Early Value Assessment: Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates

Produced by Newcastle Technology Assessment Review Group

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Abbreviations

AABR	Automated auditory brainstem response
AIHL	Aminoglycoside-induced hearing loss
AIO	Aminoglycoside-induced ototoxicity
ALSPAC	Avon Longitudinal Study of Parents And Children
AOAE	Automated otoacoustic emission
BNF	British National Formulary
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence Interval
CPIC	Clinical Pharmacogenetics Implementation Consortium
CR	Clear response
CT	Computerised Tomography
dB HL	Decibels hearing level
DG	Diagnostic Guidance
DNA	Deoxyribonucleic Acid
EAG	Evidence Assessment Group
ENT	Ear, Nose and Throat
EVA	Early value assessment
GP	General Practitioner
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HUI2	Health Utilities Index Mark 2
HUI3	Health Utilities Index Mark 3
ICER	Incremental cost-effectiveness ratio
MHRA	Medicines and Healthcare products Regulatory Agency
MIB	Medtech innovation briefing
MRI	Magnetic resonance imaging
mtDNA	Mitochondrial DNA
MTG	Medical Technology Guidance
NCR	No Clear response
NHS	National Health Service
NHSP	Newborn hearing screening programme
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
PALOH	Pharmacogenetics to Avoid Loss of Hearing (*reference to the trial)*
POCT	Point of care test
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
QALY	Quality Adjusted Life Years
QoL	Quality of life
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
ROBINS-I	Risk Of Bias In Non-randomized Studies - of Interventions
SD	Standard Deviation
SLT	Speech and Language Therapy
TTO	Time Trade Off
UK	United Kingdom
UKCISG	UK Cochlear Implant Study Group
VAS	Visual Analogue Scale
VAT	Value-Added Tax
WHO	World Health Organization

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ABSTRACT

Sepsis and bacterial infections are a significant cause of mortality and morbidity in neonates. Neonates with suspected infection or sepsis are commonly treated with gentamicin, an antibiotic of the aminoglycoside family. These antibiotics are associated with a very high risk of damage to the ear (ototoxicity), including profound bilateral deafness, in people with the MT-RNR1 gene m.1555A>G mitochondrial genetic variant. The overall aim of this early value assessment was to summarise and critically appraise existing evidence on the clinical-effectiveness and cost-effectiveness of the Genedrive MT-RNR1 ID Kit for identifying the gene m.1555A>G variant in neonates and in mothers of neonates who need antibiotics or are anticipated to need antibiotics. Following clinical comment in the scoping workshop and specialist assessment sub-group meeting, we also considered the Genedrive MT-RNR1 ID Kit for identifying the m.1555A>G variant in mothers prior to giving birth. For clinical effectiveness, Wwe searched three major databases (Medline® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions; Embase and CINAHL). For cost-effectiveness, in addition to the three mentioned databases, we searched Cochrane Library and RePEc-IDEAS. One study was included in the clinical effectiveness review and no studies were included in cost-effectiveness review. All except one outcome (test failure rate: low risk of bias) were rated as moderate risk of bias. The economic component of this work has identified some key evidence gaps that require addressing before a robust economic evaluation can be conducted. These include the sensitivity of the Genedrive MT-RNR1 ID Kit for identifying the gene m.1555A>G variant in neonates, the magnitude of risk for aminoglycoside induced hearing loss (AIHL) in neonates with m.1555A>G, and the prevalence of them.1555A>G genetic variant. Other potential important gaps include how data regarding maternal inheritance may potentially be used in the clinical pathway This early value assessment (EVA) suggests that the Genedrive MT-RNR1 ID Kit has the potential to identify the m.1555A>G variant and to be cost-effective. Nevertheless, as anticipated, there is insufficient evidence to conduct a full diagnostic assessment of the clinical- and cost-effectiveness of Genedrive MT-RNR1 ID Kit in neonates directly, or their mother. This report includes a comprehensive list of research priorities, both to reduce the uncertainty around this EVA and to provide the additional data needed to inform a full Diagnostic Assessment, including cost effectiveness modelling.

PLAIN ENGLISH SUMMARY

Our immune system usually fights off invading germs, such as bacteria, viruses, fungi, or parasites, in order to prevent infection. Sometimes the immune system stops fighting the "invaders," and begins to turn in on itself. This life-threatening reaction, is known as sepsis. Bacterial infections and sepsis are significant causes of death and illness in newborns. Newborns with suspected bacterial infection or sepsis are normally treated with an aminoglycoside antibiotic called gentamicin (a type of medicine that is meant to kill bacteria). These antibiotics are associated with a very high risk of ototoxicity (damage to the ear, including deafness) amongst people with the m.1555A>G MT-RNR1 gene variant (a specific change to the small section of DNA storing biological information) within their mitochondrial DNA (small circles of DNA located in the mictochondria, the cell's energy producer). The aim of this review was to summarise and critically evaluate existing evidence on how effective (the degree to which a test does more harm than good) and cost effective (how effective a test is in relation to its cost) the Genedrive MT-RNR1 ID Kit is for identifying the m.1555A>G gene variant in newborns, or their mothers. We collected and analysed all relevant research studies, one moderate quality study was included in the clinical effectiveness review and no studies were included in the cost-effectiveness review. The quality of the included study was assessed as moderate for most of the outcomes (things measured to monitor the degree to which the test does more good than harm) reported due to uncertainty regarding the failure rate of the test. This review shows that the Gendrive MT-RNR1 ID Kit has the potential to identify the

m.1555A>G variant and the potential to provide value for money for the NHS. However, as expected, there is not enough evidence to conduct a full assessment of the clinical and cost-effectiveness of Genedrive MT-RNR1 ID Kit in newborns directly, or their mothers.

SCIENTIFIC SUMMARY

Background

Sepsis and bacterial infections are a significant cause of mortality and morbidity in neonates (up to and including 28 days corrected gestational age). Expert opinion suggests the incidence of culture-confirmed neonatal infection is around 1 in 2,000 deliveries. But a larger proportion of babies will go on to receive precautionary antibiotic treatment for suspected infection (e.g., 30-60 in 1,000 for those admitted to neonatal intensive care units; (NICUs)). Treatment for suspected infection or sepsis is commonly conducted using gentamicin, an antibiotic of the aminoglycoside family. These antibiotics are associated with a high risk of ototoxicity in those with a genetic variation of the mitochondrial MT-RNR1 gene, specifically m.1555A>G. The purpose of this assessment was to investigate the usage of the Genedrive MT-RNR1 ID Kit in identifying the m.1555A>G variant in neonates with suspected infection or sepsis. This technology has the potential to identify those at most risk of ototoxicity from aminoglycoside antibiotics and inform treatment decisions within the time frame recommended by NICE guidance.

Aim

The overall aim of this early value assessment was to summarise and critically appraise existing evidence on the clinical-effectiveness and cost-effectiveness of the Genedrive MT-RNR1 ID Kit for identifying the gene m.1555A>G variant in neonates or mothers.

Methods

Rapid review methodology was utilised to identify eligible studies for clinical- and cost-effectiveness. Databases searches were conducted on Medline, Embase, and CINAHL for both aspects of the review; additionally, the cost-effectiveness review searched the Cochrane library and RePEc-IDEAS, from 2010 to November 2022. Search results were screened by two independent reviewers. Only one study met the inclusion criteria for the clinical-effectiveness rapid review, and no studies met the eligibility criteria for the cost-effectiveness rapid review. Data extraction and quality appraisal of the clinical-effectiveness study were completed by one reviewer and checked for accuracy by another. Quality appraisal was conducted per outcome, the QUADAS-2 tool was used to assess diagnostic test accuracy outcomes, and the ROBINS-I tool for all other outcomes. Meta-analyses were not possible as only one study was included in the clinical effectiveness rapid review.

Care pathways with and without the use of the Genedrive MT-RNR1 ID Kit were developed and from these a conceptual economic evaluation model was developed. This was used to identify the information requirements to parameterise the model. Attempts were then made to identify relevant parameter values and evidence gaps where no or little data were identified. Using available information, an early health economic model was developed to provide initial estimates of the incremental cost per quality adjusted life year (QALY) gained for the comparison of the use of Genedrive MT-RNR1 ID Kit with current standard care.

Results

The evidence to inform this EVA was extremely limited, only one study was included in the clinical effectiveness rapid review for which risk of bias was rated as being moderate for most of the outcomes measured.

The included study suggested high diagnostic test accuracy (Sensitivity = 100%, Specificity = 99.2%). Estimates of sensitivity were very uncertain, due to a small number of positive cases (i.e. people with the m.1555A>G variant) but no false negatives were identified. However, there were some false positives (n = 5 of 8), the specificity estimate was very high with sufficient precision.

This was established from 424 successful tests, with a test failure rate of 17.1% (90 patients). The failure rate was reduced to 5.1% in repeated testing of samples post after modifications were made to the assay buffer and the test cartridge was redesigned. Overall, three neonates were identified with the genetic variant. The trial research team were able to genotype the m.1555A>G variant using the Genedrive MT-RNR1 ID Kit in 26 minutes. Time to antibiotics when using the Genedrive MT-RNR1 ID Kit did not differ from normal practice (i.e. not using the test kit). Difference between groups was not statistically significant (mean difference=-0.87 minutes, 95% CI: -5.96 to 4.23 minutes) and the 95% CI was within the predefined boundary for statistical equivalence.

Superseded

We did not identify any studies that reported on the following intermediate, clinical or patient related outcomes: impact of test implementation and use on healthcare resources, , usability of the test, mortality and morbidity. Additionally, no studies assessed the usage of the point of care test in mothers.

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No relevant economic evaluations were identified. From the conceptual economic model key evidence gaps were identified. These include the sensitivity of the Genedrive MT-RNR1 ID Kit for identifying the gene m.1555A>G variant in neonates, the magnitude of risk for aminoglycoside induced hearing loss (AIHL) in neonates and mothers with m.1555A>G, and the prevalence of the gene m.1555A>G variant. Other potential important gaps include how data regarding maternal inheritance may potentially be used in the clinical pathway. The early health economic model focused on some of those parameters, where on consideration of the available data, the estimates of cost-effectiveness would be most sensitive to changes. The results of this model showed that the use of the Genedrive MT-RNR1 ID Kit for identification of the m.1555A>G genetic variant could potentially be cost-effective. In a deterministic sensitivity analysis, the results were shown to be most sensitive to changes in the time horizon, the sensitivity of the Genedrive MT-RNR1 ID Kit system, the proportion of neonates with m.1555A>G variant suffering from AIHL after being exposed to aminoglycosides and the prevalence of the m.1555A>G variant in the UK population.

Conclusions

There is limited evidence for the assessment of the Genedrive MT-RNR1 ID Kit for identification of the m.1555A>G genetic variant. However, there is evidence to suggest the usage of the Kit did not substantially impact on time to antibiotics, but this work was conducted in two large NICUs and may not be generalisable to smaller NICUs or other hospitals. While there were modifications made to the Kit to reduce failure rate, when used in the clinical setting this was not completely eradicated. Therefore, the usage of the Genedrive MT-RNR1 Kit should be investigated further in varying settings. There were no existing economic evaluations that addressed this topic. The total cost per test to the NHS was estimated to be £130, however there is uncertainty surrounding this estimate given this cost is likely to vary by size and type of site. The results of the early economic evaluation model suggests that the use of the Genedrive MT-RNR1 ID Kit for identification of the m.1555A>G genetic variant could

potentially be cost-effective. Once evidence regarding the reported evidence gaps have been identified, a full diagnostic assessment of the cost-effectiveness should be undertaken to establish the cost-effectiveness of the Genedrive MT-RNR1 ID Kit.

Suggested priorities for further research

This report identifies two key priorities for research required to reduce the uncertainty around this EVA and to provide the additional data needed to inform a full Diagnostic Assessment, including cost effectiveness modelling.

The risk and severity of AIHL in neonates with the m.1555A>G variant was identified as key uncertainties in the economic model. Limitations of the current literature, primarily based on case-control studies in hearing impaired populations with the m.1555A>G variant are provided in more detail below. Future studies, perhaps including existing cohorts in the UK, are required to identify sufficient numbers of people with the m.1555A>G variant who have been exposed to aminoglycosides in a sample that includes participants with and participants without hearing impairment.

A second priority for research is further validation of the Genedrive MT-RNR1 ID Kit in both neonates and mothers of neonates who need or may need aminoglycoside treatment. Uncertainties regarding the sensitivity of the test was an important uncertainty in the economic model. Further studies including more people with the m.1555A>G variant will increase the precision of the estimated sensitivity of the test. In addition, only the PALOH study has investigated the validity of the Genedrive MT-RNR1 ID Kit. This study was conducted in two large NICUs, further research is needed to assess if the findings of the PALOH study generalise to smaller NICUs and other relevant hospital settings. In addition, our focus group with parents and review of parents comments on internet forums identified that further work may be required to obtain informed consent.

A final area for further research is to provide updated and more comprehensive estimates of health state utility values. Data that are currently available are restricted in terms of health states considered or use health-related quality of life (HRQoL) tools whose relevance to the UK decision makers may be limited.

1 Background and definition of decision problem

1.1 Background to decision problem

Infection can develop into sepsis, which is the body's potentially life-threatening response to an infection. Sepsis and bacterial infections are significant causes of mortality and morbidity in neonates (up to and including 28 days corrected gestational age). Expert opinion suggests the incidence of culture-confirmed neonatal infection is around 1 in 2,000 deliveries. But a larger proportion of babies will go on to receive precautionary antibiotic treatment for suspected infection. For example, approximately 30 to 60 of every 1,000 blood culture samples taken in Neonatal Intensive Care Units (NICUs) 2020-2022 were positive.[1]

1.1.1 Prevalence of m.1555A>G variant and risk of aminoglycoside-induced hearing loss (AIHL)

Superseded

Neonates with suspected infection are commonly treated with gentamicin, an antibiotic of the aminoglycoside family. These antibiotics are associated with a very high risk of damage to the ear (ototoxicity), including profound bilateral deafness, in people with the MT-RNR1 gene m.1555A>G mitochondrial variant.[2, 3]

– see

Cohort studies in various countries suggest the variant is rare. For example in the UK, Rahman and colleagues have found similar prevalence rates of m. 1555A>G in two representative samples of the UK Population: the Avon Longitudinal Study of Parents And Children (ALSPAC), 0.19% (95% CI 0.10 to 0.28, 18/9371 participants);[4] and the 1958 Birth Cohort study, 0.26% (95% CI 0.14% to 0.38%, 19/7350 participants).[5]

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Given these low prevalence rates, it is unsurprising AIHL has been investigated primarily in case-control studies, in families who have experienced hearing impairment due to maternal inheritance of the m.1555A>G variant. These studies have found all people exposed to aminoglycosides experienced hearing loss.[2, 3] However, these study designs are likely to overestimate the risk of aminoglycoside exposure. Cohort studies of hearing loss in people with the m.1555A>G genetic variant in broader populations (e.g. preterm infants, neonates in NICUs not selected on the basis of existing hearing impairment) have suggested greater uncertainty on the risk of AIHL.

A German study of preterm infants found only three of ten infants with the m.1555A>G variant, and exposed to aminoglycosides, failed the newborn hearing screening test.[6] Two American studies conducted in NICUs also suggest not all infants with the variant, and exposed to aminoglycosides, experienced hearing loss. Ealy et al 2011 identified two infants with the m.1555A>G genetic variant who received aminoglycosides. Both passed their newborn hearing screening test. Johnson et al 2010 identified three infants with the m.1555A>G genetic variant, all were exposed to aminoglycosides. Only one of these infants failed their newborn hearing screening test.

However, these studies also have multiple limitations. For example, later hearing loss due to neonatal exposure to aminoglycosides cannot be ruled out in those infants who passed newborn hearing screening tests. In addition, these studies are based on very small samples of people with the m.1555A>G variant. Therefore, there is substantial uncertainty regarding how many neonates with the m.1555A>G variant and exposed to aminoglycosides are likely to experience hearing loss.

1.1.2 m.1555A>G variant and nonsyndromic hearing loss (without exposure to aminoglycosides)

The prevalence of nonsyndromic hearing loss in people with the m.1555A>G variant is a further uncertainty.

Case control studies in people with the m.1555A>G genetic variant experiencing hearing impairment, suggest AIHL may not explain all hearing impairment in these populations. For example, one Spanish study found that 65% (45/69) of families who carried the variant experienced hearing impairment despite no exposure to aminoglycosides.[2] In another case control study of 70 Spanish families, Estivill et al[3] estimated that 39.9% of carriers of the variant, without exposure to aminoglycosides, still experienced hearing loss. However, they found a much lower median age for hearing loss (5 years) in those treated with aminoglycosides compared to those not treated with aminoglycosides (20 years).

As above, case-control studies may overestimate the risk of nonsyndromc hearing loss. For example, no evidence of hearing loss was found in people with the m.1555A>G variant in two UK population cohort studies conducted by Rahman and colleagues.[4,5] However, no data on aminoglycoside use were available and the sample size of people with the variant was small in both studies. The Australian Blue Mountains Hearing Study had contrasting findings. Six participants (total sample size = 2,856 participants) identified with the m.1555A>G variant all experienced hearing loss, yet none reported aminoglycoside use. After statistical adjustment, three of six carriers of the m.1555A>G variant were found to have mean auditory thresholds higher than the general population.

1.1.3 Maternal inheritance of m.1555A>G variant

The m.1555A>G variant, since it is a variant of mitochondrial DNA (mtDNA), is inherited maternally. Mitochondrial DNA variants are commonly heteroplasmic (when mtDNA varies widely within the same cell and mitochondrion). Therefore, most children have similar but not identical mtDNA to their mothers and other maternal relatives. However, some mitochondrial variants are homoplasmic (when all or most copies are identical throughout mtDNA), resulting in greater penetrance of the variant.

Most studies of this variant have found people are homoplasmic for the G allele (for example, Matsunaga et al).[7] However, people with a heteroplasmic variant have been identified in several studies including in Spanish families with m.1555A>G and hearing impairment,[8] and a large genetic screening study (24,349 neonates) in a Chinese hospital.[9] Del Castillo et al found in six families there were 19 people with heteroplasmy for the variant and 12 people with the variant in homoplasmy.[8] The proportion of variant copies differed widely in the heteroplasmic participants (3.75% - 96.60%). Although Del Castillo et al found correlations between variant load and hearing thresholds, the small sample size makes these data difficult to interpret. Luo et al found that most neonates (39/46 people)with m.1555A>G were homoplasmic and 7/46 people heteroplasmic.[8]

1.2 Description of current practice

MT-RNR1 testing is more commonly conducted retrospectively, although prospective testing is currently used for people who have a predisposition to gram-negative infections. Current genetic testing varies between different laboratories but may include techniques such as restriction enzyme assay and sequence analysis. Laboratory testing is estimated to take 2-6 weeks. Such testing is unable to provide results within the time frame required to impact treatment for infection or sepsis, as antibiotics are recommended within 1 hour of decision to treat. The company states that the Genedrive MT-RNR1 ID Kit has a run time of 26 minutes. Therefore, this technology has the potential to identify those at most risk of ototoxicity from aminoglycoside antibiotics and inform treatment decisions within the time frame recommended by NICE guidance.

Superseded
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1.3 Description of interventions

This assessment evaluated whether the Genedrive MT-RNR1 ID Kit can be used to assess the presence of the m.1555A>G variant in neonates with suspected infection or sepsis or in mothers prior to giving birth. This technology aims to identify those with the m.1555A>G gene variant. The test requires a buccal swab sample. The test is reported to take 26 minutes to complete, fitting in the time frame of antibiotic prescribing within 1 hour of identification of possible infection or sepsis. There are no other tests of a similar nature that can accomplish this. The Genedrive MT-RNR1 ID Kit would therefore be the first of its kind to be used as a point of care test in practice, with the possibility of informing prescribing decisions.

1.4 Population and relevant subgroups

The population under consideration was neonates with suspected infection or sepsis who need antibiotics (that is, a decision to start antibiotics has already been made) or who were anticipated to need antibiotics (that is, a decision to start antibiotics has not already been made). Also, mothers prior to giving birth.

Where data permitted, the following subgroups were to be considered:

- Neonates who need antibiotic treatment (that is, a decision to start antibiotics has already been made)
- Neonates who are anticipated to need antibiotics (that is, a decision to start antibiotics has not already been made)
- Babies of different ethnicities
- Babies with early-onset neonatal infection
- Babies with late-onset neonatal infection

However, there were insufficient data to consider any of these subgroups.

1.5 Place of intervention in current pathway: treatment for neonatal infections and sepsis

NICE guidance (NG195) is available on the antibiotic treatment of suspected infections and sepsis for neonates.[10] Investigations prior to starting antibiotics include a blood culture to test for bacteria in the blood, measurement of baseline C-reactive protein concentration and, if safe, lumbar puncture when there is a strong clinical suspicion of early onset neonatal infection and clinical symptoms or signs suggesting meningitis. If an infection or sepsis is suspected, antibiotics must be given within 1 hour of the decision to treat with antibiotics.

For the treatment of early onset infection, intravenous benzylpenicillin with gentamicin is recommended as the first-choice antibiotic regimen. The starting dose of gentamicin should be 5mg/kg every 36 hours administered in a single dose. If a second dose of gentamicin is given, this should be 36 hours after the first dose, however, a shorter interval can be used if clinical judgement suggests this is needed. NICE guidance also recommends, in those receiving antibiotics because of risk factors for early-onset infection or clinical indicators of possible infection, to consider stopping antibiotics at 36 hours.

For babies with late onset infection who are already in a neonatal unit, a combination of narrow-spectrum antibiotics, such as intravenous flucloxacillin plus gentamicin, is recommended as first-line treatment. Local antibiotic susceptibility and resistance data should be taken into account when deciding

which antibiotics to use. NICE guidance recommends considering stopping antibiotics at 48 hours for those with suspected late onset infection.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Aminoglycosides and MT-RNR1 recommends that aminoglycoside antibiotics should be avoided in individuals with the MT-RNR1 variant unless the high risk of permanent hearing loss is outweighed by the severity of infection and lack of safe or effective alternative therapies.[11]

Alternative antibiotic therapies may be used instead of aminoglycosides in cases of neonatal infection. However, clinical experts have advised that there are strong clinical concerns regarding antibiotic resistance to these. Alternative antibiotics include:

Cefotaxime a third-generation cephalosporin is effective against gram-negative bacteria but is less effective against gram-positive bacteria such as Staphylococcus aureus.

Meropenem is a type of carbapenem. It is not licensed for children under 3 months of age, but its efficacy, safety and tolerability have been studied in this age group.

Imipenem with cilastatin which may be used to treat aerobic and anaerobic Gram-positive and Gram-negative infections in neonates.

The Genedrive MT-RNR1 Kit could be used before antibiotic treatment to confirm the existence of the m.1555A>G variant. During the scoping workshop, and assessment subgroup meeting, clinical experts raised the possibility that Genedrive MT-RNR1 Kit could also be used to test mothers of neonates at risk of sepsis providing information on the likelihood of neonates inheriting the m.1555A>G variant. This could enable informed decisions regarding antibiotic prescription, specifically whether to prescribe an alternative to aminoglycosides.

