Evidence overview: Early value assessment - Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates to guide use of aminoglycosides

This overview summarises the main issues the diagnostics advisory committee needs to consider. It should be read together with the final scope and the early value external assessment report.

1 Aims and scope

Neonatal bacterial infection is a significant cause of mortality and morbidity in newborn babies. Neonates (babies up to and including 28 days corrected gestational age) with suspected infection or sepsis may be treated with gentamicin. NICE guidance on neonatal infection recommends that if a baby needs antibiotic treatment, this should be given as soon as possible and always within 1 hour of the decision to treat.

Individuals who have a genetic variant in the mitochondrial *MT-RNR1* gene (m.1555A>G) are at increased risk of profound bilateral deafness caused by damage to the ear (ototoxicity) when exposed to the aminoglycoside family of antibiotics, which includes gentamicin. However, currently available laboratory testing for m.1555A>G cannot provide results quickly enough if a decision to treat a neonate with antibiotics has already been made or is likely.

The Genedrive MT-RNR1 ID Kit is a qualitative in vitro molecular diagnostic test for the detection of the *MT-RNR1* m.1555A>G variant. It is intended to be used by healthcare professionals in a near patient setting using a buccal (cheek) swab sample. The company states that the kit provides a result within about 26 minutes. This could help ensure that neonates who have the m.1555A>G variant, receive alternative antibiotics and avoid irreversible,

lifelong hearing loss due to ototoxicity. This may improve the standard of care and clinical outcomes in maternity and neonatal care and reduce treatment costs associated with aminoglycoside induced hearing loss.

This topic is presented as an early value assessment. The decision question that would need to be answered in guidance is presented below.

Decision question

Does testing to determine the *MT-RNR1* m.1555A>G status of neonates before they have aminoglycosides have the potential to be clinically and cost-effective?

What evidence is available to support the value proposition outlined in the scope and where are the evidence gaps?

Populations

Neonates who need antibiotic treatment (that is, a decision to start antibiotics has already been made) or who are anticipated to need antibiotics (that is, a decision to start antibiotics has not already been made) and who are being considered for treatment with aminoglycosides. Where data permits, the following subgroups may 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

Interventions

Genedrive MT-RNR1 ID test 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.

Healthcare setting

The healthcare settings for the intervention are secondary care (hospital, neonatal unit) and clinical laboratories.

Further details, including descriptions of the interventions, comparator, care pathway and outcomes, are in the final scope for Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates.

2 Clinical effectiveness evidence

The EAG did a rapid review to identify evidence on the clinical effectiveness and diagnostic accuracy of the Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates. Find the full review results on page 20 of the external assessment report.

Overview of included studies

Only 1 study, reported in a peer reviewed publication and as a conference abstract was included in the review (McDermott et al. 2022). This study was a prospective observational implementation trial based in 2 large specialist neonatal intensive care units. It included 749 neonates, with 526 needing treatment with antibiotics. The accuracy of the Genedrive MT-RNR1 ID kit was compared with Sanger sequencing. Out of the 526 needing treatment with antibiotics 424 (80.6%) were genotyped and antibiotics were prescribed. Of those neonates that were tested, 3 were found to have the *MT-RNR1* m.1555A>G variant (confirmed by Sanger sequencing) and 416 did not. The

median age of participants was 2.5 days (range, 0 to 198 days). The study did not report on the sex or ethnicity of participants.

Study quality

The EAG assessed the quality of the included study per outcome. For diagnostic test accuracy it used the QUADAS-2 tool and for other clinical outcomes the ROBINS-I tool was used.

The McDermott et al. 2022 study was rated as low risk of bias for patient selection and index test. The risk of bias for the reference standard was reported as unclear because there was no information reported on whether those interpreting the test had knowledge of the index test result. The risk of bias for flow and timing was rated as high because of the reported variation in numbers of people tested, compared with those not included in the analysis.

In terms of other intermediate outcomes, only test failure rate was rated as having a low risk of bias. All other outcomes were rated as having a moderate risk of bias. This was because the failure rate, which was 17.1%, was not included in the analyses of the outcomes and this could affect the other outcome results. See pages 22 to 23 of the external assessment report for more information.

Intermediate outcomes

Diagnostic test accuracy

The study reported that the test had a sensitivity of 100% (95% CI: 29.2 to 100), a specificity of 99.2% (95% CI: 98 to 99.7), and an accuracy of 99.2% (95% CI: 98 to 99.7). Out of the 424 neonates included in the analysis, 5 false positives and no false negatives were reported.

Throughout the trial, the Genedrive 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 authors stated that the issue was resolved by an updated buffer and cartridge design.

