Healthcare Improvement Scotland | SHTG Advice on health technologies

SHTG Assessment
October 2024

In response to enquiry from the Accelerated National Innovation Adoption (ANIA) collaborative

Genotype testing to guide antibiotic use and prevent hearing loss in neonates

Key messages

1. Newborn babies (neonates) with a specific MT-RNR1 gene variant (m.1555A>G) have an increased risk of permanent hearing loss after receiving aminoglycoside antibiotics such as gentamicin. The m.1555A>G variant is estimated to be present in 1 in 500 newborns.
2. In an implementation trial testing 424 neonates, point of care MT-RNR1 genotype testing had a sensitivity of 100% and specificity of 99.2%. There is some uncertainty about the sensitivity of the test because of the wide confidence interval around this estimate.
3. The time needed to test a neonate's genotype and review the result is approximately 26 minutes. This means point of care testing can be carried out without delaying antibiotic treatment.
4. Hearing loss in neonates has a considerable impact on the quality of life of affected children and their families. It affects a child's ability to communicate, their social and emotional development, and their opportunities in life. Children with hearing loss need to wear hearing aids or cochlear implants throughout their life. Wider societal costs and benefits, such as the impact on quality of life and educational attainment of the child, are beyond the scope of our analysis.
5. Using current cost estimates and a 3 year model, introducing Genedrive MT-RNR1 point of care genotype testing to neonatal intensive care units (NICUs) is estimated to have a net resource impact of £29,000 in NHSScotland. This is based on three fewer neonates experiencing aminoglycoside induced hearing loss. The net increase in the resource costs over 3 years is attributable to device acquisition costs in the first year. In subsequent years, the ongoing cost of testing is less than the value of resource savings associated with cochlear implants and managing hearing loss. Extending MT-RNR1 genotype testing to other neonatal care settings could potentially increase the number of babies prevented from experiencing aminoglycoside induced hearing loss.
6. While equally effective antibiotics are available to replace gentamicin when treating neonates with the m.1555A>G gene variant, the main alternative is associated with higher rates of antibiotic resistance.

What were we asked to look at?

We were asked to review the evidence for point of care MT-RNR1 genotype testing in neonates (babies 0–28 days old) who need treatment with aminoglycoside antibiotics, such as gentamicin.

Why is this important?

Aminoglycoside antibiotics are known to have ototoxic side effects.[1] Neonates who have the mitochondrial MT-RNR1 m.1555A>G gene variant are at increased risk of aminoglycoside induced hearing loss. Neonates with signs of a serious infection need antibiotics within 1 hour of the decision to treat. Only a point of care test can provide a genotype result quickly enough to inform the choice of antibiotic in neonates within this timeframe. Preventing aminoglycoside induced hearing loss in neonates means these children will not experience a lifetime of deafness, with the associated need for hearing aids or cochlear implants.

What was our approach?

We reviewed the published literature on the clinical effectiveness, cost effectiveness, safety and patient experience of genotype testing to guide antibiotic use in neonates. We conducted a resource impact analysis using modelling work done by the National Institute for Health and Care Excellence (NICE). More information about SHTG assessments can be found on our website.

What next?

Our assessment will be used to inform an ANIA value case. The value case will inform decision making on the rollout of neonatal MT-RNR1 genotype testing in NHSScotland.

Key points from the evidence

1. Evidence on point of care MT-RNR1 genotype testing in neonates to guide antibiotic treatment comes from an implementation trial in two large NICUs in Manchester, England.
    - All neonates were tested for the MT-RNR1 m.1555A>G gene variant by a nurse using the point of care test on admission to one of the participating NICUs.
    - Sensitivity of the genotype test was 100% with uncertainty around the estimate (95% confidence interval (CI) 29.2% to 100%). Specificity was 99.2% (95% CI 98.0% to 99.7%).
    - Of 424 neonates successfully tested, three tested positive for the m.1555A>G gene variant and were given alternative antibiotics. There were five false positives and no false negatives.
    - Average time to initiating antibiotic treatment (including genotype testing) was 55.18 minutes. There was no statistically significant difference in time to treatment before and after introducing genotype testing (p=0.74).
2. The NICUs that trialled genotype testing report a test failure rate of 1.81% (95% CI 0.6% to 5.18%) since completion of the trial. This low rate may not generalise to less specialist neonatal care settings.
3. Aminoglycoside induced hearing loss has a considerable lifelong impact on the quality of life of affected children and their families. This can include children's ability to communicate, their social and emotional development, and their education and employment opportunities.
4. Parents of neonates needing extra care want more information about gene variant prevalence, genotype testing, the risks associated with hearing loss and infection, and the effectiveness of different antibiotics.
5. In a NICE cost-utility analysis, Genedrive MT-RNR1 genotype testing generated 0.01 more quality adjusted life-years (QALYs) at a lower cost (-£62.61) compared with no testing over a 50-year time horizon.
6. In a resource impact analysis for Scotland, introducing Genedrive MT-RNR1 genotype testing for neonates in NICUs who need antibiotics is associated with a resource impact of £29,000 over 3 years and prevents three babies experiencing aminoglycoside induced hearing loss.

