6.4.4 Breakdown the most common causes of syndromic hearing loss into inheritability types. CB
From UTMB

Syndromic Hearing Loss

Autosomal Dominant Syndromes

**Waardenburg syndrome**: Characterized by sensorineural hearing loss, abnormal pigmentation of the skin and hair, dystopia canthorum (eye inner canthi are displaced laterally), heterochromia iridis (iris colors do not match), and pinched nose. This syndrome occurs anywhere from 1 in 20,000 to 1 in 40,000 and accounts for 1-2% of people with profound hearing loss. The hearing loss can be unilateral or bilateral of varying severity. The syndrome has 4 subtypes classified according to the presence or absence of other abnormalities. In Type 1, every patient exhibits dystopia canthorum. The Type 2 phenotype is void of dystopia canthorum while Type 3 exists with upper extremity abnormalities in conjunction with Type 1 characteristics. Type 4 exhibits pigmentation abnormalities, Hirschsprung’s disease, plus findings shown in Type 2. Types 1 and 3 are linked to gene mutations in the PAX3 gene, while Types 2 and 4 are linked to the MITF and EDNRB genes respectively.

**Branchio-oto-renal syndrome**: This syndrome is estimated to be present in 2% of profoundly deaf children. The syndrome displays high penetrance although variable expressivity has been shown in families. Hearing impairment is estimated to be present in 70-93% of affected people but the age of onset ranges from early childhood to young adulthood. Likewise, there is varied severity ranging from mild to profound and the nature can be conductive, sensorineural or mixed. Common characteristics of the BOR phenotype include cup-shaped pinnae, preauricular pits, branchial cleft fistulae and bilateral renal anomalies. Other features displayed are preauricular tags, lacrimal duct stenosis, deep overbite and a long, narrow face. Inner ear anomalies like Mondini’s dysplasia and stapes fixation can also be present. The genetic etiology of this syndrome can be traced to the EYA1 gene. Based on the phenotypic anomalies, criteria have been developed for EYA1 testing: affected individuals must have at least 3 major criteria; two major criteria and at least two minor criteria; or one major criterion with one first- degree family member meeting BOR criteria (see accompanied POWERPOINT SLIDE SHOW presentation for table of criteria).

**Stickler Syndrome (STL)**: In addition to having sensorineural hearing loss that is progressive, these patients usually display a cleft palate, abnormal development of the epiphysis, vertebral abnormalities and osteoarthritis. There are three clinical subtypes that exist. Type 1 develops progressive myopathy, retinal detachment and vitreoretinal degeneration. Retina detachment is nonexistent in type 2 due to lack of the COL11A2 gene in the retina. In Type 3 shares eye and ear findings present in type 1 but has facial abnormalities. The absence of COL11A2 in the vitreous humor is the reason for the differing ocular phenotypes between Stickler types 1 and 3, and Stickler type 2. The genes with loci responsible for STL 1, 2 and 3 are COL2A1, COL11A1, and COL11A2 respectively.

**Treacher Collins (TC)**: Also known as Fraceschetti-Zwahlen-Klein Syndrome or Mandibulo-Facial Dysostosis, this autosomal dominant entity is liked to mutations on chromosome 5q11 and some reports mention an association of maternal vitamin A hypersensitivity.
Diagnostic criteria include microtia and malformed ears, midface hypoplasia, downslanting palpebral fissures, coloboma of outer 1/3 of lower eyelids, and micrognathia. The upper airway narrowing can be a major issue in infancy. The size of the nasopharynx is 50% smaller than normal and affected infants are more prone to OSA and SIDS. Hearing loss in this syndrome is usually conductive with a wide array of middle ear anomalies present such as monopodal stapes, ankylosed foot plate, malformed incus, cochlea and vestibule abnormalities. The EAC may be absent or stenosed. If sensorineural hearing loss is present, it usually occurs at high frequencies.

