Precision medicine approach to cochlear implantation

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Highlights

- The precision medicine approach to cochlear implantation (CI) refers to a series of processes that determine and customize the preoperative planning of CI.

- Appreciation of relevant genotype-phenotype correlations could provide clinically useful diagnostic and prognostic information.

- Information gathered from a thorough evaluation of imaging studies can direct timing of surgery, device selection, and insertion techniques to maximize CI outcome.

- For certain types of inner ear malformations, the electrophysiological parameters obtained intraoperatively provides clues to the appropriate positioning of the electrodes and the timing of the initial switch-on of the device.
Abstract

In the early days of cochlear implantation (CI) surgery when the types of electrodes were limited and the etiology of sensorineural hearing loss (SNHL) was not well understood, the one-size-fits-all approach to CI held true like all other fields. However, in the era of personalized medicine, there have been attempts to associate CI performance with etiology of SNHL and to establish customized surgical techniques that can maximize performance according to individual cochlear dimensions. Personalized genomic-driven assessment of CI candidates and better understanding of genotype-phenotype correlations could provide clinically applicable diagnostic and prognostic information about questions such as who, how, and when to implant. Rigorous and strategic imaging assessments also provide a better insight into anatomic etiology of SNHL and cochlear dimensions, leading to individualized surgical techniques to augment CI outcome. Further, precision medicine approach to CI is not necessarily limited to preoperative planning but can be extended to either intraoperative electrode positioning or even decision of a timing of initial switch-on. In this review, we will discuss the implications of personalized diagnosis (both genetic and nongenetic) on planning and performance of CI in prelingual and postlingual SNHL.

Keywords: precision medicine, cochlear implantation, hearing loss, genotype-phenotype correlation, cochlear parameters, etiology of hearing loss.
Introduction

For subjects with severe-to-profound hearing loss that no longer benefit from the use of hearing aids, cochlear implantation (CI) is a better habilitation method for improved speech outcome [1]. CI is a commonly performed procedure with its indication criteria continuously expanding. Speech performance after CI is influenced by a complex array of factors, including duration of hearing loss, age at implantation, residual hearing, age at onset of hearing loss, type of implant, and socioeconomic status [2,3]. Unfortunately, about 3-7% of cochlear implantees do not benefit from the use of their device [4,5]. Although realistic expectations of CI performance can somewhat be predicted based on prognostic factors, currently there are no available methods to identify these potential nonusers prior to surgery.

In the era of personalized medicine, there have been attempts to associate CI performance with etiology of hearing loss [6-8] and to establish surgical techniques that can maximize performance according to individual cochlear dimensions [9,10]. In this review, we will discuss the implications of personalized diagnosis (both genetic and nongenetic) and how it relates to the performance of CI and decision making in prelingual and postlingual hearing loss (Table 1).

Molecular genetic diagnosis and cochlear implantation in prelingual deafness

The introduction of next generation sequencing (NGS) technology has allowed implementation of genetic diagnosis in various fields of medicine including hearing loss [11,12] Now molecular genetic testing (MGT) has become an important step in the diagnostic workup of CI candidates providing invaluable information regarding the etiology of hearing loss and prognosis of CI [13]. This information can foretell the natural course of hearing loss, guide patient selection and aid in
determining the timing of CI [14-16].

Hereditary deafness with variants in certain genes is related to especially successful CI outcome—specifically congenital deafness with variants of GJB2 or SLC26A4, the two most common deafness causing genes, yield excellent results [17-21]. Wu et al. found that age at implantation was another important factor determining good CI outcome even in patients with pathogenic variants of allegedly good prognosis-bearing genes, GJB2 and SLC26A4 [18,19]. Children that received CI before the age of 3.5 years demonstrated better auditory performance at 3- and 5-years post-CI than those without documented pathogenic variants, whereas no differences were observed between children that received CIs after 3.5 years of age [18,19].

However, in another study of Korean children with GJB2 and SLC26A4 variants that underwent CI, excellent results were also observed in late cochlear implantees [17]. The discrepancy in these findings were attributed to the fact that most late implantees, especially the children with SLC26A4 variants, had a history of progressive or fluctuating hearing loss and their pre-CI hearing experience could be associated with their good CI outcomes.