- In year 1, the introduction of point of care genotype testing is associated with a net cost. Genotype testing was associated with resource savings in years 2 and 3.
- The cost of the testing kit (fixed and per test costs), the number of babies tested and the proportion of babies at risk for aminoglycoside induced hearing loss were key drivers of the resource impact analysis. This meant that our analyses were highly sensitive to assumptions around the acquisition cost of Genedrive devices and testing kits, the proportion of babies who receive antibiotics in NICU settings in Scotland and the testing strategy adopted.
- While the evidence base for MT-RNR1 genotype testing was generated in the NICU setting, expanding the use of testing to other settings where neonates are treated for infections, such as special baby care units or paediatric wards, may increase the number of babies avoiding hearing loss and generate additional resource savings.

Contents

Definitions

Aminoglycosides	Broad spectrum antibiotics that are commonly prescribed for children.[2] Aminoglycosides include gentamicin, amikacin, tobramycin, neomycin and streptomycin. Gentamicin is the most used antibiotic in UK neonatal units.
Gene variant	A permanent change in the deoxyribonucleic acid (DNA) sequence of a gene.[3] These used to be called gene mutations.
Genotype	The complete set of genes that make up an individual.[4] Genotype can also refer to the variant forms of a gene carried by an individual.
Mitochondria	Membrane-bound cell organelles.[5] Each mitochondrion contains DNA. Mitochondria are generally maternally inherited.
Neonate	A newborn baby is referred to as a neonate for the first 4 weeks (28 days) of their life.[6]
Nephrotoxicity	Rapid deterioration in kidney function caused by the toxic side effects of medication or chemicals.[7]
Ototoxicity	Damage to the inner ear caused by medication side effects.[8] It can cause symptoms such as ringing, hearing loss and balance problems.
Premature / preterm babies	Any baby born alive before 37 weeks of pregnancy.[9] Extremely preterm/premature babies are born before 28 weeks of pregnancy.

Definitions of terms relating to diagnostic test accuracy are provided in *Appendix 2*.

Introduction

Bacterial infections and sepsis are a significant cause of mortality and morbidity in neonates.[1] Neonates with a suspected infection are often treated with gentamicin, an antibiotic from the aminoglycoside family.[1, 10] Aminoglycosides have known side effects including ototoxicity and nephrotoxicity.[11, 12]

Neonates with the mitochondrial MT-RNR1 m.1555A>G gene variant are at increased risk of aminoglycoside induced hearing loss when given gentamicin.[1] Neonates with the m.1555A>G variant can develop profound and irreversible hearing loss after a single dose of an aminoglycoside.[13]

Equally effective antibiotics are available to replace gentamicin when treating neonates with the m.1555A>G gene variant.[1] The main alternative is cefotaxime.[1, 10, 13] Cefotaxime is associated with higher rates of antibiotic resistance than gentamicin.[1, 10]

Neonates with signs of an infection need to be given antibiotics within 1 hour of the decision to treat.[1] Laboratory testing is unable to provide genotype results within the required turnaround time.

This assessment reviews the evidence for point of care testing for the MT-RNR1 m.1555A>G genotype in neonates.

Genetics of aminoglycoside induced hearing loss

Every cell in the human body contains genetic material in two locations: the cell nucleus and the mitochondria. The nucleus has two copies of each gene, one from each parent. Mitochondrial genes are inherited only from the mother.[1]

One mitochondrial gene is called MT-RNR1.[1, 11] Changes in a gene can occur spontaneously when copying the gene for a new cell. These altered genes are called variants. The MT-RNR1 gene variant most often linked to an increased risk of aminoglycoside induced hearing loss is called m.1555A>G.[1, 11]

The m.1555A>G variant causes the mitochondria to produce a protein that closely resembles a bacterial protein which aminoglycosides bind with to destroy the bacterium.[1, 11] This results in increased ototoxic (damaging to the ear) effects in people who have this gene variant.

Research question

What is the clinical effectiveness, cost effectiveness and safety of aminoglycoside (gentamicin) genotype testing compared with no testing in neonates?

Literature search

A systematic search of the secondary literature was carried out between 24 and 26 April 2024 to identify systematic reviews, health technology assessments and other evidence-based reports. Medline and Embase databases were also searched for systematic reviews and meta-analyses.

The primary literature was systematically searched between 24 and 26 April 2024 using the Medline and Embase databases. Results were limited to English language articles published from 2022 onwards.

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials.

Concepts used in all searches included neonatal/newborn, point of care testing, gentamicin, aminoglycoside and hearing loss. A full list of resources searched and terms used is available on request.

Health technology description

The Genedrive MT-RNR1 ID Kit (Genedrive plc) is a portable point of care diagnostic test for detecting the MT-RNR1 m.1555A>G gene variant.[1] Each kit contains all the materials needed to complete the test.

A swab sample is taken from the neonate's cheek.[1] The sample is mixed with buffer solution and reagents and placed in a cartridge.[13] The cartridge is then inserted into the machine.

The test is automated and provides a simple 'detected' or 'not detected' result.[1, 13] The kit provides a genotype result within about 26 minutes per baby tested.

Cartridges for the Genedrive system need to be stored at 2–30°C.[13] Once the cartridge has been removed from the pouch it comes in, it is stable up to 40°C for up to 3 hours. All cartridges and test kits are single use, which has potential implications for environmental sustainability.

