NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

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

Final scope

September 2022

1 Introduction

The Genedrive MT-RNR1 ID Kit is manufactured by Genedrive plc. The topic selection oversight panel identified this test as suitable for evaluation by the Diagnostics Assessment Programme. Following scoping of the topic it was decided that the topic should be assessed using the NICE early value assessment approach. This allows the NICE diagnostics advisory committee to consider the technology more quickly, and outline further data needed, potentially alongside use of the test in the NHS.

A glossary of terms and a list of abbreviations are provided in appendices A and B.

The revised scope was informed by discussions at the scoping workshop on 10th August 2022 and the assessment subgroup meeting held on 25th August 2022.

2 Description of the technology

This section describes the properties of the diagnostic technology based on information provided to NICE by manufacturers and experts, and information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technology

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, to

give this as soon as possible and always within 1 hour of the decision to treat. Individuals who have a genetic variant in the *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. Currently available laboratory testing for m.1555A>G cannot provide results quickly enough if a decision that a neonate needs antibiotics has already been made or is likely to be imminent.

Rapid genetic testing for the m.1555A>G variant could mean neonates who have this variant can have alternative antibiotics and avoid irreversible, lifelong hearing loss due to ototoxicity. Preventing hearing loss will mean neonates will not require lifelong use of cochlear implants, won't experience the lifelong impacts of hearing loss, and won't require surgeries associated with treating severe or profound hearing loss. This could have long-term benefits in preventing any lifelong financial, educational, and employment impacts of hearing loss. Identifying a neonate with this genetic variant could also inform other family members of their status, potentially preventing aminoglycoside induced hearing loss.

Rapid *MT-RNR1* gene testing may benefit health professionals in giving them confidence that they have made the right treatment decision for a patient in a clinically relevant time frame. This may improve the standard of care and clinical outcomes in maternity and neonatal care.

Costs to the NHS could also be reduced. The costs associated with treating people with damage to their ears caused by antibiotics could be reduced with preventative testing. Incidence of antimicrobial resistance in the healthcare setting could be improved if testing reduces the use of gentamicin alternatives.

2.2 Product properties

2.2.1.1 Genedrive MT-RNR1 ID Kit

The Genedrive MT-RNR1 ID Kit is a qualitative in vitro molecular diagnostic test for the detection of the single nucleotide polymorphism (SNP) m.1555A>G in the mitochondrial gene *MT-RNR1*. It is intended to be used by healthcare professionals within a near patient setting. The kit is intended for use on fresh human buccal (cheek) cells collected using the provided buccal swab. The test is used with the Genedrive System to provide an automated assessment of an individual's *MT-RNR1* m.1555 variant status to inform a clinician ahead of antibiotic treatment decisions.

The Genedrive system is a benchtop gene amplification platform for molecular testing in an emergency care setting. Each Genedrive MT-RNR1 ID Kit includes all the necessary consumables and reagents needed to perform the amplification and detection of the m.1555A>G variant. These include a buccal swab and sample collection tube containing lysis buffer, Genedrive assay cartridge (containing lyophilised reagents), minivette and assay cartridge lid. The sample handling and preparation procedure begins with a buccal swab taken from the patient which is submerged in the lysis buffer in the sample collection tube. This is then swirled for 30 seconds to release the buccal cells into the solution. The Genedrive lysis buffer and patient samples are mixed by inverting the collection tube several times. The sample is then collected from the tube using the minivette and dispensed into the assay cartridge. The assay cartridge is then inserted into the Genedrive System and the test can start. The test consists of a target DNA amplification step followed by an end-point melt curve analysis.

The results are interpreted by the Genedrive system software and displayed on the screen. Integration of the test result into patient records may be done by printing off a label using an optional printing accessory and attaching to relevant records. Electronic transmission and integration with hospital records may also be possible.

The company states that the kit provides a result within about 26 minutes. Results are displayed on the Genedrive system as one of 3 possible test outcomes: detected, not detected or test failed. If the test has failed the company recommends that the test is repeated. Clinical experts commented that if there is not enough time to wait for a second test result if the initial test fails, a decision should be made by the healthcare professional as to whether gentamicin should be prescribed regardless, or whether an alternative antibiotic should be used.