**Osteogenesis imperfecta (OI):** This is an autosomal dominant disorder displaying the triad of bone fragility, blue sclerae and hearing impairment. Other characteristics include triangular face, short stature, hypermobile mobile joints, cardiovascular abnormalities and skin disorders. The incidence is estimated to be 1 in 20,000 to 1 in 30,000. Causative mutations involve the COL1A1 or COL1A2 gene which regulate formation of type 1 collagen. Hearing loss is usually mixed and has a prevalence ranging from 26-78%. The hearing loss usually presents itself during the late 20s or early 30s. The conductive component of the hearing loss is attributed to the thickened and fixed stapes footplate, similar to what is seen in otosclerosis. The sensorineural component usually results from cochlear hair cell atrophy and atrophy of the stria vascularis. Also, anomalous bone formation in and around the cochlea may contribute to the sensorineural component of the hearing loss.

**Neurofibromatosis Type II (NF 2):** Bilateral vestibular schwannomas are the hallmark of this disease with a prevalence of 1 in 210,000 people. Other features include meningiomas (intracranial and spinal), ependymomas, gliomas, presenile lens opacities, and schwannomas located in the cranial, spinal and peripheral nerves. The skin can also manifest café-au-lait spots but not to the extent found in neurofibromatosis type I. This disease is caused by an NF 2 tumor-suppressor gene mutation on chromosome 22. Affected patients usually present in the 2nd and 4th decade. Up to 41% present with unilateral sensorineural hearing loss rather than bilateral sensorineural hearing loss due to the fact that this percentage of patients do not present with bilateral vestibular schwannomas. Patients can also have tinnitus, disequilibrium, headache and cranial nerve symptoms. Children < 15 years old may commonly present with skin or spinal tumors prior to the onset of hearing loss or development of vestibular schwannomas. In addition to the Manchester criteria for diagnosis (see accompanied power point presentation) patients who are suspicious for having NF 2 should undergo audiometry and MRI with gadolinium enhancement of the internal auditory canals.

Autosomal Recessive Syndromes

**Usher Syndrome:** Usher syndrome is the most common cause of autosomal recessive hearing loss. The incidence of Usher syndrome is approximately 3-5 per 100,000 in the general population and 1-10% among profoundly deaf children. The syndrome has several subtypes based on severity of the deafness and the onset of retinitis pigmentosa (gradual retinal degeneration leading to decreased night vision, loss of peripheral vision, and blindness). Type 1 has severe hearing loss and vestibular dysfunction. The onset of retinitis pigmentosa is in childhood as opposed to type 2 where it begins after childhood. Mild to moderate hearing loss characterizes type 2 along with normal vestibular function. In type 3, hearing loss is progressive as is the vestibular dysfunction. Retinitis pigmentosa can occur anytime in life.
**Pendred syndrome:** Characterized by hearing impairment associated with abnormal iodine metabolism. The responsible gene is SLC26A4 (PDS). This encodes a protein named pendrin which helps regulate iodine and chloride ion transport. Most patients have a euthyroid goiter which is sometimes detected at birth but often is not clinically evident until 8 years of age. Diagnosis of the thyroid abnormality used to depend on perchlorate discharge tests (indicates abnormal organification of nonorganic iodine) but this test is not specific for Pendred syndrome and the sensitivity is unknown. Instead, thyroid function tests are used. The hearing loss in this syndrome is severe and can be present at birth or progress with age. In addition, CT scans have revealed cochlear dysplasia (Mondini’s) an enlarged vestibular aqueduct or both.

**Jervell and Lange-Nielsen Syndrome:** This syndrome, although rare, should be suspected in a child with hearing loss and seizures of unknown origin and/or a family history of sudden death. Patients are characterized by severe-profound hearing loss and prolongation of the QT interval EKG. The syncopal episodes are due to a cardiac conduction defect which can manifest as early as the 2nd or 3rd year of life. The cardiac conduction defects can be attributed to mutations in potassium channel genes traced back to loci on the KVLQT1 and KCNE1 genes located on chromosomes 11p15.5 and 21q22 respectively.

**Biotinidase Deficiency:** Infants with severe biotinidase deficiency will display skin rashes, seizures, hair loss, hypotonia, emesis and acidosis in the first few months of life. This syndrome occurs because the infant lacks the enzyme responsible for proper biotin metabolism. Approximately 75% of affected infants will develop hearing loss if left untreated. The significance of this disorder is that if it is recognized, all the sequelae can be avoided with biotin supplementation.