Point of care testing for the MT-RNR1 m.1555A>G testing is not currently used in NHSScotland. The Dundee regional genetic testing laboratory provides laboratory-based testing for MT-RNR1 gene variants for patients expected to have significant exposure to aminoglycosides.

Epidemiology

Neonates, babies aged less than 28 days old, can be cared for in neonatal care, paediatric care or maternity settings. Babies are admitted for specialist neonatal care when they are born prematurely, have a low birth weight or are unwell.[14] In Scotland, there were 45,061 births in the year 2022–2023.[15] Of these babies, 4,009 (8.9%) needed extra neonatal care (*Table 1*).

Table 1: Babies needing extra neonatal care in Scotland 2022–2023[15]

Type of neonatal care	n babies	% babies born
NICU	812	1.8%
Special baby care unit (SCBU)	1,948	4.3%
High dependency unit (HDU)	1,081	2.4%
Postnatal ward or transitional care units (alongside mother)	72	0.2%
Unknown level of neonatal care	96	0.2%
Total	**4,009**	**8.9%**

The global incidence of early onset sepsis in neonates ranges from 0.3 to 0.9 per 1,000 live births.[16] Most regions of the UK report incidence as 0.5 per 1,000 live births (1 in 500 births). A higher proportion of babies admitted to NICUs will be given precautionary antibiotics for suspected infections.[1, 13] In a study in Manchester, 80.6% of neonates admitted to a NICU were prescribed antibiotics for a suspected infection.[13] This is likely to be an overestimate of the actual rate of infection in neonates admitted to a NICU, because only 30 to 60 out of every 1,000 blood culture samples tested in NICUs in England in 2020–2022 were positive for infection.[1]

The m.1555A>G variant is a risk factor for aminoglycoside induced hearing loss.[1] The evidence for this association comes from small retrospective cohort and case-control studies.[1, 11] Consequently, there is a lot of uncertainty about the level of risk associated with having this gene variant.[1]

- In a study of 12 Spanish families with maternally transmitted hearing loss, everyone who had the m.1555A>G gene variant and received treatment with aminoglycosides became deaf.[17]
- In a large cohort (n=7,056) of premature babies in Germany, 788 (11%) developed permanent hearing loss. Of the ten babies who had the m.1555A>G gene variant and were given aminoglycosides, three (30%) failed their newborn hearing test. The combination of aminoglycoside treatment and having the m.1555A>G gene variant was a significant predictor of hearing loss (odds ratio (OR) 1.26, 95% CI 1.07 to 1.49).

- Two studies in the United States (US, n=1,139) found that one in five (20%) neonates who had the m.1555A>G variant and received aminoglycosides went on to have an abnormal newborn hearing test.[17]
- In a Finnish study, ten out of 19 children who had the m.1555A>G variant went on to develop permanent hearing loss at a median age of 3.7 years old despite never being treated with aminoglycosides.[17]

Two large UK-based cohort studies estimated the prevalence of the MT-RNR1 m.1555A>G variant in the UK population to be 0.2%.[1, 12] The Avon Longitudinal Study of Parents and Children (ALSPAC) estimated the prevalence as 0.19% (95% CI 0.10% to 0.28%, 18/9,371 participants) and the 1958 Birth Cohort estimated prevalence as 0.26% (95% CI 0.14% to 0.38%, 19/7,350 participants). It is likely that both cohorts were people from a predominantly white ethnic background that may not represent the ethnic diversity of the current Scottish population.

The prevalence of MT-RNR1 gene variants appears to differ between groups of people from different geographical regions.[18] Genotype testing may be particularly beneficial for people with east Asian (Indonesian, Korean or Chinese) or south African heritage given the higher prevalence estimates in these populations (1.8% and 0.3% respectively).

Links between other MT-RNR1 variants and aminoglycoside induced hearing loss are based on single studies and remain uncertain.[1, 11]

Other risk factors for aminoglycoside induced hearing loss include premature birth, renal impairment, severe inflammatory response syndrome, prolonged treatment regimens and blood plasma drug concentrations higher than the dose needed for effective treatment.[11]

Inequalities

Mothers from more deprived socioeconomic backgrounds are at a higher risk of their baby needing extra neonatal care after birth.[15] In 2022–2023, nationally collected data showed that 10.9% of babies born to mothers from the most deprived category in the Scottish Index of Multiple Deprivation (SIMD) needed extra neonatal care, compared with 7.5% of babies born to mothers from the least deprived SIMD category. Babies of mothers from a lower socioeconomic background may also have an increased risk of neonatal infection.[1]

Clinical effectiveness

Evidence on MT-RNR1 genotype testing in neonates to guide antibiotic treatment comes from the Pharmacogenetics to Avoid the Loss of Hearing (PALOH) study in two large NICUs in Manchester, England.[13] The PALOH study formed the basis of a NICE Early Value Assessment for NHS England and Wales.[1]

The PALOH study consisted of two parts, a preclinical validation of the Genedrive MT-RNR1 ID Kit and an implementation trial of genotype testing.[1, 13] The Genedrive point of care test was validated using a case-control study design. Cheek swabs were prospectively collected from 74 adults and 53 neonates known not to have the m.1555A>G variant and 32 adults known to have the m.1555A>G variant. Laboratory-based genetic testing was used as the reference standard to calculate diagnostic accuracy.