The company also provide a MT-RNR1 control kit, purchased separately to the kit, which contains positive and negative controls for quality control testing. The company recommends running a positive control and negative control every month or in line with local quality control policy.

Clinical experts commented that while the Genedrive system 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 housed in a laboratory, rather than near care setting, this could impact on how quickly the test is done.

Clinical experts also commented that the point-of-care test result is intended to be used to guide treatment in the first instance, and the extent that

laboratory testing may follow a point-of-care test to confirm a positive test result if the test was adopted into clinical practice is uncertain. An expert commented that it is likely that any impact on confirmatory laboratory-based testing following a positive point-of-care test result would be small due to the low prevalence of the m.1555A>G variant in the general population. Experts suggested that the extent of confirmatory testing done is likely to depend on how confident clinicians are in the accuracy of the test and may change over time, for example as more data on test performance becomes available.

Confirmatory testing is not currently included in NHS England's National genomic test directory, which specifies which genomic tests are commissioned by the NHS in England, and the patients who will be eligible to access to a test (see section 3.2).

3 Target conditions

3.1 Neonatal infection

Neonatal bacterial infection is a significant cause of mortality and morbidity in newborn babies (up to and including 28 days corrected gestational age). Experts have suggested that 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. The NICE guideline on neonatal infection defines neonatal infection as early-onset (that is less than 72 hours after birth) or late-onset (72 hours or more after birth). For both early-onset and late-onset neonatal infection, the guidance details risk factors and clinical indicators that may lead to a decision to treat with antibiotics.

Infection can develop into sepsis, which is potentially life-threatening. Sepsis begins when an infection makes its way into the bloodstream. Bacterial infections cause most cases of sepsis, with causative organisms including Group B *Streptococcus*, Gram negative bacteria (for example, *Escherichia coli*), *Staphylococcus aureus*, other *streptococci* and Listeria. There may also be other causes such as viral infections (for example, influenza and SARS-CoV-2). Early-onset infection may be a result of transmission from the mother, typically caused by group B *streptococci* carried vaginally, which can infect the amniotic fluid even if membranes are intact, or can infect the baby during delivery, causing sepsis, pneumonia, or meningitis. Late-onset is acquired from the baby's surroundings and is less often fatal compared with early infection, with *Escherichia coli* and *Staphylococcus aureus* being more frequent causes.

3.2 Aminoglycoside-induced hearing-loss

Aminoglycosides are a class of drugs which are commonly used worldwide to treat gram-negative infections. Examples include gentamicin, tobramycin and kanamycin. They can cause toxicity, including nephrotoxicity (kidneys) and ototoxicity (hearing). This effect is related to the dose and duration of treatment and is made worse by renal or hepatic impairment and is more likely in elderly people and neonates (Aminoglycosides: increased risk of deafness in patients with mitochondrial mutations, MHRA drug safety update, accessed July 2022).

Aminoglycosides work by disrupting bacterial protein synthesis as they bind to the 16s ribosomal RNA (rRNA) subunit of the bacterial 30S ribosome. In human cells, mitochondria have a version of this 16s rRNA subunit, called the 12s rRNA subunit which is encoded by the *MT-RNR1* gene in the mitochondrial genome. The m.1555A>G variant changes the structure of the mitochondrial 12S rRNA subunit, so that it more closely resembles the bacterial 16S rRNA subunit, allowing aminoglycosides to bind. The impact of this is damage to the hair cells in the inner ear, leading to permanent sensorineural deafness. Although sound travels through the ear in the usual way, the hair cells are not stimulated and so no nerve impulse is sent to the brain. Problems with the hair cells make it more difficult to hear quiet or subtle sounds, and in some cases very loud sounds.

The *MT-RNR1* m.1555A>G variant is the most common mitochondrial DNA variant, with an estimated prevalence of 0.2% in the general population (Bitner-Glindzicz et al, 2009). The PharmGKB allele frequency table for the MT-RNR1 gene reports that the frequencies of the m.1555A>G variant by biogeographical group are 0.11% (Central/South Asian family background), 1.81% (East Asian family background), 0.11% (European family background), 0.14% (Near Eastern family background) and 0.3% (Sub-Saharan African family background).