X-Linked syndromes

**Alport syndrome:** As a result of the mutation in type IV collagen gene COL4A5, patients with Alport syndrome exhibit renal disorders and ocular abnormalities in addition to progressive sensorineural hearing loss. Renal disorders include glomerulonephritis, hematuria (“red diaper”), and renal failure. Early diagnosis is essential because the renal disease is usually more severe in males causing death secondary to uremia prior to 30 year old. Congenital cataracts are also common. The progressive sensorineural hearing loss mentioned earlier usually has an onset beginning in the 2nd decade of life.

Non-genetic Syndromes

**Down’s syndrome:** This is the most common of the chromosome abnormality syndromes typified by a wide range of abnormalities. Otolaryngologic findings are numerous in these patients and can affect every region of the head and neck. This includes small ears with over folding of the superior helix, stenotic EAC and eustachian tube dysfunction. There is also an increased incidence of chronic ear disease in affected children due to increased incidence of upper respiratory infections, reduction of B and T cell function (immune system immaturity), and eustachian tube dysfunction. The hearing loss in DS is usually conductive secondary to the chronic middle ear disease but can also be due to ossicular chain abnormalities, especially the stapes. Upper airway obstruction and OSA are also problems encountered by children with DS due to the midface hypoplasia, and relative enlargement of the
tongue, tonsils and adenoids in a constricted naso/oropharynx. Other systems affected include cardiovascular (ventricular-septal defect, tetrology of Fallot, patent ductus arteriosus), genitourinary (micropenis, low testosterone, infertility), musculoskeletal (atlanto-axial instability, short metacarpals and phalanges) and ocular (speckled iris; Brushfield spots). In terms of speech and behavior, most Down’s syndrome patients exhibit dysarthria and articulation deficits in conjunction with some degree of mental retardation (IQ 30-50).

**Fetal Alcohol Syndrome (FAS):** Of children born to alcoholic mothers, 30-40% suffer this syndrome. The amount of alcohol intake required to cause FAS has not been clearly established. Alcohol and its major metabolite, acetaldehyde, may be teratogenic. The alcohol induced developmental abnormalities can be the result of restriction of cell growth during critical periods. Characteristics of the syndrome include prenatal and postnatal growth deficiency, microcephaly, and mental retardation (average IQ of 63). Behavior is also affected as irritability and hyperactivity are common. Neural tube defects and seizure disorder may also be present. From an ophthalmology perspective, this syndrome causes hypoplasia of the optic nerve, increased tortuosity of the retinal vessels, severe microphthalmia and colobomas. Almost no system is guaranteed to be spared as cardiac, renal and skeletal anomalies may manifest themselves as well as malignant neoplasms of embryonal origin. Common facial dysmorphisms include narrow forehead, short palpebral fissures, ptosis of eyelids, midface hypoplasia, short nose, smooth philthrum, thin upper lip and hypoplastic mandible. In addition, cleft palate or cleft lip may exist. Ten percent of patients have hearing loss that may be either conductive or sensorineural.

**Goldenhar’s Syndrome:** Also referred to as facioauriculovertebral dysplasia (FAVD) and hemifacial microsomia (HFM), this disorder results from aberrant development of the first and second branchial arches. HFM is estimated to occur in 1 in 5600 live births, perhaps making it the most significant asymmetric craniofacial disorder. Otologic manifestations include microtia/anotia, preauricular tags, ossicular abnormalities, abnormal facial nerve course, and hearing loss (conductive > sensorineural). The hearing loss is predominantly conductive secondary to the abnormal development of the structures derived from the first and second branchial arches. Facial abnormalities include unilateral hypoplasia of the maxilla, malar and temporal bones in addition to mandibular ramus and condyle hypoplasia. Macrostomia or pseudomacrostomia (lateral cleft-like extension of the oral commissures), cleft lip or palate and delayed dental development. Lastly, the mastoid is poorly pneumatized and their may exist agenesis of the parotid gland or displacement of the gland. In terms of non-head and neck features, affected individuals can also have cardiac abnormalities such as coarctation of the aorta, ventricular septal defect, tetrology of Fallot, and patent ductus arteriosus. Renal ectopia and hydronephrosis can encompass the renal abnormalities. Limb deformities can be present as well as cerebral malformation and mental retardation. Ocular abnormalities include blepharoptosis, microophthalmia, epibulbar tumors, and retinal abnormalities leading to reduced visual acuity.