Also subjects with auditory neuropathy spectrum disorder (ANSD) segregating OTOF variants (DFNB9) show consistent benefit from CI when implanted at an appropriate age [22]. But the sensitive period for good CI outcome for DFNB9 subjects may be narrower than that for GJB2- and SLC26A4-related deafness [17,23-25]. 50% of Korean DFNB9 children implanted after 2 years of age showed a notably poor outcome (categories of auditory performance) (CAP) scores of 3 and 4) at 24 months post-CI when compared to CAP scores of 6 and 7 achieved by children implanted early [17]. Furthermore, implantation before the age of 18 months was associated with a more rapid catchup in speech abilities after CI [26]. In a recent pilot study
investigating the central auditory development of DFNB9 patients after CI, the cortical auditory evoked potential-based P1 component of children implanted after the age of 2 years tended to show “absent” or “anomalous” P1 components almost always associated with delayed language development [24]. Another interesting finding was that when the P1 component was repeatedly measured in DFNB9 patients, even the children that underwent timely implantation (before the age of 12 months) did not achieve sufficient cortical maturation with six to seven months of device use. This suggests the need for sustained rehabilitation in DFNB9 patients compared to patients with other molecular etiologies.

Bi-allelic *PCDH15* pathogenic variants and p.G292R variant of *DFNB59* are reported to be associated with poor CI performance [18]. Pejvakin-deficient mice and humans have been shown to be hypervulnerable to sound because they lacked oxidative stress-induced pejvakin-dependent proliferation of peroxisomes that contributes to physiological response to sound exposure [27]. Amplification of sound using hearing aids or CI may paradoxically worsen hearing impairment in patients with DFNB59 due to sustained injury to the hair cells, spiral ganglion neurons, and auditory nerve by uncontrolled oxidative stress, therefore the authors suggested antioxidant protection in cases of peroxisomal deficiency, for specific protection against redox homeostasis failure [27].

All in all, implantees with identified genetic etiology tend to achieve better speech outcome compared to those with an unidentified etiology [6,7,17] although some variants are related with poor CI outcome [18]. The information acquired from MGT can also be used to counsel patients and their family on expected outcome after CI and the time required to reach those results. MGT can also identify appropriate candidates for personalized and customized
auditory rehabilitation for deaf patients.

Cochlear implantation in congenital cytomegalovirus infection

Congenital cytomegalovirus (cCMV) infection is a common congenital infection found in 0.5 to 2% of all live births [28,29]. Some children with cCMV infection can manifest permanent disabilities, including sensorineural hearing loss (SNHL), vision loss, and neurodevelopmental delay, with SNHL being the most common manifestation [30]. Based on the presence of clinical manifestation at birth, cCMV infection can be classified as symptomatic or asymptomatic. Approximately 10% of neonates with cCMV infection are symptomatic (they are born with clinically apparent sequelae) while the remaining 90% are asymptomatic at birth [31]. However, about 6-23% of neonates with asymptomatic cCMV infection can also develop late-onset SNHL, while 33-63% of symptomatic patients develop SNHL [30,32,33].

Resultantly, congenital CMV infection accounts for approximately 40% of nongenetically caused congenital SNHL, representing about 20% of all congenital SNHL [34]. A substantial portion of SNHL due to cCMV infection manifests as asymmetrical and progressive hearing loss with significant residual hearing [35]. Indeed, in a study of audiological characteristics in a Korean cohort with cCMV infection, 33.3% of patients had SNHL, 38% asymmetric hearing loss, 29% of late-onset hearing loss, and a diverse spectrum of SNHL severity, ranging from mild to profound [36,37].

Children with significantly delayed speech development due to cCMV related SNHL are also potential candidates for CI. However, predicting the outcome of prelingual bilateral profound hearing loss due to cCMV infection is not so straightforward. Some studies have
shown that the cCMV patients can achieve comparable CI outcome to the groups with idiopathic SNHL [38,39] or SNHL by GJB2 variants [40,41]. But other studies report variable outcomes of CI [42,43]. Specifically, Lee et al found that 64% of children with CMV-related hearing loss were able to recognize open-set words after 4 years of device use, suggesting a wide spectrum of outcome [44]. Similarly Viccaro et al also showed that after around 10 years of CI usage, the ability to recognize open-set words improved in most patients [45]. This wide outcome spectrum could be attributed to neurodevelopmental delay and cognitive impairment which cCMV infection can also manifest. In this sense, brain abnormalities seen on magnetic resonance imaging are considered poor prognostic markers of speech performance after CI [41,46] and were shown to be correlated with CI outcomes to some extent [47]. In detail, patients with a normal or partial white matter abnormality on magnetic resonance imaging showed good speech perception performance after CI at least comparable to the performance obtained by idiopathic SNHL patients [47].