1.6 Objectives

The overall aim of this early value assessment was to summarise and critically appraise existing evidence on the clinical-effectiveness and cost-effectiveness of the Genedrive MT-RNR1 ID Kit for identifying the gene m.1555A>G variant in neonates.

The following objectives were proposed:

Clinical effectiveness:

- To undertake a rapid review and, if feasible, a meta-analysis of the usability and accuracy of the Genedrive MT-RNR1 ID Kit
- To identify evidence gaps to support further evidence generation

Cost-effectiveness:

- To conduct a rapid review of existing economic evaluations studies of the use of Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates
- To estimate the costs of Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates
- To develop an early economic model to identify key drivers, and identify evidence gaps, of the cost-effectiveness of Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates

2. Methods for synthesising evidence of clinical effectiveness

A rapid review of the available evidence was conducted based on Cochrane rapid review guidance.[12]

2.1 Search Strategy

An experienced information specialist designed the search in Medline in collaboration with the project team, and a second information specialist reviewed them. The search used the following concepts:

- Point of care testing
- Gene of interest
- Antibiotic treatment
- Hearing loss

We searched the following bibliographic databases on the 13th October 2022:

- Medline® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to October 12, 2022 via OVID
- Embase (1974 to 2022 October 12) via OVID
- CINAHL (1982 to October 2022) via EBSCO

We designed the search using database thesaurus headings and keywords on MEDLINE and translated the strategy as appropriate to other databases. An example of the full search strategy can be found in Appendix A.

We also searched the following resources:

Trial registries:

- Clinicaltrials.gov
- EudraCT (European Union Drug Regulating Authorities Clinical Trials Database)
- WHO ICTRP (World Health Organization International Clinical Trials Registry Platform
- ISRCTN (International Clinical Trials Registry Platform) registry

We restricted the search to 2010 onwards. All search results were downloaded to Endnote X9.0[13] and de-duplicated.

2.2 Eligibility criteria

Population

Any babies being considered for treatment with aminoglycosides. Possible subgroups of these patients including those who present with early- (≤72 hours post birth) or late-onset (≥72 hours post birth) neonatal infection; neonates who need antibiotic treatment (that is, a decision to start antibiotics has already been made); neonates who are anticipated to need antibiotics (that is, a decision to start antibiotics has not already been made); neonates of different ethnicities. Additionally, we planned on including mothers tested for the variant pre-birth of the neonate. However, none of the subgroups were possible due to the lack of data.

Intervention

Genedrive MT-RNR1 ID Kit used to determine a neonate's MT-RNR1 m.1555A>G status, when used to test:

- the neonate directly, or
- their mother (pre-birth of the neonate)

Comparator

No testing done to determine a neonate's MT-RNR1 m.1555 variant status prior to them receiving aminoglycosides.

Outcomes

The outcomes of interest were divided into intermediate measures of the usage of the equipment and its effects on antibiotic treatment plans, clinical outcomes, patient reported outcomes, and patient experience (for further details see Table 1).

Timing

Antibiotic treatment for neonates is recommended within one hour of the decision to treat. Therefore, the test is time sensitive.

Reference standard (for test accuracy data)

Laboratory based confirmatory genetic testing. Approaches may differ across genetic laboratory testing centres including techniques such as restriction enzyme assay, and sequence analysis (such as Sanger sequencing).

Study Design(s)

We considered all study designs that provide relevant outcome data as listed inTable 1

Setting(s)

Secondary care (hospital, neonatal unit)

Table 1 Outcomes eligible for inclusion

Outcome Type	Outcome(s) Assessed
Intermediate	Number or proportion of neonates successfully tested Number or proportion of mothers successfully tested (evidence not available) Test failure rate Test accuracy Impact of test result on decisions about care (for example, antibiotic use) Impact of test implementation and use on healthcare resources (for example, time taken to do and interpret test) Time to obtaining a sample for testing Time to results Time to antibiotic treatment Number of neonates identified with m.1555A>G Usability of the test (evidence not available)
Clinical	Morbidity (such as hearing loss) (evidence not available) Mortality (evidence not available)
Patient-reported	Health-related quality of life (evidence not available) Patient experience (evidence not available)

2.3. Study Selection

The deduplicated citations in Endnote were exported to Rayyan, an online tool used to speed up the review process, for title and abstract screening.[14] We planned to screen twenty percent of citaions in duplicate, by two reviewers independently, with conflict resolution before moving on to a single screener approach. However, owing to the small number of records, all titles and abstracts were screened by two reviewers independently. Full text copies of studies included at title and abstract screening stage were obtained and eligibility further assessed by two independent reviewers. Disagreements, at either stage, were resolved through discussion.

2.4. Data extraction

A data extraction form was designed, piloted, and finalised to facilitate standardised data extraction. Basic study information (e.g., author, year), study design, patient characteristics, recruitment method, analysis information, results, and interpretation were extracted. One reviewer extracted the data and a second reviewer checked extracted data for accuracy. Any disagreements were resolved through discussion.

2.5. Quality assessment

Consistent with Cochrane Rapid Review guidance, we conducted quality assessment only on key outcomes: test accuracy, test failure rate, and impact of test result on decisions about care.

The risk of bias for diagnostic accuracy outcomes were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[15]

For all other outcomes reported in non-randomised studies, risk of bias was assessed using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool.[16]

Risk of bias assessment was completed by one reviewer and independently checked by a second reviewer. Any disagreements were resolved through discussion and, where necessary, consultation with a third reviewer.

2.6. Method of analysis/synthesis

Where possible, we planned to present results in structured tables and pool data using appropriate meta-analytic techniques. However, due to a lack of evidence, all the outcomes were summarised narratively.

3. Clinical effectiveness review results

3.1 Results of the search

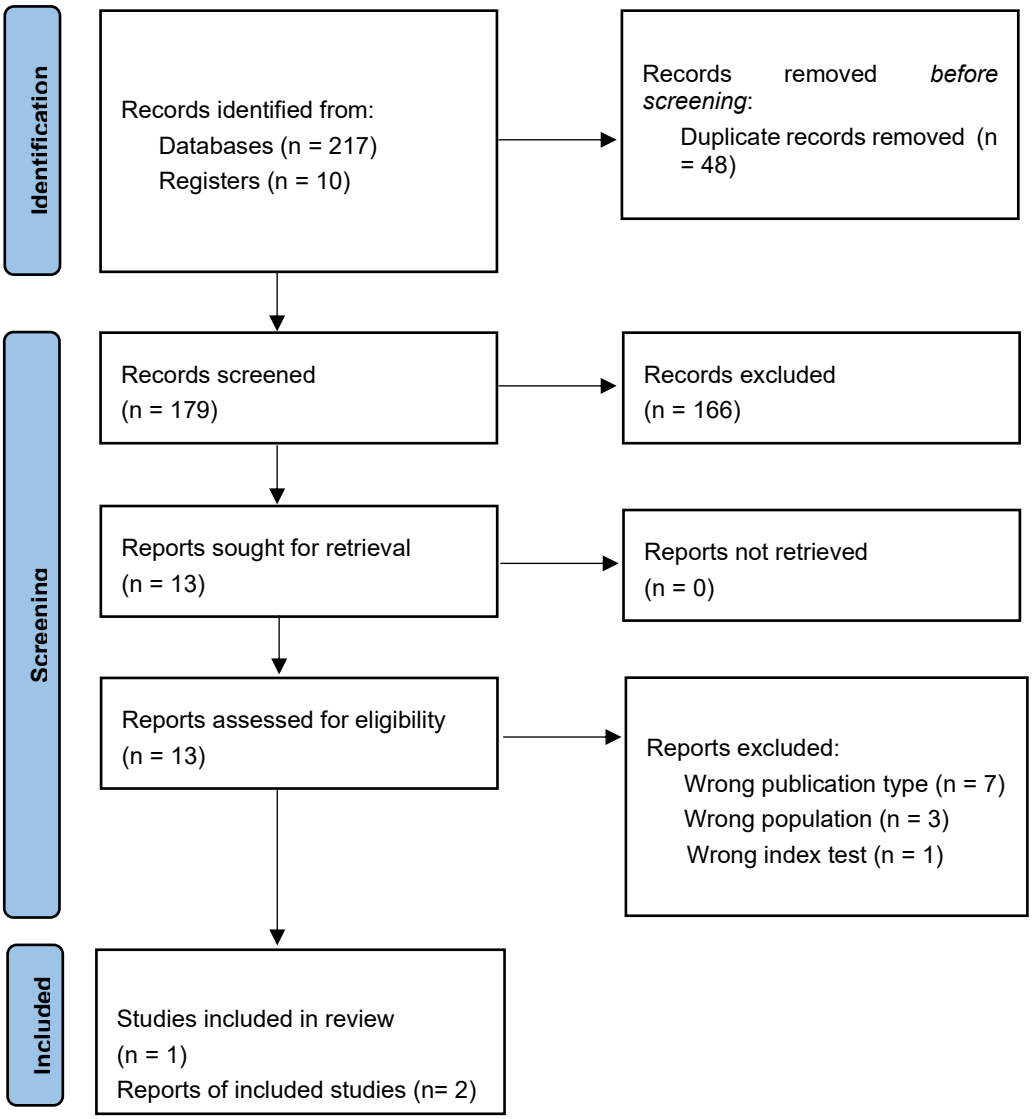


Figure 1: PRISMA flow chart clinical effectiveness review

Overall, database searching retrieved 179 records (after de-duplication) for title and abstract screening. Of these, 13 were sought for full text assessment. Two records were included, one of which was a linked conference abstract (McDermott 2022a). Meaning one study, with two associated records, was included in the review (McDermott 2022a, McDermott 2022b).[17, 18] The data were only extracted from McDermott 2022b[18] record as it provided more information (see Supplementary material 1), and in order not to double-count study participants.

Studies were excluded for the following reasons: wrong publication type (n = 7), wrong population (n = 3), and wrong index test (n = 1). A list of excluded records is available in Appendix C. See Figure 1 for flow of the studies through the selection process.

3.2 Overview of the included study

A single study met the eligibility criteria.[17, 18] The study assessed neonates who were admitted to two NICUs between January and November 2020. The Genedrive MT-RNR1 ID Kit was utilised as the index text, while Sanger sequencing was the reference standard. The study recruited 749 neonates, with 526 needing treatment via antibiotics. Due to failed tests or not testing eligible patients, 424 were genotyped and antibiotics were prescribed; 416 did not have the M.1555G variant and 3 were confirmed to possess the variant.

Data on ethnicity and gender were not provided. Participants' median (range) age was 2.5 (0-198) days at the time of recruitment. Mean (standard deviation) gestational age at time of delivery was 37 (4) weeks.

3.3 Study quality

Study quality for the included study was evaluated per outcome. To accomplish this, we utilised the QUADAS-2[15] for diagnostic test accuracy. For other clinical outcomes the ROBINS-I was complete.[16]

3.3.1 Diagnostic test accuracy

For patient selection the study by McDermott 2022b was rated as low risk of bias. This was based on the assumption that consecutive sampling was used, although it is not explicitly stated. Additionally, while a case-control design was used for the preclinical trial, a prospective study design was used for the implementation, from which the diagnostic accuracy results are presented.

The index test was also rated as low risk of bias, the question regarding thresholds was not considered for this assessment as it is a genetic variant that is either present or not. The reporting of the conduct and interpretation of the test was reported in adequate detail. Details regarding the reference standard are unclear, with no information reported on whether those interpreting the test had knowledge of the index test result. Therefore, the reference standard is at unclear risk of bias. The final domain of flow and timing was rated as high risk of bias. This was due to the reported variation in numbers who underwent the test, compared with those not included in the analysis.

3.3.2 Other clinical outcomes

All outcomes except one (test failure rate, which was rated as low risk of bias) were rated as moderate risk of bias. This is because failure rate, which was 17.1%, was not included in the analyses of the outcomes illustrated in Figure 2. Consequently, not including failure rate could affect the outcome results. All of the other risk of bias domains seemed to be reported adequately. See Figure 2 for risk of bias visualisation using ROBINS-I tool.[16]

Figure 2: ROBINS-I tool visualisation by outcomes

3.4 Intermediate outcome results

3.4.1 Diagnostic test accuracy

In the preclinical trial buccal samples were collected and genotyped from 159 participants, with 304 samples. The controls were split into two groups, firstly, people who had confirmation that they did not carry the m.1555A>G genetic variant (assessed via normal clinical laboratory processes; n = 74). Secondly, children on the NICU were recruited (n = 55, 110 individual specimens) to ensure there are no factors specific to neonatal swab sampling that would impair the assay. The cases were individuals who previously had confirmation for carrying the m.1555A>G genetic variant (n = 32, 62 individual specimens). The Genedrive MT-RNR1 ID Kit was validated for both adults and neonatal populations in this case-control study. The sensitivity was reported as 100% (95% CI: 93.9-100) and specificity reported as 100% (95% CI: 98.5-100). This part of the study was not assessed in the quality appraisal above.

In the prospective study, 424 of the 526 (80.6%) neonates who received antibiotic treatment were included in the analysis. Three neonates were identified to have the m.1555A>G variant and confirmed by Sanger sequencing. There were five false positives and no false negatives. The assay produced a sensitivity of 100% (95% CI: 29.2-100), a specificity of 99.2% (95% CI: 98-99.7), and an accuracy of 99.2% (95% CI: 98-99.7). Throughout the trial, the MT-RNR1 assay was updated to improve efficiency, this process led to the identification of an issue with the buffer and cartridge, which was linked to the false positive rates. The issue was resolved via an updated buffer and cartridge design.

3.4.2 Number successfully tested

Only neonates were assessed in this included study. With 424 successful tests of 526 admissions. Of the 526 admissions, there were 12 who did not have an index test (no further information provided regarding the reasons). The remaining tests were failed (unsuccessful genotyping), see section 4.4.3.

No mothers were tested.

3.4.3 Test failure rate

Of the 526 admissions that had antibiotics, 90 (17.1%) failed tests were reported. For the whole cohort (n = 749) the failure rate was 128 (17.1%). The failure rate was determined to be caused by low signal intensity during the melting phase, which was resolved post recruitment period via modifications to the assay buffer and a redesigned cartridge. Repeated testing of samples where genotyping previously failed lead to a reduced failure rate of 5.7% in a clinical setting and 0% when performed in the laboratory.[18]

3.4.4 Impact of test result on decisions about care

The study reports (McDermott 2022b, p.489) that "in all cases where a m.1555A>G genotype was identified, aminoglycoside antibiotics were avoided and alternative cephalosporin-based regimens were used".[18]

3.4.5 Impact of test implementation and use on healthcare resources

The MT-RNR1 point of care test analysis is automated without any user interpretation, providing the user with a “detected” or “not detected” actionable result in 26 minutes of initiating the analysis. The authors suggest an approximate 30 minutes from collection to an actionable result.[18]

No further data regarding the impact of the test implementation and use on healthcare resources is reported.

3.4.6 Time to obtaining a sample for testing

The median time to swab throughout the study was 6 minutes (inter quartile range = 3 to 16 minutes).

3.4.7 Time to results

The MT-RNR1 point of care test was able to genotype the m.1555A>G variant in 26 minutes.

3.4.8 Time to antibiotic treatment

Study authors report that prior to implementation, the mean time to antibiotic therapy was 55.87 (SD=22.56) minutes based on 95 consecutive acute admissions over 1 month. During the study, the corresponding mean time to antibiotic therapy was 55.18 (SD=23.82) minutes. The difference was not statistically significant, before and after implementation of the MT-RNR1 assay, in mean time to antibiotic therapy was −0.87 minutes (95% CI,−5.96 to 4.23 minutes). The 95% CI was within the prespecified boundaries of statistical equivalence.

3.4.9 Number of neonates identified with m.1555A>G

There were three neonates identified with the variant, five false-positives and no false-negatives.

3.4.10 Usability of the test

The study did not report on this outcome.

3.5 Clinical outcome results

3.5.1 Mortality

The study did not report on this outcome.

3.5.2 Morbidity

The study did not report on this outcome.

3.6 Patient-reported outcome results

3.6.1 Health related quality of life

The study did not report on this outcome.

3.6.2 Patient experience

The study did not report on this outcome.

4. Methods for synthesising evidence of cost-effectiveness

4.1 Decision problem

The economic evaluation assessed the cost-effectiveness of Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates compared to current clinical standard (no testing). The decision problem for the economic evaluation is summarised in Table 2.

Table 2 Decision problem addressed by the economic evaluation

Item	Description
Populations	Neonates who need antibiotic treatment or who are anticipated to need antibiotic treatment, and who are being considered for treatment with aminoglycosides
Intervention	Genedrive MT-RNR1 ID Kit used to test for single nucleotide polymorphism m.1555A>G variant status, when used to test the neonate directly, or their mother (pre-birth of the neonate)
Comparators	No point of care testing for single nucleotide polymorphism m.1555A>G prior to them receiving aminoglycosides
Perspective	NHS England and personal social services
Time horizon	Lifetime
Outcomes	Cost per Genedrive MT-RNR1 ID Kit Incremental cost per hearing loss case prevented Incremental cost per QALY gained
Abbreviations: NHS = National Health Service; QALY = Quality Adjusted Life Year	

The decision problem consists of neonates in need of antibiotic treatment (both early-onset and late-onset infection) and who are being considered for treatment with aminoglycosides. The economic assessment was undertaken from the perspective of the NHS and Personal Social Services. The main economic questions to be addressed were:

1. What existing, published cost-effectiveness studies are available about Genedrive MT-RNR1 ID Kit, for detecting single nucleotide polymorphism m.1555A>G in neonates?

2. What are the costs, from a UK NHS and Personal Social Services perspective, of Genedrive MT-RNR1 ID Kit, for detecting single nucleotide polymorphism m.1555A>G in neonates?

3. What are the key drivers of the cost and effectiveness of Genedrive MT-RNR1 ID Kit roll-out for detecting single nucleotide polymorphism m.1555A>G in neonates.

4.2 Rapid review of cost-effectiveness studies

We utilised the search from the clinical effectiveness review and combined it with an economics filter (please see Appendix B for a list of economic filters used). We searched the following bibliographic databases on the 3rd November 2022:

- Medline ® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to November 02, 2022 via OVID
- Embase (1974 to 2022 November 02) via OVID
- CINAHL (1982 to November 2022) via EBSCO
- Cochrane Library (via Wiley)

We also searched the following resources:

- RePEc-IDEAS (https://ideas.repec.org/)

In both cases, we restricted the search to 2010 onwards. All search results were downloaded to Endnote X9.0[7] and de-duplicated.

The above sources were also searched using the clinical effectiveness search with Health-Related Quality of Life and Hearing Loss filter terms in a targeted search to inform the utility values to be used in the early economic model (please see Appendix B for a list of HRQoL and hearing loss filter terms). No restrictions were made in relation to year of publication. Once more, all search results were downloaded to Endnote X9.0[7] and de-duplicated.

4.3 Development of an early health economic model

In order to identify the key drivers of cost and effectiveness of Genedrive MT-RNR1 ID Kit roll-out for detecting single nucleotide polymorphism m.1555A>G in neonates, the EAG developed an economic model. This economic model reflected the pathways of care that individuals follow under standard practice in the UK NHS and how the use of the Genedrive MT-RNR1 ID Kit might change those pathways of care. The purpose of the model was threefold. First, to outline the structure and parameter requirements for a model. Second to use that model to help define the utilities, costs and probabilities needed to populate that model. Third, to use the available data, accepting that there would be insufficient information to complete a full economic evaluation, to conduct an early economic evaluation modelling exercise. The purpose of this model was to provide an early indication as to whether the use Genedrive MT-RNR1 ID Kit could potentially be cost-effective and to identify key drivers of cost-effectiveness.

In line with the decision problem set out in Table 2, outcomes included the lifetime impact on costs for the NHS and personal social services (PSS) of aminoglycoside-induced hearing-loss in neonates, impact on number of cases of aminoglycoside-induced hearing-loss avoided and the lifetime impact on quality adjusted life years (QALYs) of aminoglycoside-induced hearing-loss in neonates.

The full model incorporated the risk of ototoxicity/hearing loss for people with and without the m.1555A>G variant who have (1) aminoglycoside and (2) non-aminoglycoside alternatives; the likely prevalence of MT-RNR1 gene m.1555A>G variant in neonates (and how this varies across different groups); and diagnostic failure as well as diagnostic accuracy. The capacity to explore the time to antibiotic delivery using the Genedrive MT-RNR1 ID Kit was incorporated in the full model. Within the early economic model, however, it was assumed that all neonates will receive antibiotics in one hour, irrespective of a successful or failed test. For those with successful test results, it was assumed that neonates identified with the m.1555A>G variant would receive non-aminoglycoside alternatives, and those neonates identified without the m.1555A>G variant would receive aminoglycoside. If the 1st test (and 2nd test) failed, it was assumed (after consulting with clinical experts) that the neonates could receive non-aminoglycoside alternatives in order to “play it safe”. However, as described in section 5, the early economic evaluation model was much simplified due to the limited data available to explore some issues including some of the ones noted in this paragraph e.g., how prevalence of MT-RNR1 gene m.1555A>G variant varies across groups.

Cost data relating to the Genedrive system (Genedrive MT-RNR1 ID Kit to detect m.1555A>G variant and Genedrive system software), the medical management of people with suspected/diagnosed hearing loss and the need for Cochlear implants in the long-term were included. To identify cost and resource use evidence, the EAG searched the same sources identified for the economic evidence supplied by the test manufacturers together with NHS reference costs, the unit costs of health and social care and the British National Formulary. All costs were updated to the price year 2021/22. Data on HRQoL were extracted from the rapid review of cost-effectiveness studies and the targeted literature search for publications reporting HRQoL or health state utilities for the populations of interest.

The early economic model was developed according to standard modelling guidelines.[49] The model structure was reviewed by clinical and methodological experts for appropriateness to the current NHS clinical and diagnostic pathway and the face validity of the model was checked by clinical experts.