Number of neonates successfully tested

Of the 526 neonates who needed treatment with antibiotics, 12 (2.3%) did not have the Genedrive MT-RNR1 ID Kit test because they were missed. The EAG said that no further information was provided to explain the reason for this. There were 90 (17.1%) tests that failed due to unsuccessful genotyping. No mothers were tested as part of the study.

Test failure rate

Of the 526 neonates who had antibiotics, 90 (17.1%) failed tests were reported. McDermott et al. suggested that the failure rate was caused by low signal intensity during the melting phase of the assay. The authors said this was resolved after the recruitment period by modifications to the assay buffer and a redesigned cartridge. Repeated testing of samples that had previously failed lead to a reduced failure rate of 5.7% in a clinical setting and 0% when performed in the laboratory.

Test implementation considerations

The study by McDermott et al. reported a test run time to actionable result of 26 minutes and a median time to swab of 6 minutes (inter quartile range = 3 to 16 minutes). No further data on the effect of the test implementation and use on healthcare resources was reported. The study reported that in all cases where the m.1555A>G variant was identified, aminoglycoside antibiotics were avoided and alternative cephalosporin-based regimens were used.

Time to antibiotic treatment

The time to antibiotic treatment when using the test was 55.18 (SD=23.82) minutes, compared with 55.87 (SD=22.56) minutes before the test was implemented. The difference in mean time to antibiotic treatment was not

statistically significant at −0.87 minutes (95% CI,−5.96 to 4.23 minutes). The study did not report data on the usability of the test.

Clinical outcomes

The study did not report on mortality or morbidity outcomes.

Health-related quality of life outcomes

The study did not report on health-related quality of life or patient experience outcomes.

Cost effectiveness evidence

The EAG did a rapid review to identify any published economic evaluations of the Genedrive MT-RNR1 ID Kit but no studies were identified.

Economic analysis

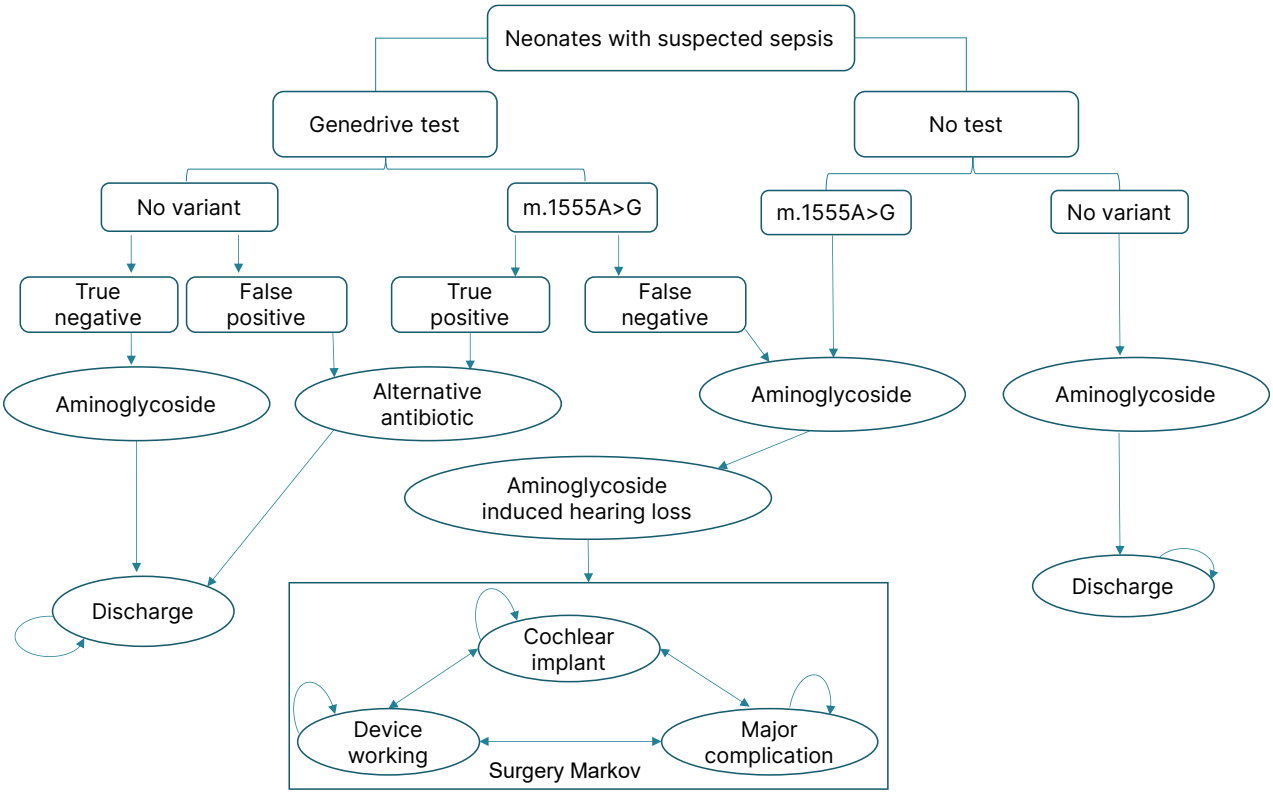
The EAG developed an early economic model to provide an indication of whether the Genedrive MT-RNR1 ID Kit could potentially be cost-effective and to identify key drivers and uncertainties of cost-effectiveness. To aid in the development of the early economic model the EAG constructed conceptual clinical pathway models for standard care and when the Genedrive MT-RNR1 ID Kit is used.