Other than m.1555A>G, additional variants associated with aminoglycoside-induced hearing-loss include m.1095C>T and m.1494C>T. These variants are less common than the m.1555A>G variant. The PharmGKB allele frequency table for the MT-RNR1 gene reports that the m.1494C>T variant has frequencies of 0.07% (Central/South Asian family background) and 0.03% (European family background). The m.1095C>T variant has reported frequencies of 0.07% (Central/South Asian family background), 0.15% (East Asian family background) and 0.06% (European family background).

An MHRA drug safety update (accessed July 2022) states that evidence suggests an increased risk of aminoglycoside-associated ototoxicity in

patients with mitochondrial variants (particularly m.1555A>G), including cases in which the person's aminoglycoside serum levels were within the recommended range. The penetrance of the variant (how likely it is that someone who has the variant and has an aminoglycoside will become deaf) is stated to be uncertain. A clinical expert commented that penetrance of the observed ototoxic effect due to the m.1555A>G variant is unclear and may change with age.

The CPIC guideline for the use of aminoglycosides based on *MT-RNR1* genotype suggests that people with no detectable *MT-RNR1* variant should still be considered at risk of aminoglycoside-induced hearing loss. Other risk factors include prematurity, renal impairment, severe inflammatory response syndrome, prolonged therapy regimens, and high aminoglycoside plasma concentrations. Clinical expert suggested that preterm babies are those most likely to be affected by aminoglycoside-induced hearing loss, even if they do not carry genetic variants. Preterm babies may not have fully developed immune systems which may increase their risk of infection. This may mean a higher risk of ototoxicity as they are more likely to receive treatment with gentamicin.

Current *MT-RNR1* variant testing in the NHS

Genomic testing in the NHS is delivered through a network of 7 Genomic Laboratory Hubs (GLHs). The National Genomic Test Directory outlines the genomic tests that are commissioned for the NHS in England, specifying which tests are available and the patients who are eligible to access a test. For testing for aminoglycoside exposure posing risk to hearing (R65), the testing criteria is for significant exposure to aminoglycosides posing risk of ototoxicity, for:

1. individuals with a predisposition to gram negative infections for example due to known respiratory disease (e.g. bronchiectasis, cystic fibrosis) or due to structural or voiding genitourinary tract disorders, or

2. Individuals with hearing loss who have been exposed to aminoglycosides.

Clinical experts commented that testing is not currently commissioned for use in people who have a known family history of susceptible gene variants, hence cascade testing for families of neonates identified to carry the m.1555A>G may not be done.

3.3 Diagnostic and care pathway

Current practice

3.3.1 Assessing possible neonatal infection

NICE guidance on neonatal infection lists risk factors and clinical indicators that suggest early-onset or late-onset neonatal bacterial infection (including 'red flag' risk factors or clinical indicators). Based on this, a framework is provided to help make antibiotic management decisions. This includes investigations into possible other causes that should be done (see the NICE guidance for details).

Clinical experts also highlighted that there are some neonates for whom a decision to treat with antibiotics may not already have been made, but are still anticipated to potentially need antibiotics during their stay in hospital (that is, the likelihood of needing antibiotics is greater than for neonates in general, but less than 100%). For example, experts commented that a high proportion of babies admitted to a NICU would need antibiotics. All babies admitted to NICU were eligible for recruitment into the PALOH study of the Genedrive MT-RNR1 ID Kit, even though not all went on to receive antibiotics (McDermott et al., 2022).

Some risk factors for early-onset neonatal infection detailed in the NICE guidance are based on maternal signs (see Box 1), for example confirmed rupture of membranes for more than 18 hours before a pre-term birth. Clinical experts commented that these signs indicate if a neonate will, or is likely to, need antibiotics. They further commented that testing the mother using the Genedrive MT-RNR1 test prior to birth (if there is no time for laboratory based testing) could be a way to provide an indication of the neonate's genotype without having to wait for the birth; that is, prescribing decisions for the neonate could be based on their mother's m.1555A>G status. This would provide information on genotype quicker but would be associated with uncertainty about how the neonate's genotype matched its mother (see section 3.3.4).