**Rubella:** Consists of a triad characterized by deafness, congenital cataracts and heart defects. This disease is caused by an RNA togavirus and is transmitted postnatally via respiratory secretion, saliva, or direct contact. Transplacental transmission is the route responsible for congenital infection which can involve more sequelae if infection is present during the first trimester. In terms of diagnosis, positive viral culture must be obtained, rubella-specific IgM antibody, or demonstration of significant rise in IgG
antibody in acute (7-10 days) and convalescent phase (2-3 weeks later). The virus can be cultured from blood, nasal secretions, urine, throat swab or CSF. In addition to the above listed triad, other abnormalities that may manifest are microcephaly, motor and neural retardation, hepatosplenomegaly, thrombocytopenia, encephalitis and interstitial pneumonia. The hearing loss in rubella is typically asymmetric and sensorineural with variable severity. The 500-2000 Hz frequencies are the most commonly affected. This hearing deficit usually manifests by 5 years of age and can be an isolated finding in 22%. Approximately 25% of patients will experience a progressive form of hearing loss.

**Cytomegalovirus (CMV):** CMV has an incidence of 0.2%-2.3% of live births making it one of the most frequently occurring viruses worldwide and the leading cause of congenital malformations and mental retardation in developed countries. Of all the TORCH infections, CMV is the most common. Microcephaly, intrauterine growth restriction (IUGR), petechiae, encephalitis, hepatosplenomegaly, and deafness are some of the physical characteristics of a congenital CMV infection. CMV is estimated to account for 1/3 of sensorineural hearing loss in young children. Hearing impairment in CMV can be delayed (occurring months-years after birth), or fluctuating and progressive. Interesting to note, infants with petechiae and IUGR are 2-3 times more likely to have sensorineural hearing loss. Post mortem temporal bone studies on infants who died from cytomegalic inclusion disease have revealed inclusion bodies in the stria vascularis, Reissner’s membrane, saccule, utricle and semicircular canals. Endolympathic hydrops was noted in the cochlear ducts.

6.4.15 What is the significance of connexin 26? Who should be screened for this mutation? What are the limitations of testing? CB

Congenital hereditary hearing loss must be differentiated from acquired hearing loss. More than half of all cases of prelingual deafness are genetic. The remaining 40-50% of all cases of congenital hearing loss are due to nongenetic effects, such as prematurity, postnatal infections, ototoxic drugs, or maternal infection (with cytomegalovirus [CMV] or rubella). Most cases of genetic hearing loss are autosomal recessive and nonsyndromic. Hearing loss that results from abnormalities in connexin 26 and connexin 30 proteins likely account for 50% of cases of autosomal recessive nonsyndromic deafness in American children.

Mutations in CX26 are the most common cause of autosomal recessive deafness throughout the world. This gene is believed relevant to half of all cases of hereditary deafness. CX26 shows diverse mutations, but one mutation occurs very frequently in Europe—the 35delG mutation. Average carrier frequency in Europe is 1:51 (north/middle Europe 1:79, south Europe 1:35) (Table 6). In the Mediterranean countries the carrier frequency exceeds even that of the ΔF508 mutation in the CFTR gene which causes cystic fibrosis. Carrier frequencies in North America and Australia are comparable to those in north/middle Europe. In oriental populations and Ashkenazi Jews, other mutations in the same gene play a more important role (234delC and 176delT, respectively). The high frequency of connexin-26-related hearing impairment in certain populations may be the result of the tradition of marriages between hearing-impaired persons. The 35delG mutation gives rise to a severely shortened, non-functional protein. More than sixty other, far less frequent, mutations have been described in CX26. Uncertainty about the pathogenicity of some of the mutations complicates interpretation of mutation analysis.
Carrier frequency of mutation 35delG in the GJB2 gene in 17 European countries (adapted from Ref. 12)

Denoyelle et al.\textsuperscript{7} found mutations in the CX26 gene in 49% of the families from France, Great Britain and New Zealand who had severe to profound prelingual hearing loss. CX26 mutations were present in 51% of the group with, versus 31% in the group without, a clear familial history of hearing impairment; 86% of the CX26 mutations were 35delG mutations. Mueller et al.\textsuperscript{19} studied a group of 284 English patients with early childhood hearing impairment or deafness, with and without hereditary causes. They found CX26 mutations in 27.8% of the familial cases and in 7.9% of the sporadic cases; 70% of the CX26 mutations were 35delG mutations. This difference can be explained by the fact that families with different ethnic backgrounds were included in the study. The prevalence of non-familial, sporadic hearing impairment based on CX26 mutations in an English—Belgian population of 68 children was 10%.\textsuperscript{20}

