ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Auditory Brainstem Implantation for Adults With Neurofibromatosis 2 or Severe Inner Ear Abnormalities: A Health Technology Assessment

KEY MESSAGES

What Is This Health Technology Assessment About?

Neurofibromatosis 2 (NF2) is a rare genetic disease that causes tumours to develop in both hearing nerves and sometimes in other nerves as well. People with this condition slowly lose their hearing and become completely deaf. Other rare abnormal conditions in the inner ears can also cause deafness that, like NF2, cannot be treated with a cochlear implant.

An auditory brainstem implant is the only treatment to help these deaf people hear. The treatment includes surgery to implant a set of electrodes into the base of the brain. The person then wears an ear-piece that picks up sounds and sends them wirelessly to the implant. The device does not restore normal hearing, but it can help people hear sounds such as car horns and telephone rings and sometimes recognize speech when they use lip-reading at the same time.

This health technology assessment looked at how safe and effective auditory brainstem implants are for adults with NF2 or severe inner ear abnormalities who cannot use a cochlear implant. We also looked at what would be the budget impact of publicly funding these devices in Ontario and at the experiences, preferences, and values of adults with these two conditions.

What Did This Health Technology Assessment Find?

The best available evidence shows auditory brainstem implants helped adults with NF2 or severe inner ear abnormalities to recognize sounds and understand speech, especially when they also used lip-reading. These improvements allowed them to be aware of their environments, helped them communicate, and improved their hearing-specific quality of life.

Publicly funding auditory brainstem implants for adults with NF2 or severe inner ear abnormalities would lead to a small budget increase in Ontario, about $130,000 to $260,000 per year, because only a few people each year would be candidates for this surgery.

Hearing loss from NF2 and inner ear abnormalities can have a large negative impact on the people affected, causing emotional distress and challenges in activities of daily living. We spoke with six people, including two who had received an auditory brainstem implant. They said it restored some hearing ability and improved their quality of life, though they also reported ongoing challenges in using the device and side effects from the procedure.

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ABSTRACT

Background

Neurofibromatosis 2 (NF2) is a rare genetic disorder that causes vestibular schwannomas to develop in both eighth cranial nerves. Almost all people with NF2 eventually become completely deaf as a result of progressive tumour enlargement or following surgical or radiotherapy treatment. Other rare abnormal conditions in the inner ears can also cause complete deafness. For people with either indication who are not candidates for cochlear implantation, auditory brainstem implantation is the only treatment option to restore some functional hearing. We conducted a health technology assessment of auditory brainstem implantation for adults with NF2 and severe inner ear abnormalities, which included an evaluation of effectiveness, safety, cost-effectiveness, the budget impact of publicly funding auditory brainstem implantation, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using the Risk of Bias in Non-randomized Studies—of Interventions (ROBINS—I) tool and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search. We did not conduct a primary economic evaluation because the outcomes identified in our clinical evidence review were difficult to translate into measures appropriate for health economic modelling. We also analyzed the net budget impact of publicly funding auditory brainstem implantation over the next 5 years in Ontario, including the device, presurgical assessment, surgical procedure, and postsurgical rehabilitation. To contextualize the potential value of auditory brainstem implants, we spoke with six people with lived experience of NF2 and severe inner ear abnormalities.

Results

We included 22 publications (16 in NF2, five in severe inner ear abnormalities, and one in complications of auditory brainstem implantation) in the clinical evidence review. In adults with NF2, auditory brainstem implantation when compared with no intervention allows any degree of improvement in sound recognition (GRADE: High), allows any degree of improvement in speech perception when used in conjunction with lip-reading (GRADE: High), and provides subjective benefits of hearing (GRADE: High). It likely allows any degree of improvement in speech perception when using the implant alone (GRADE: Moderate) and may improve quality of life (GRADE: Low). In adults with severe inner ear abnormalities, auditory brainstem implantation when compared with no intervention likely allows any degree of improvement in sound recognition (GRADE: Moderate) and in any speech perception when using the implant alone (GRADE: Moderate). It may allow any degree of improvement in speech perception when used in conjunction with lip-reading (GRADE: Low), provide subjective benefits of hearing (GRADE: Low), and improve quality of life (GRADE: Low).

We did not identify any economic studies on auditory brainstem implantation for adults with NF2 or adults with deafness due to severe inner ear abnormalities. We estimated that the annual net budget impact of publicly funding auditory brainstem implantation in Ontario over the next 5 years would range from about $130,000 in year 1 for two procedures to about $260,000 in year 5 for four procedures.

People with whom we spoke who had received an auditory brainstem implant reported that it restored some hearing ability and improved their quality of life, though they also reported ongoing challenges in using the device or side effects from the procedure.

Conclusions

When compared with no intervention, auditory brainstem implantation provides some benefit for completely deaf adults with NF2 or severe inner ear abnormalities who are not candidates for cochlear implantation. Based on evidence of moderate to high quality, auditory brainstem implants allow any degree of improvement in sound recognition and in speech perception when used in conjunction with lip-reading for people with NF2. The quality of evidence on these outcomes was low to moderate for people with severe inner ear abnormalities. These functional outcomes lead to subjective benefits of hearing which are consistently reported in the literature and in interviews with patients. We were unable to determine the cost-effectiveness of this treatment. We estimate that publicly funding auditory brainstem implantation in Ontario would result in additional costs of about $130,000 to $260,000 annually over the next 5 years.

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OBJECTIVE

This health technology assessment looked at the effectiveness and safety of auditory brainstem implantation in adults with neurofibromatosis 2 or severe inner ear abnormalities (i.e., nontumour indications) who are not candidates for cochlear implantation. It also evaluated the budget impact of publicly funding auditory brainstem implantation and the experiences, preferences, and values of adults with neurofibromatosis 2 or severe inner ear abnormalities.

BACKGROUND

Health Condition, Clinical Need, and Target Population

Neurofibromatosis 2

Neurofibromatosis 2 (NF2) is a genetic disorder that affects chromosome 22, which encodes the gene responsible for the production of a tumour suppressor protein that is integral to the normal structural function of nerves.[1]

People with NF2 develop tumours, known as vestibular schwannomas or acoustic neuromas, on both of their eighth cranial nerves (the auditory-vestibular nerves). These nerves, one on each side of the head, are essential to a person's sense of hearing and balance. As the tumours grow, people commonly experience progressive hearing loss and imbalance, the defining features of NF2. The genetic mutation can also cause tumours that affect the nerve roots of the spinal cord, the head and neck regions, and other anatomical sites.

People with NF2 can present a wide spectrum of symptoms. The condition is progressive in nature leading to multiple disabilities. In particular, it results in hearing loss and subsequent communication difficulties.[2] Almost everyone with NF2 will eventually become completely deaf as the tumours grow or following surgery or radiotherapy used to treat the tumours. These people have decreased health-related quality of life in physical, social and mental domains.[3] In addition, those who have more hearing loss and imbalance report significantly lower quality of life.[4] Difficulties with communication from profound hearing loss often lead to social isolation resulting from avoiding social situations, which further compromises quality of life.[5]

Historically, the prevalence of NF2 was estimated to be approximately 1 in 200,000 people; however, the prevalence has increased to approximately 1 in 60,000 due to earlier diagnosis and better survival with improved treatment.[6] Based on this prevalence and the Ontario population, it is estimated that about 250 people are living with NF2 in the province.

Nontumour Indications

Several types of rare congenital or acquired condition in the inner ears can cause bilateral (two-sided) deafness. These conditions may be caused by structural or neural defects, such as cochlear or cochleovestibular nerve aplasia or hypoplasia (lack of or underdevelopment of the cochlea, a part of the hearing organ in the inner ear), traumatic damage to the cochlear nerves, or an ossified cochlea (a complication in which the normal fluid in the cochlea is replaced by bone) due to meningitis, trauma, or advanced otosclerosis. It is difficult to estimate the prevalence of these conditions because of their different etiology (underlying causes).

Current Treatment Options

Hearing aids are the most common treatment for people with moderate to severe hearing loss associated with NF2 or with an inner ear condition that affects the cochlear nerve. But hearing aids become less effective when a person's ability to understand speech falls below 50% and their threshold for detecting sound rises above 70 decibels (dB). When hearing loss reaches the severe to profound stage (> 70 decibels in hearing level [dB HL]), hearing aids are generally considered of little benefit. Lip-reading, texting, written communication, and manual communication or sign language are communication strategies to supplement hearing aids.

For a small number of people with less aggressive forms of NF2, whose tumours are stable in size and who get little benefit from hearing aids, cochlear implantation (a surgical procedure to implant a device that sends sound signals to the brain) may be an option. Candidates must have the appropriate clinical presentation and treatment profile, and they must have at least one intact cochlear nerve that could potentially be stimulated.

An auditory brainstem implant (ABI) (described below, Health Technology Under Review) is the only treatment option to provide partial hearing recovery in people with NF2 who are completely deaf and are precluded from cochlear implantation due to nonfunctional cochlear nerves. The ABI procedure is often performed simultaneously with tumour resection (surgery to remove the tumours), but it can also be done as a stand-alone procedure. An ABI is also the only treatment option for people with severe inner ear abnormalities who are not candidates for cochlear implantation.

Health Technology Under Review

An auditory brainstem implant is a bio-electric device that is implanted under the skin at the base of the brain. Similar in construction and stimulation strategy to a cochlear implant, it is designed to directly stimulate the hearing pathways in the brainstem and allow the person to detect sounds, bypassing the inner ear. The brainstem is the stalk-like part of the brain that connects the two hemispheres to the spinal cord.

An ABI is designed with a flat electrode paddle connected to a receiver-stimulator that is surgically placed within the lateral recess between the brainstem and the cerebellum. During surgery, electrical impulses are used to stimulate the auditory pathway, while the brain's responses are recorded to verify the correct placement over the cochlear nucleus, where the processing of acoustic information begins.

The three-dimensional tonotopicity (the spatial arrangement that allows different tone frequencies to be transmitted) of the cochlear nucleus is less well defined than in the inner ear. Furthermore, the cochlear nucleus lies deep under the surface of the brainstem, making accurate electrical stimulation more challenging, especially when the brainstem is compressed by a tumour and during tumour surgery. This could explain why auditory performance with an ABI is inferior to a cochlear implant.

Most people with NF2 who are referred for consideration for an ABI are already deaf in one ear as a result of the tumour on that side or treatment for the tumour (surgery or radiation), and they are experiencing tumour enlargement and progressive hearing loss on the second side. If the person is being considered for a second surgery to remove a tumour, an ABI could be performed simultaneously. If the tumour is very large and compressing the brainstem, the ABI and tumour removal surgeries would have to be two separate operations. In nontumour

indications, the ABI procedure is generally shorter and less complicated because the person has minimal to no brainstem compression.

The implanted device communicates with an externally worn ear-piece that contains a microphone, a sound processor, and a power source. The ear-piece and the sound processor are the same as those used for a cochlear implant. The ear-piece converts sounds into digital signals, which are then transmitted wirelessly to the internal implant. The resulting electrical stimulation of the cochlear nucleus provides auditory sensation but does not restore normal hearing. Depending on the etiology of the person's deafness and their clinical condition, the primary therapeutic goal of ABI is to help them detect environmental sounds such as a car horn or telephone ring and, when the device is used in conjunction with lip-reading, comprehend speech.[7]

The implant is typically activated 4 to 6 weeks after surgery to assess the person's subjective behavioural responses and to determine if the electrical impulses result in any nonauditory side effects such as a physical sensation or feeling. Testing, programming, and adjustment of the device require a team that comprises an electrophysiologist, a cochlear implant audiologist, and auditory rehabilitation personnel. Extensive auditory rehabilitation—training the brain to learn to hear through the implant—is required for optimal outcomes and to meet the expectations of the person and the implant team. Identifying candidates with strong motivation to follow through with long-term rehabilitation is crucial. (Joseph Chen, MD, email communication, May 2018).

After the initial activation, people typically see their audiologist at 1 month, 2 months, 3 months, 6 months, and 1 year, and then annually thereafter. At each follow-up visit, the implant settings are adjusted to improve the sound quality and patients have speech perception tests to determine the benefit of the ABI. Patients receive rehabilitative materials to work with at home to try to improve their hearing perception; this may involve online listening games or programs, listening activities with friends and family, or listening to audiobooks while following the text (Kari Smilsky, MClSc, email communication, May 2018).

Regulatory Information

Two auditory brainstem implant systems are currently available and used in clinical practice in Canada:

- Nucleus ABI541 Auditory Brainstem Implant by Cochlear Limited (Sydney, Australia) is indicated for use as a prescription-only, single-use (nonsterilizable) device intended for chronic implantation under the skin in the mastoid region on either side of the head (Health Canada license number 97717, Class III device). The brainstem implant is intended to restore a level of auditory sensation via electrical stimulation of the cochlea for individuals 12 years of age or older who have been diagnosed with NF2. Implantation may occur during tumour removal on the first or second side or in people with previously removed bilateral acoustic tumours. Because the surgical procedure for tumour excision and electrode placement eliminates residual hearing, preoperative audiological criteria are not relevant. Prospective implant recipients and their families should have appropriate expectations regarding the potential benefits of an auditory postoperative rehabilitation process.
- Synchrony Auditory Brainstem Implant by MED-EL AG (Innsbruck, Austria) is indicated for electrical stimulation of the cochlear nucleus via an implanted stimulator and a specially designed electrode array to evoke auditory sensations in patients with nonfunctional cochlear nerves (Health Canada license number 104052, Class IV

device). This ABI system has an MR-conditional magnet that will self-align with the magnetic field of a magnetic resonance imaging (MRI) machine; patients do not have to remove the magnet to have MRI scans, an important feature as people with NF2 require frequent follow-up MRI studies. In addition, it has a probe electrode which is placed before the full electrode array and used in conjunction with electrical auditory brainstem response to help locate the best position for the full electrode array. The MED-EL ABI system was CE marked (i.e., licensed in Europe) in 2014 for use in people 15 years or older with two nonfunctional auditory nerves due to NF2. Expanded indications were CE marked in 2017 for people 12 months or older who cannot benefit from a cochlear implant and have a nonfunctional auditory nerve due to auditory nerve aplasia or hypoplasia, head trauma, a non-NF2 tumour or severe cochlear ossification.

These devices have a number of differences in design and signal processing strategy[7] (Table 1).

Table 1: Characteristics of Auditory Brainstem Implant Systems Used in Canada

	Cochlear ABI	MED-EL ABI
Electrode number	21	12
Electrode array size	8.5 mm × 3 mm	5.5 mm × 3 mm
Stimulation strategy	SPEAK	High-rate CIS

Abbreviations: ABI, auditory brainstem implant; CIS, continuous interleaved sampling; SPEAK, spectral peak coding strategy.

We reviewed ABI as an overall class of technology instead of reviewing individual models of manufacturers.

Ontario, Canadian, and International Context

Auditory brainstem implants have been approved by Health Canada for treatment of NF2 for over two decades. However, the procedure is not publicly funded in Ontario or in any other Canadian province. Ontario and Quebec are the only two provinces that have the surgical experience to perform ABI.

Historically, Canadians seeking an ABI have gone to the United States, Germany, and Italy as ABI was unavailable or not publicly funded. Several children and adults in Ontario have gone abroad for this treatment (Joseph Chen, MD, email communication, May 2018).

In 2010, the Ontario Cochlear Implant Program identified Sunnybrook Health Sciences Centre as the lead in an initiative to provide auditory brainstem implantation in Ontario because the expertise and infrastructure were already in place, with a large cochlear implantation program supported by otolaryngology and neurosurgery specialized in skull-base surgical procedures. As of March 2020, four adults have received an ABI at Sunnybrook Health Sciences Centre. Among these four people, two (both with NF2) were implanted with Cochlear Nucleus 24 ABI. The other two (one with NF2 and one with a nontumour indication) were implanted with a MED-EL ABI through Health Canada's Special Access Program. The four cases were funded through clinical savings of the cochlear implantation program at Sunnybrook Health Sciences Centre and through the hospital's budget.

Based on historical caseloads, the Ontario Cochlear Implant Program estimates the clinical need for ABI for adults with NF2 or severe inner ear abnormalities to be fewer than 5 procedures per year.

Careful clinical selection of candidates based on age, expectations, comorbidities, family support, and motivation to undertake auditory rehabilitation are critical in optimizing hearing outcomes for people receiving an ABI. The Ontario Cochlear Implant Program has specified the following criteria for ABI:

- NF2 population (bilateral acoustic neuromas)
    - Adults aged less than 50 years
    - Committed to 2 or more years of auditory rehabilitation
    - Bilateral profound deafness (for less than 1 year) with no perceived benefits from hearing aids
    - Generally healthy with a favourable life-expectancy
    - Favourable anatomy: no significant brainstem or cerebellar compression (small to medium size tumour)
    - No prior radiation exposure on the implant side
    - Not a candidate for cochlear implantation due to nonfunctional cochlear nerves

- Nontumour (severe inner ear abnormalities) population
    - Adults aged less than 50 years
    - Committed to 2 or more years of auditory rehabilitation
    - Bilateral profound deafness with no perceived benefits from hearing aids
    - Generally healthy
    - Not a candidate for cochlear implantation due to severe inner ear deformity or absent cochlear nerves

In the United Kingdom, ABI has been publicly funded for people with NF2 and those with congenital abnormalities of the auditory nerves of cochleae.[8,9] Public funding for ABI is also available across Europe, the United States, Australia, and a number of Asian countries.

Expert Consultation

We engaged with experts in the specialty areas of audiology, otology, and neurosurgery to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROPSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD # 42018103498), available at https://www.crd.york.ac.uk/PROSPERO.

CLINICAL EVIDENCE

Research Questions

- What are the clinical effectiveness and safety of auditory brainstem implantation for adults with neurofibromatosis 2 (NF2) who are not candidates for cochlear implantation?
- What are the clinical effectiveness and safety of auditory brainstem implantation for adults with severe inner ear abnormalities who are not candidates for cochlear implantation?

Methods

We developed the research questions in consultation with patients, health care providers, clinical experts, and other health system stakeholders.

Clinical Literature Search

We performed a clinical literature search on June 21, 2018, to retrieve studies published from database inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the CRD Health Technology Assessment Database, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer reviewed using the PRESS Checklist.[10]

We created database auto-alerts in MEDLINE and Embase, and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites as well as clinical trial and systematic review registries. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception to June 21, 2018
- Health technology assessments, systematic reviews, meta-analyses
- Randomized controlled trials
- Prospective or retrospective observational studies
- Case series with 5 or more patients

Exclusion Criteria

- Animal and in vitro studies
- Case reports, editorials, letters, commentaries, abstracts, conference papers, narrative reviews
- Case series with less than 5 patients
- Studies that reported combined data for adults and children where data for the specific population cannot be abstracted
- Studies that reported combined data for NF2 and nontumour cases where data for the specific population cannot be abstracted

Participants

- Adults with NF2 who are not candidates for cochlear implantation
- Adults with severe inner ear abnormalities who are not candidates for cochlear implantation

Interventions

- Auditory brainstem implantation

Outcome Measures

- Sound recognition
- Speech perception
- Subjective benefits of hearing
- Quality of life
- Adverse events

Literature Screening

A single reviewer reviewed the abstracts and, for those studies meeting the eligibility criteria, we obtained full-text articles. We also examined reference lists for any additional relevant studies not identified through the literature search.

Data Extraction

We extracted relevant data on the included studies—including study design, populations, interventions, comparators, outcomes—and summarized them in tables. We extracted only data relevant to the research questions and data on devices currently available in Canada. To minimize data from overlapping study populations, we included only studies with the largest sample size and the latest publication date that reported the same outcomes from the same research group. We contacted study authors to provide clarification as needed.

Statistical Analysis

We did not pool the results of the included studies because of differences in testing conditions and outcomes measurements. We summarized the results in tables and described them in the text.

