).

In Germany a similar term exists. Special needs children are called "besondere Kinder" ("special children").
Establishment of a System
19% of Americans are classified as a person with a special need, which equals the population of the states of FL and CA combined

41% of children with developmental difficulties have multiple special needs

17% of Americans will experience a communication disorder at some point in their life, which includes sensing, interpreting and responding (i.e. auditory processing disorder).
Isolated hearing loss may not be the most common form of hearing loss in the future.
## Other Diagnoses Associated with Hearing Loss

Gallaudet Research Institute, 2003

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning difficulties</td>
<td>10.7</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>9.8</td>
</tr>
<tr>
<td>Attention difficulties</td>
<td>6.6</td>
</tr>
<tr>
<td>Blindness and low vision</td>
<td>3.9</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>3.5</td>
</tr>
<tr>
<td>Emotional disturbance</td>
<td>1.5</td>
</tr>
<tr>
<td>Other conditions</td>
<td>12.1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>48.1</strong></td>
</tr>
</tbody>
</table>
Genetics: A case against perfection

"Congratulations, it's a Versace!"
Developments

1) Molecular/genetic understanding of hereditary hearing loss vastly enhanced over last 10 years

- Genetic testing and Genetic Evaluation is now an integral part on the assessment of children with hearing impairment

2) Early intervention [medical vs. surgical] now standard of care with limitations

3) Genetic treatment may be the choice in the future
“You look different—have you been evolving or something?”
Definition of Evolution

“Evolution is a process that results in heritable changes in a population spread over many generations”
Evolution and Birth Defects

Birth defects are suppose to happen
Birth defects can be advantageous
Birth defects can be deleterious
In search of individuality
Birth defects can be silent
Mutated miR-96 gene
14 April 2009. Chrissie Giles
Stage 12-4th week of gestation
Embryology of the ear placode

Images of the lateral view of the human embryonic head from week 5 (stage 14) through to week 8 (stage 23)
RNA in situ hybridization of Pds in noncochlear regions of the mouse inner ear.

Everett L A et al. PNAS 1999;96:9727-9732

©1999 by National Academy of Sciences
Mutations in \textit{OTOGL}, Encoding the Inner Ear Protein Otogelin-like, Cause Moderate Sensorineural Hearing Loss

Kemal O. Yariz et al. AJHG \textbf{Volume 91, Issue 5}, 2 November 2012, Pages 872–882
Newborn mice lacking the \textit{Slitrk6} gene (right) have severe reductions in the numbers of nerve fiber bundles innervating the inner ear compared to wild-type animals (left).
The ATP-dependent chromatin remodeling enzyme CHD7 regulates pro-neural gene expression and neurogenesis in the inner ear.
<table>
<thead>
<tr>
<th>Statoacoustic ganglion</th>
<th>Otocyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal turn of the cochlea</td>
<td></td>
</tr>
<tr>
<td>Tip of digits</td>
<td>Vibrissae</td>
</tr>
<tr>
<td>Nasal/Oral epithelia</td>
<td>Amniotic membrane</td>
</tr>
</tbody>
</table>
Multi-system gene expression: 30,000 genes

Samin Ahmed Sajan, PhD.
University of Washington, May 2008
Microarray technology

Mouse cochleas were examined at two developmental stages (P2 and P32) using GeneChip oligonucleotide arrays

> 10,000 genes were found to be expressed in the cochlea
Gene Function and Hearing

Developmental Time
Gene Expression
Gene Expression Transformation
Gene Regulation
Genetic susceptibility
Identifying Infants with Hearing Loss

Undetected hearing loss can delay speech and language development

All states and U.S. territories also have established Early Hearing Detection and Intervention (EHDI) programs
Infant Hearing Loss
Hearing Loss
Case 5 - CATSHL

- Camptodactyly
- Tall Stature
- Congenital bone abnormalities
- Congenital hearing loss – diagnosed as isolated non-syndromic at birth (moderate bilateral SNHL)

Toydemir, et al. A Novel Mutation in FGFR3 Causes Camptodactyly, Tall Stature, and Hearing Loss (CATSHL) Syndrome, AJHG 2006; 79, 5
Mutation in **FGFR3** (1862G→A): CATSHL syndrome
CATSHL syndrome

Mutation in the FGFR3 gene

Chromosome 4
ENT Medical Work UP

ABR testing - moderate CHL right and normal hearing left

CT scan of temporal bones
- bilateral dysplasia of bony labyrinths
- normal cochleae, IACs, vestibular aqueducts, and ossicles
- Possible anomaly of right facial nerve

Testing for Pendred Syndrome - Insurance company rejected testing unless recommended by Medical Genetics

Referral to Genetics
Medical Genetics Findings

1. Cervical fusion – fusion of C1-C2, retrolisthesis of C3 on C4, C6 and C7 fusion
2. Facial asymmetry
3. Speech/language delay
4. Hand and arm anomalies
5. DX: Klippel Feil Syndrome
6. No Genetic testing needed
# Klippel-Fiel Syndrome

## Most Common Associated Abnormalities

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital scoliosis</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Rib abnormalities (excluding cervical ribs)</td>
<td>33%</td>
</tr>
<tr>
<td>Deafness</td>
<td>30%</td>
</tr>
<tr>
<td>Genitourinary abnormalities</td>
<td>25-35%</td>
</tr>
<tr>
<td>Sprengel’s deformity</td>
<td>20-30%</td>
</tr>
<tr>
<td>Synkinesia</td>
<td>15-20%</td>
</tr>
<tr>
<td>Cervical Ribs</td>
<td>12-15%</td>
</tr>
<tr>
<td>Cardiovascular abnormalities</td>
<td>4-29%</td>
</tr>
</tbody>
</table>

Genetic Testing vs. Genetic Evaluation
Iris Colobomas

- Cat-Eye syndrome
- Preauricular tags/pits
- Stenotic ear canals
- 22q deletion
- Mixed Hearing loss
Robin Sequence

Micrognathia
Cleft palate
Apnea
Stickler Syndrome

- Micrognathia
- Hypermobility
- Mixed hearing loss
- Mutation in Collagen gene
Clefting

Cleft lip/palate

Van Der Wood syndrome
Genetic Evaluation:

Dysmorphology Exam

Team agrees on Isolated hearing loss
- 1. Otochip
- 2. Clinical Follow up
- 3. Metabolic testing

Hearing loss + recognizable syndrome
- 1. Targeted gene testing
- 2. Clinical Follow up
- 3. Management of comorbidity

Hearing loss + other findings but not recognizable syndrome
- 1. Microarray analysis
- 2. Karyotype
- 3. Exome Sequencing
The end