Model structure

The Markov model simulates the patient pathway from the initial diagnosis of neonates with the m.1555A>G variant to treatment for aminoglycoside induced hearing loss for a patient's lifetime. Neonates with or without the m.1555A>G variant enter the model with suspected sepsis. They may then follow standard care (no test) or have the Genedrive MT-RNR1 test. For those neonates without the variant, in standard care they are not tested for m.1555A>G, so receive an aminoglycoside and are then discharged. If this group have the Genedrive test, they may get either a true negative result (followed by aminoglycoside treatment and discharge) or they may get a false

positive result. In this case they will receive an alternative antibiotic before being discharged. For those neonates with the m.1555A>G variant, standard care results in aminoglycoside induced hearing loss and so they progress into the treatment state. Neonates with the m.1555A>G variant who have the Genedrive test may get a true positive result (followed by alternative antibiotic treatment and discharge). They may also get a false negative result and so receive aminoglycosides leading to hearing loss and treatment. Figure 1 shows a simplified outline of the model. The key long-term implications considered by the model are those that follow aminoglycoside induced hearing loss. The time horizon is the patient lifetime and the cycle length used in the model is 1 year.

Figure 1 Simplified schematic outline of the Markov model



Population

In the early economic model, the EAG included neonates who need antibiotic treatment and are being considered for treatment with aminoglycosides.

Comparator

The comparator was no testing done to determine a neonate's m.1555 variant status prior to them receiving aminoglycosides.

Model inputs

Find the full list of model parameters in tables 16 to 19 on pages 52 to 54 of the external assessment report. Tables 1 and 2 below show the model population characteristics and test specific parameters used in the early economic model.

Table 1 Model population characteristics

Parameter	Base case value	Sensitivity analysis values (low – high)	Source
Prevalence of MT-RNR1 variant m.1555A>G in the UK population	0.20%	0.10% to 0.28%	Bitner-Glindzicz et al (2009)
Probability of aminoglycoside induced hearing loss for neonates with the m.1555A>G variant prescribed with aminoglycoside	100%	30% to 100%	Model assumption, Gopel et al 2014
Probability of aminoglycoside induced hearing loss for neonates with the m.1555A>G variant prescribed with other antibiotics	0%	0% to 30%	Model assumption, Ballana 2006
Proportion of cases with bilateral cochlear implant	100%	50% to 100%	Model assumption
Probability of unilateral or bilateral cochlear implant being successful	97%	80% to 100%	Wang et al (2014)
Probability of death for the model cohort	UK Lifetable Mortality 2022	-	National life table UK

Table 2 Test specific parameters

Parameter	Base case value	Sensitivity analysis values (low – high)	Source
Genedrive MT-RNR1 ID Kit Price (Per Test)	£102	£50 to £150	See table 3
Cost for the staff (nurse) doing the test	£28	£15 to £40	Unit Costs of Health and Social Care 2021
Probability of 1st Genedrive MT-RNR1 ID Test being successful	94.3%	50% to 100%	PALOH study
Probability of 2nd Genedrive MT-RNR1 ID Test being successful	100%	80% to 100%	Model assumption
Genedrive MT-RNR1 ID Kit Accuracy (Sensitivity)	1	0.292 to 1	PALOH study
Genedrive MT-RNR1 ID Kit Accuracy (Specificity)	0.992	0.980 to 0.997	PALOH study

Costs

The EAG said that the resource use consequences of adopting the Genedrive MT-RNR1 ID Kit would vary depending on the NHS trust and how much the test is used. A number of assumptions were made about test usage and staff costs, so the model and therefore the costs presented are unlikely to be generalisable to all sites. In the early economic model, the EAG assumed that the test would be implemented in a neonatal intensive care unit (or similar) and that only 1 Genedrive device would be required. Some units may require more than 1 device, however, this is unlikely to have any material effect on the cost effectiveness results due to the low cost per test. Find the full list of costs used in the model in tables 8 to 13 (pages 40 to 44) of the external assessment report.