Critical Appraisal of Evidence

We assessed the risk of bias using the Risk of Bias in Non-randomized Studies—of Interventions tool (ROBINS-I).[11] We evaluated the level of quality of the body of evidence for each outcome according to the *Grading of Recommendation, Assessment, Development and Evaluation* (GRADE) *Handbook*.[12] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Results

Clinical Literature Search

The clinical literature search yielded 311 citations published from inception to June 21, 2018, after removing duplicates. We reviewed 61 articles for further assessment and 22 studies met the inclusion criteria. We reviewed the reference lists of the included studies, but we did not identify any additional relevant studies. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

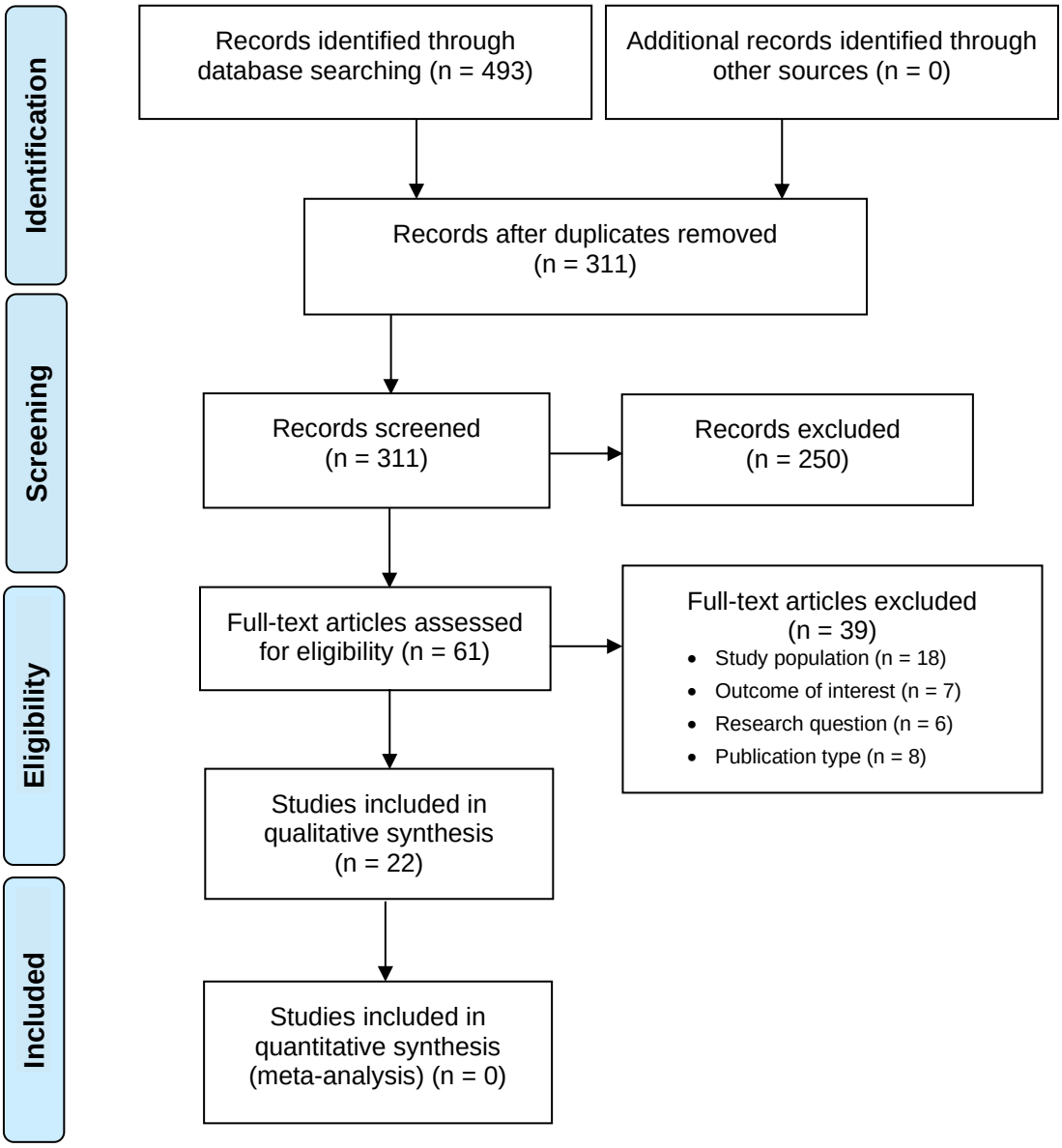

Figure 1: PRISMA Flow Diagram—Clinical Search Strategy

Source: Adapted from Moher et al.[13]

Characteristics of Included Studies

The literature search identified 22 primary studies for inclusion in this clinical evidence review.[14-35] Among these 22 primary studies, one described complications of auditory brainstem implants in patients with NF2 or nontumour indications,[32] two reported clinical benefits in patients with NF2 or nontumour indications,[15,16] three reported clinical benefits in patients with nontumour indication only,[33-35] and 16 reported clinical benefits in patients with NF2 only.[14,17-31]

The literature search also identified two systematic reviews.[36,37] The systematic review by Lloyd et al[36] reviewed the hearing outcomes of all treatments for vestibular schwannomas in NF2. Fifteen studies included in the systematic review reported hearing outcomes of ABI in patients with NF2, combining data for adults and children. The mean word scores (% correct) with ABI and lip-reading and with ABI only were 73% and 35%, respectively. The mean sentence scores (% correct) with ABI and lip-reading and with ABI only were 58% and 12%, respectively. The authors noted that the auditory benefits continued to improve over several years.

The systematic review by Lovell and Refair[37] included six studies that reported speech perception outcomes in adults and children with tumour or nontumour indications. The authors concluded that speech perception improved after ABI for at least one year.

Because these two published reviews[36,37] did not fit our inclusion criteria (they presented combined data for tumour and nontumour cases and/or combined data for adults and children), or they did not include more recent studies beyond 2016, we undertook an evaluation of the 22 primary studies.

Risk of Bias in the Included Studies

Appendix 2, Table A1, presents results of the risk of bias assessment for the included studies. We rated 5 studies as having moderate risk of bias due to missing data.[14,18,20,23,24] Thirteen studies were rated as having moderate risk of bias due to outcome measurement.[15,16,19-25,27,30,31,34] Four studies were rated as having moderate risk of bias due to selection of reported results.[14,18,21,31]

Auditory Brainstem Implantation: Neurofibromatosis 2

Table 2 summarizes the characteristics of the 19 included studies for NF2.

Six of the included studies were prospective observational studies.[14,18,19,22,25,26] Of these six studies,[14,18,19,22,25,26] two were multicentre cohorts.[22,25] Another 11 included studies were in retrospective design, either as a cohort or a chart review.[15-17,21,24,27-32] The remaining two included studies were cross-sectional surveys conducted within existing patient cohorts.[20,23]

Four studies reported patients' usage patterns for their ABI.[17,19,23,25] The average duration of use ranged from 8.5 hours to 13 hours per day.[17,19,23,25] All patients stated that they used ABI in quiet environments, but approximately 20% of patients switched off the ABI in noisy environments,[19,23,25] and approximately 50% switched it off when they were tired.[19,23]

Table 2: Observational Studies on Auditory Brainstem Implantation for Neurofibromatosis 2

Author, Year	Sample Size,[a] N	ABI Users,[b] n	Study Period	Age at Implantation, Years	Duration of Deafness	ABI Type	Outcomes	Follow-Up	Study Design
Behr et al, 2007[14]	20	14	1997–2004	18–56	0.5–24 years	MED-EL Combi 40+ ABI	Speech perception Nonauditory side effects Surgical complications	6, 12, 24 months	Prospective
Colletti et al, 2009[15]	32	32	1997–2007	NR	3.2–8.5 years	Cochlear Nucleus ABI22 Cochlear Nucleus ABI24	Speech perception	1–10 years[c]	Retrospective
Colletti et al, 2010[32]	34	34	1997–2008	21–70	NR	Cochlear Nucleus ABI22 Cochlear Nucleus ABI24	Surgical complications	1–10 years[c]	Retrospective
Grayeli et al, 2008[16]	23	16	1996–2006	17–59	NR	Cochlear Nucleus ABI22 Cochlear Nucleus ABI24	Speech perception	12–120 months[c]	Retrospective
Kanowitz et al, 2004[17]	18	11	1994–2003	15–55	NR	Cochlear Nucleus ABI22 Cochlear Nucleus ABI24	Speech perception Nonauditory side effects Surgical complications	2–78 months[c]	Retrospective
Lenarz et al, 2001[18]	14	13	1996–2000	22–61	2–144 months	Cochlear Nucleus ABI22 Cochlear Nucleus ABI24 Advanced Bionics Clarion ABI	Speech perception Nonauditory side effects Surgical complications	1–41 months[c]	Prospective
Lenarz et al, 2002[19]	14	11	1996–2000	24–62	2–144 months	Cochlear Nucleus ABI22 Cochlear Nucleus ABI24 Advanced Bionics Clarion ABI	Subjective benefits of hearing	6–41 months[c]	Prospective
Lundin et al, 2016[20]	11	8	1993–2013	NR	NR	Cochlear Nucleus ABI22 Cochlear Nucleus ABI24	Subjective benefits of hearing	NA	Cross-sectional survey
Maini et al, 2009[21]	11	10	1995–2009	17–46	NR	Cochlear Nucleus ABI22 Cochlear Nucleus ABI24	Speech perception	1–12 years[c]	Retrospective
Matthies et al, 2013[22]	32	27	2001–2009	19–66	NR	MED-EL Combi 40+ ABI	Sound recognition Speech perception Subjective benefits of hearing Nonauditory side effects	1, 3, 6, 12 months	Prospective multicentre
McSorley et al, 2015[23]	57	31	1994–2009	13–73	0–50 years[d] (contralateral side) 0–10 years[d] (implanted side)	Cochlear Nucleus ABI22 Cochlear Nucleus ABI24	Subjective benefits of hearing Nonauditory side effects	NA	Cross-sectional survey

Author, Year	Sample Size,[a] N	ABI Users,[b] n	Study Period	Age at Implantation, Years	Duration of Deafness	ABI Type	Outcomes	Follow-Up	Study Design
Nakatomi et al, 2016[24]	10	9	1999–2011	25–64	0–16 years	Cochlear Nucleus ABI MED-EL ABI	Sound recognition Speech perception	NR	Retrospective
Nevison et al, 2002[25]	27	25	1992–1997	17–58	NR	Cochlear Nucleus ABI	Speech perception Subjective benefits of hearing Nonauditory side effects Surgical complications	3, 6, 9, 12 months, then annually	Prospective multicenter
Otto et al, 2002[26]	61	55	1992–2000	12–71	NR	Cochlear Nucleus ABI22 Cochlear Nucleus ABI24	Sound recognition Speech perception Nonauditory side effects Surgical complications	6 months –8 years[c]	Prospective
Ramsden et al, 2016[27]	49	29	1994–2009	12–71	< 12 months –20 years	Cochlear Nucleus ABI22 Cochlear Nucleus ABI24	Sound recognition Speech perception Surgical complications	3–18 years[e]	Retrospective
Sanna et al, 2012[28]	25	19	1986–2010	18–69	NR	Cochlear Nucleus ABI24	Sound recognition Speech perception Nonauditory side effects	2–53 months[c]	Retrospective
Shannon et al, 1993[29]	25	16	1979–1991	NR	NR	Cochlear Nucleus ABI	Sound recognition Speech perception Nonauditory side effects	NR	Retrospective
Siegbahn et al, 2014[30]	20	17	1993–2013	15–75	NR	Cochlear Nucleus ABI	Speech perception Nonauditory side effects Surgical complications	0–16 years[c,f]	Retrospective
Thong et al, 2016[31]	8	8	1997–2014	22–54	NR	Cochlear Nucleus ABI24	Sound recognition Speech perception Subjective benefits of hearing Nonauditory side effects Surgical complications	6 months, 1 year, 2 years	Retrospective

Abbreviations: ABI, auditory brainstem implantation; LR, lip-reading; NA, not applicable; NR, not reported.

[a]Sample size refers to the number of patients with ABI.

[b]ABI users refers to the number of patients with ABI, excluding those without auditory sensations, those with a sleeper device (implanted but not activated), and those who died during the study period.

[c]Data obtained from the last follow-up visit.

[d]0 years refers to deafness secondary to surgery.

[e]Best scores achieved were used for analyses regardless of time post-implantation.

[f]One patient had a sleeper ABI (implanted but not activated); therefore, this patient did not have any follow-up visit

Sound Recognition

Seven studies reported on sound recognition,[22,24,26-29,31] and Table 3 summarizes their results. Despite the use of different test materials (different types of sounds) across the studies, most patients could achieve approximately 50% or more sound recognition with their ABI.[22,24,26-29,31] In addition, Matthies et al[22] reported a steady increase in sound recognition from ABI activation to 1-year follow-up, and this improvement was statistically significant.

The quality of the evidence for any degree of improvement in sound recognition was high (Appendix 2, Table A2). We upgraded this evidence because of large magnitude of effects: the ABI allowed people who were completely deaf to perceive sounds, and—considering all outcomes we evaluated—the ability to hear led to improvement in both objective and subjective benefits of hearing.

Table 3: Sound Recognition—Neurofibromatosis 2

Author, Year	Test Measures	Sample Size, N	Results,%
Matthies et al, 2013[22]	Closed-set sound effects recognition test[a] (mean, % correct)	26	Initial: 44 1 month: 57 3 months: 62 6 months: 75 12 months: 70 *P* = .009 (12 months vs. initial)
Nakatomi et al, 2016[24]	Closed-set sound recognition test (range, % correct)	7 3	ABI only: 29–88 ABI + LR: 90–100
Otto et al, 2002[26]	Sound effects recognition test[b,c]	61	80% were able to recognize sound at or above 50% correct level
Ramsden et al, 2016[27]	Environmental sounds test[d] (mean [range], % correct)	29	46 (0–85)
Sanna et al, 2012[28]	Environmental sound detection test[e] (range, % correct)	19	40–100
Shannon et al, 1993[29]	Environmental sounds test[f] (range, % correct)	16	18–70
Thong et al, 2016[31]	Environmental sound discrimination (mean [range], % correct)	8	75% of patients were able to differentiate sounds 6 months: 46 (28–60) 12 months: 57 (36–76) 24 months: 48 (24–76)

Abbreviations: ABI, auditory brainstem implantation.
[a]A closed-set test used recorded test materials of environmental sounds which consisted of 3 different lists of 10 items each. Maximum score was 10. Data presented were converted to % for comparison purposes.
[b]Numeric data were estimated from figures.
[c]A four-alternative test of environmental sound discrimination with a chance performance level of 25%.
[d]An open-set test whereby patients tried to identify common sounds, such as a door bell, out of a possible 20 different sounds.
[e]Patients were asked to respond to the presence or absence of sounds of different frequencies delivered at an intensity of 70 dB HL (drum for low frequencies, bell for medium frequencies, and rattle for high frequencies).
[f]The environmental sounds test presented a single nonspeech sound and required the patient to choose from among 5 foils.

Speech Perception

Fifteen studies reported on speech perception,[14-18,21,22,24-31] and Table 4 summarizes their results. There was a lot of variability in speech perception results. The clinical benefits of ABI in closed-set speech perception (where the patient selects the correct response from a forced-choice or multiple-choice list) were more consistent when people used ABI in conjunction with lip-

reading.[14,16,21,22,27] In addition, patients showed substantial gains in open-set speech perception (correctly repeating words or sentences without being presented with a set to choose from) when ABI was added to lip-reading.[18,21,27] When using ABI only, most patients were able to understand some speech in closed-set word and sentence tests.[14,22,24-27]

Open-set speech perception better resembles communication in real life. While a number of studies reported that few patients were able to achieve open-set speech perception with ABI only,[21,24,25,27,31] there were also studies that showed excellent open-set performance in some patients.[16,22]

Grayeli et al[16] stratified the speech results by performance (i.e., excellent, good, and poor) and documented that some patients could achieve excellent or good open-set sentence perception using ABI with or without lip-reading. Furthermore, Sanna et al[28] and Siegbahn et al[30] reported that a small number of patients could even use the telephone with familiar speakers.

Auditory performance (hearing ability) improved over time in both closed-set and open-set speech perception.[14,15,17,18,21,22] Lenarz et al[18] showed that patients were able to develop better speech perception with the help of lip-reading as soon as 2 weeks after ABI activation, and that it took about 2 years for some patients to develop the open-set perception ability. In another study by Otto et al,[26] improvement in closed-set word test scores continued for as long as 8 years after patients received an auditory brainstem implant. Patients with more than 2 years of experience with an ABI performed better on all speech perception tests than those with less experience. These results highlighted the importance of long-term auditory rehabilitation on hearing outcomes.[18,26]

More recently published studies also showed overall improved speech perception outcomes,[22,27] which could be related to improved implant designs and refined surgical techniques.

The quality of the evidence for any degree of improvement in speech perception with an ABI used in conjunction with lip-reading was high (Appendix 2, Table A2). We upgraded this evidence because of large magnitude of effects: the ABI allowed completely deaf people to perceive speech.

The quality of the evidence for any degree of improvement in speech perception with ABI only was moderate (Appendix 2, Table A2). As with ABI plus lip-reading, we upgraded this evidence because of large magnitude of effects. However, we downgraded for inconsistency as speech perception with ABI only varied considerably between studies. Patient, surgical, and device-related factors could affect auditory performance (e.g., tumour size, local anatomical conditions, duration of auditory deprivation, number of activated electrodes), and it was difficult to distinguish whether the varied results were due to any of these factors or to differences in the ways studies were conducted.

Table 4: Speech Perception—Neurofibromatosis 2

Author, Year	Test Measures	Sample Size, n	Results
Behr et al, 2007[14]	Innsbruck sentence tests[a] (mean, % correct)		*ABI only*
		4	6 months: 46.0%
		8	24 months: 42.7%
			ABI + LR
		9	6 months: 59.6%
		9	24 months: 67.5%
	Numbers (mean, % correct)		*ABI only*
		8	6 months: 40.1%
		9	24 months: 51.7%
			ABI + LR
		9	6 months: 62.9%
		5	24 months: 81.3%
Colletti et al, 2009[15]	Open-set sentence recognition (range, % correct)	32	5%–31% over time
Grayeli et al, 2008[16]	Open-set word discrimination (range, % correct)[b]	8	Excellent performance group[c] *ABI only:* 30%–70%
			ABI + LR: 50%–100%
		5	Good performance group[c] *ABI only:* 0%–40%
			ABI + LR: 40%–90%
		2	Poor performance group[c] *ABI only:* 0%–10%
			ABI + LR: 10%–30%
	Open-set sentence discrimination (range, % correct)[b]	8	Excellent performance group *ABI only:* 10%–80%
			ABI + LR: 25%–100%
		5	Good performance group *ABI only:* 0%–15%
			ABI + LR: 10%–100%
		2	Poor performance group *ABI only:* 0%–10%
			ABI + LR: 30%–40%
Kanowitz et al, 2004[17]	MTS word test[d] (mean ± SD, % correct)	8	*Cochlear N22 ABI* Initial: 22.1 ± 9.0, *P* = .002[e]
			Follow-up: 30.8 ± 17.0, *P* = .003[e]
			Cochlear N24 ABI
		3	43.2 ± 18.8, *P* = 0.04[e]
	MTS stress test[d] (mean ± SD, % correct)	8	*Cochlear N22 ABI* Initial: 52.6 ± 17.0, *P* = .007[e]
			Follow-up: 62.5 ± 12.0, *P* < .001[e]
			Cochlear N24 ABI
		3	80.7 ± 14.6, *P* = .02[e]
	NU-CHIPS test[f] (mean ± SD, % correct)	8	*Cochlear N22 ABI* Initial: 33.5 ± 7.0, *P* = .005[e]
			Follow-up: 32.8 ± 7.6, *P* = .01[e]
		3	*Cochlear N24 ABI* 45.3 ± 11.0, *P* = .04[e]
Lenarz et al, 2001[18]	Closed-set vowel test[g] (mean ± SD, % correct)	13	*LR only:* 78% ± 14%
			ABI + LR
		13	2 weeks: 84% ± 12%
		11	6 months: 92% ± 7%