5. Cost-effectiveness

5.1 Results of the cost-effectiveness studies search

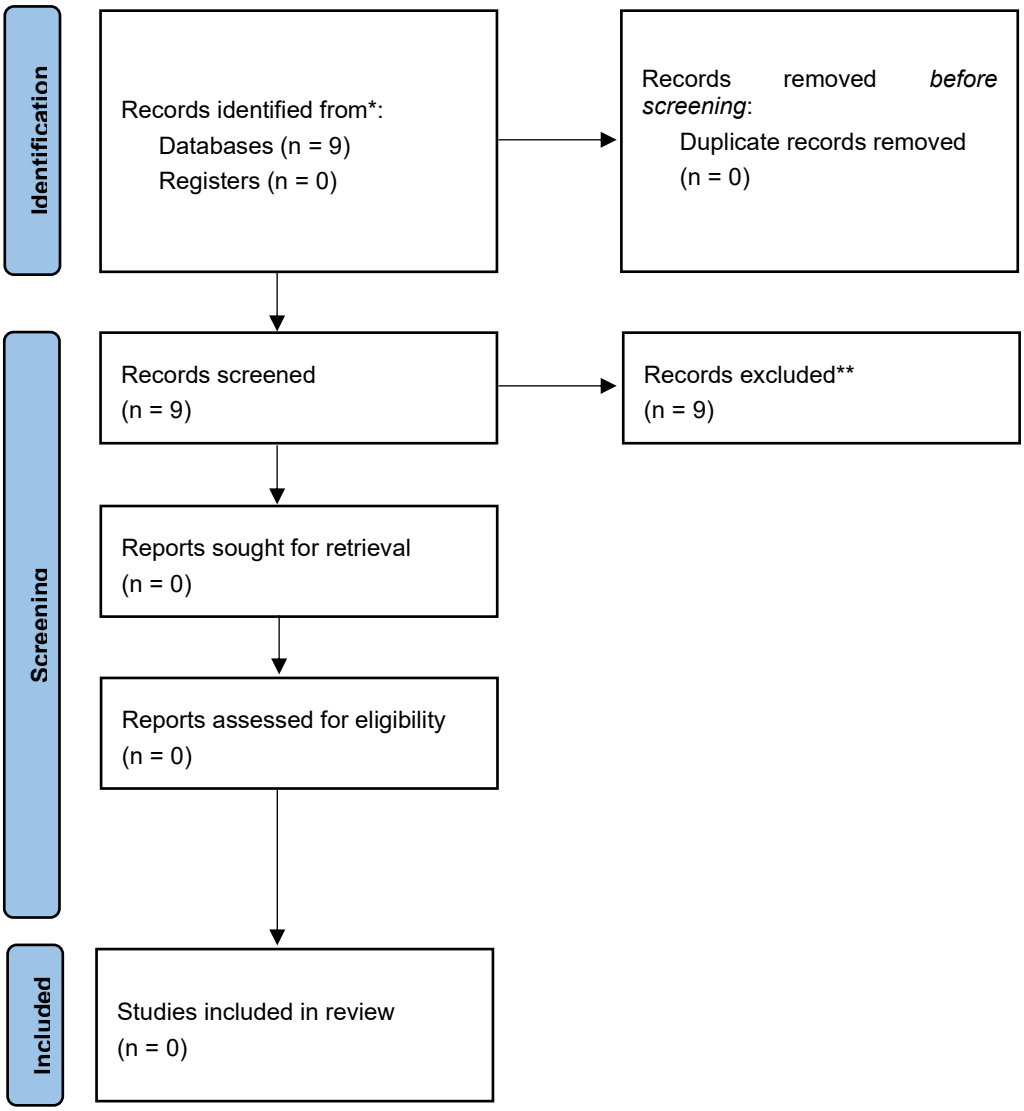


Figure 3: Flow diagram of cost-effectiveness review

Overall, database screening retrieved nine records for title and abstract screening. No studies were sought for full text assessment as no records were judged relevant (see Figure 3).

5.2 Developing a clinical pathway and economic model

Given the lack of economic evaluations the EAG went on to consider how an economic evaluation model might be structured in order to identify the information needs for this model, the availability of these data and from that the information gaps that exist. Given the anticipated information gaps an early economic evaluation model was developed to provide an indication as to whether the use of the Genedrive MT-RNR1 ID Kit could plausibly be cost-effective and explore the impact of key uncertainties on estimates of cost-effectiveness.

The first stage in developing the economic evaluation model was to develop conceptual models of the clinical pathways for situations representing the current standard of care and for when the Genedrive MT-RNR1 ID Kit is used.

5.2.1 Developing a clinical pathway

To develop the clinical pathway (using GitMind[20]) for using the Genedrive MT-RNR1 ID Kit to detect the m.1555A>G in neonates, we reviewed related documents to map out the treatment pathway in the NHS for the target population. This clinical pathway was checked with clinical experts consulted by the EAG and revised following their comments. The main documents that we initially used to develop clinical pathway are as follows:

1. NICE advice Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in newborn babies[21]
2. NG195: Neonatal infection: antibiotics for prevention and treatment NICE guideline [NG195] Published: 20 April 2021[10]
3. Clinical Pharmacogenetics Implementation Consortium Guideline for the Use of Aminoglycosides Based on MT- RNR1 Genotype[11]
4. Pharmacogenetics to Avoid Loss of Hearing (PALOH) trial: a protocol for a prospective observational implementation trial[22]
5. WHO report; Childhood hearing loss: strategies for prevention and care.[23]
6. New-born hearing screening programme (NHSP): care pathways for babies in neonatal intensive care units (NICU) Guidance[24]

5.2.1.1 Pathway for the current standard of care

A simple structure of clinical pathway for the current standard of care is shown in Figure 4. In the current standard pathway neonates with suspected infection or sepsis will receive an aminoglycoside, such as gentamicin, irrespective of if they have MT-RNR1 gene m.1555A>G mitochondrial genetic variant. The current pathway also considered administration of antibiotics to women during labour at risk of early onset neonatal infection. Risk factors for early-onset neonatal infection for women in labour are set out in the NICE guideline (NG195; Box 1).

Due to the inheritance pattern of MT-RNR1, the current pathway included mitochondrial mutation screening for neonates with a mitochondrial or mutations maternal history of deafness, or both, who need aminoglycoside prescription. The current pathway also considered the findings of any previous genetic test to determine an antibiotic prescription. For example, children with cystic fibrosis are tested for the variant once they are identified as having cystic fibrosis as it is expected that these individuals will require aminoglycoside antibiotics at some stage in their lives.

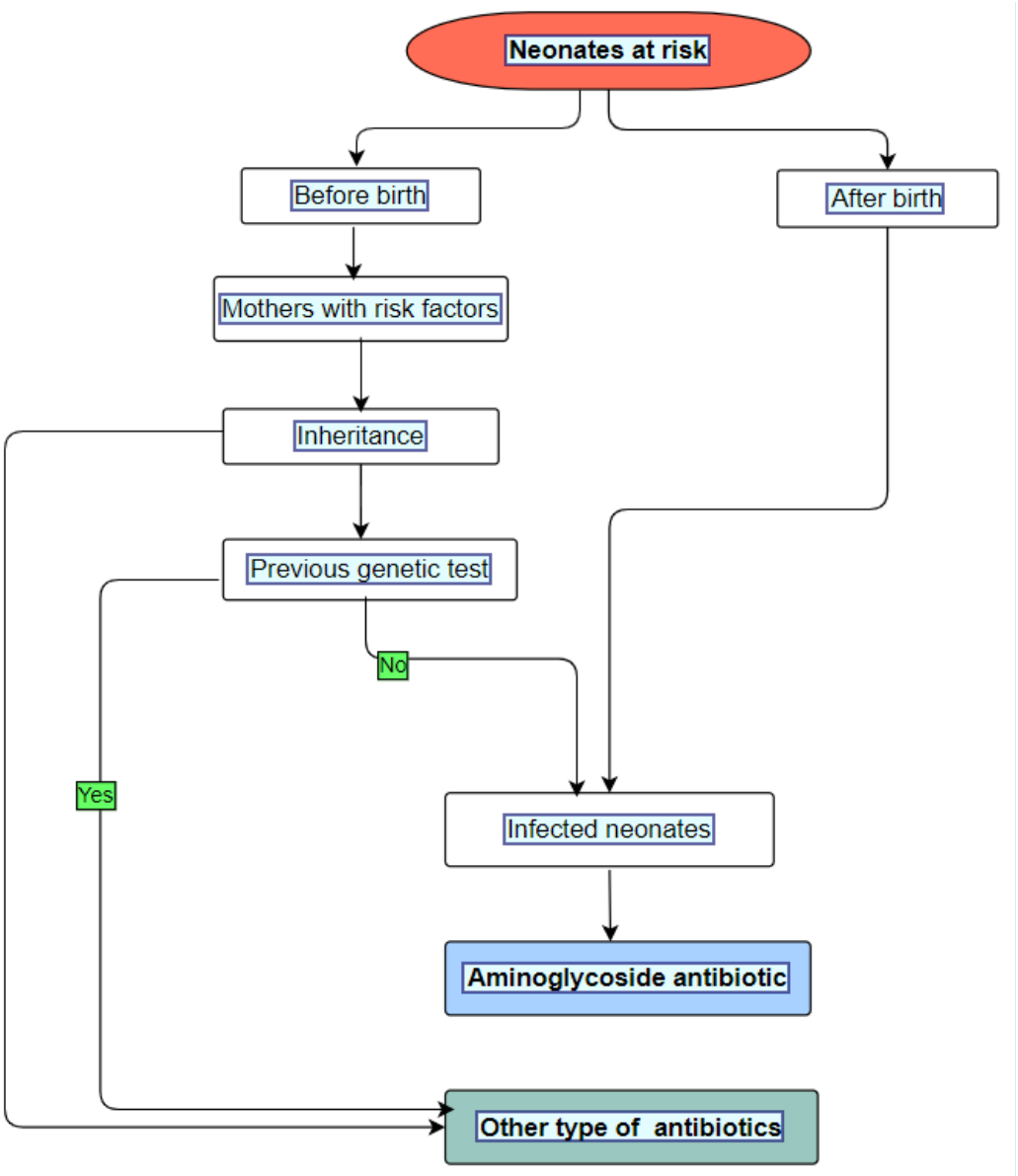


Figure 4: Clinical pathway for the normal standard of care

5.2.2.2 Pathway when using the Genedrive MT-RNR1 ID Kit

A simple structure of clinical pathway for the integration of the Genedrive MT-RNR1 ID Kit into the clinical pathway is shown in Figure 5. In common with the current standard of care, inheritance data and previous genetic tests for mothers with relevant risk factors are considered when deciding whether or not to prescribe aminoglycoside to neonates with suspected infection or sepsis. Although the time taken to administer the Genedrive MT-RNR1 ID Kit is short (26 minutes), for some of the neonates who present with suspected infection or sepsis there is insufficient time to use the Genedrive MT-RNR1 ID Kit as they are in immediate need. This issue was discussed by clinical experts consulted by the EAG. Their view was that using the Genedrive MT-RNR1 ID Kit may cause a delay for some neonates, however less than five percent of neonates will need immediate antibiotics.

As shown in Figure 5, antibiotic prescription for neonates will be based on Genedrive MT-RNR1 ID Kit results, with aminoglycosides being prescribed only if the test results are negative. As also shown in Figure 5, there is the possibility that the Genedrive MT-RNR1 ID Kit will be conducted for the second

time if the first test were to fail. If both the 1st test and the 2nd test were to fail, then there would be no more time for any extra tests within the golden hour for the administration of the antibiotics. Clinical experts consulted by the EAG noted that in this situation, neonates with suspected infection or sepsis would almost certainly be provided with other alternative antibiotics, due to the need to 'play it safe'.

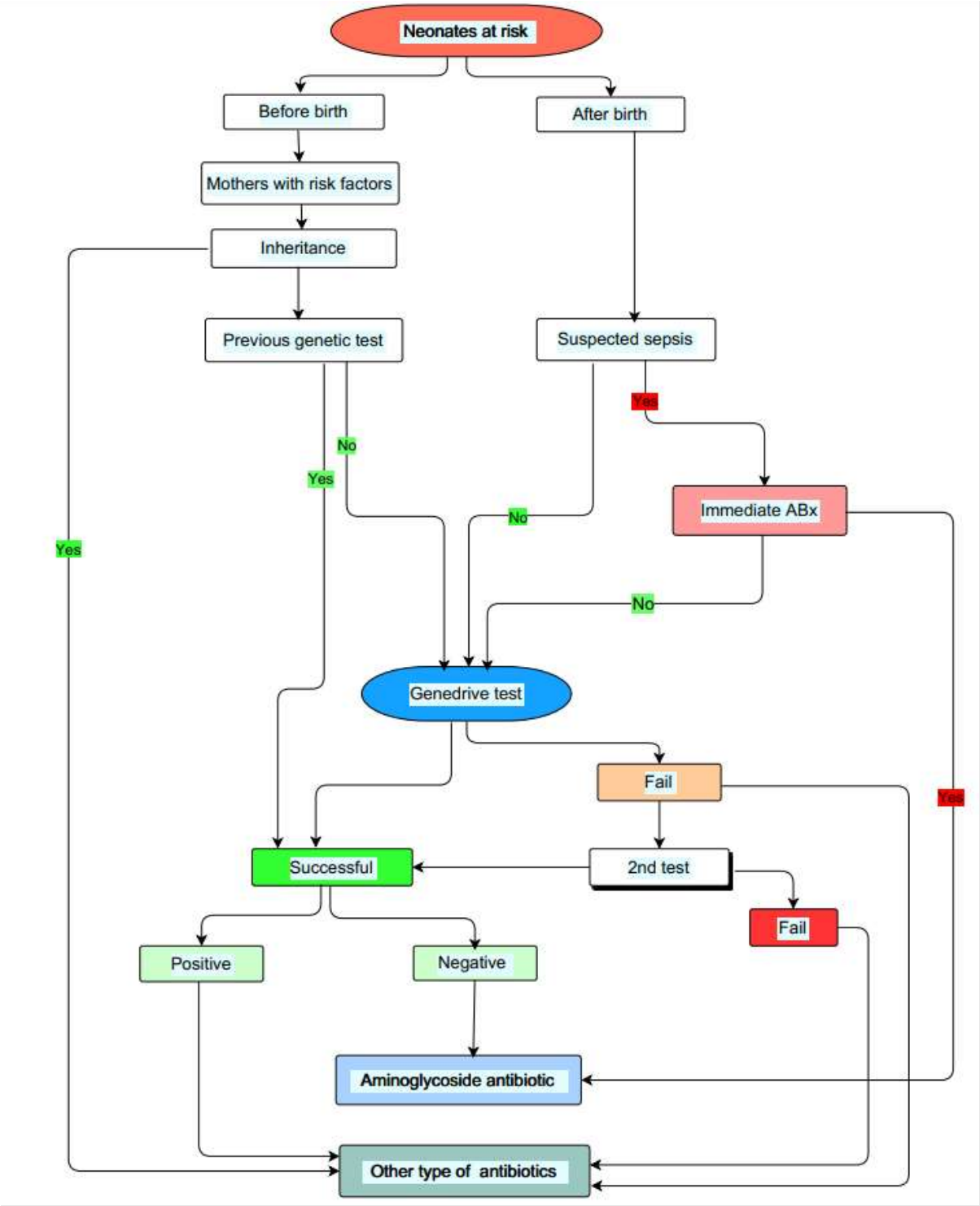


Figure 5: Clinical pathway when using the Genedrive MT-RNR1 ID Kit

5.2.2 Developing an economic evaluation model

In the following subsection we outline the structure and key assumptions for a full economic model. The proposed economic model seeks to capture the components of the care pathways described above and then consider the long-term implications of to the child over their entire lifetime of preventing the use of an aminoglycoside antibiotic for a child presenting with suspected infection or sepsis who has the m.1555A>G variant. Figure 6 below provides a schematic, but simplified representation of this model. In this model the key long-term implications considered by the model are the those that follow aminoglycoside induced hearing loss.

The model was developed according to standard modelling guidelines.[25, 26] The face validity of the economic model structure was checked by our clinical experts and methodological experts for appropriateness to the current NHS clinical and diagnostic pathways. The model's calculations and proposed data inputs were also checked for technical correctness.

The model simulates the patient pathway from the initial diagnosis of neonates with the m.1555A>G gene variant to treatment for AIHL (e.g., a cochlear implantation) for a patient's lifetime. As per NICE scope, the population that were defined in the model are neonates with suspected infection or sepsis. The patient pathway described by the Markov model involves a series of mutually exclusive health states that a patient may move between over time (Figure 6). Once someone is in a state then they stay in that state for a defined period of time called the cycle length. We have defined 1-year cycle length, as it was thought that an annual period is sufficient to capture both cost and effectiveness impacts in the model.

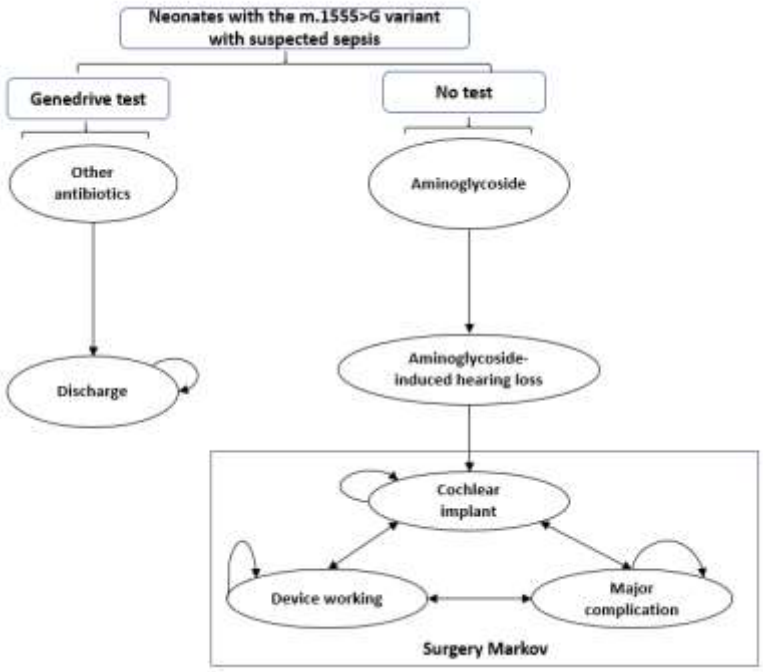


Figure 6: Schematic outline of the Markov model

Each Markov model includes at least one absorbing state. This is a state that a person can enter but cannot leave. In the context of a chronic disease, the absorbing state might be death. In our model, the probability of movement to death was informed by the UK National Life Table.[71] All the programming for the model was implemented in TreeAge Pro 2022 (Williamstown, MA, USA).

Set out below are some key features for the proposed economic model:

- The population modelled are neonates with early onset and late onset infection who need antibiotic treatment and who are being considered for treatment with aminoglycosides
- Some neonates will require antibiotic administration immediately (i.e., there is no time for the Genedrive MT-RNR1 ID Kit before antibiotics must be started)
- Increased time to antibiotics will increase the risk of death for neonates with sepsis
- The clinical pathway for neonates with early onset and late onset infection are different (in terms of duration of antibiotic prescription)
- There is a chance the Genedrive MT-RNR1 ID Kit will give a false negative result
- There is a chance the Genedrive MT-RNR1 ID Kit will give a false positive result
- There is a chance that the Genedrive MT-RNR1 ID Kit will fail to give a result
- If the first Genedrive MT-RNR1 ID Kit fails to give a result, there is time for a second test
- If both the first Genedrive MT-RNR1 ID Kit and the second Genedrive MT-RNR1 ID Kit fail, there will be insufficient time for further testing and neonates with suspected infection will not be treated with aminoglycosides and receive other antibiotics (such as cefotaxime)
- An increased time to antibiotics will increase the risk of death for neonates from sepsis
- Where neonates are identified as not having the m.1555A>G variant using the Genedrive test, aminoglycosides (such as gentamicin) will be used
- Where neonates are identified as having the m.1555A>G variant using the Genedrive test, alternative antibiotics (such as cefotaxime) will be used
- Different antibiotics will have different adverse event profiles
- For neonates with the m.1555A>G variant treated with aminoglycosides, there is a risk of AIHL
- For neonates with the m.1555A>G variant not treated with aminoglycosides, there is a risk of nonsyndromic hearing loss
- For neonates who suffer hearing loss, the severity may vary
- Women with risk factors (for sepsis) are eligible for MT-RNR1 ID Kit, but antibiotic prescription will be for neonates (after birth)
- Maternal inheritance may be considered before testing
- The use of the Genedrive MT-RNR1 ID Kit, other than affecting time to administration and the type of antibiotic used, does not affect normal standard of care for neonates presenting with suspected infection or sepsis
- There will be training costs for staff to carry out the test, which will vary by the size of type of hospital ward
- Staff time is required to carry out the test, which will vary by the size of type of hospital ward
- Additional audiological monitoring will be required for infants with AIHL
- AIHL has associated adverse events
- If AIHL occurs, neonates will require hearing aids, unilateral cochlear implants or bilateral cochlear implants
- HRQoL will vary by age, level of hearing loss, type of cochlear implant and time since cochlear implant has been implanted
- To demonstrate no adequate benefit from hearing aids, children need to have had a valid trial of an acoustic hearing aid for at least three months

- There are pre-procedure, procedure and post-procedure costs associated with both unilateral and bilateral cochlear implants
- There is a chance that the cochlear implant surgery will not be successful
- It is possible to upgrade cochlear implants after they have been fitted
- There may be complications associated with the implantation of cochlear implants (i.e., internal or external device failure, death)
- There are short-term and long-term adverse events associated with cochlear implants such as Dysgeusia and Vertigo which will impact both costs and utilities

In the next sections information on the health state utilities and costs required to populate the model are set out. As is described below not all of these are used in the early economic model.

5.3 Results of the targeted search for HRQoL studies

Overall, database screening retrieved 465 records (after deduplication) for title and abstract screening. Of these studies, 46 were sought for full text assessment. Following discussion with the project team it was decided that utility data would only be considered for inclusion from studies based in the United Kingdom (UK) as these were most relevant to the decision problem. Eight studies were therefore initially identified with utility data that could potentially be used in the early economic model. On review of citations of these identified studies, three additional studies were identified. These eleven studies are briefly summarised in Table 3.

Table 3 Summary of studies included in targeted review of HRQoL literature

Study	Population	Description	Utility Measure(s) Used
Summerfield *et al* (2002)[27]	Adults	Cost-utility modelling study of unilateral cochlear implantation	Health Utilities Index Mark 2 (HUI2)[28], Time Trade Off (TTO)
UK Cochlear Implant Study Group (2004)[29]	Adults	Prospective cohort study of unilateral cochlear implantation	Health Utilities Index Mark 3 (HUI3)[30]
Barton *et al* (2004)[31]	Adults	Study comparing utility in hearing-impaired adults before and after being provided with a hearing aid	EQ-5D-3L,[32] HUI3,[30] SF-6D[33]
Summerfield *et al* (2006)[34]	Adults	Randomised control trial of benefits of successive bilateral cochlear implants	HUI3,[30] VAS
Barton *et al* (2006)[35]	Children	Cost-utility analysis of paediatric cochlear implantation	HUI3[30]
Petrou *et al* (2007)[36]	Children	Study looking at the impact of bilateral heating impairment on HRQoL	HUI2,[28] HUI3[30]
Bond *et al* (2009)[37]	Children and Adults	Cost-utility analysis of cochlear implants for severe to profound deafness	HUI3[30] – taken from UKCISG (2004) and Barton *et al* (2006)
Lovett *et al* (2010)[38]	Children	Study looking at the impact of cochlear implants for deaf children	HUI3,[30] VAS
Summerfield *et al* (2010)[39]	Children	Cost-utility analysis of paediatric bilateral cochlear implantation	Time Trade Off (TTO), Visual Analogue Scale (VAS)

Petrou *et al* (2021)[40]	Children	Study looking at the impact of permanent bilateral hearing loss of HRQoL	HUI2,[28] HUI3[30]
Cutler *et al* (2022)[41]	Adults	Cost-utility analysis of unilateral cochlear implants	HUI3[30] – taken from UKCISG (2004)

The studies identified in the targeted review and gathered through a review of citations were mainly a mixture of cost-effectiveness analyses (Summerfield *et al* 2002,[27] Barton *et al* 2006, Bond *et al* 2009, Summerfield *et al* 2010, Cutler *et al* 2022) and standalone studies with the objective of measuring the HRQoL associated with different levels of hearing impairment and/or the implementation of different types of cochlear implant in either children or adults (UKCISG 2004, Barton *et al* 2004,[37] Petrou *et al* 2007,[36] Lovett *et al* 2010,[38] Petrou *et al* 2021[40]). Summerfield *et al* (2006)[34] was a randomised control trial of the effects of successive cochlear implants.