Cost of Genedrive

A breakdown of the costs associated with the implementation of Genedrive used in the early economic model are shown in table 3.

Upfront costs for Genedrive include:

- Cost of Genedrive MT-RNR1 ID System £4,995
- Cost of Bluetooth printer £400

These costs were converted using the equivalent annual cost methodology into an annual sum which equals the resources and investment plus their opportunity cost. The lifespan of the equipment was assumed to be 6 years based on information provided by the company.

Other costs of associated with the use of Genedrive include:

- Annual warranty fee for equipment (years 2 to 6) £750 per year
- Genedrive MT-RNR1 Control Kit (one kit per system per month) £35
- Genedrive MT-RNR1 ID Kit (per test) £100
- Custom labels (200 per pack) £40

For the staff costs associated with use of the test, the EAG assumed a 30-minute duration and an hourly cost based on the midpoint between a band 5 and band 6 nurse. This resulted in a total staff cost per test of £28 (see table 9 in the external assessment report).

Table 3 Costs associated with implementation of Genedrive test used in the model

Item	Opportunity cost of capital equipment	Annual cost of capital equipment	Cost per test
Opportunity cost of Genedrive MT-RNR1 ID System	£5624.42	£937.61	£0.86
Opportunity cost of bluetooth printer and charging cable	£450.40	£75.07	£0.07
Cost of warranty per test (assume three tests per day)	-	-	£0.57
Genedrive MT-RNR1 Control Kit per test (assume three tests per day)	-	-	£0.38
Genedrive MT-RNR1 ID Kit (per test)	-	-	£100.00
Cost of custom Label (one per test)	-	-	£0.20
Non staff totals	**£6074.82**	**£1012.68**	**£102.08**
Staff costs for doing the test (see table 2)	-	-	£28
Total cost of Genedrive	-	-	**£130.08**

Implementation costs

It was assumed that there were no costs associated with modifying existing infrastructure to accommodate the Genedrive system. Staff training costs were not considered in the early economic model. However, the manufacturer provides free training and this would be a relatively short duration (15 minutes to 1 hour), so the training costs per neonate tested would be negligible. Therefore, it is only staff time for collecting the samples and running the test that would be incurred.

Costs of laboratory testing

There is no current standard care for MT-RNR1 testing in neonatal sepsis. Retrospective testing for people with hearing loss who have been exposed to aminoglycosides may be done using methods such as pyrosequencing or

Sanger sequencing. The EAG found the costs to be similar for the 2 methods so assumed that Sanger sequencing would be used at a cost of £191. In the early economic model this cost was only applied to neonates with the m.1555A>G variant that were treated with aminoglycosides, leading to aminoglycoside induced hearing loss (that is, false negative cases in the Genedrive arm and all cases of aminoglycoside induced hearing loss in the standard care arm). During scoping of the assessment, it was suggested that positive results with Genedrive may be followed up with confirmatory laboratory testing. The EAG did not include this in the model but noted that they would expect it to have a negligible impact on the results of the model due to the low number of expected positive results.

Costs of antibiotics

The EAG did not include the antibiotic costs in the early economic model because the various antibiotics that may be used are relatively inexpensive and so would be predicted to have a negligible effect on cost-effectiveness.

Costs of hearing aids

The EAG assumed that all neonates with aminoglycoside induced hearing loss would be fitted with 2 acoustic hearing aids for a trial period. The cost of a pair of hearing aids was estimated to be £396, with a fitting cost of £249. It was assumed that hearing aids have a lifetime of 5 years, and so only 1 pair would be needed per neonate.

Costs of cochlear implants

The cost of fitting a cochlear implant included pre-surgery costs of £1,749 to cover initial assessments and testing and consultations with a surgeon and GP. Procedure and post-procedure costs were taken from TA566. The EAG assumed all implants in the model were bilateral in the base case (rather than a mix of unilateral and bilateral). This assumption was tested in sensitivity analysis. The cost estimate for a bilateral cochlear implant procedure and assessment was £61,268 (the corresponding cost for a unilateral cochlear

implant was estimated to be £37,699). The cost in the first year post-procedure was £4,283 and the ongoing annual cost after year 1 was £947. A full breakdown of these costs is shown in tables 12 and 13 of the external assessment report.