Author, Year	Test Measures	Sample Size, n	Results
	Closed-set consonant test[h] (mean ± SD, % correct)	13	*LR only:* 57% ± 10%
			ABI + LR
		13	2 weeks: 68% ± 13%
		11	6 months: 75% ± 14%
	Open-set speech tracking test[i] (mean ± SD, words/min)	13	*LR only:* 15.3 ± 7.3 words/min
			ABI + LR
		13	2 weeks: 19.6 ± 9.7 words/min
		11	6 months: 25.8 ± 14.8 words/min
	Open-set Freiburger numbers test[j]	10	6 months: 50% of patients scored above 0
Maini et al, 2009[21]	Open-set sentence test[b,k] (mean, % correct)	3	Cochlear Nucleus ABI22
			LR only
			1 year: 23%
			Later follow-up[l]: 26%
			ABI only
			1 year: 2%
			Later follow-up[l]: 2%
			ABI + LR
			1 year: 54%
			Later follow-up[l]: 62%
		7	Cochlear Nucleus ABI24
			LR only
			1 year: 18%
			Later follow-up[l]: 19%
			ABI only
			1 year: 2%
			Later follow-up[l]: 8%
			ABI + LR
			1 year: 40%
			Later follow-up[l]: 60%
Matthies et al, 2013[22]	Closed-set MTP test[m] (mean ± SD, words repeated correctly)		*ABI only*
		21	Initial activation: 11.7 ± 6.4
		24	1 month: 15.4 ± 5.3
		24	3 months: 16.1 ± 6.2
		23	6 months: 17.9 ± 4.8
		24	12 months: 19.6 ± 4.2
			$P < .001$ (12 months vs. first fitting)
			ABI + LR
		21	Initial activation: 23.2 ± 1.0
		24	1 month: 23.2 ± 2.1
		24	3 months: 23.2 ± 2.1
		23	6 months: 23.8 ± 0.6
		24	12 months: 23.6 ± 1.0
			$P = .1$ (12 months vs. first fitting)
	Open-set sentence test[n] (mean ± SD, % correct)		*ABI only*
		12	Initial activation: 5.2% ± 8.3%
		17	1 month: 19.9% ± 30.2%
		18	3 months: 13.3% ± 17.1%
		19	6 months: 27.6% ± 30.8%
		20	12 months: 36.9% ± 32.8%
			$P < .001$ (12 months vs. first fitting)

Author, Year	Test Measures	Sample Size, n	Results
			ABI + LR
		17	Initial activation: 47.7 ± 31.3
		21	1 month: 66.2 ± 23.6
		19	3 months: 68.8 ± 26.2
		22	6 months: 66.6 ± 30.1
		21	12 months: 76.8 ± 25.3
			P = .001 (12 months vs. first fitting)
Nakatomi et al, 2016[24]	Closed-set word recognition (range, % correct)	6	*ABI only* (60% of patients): 4%–77% *ABI + LR* (60% of patients): 14%–100%
	Open-set sentence recognition (range, % correct)	6 8	*ABI only* (60% of patients): 0%–31% *ABI + LR* (80% of patients): 0%–98%
Nevison et al, 2002[25]	Closed-set MTS word test	16	*ABI + LR* 94% of patients scored 90%–100% correct in identifying stress-pattern
	Vowel confusion test	17	*ABI only* 87% of patients scored well above chance level
	Consonant confusion test	17	*ABI only* 57% of patients scored well above chance level
	Closed-set word identification test	20	*ABI + LR* 50% of patients scored 100% correct 50% scored between 66% and 100% correct
	Open-set sentence recognition test	17	*ABI + LR* 47% of patients scored at or above 50% correct 24% of patients scored above 80% correct
	Word recognition test	20	*ABI + LR* 70% of patients scored above 50% correct 55% of patients scored above 70% correct
Otto et al, 2002[26]	Closed-set MTS word test[d]	55	*ABI only* 87% of patients scored significantly above chance level
	Closed-set MTS stress test[d]	55	*ABI only* 98% of patients scored significantly above chance level
	Closed-set NU-CHIPS test[f]	55	*ABI only* 84% of patients scored significantly above chance level
	Closed-set CUNY sentence test[o]	55	*ABI + LR* 31% of patients scored > 70% correct
	Vowel recognition test[p]	55	*ABI only* 51% of patients scored significantly above chance level
	Consonant recognition test[q]	55	*ABI only* 87% of patients scored significantly above chance level
Ramsden et al, 2016[27]	Three-alternative forced-choice syllable test[r] (mean and range, % correct)	29	83% (30%–100%)
	Arthur Boothroyd monosyllabic words test[s] (mean and range, % correct)	29	*ABI only:* 21% (0%–63%) *LR only:* 44% (21%–69%) *ABI + LR:* 63% (27%–96%)
	CUNY sentence test[o] (mean and range, % correct)[b]	29	*ABI only:* 10% (0%–85%) *LR only: 20*% (0%–55%) *ABI + LR: 45*% (0%–100%)

Author, Year	Test Measures	Sample Size, n	Results
Sanna et al, 2012[28]	Bisyllabic word recognition test[t]	19	58% were able to recognize words; % correct ranged from 10 to 90
	Open-set common phrases comprehension[u]	19	47% were able to respond to common phrases; % correct ranged from 10 to 100
	Open-set speech recognition[v]	19	42% were able to recognize speech; % correct ranged from 20 to 100 Among these, 50% could use telephone and achieved 70%–100% correct
Shannon et al, 1993[29]	MTS word score[d]	16	81% were able to recognize words; % correct ranged from 40 to 75
	MTS stress score[d]	16	100% were able to recognize stress patterns; % correct ranged from 48 to 98
	CUNY sentence test[o] (range, % correct)	16	*LR only*: 4%–60% *ABI + LR*: 12%–80%
Siegbahn et al, 2014[30]	Categories of Auditory Performances[w]	17	94% had awareness of environmental sound 12% were able to respond to speech sounds 41% were able to identify environmental sounds 35% were able to discriminate speech sounds without lip-reading 6% were able to use telephone with familiar speaker
Thong et al, 2016[31]	Closed-set word identification	8	*ABI only* 6 months: 39% (12%–72%) 12 months: 68% (48%–92%) 24 months: 62% (28%–100%)
	Open-set sentence identification	8	*ABI only* 6 months: 49% (27%–67%) 12 months: 31% (12%–79%) 24 months: 35% (12%–67%)

Abbreviations: ABI, auditory brainstem implantation; CUNY, City University of New York; LR, lip-reading; MTP, Monosyllabic Trochee Polysyllabic; MTS, Monosyllable, Spondee, Trochee; NR, not reported; NU-CHIPS, the Northwestern University Children's Perception of Speech; SD, standard deviation.

[a]The Innsbruck Sentences test consists of 10 lists of 10 short sentences with an average number of 5 words per sentence spoken by a female voice.

[b]Numeric data were estimated from figures.

[c]Excellent performance group achieved 50% or higher discrimination scores for open-set dissyllabic words or sentences with ABI only. Good performance group achieved 50% or higher discrimination scores for open-set dissyllabic words or sentences with ABI and LR. Limited performance group had less than 50% word and sentence discrimination with ABI and LR, but benefited from an environmental sound awareness.

[d]The MTS test consists of two presentations of 12 pictured words: 4 monosyllables, 4 trochees (a stressed and unstressed syllable), and 4 spondees (two stressed syllables). Two scores were obtained that reflected the number of times that patients recognized the correct stress pattern (MTS stress) and the number or words correctly identified (MTS words).

[e]Statistically significant when compared with chance level (i.e., patients could get the correct answers by randomly guessing).

[f]The NU-CHIPS test examines word recognition with stimuli comprising the most frequently occurring phonemes in the English language. The test consists of 4 lists of 50 words each, and the patients were required to identify the stimulus presented from a choice of 4 pictures.

[g]10 monosyllable vowels, composed of 5 long (BAAT, GAAT) and 5 short (BAT, GAT) words, were read for the patient 4 times through live voice.

[h]13 meaningless consonant words (ABA, AGA) were read for the patients 4 times through live voice.

[i]A story was read through live voice to the patient who was supposed to repeat the sentences or words correctly. The number of correct words in 5 minutes was calculated and divided by 5 to measure the number of correct words per minute. The score for a normal hearing person is 70 to 80 words per minute.

[j]A standardized open-set test in German, composed of 20 numbers between 13 and 99 (2 to 4 syllables), were presented at comfortable loudness level through a CD player directly connected to the input tract of the speech processor. Patients were supposed to repeat the numbers correctly and each correct answer was equivalent to 5%.

[k]Audiological tests included phoneme recognition tests (vowel and consonant confusion tests), the Arthur Boothroyd word list test, the Bamford-Kowal-Bench (BKB) sentence test, and the CUNY sentence test.

[l]Later follow-up referred to follow-up between 1 and 7 years post-ABI.

[m]The MTP test assessed words and number of syllables recognized and consisted of a closed set of 12 words offered twice each in a random order.

[n]Open-set sentences tests used were the Hochmair-Schulz Moser test, the Polish Hochmair-Schulz-Moser, the Technical Committee on Cochlear Implant in Japan test, the open-set sentence recognition test, the Institute of Hearing Research sentence test.

[o]The CUNY test consisted of lists of 12 everyday sentences.

[p]8 vowel sounds were included in the test and were embedded in an hVd context (heed, had, hid, and so on).

[q]16 consonant sounds were included and were embedded in an aCa context (aPa, aSa, aFa, aJa, and so on).

Notes continued on next page.

Notes for Table 4 continued:

[r]In the three-alternative forced-choice syllable test, patients listened to a single word or a phrase and were asked to decide whether it was single or multisyllabic.

[s]In the Arthur Boothroyd monosyllabic words test, patients were asked to identify phonemes of the words.

[t]Bisyllabic word recognition test used the Italian version of the Northwestern University Phonetically Balanced Word List.

[u]The open-set common phrases comprehension test was based on common and simple interrogative phrases (e.g., "How are you feeling?") to which the patient had to respond.

[v]The open-set speech recognition test, a list of 10 uncommon sentences, was presented to the patient; each list contained 100 words and was scored for the total number of words correctly repeated.

[w]Categories of Auditory Performance is an outcome measure of auditory receptive abilities. Medical social workers and speech language pathologists rated the developing auditory abilities according to eight categories of increasing difficulty. A score of 0 corresponds with "displays no awareness of environmental sounds" and a score of 7 corresponds to "can use the telephone with a familiar speaker."

Subjective Benefits of Hearing

Five studies measured subjective benefits of hearing, using questionnaires,[19,20,22,23,25] and Table 5 summarizes their results.

In the studies reviewed, most patients could differentiate speech from environmental sounds, distinguish among environmental sounds, and distinguish the difference between various voice qualities (e.g., man vs. woman, adult vs. child).[19,20]

Patients found ABI to be considerably helpful in understanding speech in quiet environments, especially with familiar voices. The results were less satisfying in noisy environments, according to the study authors.[19,23,25] Compared to using ABI only, patients reported that lip-reading enhanced their speech perception with both familiar and unfamiliar voices, and in both quiet and noisy environments.[23,25,31]

Some patients also reported that ABI helped them control their voice volume, to understand speech more easily, to hear certain words without seeing the speaker, to recognize certain voices, and to listen to music.[20] With respect to adjusting to hearing with an ABI, Matthies et al[22] reported that it took patients some time and some difficulty to adjust. Approximately half their study population described a positive change in emotional state. Most patients found that ABI improved their listening in individual conversations, and some found it useful in group conversations. However, only a few found it useful in noisy environments. Despite these varied benefits, all patients said they were "adequately" or "very" satisfied with the ABI.

Behr et al[14] commented that "there was a lot of variability which could not be expressed adequately by means and standard deviations [of test scores]" and that "individual expectations and the individual degree of satisfaction must be taken into consideration when evaluating the benefits from ABI." In two publications on the same cohort of patients, subjective measurement of patient satisfaction did not directly correlate with the results of the objective auditory tests.[18,19] Objective measurement only accounted for auditory perception; however, patients' actual auditory performance in daily life depended on factors such as the speed of conversation, tone of voice, and environmental conditions. These factors could affect the way patients cope with the ABI in everyday situations and, hence, influence their satisfaction with the implant.[18,19]

Six included studies described patients' subjective benefits narratively.[14,16,19,20,23,25] While this information may be subject to potential reporting bias, as it was not systematically collected, it may add value in presenting a dimension of patients' values and preferences. Some of these narratives were collected as part of the survey questionnaire,[23] while others were captured in quotes from the patients themselves or described by the authors, as in the following examples:[14,16,19,20,25]

The implant makes me feel safe.[20]

It gives me more control of what happens around me.[20]

It feels like I'm in a bubble without the implant.[20]

If the implant would have worked as it did in the beginning, I would make the same decision again [to get an implant].[20]

It was tiring to go through the surgery and the fitting of the ABI, but I do not regret it for a second as it makes me feel safe and gives me self-confidence.[20]

Can discriminate some sounds in the right environment. If it is a lot of background noise, it is hard to sort the sounds.[20]

Has taken the implant off in noisy environments.[20]

[A patient] achieved … 65% sentences (all open set) without LR [lip-reading] 1 year after the first fitting. She learned a foreign language … by using audiocassettes and a text book and can use the telephone with familiar people.[14]

[A patient] had only limited speech discrimination and had been deaf for a very long time … Before implantation she had felt very isolated, did not leave her house, had very limited social contacts, and had distressing tinnitus. After tumour resection and ABI implantation her life changed. The tinnitus was almost completely masked … and she was no longer afraid to leave her house as she was now able to identify traffic noise. Most important, she is now confident to walk with her grandson and to play with him outside.[14]

[A patient] had a severe form of NF2. She had no LR [lip-reading] ability, and her blindness greatly hampered the [ABI] training. Her performances were limited to environmental sound awareness. Even if the auditory performances with ABI were poor, ABI changed the everyday life of this patient whose environmental awareness was limited to touch before ABI.[16]

Most ABI users informally reported to clinic staff that they were happy to have received the implant. Even those who did not score highly on objective tests found the ABI provided increased awareness of their surroundings.[25]

Most of our patients believed that the ABI was helpful in fighting isolation and supported them in dealing better with their neurofibromatosis type 2.[19]

The quality of the evidence for subjective benefits of hearing was high (Appendix 2, Table A2). We upgraded this evidence because of large magnitude of effects: the ABI allowed these completely deaf people to regain the ability to hear.

Table 5: Subjective Benefits of Hearing—Neurofibromatosis 2

Author, Year	Test Measures	Sample Size, n	Results
Lenarz et al, 2002[19]	Self-reported questionnaire on subjective rating of hearing ability[a]	11	*Recognition of speech and its quality:* Able to differentiate speech from environmental sounds: 100% Able to differentiate adult's voice from children's voice: 73% Able to differentiate men's voice from women's voice: 64%
		11	*Differentiating various environmental sounds:* Score 6 (82%); score 5 (18%)
		11	*Usefulness in enhancing lip-reading ability:* Understand familiar voice in quiet: score 6 (82%); score 5 (18%) Understand familiar voice in noise: score 6 (36%); score 5 (18%); score ≤ 4 (45%) Understand unfamiliar voice in quiet: score 6 (54%); score 5 (9%); score ≤ 4 (36%) Understand unfamiliar voice in noise: score 6 (27%); score 5 (9%); score ≤ 4 (64%)
		11	*Ability to converse by telephone:* yes, with familiar voice (18%)
Lundin et al, 2016[20]	Self-reported questionnaire on perception of environmental sounds and the benefits of ABI[b]	8	*Can you hear these sounds with the ABI only?* Voices: yes (88%), sometimes (12%) Foot steps: yes (50%), sometimes (38%) Doors opening/closing: yes (62%), sometimes (12%) Pouring water: yes (88%), sometimes (12%) TV/radio: yes (50%), sometimes (50%) Knocking on the door: yes (50%), sometimes (25%) Door bell: yes (38%), sometimes (38%) Telephone ringing: yes (50%), sometimes (50%) Car engine: yes (50%), sometimes (38%) Emergency vehicle: yes (38%), sometimes (12%) Birds singing: yes (38%), sometimes (38%) Music: yes (62%), sometimes (12%)
		8	*Can you hear the difference between these sounds with the ABI only?* Male vs. female voice: yes (25%), sometimes (12%) Adult vs. child voice: yes (38%), sometimes (12%) Telephone vs. door bell: yes (38%), sometimes (25%) Speech vs. music: yes (62%), sometimes (12%)
		8	*Does the ABI help you to control the volume of your voice?* Yes (75%), sometimes (12%)
		8	*Is it easier to understand speech when using the ABI?* Yes (100%)
		8	*Can you hear certain words with the ABI without seeing the speaker?* Yes (38%), sometimes (25%)
		8	*Can you recognize certain voices with the ABI?* Yes (25%), sometimes (25%)
		8	*Do you use the ABI to listen to music?* Yes (25%), sometimes (12%)
Matthies et al, 2013[22]	Subjective benefit questionnaire[c]	14	*About how long would you say it took for you to adjust to your ABI?* No time (21%) Hardly any time (21%) Moderate amount of time (36%) Quite some time (21%) A very long time (0%)
		15	*How difficult was this adjustment for you?* Not difficult (27%) Somewhat difficult (47%) Moderately difficult (13%) Quite difficult (7%) Very difficult (7%)

Author, Year	Test Measures	Sample Size, n	Results
		16	*How would you rate the changes in your emotional state since you began wearing an ABI?* Very positive (25%) Somewhat positive (25%) Neutral (44%) Somewhat negative (6%) Very negative (0%)
		16	*Has your ABI improved listening in individual conversation?* Not at all (0%) Hardly (6%) Sometimes (38%) Often (56%) Not applicable (0%)
		16	*Has your ABI improved listening in groups?* Not at all (13%) Hardly (31%) Sometimes (38%) Often (13%) Not applicable (6%)
		15	*Has your ABI improved listening in noisy environments?* Not at all (27%) Hardly (40%) Sometimes (20%) Often (7%) Not applicable (7%)
		15	*How satisfied are you in general with your ABI?* Very satisfied (33%) Fairly satisfied (40%) Adequately satisfied (27%) Hardly satisfied (0%) Not at all satisfied (0%)
McSorley et al, 2015[23]	ABI Performance Questionnaire[d] (median score)	22	*Usefulness with a familiar speaker in a quiet place:* 4.0 (ABI only) vs. 5 (ABI + LR)
		22	*Usefulness with a familiar speaker in a noisy place:* 2.5 (ABI only) vs. 3.5 (ABI + LR)
		22	*Usefulness with an unfamiliar speaker in a quiet place:* 1.5 (ABI only) vs. 3.0 (ABI + LR)
		22	*Usefulness with an unfamiliar speaker in a noisy place:* 1.0 (ABI only) vs. 2.0 (ABI + LR)
Nevison et al, 2002[25]	Subjective performance questionnaire[a] (mean score)	11	*Usefulness with a familiar speaker in a quiet place:* 2.9 (ABI only) vs. 4.9 (ABI + LR)
		11	*Usefulness with a familiar speaker in a noisy place:* 1.5 (ABI only) vs. 2.8 (ABI + LR)
		11	*Usefulness with an unfamiliar speaker in a quiet place:* 2.6 (ABI only) vs. 4.0 (ABI + LR)
		11	*Usefulness with an unfamiliar speaker in a noisy place:* 1.2 (ABI only) vs. 2.8 (ABI + LR)
		11	*Environmental sounds:* 4.8 (ABI only)

Abbreviations: ABI, auditory brainstem implantation; LP, lip-reading.

[a]Scoring system composed of 6 scores with 1 indicating no benefits and 6 indicating very useful.

[b]The 4 responses of the questionnaire were yes, sometimes, no, and don't know.

[c]The questionnaire consisted of 7 questions assessing the time needed to become accustomed to the ABI, the influence of the ABI on daily life and listening capacity, and the patient's overall impression of the ABI.

[d]Patients were asked to rate the usefulness of ABI in each situation using a grading system from 1 (not useful) to 6 (very useful).

Quality of Life

One study reported on quality of life,[20] and Appendix 3, Table A4, summarizes its results. Lundin et al[20] measured quality of life in patients with NF2 using the validated, disease-specific Neurofibromatosis 2 Impact on Quality of Life (NFTI-QOL) questionnaire.[38] Hearing problems had the largest negative effect on quality of life in this patient population, with 91% of patients reporting that hearing problems disrupted their usual activities. Approximately 73% of patients perceived that NF2 affected their role and outlook on life (e.g., confidence, career, relationships), leading to poorer quality of life. However, there was no correlation between the NFTI-QOL score and ABI use: mean scores were equal for users (11.0) and nonusers (10.8), out of a maximum possible score (poorest quality of life) of 24.

The quality of the evidence for quality of life was low (Appendix 2, Table A2). We upgraded this evidence because of large magnitude of effects: the ABI allowed these completely deaf patients to hear which led to improvement in both objective and subjective outcomes of hearing. However, we downgraded for indirectness because these results combined both ABI users and nonusers, which did not allow us to delineate the impact of ABI on quality of life for patients with NF2 in this study. We also downgraded for imprecision because of small sample size.