Go to:

**DIAGNOSIS**

An increasing number of medical centres can perform mutation analysis to determine involvement of the CX26 gene in congenital hearing impairment. This method has been available for several years at the department of medical genetics in Nijmegen. We retrospectively analysed the outcome of ninety-one CX26 mutation analysis requests covering a fixed period of time. Nineteen unrelated cases were shown to have two mutations in the gene. Twelve of them turned out to be homozygous, whereas four others were heterozygous for the 35delG mutation. Overall, the 35delG mutation was involved in 84% of the cases; thirteen cases originated from multiaffected families, whereas three others were sporadic cases. Information on the remaining three families could not be retrieved. Table 7 gives an overview of the CX26 mutations found in Nijmegen.

The uncertainty about the pathogenicity of the mutation demands close collaboration with geneticists who are familiar with deafness\textsuperscript{18}. Nevertheless, CX26 mutation analysis provides a good starting-point in the molecular diagnosis of patients with non-syndromic congenital deafness.

6.4.16 What is mitochondrial deafness? CB from sick kids.com- pediatric lab medicine

Non-syndromic mitochondrial hearing loss is characterized by moderate-to-profound hearing loss, a lack of other systemic clinical findings, and a mutation in either the MTRNR1 or MTTS1. The MTRNR1 gene encodes the 12S ribosomal RNA and the MTTS1 gene encodes transfer RNA for serine, both of which are important in mitochondrial protein synthesis. Several recurrent
mutations have been reported to cause nonsyndromic mitochondrial hearing loss, including recurrent mutations in the MTRNR1 gene (m.C1494T, m.A1555G, m.961delT+Cn) and MTTS1 gene (m.A7443G, m.G7444A, m.A7445C, m.T7510C, m.T7511C).

Individuals with an MTRNR1 mutation may have a predisposition to aminoglycoside ototoxicity causing deafness and/or late onset sensorineural hearing loss. In these individuals, hearing loss associated with aminoglycoside ototoxicity is bilateral and severe to profound and occurs within a few days to weeks after administration of any amount of aminoglycoside antibiotic. Individuals with an MTTS1 mutation generally have an onset of sensorineural hearing loss during childhood. Variability in clinical findings may be due to the presence of variable numbers of mitochondria containing mutations in different tissues of the body (heteroplasmy).

Since non-syndromic mitochondrial sensorineural hearing loss is due to mutations in mitochondrial DNA (mtDNA) it is transmitted by maternal inheritance. In most cases, the mother of a proband has a disease-causing mtDNA mutation, and may or may not have hearing loss. All offspring of females with a mtDNA mutation are at risk of inheriting the mutation. Offspring of males with a mtDNA mutation are not at risk of inheriting the mutation.

The strategy used for testing for mutations causing non-syndromic mitochondrial hearing loss is direct mtDNA sequencing to identify recurrent mutations in the MTRNR1 and MTTS1 genes.

**Who should be tested**

- individuals clinically suspected of being affected with non-syndromic mitochondrial hearing loss
- relatives of probands with identified MTRNR1 or MTTS1 mutations

**Testing Methodology**

**Direct Mutation Analysis:** Patient samples are analyzed by direct mtDNA sequencing. For the MTRNR1 gene, the region sequenced encompasses nucleotides 860–1226 and 1313–1601 of the mitochondrial genome. For the MTTS1 gene, the entire gene is sequenced including the exon/intron boundaries.

**Test Sensitivity:** Of individuals affected with mitochondrial non-syndromic hearing loss, three mutations in the MTRNR1 gene (m.C1494T, m.A1555G, m.961delT+Cn) account for ~70 per cent of mutations, while five mutations in the MTTS1 gene (m.A7443G, m.G7444A, m.A7445C, m.T7510C, m.T7511C) account for a further ~14 per cent of mutations. A negative result does not rule out the possibility that the individual has a different MTRNR1 or MTTS1 mutation, or a mutation in another gene, not detected in the assay and is affected with non-syndromic mitochondrial hearing loss. In addition, sequencing analysis will not detect low levels of heteroplasmic mutant mitochondria.