Table 4 Other cost values used in the model base case and sensitivity analyses

Parameter	Base case value (£)	Sensitivity analysis values (low – high)	Source
Cost of Sanger sequencing	191	150 to 250	Medtech briefing document
Cost of unilateral hearing aids	447	400 to 500	Cutler et al (2022)
Cost of bilateral hearing aids	645	600 to 700	Cutler et al (2022)
Cost of bilateral cochlear implant (procedure plus assessment total)	61,268	40,000 to 80,000	TA566
Cost of bilateral cochlear implant (first year post procedure)	4,283	2,000 to 6,000	TA566
Annual ongoing cost of bilateral cochlear implant	947	500 to 1,500	TA566
Aggregated pre-surgery costs associated with bilateral cochlear implants	1,749	1,500 to 2,000	Cutler et al (2022)

Utility values

Health-related quality of life

Eight studies were initially identified with utility data that could potentially be used in the early economic model (see table 3, pages 34 to 35 of the external assessment report). The most common health-related quality of life questionnaire used to measure utility was the health utilities index mark 2 and mark3 (HUI2 and HUI3). In the early economic model, the EAG used utility values from the study by Bond et al. 2009. This is a NIHR health technology assessment investigating the effectiveness and cost-effectiveness of cochlear

implants for severe to profound deafness in both children and adults. The utility values for profound hearing loss, unilateral cochlear implants and bilateral cochlear implants for children used in Bond et al. are from 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 (Barton et al. 2006). The adult utility values for profound hearing loss, unilateral cochlear implants and bilateral cochlear implants used in Bond et al. 2009 are taken from a UK Cochlear Implant Study Group study.

The EAG said that, although EQ-5D is NICE's preferred method of measuring utility in the reference case, HUI3 directly captures the impact of hearing on quality of life in a way that the EQ-5D does not. Therefore EQ-5D is unlikely to be an appropriate measure of utility for aminoglycoside induced hearing loss.

Tables 5 and 6 show the utility values used in the early economic model for children and adults, respectively.

Table 5 Utility values for children used in the model

Parameter	Value	Source
No hearing loss (population norm)	0.908	Pogany et al (2006)
Profound/significant hearing loss	0.421	Barton *et al* (2006)
Unilateral cochlear implant (less than 2 years since implant)	0.487	Barton *et al* (2006)
Unilateral cochlear implant (2 to 4 years since implant)	0.633	Barton *et al* (2006)
Unilateral cochlear implant (over 4 years since implant)	0.653	Barton *et al* (2006)
Bilateral cochlear implant (less than 2 years since implant)	0.490	Barton et al (2006), Bond et al (2009)
Bilateral cochlear implant (2 to 4 years since implant)	0.636	Barton et al (2006), Bond et al (2009)
Bilateral cochlear implant (over 4 years since implant)	0.656	Barton et al (2006), Bond et al (2009)

Table 6 Utility values for adults used in the model

Parameter	Value	Source
No hearing loss (population norm)	0.850	Pogany et al (2006)
Profound/significant hearing loss	0.433	UKCISG (2004)
Unilateral cochlear implant (note only used in sensitivity analysis)	0.630	UKCISG (2004)
Bilateral cochlear implant	0.633	Summerfield (2006)

In the early economic model, the EAG varied the utility values by time of implementation in childhood, but did not adjust the values for age to reflect a decrease in health-related quality of life with increasing age. The EAG noted that using a single age-independent value for the utility increment associated with cochlear implants may result in a situation where the utility for a cochlear implant recipient may be higher than that of someone without hearing loss.

The EAG did not include the disutilities and costs of adverse events associated with the implementation of cochlear implants in the early economic model. This is because they were not expected to have a meaningful impact on the results of the model because of the relatively short duration of these events, relatively low probability of them occurring and their relatively low cost. Further details are on pages 37 to 38 of the external assessment report.

Key assumptions in the early economic model

For the early economic model, the EAG made a number of simplifying assumptions for parameters that were considered unlikely to effect cost effectiveness or where there were evidence gaps. These assumptions were as follows:

- Time to antibiotics was not included
- A second Genedrive MT-RNR1 ID test was assumed to never fail and also not to delay antibiotic treatment

- Neonates with the m.1555A>G variant treated with aminoglycosides experience aminoglycoside induced hearing loss. This assumption was tested in the deterministic sensitivity analysis
- Neonates with the m.1555A>G variant treated with an alternative antibiotic do not develop hearing loss. This assumption was tested in the deterministic sensitivity analysis
- If aminoglycoside induced hearing loss occurs, it results in severe or profound irreversible deafness
- Utility values for children aged 5 years and above were used as proxies for children under 5. Different utility values were used for those under 18 and 18 and over. No further age-adjustment was used.

Base case results

Estimation of cost effectiveness

The EAG provided 2 estimates of cost effectiveness:

- Incremental cost per case of aminoglycoside induced hearing loss avoided
- Incremental cost per QALY gained

The base case results for these estimates are shown in tables 7 and 8. The results show that testing for the m.1555A>G genetic variant using the Genedrive MT-RNR1 ID Kit is estimated to be cost saving over the lifetime of the neonate.