For those standalone studies, all studies used parent proxy-reported outcomes. The most common HRQoL questionnaire used to measure utility was the HUI3 and its predecessor the HUI2. Barton *et al* (2004)[31] additionally used the EQ-5D-3L and SF-6D, however neither of these measures include a question specifically related to hearing and therefore may not be sensitive to changes in utility related to hearing loss (the EAG note that a hearing bolt on is under development for the EQ-5D).[42] Summerfield *et al* (2010)[39] and Lovett *et al* (2010)[38] additionally used the Visual Analogue Scale (VAS), an assessment of general health scored between 0 and 100.

For cost-effectiveness studies, the utility values were gathered from several sources. Summerfield *et al* (2002)[27] collected HUI2 and TTO data from a sample of adults. Barton *et al* (2006)[35] collected HUI3 data from the parents of children with hearing loss with and without cochlear implants. Bond *et al* (2009)[37] used the child utility values from Barton *et al* (2006)[35] and the adults utility values from UKCSIG (2004).[29] Summerfield *et al* (2010)[39] used the Time Trade Off (a choice-based method of eliciting health state utility commonly used in health economic studies) and the VAS. Cutler *et al* (2022)[41] used the utility values from UKCISG (2004).[29]

5.4 Health-Related Quality of Life

5.4.1 Utility Values

The utility values used in the early economic model are based on those used in Bond *et al* (2009),[37] a highly cited NIHR Health Technology Assessment investigating the effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in both children and adults. Bond *et al* (2009)[37] was the health economic evaluation submitted as part of TA166 ('Cochlear implants for children and adults with severe to profound deafness'),[43] which was subsequently updated in TA566.[44] These utility values are shown in Table 5. Further description of these utility values is provided below.

The utility values for profound hearing loss, unilateral cochlear implants and bilateral cochlear implants for children used in Bond *et al* (2009)[37] are taken from Barton *et al* (2006),[35] a cross sectional study in which the parents of a representative sample of hearing-impaired children assessed the health-related quality of life of their children using the HUI3. The HUI3 is the HRQoL measure considered to be the most sensitive for the effects of hearing treatment on overall health status.[45] As reported in Bond *et al* (2009),[37] the utility increment from cochlear implants in childhood will vary by time since implantation and whether the child has a unilateral or bilateral cochlear implant, and therefore different utility values are provided for 'less than two years since implant', 'two to four years since implant' and 'over four years since implant'.

The utility value for no hearing loss in childhood is taken from Pogany *et al* (2006),[46] which is the source of the HUI3 population norms reported on the website of the HRQoL tool.[47] Pogany *et al* (2006)[46] reports the HUI3 population norms for the Canadian general population by age band.[46] The value of 0.908 is a weighted average of the 5-12, 13-15 and 16-19 age bands. As this value is taken from the Canadian value set, there are likely to be small differences between the health preferences for those from Canada and those from the UK, impacting the generalisability of this utility value. However, the HUI3 was the measure used in the Barton *et al* (2006)[35] study and there is no UK value set for the HUI3. It is worth noting that for all child utility values used in the early economic model it is assumed that the values for those aged five and above generalise to those below the age of five. This is clearly a strong assumption.

Table 4. Utility Values for use in Early Economic Model

Parameter	Value	Source
Children (Under 18)		
No hearing loss (population norm)	0.908	Pogany *et al* (2006)[46]
Profound/significant hearing loss	0.421	Barton *et al* (2006)[35]
Unilateral cochlear implant (less than two years since implant)	0.487	Barton *et al* (2006)[35]
Unilateral cochlear implant (two to four years since implant)	0.633	Barton *et al* (2006)[35]
Unilateral cochlear implant (over four years since implant)	0.653	Barton *et al* (2006)[35]
Bilateral cochlear implant (less than two years since implant)	0.490	Barton *et al* (2006)[35], Bond *et al* (2009)
Bilateral cochlear implant (two to four years since implant)	0.636	Barton *et al* (2006)[35], Bond *et al* (2009)
Bilateral cochlear implant (over four years since implant)	0.656	Barton *et al* (2006)[35], Bond *et al* (2009)
Adults (18 years of age and over)		
No hearing loss (population norm)	0.850	Pogany *et al* (2006)[46]
Profound/significant hearing loss	0.433	UKCISG (2004)[29]
Unilateral cochlear implant	0.630	UKCISG (2004)[29],
Bilateral cochlear implant	0.633	Summerfield (2006)[34]

The adult utility values for profound hearing loss, unilateral cochlear implants and bilateral cochlear implants used in Bond *et al* (2009)[37] are taken from a UK Cochlear Implant Study Group study[29] which estimated the cost-effectiveness of unilateral cochlear implants for deaf adults using the HUI3. It is worth noting that these utility values were also used in the recent Cutler *et al* (2022)[41] study, which investigated the cost-effectiveness of unilateral cochlear implants in UK adults. The utility value of being profoundly deaf was estimated to be 0.433. There are utility increments associated with both unilateral (0.630) and bilateral (0.633) cochlear implants. It is worth noting that a recent network meta-analysis of both UK and non-UK studies estimated the utility increment of bilateral cochlear implants compared to unilaternal cochlear implants to be 0.08 (Dixon *et al* 2022), slightly higher than the 0.03 increment reported in Bond *et al* (2009)[37] and used in the early economic model.

The utility value for no hearing loss (the adult population norm) was estimated to be 0.850, the HUI3 population norm value for adults reported in Pogany *et al* (2006).[46] Once more, as this value is taken

from the Canadian HUI3 value set this is unlikely to be full representative of the UK population given differences in health preferences across countries. However, the HUI3 is the HRQoL measure used in the UKCISG study and there is no UK value set for the HUI3.

It has previously been shown that health-related quality of life decreases with age.[48] As argued in Bond *et al* (2009),[37] using a single age-independent value for the utility increment associated with cochlear implants may result in a counterintuitive position where the utility for a cochlear implant recipient may be higher than that of their normal-hearing peers. As this is an early value assessment, aside from varying the utility values by time of implementation in childhood, age-adjustment has not been considered in the early economic model. In a definitive study, age-adjustment should be implemented in line with modelling good practice guidelines and NICE guidance.[25, 26, 49]

5.4.2 Adverse Event Disutility Values

As noted in Cutler *et al* (2022),[41] there are adverse events associated with the implementation of cochlear implants that may be included in an economic model. The disutility values associated with these adverse events and the probability of these adverse events are shown in Table 5 and Table 6. The disutility values used in Cutler *et al* (2022)[41] and their duration are sourced from a number of previously published health preference studies (Swan *et al* 2012),[50] Happich *et al* 2009),[51] (Prosser *et al* 2004)[52]. The probabilities of the adverse events used in Cutler *et al* (2022) were sourced from a series of clinical studies reporting complications associated with cochlear implants (Hansen *et al* 2010, Jepperson *et al* 2013, Farientti *et al* 2014 and Venail *et al* 2008).[53-56]

Given the relatively short duration of many of these events (with the exception of long-term vertigo), the relatively low probability of occurrence and relatively low cost of these adverse events (as shown in Table 6), the disutilities and costs associated with adverse events are not included in the early economic model. In a definitive study, the disutilities and costs associated with adverse events should be included in line with standard methods guidelines.[25, 26, 49] Given the data in Table 5 on utilities and Table 6. This suggests adverse effects that may be included in a definitive economic model may only have a negligible impact on the overall conclusions regarding cost-effectiveness.

Table 5 Disutility Decrements of Adverse Events

Adverse Event	Value	Duration	Source
Dysgeusia	0.020	Six months	Cutler et al (2022)[41]
Vertigo (Short Term)	0.033	Six months	Cutler et al (2022),[41] originally sourced from Swan et al (2012)[50]
Tinnitus	0.050	Six months	Cutler et al (2022),[41] originally sourced from Happich et al (2009)[51]
Wound Infection	0.042	Six months	Cutler et al (2022),[41] originally sourced from Prosser et al (2004)[52]
Vertigo (Long Term)	0.033	Lifetime	Cutler et al (2022),[41] originally sourced from Swan et al (2012)[50]
Source: Disutility estimates taken from Table 3 of Cutler et al (2022)[41]			

Table 6 Probability of Adverse Events related to Cochlear Implants for use in Economic Model

Adverse Event	Probability	Source
Dysgeusia	0.065	Cutler et al (2022),[41] originally sourced from Hansen et al (2012),[53] Jeppesen et al

		(2013),[54] Farinetti et al (2014)[55]
Vertigo (Short Term)	0.194	Cutler et al (2022),[41] originally sourced from Hansen et al (2012),[53] Jeppesen et al (2013),[54] Farinetti et al (2014),[55] Venail et al (2008),[56] Stamatiou et al (2011)[57]
Tinnitus	0.036	Cutler et al (2022),[41] originally sourced from Jeppesen et al (2013),[54] Farinetti et al (2014),[55] Venail et al (2008)[56]
Wound Infection	0.015	Cutler et al (2022),[41] originally sourced from Hansen et al (2012),[53] Jeppesen et al (2013),[54] Stamatiou et al (2011), Farinetti et al (2014),[55] Venail et al (2008)[56]
Vertigo (Long Term)	0.014	Cutler et al (2022),[41] originally sourced from Hansen et al (2012),[53] Jeppesen et al (2013)[54]
Source: Probability of adverse events estimates taken from Table 4 of Cutler *et al* (2022)[41]		

Table 7 Costs Associated with Adverse Events related to Cochlear Implants in Economic Model

Adverse Event	Cost	Source
Dysgeusia	£31	Unit Costs of Health and Social Care 2018[58]
Vertigo (Short Term)	£31	Unit Costs of Health and Social Care 2018[58]
Tinnitus	£31	Unit Costs of Health and Social Care 2018[58]
Wound Infection	£41	Unit Costs of Health and Social Care 2018,[58] NHS prescription charge 2017[59]
Vertigo (Long Term)	£31	Unit Costs of Health and Social Care 2018[58]
Source: Cost estimates for adverse events taken from Table 10 of Cutler *et al* (2022).[41] All costs inflated to a common price year of 2022 using the Bank of England Inflation Calculator where appropriate.		

5.5 Health Resource Use

Following a request for information by NICE, the costs related to the Genedrive MT-RNR1 ID Kit were provided to the EAG by the test manufacturer, including the cost of purchasing the Genedrive MT-RNR1 ID Kit itself, the cost of the other equipment required to carry out the diagnostic test and the annual warranty fee. In addition, a 'Health Economic Utility' paper was also provided to NICE by the manufacturer, which reported on the implementation of the test and the potential impact on routine clinical care with the prescribed golden hour for the administration of an antibiotic. As mentioned in the NICE Medtech Information Briefing (MIB) document,[21] estimating the resource consequences from

adopting the technology will vary depending on the NHS Trust and how much it is used. Several pragmatic assumptions have been made in this analysis related to test usage and staff costs. Therefore, the costs presented are unlikely to be generalisable to all sites.

5.5.1 Non-Staff Costs of Diagnostic Test

Using the information provided by the test manufacturers and information gathered from various other sources (including NHS reference costs and the unit costs of health and social care), the cost of implementing the Genedrive MT-RNR1 ID Kit was micro-costed (see Table 9). The work reported in this sub-section addresses the first objective for the cost-effectiveness set out in Section 1.6.

The costs of the diagnostic test were assumed to include:

- Cost of the Genedrive MT-RNR1 ID System (GS-002)
- Cost of the Genedrive MT-RNR1 ID Kit
- Cost of the Genedrive MT-RNR1 Control Kit
- Cost of a Bluetooth Printer
- Cost of Custom Labels
- Annual Warranty fee for the Genedrive equipment

Capital costs for the Genedrive MT-RNR1 ID System and Bluetooth Printer were calculated using the equivalent annual cost methodology.[60] This method converts the initial capital cost into an annual sum which equals the resources and investment plus their opportunity cost. The equivalent annual cost of implementing the Genedrive MT-RNR1 ID Kit was calculated under the following assumptions:

- Lifespan of the Genedrive MT-RNR1 ID System and Bluetooth Printer: six years
- Capital costs spread over its lifespan (six years)
- Weeks per year in use: 52 weeks
- Genedrive MT-RNR1 ID Kit usage: three times per day
- Warranty fee would
- Discount factor of 3.5% (in line with NICE reference case)

Following a request for information from the manufacturer, the lifespan of the Genedrive MT-RNR1 ID System was assumed to be six years. In documentation provided by the manufacturer, the company recommends running a positive and negative control (both contained in a single Genedrive MT-RNR1 Control Kit) once per month to confirm that the Genedrive MT-RNR1 ID System is working correctly. It was therefore assumed that each site would undertake the recommended quality control using the control kit once per month. It was also assumed that each site would purchase a Bluetooth printer to print labels (together with a charging cradle) and custom labels provided by the company would also be purchased. It was further assumed that lifespan of the Bluetooth printer would also be six years, in line with the lifespan of the Genedrive MT-RNR1 ID System. As specified by the manufacturer, the Genedrive System has been designed to be easily integrated into a NICU and does not need special storage for either the Genedrive MT-RNR1 ID System itself or the Genedrive MT-RNR1 ID Kit, and therefore it was assumed that there were no costs associated with modifying existing infrastructure to accommodate the system.

It was assumed that the Genedrive MT-RNR1 ID Kit would be in use throughout the year. However, estimating the test usage at a site level is complicated by the fact that usage will be determined by the size, type and geographical location of each site. In the NICE Medtech innovation briefing document for Genedrive it was assumed there are approximately 90,000 annual admissions to NICUs for neonates

with suspected infection in the UK.[21] Given that there are currently estimated to be 72 Level 3 NICUs in the UK,[61] this indicates that the average number of eligible admissions per NICU per day may be between three and four. In the PALOH study,[18] 751 neonates were recruited from two centres in an eleven-month period (January 2020 to November 2020). Due the COVID-19 pandemic, the majority (n=713, 94.9%) of these admissions were from a single centre, giving an average number of admissions to the participating site per day between two and three.

Given the information from both the MIB document and the PALOH study,[18, 21] in the early economic model, it was assumed that the Genedrive MT-RNR1 ID Kit was used three times per site per day. It is worth emphasising that this estimate is subject to a significant level of uncertainty, given that the use of the equipment per site could vary markedly. However, it is also worth emphasising that because the Genedrive MT-RNR1 ID System itself is a relatively inexpensive medical device, the cost per neonate tested of the Genedrive MT-RNR1 ID System would be negligible over the lifetime of its use even in very small sites, and therefore should not materially impact the cost-effectiveness results.

Table 8 Non-staff costs associated with implementation of Genedrive Test

Item	Cost (£)
Purchase Costs	
Genedrive MT-RNR1 ID System (GS-002)	£4995
Bluetooth Printer + Charging Cradle	£400
Annual warranty fee for equipment (Year 2 – Year 6)	£750
Genedrive MT-RNR1 ID Kit (per test)	£100
Genedrive MT-RNR1 Control Kit (one kit per system per month)	£35
Custom Labels (200 per pack)	£40
Capital Costs	
Opportunity Cost of Genedrive MT-RNR1 ID System (assume six years equipment life)	£5624.42
Annual Cost of Genedrive MT-RNR1 ID System (assume six years equipment life)	£937.61
Cost Per Test of Genedrive MT-RNR1 ID System (assume three tests per site per day)	£0.86
Opportunity Cost of Bluetooth Printer + Charging Cable (assume six years equipment life)	£450.40
Annual Cost of Bluetooth Printer + Charging Cable (assume six years equipment life)	£75.07
Cost Per Test of Bluetooth Printer + Charging Cable (assume three tests per day)	£0.07
Other Costs	
Cost of Genedrive MT-RNR1 Control Kit per test (assume three tests per day)	£0.38
Cost of Custom Label (one per test)	£0.20
Cost of Warranty per Test (assume three tests per day)	£0.57
Estimated Total Non-Staff Cost Per Test	£102.08
Notes: All prices exclusive of VAT	

5.5.2 Staff Costs

There are significant staffing requirements in NICUs, with NICE quality standards stating that the minimum standard should be 1:1 nursing for all neonates.[62] Additional time for nursing staff to be trained and undertake the diagnostic testing will have cost implications.

5.5.2.1 Training Costs

In terms of training, in the protocol for the PALOH study[22] it was stated that a minimum of 80% of all relevant nursing and medical staff within the two NICUs involved in the PALOH study would be trained with this training including practical use and interpretation of the assay, with Standard Operating Procedures for use integrated into the standard admission procedure. It was also stated that a 'train the trainer' approach will be adopted, where a number of experienced NICU research nurses plus additional clinical nursing staff identified as 'super-users' will receive training directly from representatives of the device manufacturer, who would then cascade training to the remaining nursing and medical staff. The Genedrive MIB document states that the manufacturers would provide training for free and that this training would last between 15 minutes and one hour.[21] In the Genedrive MIB document, two of the three experts consulted stated that minimal training would be needed for staff using the technology as it is similar to other point of care testing currently used in practice. Estimating the training costs at a site level is difficult to determine, given that different size, type, and structures of the different sites. As this is an early value assessment, training costs were not considered for inclusion in the early economic model. However, given the estimated relatively short time for training and the high potential use of the Genedrive MT-RNR1 ID Kit, it is likely that the training costs per neonate tested would be negligible, even in smaller sites.

5.5.2.2 Staff Costs of Implementing the Test

In terms of staff time to implement the diagnostic tests, in the 'Health Economic Utility Paper' document provided by the test manufacturers to NICE, the manufacturers stated no increase in nursing time was required to implement the assay into practice, pointing to evidence from the PALOH study.[17]However, the sites used in the PALOH trial were large academic teaching hospitals with extensive experience of the implementation of new technologies. Therefore, clinical experts consulted by the EAG, considered it unlikely that staffing requirements for these hospitals will be generalisable to smaller sites with less experience of research activity. The Genedrive Medtech innovation briefing document,[21] reported differing views of clinical experts regarding the impact of Genedrive on staffing levels. One expert noted that although the technology itself was relatively simple, implementation may be hindered by the need to communicate the findings across the health care system. One of the clinical experts consulted by the EAG stated that the assumption of no increase in nursing time was very strong, given that a member of staff would need to physically implement the test. In the final scope for Genedrive, experts commented that while the Genedrive MT-RNR1 ID Kit may be intended to be used in a near patient setting, for some hospitals this may not be possible, for example because of a lack of space on neonatal units. If the Genedrive System was instead housed in a laboratory rather than near care setting, this could increase the staff time required to implement the test.

In the early economic model (see Table 9), it was assumed that 30 minutes of nurse time would be required to implement each diagnostic test, inclusive of collecting the buccal swab from the neonates, entering the assay into the Genedrive MT-RNR1 ID System, reporting the results and communicating the findings to the other members of the team. In the 'Health Economics Utility Paper' provided by the test manufacturers, this was average analysis time reported from sample collection to result. In the early economic model, it was assumed that either Band 5 or Band 6 Nurses would be responsible for carrying out the diagnostic test. Due to uncertainties regarding the proportion of different bands of nurses working at different sites, it was pragmatically assumed that an equal proportion of Band 5 and Band 6 Nurses would undertake the test, and therefore the hourly cost used is the midpoint of the two cost bandings.

Table 9: Estimated staff costs associated with implementation of Genedrive MT-RNR1 ID Kit

Item	Minutes	Hourly Cost	Total Cost	Source
Staff Costs				
Nurse (Band 5)	30	£50	£25	Unit Costs of Health and Social Care 2021[63]
Nurse (Band 6)	30	£62	£31	Unit Costs of Health and Social Care 2021[63]
Total Staff Cost Per Test			£28	
Notes: All costs inflated to a common price year of 2022 using the Bank of England Inflation Calculator where appropriate.				

5.5.3 Cost of Standard of Care

Although there is no current standard care for MT-RNR1 testing in neonatal sepsis, expert opinion and company information suggests that Pyrosequencing and Sanger sequencing are the two closest comparators in the NHS.[21] The total estimated costs of Pyrosequencing and Sanger sequencing are shown in Table 10 below. This is a retrospective investigation of the cause of hearing loss. Given the uncertainty regarding current standard care, in the economic model it was pragmatically assumed that Sanger sequencing was used, as this was the sequencing method used to confirm the results from the Genedrive MT-RNR1 ID Kit in the PALOH study.[18] Given the relatively small difference in the costs between Pyrosequencing and Sanger sequencing, this assumption is likely to have little impact on the results from the early economic model. As well as being used retrospectively in standard care to confirm the cause of hearing loss, it was also assumed that a retrospective investigation of hearing loss would also be used to confirm any positive results from the Genedrive MT-RNR1 ID Kit.

Table 10 Costs of standard care

Diagnostic Testing (Standard Care)		
Pyrosequencing	£212	MIB Genedrive Document[21]
Sanger Sequencing	£191	MIB Genedrive Document[21]
Notes: All costs inflated to a common price year of 2022 using the Bank of England Inflation Calculator where appropriate.		

5.5.4 Costs of Antibiotics

The implementation of the Genedrive MT-RNR1 ID Kit will have an impact on the antibiotics given to neonates. For early onset infection, the first-choice antibiotic regime for empirical treatment for suspected early-onset infection (less than 72 hours) is intravenous benzylpenicillin with gentamicin. The starting dosage for this antibiotic regime is 5mg/kg every 36 hours administered in a single dose. A second dose may be given after 36 hours. A shorter interval can be used if clinical judgement suggests that this is needed. According to the British National Formulary (BNF),[64] the price of a single vial of Benzylpenicillin is between £3 and £4 and the price of a single vial or ampoule of Gentamicin is between £1 and £3 depending on the specific brand. For late onset infection, the first-choice antibiotic regime is a narrow-spectrum antibiotic such as intravenous flucloxacillin with gentamicin. The starting dose for this antibiotic regime is 50mg/kg every 6 – 12 hours. According to the BNF,[64] the price of a single vial is between £1 and £4 depending on the specific brand.