The decision to undergo CI in unilateral and asymmetric hearing loss due to cCMV is even more complicated. In these cases, since substantial speech development has already been achieved, the decision to implant should be determined by weighing the potential benefits on speech development (i.e., pronunciation or expressive language) that can be obtained through CI against the limitations of the development due to cognitive impairment. Specifically, we need to be cautious about performing CI on the worse hearing ear in a cCMV child with asymmetric hearing loss who has significant cognitive impairment.

**Cochlear implantation in cochlear nerve deficiency**
Cochlear nerve deficiency, typically defined as a small or absent cochlear nerve in the internal auditory canal (IAC) documented by magnetic resonance imaging, is a known cause of congenital deafness [48,49] and prevails in up to 18% of congenital SNHL [50]. The status of the cochlear nerve can be graded based on the number of nerves visualized in the IAC [51]. Grade 0 is indicated when no nerves are identified in the IAC, grade I when there is one nerve present, grade II when there are two nerves present, grade III when there are three nerves present, grade IV when there are four nerves present with a hypoplastic nerve, and grade V when all four normal sized nerves are present in the IAC [51]. However, limited resolution of magnetic resonance imaging may not accurately reflect the status of the nerves in the IAC [52] and some patients with auditory nerve aplasia do in fact respond to electrical stimulation when implanted with a CI [53,54].

Management of hearing loss in children with cochlear nerve deficiency accompanies many challenges. Because the cochlear nerve is absent or hypoplastic, the electrical signal from the implant provides limited stimulation. Cochlear nerve deficiency can accompany other inner ear malformations, craniofacial anomalies and neurodevelopmental problems which will further influence the outcome of CI [55,56]. Cochlear nerve deficiency was once considered a contraindication for CI [57] but a growing body of evidence suggest successful CI outcome in these patients despite imaging evidence of deficient cochlear nerve [58].

Children with cochlear nerve deficiency require obviously higher stimulation levels than that required by those with normal cochlear nerve dimensions [59-61]. These results support the importance of 1) proper device choice such as modiolar hugging electrodes with better modiolar proximity and 2) appropriate initial switch-on strategies to ensure earlier stabilization of mapping
parameters and to thereby maximize the patients’ performance [62,63].

**Cochlear implantation in common cavity (CC) or cochlear aplasia with dilated vestibule (CADV): Exploring the neural tissue**

CI is generally considered a valid option for common cavity (CC) deformities [64,65], albeit with varying outcomes reported thus far. Cochlear aplasia with dilated vestibule (CADV) is traditionally regarded as a contraindication to CI, however still some satisfactory outcomes have been reported in very small numbers [66,67]. For patients with CC or CADV, the status of the cochlear nerve and the positioning the electrode can potentially affect CI outcome [65].

The auditory neural tissues are distributed along the wall of these anomalous cavities [68], which is in line with the clinical observation that a full-band straight electrode outperforms modiolar hugging electrodes in eliciting electrically evoked compound action potential (ECAP) responses in CI subjects with CADV [69]. Using electrical auditory brainstem response recording, Yamazaki et al. suggested that the auditory neuronal tissue was distributed in the anteroinferior part of CC deformities, mainly near the inner wall of the cavity in all cases [70]. The authors suggested using electrical auditory brainstem response testing to achieve the optimal electrode array placement and to adjust programming parameters of the implanted device.

During CI surgery for CC/CADV, the electrode should be inserted in a way that enables maximum contact of the CI electrode with the inner wall of the cavity [69,71]. Previously, lower maximum comfortable level and better behavioral outcomes were related to a shorter distance between the inner wall of the CC/CADV cavity and the electrode [72]. Intraoperative ECAP-based positioning of full-band straight electrodes can be implemented into surgical practice to
guide the optimal electrode positioning in each individual CC/CADV allowing successful CI [69].

Taken together, achieving the maximum CI outcomes in CC/CADV depends on the presence of auditory neural tissue and proper positioning of the electrode which could be assisted by ECAP measurements so that the neural tissues can be fully stimulated.