A total of 304 samples, from 159 people, were collected and tested.[1, 13] Sensitivity was estimated to be 100% (95% CI 93.9% to 100%). Specificity was also 100% (95% CI 98.5% to 100%) in the case-control study. In the implementation trial, sensitivity remained 100% but with greater uncertainty around the estimate (95% CI 29.2% to 100%) because the gene variant is rare and only three babies in the trial tested positive. Specificity was slightly lower at 99.2% (95% CI 98.0% to 99.7%).

Both participating NICUs follow NICE guidelines on treating neonatal infections which recommend gentamicin-based treatment regimens. All neonates admitted to the participating NICUs between January and November 2020 were enrolled in the PALOH implementation trial. The Genedrive point of care test was performed by a nurse for all babies on admission to the NICU. If the m.1555A>G gene variant was detected, and the baby went on to need antibiotics, the baby was treated with an alternative antibiotic.

The trial was not powered to ensure detection of all babies with the relatively rare m.1555A>G gene variant.[13] It was powered to detect a difference in time to antibiotic administration before and after implementation of the point of care test.

A total of 749 babies were recruited into the trial; 711 babies (94.9%) were from one NICU.[1, 13] Median participant age was 2.5 days (range 0 to 198 days). Gender and ethnicity were not recorded. A total of 526 babies (70%) were treated with an antibiotic as part of their care. Of these, 424 were successfully tested for the m.1555A>G gene variant. Twelve neonates were not tested and 90 neonates had a failed test (17.1%). The high test failure rate was determined to be caused by the cartridge not being completely inserted into the machine. The design of the cartridge was changed during the trial and the subsequent test failure rate was 5.7%.[1, 13] It is not clear if neonates where retested after a test failure or were given aminoglycosides under the assumption they did not have the variant.

Three neonates were found to have the m.1555A>G variant. All three were treated with cefotaxime instead of gentamicin. There were five false positive test results (confirmed by laboratory testing) and no false negative results. The five infants with false positive results were assumed to have been treated with an alternative antibiotic unnecessarily.

Before the implementation trial, the average time to antibiotic initiation was 55.87 minutes (standard deviation (SD) 22.56 minutes) for 95 babies admitted to the NICUs.[1, 13] During the trial, the time to starting antibiotic treatment was 55.18 minutes (SD 23.83). There was no statistically

significant difference in time to antibiotic treatment before and after introducing genotype testing (mean difference -0.87 minutes, p=0.74). This result will have been strongly influenced by the decision to test all neonates on admission to the NICU, rather than testing each baby after it was decided they needed antibiotics; the 26 minute test time is incurred at admission and not part of the time to treatment estimate in the trial.

The limitations of the PALOH study were noted in the NICE Early Value Assessment.[1, 13] It is unclear whether consecutive neonates admitted to the NICUs were recruited to the trial. It is also unclear whether people conducting the laboratory testing knew the results of the point of care test. The trial was conducted in large NICUs so the results may not generalise to other neonatal care settings. The study results are based on only three babies with the gene variant because the m.1555A>G variant is rare. Finally, there has been no confirmation of negative test results to determine if a child went on to develop hearing loss that could be attributed to having the gene variant (a possible false negative test result).

Recommendations

The NICE Early Value Assessment makes recommendations based on the PALOH study:[1, 13]

> 'The Genedrive MT-RNR1 ID Kit can be used while further evidence is generated as an option for detecting the genetic variant m.1555A>G to guide antibiotic (aminoglycoside) use and prevent hearing loss in newborns who are being considered for treatment with aminoglycosides.
>
> Healthcare professionals should tell parents about the possible implications of positive test results for their baby and their family at an appropriate time, and give support and information.
>
> Positive results should be confirmed by laboratory testing.
>
> The recommendation is conditional on further evidence being generated on:
>
> - how the test affects time to antibiotics
> - how the test result affects antibiotic prescribing decisions
> - the technical performance and accuracy of the test.'[1]

The Clinical Pharmacogenetic Implementation Consortium (CPIC)* has published a guideline on aminoglycoside therapy for people of all ages with MT-RNR1 gene variants.[11] The guideline is based

* CPIC is an international consortium of volunteers who are interested in facilitating pharmacogenomic testing for patient care.

on a review of 94 studies investigating the relationship between MT-RNR1 gene variants and aminoglycoside induced hearing loss. The guideline describes these studies as mainly small retrospective cohort studies with methodological flaws.

The CPIC guideline makes a strong recommendation that people with the MT-RNR1 m.1555A>G gene variant should avoid aminoglycosides unless the increased risk of permanent hearing loss is outweighed by the risk of infection without safe or effective alternative therapies.[11] The guideline notes the possibility that a lack of hearing loss in a person with the m.1555A>G variant who has previously been treated with aminoglycosides does not mean they will not develop hearing loss after subsequent doses. The guideline also notes that the impact of aminoglycosides on children with the m.1555A>G variant is likely to be greater than the impact on adults.