If m.1555A>G were to be detected, CPIC guidance recommends that the use of aminoglycosides should be avoided unless the level of infection is very severe and there is a lack of safe or effective alternative therapies.[11] Therefore, alternative antibiotic therapies would be administered. Alternative antibiotic therapies include cefotaxime and amoxicillin, with the exact antibiotic regime used depending on local antimicrobial guidelines. In the PALOH study, when an infant was identified to carry m.1555A>G, they were prescribed with cefotaxime, which is considered to have comparable antimicrobial coverage to benzylpenicillin with gentamicin.[18] The starting dosage for cefotaxime is 50mg/kg administered in a single dose. According to the BNF, the price of a single vial is between £2 and £4 depending on the specific brand.[64]

As this is an early value assessment and the costs of the various antibiotics that may be used are relatively inexpensive, the antibiotic costs were not included in the early economic model, as their impact on the cost-effectiveness was predicted to be negligible. In a definitive study these costs should be included.

5.5.5 Costs of Testing for Hearing Loss

As part of the NHS Newborn screening programme, all neonates should be screened within 26 days of birth for possible hearing loss.[24] An automated otoacoustic emissions test (AOAE) is commonly used in the first instance. If the results are not clear, a second AOAE test may be conducted, or an auditory brainstem response (ABR) test may be used. Clinical experts commented that babies with AIHL may have discordant results and that all those with a known m.1555A>G variant should therefore be referred for immediate follow-up and additional audiological monitoring. The exact health resource requirements for this additional audiological monitoring is unclear. As all neonates are assumed to be screened as part of the NHS Newborn screening programme, the costs of attending the Newborn screening programme and the associated AOAE and ABR tests are not included in the economic analysis. Moreover, as the additional monitoring for those with a known m.1555A>G variant is not predicted to differ between current standard care and the proposed care pathway with the Genedrive MT-RNR1 ID Kit, these costs are also not included in the economic analysis.

5.5.6 Costs of Hearing Aids and Cochlear Implants

5.5.6.1 Hearing Aids

For those children with severe to profound deafness, NICE guidelines state that bilateral hearing aids are recommended for those who do not benefit from acoustic hearing aids.[44] The age at cochlear implant surgery was assumed to be one year, in order to demonstrate no adequate benefit from hearing aids, children need to have had a valid trial of an acoustic hearing aid for at least three months.[65] It was therefore assumed that all neonates with AIHL would be fitted with two acoustic hearing aids for a trial period. The cost of a pair of hearing aids was estimated to be £396 (£198 per individual hearing aid), together with a fitting cost of £249 (see Table 11). It was assumed that hearing aids have a lifetime of five years, and therefore only one pair would be needed per neonate.[37, 41]

Table 11 Costs associated with hearing aids

Item	Cost	Source
Pair of Hearing Aids	396	NHS National Schedule of Reference Costs
Fitting of Hearing Aids	249	NHS National Schedule of Reference Costs

Source: Cost estimates taken from Table 7 of Cutler *et al* (2022). All costs inflated to a common price year of 2022 using the Bank of England Inflation Calculator where appropriate.

5.5.6.2 Cochlear Implants

For cochlear implants, cost estimates were gathered for pre-procedure health resource use, the cost of the procedure itself and post-procedure resource use. Estimates for the pre-implant resource use were taken from Cutler et al (2022),[41] a cost-effectiveness analysis of unilateral cochlear implants in UK adults. These estimates were based on clinical expert sought within the development of the clinical pathway for that study. The unit costs used in Culter et al (2022)[41] were derived from clinical expert opinion, literature reviews, NHS National Schedule of Reference Costs,[66] NHS National Tariffs,[67] and the Unit Costs of Health and Social Care publication.[58]

As outlined by Culter et al (2022),[41] the cost of fitting a cochlear implant can be split into a number of different stages. These include an initial assessment with an audiologist, testing, electrophysiologic assessments, surgeon and general practitioner (GP) consultation and a pre-procedural assessment. Although these estimates were gathered specifically in relation to adult testing, the costs are estimated to be broadly similar to those for children. A previously published budget impact assessment of cochlear implants in children in Scotland estimated the total costs of pre-surgery assessments to be £1,575 (inflated to 2022 prices). This estimate is broadly in line with the costs presented in Table 12 below.[68]

Table 12 Pre-surgery costs associated with cochlear implants

Item		Cost	Source
Stage 1: Initial Assessment			
Audiologist initial assessment		100	NHS National Schedule of Reference Costs[66]
Speech and language therapist		114	NHS National Schedule of Reference Costs[66]
Stage 2: Testing			
Vestibular assessment and tests		100	NHS National Schedule of Reference Costs[66]
Radiologist		105	Unit Costs of Health and Social Care[58]
MRI scan		164	NHS National Schedule of Reference Costs[66]
CT scan		105	NHS National Schedule of Reference Costs[66]
Stage 3: Electrophysiology			
Audio scientist		100	NHS National Schedule of Reference Costs[66]
Electrophysiology assessment		84	Unit Costs of Health and Social Care[58]
Stage 4: Medical Assessment			
Audiologist pre-operative assessment		100	NHS National Schedule of Reference Costs[66]
ENT surgeon consultation		124	NHS National Schedule of Reference Costs[66]

Anaesthetist consultation		155	NHS National Schedule of Reference Costs[66]
Multidisciplinary team meeting (Audiology, SLT, ENT)		338	NHS National Schedule of Reference Costs[66]
GP consultation		37	Unit Costs of Health and Social Care[58]
Meningitis vaccination		71	NHS Vaccine Price List
Stage 5: Pre-Procedural Assessment Outcome Discussion			
Cochlear implant surgery coordinator		52	Unit Costs of Health and Social Care[58]
Total pre-surgery costs		1,749	
Source: Cost estimates taken from Table 5 of Cutler *et al* (2022).[41] All costs inflated to a common price year of 2022 using the Bank of England Inflation Calculator where appropriate.			

The procedure and post-procedure costs were taken from TA566[44] (a partial review of TA166) and originally based on the assumptions made in Bond et al (2009)[37] regarding the long-term cost implications of cochlear implants. These include the costs of the procedures themselves, multiple hearing assessments in the first-year post procedure, as well as post-procedure, annual maintenance and rehabilitation costs. It should be noted that the resource associated with cochlear implant surgery and, subsequently used in TA566 and this report (see Table 13), are lower than those used in Barton et al (2003)[69] when considering inflation and higher than those used in Cutler et al (2022).[41] The cost estimates in these studies were also based on clinical expert opinion.

Table 13 Surgery and post-surgery costs associated with cochlear implants

Item	Cost (£)	Source
Unilateral Cochlear Implant		
Procedure (assuming Children's Services Surgery Multiplier of 34.38%)	36,049	TA566 Resource Impact Template[44]
Audiometry or Hearing Assessment	1,650	TA566 Resource Impact Template[44]
Cochlear implant maintenance and programming – Year 1	3,290	TA566 Resource Impact Template[44]
Cochlear implant maintenance and programming – Year 2 (ongoing)	823	TA566 Resource Impact Template[44]
One to one rehabilitative Audiology Service – Year 1	993	TA566 Resource Impact Template[44]
One to one rehabilitative Audiology Service – Year 2 (ongoing)	124	TA566 Resource Impact Template[44]
Procedure + Assessment Total	37,699	
Costs in First Year Post Procedure	4,283	
Ongoing Yearly Costs after Year 1	947	
Bilateral Cochlear Implant		
Procedure (assuming Children's Services Surgery Multiplier of 34.38%)	59,618	TA566 Resource Impact Template[44]

Audiometry or Hearing Assessment	1,650	TA566 Resource Impact Template[44]
Cochlear implant maintenance and programming – Year 1	3,290	TA566 Resource Impact Template[44]
Cochlear implant maintenance and programming – Year 2 (ongoing)	823	TA566 Resource Impact Template[44]
One to one rehabilitative Audiology Service – Year 1	993	TA566 Resource Impact Template[44]
One to one rehabilitative Audiology Service – Year 2 (ongoing)	124	TA566 Resource Impact Template[44]
Procedure + Assessment Total	61,268	
Costs in First Year Post Procedure	4,283	
Ongoing Yearly Costs after Year 1	947	
Source: Cost estimates taken from TA566 resource impact template.[44] All costs inflated to a common price year of 2022 using the Bank of England Inflation Calculator where appropriate.		

5.6 Early Economic Modelling

In Section 5.2.2 key features of the economic model required for the full economic evaluation were outlined. For some of these data are sparse or lacking altogether. Table 14 outlines key parameters for which good quality evidence is needed for a full economic evaluation but which is currently not available.

Table 14 Likely key evidence gaps for the full economic evaluation model

Evidence Gaps
Proportion of neonates who require antibiotics immediately and therefore will not be tested using the Genedrive MT-RNR1 ID Kit
Proportion of neonates with the m.1555A>G variant treated with aminoglycosides who suffer AIHL
Proportion of neonates with the m.1555A>G variant treated with aminoglycosides who suffer mild/moderate/severe/profound AIHL
Proportion of neonates with the m.1555A>G variant not treated with aminoglycosides who suffer nonsyndromic hearing loss
Proportion of neonates with the m.1555A>G variant not treated with aminoglycosides who suffer mild/moderate/severe/profound nonsyndromic hearing loss
The proportion of neonates with either AIHL or nonsyndromic hearing loss who require hearing aids, unilateral cochlear implants and bilateral cochlear implants
Valid utility values for children under five with different degrees of hearing loss (either AIHL or nonsyndromic) and different types of cochlear implant
The impact of adverse events related to AIHL on costs and utilities
Proportion of neonates who are considered for treatment with aminoglycosides
Proportion of women in labour who are identifiable with risk factors (for infection or sepsis of the neonate)
Proportion of women in labour where maternal inheritance data exists
Proportion of neonates where maternal inheritance data exists

Given the evidence gaps shown in Table 14 an early economic model was used rather than attempting to conduct a full economic model. Early economic evaluation provides an initial assessment of whether a technology has the potential to be cost effective (and under what conditions) and can help prioritise further research that is required and the evidence needed to populate a full economic model.

The early economic model used in this assessment is a simplification of the proposed economic model set out in Section 5.2.2 and illustrated in Figure 6. It follows the same fundamental structure set out in Figure 6 but makes a series of simplifying assumptions. These are set out in Table 15 below, where we describe some key features of the proposed full economic model and how these have been adapted for the early economic model. These simplifications have been made following consideration of when inclusion of a given model feature would be unlikely to change estimates of cost-effectiveness or where there is an evidence gap (see Table 14). As already noted, these evidence gaps would need to be addressed before a full economic model could be conducted.

Table 15 Differences in features between the full economic model and early economic model

Key features of the full economic model	Changes in early economic model
The population modelled are neonates with early onset and late onset infection who need antibiotic	No change.

treatment and who are being considered for treatment with aminoglycosides.	
Some neonates will require antibiotic administration immediately (i.e., there is no time for the test before an antibiotic must be started).	No neonates required antibiotic administration immediately – it was assumed that all neonates were tested.
Increased time to antibiotics will increase the risk of death for neonates with sepsis	Time to antibiotics was not included as part of the early economic model.
There is a chance the Genedrive MT-RNR1 ID Kit will give a false negative result.	In the base-case, the Genedrive MT-RNR1 ID Kit was assumed to have a perfect accuracy. This assumption was tested in the deterministic sensitivity analysis.
There is a chance the Genedrive MT-RNR1 ID Kit will give a false positive result.	No change.
There is a chance that the Genedrive MT-RNR1 ID Kit will fail to give a result.	No change.
If the first Genedrive MT-RNR1 ID Kit fails to give a result, there is time for a second test.	No change.
The clinical pathway for neonates with early onset and late onset infection are different (in terms of duration of antibiotic prescription)	We assumed the same clinical pathway for neonates with early onset and late onset infection.
If both the first Genedrive MT-RNR1 ID test kit and the second Genedrive MT-RNR1 ID test kit fail, there will be insufficient time for further testing and neonates with suspected infection will not be treated with aminoglycosides and will receive other antibiotics.	The second Genedrive MT-RNR1 ID test was assumed to never fail.
Where neonates are identified as not having the m.1555A>G variant using the Genedrive MT-RNR1 ID Kit, aminoglycosides will be used.	No change.
Where neonates are identified as having the m.1555A>G variant using the Genedrive MT-RNR1 ID Kit, alternative antibiotics will be used.	No change.
Different aminioglycosides will have different adverse event profiles.	All classes of aminoglycoside (gentamicin, amikacin, tobramycin, and neomycin) were assumed to have the same adverse reaction profile.
For neonates with the m.1555A>G variant treated with aminoglycosides, there is a risk of AIHL.	In the base-case it was assumed that all neonates with the m.1555A>G variant treated with aminoglycosides would suffer AIHL. This assumption was tested in the deterministic sensitivity analysis.
For neonates with the m.1555A>G variant not treated with aminoglycosides, there is a risk of nonsyndromic hearing loss.	In the base-case it was assumed that no neonates with the m.1555A>G variant not treated with aminoglycosides would suffer hearing loss. This assumption was tested in the deterministic sensitivity analysis.
For neonates with AIHL, the severity of the hearing loss may vary.	In the base-case it was assumed that if AIHL occurs it will result in severe/profound irreversible deafness.

Women with risk factors (for sepsis) are eligible for Genedrive MT-RNR1 ID Kit, but antibiotic prescription will be for neonates (after birth)	We assume the same prevalence of disease (suspected to sepsis) and gene mutation in mothers and neonates.
Maternal inheritance may be considered before testing.	Maternal inheritance will not be considered before testing.
An increased time to antibiotics will increase the risk of death for neonates.	Time to antibiotics was not included in the early economic model.
The use of the Genedrive MT-RNR1 ID Kit, other than affecting time to administration and the type of antibiotic used, does not affect normal standard of care for neonates presenting with suspected infection or sepsis.	No change.
There will be training costs for staff to carry out the test.	Training costs were excluded. It was assumed that training costs would not have a large impact on the cost-effectiveness results from the model.
Staff time is required to carry out the test.	No change.
Additional audiological monitoring will be required for infants with AIHL.	The costs of this additional monitoring were not included.
There are pre-procedure, procedure and post-procedure costs associated with both unilateral and bilateral cochlear implants.	No change.
AIHL has several associated adverse events	It was assumed the adverse events of AIHL would not have a large impact on the cost-effectiveness results from the model
If AIHL occurs, neonates will require hearing aids, unilateral cochlear implants or bilateral cochlear implants	In the base-case it was assumed that if AIHL occurs all neonates would require bilateral cochlear implants. This assumption was tested in the deterministic sensitivity analysis.
HRQoL will vary by age, level of hearing loss, type of cochlear implant and time since cochlear implant has been implanted	It was assumed that hearing loss could vary by type of cochlear implant and time since the cochlear implant was implanted. It was assumed that all neonates with AIHL would suffer profound hearing loss. Utility values for children five and above were used as proxies for children under five. Different utility values were used for those under 18 and 18 and over, however no further age-adjustment was used.
To demonstrate no adequate benefit from hearing aids, children need to have had a valid trial of an acoustic hearing aid for at least three months	No change.
There is a chance that the cochlear implant surgery will not be successful.	No change.
It is possible to upgrade cochlear implants after they have been fitted.	It was assumed it was not possible to upgrade cochlear implants.

There may be complications associated with the implantation of cochlear implants (i.e., internal or external device failure, death)	It was assumed there are no complications associated with the implantation of cochlear implants.
There are short-term and long-term adverse events associated with cochlear implants.	Adverse events related to cochlear implants were not included.

The early economic Markov model was informed by the key features described in Table 15. The model starts with the presentation of a neonate with suspected infection or sepsis. For the Genedrive pathway in the model the neonate is receives the Genedrive test (Figure 7). All the events described in Figure 7 are assumed to occur in the first cycle (i.e., year one) of the model. Although not shown in Figure 7, neonates may also receive an additional test to confirm AIHL (Sanger Sequencing). In terms of cost, we excluded costs associated with the different antibiotics that may be prescribed to the neonate with suspected infection or sepsis as their impact on the cost-effectiveness was predicted to be negligible.

As shown in Figure 7, the destination of the neonate in terms of which Markov state they transition to is based on the results of the Genedrive test. For (true) positive cases, alternative antibiotic therapies (such as cefotaxime) are prescribed instead of aminoglycosides, and neonates move to the "discharge" state. These neonates will not suffer AIHL. The model structure allows the possibility that some neonates with gene mutation may suffer hearing loss even if they received other types of antibiotics. These children would to the to the cochlear implant state in the next cycle. However, in the base-case analysis the probability of this occurring is set to zero.

For (false) negative cases, neonates will be prescribed aminoglycosides. This may result in AIHL, and these neonates also move to the cochlear implant state in the next cycle. Again, the model allows the possibility that some neonates with gene mutation will not suffer AIHL even if they have received aminoglycosides. In the base-case analysis we assumed that the Genedrive test has a near perfect test accuracy. We also assumed that all neonates with the gene mutation that received aminoglycosides will result in AIHL and that none of neonates that have been prescribed with other antibiotics will result in hearing loss.

As part of the early economic model, we also modelled what would happen if the first test failed to provide a result. Here we allowed the possibility that a second test could be conducted. If the second test was successful, the neonate followed the same pathway they would have done had the first test been successful. If the second test failed, we assumed that there would be no time to conduct a third test and that neonates would not be prescribed aminoglycosides and be prescribed alternative antibiotics such as cefotaxime.

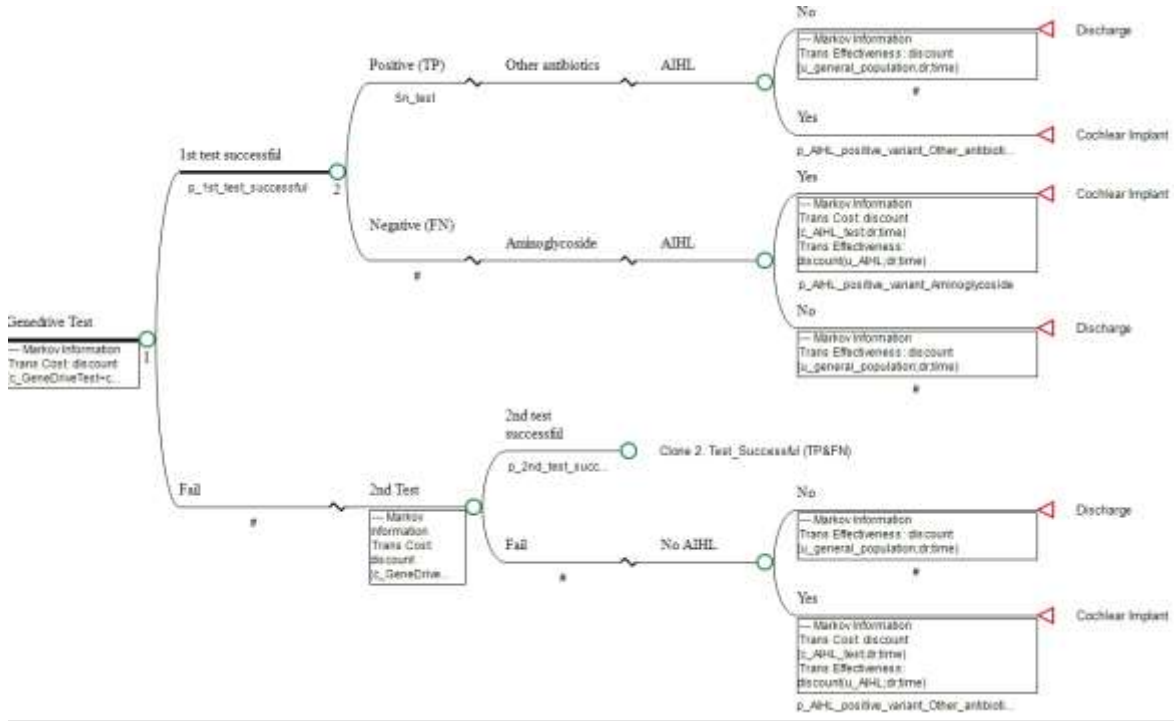


Figure 7 Decision tree of using Genedrive MT-RNR1 ID Kit in the Markov model

For neonates that follow the standard pathway, the Genedrive MT-RNR1 ID Kit, is not used and those with the m.1555A>G variant receive an aminoglycoside and AIHL occurs. Those without the variant likewise receive an antibiotic but do not experience AIHL and are discharged from care. Thus, the pathway here is a simplification of that described in Figure 7.

After the sequence of events described in Figure 7, occurs the individual modelled can move to one of two states: Discharge or cochlear implant. Those who move to the Discharge state stay there for the rest of their life. For those that move to the cochlear implant state (i.e., infants with AIHL) they follow receive a unilateral/bilateral cochlear implantation. In either case the implant has a probability of failing. In this situation other forms of hearing support are used. This process of care is described in Figure 8 and is assumed to all take place in a single cycle of the model. At the end of the cycle individuals move to states where the cochlear implant is working, or it is not, and other forms of hearing support are needed. Within the base–case analysis individuals stay in these states for the rest of their lives.

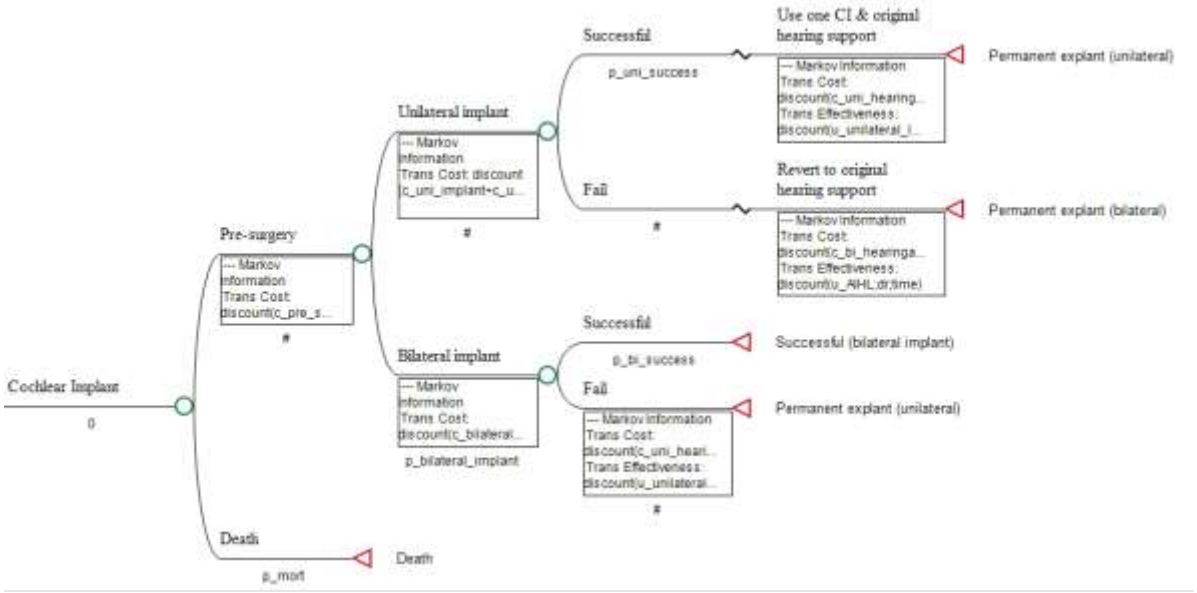


Figure 8 Decision tree for the cochlear implant state with the Markov model

5.7 Model Parameters

The parameters used in the early economic model are shown in Table 16, Table 17, Table 18, Table 19.