**Molecular genetic diagnosis and cochlear implantation in postlingual deafness**

Some genetic variants have been reported to be associated with good auditory performance after CI in postlingual deafness [73-75]. Therefore, identification of pathogenic variants via MGT can be a crucial component in the preoperative evaluation of CI from the prognostic viewpoint. For example, CI is believed to provide satisfactory results in postlingual adult DFNA9 cochlear implantees carrying a variant of COCH which is expressed also in the dendrites of the spiral ganglion neuron (SGN) in addition to the spiral limbus and the lateral wall [76]. Pecci et al. reported that CI is safe and effective in most patients with MYH9-related disease and deafness [77]. Miyagawa et al. found that four patients with a variant in MYO15A, TECTA, TMPRSS3, or ACTG1 genes showed relatively good auditory performance after CI including electric acoustic stimulation [13].

A comprehensive MGT protocol, including exome sequencing, can potentially identify the genetic etiology in approximately 50% of patients with postlingual deafness [8]. Molecular etiologic heterogeneity involving 14 deafness genes in 21 subjects was noted in this Korean cohort [8]. In contrast with a high proportion of variants of two genes, GJB2 and SLC26A4, accounting for up to 38% of prelingual SNHL [17], there is extreme genetic heterogeneity in
postlingual deafness [73,74]. Given the nature of this heterogeneity, exome sequencing is often required to identify pathogenic variants.

Implantees whose causative variants were identified among the known deafness genes yielded better CI outcomes than those without identifiable variants [8]. However considerable variation in CI outcome is observed among subjects with the same genotype, meaning that the genetic etiology alone may not be sufficient in predicting the CI outcome. The duration of deafness is negatively associated with the CI outcomes, especially in subjects with identified causative variants among known deafness genes, however, not in those who remain undiagnosed. Therefore, early timely CI is recommended in subjects with a known genetic etiology.

CI outcome is also related to the gene expression site in postlingually deafened cochlear implantees [78]. According to a previously suggested classical hypothesis, the prediction of CI outcomes could be postulated based on the SGN health [73]. Membranous labyrinth-related deafness genes, which may inflict a relatively weaker damage on the SGN health if mutated, are considered to yield favorable CI outcomes [8]. Further, even subjects with SGN-related deafness genes, including COCH [76], TMPRSS3 [79], and NF2 [80], can attain some extent of audiological benefit from CI.

**Postlingual auditory neuropathy spectrum disorder and cochlear implantation**

Perhaps the biggest beneficiary of the precision medicine approach to CI is postlingual ANSD. Unlike prelingual ANSD which is mainly caused by OTOF variants or cochlear nerve deficiency, numerous causative genes of postlingual ANSD have been reported and they are largely divided into genes expressed in 1) inner hair cells themselves, 2) inner hair cells-afferent dendrite
junctions, 3) regions more central to the inner hair cells-afferent dendrites synaptic junctions, depending on their expression sites.

A representative ANSD gene expressed only in inner hair cells itself is the *DIAPH3* gene, which causes lesions limited to the stereocilia of inner hair cells [81]. Many currently known ANSD genes are usually expressed at the inner hair cell-afferent dendrite junction. For example, *SLC17A8*, which encodes VGLUT3, and *DMXL2*, which encodes Rabconnectin-3, are expressed in the synaptic vesicle membrane and are known to cause, if altered, DFNA25 and DFNA71, respectively, in humans [82,83]. In addition to those expressed in the inner hair cells and the junction itself, there are also the genes expressed in the supporting cells adjacent to the inner hair cells such as border cells and inner phalangeal cells. The classic example of this is *TMEM43* [84]. It is not surprising that favorable CI outcome is reported among these presynaptic ANSD cases that are not amenable to conventional hearing aids.

The two genes, *ATP1A3* and *OPA1* merits special attention since these are known to cause syndromic hearing loss. *ATP1A3* is the causative genes of CAPOS syndrome (Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy and Sensorineural hearing loss), however, the p.Glu818Lys variant of *ATP1A3* leads to manifestation of ANSD with minimal syndromic features in Koreans. In fact, it frequently appears in the form of nonsyndromic ANSD [85]. Since *ATP1A3* and *OPA1* genes are expressed in the spiral ganglia as well as in the nerve endings of afferent dendrites, the results of CI have been questioned, but satisfactory results have been reported [85,86].