3.3.2 Treatment of babies with suspected infection

The NICE guidance on neonatal infection recommends that antibiotics should be given as soon as possible and always within 1 hour of the decision to treat with antibiotics. Clinical experts explained this can often be a challenge as it takes time to prepare the correct antibiotic dose based on the baby's weight and also find a suitable vein.

Early onset infection

The NICE guidance on neonatal infection recommends that the first-choice antibiotic regimen for empirical treatment of suspected early-onset infection (less than 72 hours after birth) is intravenous benzylpenicillin with gentamicin, unless microbiological surveillance data show local bacterial resistance patterns that indicate the need for a different antibiotic.

Further recommendations on antibiotic use are described in this guidance. This includes a statement that evidence reviewed for the guideline supported a starting dosage for gentamicin of 5 mg/kg every 36 hours administered in a single dose, and that, a dosage of 5 mg/kg every 36 hours is an off-label use of gentamicin. If a second dose of gentamicin is given this should usually be 36 hours after the first dose. But a shorter interval can be used if clinical judgement suggests this is needed (for example if the baby appears very ill or the blood culture shows a Gram-negative infection). The guidance also recommends that for babies given antibiotics because of risk factors for early-onset infection or clinical indicators of possible infection, to consider stopping the antibiotics at 36 hours (factors to consider are listed in the guidance).

Late onset infection

NICE guidance on neonatal infection recommends that for suspected late-onset infection (72 hours or more after birth) in babies who are already in a neonatal unit, a combination of narrow-spectrum antibiotics (such as intravenous flucloxacillin plus gentamicin) is recommended as the first-line treatment. Local antibiotic susceptibility and resistance data (or national data if local data are inadequate) should be used when deciding which antibiotics to use. The guidance also recommends that for babies given antibiotics because of suspected late-onset infection, stopping the antibiotics at 48 hours should be considered (factors to consider are listed in the guidance).

For babies with suspected late-onset neonatal infection or meningitis who have been admitted from home, recommendations on treatment are given in the NICE guideline on sepsis. Neonates who are more than 40 weeks corrected gestational age who present with community acquired sepsis should be given ceftriaxone 50 mg/kg unless already receiving an intravenous calcium infusion at the time. Neonates who are 40 weeks corrected gestational age or below or receiving an intravenous calcium infusion should be given cefotaxime 50 mg/kg every 6 to 12 hours, depending on the age of the neonate. A clinical expert explained that neonates readmitted from home may follow a different antibiotic prescribing regimen, such as flucloxacillin or

vancomycin if Staphylococcus is suspected. A research recommendation was made for this guidance in 2021 on what the optimal antibiotic treatment regimen for suspected late-onset neonatal infection is.

To minimise the risk of ototoxicity with systemic aminoglycosides (even in those without detectable *MT-RNR1* variants), regular serum concentration monitoring is recommended to maintain aminoglycoside levels below the toxic threshold for the cochleo-vestibular system (MHRA safety update, 2021). The product information for each medicine provides dosing considerations and recommendations for toxicity thresholds. The NICE guideline on neonatal infection includes recommendations on therapeutic drug monitoring for babies receiving gentamicin. Longer duration of gentamicin exposure may increase the likelihood of hearing failure, in both those with and without *MT-RNR1* variants (Johnson et al, 2010).

3.3.3 Alternative antibiotics if m.1555A>G detected

The CPIC Guideline for Aminoglycosides and *MT-RNR1* recommends that in those with *MT-RNR1* increased risk of aminoglycoside-induced hearing loss, aminoglycoside antibiotics should be avoided unless the high risk of permanent hearing loss is outweighed by the severity of infection and lack of safe or effective alternative therapies. Alternative antibiotic therapy may be used instead of gentamicin in cases of neonatal infection. However, clinical experts have advised that there are strong clinical concerns regarding antibiotic resistance to these. Alternative antibiotic prescribing decisions may vary between centres and may be influenced by local antibiotic resistance statistics. Clinical experts have commented that there are alternative antibiotics to aminoglycosides that could be used, including (but not limited to):

- **Cefotaxime** is a third-generation cephalosporin. It is effective against gram-negative bacteria but is less effective against gram-positive bacteria such as *Staphylococcus aureus*. A study on point-of-care testing for the m.1555A>G variant gives details of an alternative cephalosporin-based regimen used when the Genedrive MT-RNR1 test gave a positive result (McDermott et al, 2022). A clinical expert commented that amoxicillin may be used with cefotaxime for Listeria.