Table 16 Model setting parameters and population characteristics

Parameter	Base-case value	Sensitivity analysis values (low – high)	Source
Time Horizon (Years)	100	1-100	Model Assumption
Starting Age (Years)	0	-	Model Assumption
Discount Rate (%)	0.035	0.015-0.05	Model Assumption
Prevalence of MT-RNR1 variant m.1555A>G in the UK population	0.0019	0.0010-0.0028	Bitner-Glindzicz *et al* (2009)[4]
Probability of 1st Genedrive MT-RNR1 ID Test being successful	0.943	0.5-1	PALOH Study[18]
Probability of 2nd Genedrive MT-RNR1 ID Test being successful	1	0.8-1	Model Assumption
Probability of AIHL for neonates with the m.1555A>G variant prescribed with aminoglycoside	1	0.3-1	Model Assumption, Gopel et al 2014[6]
Probability of AIHL for neonates with the m.1555A>G variant prescribed with other antibiotics	0	0-0.30	Model Assumption, Ballana 2006[2] Estivill 1998[3]
Proportion of cases with bilateral cochlear implant	1	0.5-1	Model Assumption

Probability of unilateral or bilateral cochlear implant being successful	0.97	0.8-1	Wang *et al* (2014)[70]
Probability of death for the model cohort	UK Lifetable Mortality 2022	-	National Life Table UK[71]

Table 17 Test specific parameters

Parameter	Base-case value	Sensitivity analysis values (low – high)	Source
Genedrive MT-RNR1 ID Kit Price (Per Test)	£102	£50 - £150	Model Assumption
Genedrive MT-RNR1 ID Kit Accuracy (Sensitivity)	1	0.292-1	PALOH Study[18]
Genedrive MT-RNR1 ID Kit Accuracy (Specificity)	0.992	0.980-997	PALOH Study[18]

Table 18 Cost values used in the model

Parameter	Base-case value (£)	Sensitivity analysis values (low – high)	Source
Cost of Sanger Sequencing	191	150 - 250	Medtech Briefing Document[21]
Cost of unilateral hearing aids	447	400 - 500	Cutler *et al* (2022)[41]
Cost of bilateral hearing aids	645	600 - 700	Cutler *et al* (2022)[41]
Cost of unilateral cochlear implant (Procedure + Assessment Total)	37,699	20,000 – 50,000	TA566[44]
Cost of bilateral cochlear implant (Procedure + Assessment Total)	61,268	40,000 – 80,000	TA566[44]
Cost of unilateral cochlear implant (First Year Post Procedure)	4,283	2,000 – 6,000	TA566[44]
Cost of bilateral cochlear implant (First Year Post Procedure)	4,283	2,000 – 6,000	TA566[44]
Annual ongoing cost of unilateral or bilateral cochlear implant	947	500 – 1,500	TA566[44]
Cost for the staff (nurse) doing the test	28	15 – 40	Unit Costs of Health and Social Care 2021[63]
Aggregated pre-surgery costs associated with unilateral or bilateral cochlear implants	1,749	1,500 – 2,000	Cutler *et al* (2022)[41]

Table 19 Utility values used in the model

Parameter	Base-case value	Sensitivity analysis values (low – high)	Source
Children (Under 18)			

No hearing loss (population norm)	0.908	0.899 – 0.917	Pogany *et al* (2006)[46]
Profound/significant hearing loss	0.421	0.398 – 0.452	Barton *et al* (2006)[35]
Unilateral cochlear implant (less than two years since implant)	0.487	0.408 - 0.565	Barton *et al* (2006)[35]
Unilateral cochlear implant (two to four years since implant)	0.633	0.582 - 0.684	Barton *et al* (2006)[35]
Unilateral cochlear implant (over four years since implant)	0.653	0.605 - 0.701	Barton *et al* (2006)[35]
Bilateral cochlear implant (less than two years since implant)	0.490	0.411 – 0.568	Barton *et al* (2006)[35], Bond *et al* (2009)[37]
Bilateral cochlear implant (two to four years since implant)	0.636	0.585 - 0.687	Barton *et al* (2006)[35], Bond *et al* (2009)[37]
Bilateral cochlear implant (over four years since implant)	0.656	0.608 - 0.704	Barton *et al* (2006)[35], Bond *et al* (2009)[37]
Adults (18 and over)			
No hearing loss (population norm)	0.850	0.841 - 0.859	Pogany *et al* (2006)[46]
Profound/significant hearing loss	0.433	0.407 – 0.468	UKCISG (2004)[29]
Unilateral cochlear implant	0.630	0.609 – 0.651	UKCISG (2004)[29],
Bilateral cochlear implant	0.633	0.585 – 0.734	Summerfield (2006)[34]

5.8 Estimation of cost-effectiveness and sensitivity analysis

5.8.1 Estimation of cost-effectiveness

Using the data set out in Tables 16-19 two estimates of cost-effectiveness were produced:

- Incremental cost per case of AIHL avoided
- Incremental cost per QALY gained

For each point estimates of costs and effects for neonates that follow either current standard of care or use the Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G were estimated. From these incremental costs, effects and incremental cost effectiveness were calculated.

Deterministic sensitivity analysis

We also conducted a deterministic sensitivity analysis to explore the uncertainty regarding key parameters in the early economic model, using the sensitivity analysis values shown in Tables 16-19. This sensitivity analysis focused on costs, QALYs and incremental cost per QALY only. Due to the uncertainty regarding the majority of the parameters in the early economic model, a probabilistic sensitivity analysis was not implemented.

For the prevalence of the m.1555A>G variant, the high and low values used in the sensitivity analysis were the 95% confidence intervals from Bitner-Glindzicz *et al* (2009).[4] For the sensitivity and specificity values, the high and low values used in the sensitivity analysis were the 95% confidence intervals reported in the PALOH study.[18] For the utility values, the high and low values for the sensitivity analysis were the 95% confidence intervals from the original studies from which the values were sourced.

For the parameter related to the probability of AIHL for neonates with the m.1555A>G variant prescribed with aminoglycosides, the lower bound estimate (0.3) was taken from Gopel *et al* (2014), a prospective cohort study in a German population.[6] For the other parameters (including all of the cost parameters), reasonable high and low values were chosen to explore the potential uncertainty related to these parameters.

5.9 Model Results

5.9.1 Base-case results

Using the parameters shown in Section 5.7, the base-case results from the early economic model are shown in Table 20 for the cases of AIHL avoided and Table 21 for QALYs. In terms of AIHL, the results show that using the Genedrive MT-RNR1 ID Kit is estimated to be cost saving over the lifetime of the neonate tested for the m.1555A>G genetic variant with the Genedrive MT-RNR1 ID Kit.

Table 20 Base-case economic analysis – cases of AIHL avoided (Genedrive MT-RNR1 ID Kit vs Normal standard of care)

Strategy	Total costs (£)	Cases of AIHL	Incremental cost (£)	Incremental AIHL avoided	ICER (£)
GeneDrive MT-RNR1 ID Kit	151.45	0	-58.48	0.00	Dominant
Normal standard of care	209.93	0.002			
Source: Produced by EAG					

Superseded

In terms of cost of per QALY, the results show that the Genedrive MT-RNR1 ID Kit dominates the current standard of care over the lifetime, as it is less costly and more effective (Table 21).

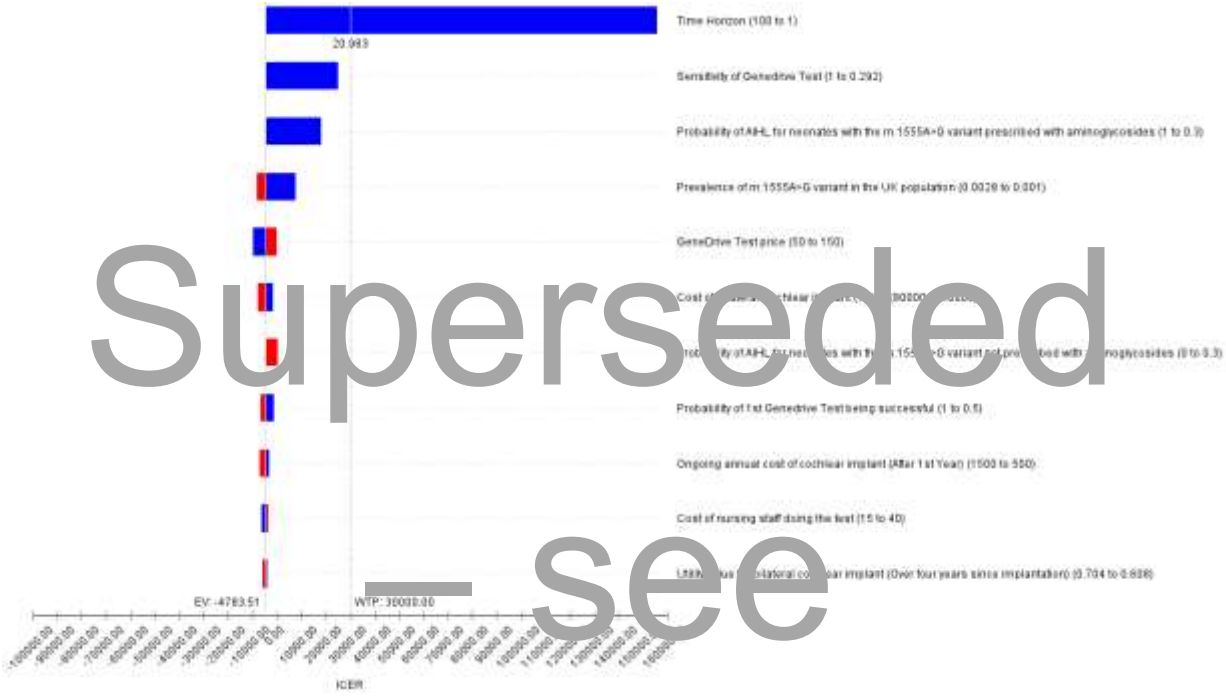
– see erratum

Table 21 Base-case economic analysis - QALYs gained (Genedrive MT-RNR1 ID Kit vs Normal standard of care)

Strategy	Total costs (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)
Genedrive MT-RNR1 ID Kit	151.45	23.12	-58.48	0.01	Dominant
Normal standard of care	209.93	23.11			
Source: Produced by EAG					

Results from deterministic sensitivity analysis

The results from the deterministic sensitivity analysis are presented in a Tornado plot (Figure 9). The Tornado shows the impact of the high and low parameter values specified in Tables 14 – 18 on the estimated ICER.



Superseded – see erratum

Figure 9 Tornado Diagram Genedrive MT-RNR1 ID Kit pathway vs. Standard pathway

As shown in Figure 9, the parameter values which have the largest impact on the ICER are the time horizon of the model, the sensitivity of the Genedrive MT-RNR1 ID Kit, the probability of neonates with the m.1555A>G variant prescribed with aminoglycosides suffering from AIHL, the prevalence of the m.1555A>G variant across the population and the cost of the Genedrive MT-RNR1 ID Kit. As Figure 9 shows, varying other parameter values (for example the utility values associated with bilateral cochlear implants and the probability of cochlear implants being successful) did not appear to materially impact the incremental cost per QALY.

The sensitivity of the results to the time horizon reflects the fact that from an NHS resource use perspective, there are significant costs required in order to identify one neonate with the m.1555A>G variant, while the benefits (specifically cost savings related to cochlear implants avoided and utility gains from avoiding AIHL) are likely to only be felt in the medium to long-term. Table 22 illustrates this by showing the impact on cost-effectiveness of varying the time horizon between one, ten and 50 years. As shown in Table 22, although the Genedrive MT-RNR1 ID Kit has a very large ICER when compared to normal standard of care for a one-year time horizon, the Genedrive MT-RNR1 ID Kit has an incremental cost per QALY of just over £100 when using a ten-year time horizon and dominates the current normal standard of care when using a 50-year time horizon.

Table 22 Base-case economic analysis: QALYs gained for different time horizons (Genedrive MT-RNR1 ID Kit vs Normal standard of care)

Time Horizon	Strategy	Total costs (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)

One Year Time Horizon	Genedrive MT-RNR1 ID Kit	151.45	0.90	151.07	0.00	155,767
	Normal standard of care	0.38	0.90			
Ten Year Time Horizon	Genedrive MT-RNR1 ID Kit	151.45	7.78	0.62	0.01	103
	Normal standard of care	150.83	7.77			
50 Year Time Horizon	Genedrive MT-RNR1 ID Kit	151.45	20.42	-48.43	0.01	Dominant
	Normal standard of care	199.88	20.41			
Source: Produced by EAS						

Superseded — see erratum

The impact of the sensitivity of Genedrive MT-RNR1 ID Kit on the cost-effectiveness results reflects the fact that the real-world sensitivity of the Genedrive Test (as reported in the PALOH study[18]) is highly uncertain due to the very small number of positive cases. This uncertainty was reflected in the reported wide confidence intervals used as the high and low values in the deterministic sensitivity analysis.

The sensitivity of the results to the proportion of neonates with m.1555A>G variant suffering from AIHL after being exposed to aminoglycosides reflects the inherent uncertainty related to this parameter. As discussed in Section 1.1.1, although there is clear evidence that m.1555A>G variant is a risk factor for AIHL, most evidence comes from case-control studies which may overestimate this risk, and therefore the precise level of this risk is unknown.

With respect to the results being sensitive to the prevalence of the m.1555A>G variant across the population, this parameter affects how many neonates need to be tested to detect a single neonate with the m.1555A>G variant. As the probability increases, fewer neonates need to incur the cost of testing to detect a neonate with the variant and hence cost-effectiveness of using the Genedrive MT-RNR1 ID Kit improves. Although no data were available to consider how cost-effectiveness varied by different sub-groups, this sensitivity analysis helps illustrate how cost-effectiveness might vary if testing were focused on sub-groups where the m.1555A>G variant is more prevalent.

For the cost of the Genedrive MT-RNR1 ID Kit , the analysis made some simplifying assumptions about what costs were included. Although there is some variation in the incremental cost per QALY, the sensitivity analysis shows that inclusion of these costs would not substantially alter the cost-effectiveness results over the lifetime horizon.

6. Public Involvement

6.1 Methods

Public involvement took place at a single time point, at an influencing level as described within the ACTIVE continuum of involvement using two different approaches.[72]

The first approach was to scan data held upon social media forums. A total of 40,346 individual posts (39,374 from the children's health section of Mumsnet and 972 posts from the National Deaf Children's Society forum) were collected using a custom web scraping script written in Python.[73] Posts were then filtered using search terms generated by an information specialist (Concepts as follows: newborn; infection; antibiotics; hearing loss) applied with gestalt pattern matching, with an 80% match or above considered relevant.[74, 75] A second filter was applied using two regular expression searches ('(\d+) year[s]? old' and '(\d+) month[s]? old') to identify posts mentioning children under one. Less relevant posts identified by broader terms reflective of only two concepts 'antibiotics' and 'baby' were removed. This left 92 individual posts which were manually screened and thematically analysed using a reflexive, inductive approach by a single researcher.[76]

The second approach was a focus group. Recruitment was facilitated through contact with organisations and individuals relevant to the early value assessment scope population. Present at the focus group were mothers of newborns (n=1), mother of toddlers (n=3), professionals who care for newborns and their families (n=2) and an effectiveness reviewer (n=1). Participants consented to recording via Zoom, handwritten notes were also taken, and Zoom chat messages were monitored and saved. Introductions were undertaken to establish a climate of trust between attendees and begin active listening. To orientate participants, they were given a high-level overview of: NICE technology appraisal and early value assessment; diagnostic test accuracy review; bacterial infection, sepsis and its treatment; the MT-RNR1 gene variant m.1555A>G and the proposition of testing for this within the infection or sepsis care pathway. Opportunities were given at regular intervals for participants to ask questions about the information being presented. Participants were then asked to share their thoughts and feelings about testing for m.1555A>G during the infection or sepsis care pathway. Facilitation was neutral to allow for open discussion. However, discussion of how participants would make decisions on: test use; treatment prior or subsequent to testing and outcomes of importance was probed. Recordings were transcribed by a single researcher using rapid intelligent verbatim transcription.[77] One researcher then thematically analysed data, abstracting and organising concepts into broad themes, then seeking cross-cutting commonalities using a reflexive, inductive approach. Identified codes and themes were reviewed and relevance agreed upon by other researchers in the team.

6.2 Findings

Social Media Posts

The 92 social media posts centre around three descriptive themes: neonatal sepsis experiences; infection causing hearing loss; and hearing loss from gentamycin use.

Neonatal sepsis experiences

Families of infants who have had sepsis are using social media to:

- Share experiences of neonatal sepsis, connect with other parents with shared experiences

  "After a load of tests...sepsis, a week on two broad spectrum antibiotics...."

  "...other mums of sepsis babies...?"

- Understand and express fear of perceived long-term consequences of sepsis

- Future infection rate and impact
  "...still suffers a lot of viral infections and bacterial infections now aged 3..."

- Potential side effects of antibiotic treatment on feeding and digestion.
  "*...what is wrong with Lo and his feeding...One of the things that I've read can cause it is antibiotics in early life..."*

Infection (sepsis or meningitis) as a cause of hearing loss

Families of infants who have had sepsis or meningitis and now have hearing loss are using social media to:

- Explore the aetiology of their child's hearing loss
- Share experience of difficulties finding childcare
  "...childminders are not getting back to me..."

- Share experience of difficulties using hearing aids
  "...hair is now brushing the back of the aids I wonder if that is causing distress..."

- Express a need for earlier hearing loss testing after infection
  "...trying to arrange a hearing test but ... audiology department is not being particularly forthcoming..."

Hearing loss and gentamicin use

Families of infants with hearing loss potentially due to gentamicin use:

- Express a preference for treatment with gentamicin, with a perceived trade-off between side effects and effective treatment
  "...antibiotics are given with best intentions at the time, and ... was very poorly so I would rather ... had the antibiotics..."

  - Have a lack of clarity on alternate treatment options and comparative effectiveness
    "...i'm not sure if there are options for other antibiotics which are strong enough..."

- Want use of treatments with ototoxic potential to be after informed consent given
  "...doctor should have advised and obtained informed consent..."

- Indicate a lack of clarity on safe dosing
  "doctor told us that...didn't receive 'too much' however we don't know the impact of what...did receive"

  - Indicate the utility of test to inform future treatment for individual and offspring
    "have it (variant)*... this done as could have issues if needed...these drugs again...could pass this to...children"*

- Desire clarity on the aetiology of hearing loss
  - Emotional support dealing without clarity and moving on from search for a cause
    "I haven't thought about it for a long time...move on from finding a cause...is what it is'..."

  - Identify testing for the variant may not give this
    "tested negative so we were no further forward"

Focus Group Discussion

Two overarching analytical themes emerged from focus group discussion: Information need to inform parents decision to test and, or, treat; and testing desirability dependent on context.

Information need to inform parents decision to test and, or, treat.

Information was wanted on:

- The prevalence of the variant (see section 1.1.1, evidence available).

"what is the chance of having the variant where you might be predisposed to losing your hearing."

- Test accuracy and safety both for use in children (see section 3.4.1, limited evidence) and mothers (see Table 1, no evidence).

"So I suppose i'm just asking how...safe is this test"
"...it would be a non-starter for me if there was any question on the accuracy of the test..."
"...how accurate it is when they test the mother..."

- The chance of hearing loss developing after taking aminoglycosides without the variant (see section 1.1.1, limited evidence) and with the variant (evidence not sought).

"...the risk of taking the initial drug and losing your hearing..."

- The chance of spontaneous hearing loss with the variant (see section 1.1.2, limited evidence) and without the variant (evidence not sought). This links to social media comments on desire for clarity on hearing loss aetiology

"...I didn't have the numbers of what the chance of them having hearing loss was I would want to know that chance..."

- The chance of morbidity and mortality from infection and from sepsis. As well as, if and how this changes based on time to treatment initiation.

"...i'm presuming that within that hour the quicker, the better it is even within that hour..."
"What other risks are there then? What other repercussions for your child?"
"...so, chances of like the long term health effects increase the longer you wait?"

- The longer-term health risks of infection and sepsis.

"What are the other long-term or like health risks of having"

- The comparative effectiveness and tolerability of antibiotics (see section 1.5, limited evidence). This links with the lack of clarity expressed about treatment options and comparative effectiveness in social media posts.

"I'd want to know the differences between the 2 drugs...taking the second one, does that increase the chance of mortality?"
"...why wouldn't you just use the second antibiotic, whatever that might be, if that was equal..."
"...You want to know which outweighs the other..."

- The certainty in aetiology of hearing loss after testing. This links with social media data on the lack of clarity testing for the variant may give upon hearing loss aetiology

"Obviously they do a hearing test on newborn babies not long after they've been born. How do they know that it's a drug that caused the hearing loss..."

Testing desirability dependent on context
Testing undesirable if:

- Variant prevalence is low (with evidence showing this is the case, see section 1.1.1), test not very accurate, chance of failure and poor safety.

"...because if that's (prevalence) *incredibly low...the majority of people would not want to go down that route* (testing) *if the chance of actually having the genetic variant is incredibly low."*
"...So do we know what the failure of it is, what is it?"

- Within the care pathway for infection and sepsis and parents unable to make truly informed choices about testing due to stress of the situation. Parents wanted to make the decision on whether testing was undertaken and to then be guided by clinical expertise on how or if this should inform treatment. This links to the desire for discussion of potential side effects of treatment and sought consent in social media data.

"...is there somewhere that this test is offered to before giving birth, to determine whether this gene might be there on the newborn prior to any possible infection. So things can be looked at in advance and thought about, rather than in a panic..."

"Is it you know this is what we could treat your baby with, but the the risks are of them potentially having hearing loss..."

"...if I was in that position I would want to make a decision, but I think I would be guided by the other people around..."

- If there is a decline in outcomes from infection or sepsis over time to treatment initiation, parents did not want any treatment delay even if this led to adverse events. A second test was not deemed acceptable. This links with the preference for treatment regardless of trade off against side effects expressed in social media posts.

"...save that 26 min, or the the 52, whatever it might be to stop the risk of the whole situation getting worse..."

Testing desirable if:

- Undertaken upstream of infection amongst neonates at high risk of infection or mothers at risk of giving birth to a neonate at high risk of infection. There is evidence on testing at this upstream point in the pathway although not with Genedrive MT-RNR1 ID Kit. However, evidence indicates this mtDNA variant could potentially be heteroplasmic which would affect the accuracy of testing mothers as a proxy for newborn (see section 1.1.3).

"...why this test isn't given to pregnant mothers, that's my personal point of view... if it was down to the cost effectiveness of that test when the mother is pregnant that would make me so mad... and that hearing loss is avoidable...obviously you have your babies here. But if you could have avoided hearing loss..."

"... Comes back to what Z said earlier...It's maybe not the time when parents would want that test to be happening."