In contrast, when ANSD occurs due to alteration of genes mainly expressed more central to the synaptic region such as the SGN or the cochlear nerve, the outcome of CI is theoretically unpredictable with residual hearing at risk of aggravation. There is no definitive data on whether
these ANSD patients can benefit greatly from CI. Given the lack of robust clinical test to localize the main lesion of postlingual ANSD, molecular genetic diagnosis is of tremendous importance for prediction of outcome of CI and sometimes even for the decision on whether to perform CI in these patients.

**Potentially treatable sensorineural hearing loss and cochlear implantation**

A subclass of patients with progressive SNHL due to gain-of-function variants of the *NLRP3* gene warrants special attention in the management of hearing loss. The *NLRP3* gene encodes the NLRP3 protein which controls the secretion of IL-1β [87]. The cochlear autoinflammation caused by increased level of IL-1β in these patients can thus be reversed by systemic administration of IL-1β antagonist [88]. Degree of hearing loss, and responsiveness to IL-1β antagonist (Kineret® (Anakinra)) may vary from person to person, however *NLRP3* genotypes, auditory thresholds at diagnosis and radiological findings of the cochlea can collectively serve as potential predictive and prognostic factors of hearing loss progression [89]. Not infrequently, CI candidates with *NLRP3* variants show improvement of hearing to a level that can be rehabilitated with conventional hearing aids after daily injection of Anakinra, emphasizing the importance of molecular genetic diagnosis in the management of hearing loss. Subjects unresponsive to medical therapy, nevertheless show excellent audiological outcomes with rapid improvement of speech perception test result reaching plateau at 3 months after CI [90].

**Molecular genetic diagnosis and hearing preservation in CI among ski-slope type hearing loss**
A subset of postlingual hearing loss patients exhibit ski-slope type hearing loss—hearing loss with significant low-frequency residual hearing. These patients are in a unique situation because hearing aids do not provide adequate amplification of the mid-to-high frequencies necessary for speech perception; however, many of these patients also do not meet the reimbursement criteria for the insurance system and sometimes do not fall within the conventional candidacy criteria for CI. Therefore, there lies a clinical dilemma in deciding when to proceed with CI and the precision genetic medicine approach can guide decision making. Specifically, a recent case series describing the effects of CI in children with TMPRSS3 variants has paved the idea of early intervention using electroacoustic stimulation implants in cases where the natural course of hearing loss can be predicted by the genetic etiology [91].

The detection rate of molecular genetic testing in a Korean cohort of ski-slope hearing loss was 37.8% [92]. This number is significantly lower than detection rates of 48–65% previously reported for SNHL that were diagnosed through the same molecular diagnostic platform [8,15,93]. Considering that around 80% of hearing loss cases are of genetic origin [94], there may be a yet-to-be-found Mendelian genetic disorder behind ski-slope hearing loss; or alternatively, environmental or polygenic factors could play a role in the pathophysiology of ski-slope hearing loss. Nevertheless, the variants found in a ski-slope hearing loss cohort were heterogeneous and included TMC1, TMPRSS3, GSDME, MYO3A, MYO6A, MYO7A, MYO15A, LOXHD1, PTPRO, SLC26A4, P2RX2, LRTOMT, and USH2A and GPR98 digenic variants [92].

Recently minimally invasive surgery and delicate electrode array design have allowed hearing preservation in CI surgery, although the hearing preservation rate differs according to studies [95-97]. A trend toward better hearing preservation in genetically diagnosed cochlear
Implantees have been proposed, especially in patients carrying pathogenic variants of genes specifically expressed in the stereocilia of hair cells [92,98]. Yoshimura et al. found better hearing preservation scores in patients who had pathogenic variants in the CDH23, MYO7A, or MYO15A gene [98]. The authors speculated that the stereocilia function was the key component in residual hearing, and that CI insertion may not have an impact on the residual function of hair cells. However, in the Korean cohort, no significant differences in hearing preservation rates among recipients with genetic variants expressed mainly in the hair cells (MYO7A, MYO15A, PTPRQ, TMCI, and LOXHD1) and those expressed mainly elsewhere in the cochlea (SLC26A4, GSDME, and TMPRSS3) were noted [92]. This issue merits further investigation in larger cohorts.