Table 7 Base-case economic analysis: cases of aminoglycoside induced hearing loss avoided

Test approach	Total costs (£)	Cases of aminoglycoside induced hearing loss	Incremental costs (£)	Incremental cases of aminoglycoside induced hearing loss avoided	ICER (£)
GeneDrive MT-RNR1 ID Kit	136.82	0	-73.11	0.002	Dominant
Normal standard of care	209.93	0.002	-	-	-

For the cost per QALY gained, 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 8 Base-case economic analysis: QALYs gained

Test approach	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
GeneDrive MT-RNR1 ID Kit	136.82	23.12	-73.11	0.01	Dominant
Normal standard of care	209.93	23.11	-	-	-

The EAG reported that the estimated cost to identify one neonate with the variant would be around £65,000.

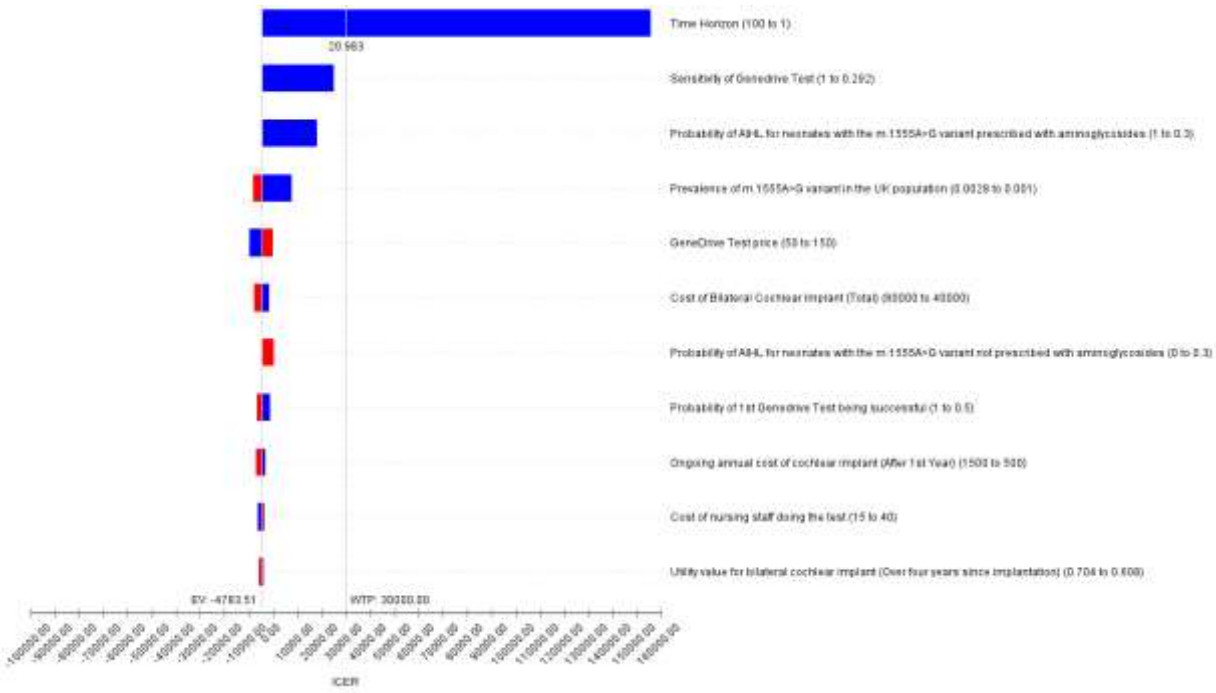
Sensitivity analyses

A deterministic sensitivity analysis was done to assess the uncertainty in key parameters in the early economic model. The EAG did not do a probabilistic

sensitivity analysis because of the uncertainty in the majority of the parameters in the early economic model.

Where they were available, confidence intervals from the relevant studies were used to inform the high and low values used. The results from the deterministic sensitivity analysis are shown in figure 2.

Figure 2 Tornado Diagram: Genedrive MT-RNR1 ID Kit pathway compared with standard pathway



The only parameter which changed the direction of the results was the time horizon used for the model. The sensitivity of the results to the time horizon reflects fact that the benefits (specifically cost savings related to cochlear implants avoided and utility gains from avoiding aminoglycoside induced hearing loss) are only likely to be felt in the medium to long-term whereas the costs of testing are incurred upfront. When the time horizon was reduced to 1 year, the ICER increased to £155,767 per QALY gained. With a time horizon of 10 years the ICER is £103 per QALY gained. Further details are in table 22 (pages 56 to 57) of the external assessment report.