Auditory Brainstem Implantation: Nontumour Indications

Six observational studies investigated ABI for nontumour indications,[15,16,33-35] and Table 6 summarizes their characteristics. Three studies were conducted only in patients with postmeningitis totally ossified cochleae,[33-35] while the other two studies were conducted in patients with deafness due to various nontumour causes.[15,16] Patients were followed from 6 months to 10 years, with data from the latest follow-up being reported.[12,13,20-22] One study was on surgical complications of ABI.[32]

Table 6: Observational Studies on Auditory Brainstem Implantation for Nontumour Indications

Author, Year	Sample Size,[a] N	ABI Users,[b] n	Study Period	Age at Implantation, Years	Duration of Deafness, Years	ABI Type	Indications	Outcomes	Follow-Up	Study Design
Bayazit et al, 2016[33]	9	5	2007–2014	17–47	1.5–29	MED-EL Concerto, Pulsar Neurelec Digisonic SP	Postmeningitis bilateral ossified cochlea	Sound recognition Speech perception	6–69 months[c]	Retrospective cohort
Colletti et al, 2009[15]	48	48	1997–2007	NR	1.2–19.8	Cochlear Nucleus ABI22 Cochlear Nucleus ABI24	Head trauma Auditory neuropathy Cochlear malformation Altered cochlear patency	Speech perception	1–10 years[c]	Retrospective cohort
Colletti et al, 2010[32]	39	39	1997–2008	21–70	NR	Cochlear Nucleus ABI22 Cochlear Nucleus ABI24	Head trauma Auditory neuropathy Cochlear malformation Altered cochlear patency	Surgical complications	1–10 years	Retrospective cohort
Fernandes et al, 2017[34]	7	7	NR	21–56	NR	Cochlear ABI	Postmeningitis	Patient satisfaction Quality of life	1–4 years[c]	Cross-sectional descriptive
Grayeli et al, 2008[16]	8	6	1996–2006	37–71	0–33	Cochlear Nucleus M22, M24	Postmeningitis bilateral ossified cochlea Solitary vestibular schwannomas on the only hearing ear Inner ear malformation Bilateral cochlear destruction by otosclerosis	Speech perception	6–100 months[c]	Retrospective cohort
Malerbi et al, 2018[35]	8	7	2009–2015	21–56	2.0–18.5	Cochlear Nucleus M24	Postmeningitis bilateral ossified cochlea	Pure tone audiometry Speech perception Nonauditory effects Surgical complications	22–60 months[c]	Prospective before-and-after

Abbreviations: ABI, auditory brainstem implantation; NR, not reported.
[a]Sample size refers to the number of patients with ABI.
[b]ABI users refers to the number of patients with ABI excluding those without auditory sensations, those with a sleeper device (implanted but not activated), and those who died during the study period,
[c]Data obtained from the last follow-up visit.

Sound Recognition

Two studies reported on sound recognition,[33,35] and Table 7 summarizes their results. The sound field thresholds reported by Bayazit et al[33] suggested that these patients could hear quiet conversational speech with ABI. In addition, most of these patients were able to detect the Ling 5 sounds (/a/, /ee/, /u/, /sh/ and /s/). In a before-and-after study, Malerbi et al[35] reported a significant improvement in sound thresholds measured by pure tone audiometry after ABI.

The quality of the evidence for any degree of improvement in sound recognition was moderate (Appendix 2, Table A3). We upgraded this evidence because of large magnitude of effects: the ABI allowed these completely deaf people to perceive sounds, and—as with NF2 patients—this ability contributed to improvement in both objective and subjective benefits of hearing. However, we downgraded for imprecision because of small sample sizes.

Table 7: Sound Recognition—Nontumour Indications

Author, Year	Test Measures	Sample Size, n	Pathological Conditions	Results
Bayazit et al, 2016[33]	Ling 5 sound detection	5	Cochlear ossification	60% able to detect 5 out of 5 sounds 20% able to detect 4 out of 5 sounds
	Sound field thresholds[a] (range, dB HL)	4	Cochlear ossification	250 Hz: 30–45 dB HL 500 Hz: 25–45 dB HL 1 kHz: 35–45 dB HL 2 kHz: 30–55 dB HL 4 kHz: 30–75 dB HL 6 kHz: 25–40 dB HL
Malerbi et al, 2018[35]	Pure tone audiometry[a]	7	Cochlear ossification	*Pre vs. post ABI* 103–130 vs. 45–65 dB HL *P* < .05

Abbreviations: ABI, auditory brainstem implantation; dB HL, decibels in hearing level.
[a]The lower the sound threshold in dB HL, the better the hearing.

Speech Perception

Four studies reported on speech perception[15,16,33,35] (Table 8). In patients with cochlear ossification, speech perception significantly improved after ABI, compared with pre-implantation.[35] The magnitude of improved speech perception after ABI appeared to differ by underlying pathological condition. In general, patients with altered cochlear patency (e.g., those with cochlear ossification) attained better speech perception with ABI than those with cochlear malformation.[15,16] (*Cochlear patency* refers to the openness of the cochlear aqueduct, a narrow channel in the hearing pathway.) When used in conjunction with lip-reading, perception of words and sentences improved, especially in those with cochlear ossification.[16]

The underlying etiology of deafness also has an impact on speech perception with ABI. In a cohort of patients with NF2 and nontumour etiology, the average performance of open-set sentence recognition with ABI was significantly better in patients with nontumour etiology than those with NF2 (*P* = .0007), likely because the brainstem was not compressed in nontumour cases.[15]

The quality of the evidence for any degree of improvement in speech perception with ABI used in conjunction with lip-reading was low (Appendix 2, Table A3). We upgraded this evidence

because of large magnitude of effects: the ABI allowed these completely deaf people to perceive speech. However, we downgraded because of imprecision from small sample sizes.

The quality of the evidence for any improvement in speech perception with ABI only was moderate (Appendix 2, Table A3). We also upgraded this evidence because of large magnitude of effects, but we downgraded the evidence for inconsistency as speech perception with ABI only varied considerably between studies. Patient, surgical, and device-related factors (e.g., tumour size, local anatomical conditions, duration of auditory deprivation, number of activated electrodes) could affect auditory performance. It was difficult to distinguish whether the varied results were due to patient-related factors or the way the study was conducted.

Table 8: Speech Perception—Nontumour Indications

Author, Year	Test Measures	Sample Size, n	Pathological Conditions	Results, %[a]
Bayazit et al, 2016[33]	Closed-set word score (range, % correct)	4	Cochlear ossification	50–100
	Closed-set sentence score (range, % correct)	4	Cochlear ossification	70–100
Colletti et al, 2009[15]	Open-set sentence recognition (range, % correct)	7	Head trauma	32–80
		4	Auditory neuropathy	12–18
		6	Cochlear malformation	37–61
		31	Altered cochlear patency	34–100
Grayeli et al, 2008[16]	Open-set word discrimination (range, % correct)[b]	3	Cochlear ossification	10–50 *ABI + LR:* 80–90
		2	VS + contralateral hearing loss	0 *ABI + LR:* 20–22
		1	Cochlear malformation	0 *ABI + LR:* 22
		1	Advanced otosclerosis	0 *ABI + LR:* 70
	Open-set sentence discrimination (range, % correct)[b]	3	Cochlear ossification	20–32 *ABI + LR:* 72–90
		2	VS + contralateral severe hearing loss	0 *ABI + LR:* 0–6
		1	Cochlear malformation	0 *ABI + LR:* 0
		1	Advanced otosclerosis	0 *ABI + LR:* 40
Malerbi et al, 2018[35]	Suprasegmental four-choice word recognition test (range, % correct)	8	Cochlear ossification	Pre vs. post ABI: 0–25 vs.18–50 *P* = .01
	Four-choice spondee recognition test (range, % correct)	8	Cochlear ossification	Pre vs. post ABI: 0 vs. 16–50 *P* = .01
	Vowel presentation (range, % correct)	8	Cochlear ossification	Pre vs. post ABI: 0 vs. 0–53 *P* = .03

Abbreviations: ABI, auditory brainstem implantation; LR, lip-reading; NR, not reported; VS, vestibular schwannomas.
[a]All results were tested with ABI only, unless otherwise stated.
[b]Numeric data were derived from figures.

Subjective Benefits of Hearing

One study reported on various aspects of patient satisfaction with the ABI as a measure of subjective benefits of hearing (Table 9).[34] Patient satisfaction was measured by the Satisfaction with Amplification in Daily Life questionnaire. Based on the results of this survey, the study authors indicated that patients were satisfied with ABI in the subscales of positive effects (acoustic and psychological benefits), negative factors (e.g., amplification of environmental noise), and service and cost (e.g., satisfaction with professional services, cost of the device), but dissatisfied in the subscales of personal image (e.g., aesthetics) and global (overall) satisfaction. According to the authors, feelings of dissatisfaction stemmed from the way other people in a social environment perceive ABI, which negatively impacts the deaf person's self-image and personal relationship. The authors further stated that despite expressing some dissatisfaction, patients continued to use their ABI for at least 9 hours a day, suggesting the benefits may not be fully captured in the questionnaire.

The quality of the evidence for subjective benefits of hearing was low (Appendix 2, Table A3). We upgraded this evidence because of large magnitude of effects: patients were completely deaf and the ABI allowed them to regain some hearing. However, we downgraded for imprecision because of small sample size which may have created uncertainty in the study results.

The quality of the evidence for subjective benefits of hearing was low (Appendix 2, Table A3).

Table 9: Subjective Benefits of Hearing—Nontumour Indications

Author, Year	Test Measures	Sample Size, n	Pathological Conditions	Results
Fernandes et al, 2017[34]	SADL[a] (range, score)	7	Postmeningitis	Global[b]: 2.9–3.6 Positive effects[c]: 3.7–5.0 Service and cost[d]: 0–7.0 Negative factors[e]: 1.0–4.3 Personal image[f]: 2.7–4.3

Abbreviations: NR, not reported; SADL, Satisfaction with Amplification in Daily Life questionnaire.
[a]Scoring system ranges from 0 (not at all satisfied) to 7.0 (extremely satisfied).
[b]Global refers to overall satisfaction.
[c]Positive effects refer to acoustic and psychological benefits.
[d]Service and cost refer to professional competence, product price, and number of repairs.
[e]Negative factors refer to amplification of environmental noise, presence of microphony (e.g., buzzing) in telephone use.
[f]Personal image refers to aesthetics and the stigma related to use of the devices.

Quality of Life

One study reported on quality of life (Table 10).[34] The authors concluded that all ABI users rated their quality of life as good in all domains by indicating above-average values on the scales in the brief version of the World Health Organization Quality of Life questionnaire.

The quality of the evidence for quality of life was low (Appendix 2, Table A3). We also upgraded this evidence because of large magnitude of effects but downgraded for imprecision because of small sample size which may have created uncertainty in the study results.

Table 10: Quality of Life—Nontumour Indications

Author, Year	Test Measures	Sample Size, n	Pathological Conditions	Results, %
Fernandes et al, 2017[34]	WHOQOL–BREF[a] (range, score)	7	Postmeningitis	Physical: 36–100 Psychological: 46–96 Social relationship: 25–100 Environmental: 38–97 General[b]: 38–100

Abbreviations: WHOQOL–BREF, World Health Organization Quality of Life questionnaire—brief.
[a]Scoring system ranges from 0% (poor quality of life) to 100% (good quality of life).
[b]General refers to general quality of life.

Auditory Brainstem Implantation: Adverse Events in Neurofibromatosis 2 and Nontumor Indications

Nonauditory Side Effects

Fourteen studies reported nonauditory side effects (Table 11).[14,17,18,21-23,25-31,35]

Nonauditory side effects arise from stimulation of areas around the brainstem not related to hearing. In the studies reviewed, these side effects were mostly sensory in nature, frequently described as a tickle, tingle, or nonspecific vibrotactile sensation.[21,26] They were either eliminated by deactivating electrodes or were so minimal that the electrodes could be used.[17] Their magnitude often decreased over time.[17,26] The prevalence of nonauditory side effects ranged from 5% to 70% in various areas of the body.[14,17,18,21-23,25-31,35] In a few instances, patients were unable to use their implants due to nonauditory side effects.[21]

The quality of the evidence for nonauditory side effects was low because of inherent limitations in the observational study design (Appendix 2, Tables A2 and A3).

Table 11: Nonauditory Side Effects of Auditory Brainstem Implantation

Author, Year	Sample Size, n	Nonauditory Side Effects	Frequency, %
Behr et al, 2007[14]	14	Nonauditory sensations (unspecified)	8
Kanowitz et al, 2004[17]	11	Ipsilateral body tingle	28
		Facial nerve twitch	17
		Eye/visual field vibrotactile sensation	33
		Vestibular sensation	17
		Nonspecific head sensation	17
		Throat tingle and tickle	28
Lenarz et al, 2001[18]	13	Dizziness	69
		Tongue and leg tingle	38
		Pain in the head or around the ear	31
Maini et al, 2009[21]	10	Nonauditory sensations leading to ABI deactivation	20
Malerbi et al, 2018[35]	8	Throat tingle and tickle	12
		Leg and foot tingle	17
		Dizziness	13
Matthies et al, 2013[22]	27	Nonauditory sensations (unspecified)	44
McSorley et al, 2015[23]	31	Paresthesia	5
		Pain	5
		Decreased vision	5
Nevison et al, 2002[25]	25	Nonauditory sensations to head areas	73
		Nonauditory sensations to upper body areas	31
		Nonauditory sensations to abdominal areas	31
		Nonauditory sensations to lower extremities	27
Otto et al, 2002[26]	55	Nonauditory sensations (unspecified)	24
Ramsden et al, 2016[27]	29	Dizziness	55
		Nystagmus or ocular deviation	33
Sanna et al, 2012[28]	19	XI cranial nerve stimulation	46
		VII cranial nerve stimulation	8
		IX cranial nerve stimulation	21
		Vertigo	25
		Headache	8
Shannon et al, 1993[29]	16	Throat sensations (pain, vibration, constriction)	16
		Facial twitching	12
		Eye vibration	16
Siegbahn et al, 2014[30]	17	Tingling in face, tongue, and contralateral side of arms and legs	48
		Facial twitching	4
		Headache and vertigo	4
Thong et al, 2016[31]	8	Dizziness	13
		Tactile sensation in the back	13
		Stimulation of the arm; throat discomfort	25

Surgical Complications

Twelve studies reported surgical complication rates of ABI (Table 12).[14,17,18,21,25-28,30-32,35]

Colletti et al[32] presented the largest single-centre review of ABI complications which included data from 83 adult patients with NF2 (n = 34) and nontumour causes of deafness (n = 49) for 10 years. Major complications occurred in 32% (n = 11) of adult patients with NF2 and 6% (n = 3) of adult patients with nontumour etiology; none required device explantation (removal). Minor complications occurred in 58% (n = 20) of adult patients with NF2 and 18% (n = 9) in adult patients with nontumour etiology.

In the study by Colletti et al,[32] major and minor complications were both significantly less frequent in nontumour patients than in NF2 patients (major: *P* = .0004; minor: *P* = .003). It also appeared that there was no increase in the overall complication rate when implanting ABIs in NF2 patients compared with the same surgery performed only to remove a vestibular schwannoma. These differences suggested that the disease process of NF2 and the concurrent surgical removal of vestibular schwannomas contribute substantially to complication rates of the joint procedure. The authors concluded that ABI "is a safe procedure with a very low major complication rate, when performed in an experienced center with experienced adult and pediatric neurootologists, neurosurgeons, and anesthesiologists. Minor complications are easily controlled with complete resolution."[32]

Three studies reported no surgical complications in NF2 patients[18,21] and nontumour patients.[35] Among other studies, the most common complications in patients with NF2 were cerebrospinal fluid leak (3%–15%) and infection (10%–13%).[14,17,25-28,30-32] Among patients with nontumour indications, surgical complications specific to implanting the ABI device were less than 5%.[32]

The quality of the evidence for surgical complications was low because of the inherent limitations of the observational study design (Appendix 2, Tables A2 and A3).

Almost all the major and minor complications observed in the literature are common with either a suboccipital or translabyrinthine approach to any surgery around the cochlear nerve and are not specific to ABI. Potential risks specific to adding the implantation to the tumour removal surgery were local wound infection, local cerebrospinal fluid leakage and, rarely, meningitis.

Table 12: Surgical Complications of Auditory Brainstem Implantation

Author, Year	Indications for ABI	Sample Size, n	Surgical Complications	Frequency, %
Behr et al, 2007[14]	NF2	14	Pseudomeningocele	25
			Hydrocephalus	5
			Facial palsy	30
Colletti et al, 2010[32]	NF2	34	*Major complications*	
			Mortality[a]	9
			Cerebellar contusion	3
			Permanent facial palsy	3
			Meningitis	3
			Lesions of the lower cranial nerves	6
			Hydrocephalus	3
			Pseudomeningocele	6
			Minor complications	
			Cerebrospinal fluid leakage	18
			Transient hydrocephalus	21
			Wound seroma	12
			Minor infection	6
			Balance problems	32
			Infection around implant	6
			Infection surgical flap	6
			Transient facial palsy	24
			Headache	24
			Flap problems	6
	NT	49	Meningitis[b]	4
			Hydrocephalus	2
			Cerebrospinal fluid leakage	2
			Transient hydrocephalus	2
			Wound seroma	4
			Minor infection	4
			Balance problems	4
			Infection around implant	4
			Infection surgical flap	2
			Headache	6
Kanowitz et al, 2004[17]	NF2	11	Cerebrospinal fluid leakage	6
			Facial nerve weakness	28
			Wound seroma	6
Lenarz et al, 2001[18]	NF2	13	Surgical complications	0
Maini et al, 2009[21]	NF2	10	Surgical complications	0
Malerbi et al, 2018[35]	NT	8	Surgical complications	0
Nevison et al, 2002[25]	NF2	25	Facial nerve palsy	7
Otto et al, 2002[26]	NF2	55	Cerebrospinal fluid leakage	3
			Meningitis	2
Ramsden et al, 2016[27]	NF2	29	Cerebrospinal fluid leakage	6
			Meningitis	2
			Lower cranial nerve dysfunction	22

Author, Year	Indications for ABI	Sample Size, n	Surgical Complications	Frequency, %
Sanna et al, 2012[28]	NF2	19	Facial nerve injury	4
Siegbahn et al, 2014[30]	NF2	17	Facial nerve palsy	40
			Subdural haematoma	10
			Infection	10
			Cerebrospinal fluid leakage	15
Thong et al, 2016[31]	NF2	8	Facial nerve palsy	25
			Cerebrospinal fluid leakage	13
			Infection	13

Abbreviations: ABI, auditory brainstem implantation; NF2, neurofibromatosis 2; NT, nontumour etiology.
[a]Postoperative deaths unrelated to the ABI.
[b]Approximately 2 years after ABI activation.

Ongoing Studies

We found one prospective nonrandomized study on auditory brainstem implantation through a search of ClinicalTrials.gov, an international prospective registry of clinical trials. This U.S. study (ID: NCT01736267) is using a before-and-after design to investigate outcomes in adults with nontumour indications. Expected completion is November 2022.

Discussion

In this clinical evidence review, we found that ABI provided completely deaf adults with NF2 or severe inner ear abnormalities with environmental sound awareness and auditory sensation, and that it facilitated communication when used in conjunction with lip-reading. However, when people were tested with ABI only (without the aid of lip-reading), results of open-set speech perception tests were less optimal and success varied widely within and across studies. The open-set speech perception results are more consistently favourable in people with nontumour causes of deafness, likely because the brainstem is not compressed by tumours. Nevertheless, with improved device designs and refined surgical techniques, more recent studies have shown an overall improvement in auditory performance (hearing ability) for adults using ABI for both NF2 and nontumor indications.

Study authors have emphasized that subjective benefits of ABI are as important as objectively measured auditory gains, if not more so, in these populations. Indeed, in the studies reviewed, people with either condition consistently expressed satisfaction with ABI through structured questionnaires and direct quotes. The benefits of environmental sound awareness and speech perception (achieved when ABI was used in conjunction with lip-reading) reduce the sense of social isolation often experienced because of total hearing loss. This increased environmental awareness could also protect people from certain dangers and accidents, as well as give them self-confidence to face the outside world.[19] The surgery for ABI itself is reasonably safe; most surgical complications observed are commonly associated with surgeries around the cochlear nerves.

Given the rarity of NF2 and severe inner ear abnormalities, their clinical presentations, and the difficulties associated with conducting research in these populations, the existing evidence has inherent limitations such as imprecision in study results from small sample sizes, inability to mask or randomize treatment, and missing follow-up data due to listening fatigue and, in the case of NF2, disease progression.