7. Discussion

7.1 Statement of principal findings

7.1.1. Clinical effectiveness

Only one study (reported in two publications) met the eligibility criteria for our rapid review.[17, 18] The study reported on the following outcomes of interest: diagnostic test accuracy, number of successful tests for neonates, test failure rate, the impact of the results on care decisions, impact of test implementation and use on healthcare resources (for example, the time taken to do and interpret test), time to obtaining a sample for a test, time to results, time to antibiotic treatment, and number of neonates identified with m.1555A>G genetic variant. However, it did not report on the following outcomes of interest: successful test of mothers, usability of the test, mortality and morbidity.

The diagnostic test accuracy of the Genedrive MT-RNR1 was high, with no false negatives reported. However, estimates of real-world sensitivity of the test lacked precision, as only three participants with the m.1555A>G variant were identified in the study.[18]

There were five false positives, which was suggested to have been rectified by updating the cartridge used in the machine.[18] Similarly, adaptations to the Genedrive MT-RNR1 ID Kit were conducted to reduce the test failure rate. After this correction, in a laboratory based setting there were no failed tests, however, in the intended point of care a test failure rate of 5.7% was still observed.[18] Three neonates were successfully identified as carrying the genetic variant, leading to aminoglycoside antibiotics being avoided and alternative cephalosporin-based regimens being provided.[18] The time to results for the Genedrive MT-RNR1 ID Kit was consistent with predefined boundaries of statistical equivalence with standard care (mean difference = -0.87 minutes, 95% CI: -5.96 to 4.23 minutes). This finding justified the simplification of the early economic evaluation model, which did not address the impact of time to antibiotics on cost-effectiveness.

Regarding the usability of the test, the analysis provides an actionable result in 26 minutes, with an estimated time of approximately 30 minutes from collection of the buccal swab to an actionable result (i.e., genetic variant detected or not detected). However, the time to obtaining a sample can vary (median = 6 minutes, IQR = 3 to 16 minutes).

Overall, these results suggest that the Genedrive MT-RNR1 ID Kit has promise as an accurate point of care diagnostic test. In addition, it has potential to provide rapid identification within a time sensitive period required to impact treatment decisions of neonates with the m.1555A>G genetic variant.

7.1.2. Cost-effectiveness

No existing economic evaluations were identified that addressed the topic of this study.

The costs of the Genedrive MT-RNR1 ID Kit were estimated using information provided by the company and assumptions made by the EAG. Considering the equipment needed to carry out the test, it was estimated that it would cost approximately £102 per diagnostic test inclusive of capital costs. It was also estimated that 30 minutes of nurse time would be needed to carry out each diagnostic test, raising the estimated total cost per diagnostic test to approximately £130. This estimate is subject to considerable uncertainty given the different types of hospital wards in which the Genedrive MT-RNR1 ID Kit could potentially be used. Although estimated to be relatively inexpensive at an individual level, due to the rarity of the m.1555A>G genetic variant the costs of identifying one neonate with this variant are more substantial. For example, under the strong assumptions of a test with perfect diagnostic

accuracy, an estimated prevalence of the m.1555A>G genetic variant of 0.002 and an estimated cost of £130 per test, the cost to identify one neonate with the variant would be £65,000.

If the Genedrive MT-RNR1 ID Kit were to be recommended for use in clinical practice whilst further data are being collected (potentially to address some of the evidence gaps identified as part of this early value assessment), the sunk costs to the NHS would include the Genedrive System itself (£4,995) and a Bluetooth printer (£200) for each site, the bulk purchasing of the Genedrive MT-RNR1 ID Kits and any accumulated training costs for health care professionals to carry out the test. As discussed previously, the training costs even for large sites with large numbers of nursing staff are likely to be relatively minor given the predicted short time of training and the fact that this could be provided for free by the manufacturer. Estimating the total sunk costs at a national level is very difficult, given the uncertainty regarding the type and numbers of sites that would potentially use the Genedrive MT-RNR1 ID Kit System. However, if each of the reported 55 Level 3 NICUs in England were to purchase the Genedrive MT-RNR1 ID System and a Bluetooth printer, the total costs would be approximately £280,000.[61]

The EAG developed an early economic model to identify key drivers of the cost-effectiveness of Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates, and also to identify evidence gaps. A targeted literature review was undertaken to identify utility values relevant for the specific population. A detailed care pathway and model were constructed, and the evidence requirements were defined. There are several key evidence gaps that exist, including the magnitude of risk for aminoglycoside induced hearing loss (AIHL) in neonates with m.1555A>G, the risk of hearing loss for neonates with m.1555A>G genetic variant without exposure to aminoglycosides, the proportion of neonates potentially requiring different types of cochlear implants and how data regarding maternal inheritance may potentially be used in the clinical pathway.

The early economic model was constructed to explore introducing the Genedrive diagnostic test into NHS services. This model focused on likely key determinants of costs and QALYs. These key areas were arrived by considering the likely impact on average costs or QALYs for the two clinical pathways (with Genedrive MT-RNR1 ID Kit and current standard care) and focusing on these parameters which might have the greatest impact on cost-effectiveness. This model was then subject to one-way deterministic sensitivity analysis to explore the impact of changes in these key parameter values. Of note, some of the changes explored indirectly assessed whether the omission of an element could affect the model result. For example, in the early economic evaluation model the costs of training have been omitted but the cost of the test has been varied in the sensitivity analysis over a range that would include the cost of testing if the training costs had been included.

Overall, the base-case results from the early economic model suggest that the use of the Genedrive MT-RNR1 ID Kit could potentially be cost-effective, mainly driven by the high diagnostic accuracy reported in the PALOH study, estimated relatively low cost per test and the avoidance of large future health care costs associated with the fitting of cochlear implants for those infants suffering from AIHL. From a deterministic sensitivity analysis conducted as part of the early economic model, the results were most sensitive to time horizon of the model (which allows more time for the health benefits that flow from avoiding hearing impairment to accrue), the sensitivity of the Genedrive MT-RNR1 ID Kit, the probability of neonates with the m.1555A>G variant suffering AIHL after being exposed to aminoglycosides and the prevalence of genetic variant across the population. This suggests that research to identify more robust data on the sensitivity of the Genedrive MT-RNR1 ID Kit, the risk of AIHL for those with the m.1555A>G variant exposed to aminoglycosides and the prevalence of the m.1555A>G variant in the UK in particular would be useful. Given the limitations of the early economic model,

these results are not sufficient to make decisions about adoption, but they are suggestive that the generation of new data may be useful.

7.2. Limitations

7.2.1 Clinical effectiveness

There are several limitations to the current evidence base. First, there has been only one study of the use of Genedrive MT-RNR1 ID Kit. This study was conducted in two specialised large NICUs, although one NICU did drop out of the study, and therefore it is unclear if these findings can be generalised to smaller neonatal units. Especially as there is limited evidence on the implementation and use of healthcare resources associated with the test kit. Additionally, some infants are born and evaluated for infection in other venues that may not have access to this technology.[78]

Second, the test was refined during the PALOH study (for example, to reduce failure rate). Although there is preliminary evidence to suggest the benefits of these more recent iterations, further studies are needed to confirm that the reduced failure rate for the test can be replicated in different settings.

Third, our rapid review identified no evidence investigating the clinical- or cost-effectiveness of Genedrive MT-RNR1 Test Kit in mothers (prebirth of the neonates). Therefore, we have no evidence to inform the use of the Test Kit in this population. Mahmood and Leung[79] have argued it would be theoretically possible to pre-test expectant mothers with the Genedrive MT-RNR1 ID Kit. Clinical advice received by NICE also highlighted this potential application for the technology. This could be especially important when families are anticipating neonatal antibiotics based on a peripartum diagnosis, meaning those neonates who were excluded in the PALOH study for requiring antibiotics immediately[18] could be included.[79]

Fourth, prior to conducting the PALOH study[18] there were some concerns regarding ethical challenges, such as testing prior to informed consent, and the burden of responsibility placed on the practitioner and the wider societal impacts technology such as the Genedrive MT-RNR1 MT-RNR1 ID Kit.[80] However, the test is relatively simple, only needing a buccal swab,[81] and would only be used in intended point of care healthcare setting.[82] Additionally, the point of care test could be considered integral to the broad package of care offered to the unwell neonate, for which broad parental consent is provided, or if unavailable, is done in the best interest of the child.[83]

Fifth, some have raised concerns regarding the choice of antibiotics being made by the point of care test. Specifically, gentamicin is suggested to be the gold standard treatment for neonates with suspected/confirmed sepsis and giving second line care could increase risk of death.[84] This concern was also raised in our focus group with parents (see section X). Therefore, there are alternative views as to whether the usage of the Genedrive MT-RNR1 ID Kit for identification of the m.1555A>G genetic variant is required. However, our clinical advisors suggest this risk of death due to antibiotics given is low.

Finally, other variants in other genes that result in the same risk phenotype are currently not assessed by the current test.[78]

7.2.2 Cost effectiveness

Further limitations can be highlighted for the economics analyses. Foremost amongst these is that given lack of data the results generated from the early economic evaluation are highly uncertain. For example, in the base case analysis of the early economic model, the sensitivity and specificity of the test are assumed to be 100% and 99.2% respectively, despite the significant uncertainty associated with the sensitivity value. This assumption was explored in the deterministic sensitivity analysis, which showed that getting more accurate data is likely to be of high importance to the cost-effectiveness results. Other

relevant data that are highly uncertain include the precise proportion of neonates with the m.1555A>G genetic variant who will suffer from hearing loss both with and without the prescription of aminoglycosides, the staffing requirements in different sizes and types of hospital wards where the Genedrive MT-RNR1 ID Kit may be implemented and the how the Genedrive MT-RNR1 ID Kit could be used to test mothers rather than neonates.

Second, for the early economic evaluation model several parameters have effectively been omitted. These include training costs, the costs of antibiotics and the impact (in terms of both costs and utilities) of long-term adverse events related to cochlear implants. The justification for this is that it was felt that the cost per patient of adding these costs would have a minimal impact on the cost-effectiveness results. This may not however be the case for all parameters. For example, there is uncertainty surrounding the proportions of neonates who suffer some degree of hearing impairment who go on to have normal hearing aids or require unilateral/bilateral cochlear implants. The results of the sensitivity analysis show that the cost-effectiveness results could be sensitive to changes in the costs of these and by extension the results will be sensitive to the proportions receiving each form of hearing aid. These omissions would need to be addressed in a full economic evaluation.

Third, other data used in the economic model may not be strictly relevant to the NICE reference case. For example, although the long-term utility data related to deafness and cochlear implants used in the early economic model are sourced from a pivotal study, these data are based on data from the HUI3 rather than the EQ-5D.[37] This is potentially justifiable as the HUI3 directly captures the impact on hearing that the EQ-5D does not. A bolt-on for hearing is under development for the EQ-5D but not yet available and of course would not relate to NICEs preferred source of utility values. The data for the HUI3 were taken from a study that was completed around 20 years ago and technology related to cochlear implants has improved significantly since then. The utility values for the HUI3 are also approaching 30 years old and are derived from a Canadian population. It is also unclear how applicable they are to children under five years of age, as the HUI3 is only validated for those five years old and over. There is a scarcity of validated HRQoL instruments suitable for infants. Although the Infant health-related Quality of life Instrument (IQI) has recently been developed, none of the seven attributes are related to hearing and again this is not compatible with the NICE reference case.[85, 86]

Fourth, related to the cost perspective, the economic model has thus far only considered NHS costs. There are likely to be costs that fall on the personal social services relating to other aids and adaptations that may be needed. Furthermore, there may be broader societal impacts on children and families (e.g., increased caring responsibilities; possible impacts on the speech development and educational attainment of the child) that may also need to be considered.

Finally, the scope of the economic evaluation may be too narrow in terms of capturing the broader implications of integrating the test into the clinical pathway. These are likely to vary substantially according to the centre. In addition, there may be some further impacts on laboratory testing. This is uncertain as the number of neonates presenting with suspected infection or sepsis is itself uncertain. The model also has not considered the impacts on antibiotic resistance. Clinical experts have advised that there are strong clinical concerns regarding antibiotic resistance to alternative antibiotic therapies than may be prescribed instead of aminoglycosides, such as cefotaxime. Therefore the incidence of antimicrobial resistance in the healthcare setting could be improved if testing reduces the use of these alternative antibiotics.[10] How this latter impact could be captured in a definitive model is however unclear.

7.3 Evidence Gaps

Diagnostic accuracy and failure rate of test

There are several uncertainties regarding the accuracy of the Genedrive MT-RNR1 ID Kit. The NICE scope included testing mothers of neonates who may require antibiotics. We found no studies using the Genedrive MT-RNR1 ID Kit in this population.

Although the PALOH study provides data on the diagnostic accuracy of Genedrive MT-RNR1 ID Kit, estimates of sensitivity of the test is severely limited by the small number (only three neonates) identified with the m.1555A>G genetic variant.[18] Therefore, although the test may be potentially very sensitive, the 95% CI was wide (mean sensitivity=100%, 95% CI 29.2% to 100.00%) indicating very high imprecision. As the early economic evaluation shows, estimates of cost-effectiveness are very sensitive to this imprecision.

Failure rate was originally 17.1% (90 of 514 neonates) but after modifications to the assay buffer and a redesigned cartridge consumable this was reduced. In a laboratory setting the failure was zero, while in a clinical setting this reduced to 5.1%, when repeated testing was conducted.[18] This suggests that when used as the point of care test there is still a failure rate, and more than one test may be required to be performed. As the test is reported to take 26 minutes, this could cause issues with antibiotic prescribing times that are required to be within the hour. Therefore, further work is required to ascertain the number of test failures that may be expected and the impact of this on prescribing. The early economic modelling suggested that this evidence gap would only have a modest effect on cost-effectiveness.

Generalisability of results

The NICE scope included NICU and hospital wards. The PALOH study provided evidence that use of Genedrive MT-RNR1 ID Kit did not substantially impact on time to antibiotics compared with standard care.[18] A key outcome, given the need to provide antibiotics within an hour of decision to treat. However, the PALOH study was conducted in two large and well-resourced NICUs, therefore advice from some of our clinical experts indicated it was unclear whether data from time to antibiotics in this study generalise to smaller NICUs and other hospital wards.

Estimating the magnitude of risk for aminoglycoside induced hearing loss (AIHL) in neonates with m.1555A>G

There is clear evidence that the m.1555A>G genetic variant is a risk factor for aminoglycoside induced hearing loss (AIHL).[11] However, data on the magnitude of this risk is uncertain. Case control studies usually find all people with the variant experience hearing loss.[3] However, selecting participants for hearing loss may overestimate the risk associated with aminoglycosides. Studies that do not select for hearing loss suggest people with the m.1555A>G variant may not always experience hearing loss when exposed to aminoglycosides.[6] The early economic evaluation suggests that cost-effectiveness estimates are likely to be sensitive to the magnitude of this risk.

In order to understand the long-term benefits (on clinical outcomes and cost-effectiveness) of avoiding aminoglycoside use in neonates with the m.1555A>G genetic variant, more precise estimates on the magnitude of risk for AIHL in this population are required. It is also worth noting that there is an evidence gap related to hearing loss for those without exposure to aminoglycosides. However, the results from the sensitivity analysis in the early economic model indicated that this may not be important.

Maternal inheritance and use of point of care testing in mothers

The m.1555A>G variant is inherited maternally, and therefore identifying a mother's m.1555A>G status may be another way of identifying a child's m.1555A>G status. However, there are several

uncertainties and evidence gaps related to this. Firstly, there in uncertainty about how well a mother's m.1555A>G status can indicate the risk of AIHL in their child. Although there are studies related to the variant load and hearing thresholds, these studies have small sample sizes. Secondly, there is uncertainty related to the proportion of mothers for which a clinically relevant genotype has previously been identified. Finally, in relation to using point of care testing for the mother, it is unclear what proportion of woman are likely to be given aminoglycosides during labour or in other clinical settings.

Resource implications

The PALOH study provided evidence that no increase in nursing time was required to implement the assay into practice.[18] As stated previously, the PALOH study was conducted in two large and well-resourced NICUs with significant experience of conducting research. There is therefore a clear lack of evidence related to the resource implications in different sized NICUs and different hospital wards where the Genedrive MT-RNR1 ID Kit may potentially be used in the future.

Estimating the severity of AIHL in neonates with m.1555A>G and quantifying the proportion of neonates requiring different types of cochlear implants in the long term

Alongside the uncertainty related to the risk of AIHL following exposure to aminoglycosides, there is also uncertainty related to the severity of AIHL for those who suffer from it. Consequently, there is uncertainty regarding the proportion of neonates with AIHL who would require different cochlear implants of different types over the long-term. This is important, as cochlear implants have significant NHS resource implications, with substantial costs related to surgery and annual maintenance and programming. Current NICE guidance states that cochlear implants are recommended for children (and adults) with severe to profound deafness who do not gain adequate benefit from acoustic hearing aids.[44] Severe to profound deafness in this case is defined as hearing only sounds that are louder than 80 dB HL. For children, adequate benefit is defined as speech, language and listening skills appropriate to age, developmental stage and cognitive ability. It is currently unclear what proportion of neonates would require acoustic hearing aids only, unilateral cochlear implants and bilateral cochlear implants, making estimates of the long-term savings associated with preventing cochlear implants highly uncertain.

Utility values for health states related to hearing loss and cochlear implants that conform to the NICE reference case for use in an economic model

As noted in Table 5.3 (Section 5.3), the majority of previous economic evaluations identified related to hearing loss and/or cochlear implants in the UK population identified in this early value assessment have used the HUI3 HRQoL tool to measure health state utilities. The main reason for this is that the HUI3 has a specific dimension related to hearing, which other commonly used HRQoL tools such as the EQ-5D and SF-6D do not. Indeed, previous research has shown that the HUI3 has better validity and responsiveness than the EQ-5D and SF-6D in studies of patients with hearing impairments.[87]

However, although the HUI3 may have some advantages relative to the EQ-5D in respect to validity and responsiveness in this clinical area, the EQ-5D is NICE's preferred measure in the reference case. Furthermore, the value set used for the HUI3 is from a Canadian adult sample and is over 20 years old. Research is ongoing regarding the development of a hearing 'bolt-on' for the EQ-5D, however its measurement properties are yet to be established.[42]

8. Conclusion

8.1. Implications for service provision

This rapid review shows that the Gendrive MT-RNR1 ID Kit has the potential to identify the m.1555A>G variant and the potential to be cost-effective. However, as anticipated, there is insufficient evidence to conduct a full diagnostic assessment of the clinical- and cost-effectiveness of Genedrive MT-RNR1 ID Kit in neonates the neonate directly, or their mother.

The evidence to inform this EVA was limited, based on only one study that included only three neonates with the m.1555A>G variant. In addition, the study was conducted in two large specialist NICUs, it is unclear whether the benefits of the technology generalise to smaller units. Too few data are available to derive robust estimates of cost-effectiveness and whilst the Genedrive MT-RNR1 ID Kit has the potential to be cost-effective, the early economic evaluation model is subject to considerable uncertainties.

8.2. Suggested research priorities

The following studies may reduce uncertainty on the clinical and cost-effectiveness of the Genedrive MT-RNR1 ID Kit identified in this EVA.

8.2.1 Risk and severity of AIHL in people with m.1555A>G variant

Proposed eligibility criteria

Population: People with m.1555A>G variant

Exposure: aminoglycosides (either directly or by exposure through mother)

Comparator: no exposure to aminoglycosides

Outcomes: Prevalence of AIHL, severity of AIHL, health-related quality of life, costs to the NHS and PSS

Study Design: cohort studies

Why this is important

There are several uncertainties regarding the risk of hearing loss in people with m.1555A>G variant:

- Risk of AIHL in people with m.1555A>G variant exposed to aminoglycosides
- Severity of AIHL in people with m.1555A>G variant exposed to aminoglycosides

The risk of AIHL in people with AIHL was identified as an important uncertainty in the economic model (see Figure 9). Cohort studies on the risk of AIHL in people with m.1555A>G variant have identified a small number of people who meet the above criteria.[6] However, substantial uncertainty regarding the magnitude of these risks remains.

Existing cohort studies in the UK and beyond, such as the Born in Bradford study, are potentially important sources of data to identify people who meet these eligibility criteria. However, given the rarity of the variant, approximately 0.3% of the UK population, it is unlikely one single cohort study will provide a large enough sample size. Therefore, it is likely meta-analyses of future cohort studies will be required for sufficient precision of estimates..

8.2.2 Further Validation of Genedrive MT-RNR1 ID Kit

Proposed Eligibility Criteria

Population: population of the NICE scope (neonates needing or expecting to need aminoglycosides and mothers with risk factors for sepsis)

Intervention: Genedrive MT-RNR1 ID Kit

Comparator: Usual care

Outcomes: Outcomes identified in NICE scope, of particular importance for informing uncertainties in the economic model: diagnostic accuracy (sensitivity of test); failure rate; time to antibiotic use; and health resource use implications (including a detailed micro-costing). Qualitative data on barriers and facilitators of implementing the test (including obtaining informed consent for parents).

Study design: Mixed methods (quantitative and qualitative)

Why this is important

The sensitivity of the Genedrive MT-RNR1 ID Kit for identifying neonates with the m.1555A>G variant was identified as a key uncertainty in the economic model. The PALOH study, the only study identified for inclusion in the rapid review of clinical effectiveness data, identified only three participants with the variant.Therefore although the estimated sensitivity of the test was very high the 95% CI was also very uncertain (mean=1.00, 95% CI 0.29 to 1.00).

In addition, the PALOH was conducted in two large NICUs (94.9% of participants were recruited from one centre, with one dropping out part way through the study). Therefore, it is unclear whether these findings generalise to smaller NICUs or other hospital wards where service configuration may differ.

Conducting further investigations in other NICUs and hospitals of varying sizes would provide greater detailed evidence of the real-world application for the point of care test. There are also uncertainties surrounding the test failure rate. Although it was reduced after edits to the Genedrive MT-RNR1 ID Kit, in the intended clinical setting there was still some failure rate. This could impact time to treatment with antibiotics and further research could allow for reduced uncertainty on e the true test failure rate in practice.

In addition, PPIE (see section 6) identified concerns from parents about the risks and benefits of the Genedrive MT-RNR1 ID Kit. Some parents were reluctant to consent for their child to take the test, particularly when their baby was at high risk of infection. Therefore, a qualitative study alongside further evaluation of the technology would help to identify barriers to implementation and obtaining informed consent.

8.2.3 Measurement of utilities associated with hearing loss, hearing aids and cochlear implants using preference elicitation techniques to validate existing values and use in economic model

Proposed Eligibility Criteria

Population: Adult general population sample

Outcomes: Utility values for different levels of hearing loss, different types of hearing aid and different types of cochlear implant

Study Design: Patient preference study where a general population sample measure the HRQoL associated with hearing loss, hearing aids and cochlear implants using either the standard gamble of time-trade off technique

Why this is important

The majority of previous economic evaluations related to hearing loss and/or cochlear implants in the UK population identified in this early value assessment have used the HUI3 HRQoL tool to measure utility, however the EQ-5D is NICE's preferred method of measuring utility in the reference case.