Other key drivers included:

- Sensitivity of the test. This reflects the uncertainty in the estimate (as reported in the PALOH study) due to the very small number of positive cases.

- Proportion of neonates with m.1555A>G variant that develop aminoglycoside induced hearing loss after being exposed to aminoglycosides. The EAG noted that there is clear evidence that the m.1555A>G variant is a risk factor for aminoglycoside induced hearing loss, but that most evidence comes from case-control studies which may overestimate this risk, and so the precise level of this risk is uncertain.

- Prevalence of the m.1555A>G variant. No data was available to consider how cost-effectiveness varied by different sub-groups (with different frequencies of the m.1555A>G variant). However, the EAG noted that this analysis provides an indication of how the cost-effectiveness might vary with prevalence.

3 Summary

Clinical effectiveness

Only 1 study on the technology was identified (PALOH, McDermott et al. 2022). The study reported a high diagnostic test accuracy for the Genedrive MT-RNR1 ID kit, with a sensitivity of 100% (95% CI: 29.2 to 100) and specificity of 99.2% (95% CI: 98 to 99.7). No false negative results were reported. However, as only 3 neonates with the m.1555A>G variant were identified, estimates of real-world sensitivity of the test are uncertain. Five false positive results were reported and this was suggested to have been due to an issue with the assay cartridge which the authors state was corrected with an updated cartridge design. An initial failure rate of 17.1% (90 of 514

neonates) was reduced to 5.7% following modifications to the assay buffer and cartridge.

The study reported that an actionable result was available in 26 minutes. The median time taken to obtain a sample was 6 minutes (interquartile range = 3 to 16 minutes). There was no statistically significant difference in time to antibiotic treatment between standard care and using the Genedrive MT-RNR1 ID kit.

Overall, the results of the study suggest that the Genedrive MT-RNR1 ID kit has promise as an accurate point of care diagnostic test and has the potential to provide rapid identification to impact treatment decisions of neonates with the m.1555>G variant.

Cost effectiveness

The EAG did not identify any existing economic evaluations that were relevant to the decision problem.

If the technology were to be implemented, the upfront (that is “sunk costs”) to the NHS would include the Genedrive system itself (£4995) and a Bluetooth printer (£200) for each site, and training/implementation costs (unknown but training is provided for free by the manufacturer and is short in duration).

The deterministic sensitivity analysis showed that the model results were most sensitive to the following parameters:

- Time horizon of the model
- Sensitivity of the Genedrive MT-RNR1 ID Kit
- Probability of aminoglycoside induced hearing loss in neonates with the m.1555A>G variant that are treated with aminoglycosides
- Prevalence of the MT-RNR1 m.1555A>G variant
- Cost of the Genedrive MT-RNR1 ID Kit

The cost of approximately £130 per test is uncertain because of the variation in types of hospital wards in which the Genedrive MT-RNR1 ID Kit could potentially be used. Also, due to the relatively low frequency of the m.1555A>G variant in the population the cost of identifying one neonate with this variant are substantial (around £65,000).

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. The main drivers of this cost effectiveness are the high diagnostic accuracy reported in the PALOH study, the 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 with aminoglycoside induced hearing loss.

4 Issues for consideration

Clinical effectiveness

Time to antibiotic treatment

The PALOH study reported no statistically significant difference in time to antibiotic treatment between standard care and when using the Genedrive MT-RNR1 ID kit. However, the PALOH study was based in a specialist centre and in a neonatal intensive care unit. So it is uncertain whether the time to antibiotic treatment result would generalise to less specialist or smaller centres, or outside of a neonatal intensive care unit setting. .

Is further data needed to assess the time to antibiotic treatment when the Genedrive MT-RNR1 ID kit is used in different centres (for example, smaller non-specialist units) in the NHS? Could this be generated through real-world use and data collection? Is further data on time to antibiotic treatment needed to inform implementation for babies not admitted to a neonatal intensive care unit, but who are treated with antibiotics?

Diagnostic test accuracy estimates

In the PALOH study, only 3 neonates were identified with the m.1555A>G variant. Therefore the 95% confidence intervals were wide (95% CI: 29.2% to 100.00%), indicating considerable imprecision in this estimate. There were no false negative results reported in the PALOH study.

Is further evidence needed to confirm the diagnostic accuracy results reported in the PALOH study? If so, could this be generated using real-world data collection and should this include centres with patients from different ethnic backgrounds? Are there any concerns that false negative results could be an issue in smaller, non-specialist centres?

Technical performance in real-world use

During the PALOH study, modifications were made to the assay buffer and test cartridge to improve false positive rates and test failure rates.