In summary, in the context of complete deafness caused by NF2 or severe inner ear abnormalities in people who are not candidates for cochlear implantation, ABI represents the only remaining therapeutic option to provide some auditory input for this small group of people. The capacity of ABI to restore partial functional hearing is substantially relevant to patient-important outcomes, in particular to allow environmental sound awareness for personal safety and improve hearing-specific quality of life.

Conclusions

Auditory Brainstem Implantation: Neurofibromatosis 2

Based on the best evidence available, when compared with no treatment in adults with neurofibromatosis 2 who are not candidates for cochlear implantation, auditory brainstem implantation:

- Allows any degree of improvement in sound recognition (GRADE: High)
- Allows any degree of improvement in speech perception when used in conjunction with lip-reading (GRADE: High)
- Likely allows any degree of improvement in speech perception when used alone (GRADE: Moderate)
- Provides subjective benefits of hearing (GRADE: High)
- May improve quality of life (GRADE: Low)

Auditory Brainstem Implantation: Nontumour Indications

Based on the best evidence available, when compared with no treatment in adults with severe inner ear abnormalities who are not candidates for cochlear implantation, auditory brainstem implantation:

- Likely allows any degree of improvement in sound recognition (GRADE: Moderate)
- May allow any degree of improvement in speech perception when used in conjunction with lip-reading (GRADE: Low)
- Likely allows any degree of improvement in speech perception when used alone (GRADE: Moderate)
- May provide subjective benefits of hearing (GRADE: Low)
- May improve quality of life (GRADE: Low)

Auditory Brainstem Implantation: Adverse Events in Neurofibromatosis 2 and Nontumor Indications

Based on the best evidence available, auditory brainstem implantation in adults is reasonably safe (GRADE: Low).

ECONOMIC EVIDENCE

Research Questions

- What is the cost-effectiveness of auditory brainstem implantation (ABI) for adults with neurofibromatosis 2 (NF2) who are not candidates for cochlear implantation?
- What is the cost-effectiveness of ABI for adults with severe inner ear abnormalities who are not candidates for cochlear implantation?

Methods

Economic Literature Search

We performed an economic literature search on June 21, 2018, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase, and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites, clinical trial and systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception to June 21, 2018
- Cost–utility analyses, cost-effectiveness analysis, cost–benefit analyses, or cost minimization analyses

Exclusion Criteria

- Unpublished studies, narrative reviews of the literature, study protocols, guidelines, conference abstracts, and editorials

Population

- Studies in adults with NF2 or adults with bilateral deafness due to inner ear abnormalities who are not candidates for cochlear implantation

Interventions

- Studies comparing ABI to any relevant comparator

Outcome Measures

- Mean estimates of effects and costs
- Incremental costs
- Incremental effectiveness outcomes (e.g., quality-adjusted life-years [QALYs])
- Incremental cost-effectiveness ratio (ICER)
- Incremental net benefit

Literature Screening

A single reviewer reviewed titles and abstracts and did not identify any studies likely to meet the eligibility criteria.

Results

Literature Search

The literature search yielded seven citations published from inception to June 21, 2018, after removing duplicates. We excluded all seven studies based on information in the title and abstract. Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

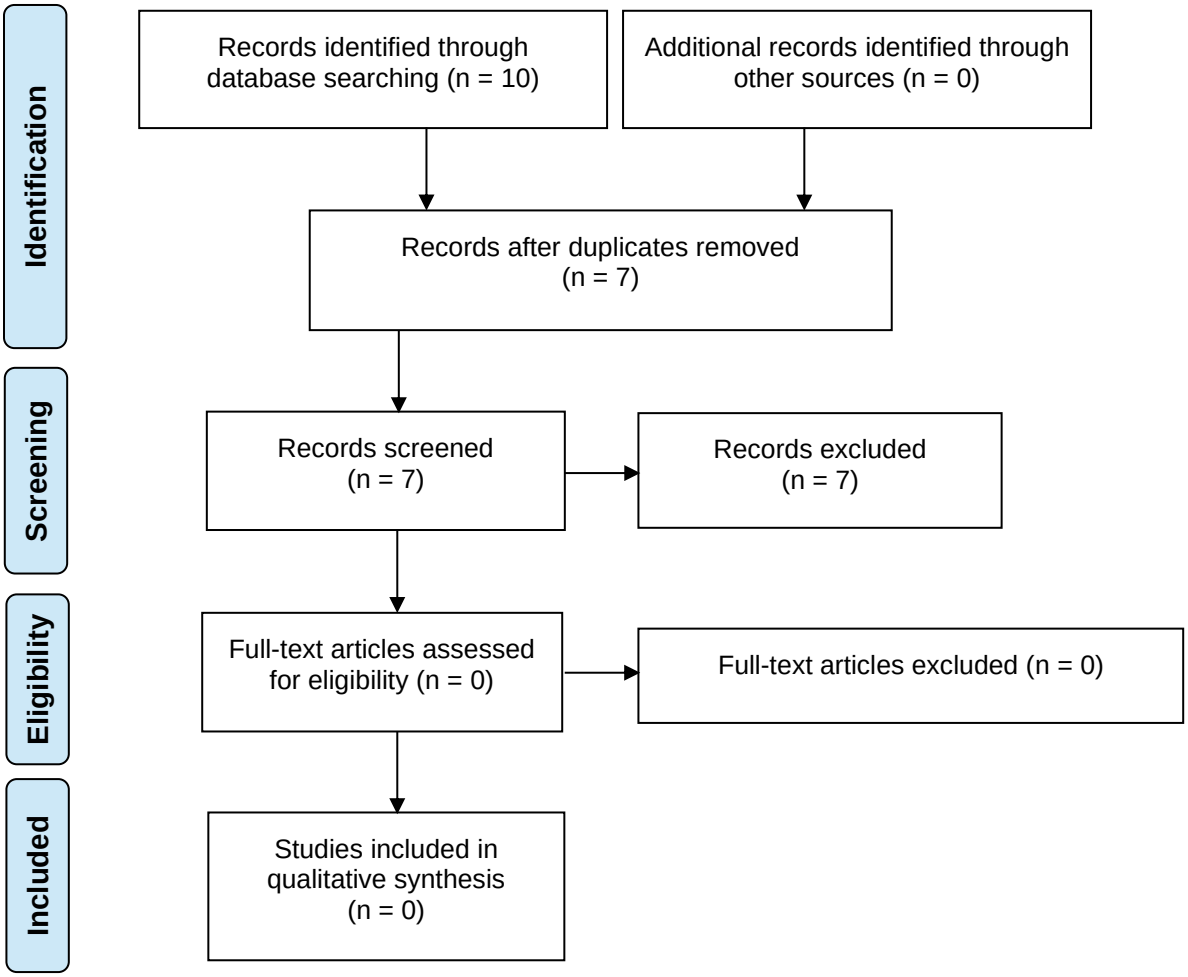

Figure 2: PRISMA Flow Diagram—Economic Search Strategy

Source: Adapted from Moher et al, 2009.[13]

Overview of Included Economic Studies

We did not identify any economic studies on ABI for adults with NF2 or severe inner ear abnormalities.

Conclusions

We did not identify any economic studies on ABI for adults with NF2 or severe inner ear abnormalities.

PRIMARY ECONOMIC EVALUATION

Our clinical evidence review found that a considerable proportion of people with neurofibromatosis 2 (NF2) and nontumour causes of deafness gained sound recognition, speech perception, and other subjective benefits of hearing by using an auditory brainstem implant (ABI). Although ABI users may experience surgery-related complications or device-related side effects, they benefited overall from improved hearing-specific health-related quality of life.[7,17,28,32,35]

However, there were no published studies that reported generic health-related quality of life data (i.e., utilities) for people with an ABI. As a result, it would be difficult to estimate the health utility associated with using an ABI and to subsequently assess the quality-adjusted life-years (QALYs) gained in a cost–utility analysis. Further, it was difficult to translate the outcomes identified in the clinical evidence review into a single effect of interest (e.g., a natural unit such as life-year) to facilitate a cost-effectiveness analysis. For these reasons, we decided to forgo conducting a primary economic evaluation and focused only on the budget impact analysis.

BUDGET IMPACT ANALYSIS

Research Question

What is the potential annual budget impact over 5 years for the Ontario Ministry of Health of publicly funding auditory brainstem implantation (ABI) for adults with bilateral deafness due to neurofibromatosis 2 (NF2) or severe inner ear abnormalities who are not candidates for cochlear implantation?

Methods

Analytic Framework

We estimated the budget impact of publicly funding ABI using the cost difference between two scenarios: (1) current clinical practice without specific public funding for ABI (the current scenario) and (2) anticipated clinical practice with specific public funding for ABI (the new scenario). Figure 3 presents the budget impact model schematic.

To date, the cost of resources associated with ABI in Ontario has been covered by the savings from other government-funded hearing aid programs and by the hospital budget at Sunnybrook Health Sciences Centre. In other words, while ABI-related costs have been covered indirectly by public funding, no specific public funding has been allocated to this treatment.

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions.

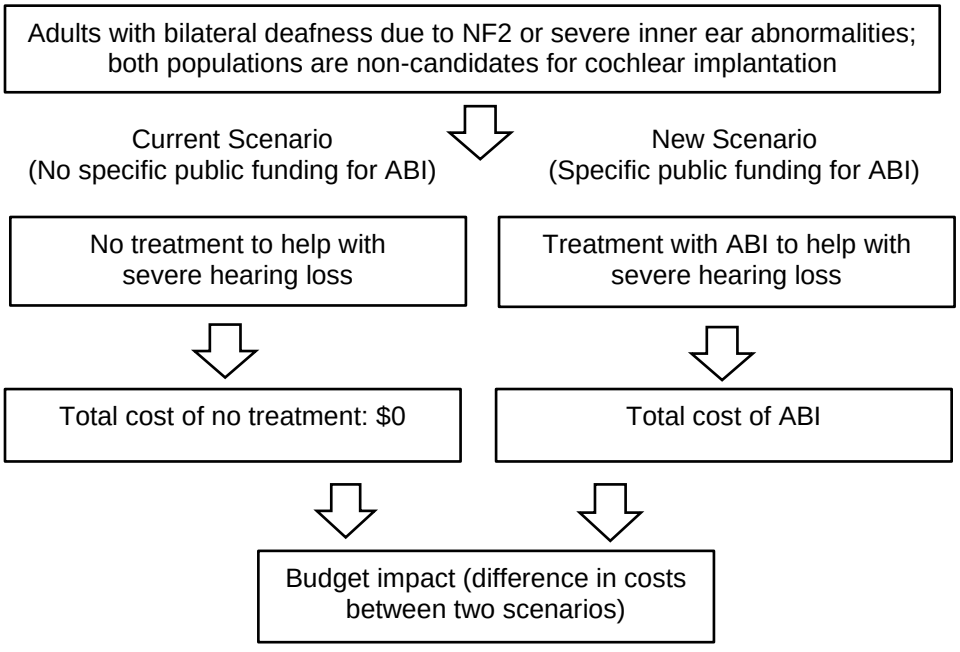

Figure 3: Budget Impact Model Schematic

Abbreviations: ABI, auditory brainstem implant; NF2, neurofibromatosis 2.

Key Assumptions

- For simplicity, we assumed in the current scenario that no public costs are incurred for adults with bilateral deafness due to NF2 or inner ear abnormalities, given that no other treatment is likely to improve hearing for people with these conditions
- We assumed that people with either NF2 or nontumour causes of deafness would incur the same costs in terms of ABI resource use
- We assumed that complications related to ABI are either uncommon (e.g., infection around the implant) or minor (e.g., dizziness, headaches, and nonauditory side effects)[32]

Target Population

We estimated the number of people expected to receive ABI based on expert consultation and trends in historical case volumes for this procedure at Sunnybrook Health Sciences Centre. This estimate took into consideration the following: (1) Sunnybrook Health Sciences Centre is the only site designated by the Ontario Cochlear Implant Program (OCIP) to conduct ABI; (2) the prevalence and incidence of our target population is relatively low (i.e., approximately 1 in 60,000 people have NF2,[6] and the nontumour population is expected to have a similarly low prevalence); and (3) only a small percentage of both NF2 and nontumour populations would be appropriate for ABI, owing to the rigorous screening of potential candidates. As outlined in the Background section of this report, the OCIP criteria include several factors that are key for ABI users to achieve successful outcomes, such as the person's physical and psychological state, their understanding of the limitations of ABI to aid in restoring some hearing, and their willingness to commit to long-term hearing rehabilitation following the procedure.[39,40]

The current annual case volume for ABI is less than one case per year. It was estimated that the annual volumes for ABI would be less than 5 cases per year if specific public funding were available for this procedure (OCIP and Joseph Chen, MD, email communications, July 2018; Cochlear Limited and MED-EL, in-person communications, October 2018). We projected that two procedures would be conducted in year 1, and four procedures would be conducted annually from year 2 to year 5 (Table 13). Based on historical trends at Sunnybrook Health Sciences Centre and expert consultation, we assumed that the projected annual volumes would include one nontumour case each year, with the rest being people with NF2.

Table 13: Expected Target Population Eligible for Auditory Brainstem Implantation

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Target population in the reference case, N	2	4	4	4	4	18

Resources and Costs

We did not identify any published economic studies on ABI, and information on the health care resources used for this procedure (e.g., length of hospital stays, length of postsurgical hearing rehabilitation sessions) was unavailable publicly or from provincial administrative databases. Furthermore, the resources required for this procedure may vary widely from patient to patient. Health-related characteristics can vary greatly among individuals who are fitted with ABI. For instance, adults with NF2 who receive an ABI may differ in the size of their tumours and in their comorbidities, which in turn may lead to significant differences in resource use (e.g., operating

room time and length of stay). Consequently, it is difficult to accurately estimate the average per-patient cost for this procedure. We therefore used crude approximations of the resource use associated with ABI, based on expert consultation.

To date, most people fitted with ABI in Ontario (three of the four procedures done, as of this writing) have been people with NF2 (Kari Smilsky, MClSc, email communication, November 2018). We therefore estimated ABI costs based on experience with people with NF2 and, as noted above, we assumed that treatment for people with nontumour causes would incur the same costs. We included direct health care costs associated with the ABI hearing implant system, from preoperative assessment to postoperative management.

We excluded costs not directly associated with the ABI, such as the costs to surgically remove tumours for people with NF2. This is an important detail in our budget impact calculations, as ABI may be implanted during the same operation to remove the NF2 tumours. As a result, it was not straightforward to separate the resource use specific to the implant procedure from the resources specific to the tumour resection. This may affect the accuracy of our resource use estimates. We also assumed that the implant system used would be divided equally between the devices manufactured by Cochlear Limited and MED-EL. This assumption is based on trends in historical ABI case volumes at Sunnybrook Health Sciences Centre.

Our per-patient cost estimate includes resources used during preoperative assessment (Table 14), the implant procedure and hospitalization (Table 15), and postoperative management such as device activation, and hearing rehabilitation (Table 16). We determined the associated unit costs of professional services from the ministry Schedule of Benefits[41] and the collective agreement between Ontario hospitals and the Ontario Public Service Employees Union (OPSEU).[42] Where the exact fee codes were unknown because ABI is not publicly funded presently, we used proxy codes.

For simplicity, we also excluded the following ABI-associated costs:

- **Postoperative complications and side effects—**In general, ABI is a safe procedure. The main complications or side effects reported are associated with disease management of NF2 or surgical complications related exclusively to the tumour removal procedure, not the implant procedure[32]
- **Device failure**—The failure rate of the ABI hearing implant system is low, at an estimated 0.08% failure rate at 4 years (Cochlear Limited, email and in-person communications, October 2018)
- **Follow-up visits after the first year—**The costs of annual follow-up visits after the first year following implantation are relatively small, compared with the total first-year costs. Therefore, we only considered costs incurred in the first year
- **ABI device replacement parts (i.e., external speech processor)**—Ontario's Assistive Devices Program provides funding assistance for replacement speech processors that are no longer serviced under manufacturer warranty after a minimum of 3 years following the implant surgery. Under this program, the Ontario Ministry of Health pays 75% of the manufacturer's invoice price up to a maximum of $5,444. While our budget impact analysis has a time horizon of 5 years, we excluded this cost after considering that an extended 5-year warranty is available from one of the ABI manufacturers (MED-EL, email communications, October 2018)[43,44]

Our reference case assumed that ABI volumes over the next 5 years would be equally divided between both makers of this technology, at an estimated $44,000 per device, based on the average ABI list prices provided by Cochlear and MED-EL. Of the four people fitted with ABI at Sunnybrook Health Sciences Centre, two received devices manufactured by Cochlear and two by MED-EL. The choice of device is guided by the professional judgement of the physician, and the real cost of devices may be lower due to compassionate pricing or discount programs. To explore the budget impact of different device costs, we included several scenario analyses that varied the price or devices used.

Table 17 summarizes the total cost per patient for auditory brainstem implantation. The average total cost per ABI procedure, including preoperative assessment and postoperative rehabilitation, was $64,807. The cost of the device (i.e., internal implant and external speech processor) contributes 68.5% ($44,400) of the total per-patient cost. All costs are reported in 2018 Canadian dollars.

Table 14: Preoperative Per-Patient Costs of Auditory Brainstem Implantation

Component	Component Breakdown	Cost per Unit, $[a] (A)	No. of Units (B)	Component Cost, $[a] (A × B)	Description	References
Surgical consult	Otolaryngologist (ENT surgeon)	160.00	3 consults	480.00	Special surgical consultation; 3 preoperative consultations	SoB[41]
	Neurosurgeon	160.00	1 consult	160.00	Special surgical consultation; 1 preoperative consultation	SoB[41]
Counselling	Audiologist	48.38	2 consults	96.76	Audiologist wage (≥ 5 years experience); 2 preoperative consultations	OPSEU[42]
	Speech pathologist	48.38	1 consult	48.38	Speech pathologist wage (≥ 5 years or more experience); 1 preoperative consultation	OPSEU[42]
Preoperative medical preparation	Pneumovax 23	20.00	1 dose	20.00	2 pneumococcal vaccines: one covered by third party, the other by OHIP	SoB, Peterborough Public Health[41,45]
	Prevnar 13	90.00	1 dose	90.00		
	Injections	4.50	2 administrations	9.00		
Total cost				**904.14**		

Abbreviations: ABI, auditory brainstem implant; ENT, ear, nose, throat; OHIP, Ontario Health Insurance Plan; OSPEU, Ontario Public Service Employees Union; SoB, Schedule of Benefits.
[a]In 2018 Canadian dollars.

