

## Supplemental information

### International expert consensus on gene therapy

#### for hereditary hearing loss:

#### Based on clinical trials

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## SUPPLEMENTAL INFORMATION

### Figure and Table Legends

**Supplemental Table S1.** Literature Used to Develop Each Consensus Statement. Related to Figure 1.

**Supplemental Table S2.** The Results of Merged and Deleted Consensus Statements in Voting Round 1. Related to Table 1.

**Supplemental Table S3.** Searches carried out in: PubMed (n=1770), Medline (n=1345), Embase OVID (n=3408), and Cochrane Library (n=2474) and manually retrieved papers (n=96) from Jan 1, 1966 to Mar 1, 2025. Related to STAR Methods.

**Table S1. Literature Used to Develop Each Consensus Statement**

Statements	Articles
1. For ethical reasons, gene therapy, an emerging treatment for hereditary HL, should comply with national regulations and laws, undergo rigorous ethical reviews, and be implemented according to standardized procedures.	Beecher et al. 1966 <sup>[S1]</sup> Emanuel et al. 2000 <sup>[S2]</sup> Lv et al. 2024 <sup>[S3]</sup> Qi et al. 2024 <sup>[S4]</sup> Wang et al. 2024 <sup>[S5]</sup>
2. Hereditary HL caused by pathogenic or likely pathogenic variants in deafness-associated genes	Lv et al. 2024 <sup>[S3]</sup> Qi et al. 2024 <sup>[S4]</sup> Wang et al. 2024 <sup>[S5]</sup> REGENERON 2024 <sup>[S6]</sup> Lilly 2024 <sup>[S7]</sup>
3. Appropriate age to receive gene therapy: The current evidence supports that the minimum age for receiving gene therapy is 10 months, whilst younger ages may be further explored.	Sharma et al. 2009 <sup>[S8]</sup> Guo et al. 2020 <sup>[S9]</sup> Alzahrani et al. 2021 <sup>[S10]</sup> Warner-Czyz et al. 2022 <sup>[S11]</sup> Roland et al. 2009 <sup>[S12]</sup> Leigh et al. 2016 <sup>[S13]</sup> Karltorp et al. 2020 <sup>[S14]</sup> Dettman et al. 2021 <sup>[S15]</sup> Anagiotos et al. 2013 <sup>[S16]</sup> REGENERON 2024 <sup>[S6]</sup> Bance et al. 2024 <sup>[S17]</sup>
4. Initially, priority is given to individuals with severe, profound or complete HL, or those severely affected by auditory synaptopathy or neuropathy, where hearing impairment often exceeds that predicted by hearing threshold. For patients with moderate to moderately severe HL, the necessity of gene therapy should be evaluated based on the progression of related hereditary HL, along with the benefits and risks of gene therapy.	Lv et al. 2024 <sup>[S3]</sup> Qi et al. 2024 <sup>[S4]</sup> Wang et al. 2024 <sup>[S5]</sup> Carlson et al. 2025 <sup>[S18]</sup> Groves 2010 <sup>[S19]</sup> Colbert 20024 <sup>[S20]</sup>
5. Guardians and/or patients should be informed of the risks and benefits with reasonable expectations of gene therapy.	Lv et al. 2024 <sup>[S3]</sup> Qi et al. 2024 <sup>[S4]</sup> Wang et al. 2024 <sup>[S5]</sup> Emanuel et al. 2000 <sup>[S2]</sup>
6. Acute inflammation of the middle ear	Lv et al. 2024 <sup>[S3]</sup> Qi et al. 2024 <sup>[S4]</sup> Wang et al. 2024 <sup>[S5]</sup>
7. Severe malformation of the inner ear or the disruption of the auditory pathway, which may limit the delivery or efficacy of the gene therapy.	Ahmed et al. 2020 <sup>[S21]</sup>
8. Severe mental, intellectual, behavioral and psychological disorders, which result in an inability to fully cooperate with gene therapy, postoperative follow-up and rehabilitation.	N/A
9. Other clinical contraindications to gene therapy, surgery or anesthesia determined by clinicians	N/A
10. The impact of pre-existing anti-AAV neutralizing antibodies on AAV-mediated gene therapy in patients with hereditary HL	Colella et al. 2018 <sup>[S22]</sup> Wang et al. 2019 <sup>[S23]</sup> Costa et al. 2020 <sup>[S24]</sup>