Safety

Aminoglycosides are known to have nephrotoxic and ototoxic side effects.[11] These effects are typically dose dependent, but a safety notice from the Medicines and Healthcare Products Regulatory Agency (MHRA) in 2021, reported cases of hearing loss in people who had aminoglycoside levels within the normal therapeutic range.[12] The MHRA notice states that genotype testing should not delay urgently needed antibiotic treatment, but may be considered when patients are expected to receive recurrent or long-term aminoglycoside therapy. The MHRA recommends continuous monitoring for toxic side effects in people of all ages treated with aminoglycosides.

The first choice alternative antibiotic used to treat neonates with an infection is cefotaxime.[1] This antibiotic is associated with an increased risk of antibiotic resistance compared with gentamicin but is considered to be equally effective against gram-negative bacterial infections. The risk of antibiotic resistance or less effective treatment of infections is likely to be small because the m.1555A>G genetic variant is rare, therefore few babies would be treated with cefotaxime.

The point of care test failure rate in the PALOH study was initially 17.1%.[1, 13] After changes were made to the Genedrive cartridge and buffer solution, the failure rate dropped to 5.7%. Since completion of the PALOH study, the NICUs in Manchester have reported a test failure rate of 1.81% (95% CI 0.6% to 5.18%) outside of a trial setting.[1] This low test failure rate may not generalise to other less specialist neonatal care settings.

Patient and social aspects

Members of the public and patient representatives involved in the NICE Early Value Assessment described parents and families feeling very stressed when a baby is admitted to neonatal care because of a suspected infection.[1] Emotions experienced by the parents of the baby who developed hearing loss included shock, confusion, anger, sadness, disbelief and guilt.

There is a recognised lifelong impact of hearing loss on a child.[1] Hearing loss can affect children's ability to communicate, their social and emotional development, their education and their employment opportunities.

The NICE Early Value Assessment reported unpublished primary research into people's perspectives on MT-RNR1 genotype testing for neonates with suspected infections.[1] Researchers scanned posts from the Mumsnet and National Deaf Children's Society forums. Ninety-two posts were manually screened and thematically analysed. It was not possible to gather any information about the demographics of the people who had written the posts.

People on these forums who were related to infants who had sepsis, sought to share their experiences and connect with others who had similar experiences.[1] They expressed fear of the long-term effects of sepsis on their child. Families of infants who had a neonatal infection and now have hearing loss wanted to find out about the causes of hearing loss, to share experiences of difficulties with finding suitable childcare and using hearing aids, and to express their desire for earlier hearing loss testing after an infection.

The families of infants with hearing loss that could be caused by gentamicin expressed a preference for treatment with gentamicin, despite the subsequent hearing loss.[1] There was a perceived trade-off between side effects and effective treatment, with a lack of understanding about alternative antibiotics.

Researchers also conducted a focus group via Zoom. Participants were mothers of newborns (n=1), mothers of toddlers (n=3), and professionals who cared for newborns and their families (n=2). Study participants were told about infection in neonates, the gene variant m.1555A>G and genotype testing. The six study participants were then asked to share their thoughts and feelings about genotype testing in the neonatal setting.

Two messages that emerged from the focus group were that parents needed information to inform their decision on testing and treating neonatal infections, and that the desirability of genotype testing was dependent on the context.

Participants in the focus group wanted more information about:

- how common the m.1555A>G variant is in neonates
- test accuracy and safety
- the chances of hearing loss after someone with the gene variant is treated with aminoglycosides
- the risk of spontaneous hearing loss without antibiotic treatment
- the chance of morbidity and mortality from neonatal infections and whether they are affected by time to treatment
- the long-term risks of neonatal infections and sepsis

- the comparative effectiveness and tolerability of different antibiotics
- how certain clinicians were about aminoglycosides causing hearing loss.[1]

Organisational issues/Context

Neonatal units in Scotland

There are three types of neonatal unit in Scotland.[19]

- SBCUs (level 1) provide care that may include tube feeding or intravenous antibiotics for babies born no more than 8 weeks premature.
- Local neonatal units (level 2) provide specialist and high dependency care, including assisted ventilation and short-term neonatal intensive care.
- NICUs (level 3) provide a full range of neonatal care, including caring for babies and families referred from other units. Pregnant women at high risk of delivering their baby before 27 weeks gestation, or where a baby is expected to have very low birth weight, are transferred to a maternity facility co-located with a NICU (if possible).

There are currently seven NICUs in Scotland. In 2023, it was decided that NICU services would be centralised at three networked locations:[20]

- Royal Hospital for Children, Queen Elizabeth University Hospital, Glasgow
- Aberdeen Maternity Hospital
- Simpson's Centre for Reproductive Health, Edinburgh Royal Infirmary.

Neonatal care units of at least one type are in approximately 15 locations across the Scottish mainland.[21] Babies that require the intensive care of a NICU are transported to the nearest facility.[20]

Staff implications of genotype testing

Workload for staff working in neonatal units and laboratories may increase if all neonates admitted to neonatal extra care and who may need treated for infection are tested for the m.1555A>G gene variant.[1] The NICE Early Value Assessment assumed that samples from babies that tested positive for the gene variant would be confirmed by laboratory testing while more data about the accuracy of the point of care test is gathered.[1] Treatment would be initiated before the laboratory test results were available.