Table 15: Implant Procedure and Hospitalization Per-Patient Costs of Auditory Brainstem Implantation

Component	Component Breakdown	Cost per Unit, $[a] (A)	No. of Units (B)	Component Cost, $[a] (A × B)	Description	References
Cortical mastoidectomy	Surgical assistant	12.04	6 units	72.24	Surgical assistant basic units associated with E320	SoB[41]
	Surgeon[b]	345.15	Flat fee	345.15	Surgical flat fee associated with E320	SoB[41]
	Anesthesiologist	15.01	6 units	90.06	Anesthesiologist basic units associated with E320	SoB[41]
Permanent cochlear prosthesis insertion	Surgical assistant	12.04	7 units	84.28	Surgical assistant basic units associated with E341	SoB[41]
	Surgeon[b]	737.30	Flat fee	737.30	Surgical flat fee associated with E341	SoB[41]
	Anesthesiologist	15.01	9 units	135.09	Anesthesiologist basic units associated with E341	SoB[41]
Infratentorial approach (neurosurgery)	Surgical assistant	12.04	15 units	180.60	Surgical assistant basic units associated with N151	SoB[41]
	Surgeon[b]	1,726.80	Flat fee	1,726.80	Surgical flat fee associated with N151	SoB[41]
	Anesthesiologist	15.01	15 units	225.15	Anesthesiologist basic units associated with N151	SoB[41]
Cranioplasty	Surgical assistant	12.04	11 units	132.44	Surgical assistant basic units associated with N161	SoB[41]
	Surgeon[b]	600.85	Flat fee	600.85	Surgical flat fee associated with N161	SoB[41]
	Anesthesiologist	15.01	11 units	165.11	Anesthesiologist basic units associated with N161	SoB[41]
Stereotaxis navigation	Surgical assistant	12.04	11 units	132.44	Surgical assistant basic units associated with N123	SoB[41]
	Surgeon[b]	538.40	Flat fee	538.40	Surgical flat fee associated with N123	SoB[41]
	Anesthesiologist	15.01	11 units	165.11	Anesthesiologist basic units associated with N123	SoB[41]
Implant of surface electrode	Surgical assistant	12.04	11 units	132.44	Surgical assistant basic units associated with N119	SoB[41]
	Surgeon[b]	901.25	Flat fee	901.25	Surgical flat fee associated with N119	SoB[41]
	Anesthesiologist	15.01	11 units	165.11	Anesthesiologist basic units associated with N119	SoB[41]
Duroplasty	Surgeon[b]	244.80	Flat fee	244.80	Surgical flat fee associated with E919	SoB[41]

Component	Component Breakdown	Cost per Unit, $[a] (A)	No. of Units (B)	Component Cost, $[a] (A × B)	Description	References
Electrophysiologic assessment	Electrophysiologist	Nil; covered by industry	n/a	Nil; covered by industry	EABR performed prior to closing wound; electrophysiologist provides feedback to surgeon	Expert opinion
Operating room		1,134 per hour	6 hours	6,804	Operating room time; cost includes nursing and support staff	Merdad et al, 2014[46]
Device (Cochlear ABI system)	Internal implant	40,200	Flat fee	40,200	n/a	List price (Cochlear Limited, email communications, Oct 2018)
	External speech processor	12,600	Flat fee	12,600	n/a	
Device (MED-EL ABI system)	Internal implant and external speech processor	36,000	Flat fee	36,000	n/a	List price (MED-EL, email communications, Oct 2018)
Postoperative recovery	Technologist	37.93	1 hour	37.93	Postoperative CT scan; registered MRI technologist wage (≥ 5 years experience)	OPSEU[42]
	Radiologist	86.60	Flat fee	86.60	Postoperative CT scan; diagnostic radiology, CT, complex head, with and without contrast	SoB[41]
	Hospitalization (postoperative recovery)	1,382 per day	3 days	4,146	3 days hospitalization (includes nursing, pharmacy, etc.)	Merdad et al, 2014[46]
Total cost				**70,649.15**	Cochlear device	
				53,849.15	MED-EL device	

Abbreviations: ABI, auditory brainstem implant; CT, computed tomography; EABR, electrical auditory brainstem response; n/a, not applicable; MRI, magnetic resonance imaging; OPSEU, Ontario Public Service Employees Union; SoB, Schedule of Benefits.

[a]In 2018 Canadian dollars.

[b]The cost of surgeon services includes services rendered by both otolaryngologist and neurosurgeon.

Table 16: Postoperative Per-Patient Costs of Auditory Brainstem Implantation

Component	Component Breakdown	Cost per Unit, $[a] (A)	No. of Units (B)	Component Cost, $ [a] (A × B)	Description	References
Follow-up at first month	Otolaryngologist	41.10	Flat fee	41.10	Surgeon flat fee associated with A243 (specific assessment)	SoB[41]
	Otolaryngologist	24.55	Flat fee	24.55	Surgeon flat fee associated with A244 (partial consultation)	SoB[41]
	Neurosurgeon	58.25	Flat fee	58.25	Surgeon flat fee associated with A243 (specific assessment)	SoB[41]
	Neurosurgeon	30.00	Flat fee	30.00	Surgeon flat fee associated with A244 (partial consultation)	SoB[41]
	Audiologist	48.38	1 hour	48.38	Audiologist wage (≥ 5 years experience)	OPSEU[42]
	Speech pathologist	48.38	1 hour	48.38	Speech pathologist hourly wage (≥ 5 years experience)	OPSEU[42]
Initial device activation at 6 to 8 weeks post-procedure	Audiologist	48.38	4 hours	193.52	Audiologist wage (≥ 5 years experience)	OPSEU[42]
	Special auditory verbal therapist	Nil; covered by third party or by patients out-of-pocket	n/a	Nil; covered by third party or by patients out-of-pocket		Expert opinion
	Electrophysiologist	Nil; covered by industry	n/a	Nil; covered by industry		Expert opinion
	Anesthesiologist	15.01	1 hour (4 units)[b]	60.04		SoB[41]
	Surgeon (standby)	12.04	1 hour (4 units)[b]	48.16		SoB[41]
	Intensive care unit	188.20	4 hours	752.80	Includes nurse in step-down unit to monitor cardiac function	CIHI[47]
Follow-up at 3 to 4 months	Audiologist	48.38	1 hour	48.38	Audiologist wage (≥ 5 years experience)	Expert opinion
	Special auditory verbal therapist	Nil; covered by third party or by patients out-of-pocket	n/a	Nil; covered by third party or by patients out-of-pocket		Expert opinion
Follow-up at 6 months	Otolaryngologist	48.60	Flat fee	48.60	Surgeon flat fee associated with A246	SoB[41]
	Audiologist	48.38	Flat fee	48.38	Audiologist wage (≥ 5 years experience)	OPSEU[42]

Component	Component Breakdown	Cost per Unit, $[a] (A)	No. of Units (B)	Component Cost, $ [a] (A × B)	Description	References
	Speech pathologist	48.38	1 hour	48.38	Speech pathologist wage (≥ 5 years experience)	OPSEU[42]
Follow-up visit at 12 months	Otolaryngologist	48.60	Flat fee	48.60	Surgeon flat fee associated with A246	SoB[41]
	Neurosurgeon	58.25	Flat fee	58.25	Surgeon flat fee associated with A046	SoB[41]
	Audiologist	48.38	1 hour	48.38	Audiologist wage (≥ 5 years experience)	OPSEU[42]
Total cost				**1,654.15**		

Abbreviations: ABI, auditory brainstem implant; CT, computed tomography; n/a, not applicable; OSPEU, Ontario Public Service Employees Union; SoB, Schedule of Benefits.

[a]In 2018 Canadian dollars.

[b]Each 15-minute period or part thereof has the following unit value: during the first hour or less = 1 unit; after the first hour = 2 units; after 2.5 hours = 3 units.

Table 17: Summary of Per-Patient Costs for Auditory Brainstem Implantation

Health Care Resource	Cost, $[a]
Preoperative assessment[b]	904
Inpatient costs of the implant procedure[c]	62,249
ABI device (50% Cochlear; 50% MED-EL)	*44,400*
Operating room	*6,804*
Professional fees during procedure	*6,775*
Hospitalization	*4,271*
Postoperative follow-up in first year[d]	1,654
Total cost	**64,807**

Abbreviation: ABI, auditory brainstem implant.

[a]In 2018 Canadian dollars.

[b]See Table 14 for detailed costs.

[c]See Table 15 for detailed costs. For the device cost, we used the average list price of the Cochlear and MED-EL devices and assumed surgeries in Ontario would use the two types equally.

[d]See Table 16 for detailed costs.

Note: Numbers may be inexact due to rounding.

Analysis

As described above, we calculated the budget impact as the cost difference between the current scenario (where ABI is not publicly funded) and the new scenario (where ABI is publicly funded) for people with NF2 or nontumour causes of bilateral deafness who are not candidates for cochlear implantation. We calculated the total cost of each scenario using the average cost per patient multiplied by the target population per year. We assumed that the costs associated with the current scenario would be zero, given that other available treatments (hearing aids) would provide little benefit to our target population. We calculated the annual budget impact for the next 5 years and estimated the total 5-year net budget impact.

In addition to the reference case, we also calculated the budget impact for the following scenarios:

- Scenario 1: A higher ABI case volume (4 cases in year 1 and 6 cases in each subsequent year)
- Scenario 2: A 30% higher implant procedure cost (assuming constant device cost) as compared with the reference case
- Scenario 3: Use of Cochlear Limited ABI device at list price for 100% of ABI procedures
- Scenario 4: Use of MED-EL ABI device at list price for 100% of ABI procedures
- Scenario 5: Use of a compassionate device rate ($24,000 in total for both the internal implant and external speech processor) for 100% of ABI procedures; this rate was based on expert consultation about current practices (Joseph Chen, MD, email communications, November 2018)
- Scenario 6: A higher cost for preoperative assessment at three times ($2,712) that of the reference case ($904), to consider that some people would be excluded during the medical and psychological assessment process for ABI
- Scenario 7: A higher cost for postoperative follow-up in the first year at double ($3,308) that of the reference case ($1,654)

Results

Reference Case

Table 18 presents the projected total costs of the resource use associated with the ABI hearing implant system over 5 years. The annual budget impact was $129,615 for 2 procedures in year 1 and increased to $259,230 subsequently to account for 4 procedures per year. The total 5-year budget impact was around $1.2 million.

Table 18: Budget Impact Analysis Results—Auditory Brainstem Implantation, Reference Case

	Budget Impact, $[a, b]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario	0	0	0	0	0	0
New scenario	129,615	259,230	259,230	259,230	259,230	1,166,534
Net budget impact	129,615	259,230	259,230	259,230	259,230	1,166,534

Abbreviations: ABI, auditory brainstem implant.
[a]In 2018 Canadian dollars.
[b]Numbers may be inexact because of rounding.

Sensitivity Analysis

Table 19 presents the results of the seven scenario analyses. Compared with the reference case, ABI would have a greater budget impact with a larger target population and higher costs for preoperative assessment, implant procedure, or postoperative follow-up. The budget impact of ABI was also sensitive to the price of the ABI device.

Table 19: Budget Impact Analysis Results—Auditory Brainstem Implantation, Scenario Analyses

	Budget Impact, $[a, b]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Scenario 1: A higher ABI case volume						
Net budget impact	259,230	388,845	388,845	388,845	388,845	1,814,608
Scenario 2: Higher implant procedure costs						
Net budget impact	140,324	280,649	280,649	280,649	280,649	1,262,919
Scenario 3: Use of Cochlear Limited ABI device for 100% of case volumes						
Net budget impact	146,415	292,830	292,830	292,830	292,830	1,317,734
Scenario 4: Use of MED-EL ABI device for 100% of case volumes						
Net budget impact	112,815	225,630	225,630	225,630	225,630	1,015,334
Scenario 5: Use of a compassionate device rate ($24,000) for 100% of case volumes						
Net budget impact	88,815	177,630	177,630	177,630	177,630	799,334
Scenario 6: A higher cost for preoperative assessment						
Net budget impact	133,231	266,463	266,463	266,463	266,463	1,199,083
Scenario 7: A higher cost for postoperative follow-up						
Net budget impact	132,923	265,846	265,846	265,846	265,846	1,196,309

Abbreviations: ABI, auditory brainstem implant.
[a]In 2018 Canadian dollars.
[b]Numbers may be inexact because of rounding.

Discussion

Auditory brainstem implantation is a treatment indicated for rare conditions, and its associated costs and resource use have not been widely reported. Therefore, we have based our budget impact estimates largely on consultation with clinical experts and on experience at Sunnybrook Health Sciences Centre, the only designated site for this procedure in Ontario.

In our budget impact analysis, we were deliberate in including only direct health care costs related to the ABI hearing implant system. Additionally, due to the critical role of screening to ensure that only appropriate candidates are fitted for the device, ABI volumes may fluctuate between 0 and 4 cases per year. Our current estimates, therefore, reflect the upper limit of expected ABI volumes over the next 5 years.

In practice, resource use associated with ABI may differ from patient to patient. People with NF2 may have the implant procedure at the same time their tumours are removed, and people with either NF2 or nontumour causes of deafness will have variations in other characteristics that may affect per-patient resource use. In addition, the total per-patient costs would increase by a moderate degree if the following costs excluded from our reference case were considered: (1) postoperative rehabilitation costs beyond the first year, (2) travel costs associated with follow-up visits incurred by people who live far from Sunnybrook Health Sciences Centre, and (3) cost of replacing the external speech processor (after manufacturer's warranty period). However, given the low case volumes projected, the total budget impact would remain small, despite the uncertainty around a summary estimate of costs for this hearing implant system.

Conclusions

We estimated that publicly funding auditory brainstem implantation for adults with bilateral deafness due to NF2 or severe inner ear abnormalities who are not candidates for cochlear implantation would lead to an annual net budget impact in Ontario ranging from about $130,000 in year 1 to $260,000 in year 5.

PATIENT PREFERENCES AND VALUES

Objective

The objective of this analysis was to explore the underlying values, needs, preferences, priorities, and values of those who have lived experience with neurofibromatosis 2 (NF2) or bilateral severe inner ear abnormalities resulting in hearing loss. The technology focus was auditory brainstem implant (ABI) devices.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat the health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[48-50] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Methods

Engagement Plan

The engagement plan for this health technology assessment focused on consultation to examine the experiences of people with NF2 or severe inner ear abnormalities, and those of their families and other caregivers. We engaged people via in-person interviews, over the phone, and through written responses.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with NF2, as well as those of their families and caregivers.[51] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of a confidential one-on-one interview methodology.

Participant Outreach

We used an approach called purposive sampling,[52-55] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of partner organizations, including Neurofibromatosis Ontario and the Brain Tumour Foundation of Canada, to spread the word about this engagement activity and to contact people with NF2 or severe inner ear abnormalities, family members, and caregivers, including those with experience of ABI treatment for hearing loss.

Inclusion Criteria

We sought to speak with people with NF2 or severe inner ear abnormalities and with family members or caregivers of people with NF2 or severe inner ear abnormalities. In particular, we

sought those who had direct experience with the ABI device, though people did not need to have direct experience with ABI treatment to participate.

Exclusion Criteria

We did not set exclusion criteria.

Participants

In the past several years, only four people have had ABI devices surgically implanted in Ontario, at Sunnybrook Health Sciences Centre in Toronto. For this project, we were able to speak to two of these people and obtained their written consent to quote them anonymously in this report. One person had NF2 while the other had undergone ABI treatment for a bilateral inner ear abnormality. We also interviewed a family member of one of the patients.

In addition, we spoke to three other people with experience with NF2: two adults with NF2 and a parent of a child with NF2. All these participants with NF2 were experiencing hearing loss, though they were not currently candidates for ABI devices.

Approach

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and, if requested, in a letter of information (Appendix 4). We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted between 15 and 60 minutes. The interview was semi-structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[56] Questions focused on the impact of NF2 or inner ear abnormalities on their quality of life, their experiences with treatments for hearing loss, as well as their decision-making values and experiences. Where applicable, we spoke about their perceptions of the benefits and limitations of ABI devices. See Appendix 5 for our interview guide.

Data Extraction and Analysis

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[57,58] We used the qualitative data analysis software program NVivo[59] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of NF2, severe inner ear abnormalities, and treatments for associated hearing loss on those we interviewed.

Results

Neurofibromatosis 2 and Its Impact

Neurofibromatosis 2 is a disease that causes tumours to grow along auditory-vestibular nerves (the nerves that send sound and balance information to the brain). These tumours can cause a variety of symptoms of different severity, depending on the size and placement of the tumours, and often require surgical removal. Participants spoke of their symptoms caused by the growth of these tumours, including balance issues, pain, loss of sensation, and diminished vision, as well as hearing loss. The monitoring and potential treatment of these tumours required regular appointments and imaging, as reported by participants, and several patients had had previous surgeries to remove tumours. This could have a significant impact on daily life:

> *If you're in a family with somebody who has NF, you're taking almost all of your free time and putting it towards going to hospital visits, getting MRIs, going to appointments … [My daughter] has upwards of eight or 10 doctors that we see regularly. So it's very difficult.*

> *I underwent a transsphenoidal resection of a meningioma in the olfactory groove (i.e., brain surgery) and had to take three months off work. While I have fully recovered from the surgery, I have permanently lost my sense of smell.*

> *Generally, there is no significant impact in my daily life, but my tumours can cause pain with and without provocation, sometimes enough to disrupt my sleep.*

Several participants reported that the rare nature of the disease was an additional burden, since accurate information about potential progression of the disease and anticipated outcomes was difficult to obtain from health care providers. And while social media and connections to other people with NF2 could be a comfort and source of information, the rare nature of the disease meant that these options were fairly limited:

> *Additionally, the burden of having a rare disease that is not widely understood has meant that I need to be my own advocate and educate myself on the disease, because few practitioners know about it. It is an exhausting and frustrating task, which is particularly unwelcome during stressful times.*

> *So just knowing that there's an organization like NFON [Neurofibromatosis Ontario] out there that does things like an annual camp where, you know, you can go and can be with people who are just like you, when you feel alone. It's a phenomenal thing.*

These challenges and the progressive nature of NF2 caused an emotional impact on the people interviewed. The ongoing growth of tumours caused fear of the future and an expectation of continuing medical challenges for several years. And the diverse potential location of tumours means that patients may face impact on various body functions:

> *[My daughter] is entering puberty, which is something that sparks tumour growth and more complications with NF. It's kind of a ticking time bomb, really, is what it is. You know, we don't know, day-to-day, what's going to happen.*

> *NF2 has caused tremendous emotional turmoil. The progression of the disease is characterized by extreme uncertainty, punctuated by heightened anxiety around MRIs and awaiting the results. NF2 has already robbed me of my sense of smell, and it has the potential to slowly strip away other vital functions, including sight, hearing, facial movement, peripheral nerve movement and other crucial motor skills … Planning my future is far from straightforward.*

Impact of Hearing Loss

For several of the participants, hearing loss was a symptom of their NF2 but not their most severe issue. Depending on the nature of the progression of NF2, hearing loss could be minor or require different treatments, such as medication or hearing aids. These participants reported managing relatively well and compensating for any hearing loss:

> *To date, my NF2 is considered relatively mild, with two surgeries to remove tumours to date. I have experienced only episodic partial hearing loss. I am currently taking a one-week dose of prednisone (oral steroids) for sudden partial unilateral hearing loss.*

> *[The tumours] are increasing in size regularly. It's a slow steady growth but it's at the point she's got hearing aids now. Something's going to have to be done.*

> *Because she's so young, you know, when you're that age and it's a gradual loss you compensate naturally. The hearing aids have been great. She actually hears a little bit too much sometimes [said jokingly]. She deals with it very well because of her age … She compensates automatically.*

However, other participants with more severe hearing loss reported greater challenges. This included the two people who had received ABI devices. Both began to lose their hearing at a young age due to their underlying conditions: one with NF2 and the other with otosclerosis. Each of these participants reported experiencing gradual hearing loss as their conditions progressed. As their hearing loss worsened, it increasingly impacted daily life and their interactions with family, friends, and coworkers. They spoke of the challenges faced at home and at work to perform routine tasks and of the accommodations they had to make in order to continue their ordinary activities such as driving, speaking on the phone, or holding a simple conversation with colleagues or friends:

> *I couldn't have a conversation on the phone. I couldn't listen to music.*

> *I spent the first few years in denial. But I couldn't hear follow-up questions at presentations that I did.*

> *I quit my managerial job … If I can't hear the problem, how can I solve it?*

Their worsening hearing also took an emotional toll. Participants spoke of feeling a sense of isolation, and an accompanying depression, as their hearing decreased. Living with hearing loss was an emotional burden that they struggled to overcome. One person also spoke of the sense of stigma, shame, and embarrassment they felt at the realization that they were unable to hear or properly communicate through conversation. They viewed the inability to hear properly as something to be hidden:

> *What would I have done without the surgery? God, I don't know … I was depressed all the time.*
>
> *I would rather [my coworkers] think I was stupid than I was deaf.*

Treatments for Hearing Loss

The participants reported on the different strategies and treatment options they attempted as their hearing loss progressed. They tried multiple options to try to cope with and manage their hearing loss. Some participants had instruction in lip-reading and received educational materials about hearing loss and their respective medical conditions. As their hearing loss progressed in both ears, they tried various kinds of hearing aids, with varying success. One person received a cochlear implant to restore some hearing in one ear:

> *In 2008 I received a cochlear implant. Got only about 30% to 40% [of hearing restored] in left ear. My right side had hearing aids, but then I started losing [hearing entirely in the] right side.*

Ultimately, for the two participants who would go on to receive ABI devices, these other treatments were unsuccessful in restoring the level of hearing they had hoped for, and they sought further treatment. Both reported feeling they were well-informed about their treatment options and knowing that an ABI device was likely the final option to restore any hearing, due to their underlying medical conditions.