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<th>Reason for referral</th>
<th>MTRNR1/MTTS1 Gene</th>
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<td>This result supports a diagnosis of <strong>non-syndromic mitochondrial hearing loss</strong></td>
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**Cautions**

Current molecular testing will not detect all possible mutations causing non-syndromic hearing loss. A negative result does not rule out the possibility that the individual has a mutation not included in the assay and is affected with non-syndromic hearing loss.

Low levels of heteroplasmic mutant mitochondria may not be detected by this testing.

Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

These tests were developed and the performance characteristics validated by the Molecular Genetics Laboratory at the Hospital for Sick Children. They have not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. These tests are used for clinical purposes.

6.4.17 Discuss the methods of newborn hearing screening including the advantages and disadvantages of each. CB

**Diagnostic Tests: The “Gold Standard” and the “Proxy Gold Standard”**

The gold standard for assessing hearing deficit in infants older than 6 months of age comprises behavioral tests that rely on operant conditioning, such as visual reinforcement audiometry (VRA). This involves testing an infant’s response to specific tones projected within a soundproof room from different directions. When performed correctly, VRA can yield accurate audiometric thresholds in children as young as 6 months of age who
have normal neurologic development. However, in Table 1.

- An illness or condition requiring admission of >48 h to a neonatal intensive care unit
- Stigmata or other finding associated with a syndrome known to include a sensorineural or conductive hearing loss
- Family history of permanent childhood sensorineural hearing loss
- Craniofacial abnormalities, including those that have morphologic abnormalities of the pinna and ear canal
- In utero infection, such as cytomegalovirus, herpes, toxoplasmosis, or rubella

Source: Joint Committee on Infant Hearing, Year 2000 Position Statement: Principles and Guidelines of Early Hearing Detection and Intervention Programs

Table 2.

- Parental or caregiver concern regarding hearing, speech, language, or developmental delay
- Family history of permanent childhood hearing loss
● Stigmata or other findings associated with a syndrome known to include a sensorineural or conductive hearing loss or eustachian tube dysfunction

● Postnatal infections associated with a sensorineural hearing loss, including bacterial meningitis

● In utero infection, such as cytomegalovirus, herpes, toxoplasmosis, rubella, or syphilis

● Neonatal indicators, specifically hyperbilirubinemia at a serum level requiring exchange transfusion, persistent pulmonary hypertension of the newborn associated with mechanical ventilation, and conditions requiring the use of extracorporeal membrane oxygenation

● Syndromes associated with progressive hearing loss (eg, neurofibromatosis, osteopetrosis, Usher syndrome)

● Neurodegenerative disorders (eg, Hunter syndrome) or sensory motor neuropathies (eg, Friedrich ataxia, Charcot-Marie-Tooth syndrome)

● Head trauma

● Recurrent or persistent otitis media with effusion for at least 3 mo

Source: Joint Committee on Infant Hearing, Year 2000 Position Statement: Principles and Guidelines of Early Hearing Detection and
Intervention Programs

**neonatology hearing screening**

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younger infants and in those who have developmental delay or certain physical disabilities, behavioral tests of any type are unreliable and have a low specificity. The auditory brainstem response (ABR) is the only test of auditory function accepted as a proxy gold standard for assessment of hearing sensitivity in newborns and infants. The ABR is an electrical waveform (an evoked potential) generated by neuronal activity in the auditory nerve and brainstem pathways following a transient sound such as a click. Its registration (via skin electrodes, electroencephalographic amplifiers, and computer averaging) does not require a behavioral response. The intensity and rate of stimulation primarily determine the response size, latency, and morphology. The presence of a detectable ABR is considered a proxy for perception of sound. The lowest stimulus level that evokes a detectable ABR is an estimator of the true perceptual threshold for various sounds. There is a high correlation between hearing impairment in infants and alteration in the ABR pattern. Overall, ABR testing provides a reasonable evaluation of thresholds over a broad range of hearing impairments and permits differentiation.
between CHL and SNHL. Many studies have demonstrated that the click ABR in early infancy is a good predictor of pure tone auditory thresholds in the 2,000 to 4,000 Hz range, although a more technically correct interpretation is that the ABR reflects the best pure tone threshold in the range of 500 to 4,000 Hz. Skill and experience are required for valid and efficient ABR testing and interpretation of results.