Furthermore, the value set used for the HUI3 is from an Canadian adults sample and is over 30 years old. Although research in ongoing regarding a hearing 'bolt on' for the EQ-5D, the measurement properties of this bolt on are still to be established.[42]

Given that the EQ-5D is unlikely to be an appropriate measure of utility for this condition, one alternative approach that could be used to generate alternative utility values for use in a future economic model could be to use either the time-trade off (TTO) or standard gamble (SG), two choice-based methods of eliciting health state utilities commonly used in health economics. These methods of measuring utility are seen to be acceptable alternatives to NICE in the absence of good quality EQ-5D data. Summerfield et al (2002) previously used the TTO in relation to unilateral cochlear implantations in adults, however the general population sample was relatively small (n=70) and only valued four health states.[27] Summerfield et al (2010) also used the TTO in relation to bilateral cochlear implantation in children, however the sample gathered was a convenience sample composing of clinicians/researchers, students, and parents of children with hearing problems (n=180) and once more they only valued four health states.[39]

A larger study with a representative general population sample (in line with the NICE reference case) and a larger range of health states to be valued (related to hearing loss, hearing aids and different sorts of cochlear implants) could potentially provide health state utility values. Such values would be more appropriate for use in a future economic model in the absence of EQ-5D data, or be used to validate the existing utility values from the literature used in economic models which have been generated using the HUI3.

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Superseded
– see
erratum

Appendix A

Clinical Effectiveness Searches

Medline

1. Point-of-Care Systems/
2. Point-of-Care Testing/
3. Genetic Testing/
4. (POCT or "point of care" or "point-of-care").ti,ab,kw.
5. genedrive*.af.
6. MIB?290.ti,ab,kw.
7. PALoH.ti,ab,kw.
8. ((pharmacogenetics or pharmacogenomics or genetic* or geno* or gene* or hear* or pyrosequenc* or sequenc*) adj4 (test* or assay* or system* or screen* or sequenc*)).ti,ab,kw.
9. or/1-8
10. "mt.1555A>G".ti,ab,kw.
11. "1555A>G".ti,ab,kw.
12. "m.1555A>G".ti,ab,kw.
13. "A1555G".ti,ab,kw.
14. "1555 A to G".ti,ab,kw.
15. MT?RNR?1.ti,ab,kw.
16. ((penetrance or snp or polymorphism or mutation) adj3 "1555").ti,ab,kw.
17. or/10-16
18. exp Aminoglycosides/
19. (Gentamicin or paromomycin or amikacin or plazomicin or tobramycin or neomycin or kanamycin or streptomycin or netilmicin).ti,ab,kw.
20. aminoglycoside*.ti,ab,kw.
21. (anti?biotic* or anti?bacterial* or anti?infective*).ti,ab,kw.
22. exp Anti-Bacterial Agents/ae, to [Adverse Effects, Toxicity]
23. or/18-22
24. induc*.ti,ab,kw.
25. ototoxicity.ti,ab,kw.
26. exp Hearing Loss/
27. exp Hair Cells, Auditory/
28. Ototoxicity/
29. Deaf*.ti,ab,kw.
30. (hear* adj2 (loss or impair*)).ti,ab,kw.
31. or/24-30
32. 9 and 17 and 23 and 31
33. "Genedrive MT-RNR1 ID".af.
34. 32 or 33
35. exp Animals/
36. exp Humans/
37. 35 not 36
38. 34 not 37
39. limit 38 to dt=20100101-20220929
40. limit 39 to english language

Embase

1. "point of care system"/
2. "point of care testing"/
3. genetic screening/
4. (POCT or "point of care" or "point-of-care").ti,ab.
5. genedrive*.af.

6. MIB?290.ti,ab.
7. PALoH.ti,ab.
8. ((pharmacogenetics or pharmacogenomics or genetic* or geno* or gene* or hear* or pyrosequenc* or sequenc*) adj4 (test* or assay* or system* or screen* or sequenc*)).ti,ab.
9. or/1-8
10. "mt.1555A>G".ti,ab.
11. "1555A>G".ti,ab.
12. "m.1555A>G".ti,ab.
13. "A1555G".ti,ab.
14. "1555 A to G".ti,ab.
15. MT?RNR?1.ti,ab.
16. ((penetrance or snp or polymorphism or mutation) adj3 "1555").ti,ab.
17. or/10-16
18. exp aminoglycoside antibiotic agent/
19. (Gentamicin or paromomycin or amikacin or plazomicin or tobramycin or neomycin or kanamycin or streptomycin or netilmicin).ti,ab.
20. aminoglycoside*.ti,ab.
21. (anti?biotic* or anti?bacterial* or anti?infective*).ti,ab.
22. exp antiinfective agent/to [Drug Toxicity]
23. or/18-22
24. induc*.ti,ab.
25. ototoxicity.ti,ab.
26. exp hearing impairment/
27. exp "hair cell (inner ear)"/
28. exp ototoxicity/
29. deaf*.ti,ab.
30. (hear* adj2 (loss or impair*)).ti,ab.
31. or/24-30
32. 9 and 17 and 23 and 31
33. "Genedrive MT-RNR1 ID".af.
34. 32 or 33
35. exp animal/
36. exp human/
37. 35 not 36
38. 34 not 37
39. limit 38 to dc=20100101-20221004
40. limit 39 to english language

Cochrane

#1 MeSH descriptor: [Point-of-Care Systems] this term only
#2 MeSH descriptor: [Point-of-Care Testing] this term only
#3 MeSH descriptor: [Genetic Testing] this term only
#4 (POCT or "point of care" or "point-of-care"):ti,ab,kw
#5 (genedrive*)
#6 (MIB?290):ti,ab,kw
#7 (PALoH):ti,ab,kw
#8 ((pharmacogenetics or pharmacogenomics or genetic* or geno* or gene* or hear* or pyrosequenc* or sequenc*) NEAR/4 (test* or assay* or system* or screen* or sequenc*)):ti,ab,kw
#9 {OR #1-#8}
#10 ("mt.1555A>G"):ti,ab,kw
#11 ("1555A>G"):ti,ab,kw
#12 ("m.1555A>G"):ti,ab,kw

#13 ("A1555G"):ti,ab,kw
#14 ("1555 A to G"):ti,ab,kw
#15 (MT?RNR?1):ti,ab,kw
#16 ((penetrance or snp or polymorphism or mutation) NEAR/3 "1555"):ti,ab,kw
#17 {OR #10-#16}
#18 MeSH descriptor: [Aminoglycosides] explode all trees
#19 (Gentamicin or paromomycin or amikacin or plazomicin or tobramycin or neomycin or kanamycin or streptomycin or netilmicin):ti,ab,kw
#20 (aminoglycoside*):ti,ab,kw
#21 (anti?biotic* or anti?bacterial* or anti?infective*):ti,ab,kw
#22 MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#23 {OR #18-#22}
#24 (induc*):ti,ab,kw
#25 (ototoxicity):ti,ab,kw
#26 MeSH descriptor: [Hearing Loss] explode all trees
#27 MeSH descriptor: [Hair Cells, Auditory] explode all trees
#28 MeSH descriptor: [Ototoxicity] this term only
#29 (deaf*):ti,ab,kw
#30 (hear* NEAR/2 (loss or impair*)):ti,ab,kw
#31 {OR #24-#30}
#32 #9 AND #17 AND #23 AND #31
#33 ("Genedrive MT-RNR1 ID")
#34 #32 OR #33

CINAHL

S36 S33 AND S34 AND S35
S35
S34
S33 S31 OR S32
S32 TX "Genedrive MT-RNR1 ID"
S31 S9 AND S13 AND S19 AND S30
S30 S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29
S29 TI (AEP or BAER or BAEP) OR AB (AEP or BAER or BAEP)
S28 TI (audit* N4 (respons* or evok* or potential*)) OR AB (audit* N4 (respons* or evok* or potential*))
S27 (MH "Evoked Potentials, Auditory, Brainstem")
S26 TI (hear* N2 (loss or impair*)) OR AB (hear* N2 (loss or impair*))
S25 TI deaf* OR AB deaf*
S24 (MH "Ototoxicity")
S23 (MH "Hair Cells")
S22 (MH "Hearing Disorders+") OR (MH "Deafness+")
S21 TI ototoxicity OR AB ototoxicity
S20 TI induc* OR AB induc*
S19 S14 OR S15 OR S16 OR S17 OR S18
S18 (MH "Antibiotics+/AE")
S17 TI (anti?biotic* or anti?bacterial* or anti?infective*) OR AB (anti?biotic* or anti?bacterial* or anti?infective*)
S16 TI aminoglycoside* OR AB aminoglycoside*
S15 TI (Gentamicin or paromomycin or amikacin or plazomicin or tobramycin or neomycin or kanamycin or streptomycin or netilmicin) OR AB (Gentamicin or paromomycin or amikacin or plazomicin or tobramycin or neomycin or kanamycin or streptomycin or netilmicin)
S14 (MH "Aminoglycosides+")
S13 S10 OR S11 OR S12
S12 TI (((penetrance or snp or polymorphism or mutation) N3 "1555")) OR AB (((penetrance or snp or polymorphism or mutation) N3 "1555"))
S11 TI MT#RNR#1 OR AB MT#RNR#1
S10 TI ("mt.1555A>G" OR "1555A>G" OR "m.1555A>G" OR "A1555G" OR "1555 A to G") OR AB ("mt.1555A>G" OR "1555A>G" OR "m.1555A>G" OR "A1555G" OR "1555 A to G")
S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S8 TI (((pharmacogenetics or pharmacogenomics or genetic* or geno* or gene* or hear* or pyrosequenc* or sequenc*) N4 (test* or assay* or system* or screen* or sequenc*))) OR AB (((pharmacogenetics or pharmacogenomics or genetic* or geno* or gene* or hear* or pyrosequenc* or sequenc*) N4 (test* or assay* or system* or screen* or sequenc*)))
S7 TI PALoH OR AB PALoH
S6 TI (MIB290 OR "MIB 290") OR AB (MIB290 OR "MIB 290")
S5 TX genedrive*
S4 TI (POCT OR "point-of-care" OR "point of care") OR AB (POCT OR "point-of-care" OR "point of care")
S3 (MH "Genetic Screening")

S2 TI point-of-care systems OR AB point-of-care systems
S1 (MH "Point-of-Care Testing")

Appendix B

Economic evaluation searches

 # MEDLINE

1. Point-of-Care Systems/
2. Point-of-Care Testing/
3. Genetic Testing/
4. (POCT or "point of care" or "point-of-care").ti,ab,kw.
5. genedrive*.af.
6. MIB?290.ti,ab,kw.
7. PALoH.ti,ab,kw.
8. ((pharmacogenetics or pharmacogenomics or genetic* or geno* or gene* or hear* or pyrosequenc* or sequenc*) adj4 (test* or assay* or system* or screen* or sequenc*)).ti,ab,kw.
9. or/1-8
10. "mt.1555A>G".ti,ab,kw.
11. "1555A>G".ti,ab,kw.
12. "m.1555A>G".ti,ab,kw.
13. "A1555G".ti,ab,kw.
14. "1555 A to G".ti,ab,kw.
15. MT?RNR?1.ti,ab,kw.
16. ((penetrance or snp or polymorphism or mutation) adj3 "1555").ti,ab,kw.
17. or/10-16
18. exp Aminoglycosides/
19. (Gentamicin or paromomycin or amikacin or plazomicin or tobramycin or neomycin or kanamycin or streptomycin or netilmicin).ti,ab,kw.
20. aminoglycoside*.ti,ab,kw.
21. (anti?biotic* or anti?bacterial* or anti?infective*).ti,ab,kw.
22. exp Anti-Bacterial Agents/ae, to [Adverse Effects, Toxicity]
23. or/18-22
24. induc*.ti,ab,kw.
25. ototoxicity.ti,ab,kw.
26. exp Hearing Loss/
27. exp Hair Cells, Auditory/
28. Ototoxicity/
29. Deaf*.ti,ab,kw.
30. (hear* adj2 (loss or impair*)).ti,ab,kw.
31. or/24-30
32. 9 and 17 and 23 and 31
33. "Genedrive MT-RNR1 ID".af.
34. 32 or 33
35. exp Animals/
36. exp Humans/
37. 35 not 36
38. 34 not 37
39. limit 38 to dt=20100101-20220929
40. limit 39 to english language

 # Embase

1 socioeconomics/
2 "cost benefit analysis"/
3 "cost effectiveness analysis"/
4 "cost of illness"/

5 "cost control"/
6 economic aspect/
7 financial management/
8 "health care cost"/
9 health care financing/
10 health economics/
11 "hospital cost"/
12 (fiscal or financial or finance or funding).tw.
13 "cost minimization analysis"/
14 (cost adj estimate$).mp.
15 (cost adj variable$).mp.
16 (unit adj cost$).mp.
17 or/1-16
18 "point of care system"/
19 "point of care testing"/
20 genetic screening/
21 (POCT or "point of care" or "point-of-care").ti,ab.
22 genedrive*.af.
23 MIB?290.ti,ab.
24 PALoH.ti,ab.
25 ((pharmacogenetics or pharmacogenomics or genetic* or geno* or gene* or hear* or pyrosequenc* or sequenc*) adj4 (test* or assay* or system* or screen* or sequenc*)).ti,ab.
26 or/18-25
27 "mt.1555A>G".ti,ab.
28 "1555A>G".ti,ab.
29 "m.1555A>G".ti,ab.
30 "A1555G".ti,ab.
31 "1555 A to G".ti,ab.
32 MT?RNR?1.ti,ab.
33 ((penetrance or snp or polymorphism or mutation) adj3 "1555").ti,ab.
34 or/27-33
35 exp aminoglycoside antibiotic agent/
36 (Gentamicin or paromomycin or amikacin or plazomicin or tobramycin or neomycin or kanamycin or streptomycin or netilmicin).ti,ab.
37 aminoglycoside*.ti,ab.
38 (anti?biotic* or anti?bacterial* or anti?infective*).ti,ab.
39 exp antiinfective agent/to [Drug Toxicity]
40 or/35-39
41 induc*.ti,ab.
42 ototoxicity.ti,ab.
43 exp hearing impairment/
44 exp "hair cell (inner ear)"/
45 exp ototoxicity/
46 deaf*.ti,ab.
47 (hear* adj2 (loss or impair*)).ti,ab.
48 or/41-47
49 26 and 34 and 40 and 48
50 "Genedrive MT-RNR1 ID".af.
51 49 or 50
52 exp animal/
53 exp human/

54 52 not 53
55 51 not 54
56 limit 55 to dc=20100101-20221004
57 limit 56 to english language
58 17 and 57

 # CINAHL

S46 S13 AND S45
S45 S43 AND S44
S44
S43 S41 OR S42
S42 S22 AND S32 AND S40
S41 TX "Genedrive MT-RNR1 ID"
S40 S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39
S39 TI (hear* N2 (loss or impair*)) OR AB (hear* N2 (loss or impair*))
S38 TI deaf* OR AB deaf*
S37 (MH "Ototoxicity")
S36 (MH "Hair Cells")
S35 (MH "Hearing Disorders+") OR (MH "Deafness+")
S34 TI ototoxicity OR AB ototoxicity
S33 TI induc* OR AB induc*
S32 S27 OR S28 OR S29 OR S30 OR S31
S31 (MH "Antibiotics+/AE")
S30 TI (anti?biotic* or anti?bacterial* or anti?infective*) OR AB (anti?biotic* or anti?bacterial* or anti?infective*)
S29 TI aminoglycoside* OR AB aminoglycoside*
S28 TI (Gentamicin or paromomycin or amikacin or plazomicin or tobramycin or neomycin or kanamycin or streptomycin or netilmicin) OR AB (Gentamicin or paromomycin or amikacin or plazomicin or tobramycin or neomycin or kanamycin or streptomycin or netilmicin)
S27 (MH "Aminoglycosides+")
S26 S23 OR S24 OR S25
S25 TI (((penetrance or snp or polymorphism or mutation) N3 "1555")) OR AB (((penetrance or snp or polymorphism or mutation) N3 "1555"))
S24 TI MT#RNR#1 OR AB MT#RNR#1
S23 TI ("mt.1555A>G" OR "1555A>G" OR "m.1555A>G" OR "A1555G" OR "1555 A to G") OR AB ("mt.1555A>G" OR "1555A>G" OR "m.1555A>G" OR "A1555G" OR "1555 A to G")
S22 S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S27 OR S28 OR S29
S21 TI (((pharmacogenetics or pharmacogenomics or genetic* or geno* or gene* or hear* or pyrosequenc* or sequenc*) N4 (test* or assay* or system* or screen* or sequenc*))) OR AB (((pharmacogenetics or pharmacogenomics or genetic* or geno* or gene* or hear* or pyrosequenc* or sequenc*) N4 (test* or assay* or system* or screen* or sequenc*)))
S20 TI PALoH OR AB PALoH
S19 TI (MIB290 OR "MIB 290") OR AB (MIB290 OR "MIB 290")
S18 TX genedrive*
S17 TI (POCT OR "point-of-care" OR "point of care") OR AB (POCT OR "point-of-care" OR "point of care")
S16 (MH "Genetic Screening")
S15 TI point-of-care systems OR AB point-of-care systems
S14 (MH "Point-of-Care Testing")
S13 S11 NOT S12
S12 PT news OR PT Letter OR PT Editorial

S11 S9 OR S10
S10 TX (cost or costs or economic$ or pharmacoeconomic$ or price$ or pricing$)
S9 S7 OR S8
S8 MW Health resource utilization OR MW Health resource allocation
S7 S1 NOT S6
S6 S2 OR S3 OR S4 OR S5
S5 (MH "Business+")
S4 (MH "Financing, Organized+")
S3 (MH "Financial Support+")
S2 (MH "Financial Management+")
S1 (MH "Economics+")

#COCHRANE

#1 MeSH descriptor: [Point-of-Care Systems] this term only 477
#2 MeSH descriptor: [Point-of-Care Testing] this term only 102
#3 MeSH descriptor: [Genetic Testing] this term only 423
#4 (POCT or "point of care" or "point-of-care"):ti,ab,kw 2583
#5 (genedrive*) 0
#6 (MIB?290):ti,ab,kw 0
#7 (PALoH):ti,ab,kw 0
#8 ((pharmacogenetics or pharmacogenomics or genetic* or geno* or gene* or hear* or pyrosequenc* or sequenc*) NEAR/4 (test* or assay* or system* or screen* or sequenc*)):ti,ab,kw 50919
#9 {OR #1-#8} 53314
#10 ("mt.1555A>G"):ti,ab,kw 0
#11 ("1555A>G"):ti,ab,kw 1
#12 ("m.1555A>G"):ti,ab,kw 1
#13 ("A1555G"):ti,ab,kw 3
#14 ("1555 A to G"):ti,ab,kw 0
#15 (MT?RNR?1):ti,ab,kw 0
#16 ((penetrance or snp or polymorphism or mutation) NEAR/3 "1555"):ti,ab,kw 1
#17 16-#16 5
#18 MeSH descriptor: [Aminoglycosides] explode all trees 9189
#19 (Gentamicin or paromomycin or amikacin or plazomicin or tobramycin or neomycin or kanamycin or streptomycin or netilmicin):ti,ab,kw 5794
#20 (aminoglycoside*):ti,ab,kw 986
#21 (anti?biotic* or anti?bacterial* or anti?infective*):ti,ab,kw 45868
#22 MeSH descriptor: [Anti-Bacterial Agents] explode all trees 13127
#23 {OR #18-#22} 55411
#24 (induc*):ti,ab,kw 187979
#25 (ototoxicity):ti,ab,kw 576
#26 MeSH descriptor: [Hearing Loss] explode all trees 1357
#27 MeSH descriptor: [Hair Cells, Auditory] explode all trees 7
#28 MeSH descriptor: [Ototoxicity] this term only 6
#29 (deaf*):ti,ab,kw 1577
#30 (hear* NEAR/2 (loss or impair*)):ti,ab,kw 4297
#31 {OR #24-#30} 192804
#32 #9 AND #17 AND #23 AND #31 2
#33 ("Genedrive MT-RNR1 ID") 0
#34 #32 OR #33 2

#REPEC
"m.1555" | "mt.1555" | "MTRNR1" | "MT-RNR-1" | "MT RNR 1" | Genedrive | PAHoL | "MIB290" | "MIB-290" | "MIB 290"

Appendix C

A list of excluded records

Parker J, Wright D. Terrible choices in the septic child: a response to the PALOH trial round table authors. Journal of Medical Ethics 2021;47:114-116. (exclusion reason: wrong publication type)

McDermott JH, Mahaveer A, James RA, et al. Rapid Point-of-Care Genotyping to Avoid Aminoglycoside-Induced Ototoxicity in Neonatal Intensive Care. JAMA Pediatrics 2022;176(5):486–492. (exclusion reason: wrong publication type)

McDermott JH. Genetic testing in the acute setting: a round table discussion. Journal of Medical Ethics 2020;46:531-532. (exclusion reason: wrong publication type)

Pillers DM. Genetic Testing in Newborns Moves From Rare to Routine Application. JAMA Pediatrics. 2022;176(5):448–449. (exclusion reason: wrong publication type)

Fischer PR. Aminoglycoside-Induced Ototoxicity: Test Before You Treat?. Infectious Disease Alert 2022; 41(8). (exclusion reason: wrong publication type)

Huang S, Xiang G, Kang D, et al. Rapid identification of aminoglycoside-induced deafness gene mutations using multiplex real-time polymerase chain reaction. International Journal of Pediatric Otorhinolaryngology. 2015; 79(7): 1067-72. (exclusion reason: wrong population)

Fan W, Zhu Y, Tang X, et al. Noninvasive test for mitochondrial DNA A1555G mutation associated with deafness. Clinical Laboratory. 2017; 63(1), 127-131. (exclusion reason: wrong population)

The Hearing Review. Genedrive Pediatric Hearing Screening Test Receives CE Marking. 2019. Available from: https://hearingreview.com/hearing-products/testing-equipment/pediatric-testing/genedrive-pediatric-hearing-screening-test-receives-ce-marking [Accessed: 1st December 2022]. (exclusion reason: wrong publication type)

Phillips LL, Glindzicz MB, Lench N, et al. The future role of genetic screening to detect newborns at risk of childhood-onset hearing loss. International Journal of Audiology. 2013; 52(2), 124-133. (exclusion reason: wrong publication type)

Kato T, Nishigaki Y, Noguchi Y. et al. Extensive and rapid screening for major mitochondrial DNA point mutations in patients with hereditary hearing loss. Journal of Human Genetics. 2010; 55, 147–154. (exclusion reason: wrong population)

Zhu Q, Li M, Zhuang X, et al. Assessment of Hearing Screening Combined With Limited and Expanded Genetic Screening for Newborns in Nantong, China. JAMA Network Open. 2021; 4(9):e2125544. (exclusion reason: wrong index test)

Superseded – see erratum