Influence of cochlear parameters in CI

A successful CI surgery requires coverage of the optimal frequency range for good audiological outcome whilst avoiding insertion trauma. To achieve good audiological outcome, closer positioning of the electrodes to the modiolus and robust scala tympani insertion are essential, while the depth of insertion is the most significant factor for the lateral wall arrays [99,100]. Intracochlear positioning of the electrode array nearer to the modiolus does lead to better hearing outcomes for CI recipients implanted with a perimodiolar electrode [101], forming the basis for the pull-back maneuver has been introduced for slim modiolar electrodes to ensure better modiolar proximity [102].

Cochlear duct length (CDL) has also been considered as another important factor that influences intracochlear position of CI electrode and therefore CI outcome [103]. Understanding
the CDL has great implications on the electrode array length selection, adjustment of angular
insertion depth, and frequency mapping [104]. However, CDL, cochlear size, shape, and spiral
characteristics varies even within normal hearing subjects according to sex and race [105-107].
Based on this, a concept for individualized CI can be presented to optimize audiological
outcomes.

Shorter CDL was noted among subjects with congenital deafness compared with those with
postlingual onset deafness [10]. Short CDL led to a “relative” over-insertion of slim modiolar
electrodes and therefore pushed the electrodes further away from the modiolus towards the
lateral wall of the cochlea. For subjects with short CDL, a further pull-back approach—in which
the electrode is pulled back by 1 or 2 mm than in conventional pull back approach—was
recommended to compensate for the “relative” over-insertion [10].

**Conclusion**

The precision medicine approach to CI refers to a series of processes that determine and
customize the preoperative planning of CI including whether to perform CI, the timing of
surgery, the position of electrodes during surgery, and the timing of the first switch-on of the
device, based on the patient's genome, imaging information, and even the electrophysiological
response obtained from the patient's cochlea intraoperatively. Appreciation of relevant genotype-
phenotype correlations could provide clinically useful diagnostic and prognostic information.
Specifically, genetic information may aid in addressing clinical questions regarding who, how,
and when to implant and also in identifying individuals with potentially treatable SNHL,
avoiding hasty CI surgery. Identifying the nongenetic causes of hearing loss also impacts CI
outcome. Information gathered from a thorough evaluation of imaging studies can direct timing
d of surgery, device selection, and insertion techniques to maximize CI outcome. For certain types
of inner ear malformations, the electrophysiological parameters obtained intraoperatively in turn
provides clues to the appropriate positioning of the electrodes and the timing of the initial
switch-on of the device has an important effect on the initial rehabilitation process.
References


Acker T, Mathur N, Savy L, Graham JJ. Is there a functioning vestibulocochlear nerve? Cochlear implantation in a child with symmetrical auditory findings but asymmetric imaging.


68. Graham JM, Phelps PD, Michaels LJTJoL, Otology. Congenital malformations of the ear and
23


75. Michalski N, Petit CJAron. Genes involved in the development and physiology of both the peripheral and central auditory systems. 2019;42(67-86).


Modiolar electrode on residual hearing in pediatric patients. 2021;278(8):2723-2732.