Decision-Making and Expectations About Auditory Brainstem Implantation

All participants reported that retaining or restoring some hearing would be the main reason they would potentially consider receiving an ABI device. For most participants, this was still an abstract decision, but something they could see happening in the future:

> *Typically, neurosurgeons offer estimates on the percentage of hearing that would be retained through the surgery. If the chances of preserving hearing are reasonably good (> 60%), then I might opt to not have an ABI implanted. However, were I to undergo neurosurgery, ABI implantation would seem to be an obvious choice (all the more so if the chances of hearing preservation are low), in that it would not require additional surgery and it would provide me with some limited ability to hear.*
>
> *The advice of the surgeon would play a crucial role in making this decision, and I would likely solicit a second opinion for further information.*

For the two participants who had already received an ABI, the impact of their hearing loss had been great, both in the activities of their daily lives and in their emotional well-being. Seeking out a permanent surgical solution for their hearing loss was seen as the best option to reduce this impact in the future. When speaking of the desire to retain and perhaps restore some hearing, one person focused more in terms of the potential impact it would have with their family, while the other spoke more in terms of the impact on work and social situations:

> *For me, I felt the space between me and [my son]. I want to hear. When my son says "Papa," I want to hear.*

> *I was desperate. I couldn't talk on the phone at work.*

Participants reported slightly different expectations as to how the ABI surgery would affect their hearing. Among those who had received an ABI, one believed their hearing would be almost fully restored, while the other simply hoped it would be better than they were experiencing through hearing aids or a cochlear implant. These expectations occurred both through discussions with their physicians and through an overall expectation of the quality of health care in Ontario. One participant also knew that they were one of the first to have the procedure done for their medical condition, so expectations were more uncertain and modest. A family member of one participant also believed that the patient's expectations going into the surgery were fairly high:

> *I'm living in one of the best countries in the world. Anything health [related], Canada is going to fix. That [is what] I think before.*

> *I asked about who before had surgery. Answer was that 82 to 85% hearing came back. I said, "I'm strong. I'm going to have 90% back."*

> *Before surgery I didn't have much expectations … Expected better than the left ear [with cochlear implant].*

> *The potential risk to ABIs is that they may not work well, in which case I have lost little, but the potential benefit of restoring some ability to hear makes it an obvious choice.*

Surgical Procedure and Impact of Auditory Brainstem Implantation

Those interviewed described the ABI procedure as long, lasting up to 10 hours. The immediate after-effects of the surgery were described as painful, frustrating, and a challenge both for the patients and their families:

> *[I took a] long time to respond after surgery. Family thinks I [am] dead. I said to my son, "You say something but I not understand what you say."*

> *[My] reaction after surgery: "This is it?" I was disappointed and I was scared … the first day was kind of a downer for me.*

> *I was in a fair bit of pain, I couldn't lie down for a week.*

Following their recovery from surgery, both participants described their regular follow-up appointments to monitor their progress and restoration of hearing ability. At the time, both people lived in the Toronto area, so attending these appointments was possible, though there were some inconveniences and costs incurred because of travel.

The first appointments were to activate the implant, and then both attended regular auditory rehabilitation sessions to begin to train the brain to recognize the signals from the device as identifiable sounds. These sessions lasted several weeks. The two participants reported that their perception of the quality of sound they were hearing improved with time, and both the patients and the family member remarked on their improved hearing in conversations and social situations. These developments had a noticeable, positive impact their quality of life. One

person described the pride they felt when they were able to communicate over the phone and book a trip for travel. Communication was better in the work environment for one person, allowing them to return to more regular work tasks and even take on more responsibility:

> *[My father's] hearing is much better after the surgery. He can hear and speak much better now in a group.*
>
> *It changed my life. It absolutely changed my life. I am very thankful.*

Both participants who had received an ABI also expressed positive views on the reliability and endurance of these devices and their components, in particular when compared to other devices. The ABI device was felt to be more reliable, even after several years of use:

> *It is so dependable. Very robust. After 5 years, I've still had the same set of batteries.*

Despite the perceived overall benefit of having an ABI, both participants expressed some ongoing concerns and challenges. One challenge was the ability to distinguish and interpret conversations in a busy environment. Another was the ability to distinguish the direction of sound, whether in conversation or in the environment. Because the implant allowed for hearing only from one ear, the participants still struggled with these challenges, which could continue to affect their daily lives. They felt this could cause safety concerns or make them avoid situations where they knew their hearing would be ineffective. Therefore, while they saw the ABI devices as an improvement and a benefit to their daily lives, the implant was not able to completely restore normal hearing:

> *When it comes to directionality, you get used to it. But I need to be in a quiet environment.*
>
> *If I hear two sounds at once, they become garbled. They mix together sometimes. I still can't have technical conversations on the phone.*

One participant also reported experiencing some side effects that he attributed to the surgery. Following the surgery, this person experienced swallowing issues, excess phlegm, eye dryness and soreness, and pain in the ear with certain movements. While grateful for the restored ability to hear, they and their family member expressed uncertainty when asked whether they regretted having the surgery done in the first place. In some ways, they felt that the restoration of some hearing was not worth the negative impact of these side effects. They reported that the feeling of regret may be due to their high expectations prior to the surgery and the sense that the expectations were not met.

> *[My father] has never said, "Oh, I wish I'd never done it." I think he is on the fence about it. There were high expectations. He feels that he was robbed.*
>
> *If now [someone was to] ask me, I say no [to having the surgery].*

Discussion

Due to the rarity of the health conditions and the surgical procedure at the centre of this assessment, our patient engagement was limited. Of the four people who have received an ABI in Ontario within the past several years, only two were available to be contacted through the surgical centre. In all, we were able to interview six people: the two surgical patients, one family member of a surgical patient, and three other participants with lived experience of NF2 (two adults with the condition and a parent of a child with NF2).

Participants were able to speak to the impact of NF2 and severe inner ear abnormalities, including the impact of hearing loss, which is one of the more common symptoms of these conditions. They reported on how it affected their daily lives as well as the various treatments and therapies they attempted to reduce this impact.

Participants were also able to speak to their decision-making when considering ABI surgery.

The two people who have received an ABI device were able to report on their decision-making process and the values they weighed in choosing to have the surgery. They were able to report on their experience with the procedure itself, the recovery period, and the impact of the device on their activities of daily living.

Conclusions

Bilateral hearing loss due to NF2 and severe inner ear abnormalities can have a large negative impact on people, causing emotional distress and challenges in activities of daily living. Both people who had an ABI perceived it as a successful means of restoring some hearing ability and improving quality of life, though they also reported ongoing challenges related to using the device or perceived side effects of the surgery.

CONCLUSIONS OF THE HEALTH TECHNOLOGY ASSESSMENT

This health technology assessment looked at the effectiveness and safety of auditory brainstem implantation (ABI) in adults with two rare conditions that can cause bilateral deafness: neurofibromatosis 2 (NF2) and severe inner ear abnormalities. It also evaluated the budget impact of publicly funding auditory brainstem implantation in Ontario, and the experiences, preferences, and values of people with NF2 or severe inner ear abnormalities.

Based on evidence of moderate to high quality, auditory brainstem implants allow any degree of improvement in sound recognition and in speech perception when used in conjunction with lip-reading in completely deaf adults with neurofibromatosis 2 who are not candidates for cochlear implantation. The quality of evidence on these outcomes was low to moderate for people with severe inner ear abnormalities. These functional outcomes lead to subjective benefits of hearing that are consistently reported in the literature.

We did not identify any economic studies on the ABI hearing implant system for adults with NF2 or with bilateral deafness due to severe inner ear abnormalities. And we did not conduct a primary economic evaluation because the outcomes identified in our clinical evidence review were difficult to translate into measures appropriate for health economic modelling. We were therefore unable to determine the cost effectiveness of ABI.

We estimated that publicly funding ABI in Ontario for adults with bilateral deafness due to NF2 or severe inner ear abnormalities who are not candidates for cochlear implantation would lead to additional costs of between $130,000 and $260,000 annually over the next 5 years.

We interviewed six people with lived experience of either NF2 or severe inner ear abnormalities, including two people who had received an ABI. These conditions and their symptoms, particularly the hearing loss, can create emotional distress and extraordinary challenges in daily living. Both people who had received an ABI perceived it as a successful means of restoring some hearing ability and improving quality of life, though they also reported ongoing challenges in using the device or with perceived side effects from the surgery.

ABBREVIATIONS

ABI	Auditory brainstem implantation
dB HL	Decibels in hearing level
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
NF2	Neurofibromatosis 2
OCIP	Ontario Cochlear Implant Program
QALY	Quality-adjusted life-year
ROBINS-I	Risk of Bias in Non-randomized Studies—of Interventions

GLOSSARY

Adverse event	An adverse event is any unexpected problem that happens during or as a result of treatment, regardless of the cause or severity.
Budget impact analysis	A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., its affordability). It is based on predictions of how changes in the intervention mix impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).
Closed-set speech perception	A closed-set hearing test is an identification task that requires the recipient to select the correct response from a forced-choice or multiple-choice list.
Cost-effective	A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.
Cost–utility analysis	A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years (QALYs), which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.
Health-related quality of life	Health-related quality of life is a measure of the impact of a health care intervention on a person's health; it assesses the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.
Health state	A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.
Incremental cost	An incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER)	In economic evaluations, the incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a consumer would have to pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.
Ministry of Health perspective	The perspective adopted in economic evaluations determines the types of cost and health benefit to include. Ontario Health (Quality) develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism, presenteeism).
Open-set speech perception	An open-set hearing test requires the recipient to repeat what is said without the aid of a predetermined set of alternative responses. This is a recognition task.
Pure tone audiometry	A hearing test used to measure hearing sensitivity. Pure-tone thresholds indicate the softest sound a person can hear at least 50% of the time. This type of test is used to diagnose the type of hearing loss a person is experiencing and thus to guide its management.
Quality-adjusted life-year (QALY)	The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.
Reference case	The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.
Scenario analysis	A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.
Sensitivity analysis	Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allow these factors to be varied and show the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario
Sound recognition	The ability to hear and correctly identify different types of sound; for example, speech versus environmental sounds.

Time horizon	In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.
Utility	Utilities are values that represent people's preferences for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.
Willingness-to-pay value	A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

APPENDICES

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: June 21, 2018

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2018>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 20, 2018>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2018 Week 25>, Ovid MEDLINE(R) ALL <1946 to June 20, 2018>

Search Strategy:

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1 Auditory Brain Stem Implants/ (451)
2 Auditory Brain Stem Implantation/ (150)
3 ((auditory brainstem or auditory brain stem) adj2 implant*).ti,ab,kf. (826)
4 ((ABI or ABIs) and (deaf* or hearing)).ti,ab,kf. (387)
5 or/1-4 (976)
6 exp Animals/ not Humans/ (15657414)
7 5 not 6 (686)
8 (exp child/ or adolescent/ or exp infant/) not exp adult/ (3791073)
9 7 not 8 (580)
10 Case Reports/ or Comment.pt. or Editorial.pt. or Letter.pt. or Congresses.pt. (4972788)
11 9 not 10 (509)
12 limit 11 to english language [Limit not valid in CDSR; records were retained] (448)
13 12 use medall,coch,cctr,clhta,cleed (221)
14 auditory brain stem implant/ (329)
15 auditory brain stem implantation/ (150)
16 ((auditory brainstem or auditory brain stem) adj2 implant*).tw,kw,dv. (839)
17 ((ABI or ABIs) and (deaf* or hearing)).tw,kw,dv. (408)
18 or/14-17 (995)
19 (exp animal/ or nonhuman/) not exp human/ (10447674)
20 18 not 19 (893)
21 exp juvenile/ not exp adult/ (2033364)
22 20 not 21 (795)
23 Case Report/ or Comment/ or Editorial/ or Letter/ or conference abstract.pt. (9886690)
24 22 not 23 (587)
25 limit 24 to english language [Limit not valid in CDSR; records were retained] (528)
26 25 use emez (272)
27 13 or 26 (493)
28 27 use medall (219)
29 27 use coch (0)
30 27 use cctr (0)
31 27 use clhta (2)

32 27 use cleed (0)
33 27 use emez (272)
34 remove duplicates from 27 (311)

Economic Evidence Search

Search date: June 21, 2018

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2018>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 20, 2018>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2018 Week 25>, Ovid MEDLINE(R) ALL <1946 to June 20, 2018>

Search Strategy:

---

1 Auditory Brain Stem Implants/ (451)
2 Auditory Brain Stem Implantation/ (150)
3 ((auditory brainstem or auditory brain stem) adj2 implant*).ti,ab,kf. (826)
4 ((ABI or ABIs) and (deaf* or hearing)).ti,ab,kf. (387)
5 or/1-4 (976)
6 economics/ (257438)
7 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (812508)
8 economics.fs. (405657)
9 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (807862)
10 exp "costs and cost analysis"/ (558895)
11 (cost or costs or costing or costly).ti. (246300)
12 cost effective*.ti,ab,kf. (291505)
13 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (191415)
14 models, economic/ (11441)
15 markov chains/ or monte carlo method/ (73601)
16 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (37484)
17 (markov or markow or monte carlo).ti,ab,kf. (117356)
18 quality-adjusted life years/ (35700)
19 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (63063)
20 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (102665)
21 or/6-20 (2394614)
22 5 and 21 (10)
23 22 use medall,coch,cctr,clhta (4)
24 5 use cleed (0)
25 23 or 24 (4)
26 (exp child/ or adolescent/ or exp infant/) not exp adult/ (3791073)

27 25 not 26 (4)
28 limit 27 to english language [Limit not valid in CDSR; records were retained] (4)
29 auditory brain stem implant/ (329)
30 auditory brain stem implantation/ (150)
31 ((auditory brainstem or auditory brain stem) adj2 implant*).tw,kw,dv. (839)
32 ((ABI or ABIs) and (deaf* or hearing)).tw,kw,dv. (408)
33 or/29-32 (995)
34 Economics/ (257438)
35 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (131929)
36 Economic Aspect/ or exp Economic Evaluation/ (432488)
37 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (832604)
38 exp "Cost"/ (558895)
39 (cost or costs or costing or costly).ti. (246300)
40 cost effective*.tw,kw. (302565)
41 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw. (199187)
42 Monte Carlo Method/ (59043)
43 (decision adj1 (tree* or analy* or model*)).tw,kw. (41254)
44 (markov or markow or monte carlo).tw,kw. (122339)
45 Quality-Adjusted Life Years/ (35700)
46 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (66857)
47 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (122156)
48 or/34-47 (2033000)
49 33 and 48 (18)
50 exp juvenile/ not exp adult/ (2033364)
51 49 not 50 (16)
52 limit 51 to english language [Limit not valid in CDSR; records were retained] (15)
53 52 use emez (6)
54 28 or 53 (10)
55 54 use medall (4)
56 54 use coch (0)
57 54 use cctr (0)
58 54 use clhta (0)
59 54 use cleed (0)
60 54 use emez (6)
61 remove duplicates from 54 (8)

Grey Literature Search

Performed: May 29–June 21, 2018

Websites searched:
HTA Database Canadian Repository, Alberta Health Technologies Decision Process reviews, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, ClinicalTrials.gov, PROSPERO, EUnetHTA, Tufts Cost-Effectiveness Analysis Registry

Keywords used: auditory brainstem, auditory brain stem, ABI, ABIs

Results (included in PRISMA): 0

Ongoing clinical trials: 5

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias[a] Among Nonrandomized Trials for Auditory Brainstem Implantation (ROBINS-I Tool)

	Pre-intervention		At Intervention		Post-intervention		
Author, Year	Confounding	Study Participant Selection	Classification of Interventions	Deviations From Intended Intervention	Missing Data	Measurement of Outcomes	Selection of Reported Results
Bayazit et al, 2016[33]	Low	Low	Low	Low	Low	Low	Low
Behr et al, 2007[14]	Low	Low	Low	Low	Moderate[b]	Low	Moderate[c]
Colletti et al, 2009[15]	Low	Low	Low	Low	Low	Moderate[d]	Low
Colletti et al, 2010[32]	Low	Low	Low	Low	Low	Low	Low
Fernandes et al, 2017[34]	Low	Low	Low	Low	Low	Moderate[e]	Low
Grayeli et al, 2008[16]	Low	Low	Low	Low	Low	Moderate[f]	Low
Kanowitz et al, 2004[17]	Low	Low	Low	Low	Low	Low	Low
Lenarz et al, 2001[18]	Low	Low	Low	Low	Moderate[b]	Low	Moderate[c]
Lenarz et al, 2002[19]	Low	Low	Low	Low	Low	Moderate[e]	Low
Lundin et al, 2016[20]	Low	Low	Low	Low	Moderate[g]	Moderate[e,h]	Low
Maini et al, 2009[21]	Low	Low	Low	Low	Low	Moderate[i]	Moderate[j]
Malerbi et al, 2018[35]	Low	Low	Low	Low	Low	Low	Low
Matthies et al, 2013[22]	Low	Low	Low	Low	Low	Moderate[k]	Low
McSorley et al, 2015[23]	Low	Low	Low	Low	Moderate[g]	Moderate[e]	Low
Nakatomi et al, 2016[24]	Low	Low	Low	Low	Moderate[b]	Moderate[l]	Low
Nevison et al, 2002[25]	Low	Low	Low	Low	Low	Moderate[k]	Low
Otto et al, 2002[26]	Low	Low	Low	Low	Low	Low	Low
Ramsden et al, 2016[27]	Low	Low	Low	Low	Low	Moderate[k]	Low
Sanna et al, 2012[28]	Low	Low	Low	Low	Low	Low	Low
Shannon et al, 1993[29]	Low	Low	Low	Low	Low	Low	Low
Siegbahn et al, 2014[30]	Low	Low	Low	Low	Low	Moderate[m]	Low
Thong et al, 2016[31]	Low	Low	Low	Low	Low	Moderate[e,l]	Moderate[c]

Abbreviation: ABI, auditory brainstem implantation; NF2, neurofibromatosis 2; ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.
[a]Possible risk of bias levels: low, moderate, serious, critical, and no information.
[b]Missing data were not accounted for.
Notes continued on next page.

Notes for Table A1 continued:
[c]Statistical testing on speech perception over time not reported.
[d]No description on test materials used for speech perception.
[e]Self-reported nature of the questionnaires for tinnitus, subjective benefits of hearing, and quality of life increased the potential for reporting bias.
[f]Potential ceiling effects in word and sentence tests with ABI and lip-reading for patients with NF2 (i.e., a large proportion of patients reached the maximum score of the tests).
[g]Nonresponse rate of survey not accounted for.
[h]ABI questionnaire was not validated; however, existing questionnaires regarding hearing were unsuitable for this patient population as the level of hearing with ABI could not be compared with hearing through a conventional hearing aid or a cochlear implant.
[i]No description on test materials used for the results reported.
[j]The sample size of the study was 10. The authors stated that 8 patients could be included in audiological analyses at 1 to 7 years post-implantation. The results were stratified by ABI models. The exact sample sizes were unclear for the results for each ABI model.
[k]Potential ceiling effects in word tests with ABI and lip-reading.
[l]No description of test materials used for sound recognition.
[m]The Categories of Auditory Performance may not be sensitive enough to evaluate hearing outcomes with ABI.

Table A2: GRADE Evidence Profile for Comparison of Auditory Brainstem Implantation and No Intervention for Neurofibromatosis 2

Number of Studies (Designs)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Sound recognition							
7 (observational)[22,24,26-29,31]	No serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	Other considerations (+2)[b]	⊕⊕⊕⊕ High
Speech perception with ABI only							
14 (observational)[14-17,21,22,24-31]	No serious limitations[a]	Serious limitations (−1)[c]	No serious limitations	No serious limitations	Undetected	Other considerations (+2)[b]	⊕⊕⊕ Moderate
Speech perception with ABI and lip-reading							
11 (observational)[14,16,18,21,22,24-27,29,31]	No serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	Other considerations (+2)[b]	⊕⊕⊕⊕ High
Subjective benefits of hearing							
5 (observational)[19,20,22,23,25]	No serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	Other considerations (+2)[b]	⊕⊕⊕⊕ High
Quality of life							
1 (observational)[20]	No serious limitations[a]	No serious limitations	Serious limitations (−1)[d]	Serious limitations (−1)[e]	Undetected	Other considerations (+2)[b]	⊕⊕ Low
Nonauditory side effects							
14 (observational)[14,17,18,21-23,25-31,35]	No serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Surgical complications							
11 (observational)[14,17,18,21,25-28,30-32]	No serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: ABI, auditory brainstem implantation; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; NF2, neurofibromatosis 2.

[a]Observational studies started at a low GRADE level because of inherent limitations in study design (e.g., lack of randomization, lack of blinding, risk of selection bias, loss to follow-up). No further downgrade of GRADE was made unless there were more substantial limitations in how the study was conducted.