The NICE Early Value Assessment also recommends that babies testing negative for the m.1555A>G variant, who still develop hearing loss, should be retested using laboratory testing to determine if they had a false negative test result or a different gene variant.[1]

Staff on neonatal units may require training on how to perform the test.[1] The PALOH study found that nursing staff could perform the point of care test with minimal training.[13]

Cost effectiveness

NICE cost effectiveness model

NICE conducted a cost-utility analysis comparing the Genedrive MT-RNR1 point of care genotype test with no testing (that is, all babies with suspected infections received aminoglycosides).[1]

The utility values used in the NICE economic model are based on studies that investigated the effectiveness of cochlear implants.[1] These values are derived from the Health Utilities Index Mark 3, a measure of the effects of treatment for hearing loss on overall health status. Profound hearing loss significantly impacts a child's quality of life, reducing utility scores on a 1 to 0 scale from the population norm of 0.908 to 0.421. Cochlear implants can partially mitigate this effect, with bilateral implants providing slightly better outcomes than unilateral implants over time.

The cost-utility model included quality of life considerations and found that Genedrive MT-RNR1 genotype testing was a dominant strategy compared with standard practice over a 50-year time horizon. In other words, genotype testing with Genedrive is cost effective because it generated more QALYs (0.01) at a lower cost (-£62.61) compared with no testing.

SHTG resource impact analysis

We conducted a resource impact analysis based on introducing the Genedrive MT-RNR1 point of care test in Scotland. The analysis is based on the NICE resource impact template published alongside their Early Value Assessment, adapted using Scottish data where possible.[1]

The assumptions underpinning the resource impact analysis are presented in *Table 2*.

The population eligible for testing in the base case analysis was neonates admitted to a NICU and treated with aminoglycosides. Figures were based on implementation of point of care testing within all seven Scottish NICU units (one machine per unit) in NHSScotland. The proportion of neonates admitted to a NICU with suspected infections or sepsis who may be treated with aminoglycosides was assumed equal to that used by NICE (80.60%).

In the year of implementation, the number of babies admitted to a NICU was based on the number observed in NHSScotland for the year 2022–23.[15] Future birth rate projections for Scotland were not available, so the birth rate was assumed to remain constant and the time horizon was limited to 3 years.

Table 2: Assumptions underpinning the resource impact analysis

	Value	Source
Number of babies admitted to NICUs, NHSScotland, year 1	812	Public Health Scotland[15]
Proportion of babies in neonatal care with a suspected infection or sepsis who may be treated with aminoglycosides	80.60%	NICE[1]
Number of babies in NICUs receiving aminoglycosides, year 1 (eligible population)	655	Calculation based on the above
	Current practice	**Future practice**
Babies tested using Genedrive MT-RNR1 ID Kit	0.00%	100.00%
Proportion of babies with the m.1555A>G variant that have received aminoglycosides and require bilateral cochlear implants	100.00%	0.00%

Genedrive test costs are presented in *Table 3*. The costs associated with current practice incorporate the costs of bilateral cochlear implants and other audiology costs. These are presented in *Table 4*.

Costs associated with the Genedrive system are uncertain and may underestimate the total costs associated with implementing point of care genotype testing for neonates in NHSScotland. The total capital and operational costs associated with the procurement of Genedrive testing are not known because published estimates exclude several components of implementation, such as delivery charges, installation costs, annual maintenance costs and staff training costs. Per test costs may also depend on volume of tests purchased per year, so these are subject to uncertainty. The Genedrive manufacturer is in discussion with NHSScotland around an agreed price for the technology and associated costs.

Table 3: Base case cost inputs used in the resource impact analysis for Scotland

Type of Cost	Cost (£)	Quantity	Total (£)	Source
Capital costs				
Genedrive MT-RNR1 ID Kit system	£5,994	7	£41,958	NICE[1]
Bluetooth printer and charging cradle	£480		£3,360	
Total	**£6,474**		**£45,318**	
Annually recurring fixed costs				
Annual warranty fee (year 2 onwards)	£750	7	£5,250	NICE[1]
Annual cost of control kits per machine (one kit per system per month)	£420		£2,940	
Total			**£8,190**	
Per test cost (year 1)				
Genedrive MT-RNR1 ID Kit (per test)	£100	655	£65,500	NICE[1]
Printer labels (four per test)	£0.20		£131	
Cost of collecting sample (5 mins, band 5 nurse)	£4.34		£2,842	PSSRU, 2022[22]
Average cost of confirmatory Sanger sequencing for 0.20% of neonates receiving test[a]	£190.81[a]	1	£190.81	NICE[1]
Total annual per test costs			**£66,663**	
First year total costs			**£114,921**	
Recurring annual costs (excluding discounting)			**£74,331**	

a: The average cost of Sanger sequencing is £190.81 at 2021/22 prices (Wallace AJ 2021. NW GLH Test Directory Price List 2021 to 2023. North west Genomic Laboratory Hub. Manchester, UK.)