- **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** may be used to treat aerobic and anaerobic Gram-positive and Gram-negative infections in neonates (BNFC, accessed August 2022)

The CPIC guideline for the use of aminoglycosides based on *MT-RNR1* genotype recommends that, if no effective alternative to an aminoglycoside antibiotic is available, hearing should be evaluated frequently during therapy and it should be ensured that all appropriate precautions are used (for example, lowest possible dose and duration, use of therapeutic drug monitoring, hydration, renal function monitoring).

The MHRA drug safety update for aminoglycosides includes advice for healthcare professionals. It states not to delay urgent treatment in order to test, and when making prescribing decisions in patients with susceptible variants, to consider the need for aminoglycoside treatment compared with alternative options available. It further states that people with known mitochondrial variants or a family history of ototoxicity are advised to inform their doctor or pharmacist before they take an aminoglycoside.

3.3.4 Testing for m.1555A>G

Currently testing for m.1555A>G is available through the National Genomic Test Directory to be carried out in individuals with a predisposition to gram negative infections or in those who have hearing loss and have been exposed to aminoglycosides (see section 3.2). Laboratory based testing may not provide results within a clinically relevant time frame for antibiotics to be given within 1 hour of the decision-to-treat. Clinical experts have commented that current genetic lab testing uses various targeted approaches to detect the m.1555A>G variant. Approaches may differ between different genomic laboratory services but may include techniques such as restriction enzyme assay, and sequence analysis.

Due to the mitochondrial inheritance pattern of *MT-RNR1*, the identification of a clinically relevant *MT-RNR1* variant in an individual will be of relevance to any of their maternal relatives (that is, mother, siblings, mother's siblings and maternal grandmother) and to all of the children of a female identified to carry the variant. CPIC guidance recommends that this should be communicated to the patient when a clinically relevant genotype is identified and the advice to avoid aminoglycosides should be cascaded to the relevant individuals within the family. Advice from a clinical genetics service can be sought to support the cascading of information within the family. Clinical experts commented that cascade testing for the *MT-RNR1* gene is not currently included in NHS England's National Genomic Test Directory (see section 3.2). Clinical experts

highlighted that any family testing done would likely be a laboratory-based test as results would not be needed imminently.

Clinical experts commented that asymptomatic babies with risk factors for neonatal infection may be more likely to receive a point-of care m.1555A>G test before gentamicin use, as there may be less imminent risk and requirement for treatment than babies presenting with symptoms of infection, with or without additional risk factors. Symptomatic babies who appear extremely unwell may be prioritised to receive antibiotics as soon as possible to maximise efficacy, but clinical experts commented that there may still be time for genetic testing to be done as gaining intravenous access can take some time.

Experts commented that the inheritance of mitochondrial DNA variants is uncertain. Due to the presence of more than 1 type of mitochondrial genome in human cells, people may inherit different levels of mitochondria containing the m.1555A>G SNP from a mother who carries this variant. There is uncertainty about how well a mother's m.1555A>G status can indicate risk of aminoglycoside-induced hearing-loss for their baby. Therefore, if a neonate's genotype is determined indirectly by testing their mother, confirmatory testing may be considered after treatment with antibiotics.

3.3.5 Babies with hearing loss

The NHS newborn hearing screening programme screens all neonates within 26 days of birth for possible hearing difficulties, with details of how babies should be tested for hearing problems, including when an audiological assessment referral may be necessary (Newborn hearing screening programme (NHSP): care pathways for babies in neonatal intensive care units).