Could real-world use and data collection be used to assess technical performance of the test in a clinical setting? The probability of someone who has a positive result having the variant (positive predictive value) may be low due to low prevalence. Are there any concerns about giving an alternative antibiotic when not all babies identified may have the variant?

Cost effectiveness

Assumptions about diagnostic test accuracy

The early economic model results are based on the high diagnostic accuracy of the test reported in the PALOH study (sensitivity of 100% and specificity of 99.2%). There is uncertainty around the sensitivity estimate due to the very small number of positive cases identified in the PALOH study (95% CI: 29.2% to 100.00%). The early economic evaluation shows that estimates of cost-effectiveness are very sensitive to the imprecision of this estimate.

Is the committee happy with this assumption in the model?

Proportion of neonates with m.1555A>G that experience hearing loss following aminoglycosides

The cost-effectiveness estimates are also based on the assumption that all neonates with the m.1555A>G variant treated with aminoglycosides will experience severe or profound hearing loss. The EAG noted that there is clear evidence that the m.1555A>G variant is a risk factor for aminoglycoside induced hearing loss. However, this evidence is from case-control studies which may overestimate this risk, and so the precise level of risk is uncertain. There is also some uncertainty related to the severity of aminoglycoside hearing loss and so around the proportion of neonates who would need different types of cochlear implants over the long-term.

Is the committee happy with these assumptions in the model? Is the committee happy with assumptions made around the long-term cost implications of aminoglycoside induced hearing loss (bilateral cochlear implants costing around £65,000 in the first year with ongoing annual costs of around £1,000).

Utility values used in the model

The model uses utility data based on the health utilities index mark 3 (HUI3) instead of EQ-5D. This is because HUI3 directly captures the impact on hearing that the EQ-5D does not.

Is the impact of aminoglycoside induced hearing loss adequately captured in the model? Are the HUI3 utility values acceptable for future economic analyses and decision making?

Results suggest Genedrive could be cost-effective but up front costs may be high

Implementation of the Genedrive MT-RNR1 ID kit test for real-world data collection would incur upfront costs (that is “sunk costs”) that are lost to the NHS. There is a substantial cost of identifying 1 neonate with this variant due

to the relatively low prevalence of the m.1555A>G variant in the population. Cost savings relate to health benefits accrued in the future (that is, the avoidance of costs associated with the fitting of cochlear implants).

Is the committee happy with the key assumptions in the model? Is the model sufficiently useful to draw any conclusions on the potential cost effectiveness of the Genedrive MT-RNR1 test?

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Race is a protected characteristic under the Equality Act (2010). The PharmGKB allele frequency table for the *MT-RNR1* gene reports that frequencies of the m.1555A>G variant differ by ethnic family background, including up to 1.81% for people of East Asian family background, so testing may be particularly beneficial in some groups. Tests that do not detect all relevant variants in the *MT-RNR1* gene could disproportionately affect different ethnic groups based on the prevalence of these alleles.

Mothers from a minority ethnic family background or those with a lower socioeconomic status may have an increased risk of early-onset neonatal infection and may be more likely to need treatment with antibiotics.

Acceptability and consent for genetic testing or treatment may differ according to personal or religious beliefs.

6 Implementation

Staff training and workload

Staff workload may be increased if all babies who are going to be treated with antibiotics, or who are likely to be treated, are offered the point-of-care test.

Staff will also need to be trained on how to use the test. A clinical expert commented that there is currently a high turnover of healthcare staff and use of agency staff, all of whom would need to be trained to use the test.

Quality assurance

A clinical expert emphasised the need for frequent quality assurance to be established to make sure the test system was functioning correctly, particularly if done outside a laboratory.

Consent

Uncertainty about the extent of information or discussion that needs to happen before giving the test, or the need to develop materials to help with this, could be a barrier to use.

Test result reporting and patient records

Determining how the test result will be recorded on patient records may be an implementation issue. Clinical experts highlighted the importance of ensuring that identification of the m.1555A>G variant is recorded to inform future decisions about antibiotic use

7 Authors

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Glossary

Aminoglycosides

A group of broad-spectrum bactericidal antibiotics. The group includes gentamicin, amikacin, tobramycin, and neomycin.

Cephalosporins

Broad-spectrum antibiotics which are used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis, and urinary-tract infections.

Mitochondria

Organelles present in human cells that are responsible for energy production. They contain their own genome and can make mitochondria specific proteins.

MT-RNR1

A gene in the mitochondrial genome that encodes the 12s ribosomal (rRNA) subunit.

Neonate

A baby up to and including 28 days from the expected date of delivery.

Ototoxicity

Damage to the hearing or balance functions of the ear by drugs or chemicals.