Table 4: Health costs for babies with aminoglycoside induced hearing loss

Health cost	Cost (£)	n babies with current practice (year 1)	Total (£)	Source
Bilateral cochlear implants	£55,109[a]	1	£55,109	NICE model[23]
Audiometry or hearing assessment, age ≤4 years	£140[b]	3	£420	
Maintenance and programming of cochlear implants	£363[c]	9	£3,267	
Rehabilitative audiology service (one to one sessions)	£155[d]	9	£1,395	
Total			**£60,191**	

a: Cost of bilateral cochlear implants include cost of procedure 2022 / 23 National tariff – procedure prices (CA41Z) which includes cochlear implant device acquisition £20,889 – from TA566 uprated to 2022 prices using the Bank of England Inflation Calculator[23]
b: 2022 / 23 National tariff – procedure prices (CA37C)
c: National Schedule of Reference Costs – Year 2020-21 – NHS trusts and NHS foundation trusts (AUD – Audiology AS13)
d: National Schedule of Reference Costs – Year 2020-21 – NHS trusts and NHS foundation trusts (AUD – Audiology AS14)

Results

The Scottish resource impact analysis results are presented in *Table 5.* The results show that the introduction of Genedrive point of care testing to guide antibiotic treatment in neonates admitted to a NICU in NHSScotland is associated with an increased cost of £29,000 over 3 years. This resource cost is based on three neonates avoiding the need for cochlear implants and other audiology costs associated with aminoglycoside induced hearing loss over this time period.

In the first year the introduction of testing is associated with a net cost of £37,000 with the initial capital costs and costs per test partially offset by cost savings associated with avoiding the cost of cochlear implants for one child. In years 2 to 3, testing was cost saving because the ongoing costs of the test (per test costs, control kit costs and device warranty) were less than the costs saved from one fewer baby requiring cochlear implants and associated costs each year.

Table 5: Base case total resource impact for NHSScotland, years 1–3

Year	Cost of current practice (£)	Cochlear implants current practice (n)	Cost of future practice (£)	Cochlear implants future practice (n)	Impact of change cost (£)
1	£78,000	1	£115,000	0	£37,000
2*	£78,000	1	£74,000	0	-£4,000
3*	£78,000	1	£74,000	0	-£4,000
Total	**£234,000**	**3**	**£262,000**	**0**	**£29,000**

**Costs for years 2 and 3 were not discounted*

A breakdown of costs, cost savings and resource savings for NHSScotland is presented in *Table 6.* Resource savings include staff and hospital resources (eg reduced need for surgeon time and audiology appointments) and these are likely to be fixed over the short term. Staff are likely to still be employed in the NHS and hospital equipment is still likely to be used. A proportion of the cost savings identified in the analysis are likely to be cash releasing from the avoided costs of purchasing bilateral cochlear implants which are estimated to be £20,889 per set of implants. Over the time horizon of the model this would be equivalent to a cash saving of £62,667.

It should be noted that additional resource costs such as training of staff and staff consultations with colleagues and parents are not accounted for in the total costs.

Table 6: Breakdown of costs against cash and resource savings for NHS Scotland, years 1–3

Year	Costs of future practice (£)	Cash savings from cochlear implants (£)	Other resource saving (£)
1	£115,000	£20,889	£57,111
2†	£74,000	£20,889	£57,111
3†	£74,000	£20,889	£57,111
Total	**£262,000**	**£62,667**	**£171,333**

†Costs for years 2 and 3 were not discounted

Scenario analysis

Scenario analyses (*Appendix 3*) were conducted to explore sensitivities in the model. Results showed that testing all babies in NICUs versus the base case of only testing those receiving antibiotics, increased the total cost over 3 years to £77,000 (*Appendix 3, Table A*). When altering the cost inputs

to 50% lower capital costs and 20% lower per test costs there was a cost saving over 3 years of £27,000.

An additional scenario (*Appendix 3, Table B*) was conducted to explore a rollout of the test according to a preferred service model described to SHTG by clinical leads within the Centre for Sustainable Delivery. The preferred service model included providing the test to all neonates being considered for an aminoglycoside antibiotic in NICUs, local neonatal units (LNUs) and SCBUs. This broader service model would require the purchase and installation of 31 Genedrive point of care devices spread across the care settings.

Maintaining all other base case assumptions, the analysis for the preferred service model resulted in the avoidance of 18 cases of aminoglycoside induced hearing loss and a net cost over 3 years of £151,000. If all neonates who presented to these settings were tested, then net costs rose to £391,000 over 3 years. The preferred service model was associated with 3-year cost savings of £133,000 when capital costs were 50% lower and the per test cost was 20% lower than in the base case.

Limitations

Resource impact input values have been applied on a Scotland-wide level. In reality, the use of resources may vary between boards and hospitals based on local practice. As the costings were estimated before implementation it is not possible to predict what local differences in cost will be.

There has not been any implementation of the Genedrive genotype test in NHS Scotland; pathways, costs and usage applied in the analysis are therefore subject to change. The base case analysis is based on the only directly relevant evidence (the PALOH study). Deviating from the Manchester service model (that is, testing all neonates on arrival at a NICU) increases the uncertainty surrounding the model inputs. Deviating from the Manchester service model also risks undermining the model assumptions, for example that testing does not adversely affect time to commencing antibiotic treatment.

Wider societal costs and benefits, such as impact on quality of life, educational attainment of the child and costs in the education sector are beyond the scope of our analysis.

Conclusion

Neonates with the MT-RNR1 m.1555A>G gene variant have an increased risk of developing permanent hearing loss if they are given gentamicin. In an implementation trial, point of care MT-RNR1 genotype testing had sensitivity of 100% and specificity of 99.2%. There remains uncertainty about the test's sensitivity because the gene variant is rare, and only three babies in the trial tested positive.