	Li et al. 2020 <sup>[S25]</sup> Whitehead et al. 2021 <sup>[S26]</sup>
11. Gene therapy can be performed on the contralateral ear in individuals with unilateral CI.	Lv et al. 2024 <sup>[S3]</sup> Qi et al. 2024 <sup>[S4]</sup>
12. Simultaneous binaural gene therapy should be based on the proven safety and efficacy of monaural gene therapy.	Dunn et al. 2008 <sup>[S27]</sup> Ma et al. 2016 <sup>[S28]</sup> Qi et al. 2024 <sup>[S4]</sup> Wang et al. 2024 <sup>[S5]</sup>
13. For individuals who cannot receive efficient auditory and speech rehabilitation, the benefits and risks of gene therapy should be considered and evaluated comprehensively, and be clearly communicated to the guardians and/or patients.	Niparko et al. 2010 <sup>[S29]</sup>
14. The patient's HL and systemic disease history should be recorded.	N/A
15. The history should include the mother's pregnancy and delivery history, the child's growth and development history, and family support for the child to comply with long-term follow-up visits.	Rawlinson et al. 2017 <sup>[S30]</sup> Chu et al. 2003 <sup>[S31]</sup> Bateman et al. 2025 <sup>[S32]</sup>
16. The periauricular area, auricle, external auditory canal and tympanic membrane should be assessed for developmental abnormalities, inflammation or other conditions that may obstruct or prevent drug delivery.	N/A
17. To allow for accurate perioperative and postoperative monitoring, the following tests are recommended, including pure tone audiometry (PTA), auditory evoked potentials, acoustic impedance and stapedial reflexes, otoacoustic emissions, and vestibular function assessment.	Hoth et al. 2017 <sup>[S33]</sup> Shi et al. 2012 <sup>[S34]</sup> Wu et al. 2022 <sup>[S35]</sup> Robbins et al. 1991 <sup>[S36]</sup> Robbins et al. 1990 <sup>[S37]</sup> Archbold et al. 1998 <sup>[S38]</sup> Mulch et al. 1979 <sup>[S39]</sup> Zellhuber et al. 2014 <sup>[S40]</sup> Weber et al. 2015 <sup>[S41]</sup> Lv et al. 2024 <sup>[S3]</sup> Qi et al. 2024 <sup>[S4]</sup> Wang et al. 2024 <sup>[S5]</sup>
18. MRI is required to assess the structure of the inner ear, auditory nerve, and central auditory system. High-resolution computed tomography (HRCT) of the temporal bone is additional required in case of malformation and can be used as a supplement or alternative (e.g., MRI incompatibility) when necessary.	Sorge et al. 2023 <sup>[S42]</sup> Joshi et al. 2012 <sup>[S43]</sup>
19. The patients' genetic variants should be identified and verified by sequencing technology, and analyzed by at least two independent experienced clinical geneticists according to the American College of Medical Genetics and Genomics / the Association for Molecular Pathology (ACMG/AMP) variant interpretation guidelines. The variants of the target gene should meet the classification of "pathogenic" or "likely pathogenic", corresponding to the inheritance pattern of the disease.	Richards et al. 2015 <sup>[S44]</sup> Riggs et al. 2020 <sup>[S45]</sup> Patel et al. 2021 <sup>[S46]</sup>
20. Speech-language skills should be assessed using well-recognized, standardized tests and validated questionnaires where appropriate.	Cox et al. 1989 <sup>[S47]</sup>