[b]Upgraded (+2) because of large magnitude of effects (from complete deafness to perception of sounds and speech) and because the ability to hear leads to improvement in both objective and subjective outcomes. The underlying trajectory of NF2 has rendered these patients completely deaf from progressive tumour enlargement or after tumour removal surgery. These patients are not candidates for cochlear implantation. ABI is the only treatment option to provide some functional hearing for these patients.

[c]Downgraded (−1) for inconsistency. Speech perception with only ABI varied considerably between studies. Various patient, surgical and device-related factors (e.g., tumour size, local anatomical conditions, duration of auditory deprivation, number of activated electrodes) could affect auditory performance. It was difficult to distinguish whether the varied results were due to the study conduct or patient-related factors.

[d]Downgraded (−1) for indirectness. Results on quality of life combined ABI users and nonusers, which did not allow us to delineate the impact of ABI on quality of life in patients with NF2.

[e]Downgraded (−1) for imprecision due to small sample sizes.

Table A3: GRADE Evidence Profile for Comparison of Auditory Brainstem Implantation and No Intervention for Nontumour Indications

Number of Studies (Designs)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Sound recognition							
2 (observational)[33,35]	No serious limitations[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	Other consideration (+2)[c]	⊕⊕⊕ Moderate
Speech perception with ABI only							
4 (observational) [15,16,33,35]	No serious limitations[a]	Serious limitations (−1)[d]	No serious limitations	No serious limitations	Undetected	Other consideration (+2)[c]	⊕⊕⊕ Moderate
Speech perception with ABI and lip-reading							
1 (observational)[16]	No serious limitations[a]	No serious limitations	No serious limitations	Serious limitations (−2)[b]	Undetected	Other consideration (+2)[c]	⊕⊕ Low
Subjective benefits of hearing							
1 (observational)[34]	No serious limitations[a]	No serious limitations	No serious limitations	Serious limitations (−2)[b]	Undetected	Other consideration (+2)[c]	⊕⊕ Low
Quality of life							
1 (observational)[34]	No serious limitations[a]	No serious limitations	No serious limitations	Serious limitations (−2)[b]	Undetected	Other consideration (+2)[c]	⊕⊕ Low
Nonauditory side effects							
14 (observational)[14,17,18,21-23,25-31,35]	No serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Surgical complications							
2 (observational)[32,35]	No serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: ABI, auditory brainstem implantation; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

[a]Observational studies started with a low GRADE level because of inherent limitations in study design (e.g., lack of randomization, lack of blinding, loss to follow-up). We did not lower the GRADE level further unless there were more substantial study limitations.

[b]Downgraded because of imprecision from small sample sizes (−1 for sound recognition, −2 for speech perception with ABI and lip-reading, −2 for subjective benefits of hearing, −2 for quality of life).

[c]Upgraded (+2) because of large magnitude of effects (from complete deafness to perception of sounds and/or speech) and because any improvement in objective and subjective outcomes would depend on the ability to hear. The underlying trajectory of severe inner ear abnormalities with various etiology rendered these patients completely deaf. These patients are not candidates for cochlear implantation. ABI is the only treatment option to provide some functional hearing for these patients.

[d]Downgraded (−1) because of inconsistency. Speech perception with only ABI varied considerably. It was difficult to distinguish whether the varied results were due to the study conduct or different etiology of underlying condition.

Appendix 3: Additional Results on Quality of Life

Table A4: Quality of Life—Neurofibromatosis 2

Author, Year	Test Measures	Sample Size, n	Results[a]
Lundin et al, 2016[20]	NFTI-QOL questionnaire[b]	11	*Do balance or dizziness problems stop you performing your usual activities?* Not present (9%) Present but causes no difficulty with usual activities (18%) Causes some difficulties with usual activities (55%) Stops usual activities (18%)
		11	*Do hearing problems stop you performing your usual activities?* Not present (0%) Present but causes no difficulty with usual activities (9%) Causes some difficulties with usual activities (64%) Stops usual activities (27%)
		11	*Does facial weakness stop you performing your usual activities?* Not present (9%) Present but causes no difficulty with usual activities (46%) Causes some difficulties with usual activities (36%) Stops usual activities (9%)
		11	*Do problems with your sight stop you performing your usual activities?* Not present (18%) Present but causes no difficulty with usual activities (36%) Causes some difficulties with usual activities (46%) Stops usual activities (0%)
		11	*Do you have any problems in mobility and walking?* Not present (46%) Present but causes no difficulty with usual activities (18%) Causes some difficulties with usual activities (27%) Stops usual activities (9%)
		11	*Has your medical condition affected your role and outlook on life? (e.g., confidence, vulnerability, relationships, caring for family, career, having children)* Not present (9%) Present but causes no difficulty with usual activities (27%) Causes some difficulties with usual activities (27%) Stops usual activities (46%)
		11	*Pain: throughout our lives, most of us have had pain from time to time, such as mild headaches, sprains and toothaches. Have you had pain other than this in the last week?* Not present (64%) Present but causes no difficulty with usual activities (27%) Causes some difficulties with usual activities (9%) Stops usual activities (0%)
		10	*Do you currently suffer from anxiety or depression?* Not present (50%) Present but causes no difficulty with usual activities (30%) Causes some difficulties with usual activities (10%) Stops usual activities (10%)

Abbreviations: NFTI-QOL, Neurofibromatosis 2 Impact on Quality of Life questionnaire.

[a]Results combined both ABI users and nonusers.

[b]The NFTI-QOL has a maximum possible score of 24 with 0 points for “not present,” 1 point for “present but causes no difficulty with usual activities,” 2 points for “causes some difficulties with usual activities,” and 3 points for “stops usual activities.” The higher the total score, the poorer the quality of life.

Appendix 4: Letter of Information

LETTER OF INFORMATION

Health Quality Ontario is conducting a review of **Auditory Brainstem Implantation** for people with brain tumors (neurofibromatosis type 2) of both ears or inner ear conditions that make it difficult for you to receive cochlear implantation. The purpose is to understand whether Auditory Brainstem Implantation surgery should be offered as a treatment by the Ontario government.

An important part of this review involves gathering perspectives of patients and caregivers. People may have had the experience of the Auditory Brain Implantation surgery or could be considering it in the future.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 30 minutes of your time for a phone, videoconference or face-to-face interview
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION INVOLVES

If you agree to share your experiences, you will be asked to have an interview with Health Quality Ontario staff. The interview will last about 30 minutes. It can be held face-to-face, over the telephone or videoconference. With your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about treatment options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

CONFIDENTIALITY

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project completion, the records will be destroyed.

RISKS TO PARTICIPATION

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experience.

IF YOU ARE INTERESTED, PLEASE CONTACT US BEFORE JANUARY 1, 2019:

Appendix 5: Interview Guide

Interview Guide for Auditory Brainstem Implantation (ABI)

Intro
Explain the purpose of Health Quality Ontario,[a] the process of health technology assessment process, and purpose of interview
History of neurofibromatosis (NF2) and hearing loss – first symptoms, background (general only)

Lived Experience
Day-to-day routine with NF2 and hearing loss
What is the impact on quality of life? Has this changed as hearing loss progressed?
Impact on family/caregivers, work?

Interventions
What previous therapies/treatments (e.g., hearing aids) are used and their impact?
How well could you manage your condition with available therapies?
Access to therapies?
Were there any associated costs/barriers?

ABI
Previous information surrounding these devices?
Decision-making for treatment. Was it difficult to weigh potential risks/benefits?
Expectations of the implant
Description of the procedure, side effects?
Results, impact, change in quality of life
After implant, do you need any further treatment? Any maintenance costs? Drawback or limitations?

[a] Health Quality Ontario is now the Quality business unit at Ontario Health.

REFERENCES

(1) Hoa M, Slattery WH 3rd. Neurofibromatosis 2. Otolaryngol Clin North Am. 2012;45(2):315-32, viii.

(2) Neary WJ, Hillier VF, Flute T, Stephens D, Ramsden RT, Evans DG. Use of a closed set questionnaire to measure primary and secondary effects of neurofibromatosis type 2. J Laryngol Otol. 2010;124(7):720-8.

(3) Merker VL, Bergner AL, Vranceanu AM, Muzikansk A, Slatter W 3rd, Plotkin SR. Health-related quality of life of individuals with neurofibromatosis type 2: results from the NF2 natural history study. Otol Neurotol. 2016;37(5):574-9.

(4) Cosetti MK, Golfinos JG, Roland JT Jr. Quality of life (QoL) assessment in patients with neurofibromatosis type 2 (NF2). Otolaryngol Head Neck Surg. 2015;153(4):599-605.

(5) Patel CM, Ferner R, Grunfeld EA. A qualitative study of the impact of living with neurofibromatosis type 2. Psychol Health Med. 2011;16(1):19-28.

(6) Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A. 2010;152A(2):327-32.

(7) Colletti L, Shannon R, Colletti V. Auditory brainstem implants for neurofibromatosis type 2. Curr Opin Otolaryngol Head Neck Surg. 2012;20(5):353-7.

(8) NHS England. NHS standard contract for neurofibromatosis type 2 service (all ages) [Internet]. London (UK): NHS England 2013 [cited 2018 Aug 2]. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/06/b13-neurofib-2.pdf

(9) NHS England. Clinical commissioning policy: auditory brainstem implant with congentital abnormalites of the auditory nerves of cochleae [Internet]. London (UK): NHS England; 2016 [cited 2018 Aug 2]. Available from: https://www.england.nhs.uk/wp-content/uploads/2016/12/clin-comm-pol-16062P.pdf

(10) McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol. 2016;75:40-6.

(11) Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

(12) Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook [Internet]. Hamilton (ON): GRADE Working Group; 2013 [cited 2017 Dec]. Available from http://gdt.guidelinedevelopment.org/app/handbook/handbook.html [Internet].

(13) Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.

(14) Behr R, Muller J, Shehata-Dieler W, Schlake HP, Helms J, Roosen K, et al. The high rate CIS auditory brainstem implant for restoration of hearing in NF-2 patients. Skull Base. 2007;17(2):91-107.

(15) Colletti V, Shannon R, Carner M, Veronese S, Colletti L. Outcomes in nontumor adults fitted with the auditory brainstem implant: 10 years' experience. Otol Neurotol. 2009;30(5):614-8.

(16) Grayeli AB, Kalamarides M, Bouccara D, Ambert-Dahan E, Sterkers O. Auditory brainstem implant in neurofibromatosis type 2 and non-neurofibromatosis type 2 patients. Otol Neurotol. 2008;29(8):1140-6.

(17) Kanowitz SJ, Shapiro WH, Golfinos JG, Cohen NL, Roland JT Jr. Auditory brainstem implantation in patients with neurofibromatosis type 2. Laryngoscope. 2004;114(12):2135-46.

(18) Lenarz T, Moshrefi M, Matthies C, Frohne C, Lesinski-Schiedat A, Illg A, et al. Auditory brainstem implant: part I. Auditory performance and its evolution over time. Otol Neurotol. 2001;22(6):823-33.
(19) Lenarz M, Matthies C, Lesinski-Schiedat A, Frohne C, Rost U, Illg A, et al. Auditory brainstem implant: part II. Subjective assessment of functional outcome. Otol Neurotol. 2002;23(5):694-7.
(20) Lundin K, Stillesjo F, Nyberg G, Rask-Andersen H. Self-reported benefit, sound perception, and quality-of-life in patients with auditory brainstem implants (ABIs). Acta Otolaryngol. 2016;136(1):62-7.
(21) Maini S, Cohen MA, Hollow R, Briggs R. Update on long-term results with auditory brainstem implants in NF2 patients. Cochlear Implants Int. 2009;10 Suppl 1:33-7.
(22) Matthies C, Brill S, Kaga K, Morita A, Kumakawa K, Skarzynski H, et al. Auditory brainstem implantation improves speech recognition in neurofibromatosis type II patients. ORL J Otorhinolaryngol Relat Spec. 2013;75(5):282-95.
(23) McSorley A, Freeman SR, Ramsden RT, Motion J, King AT, Rutherford SA, et al. Subjective outcomes of auditory brainstem implantation. Otol Neurotol. 2015;36(5):873-8.
(24) Nakatomi H, Miyawaki S, Kin T, Saito N. Hearing restoration with auditory brainstem implant. Neurol Med Chir (Tokyo). 2016;56(10):597-604.
(25) Nevison B, Laszig R, Sollmann WP, Lenarz T, Sterkers O, Ramsden R, et al. Results from a European clinical investigation of the Nucleus multichannel auditory brainstem implant. Ear Hear. 2002;23(3):170-83.
(26) Otto SR, Brackmann DE, Hitselberger WE, Shannon RV, Kuchta J. Multichannel auditory brainstem implant: update on performance in 61 patients. J Neurosurg. 2002;96(6):1063-71.
(27) Ramsden RT, Freeman SR, Lloyd SK, King AT, Shi X, Ward CL, et al. Auditory brainstem implantation in neurofibromatosis type 2: experience from the Manchester programme. Otol Neurotol. 2016;37(9):1267-74.
(28) Sanna M, Di Lella F, Guida M, Merkus P. Auditory brainstem implants in NF2 patients: results and review of the literature. Otol Neurotol. 2012;33(2):154-64.
(29) Shannon RV, Fayad J, Moore J, Lo WW, Otto S, Nelson RA, et al. Auditory brainstem implant: II. Postsurgical issues and performance. Otolaryngol Head Neck Surg. 1993;108(6):634-42.
(30) Siegbahn M, Lundin K, Olsson GB, Stillesjo F, Kinnefors A, Rask-Andersen H, et al. Auditory brainstem implants (ABIs)--20 years of clinical experience in Uppsala, Sweden. Acta Otolaryngol. 2014;134(10):1052-61.
(31) Thong JF, Sung JK, Wong TK, Tong MC. Auditory brainstem implantation in Chinese patients with neurofibromatosis type II: the Hong Kong experience. Otol Neurotol. 2016;37(7):956-62.
(32) Colletti V, Shannon RV, Carner M, Veronese S, Colletti L. Complications in auditory brainstem implant surgery in adults and children. Otol Neurotol. 2010;31(4):558-64.
(33) Bayazit Y, Kosaner J, Celenk F, Somdas M, Yilmaz I, Altin G, et al. Auditory brainstem implant in postlingual postmeningitic patients. Laryngoscope. 2016;126(8):1889-92.
(34) Fernandes NF, Goffi-Gomez MV, Magalhaes AT, Tsuji RK, De Brito RV, Bento RF. Satisfaction and quality of life in users of auditory brainstem implant. Codas. 2017;29(2):e20160059.
(35) Malerbi A, Goffi-Gomez MVS, Tsuji RK, Gomes MQT, Brito Neto R, Bento RF. Auditory brainstem implant in postmeningitis totally ossified cochleae. Acta Otolaryngol. 2018;138(8):722-6.

(36) Lloyd SKW, King AT, Rutherford SA, Hammerbeck-Ward CL, Freeman SRM, Mawman DJ, et al. Hearing optimisation in neurofibromatosis type 2: a systematic review. Clin Otolaryngol. 2017;42(6):1329-37.
(37) Lovell G, Refair AE. Speech perception outcomes following auditory brainstem implantation in both tumor and non-tumor patients: a review. Audiol Med. 2012;10(2):55-63.
(38) Hornigold RE, Golding JF, Leschziner G, Obholzer R, Gleeson MJ, Thomas N, et al. The NFTI-QOL: a disease-specific quality of life questionnaire for neurofibromatosis 2. J Neurol Surg B Skull Base. 2012;73(2):104-11.
(39) Bento RF, Neto RVB, Tsuji RK, Gomes MQT, Goffi-Gomez MVS. Auditory brainstem implant: surgical technique and early audiological results in patients with neurofibromatosis type 2. Braz J Otorhinolaryngol. 2008;74(5):647-51.
(40) MED-EL. Surgical guideline: Mi1200 SYNCHRONY ABI, Mi1200 SYNCHRONY PIN ABI [Internet]. Innsbruck (Austria) [cited 2018 Oct 31]. Available from: http://s3.medel.com/documents/AW/AW32149_10_SYNCHRONY%20ABI%20Surgical%20Guideline%20-%20EN%20English.pdf
(41) Ministry of Health and Long-Term Care. Schedule of benefits: physician services under the Health Insurance Act [Internet]. Toronto (ON): Queen's Printer for Ontario; 2015 [cited 2018 Sept 26]. Available from: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20160401.pdf
(42) Combined full-time and part-time collective agreement between [Ontario hospitals] and Ontario Public Service Employees Union [Internet]. Toronto (ON): The Union; 2016 [cited 2018 Sept 26]. Available from: https://www.oha.com/Collective%20Bargaining%20Documents/OPSEU%20Combined%20HPD%20Final%20Collective%20Agreement%20-%20March%2031,%202019.pdf
(43) MED-EL [Internet]. Durham (NC): MED-EL; c2019. Press release, MED-EL announces longest warranty on external equipment in the hearing implant industry; 2012 Jun 29 [cited 2019 Jan 3]; [about 2 screens]. Available from: https://www.medel.com/data/editor/file/press_releases_US/5-Year-Warranty.pdf
(44) Ministry of Health and Long-Term Care. Hearing devices policy and administration manual: Assistive Devices Program. Toronto (ON): The Ministry 2016 Feb.
(45) Peterborough Public Health. Vaccine price list and consult fees [Internet]. Peterborough: Peterborough Public Health; c2018 [cited 2018 Dec 10]. Available from: https://www.peterboroughpublichealth.ca/
(46) Merdad M, Wolter NE, Cushing SL, Gordon KA, Papsin BC. Surgical efficiency in bilateral cochlear implantation: a cost analysis. Cochlear Implants Int. 2014;15(1):43-7.
(47) Canadian Institute for Health Information. Care in Canadian ICUs [Internet]. Ottawa (ON): The Institute; 2016 [cited 2018 Dec 5]. Available from: https://secure.cihi.ca/free_products/ICU_Report_EN.pdf
(48) Barham L. Public and patient involvement at the UK National Institute for Health and Clinical Excellence. The patient. 2011;4(1):1-10.
(49) Messina J, Grainger DL. A pilot study to identify areas for further improvements in patient and public involvement in health technology assessments for medicines. The patient. 2012;5(3):199-211.
(50) Ontario Health Technology Advisory Committee Public Engagement Subcommittee. Public engagement for health technology assessment at Health Quality Ontario—final report from the Ontario Health Technology Advisory Committee Public Engagement Subcommittee [Internet]. Toronto (ON): Queen's Printer for Ontario; 2015 Apr [cited 2018 Apr 30]. Available from:

http://www.hqontario.ca/Portals/0/documents/evidence/special-reports/report-subcommittee-20150407-en.pdf

(51) Kvale S. Interviews: an introduction to qualitative research interviewing. Thousand Oaks (CA): Sage; 1996.

(52) Kuzel AJ. Sampling in qualitative inquiry. In: Miller WL, Crabtree BF, editors. Doing qualitative research. Thousand Oaks (CA): Sage; 1999. p. 33-45.

(53) Morse J. Emerging from the data: cognitive processes of analysis in qualitative research. In: Morse J, editor. Critical issues in qualitative research methods. Thousand Oaks (CA): Sage; 1994. p. 23-41.

(54) Patton MQ. Qualitative research and evaluation methods. 3rd ed. Thousand Oaks (CA): Sage; 2002.

(55) Strauss AL, Corbin JM. Basics of qualitative research: techniques and procedures of developing a grounded theory. 2nd ed. Thousand Oaks (CA): Sage; 1998.

(56) Health Technology Assessment International. Introduction to health technology assessment [Internet]. Edmonton (AB): Health Technology Assessment International; 2015 [cited 2018 Apr 30]. Available from: http://www.htai.org/fileadmin/HTAi_Files/ISG/PatientInvolvement/v2_files/Resource/PCISG-Resource-Intro_to_HTA__KFacey__Jun13.pdf

(57) Strauss AL, Corbin JM. Grounded theory research: procedures, canons, and evaluative criteria. Qual Sociol. 1990;13(1):3-21.

(58) Strauss AL, Corbin JM. Grounded theory methodology: an overview. In: Denzin NK, Lincoln YS, editors. Handbook of qualitative research. Thousand Oaks (CA): Sage; 1994. p. 273-85.

(59) NVivo qualitative data analysis software. QSR International. Doncaster, Victoria (Australia). Available at: https://www.qsrinternational.com/nvivo/home.

About Us

This health technology assessment was produced by the Quality business unit at Ontario Health, the government agency that when fully established will be responsible for ensuring all Ontarians receive high-quality health care where and when they need it.

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