The most common hearing test is automated otoacoustic emissions (AOAE). This test does not rely on a person's response behaviour, so the person being tested can be asleep during the test. A second test may be required if results of AOAE aren't clear. This may be a second AOAE test, or different test called auditory brainstem response (ABR). ABR can provide information about the softest level of sound the ear can hear, specifically about nerve conduction from the cochlea to the brain. Electrodes pick up responses from the hearing nerve and responses are measured by a computer to identify babies with hearing loss (NHS, 2021).

Clinical experts have commented that babies with aminoglycoside-induced hearing loss may have discordant results from AOAE and ABR, hence those

with a known m.1555A>G variant (irrespective of whether blood levels are within the therapeutic range) should be referred for immediate follow-up and audiological monitoring irrespective of screen outcome. Neonates who are given aminoglycosides but are not known to carry the m.1555A>G variant should undergo newborn hearing screening and follow-up if required, in accordance with the standard screening protocol (Guidelines for surveillance and audiological referral for infants and children following newborn hearing screen).

Babies who have had gentamicin and go on to have confirmed hearing loss following screening will have a genetic test for aminoglycoside-induced hearing loss. This will be a laboratory-based genetic test as described in section 3.3.4. A positive detection of a m.1555A>G variant will indicate that the hearing loss is a result of genetic susceptibility to aminoglycoside-induced ototoxicity.

Babies with hearing loss can be fitted with hearing aids, which amplify sounds until they can be picked up by hair cells. However, there is a limit to the amount that this can help people hear sounds clearly. NICE guidance on cochlear implants recommends that cochlear implants may be offered for babies with sensorineural hearing loss when a hearing aid is not suitable or sufficient.

A clinical expert explained that if hearing loss is present but not detected at the newborn hearing screening examination, it may take some time for signs to be detected by parents during the baby's development. If there are concerns for the baby's hearing in the early months of development, a further hearing test may be arranged between 9 months and 2.5 years of age (NHS, 2021).

3.4 Patient issues and preferences

No preventative testing is currently done in clinical practice, m.1555A>G testing could result in more babies avoiding sensorineural deafness than current care.

Acceptability and consent for genetic testing or treatment may differ according to personal or religious beliefs. Experts highlighted the need for clear information about m.1555A>G testing and the implication of test results to be available to parents and carers.

4 Comparator

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

5 Scope of the assessment

Table 1 Scope of the assessment

Decision question	Does testing to determine the *MT-RNR1* m.1555A>G status of neonates before they have aminoglycosides represent a clinical and cost-effective use of NHS resources?
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; see section 6.4) and who are being considered for treatment with aminoglycosides. Where data permits, the following subgroup 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; see section 6.4) • Babies of different ethnicities • Babies with early-onset neonatal infection • Babies with late-onset neonatal infection
Intervention	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; see section 3.3.1)

Comparator	No testing done to determine a neonate's *MT-RNR1* m.1555 variant status prior to them receiving aminoglycosides.
Healthcare setting	Secondary care (hospital, neonatal unit) Clinical laboratories
Outcomes	Intermediate measures for consideration may include: • The number or proportion of neonates successfully tested • 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 variant • Usability of the test
	Clinical outcomes for consideration may include: • Morbidity (such as hearing loss) • Mortality
	Patient-reported outcomes for consideration may include: • Heath-related quality of life • Patient experience
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Cost of investigations and ongoing care for hearing loss (for example, cochlear implants, hearing aids, need for appointments with clinicians) • Cost of treatment associated with antibiotics (including monitoring during use)

	• Cost related to testing, including:
	  ○ Device and servicing costs,
	  ○ Quality assurance and calibration related costs
	  ○ Costs related to informatics and data storage
	  ○ Costs related to training staff to do testing
	  ○ Time for staff to do testing, interpret results and explain results to parents or carers

	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

6 Other issues for consideration

6.1 Impact on laboratory-based testing

In practice, laboratory-based testing may be used to confirm the result of the Genedrive test for future antibiotic prescribing decisions, although the extent of this and how it may change over time is uncertain (see section 2.2.1.1). Currently only babies with suspected aminoglycoside-induced hearing loss receive a laboratory-based test. Any genetic testing of family members of babies with identified m.1555A>G variants that would be done would also impact on laboratory-based testing, although the extent of cascade testing that would occur in practice is also uncertain. The assessment should explore the potential impact on the number of laboratory-based tests for m.1555A>G if the Genedrive MT-RNR1 ID test is adopted.