21. Developmental and cognitive function can be evaluated by validated assessment tools. Weschler. 2003<sup>[S48]</sup>  
Wang et al. 2018<sup>[S49]</sup>  
Green et al. 2016<sup>[S50]</sup>
22. Perform blood tests, physical examinations and relevant diagnostic tests to assess the patient's overall health and identify any contraindications for gene therapy. Wang et al. 2019<sup>[S23]</sup>  
Lv et al. 2024<sup>[S3]</sup>  
Qi et al. 2024<sup>[S4]</sup>  
Wang et al. 2024<sup>[S5]</sup>
23. Glucocorticoids can be given systemically during the perioperative period to reduce possible immune and inflammatory responses. Lv et al. 2024<sup>[S3]</sup>  
Wang et al. 2024<sup>[S5]</sup>  
Bouquet et al. 2019<sup>[S51]</sup>  
George et al. 2021<sup>[S52]</sup>  
Chowdary et al. 2022<sup>[S53]</sup>  
D'antiga et al. 2023<sup>[S54]</sup>
24. Antibiotics can be given during the perioperative period. Lv et al. 2024<sup>[S3]</sup>  
Wang et al. 2024<sup>[S5]</sup>
25. General preparations for surgery and anesthesia are the same as for other inner ear surgeries. NIH guidelines 2024<sup>[S55]</sup>  
IBC 2019<sup>[S56]</sup>  
Committee TMIB 2024<sup>[S57]</sup>
26. The transmastoid facial recess approach or the external auditory canal approach is recommended for exposing the round window membrane for injection of the gene therapy drug. Lv et al. 2024<sup>[S3]</sup>  
Qi et al. 2024<sup>[S4]</sup>  
Wang et al. 2024<sup>[S5]</sup>  
Chen et al. 2025<sup>[S58]</sup>
27. As a minimum safety evaluation, the following tests are recommended: (1) Immunology (for AAV-mediated gene therapy), including anti-AAV NABs (e.g., enzyme-linked immunosorbent assays, ELISA), viral vector shedding (e.g., qPCR), and cell-mediated immunity (e.g., enzyme-linked immunosorbent spot, ELISpot); (2) Hematology, including routine blood analysis, blood biochemistry, and coagulation function, etc.; (3) Other: urinalysis. National Cancer Institute 2017<sup>[S59]</sup>  
Lv et al. 2024<sup>[S3]</sup>  
Qi et al. 2024<sup>[S4]</sup>  
Wang et al. 2024<sup>[S5]</sup>
28. Physical and ancillary examinations are necessary to evaluate surgical risks, including: (1) A thorough examination of the external auditory canal and tympanic membrane to observe surgical recovery; (2) Utilizing ear endoscopy, microscopy, or acoustic impedance to check fluid accumulation or abnormal pathology in the middle ear; (3) Evaluating facial movements and bilateral symmetry to identify potential facial paralysis; (4) Vestibular function assessment. Moore et al. 1984<sup>[S60]</sup>  
Wormald et al. 1997<sup>[S61]</sup>  
Qiu et al. 2011<sup>[S62]</sup>  
Terry et al. 2015<sup>[S63]</sup>  
Hu et al. 2020<sup>[S64]</sup>  
FDA 2020<sup>[S65]</sup>  
EMA 2024<sup>[S66]</sup>
29. Efficacy evaluation is recommended to begin from the fourth week post-operation. The commonly used audiological examinations include PTA (or pediatric behavioral audiometry), auditory evoked potentials (ABR, ASSR), acoustic impedance, OAEs, speech recognition, and assessment of vocal speech. Lv et al. 2024<sup>[S3]</sup>  
Qi et al. 2024<sup>[S4]</sup>  
Wang et al. 2024<sup>[S5]</sup>  
Lilly 2024<sup>[S7]</sup>
30. Those patients who benefit from gene therapy are recommended to undergo auditory and speech rehabilitation. Holt et al. 2020<sup>[S67]</sup>  
Holt et al. 2022<sup>[S68]</sup>  
Townsend et al. 2023<sup>[S69]</sup>

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Abbreviations: HL, hearing loss; AAV, adeno-associated virus; CI, cochlear implant; NABs, neutralizing antibodies; qPCR, quantitative polymerase chain reaction; OAEs, otoacoustic emissions.

**Table S2. The Results of Merged and Deleted Consensus Statements in Voting Round 1**

Statements	n (%) <sup>a</sup>
<b>3.3 Audiology and vestibular function examination</b>	
Statement 17: To allow for accurate perioperative and postoperative monitoring, the following tests are recommended, including:	
17.1: Pure tone audiometry (PTA)	44 (100)
17.2: Acoustic impedance and stapedial reflexes	42 (95) <sup>b</sup>
17.3: Auditory evoked potentials	44 (100)
17.4: Otoacoustic emissions	43 (98)
17.5: Vestibular function assessment	40 (91)
<b>Topic 4. Gene therapy drug delivery</b>	
<b>4.1 Preoperative preparation</b>	
Statement: Patients and/or guardians need to fully understand the benefits and risks of gene therapy and sign an informed consent form for surgery.	44 (100) <sup>c</sup>
<b>Topic 5. Follow-up</b>	
<b>5.1 Potential risks of gene therapy drugs:</b>	
Statement 27: As a minimum safety evaluation, the following tests are recommended:	
27.1: Routine testing ① Immunology: anti-AAV neutralizing antibodies, enzyme-linked immune-spot assay (ELISApot) and blood qPCR could be selected to detect AAV shedding.	44 (100) <sup>b</sup>
27.2: Routine testing ② Hematology: blood routine, blood biochemistry, coagulation function, etc.	44 (100)
27.3: Routine testing ③ Other: urine routine, etc.	38 (86) <sup>b</sup>
<b>5.2 Potential risks related to surgery:</b>	
Statement 28: Physical and ancillary examinations are necessary to evaluate surgical risks, including:	
28.1: A thorough examination of the external auditory canal and tympanic membrane to observe surgical recovery.	41 (93) <sup>b</sup>
28.2: Utilizing ear endoscopy, microscopy, or acoustic impedance to check fluid accumulation or abnormal pathology in the middle ear.	38 (86) <sup>b</sup>
28.3: Evaluating facial movements and bilateral symmetry to identify potential facial paralysis.	40 (91) <sup>b</sup>
28.4: Vestibular function assessment.	39 (89)
28.5: Taste function test.	30 (68) <sup>d</sup>