**Screening Tests: Advantages and Disadvantages**

Current screening technologies include: automated auditory brainstem response (AABR), transient evoked otoacoustic emissions (TEOAE), and distortion product otoacoustic emissions (DPOAE). The screening device objectively and automatically detects the response to sound (either an evoked potential or an otoacoustic emission), and the outcome is designated as a “pass” or “fail” (“refer”) by the automated analyser. In the screening mode, the three screening methods indicate presence or absence of a response at a specific stimulus level; they neither quantitatively estimate the severity of the hearing impairment nor distinguish conductive from sensorineural hearing impairment.

The AABR is a modification of conventional ABR testing, usually involving a single stimulus level and
automated response detection. Typically, a series of click stimuli at a level of approximately 30 to 40 dB nHL (normal hearing level is the threshold of audibility of the clicks in normal young adult listeners) is delivered. The electrical signals from at least three or four electrodes on the head are amplified and computer-processed in an attempt to extract the minute ABR from the ongoing electromyogenic and electroencephalic activity that is unrelated to the stimulus. The key technique is averaging of the waveforms recorded after several thousand stimuli, delivered very rapidly. The resultant waveform is tested statistically to determine whether it is a genuine evoked response or merely random electrical noise. Using statistical response detection eliminates the need for waveform interpretation by a highly trained professional. This is important both to reduce screening manpower costs and to increase the accuracy and consistency of response detection. A variety of automated ABR screening instruments is commercially available. TEOAE are elicited by click stimuli delivered by a probe transducer in the external ear canal. The emission or “echo” from the inner ear is a very faint sound with a complex waveform that is recorded by a sensitive, miniature microphone in an external ear probe assembly. Some method of signal enhancement, such as signal averaging,
is necessary to distinguish the otoacoustic emissions (OAE) from ambient sound.

TEOAE presence implies integrity of sound transmission through the outer and middle ear structures and functional integrity of the outer hair cells, which are the primary sensory transducers with the organ of Corti in the cochlea and are believed to be the site of emissions generation. Low ambient noise level, a clear external auditory meatus and middle ear, probe stability, appropriate choice of stimulus intensity, later postnatal testing, and cochlear maturation all improve the specificity of TEOAE screening. Because the original patent on the TEOAE method only expired recently, the variety of commercially available TEOAE screening devices is limited, although this is changing rapidly.

DPOAE are an alternative form of cochlear emission, also having their origin in the outer hair cells of the cochlea. The stimulus is two simultaneous sustained pure tones (primary frequencies of f1 and f2) typically in the 50 to 70 dB intensity range and with a frequency ratio of about 1.22. Under these conditions, a nonlinear stimulus interaction occurs within the cochlea, and a tonal distortion product at a frequency of 2f1-f2 is generated and radiates back to the external ear. Just as for the TEOAE, the DPOAE are detectable in the external
meatus. The frequency-specific nature of the DPOAE may provide more precise information than with the TEOAE, but poor recording conditions may result in inaccurate measurements. Any factor that interferes with the registration of a clear ABR or OAE will cause false-positive screening outcomes. The specificity of the AABR, TEOAE, and DPOAE improves when screening takes place at a later postnatal age and with cleaning of the external auditory meatus. This difference is believed to be due to cochlear maturation, clearance of middle ear fluid after the first 48 hours of life, or improved tympanic membrane mobility. Excessive environmental noise also decreases the specificity of TEOAE and DPOAE. There is good evidence that the TEOAE, DPOAE, and AABR are accurate tests for detection of significant hearing impairment in neonates and infants. A two-stage screening protocol tends to yield lower false-positive rates (with specificity _94%) without substantial reduction in sensitivity. Each technology is affected by environmental conditions and the age at which the screen takes place, with the OAE methods affected more than the AABR. There is more variability in the specificity with the TEOAE and DPOAE than with the AABR. That difference is reduced when a two-stage screening procedure is used and the AABR is used for the second stage of
the screen. Any of the three screening technologies may be used in a two-stage procedure to detect hearing impairment in newborns. The tests are noninvasive, brief, and inexpensive.