6.2 Antimicrobial Resistance

Any potential impact of test use on antimicrobial resistance should be considered. Alternatives to gentamicin may be broader-spectrum antibiotics so greater use of these may increase antibiotic resistance although clinical experts said, because the prevalence of *MT-RNR1* m.1555 variant is so low, any increase is likely to be small.

Clinical experts commented that use of point-of-care tests may give clinicians greater confidence to use gentamicin as first-line treatment for neonatal

infection (rather than broad-spectrum alternatives) by reducing concern about aminoglycoside-induced hearing-loss which may help to manage antimicrobial resistance.

6.3 Prevalence of m.1555A>G variant

The prevalence of the m.1555A>G variant may be higher in some ethnic groups, for whom testing may be particularly beneficial (see section 3.2). If data are not available to allow subgroup analysis to be done for babies of different ethnicities (as specified in table 1), exploratory analysis should be done varying the prevalence of the m.1555A>G variant in the population being tested to assess the expected clinical and costs effectiveness in higher prevalence groups.

6.4 Neonates who are anticipated to need antibiotics

Given the benefit of starting antibiotics for neonates as soon as possible after a decision to treat is made, testing in advance of this decision may make it more likely that m.1555A>G variant status is known in time to inform antibiotic use. But testing for neonates who are anticipated to need antibiotics rather than those for whom a decision to treat has already been made will mean that less than 100% neonates tested will go on to have antibiotics. Clinical experts have commented that indicators that antibiotics are more likely to be used include admission to a neonatal unit or NICU (see section 3.3.1). The impact of uncertainty about the proportion of neonates anticipated to need antibiotics who go on to have them should be explored in the assessment, for example through threshold analysis.

6.5 Costs and benefits falling outside the NICE reference case

Experts highlighted some costs and benefits that use of the Genedrive MT-RNR1 test could impact on that fall outside the perspective on outcomes and costs specified in the NICE reference case (see section 4.2 of the NICE health technology evaluations manual for more detail on the reference case). These include educational and societal costs associated with hearing loss. The NICE manual states that economic evaluations considered by NICE should include an analysis of results using reference-case methods. But this does not prevent additional analyses being presented when 1 or more aspects of methods differ from the reference case. However, these must be justified and clearly distinguished from the reference case. Although the reference case specifies the methods preferred by NICE, it does not prevent the committee's consideration of non-reference-case analyses if appropriate.

7 Potential equality issues

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 (see section 3.2), 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 (see section 3.4).

8 Potential implementation issues

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.

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.

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.

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.

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Appendix A Glossary of terms

Allele
An allele is a variant of a DNA sequence found at a particular place in the genome.

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

Blood culture
A test to look for infection in the bloodstream. A needle is placed in a baby's vein and a small amount of blood (one tenth of a teaspoon) is taken. The blood is put in a special bottle that detects whether any bacteria are present in the blood.

Corrected gestational age
Corrected gestational age represents the age of the child from the expected date of delivery

Group B streptococcus
A type of bacteria found in 20% of adults. If transferred to the baby during labour it can cause a life-threatening infection. This infection can be treated with antibiotics. Not all babies who are exposed to group B streptococcus develop an infection.

Early-onset neonatal infection
Neonatal infection less than 72 hours after birth

Late-onset neonatal infection
Neonatal infection 72 hours or more after birth.

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.

Penetrance
The extent to which a variant (or set of variants) is expressed in the observable characteristics of the people carrying it

Sensorineural deafness
Hearing loss due to damage of the cochlea, auditory nerve, or central nervous system

Appendix B Abbreviations

ABR: Auditory brainstem response

AOAE: Automated otoacoustic emissions

CPIC: Clinical Pharmacogenetics Implementation Consortium

NICU: Neonatal intensive care unit

Appendix C References

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