<sup>a</sup>In voting round 1, Statements 17, 27, and 28 were subdivided. After voting, the subdivided items were merged, and the agreement rates were calculated as the average of the included items.

<sup>b</sup>This item received feedback for rewording.

<sup>c</sup>This item received feedback for deletion as it overlaps with Statement 5.

<sup>d</sup>This item received feedback for deletion as the lack of reliable evaluation methods and its limited significance. Abbreviations: AAV, adeno-associated virus; qPCR, quantitative polymerase chain reaction. n, count of agreement votes.

**Table S3. Searches carried out in: PubMed (n=1770), Medline (n=1345), Embase OVID (n=3408), and Cochrane Library (n=2474) and manually retrieved papers (n=96) from Jan 1, 1966 to Mar 1, 2025**

Search Categories	#	Key words
Hearing loss-related terms	1	(hearing loss OR hereditary hearing loss OR HL OR auditory defect OR deaf OR deafness OR hard of hearing OR hearing damage OR hearing defect). ti, ab.
	2	(Hearing screening). ti, ab.
	3	OR/1-2
Gene therapy-related terms	4	(gene therapies OR gene treatment OR genetic therapy). ti, ab.
	5	(adeno-associated virus OR AAV). ti, ab.
	6	(clinical trial). ti, ab.
	7	OR/4-6
Patient selection criteria	8	3 AND 7
	9	(pathogenic OR likely pathogenic variants). ti, ab.
	10	3 AND 9
	11	(cochlear implant* OR cochlear surgery OR CI). ti, ab.
	12	age*. ti, ab.
	13	11 AND 12
	14	(severe HL OR profound HL OR complete HL). ti, ab.
	15	(moderate HL OR moderately severe HL). ti, ab.
	16	speech perception. ti, ab.
	17	language outcome*. ti, ab.
	18	risk*. ti, ab.
	19	OR/16-18
	20	14 AND 19
	21	15 AND 19
	22	acute inflammation*. ti, ab.
23	8 AND 22	
Special circumstances	24	anti-AAV neutralizing antibodies. ti, ab.
	25	binaural. ti, ab.
	26	OR/24-25
	27	3 AND 7 AND 26
Preoperative evaluation	28	audiology examination*. ti, ab.
	29	vestibular function test*. ti, ab.
	30	28 AND 29
	31	ACMG/AMP. ti, ab.
	32	speech-language. ti, ab.
	33	sound localization. ti, ab.
	34	31 AND 32 AND 33
	35	Intelligence. ti, ab.
	36	development. ti, ab.
	37	child OR children. ti, ab.

	38	(35 AND 37) OR (36 AND 37)
Preoperative preparation	39	Glucocorticoids
	40	Antibiotics
	41	(3 AND 39) OR (3 AND 40) OR 7
	42	surgery. ti, ab.
Factors that affect gene therapy	43	(Otologic surgical procedure OR Otologic surgical). ti, ab.
	44	endoscopic ear surgery
	45	mastoid surgery
	46	(relative risk* OR risk* OR risk assessment* OR health risk assessment* OR risk analysis). ti, ab.
	47	adverse event*. ti, ab.
	48	complication*. ti, ab.
	49	OR/43-48
Evaluation	50	audiological examination*. ti, ab.
Rehabilitation	51	(rehabilitation OR rehabilitation care OR recovery). ti, ab.
	52	34 AND 51

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Abbreviations: HL: Hearing loss; CI: Cochlear implant; AAV: adeno-associated virus; ACMG/AMP: the American College of Medical Genetics and Genomics / the Association for Molecular Pathology; MUSS: Meaningful Use of Speech Scale; ti: title; ab: abstract.

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