Table 1. Summary of precision medicine approach to cochlear implantation

<table>
<thead>
<tr>
<th>Type of hearing loss</th>
<th>Testing modality</th>
<th>Parameters</th>
<th>Implications</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Prelingual deafness</td>
<td>Genetic testing</td>
<td>GJB2, SLC26A4</td>
<td>Excellent results only when operated before the age of 3.5 years</td>
<td>(18,19)</td>
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<td>Excellent results even from late implantees</td>
<td>(17)</td>
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<td><strong>OTOF</strong></td>
<td>Consistent benefit when implanted at an appropriate age</td>
<td>(22)</td>
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<td>Narrow sensitive period for good CI outcome</td>
<td>(17, 23-25)</td>
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<td>Relatively poorer outcome and anomalous P1 recovery in CAEP when operated after 2 years of age</td>
<td>(17, 24)</td>
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<td>More rapid catchup in speech abilities when operated before the age of 18 months</td>
<td>(26)</td>
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<td>PCDH15 variants and p.G292R of DFNB59</td>
<td>Poor CI outcome</td>
<td>(18)</td>
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<tr>
<td></td>
<td></td>
<td>Identification of genetic etiology</td>
<td>Better speech outcome than in cases without identified genetic etiology</td>
<td>(6,7,17)</td>
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<tr>
<td>Imaging study (MRI)</td>
<td>Cochlear nerve deficiency</td>
<td></td>
<td>Not a contraindication to CI and successful CI outcome</td>
<td>(58)</td>
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<td></td>
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<td>Require higher stimulation levels than that required by those with normal cochlear nerve dimensions</td>
<td>(59-61)</td>
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<td>Proper device choice such as modiolar hugging electrodes with better modiolar proximity and better initial switch-on strategies to ensure earlier stabilization of mapping parameters</td>
<td>(62,63)</td>
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<td></td>
<td>Common cavity/CADV</td>
<td>Electrodos should be inserted in a way that enables maximum contact of the CI electrode with the inner wall of the cavity</td>
<td>(69,71)</td>
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<td>Intraoperative ECAP-based positioning of full-band straight electrodes for optimal electrode positioning</td>
<td>(69)</td>
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<tr>
<td>cCMV deafness</td>
<td>PCR, culture</td>
<td>High cCMV titer and culture positivity</td>
<td>Wide spectrum of CI outcome (64% of implantees recognize open-set words after 4 years of use)</td>
<td>(44)</td>
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<td></td>
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<td>Brain abnormalities</td>
<td>Poor prognostic outcomes after CI</td>
<td>(41,46)</td>
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<tr>
<td>Imaging study (MRI)</td>
<td>Normal or partial white matter abnormality</td>
<td>Good speech outcome</td>
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<th>Postlingual deafness</th>
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<th>COCH variants</th>
<th>Satisfactory CI results</th>
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<th>MYH9 variants</th>
<th>Safe and effective in most CI implanters</th>
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<tr>
<th>Variants in MYO15A, TECA, TMPRSS3, ACTG1</th>
<th>Relatively good CI auditory performance</th>
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<th>Identification of causative variants</th>
<th>Identification of causative variants lead to better CI outcomes. Duration of deafness is negatively associated with CI outcomes in subjects with identified causative variants.</th>
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<th>CI outcome is related to the gene expression site</th>
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<th>Spiral ganglion neuron health</th>
<th>CI outcome is predicted based on the spiral ganglion neuron health</th>
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<tr>
<th>Variants in COCH, TMPRSS3, NF2</th>
<th>Even subjects with spiral ganglion neuron-related deafness genes can attain some extent of audiological benefit from CI</th>
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<th>Variants in membranous labyrinth-related deafness genes</th>
<th>Favorable CI outcomes</th>
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<table>
<thead>
<tr>
<th>Postlingual auditory neuropathy spectrum disorder (ANSD)</th>
<th>Genetic testing</th>
<th>Gene expression in the inner hair cell themselves and surrounding supporting cells,</th>
</tr>
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<tr>
<th>TMEM43 variant</th>
<th>Successful outcome was reported</th>
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<tr>
<th>Gene expression in the Inner hair cells-</th>
<th>Favorable outcome is expected</th>
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(47) (76) (77) (13) (8) (78) (73) (76, 79, 80) (8) (81) (84) (82, 83)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Testing</th>
<th>Variant(s)</th>
<th>Description</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially treatable deafness</td>
<td>Genetic testing</td>
<td>NLRP3 variants</td>
<td>Lesser degree of cochlear autoinflammation can be amenable to Anakinra. Some CI candidates with NLRP3 variants show improvement of hearing loss to a level that can be rehabilitated with conventional hearing aids</td>
<td>(85, 86)</td>
</tr>
<tr>
<td>Ski-slope type hearing loss</td>
<td>Genetic testing</td>
<td>TMPRSS3 variants</td>
<td>Early CI is recommended.</td>
<td>(91)</td>
</tr>
<tr>
<td>All type of hearing loss</td>
<td>X-ray</td>
<td>Modiolar proximity</td>
<td>Better modiolar proximity leads to better hearing outcomes for CI recipients implanted with a perimodiolar electrode.</td>
<td>(101)</td>
</tr>
</tbody>
</table>

CI, cochlear implantation; CAEP, cortical auditory evoked potentials; CADV, cochlear aplasia with dilated vestibule; ECAP, electrically evoked compound action potential; MRI, magnetic resonance imaging; cCMV, congenital cytomegalovirus.