The safety aspects of genotype testing in neonates relates to the antibiotics used and the time to treatment, rather than safety of the test itself. The time needed for point of care MT-RNR1 genotype testing did not significantly delay starting antibiotic treatment in the PALOH study because babies were tested on admission to the unit and not when antibiotics were being considered. There was also a test failure rate of 1.8% to 5.7% which may result in babies being given a less appropriate antibiotic or having their treatment delayed.

The alternatives to aminoglycosides have a higher risk of antimicrobial resistance but this risk is likely to be low because few babies will have the gene variant. In the PALOH study, five false positive results may have meant babies were given an alternative antibiotic unnecessarily.

Aminoglycoside induced hearing loss has a considerable impact on the quality of life of affected children and their families. Hearing loss affects a child's ability to communicate, their social and emotional development, and their opportunities in life. Children with hearing loss need to wear hearing aids or cochlear implants throughout their life.

Families of neonates receiving additional neonatal care have a range of information needs. Addressing these needs could improve the perceived acceptability of genotype testing in neonatal care settings.

The benefits of identifying neonates at risk of aminoglycoside induced hearing loss likely outweigh the risks of introducing genotype testing based on a single study from a specialist NICU.

Introducing Genedrive MT-RNR1 point of care genotype testing devices to Scottish NICUs is estimated to have a resource impact of £29,000 in NHSScotland over 3 years based on three fewer neonates experiencing aminoglycoside induced hearing loss.

Identified research gaps

Additional evidence is needed on the use of MT-RNR1 genotype testing in smaller, non-specialist centres, other neonatal settings outside of NICUs and in a range of geographical areas, to verify if the results of the PALOH study are generalisable.

Larger-scale blinded studies are required to obtain more robust sensitivity and specificity estimates, and to enhance the reliability of the evidence on neonatal genotype testing.

Further evidence is needed to determine the resource and quality of life impacts of introducing MT-RNR1 genotype testing for neonates.

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Appendix 1: Abbreviations

ALSPAC	Avon longitudinal study of parents and children
ANIA	Accelerated National Innovation Adoption collaborative
CI	confidence interval
CPIC	Clinical Pharmacogenetic Implementation Consortium
DNA	deoxyribonucleic acid
HDU	high dependency unit
LNU	local neonatal unit
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICU	neonatal intensive care unit
PALOH	Pharmacogenetics to Avoid the Loss of Hearing
QALY	quality adjusted life years
SCBU	special care baby unit
SD	standard deviation
SHTG	Scottish Health Technologies Group
SIMD	Scottish index of multiple deprivation
UK	United Kingdom
US	United States

Appendix 2: Definitions of diagnostic accuracy terms

Sensitivity: the probability that a person having a disease will be correctly identified by a clinical test, that is the number of true positive results divided by the total number with the disease.[24]

Specificity: the probability that a person not having a disease will be correctly identified by a clinical test, that is the number of true negative results divided by the total number of those without the disease.[24]

Appendix 3: Scenario analysis

Table A: Base case and scenario analyses

Scenario	Year 1			Year 2		Year 3		Total over 3 years	
	Upfront costs (£)	n babies hearing loss avoided (n)	Net cost (£)	n babies hearing loss avoided (n)	Net cost (£)	n babies hearing loss avoided (n)	Net cost (£)	n babies hearing loss avoided (n)	Net cost (£)
Base case	£115,000	1	£37,000	1	-£4,000	1	-£4,000	3	£29,000
Scenario 1 *65% babies receive antibiotics*	£108,000	1	£40,000	1	£0	1	£0	3	£40,000
Scenario 2 *All babies tested*	£131,000	1	£53,000	1	£12,000	1	£12,000	3	£77,000
Scenario 3 *Capital costs 25% lower; per test costs 10% lower*	£99,000	1	£21,000	1	-£8,000	1	-£8,000	3	£5,000
Scenario 4 *Capital costs 50% lower; per test costs 20% lower*	£81,000	1	£3,000	1	-£15,000	1	-£15,000	3	-£27,000

Table B: Preferred service model for Scotland and scenario analyses

Scenario	Year 1			Year 2		Year 3		Total over 3 years	
	Upfront costs (£)	n babies hearing loss avoided (n)	Net cost (£)	n babies hearing loss avoided (n)	Net cost (£)	n babies hearing loss avoided (n)	Net cost (£)	n babies hearing loss avoided (n)	Net cost (£)
Preferred service model	£535,000	6	£169,000	6	-£9,000	6	-£9,000	18	£151,000
Scenario 1 *65% babies receive antibiotics*	£494,000	5	£174,000	5	-£3,000	5	-£3,000	15	£168,000
Scenario 2 *All babies tested*	£615,000	6	£249,000	6	£71,000	6	£71,000	18	£391,000
Scenario 3 *Capital costs 25% lower; per test costs 10% lower*	£454,000	6	£88,000	6	-£40,000	6	-£40,000	18	£8,000
Scenario 4 *Capital costs 50% lower; per test costs 20% lower*	£373,000	6	£7,000	6	-£70,000	6	-£70,000	18	-£133,000