NICE National Institute for Health and Care Excellence

Evidence-generation plan for Genedrive MT-RNR1 ID Kit for detecting a genetic variant to guide antibiotic use and prevent hearing loss in babies

Implementation support

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1 Purpose of this document

NICE's assessment of the Genedrive MT-RNR1 ID Kit recommends that further evidence is generated while it is being used in the NHS.

This plan outlines the evidence gaps for the technology and what real-world data needs to be collected for a NICE review of the technology again in the future. It is not a study protocol.

The technology developer is responsible for ensuring that data collection and data analysis takes place. Support for evidence generation will be available through a competitive process facilitated by the Office for Life Sciences, pending business case approval. This will be in the form of funding for evidence generation consortia, bringing analytical partners and implementation sites together with developers for evidence generation.

Guidance on commissioning and procurement of the technology will be provided by NHS England. NHS England is developing a digital health technology policy framework which will further outline commissioning pathways.

NICE will withdraw the guidance if the technology developer does not meet the conditions in section 4.2 on monitoring.

After the end of the evidence generation period (3 years), the developer should submit the evidence to NICE in a form that can be used for decision making. NICE will review all the evidence and assess whether or not the technology can be routinely adopted in the NHS.

2 Evidence gaps

Further evidence generation is recommended to address the evidence gaps on:

- how the test affects time to antibiotic treatment
- how the test result affects antibiotic prescribing decisions
- failure rate
- diagnostic accuracy.

Evidence gaps are described as essential, important or supportive for committee decision making.

2.1 Evidence that is essential to allow the committee to make a recommendation in future

Time to antibiotic treatment

Using the Genedrive MT-RNR1 ID Kit in specialist neonatal intensive care (the PALOH study, McDermott et al. 2022) did not affect time to antibiotic treatment. But there is no evidence in smaller centres, such as a labour or postnatal ward. Evidence is needed to check whether using the test in smaller centres delays antibiotic treatment in babies with suspected infection, which could have severe consequences.

Antibiotic prescribing decisions

Babies with a positive Genedrive MT-RNR1 test result would have an alternative antibiotic to gentamicin. If the false positive rate with the Genedrive System is low, it is likely that only a few additional babies would also have an alternative antibiotic. Experts were not concerned that this would lead to increased antibiotic resistance. But generating further evidence on how the test might affect antibiotic use is essential.

Failure rate

The failure rate of the current Genedrive MT-RNR1 ID Kit is uncertain, so further evidence is needed. This is because failed tests could delay antibiotics, or result in an alternative antibiotic (in line with NICE's guideline on neonatal infection and local protocols) being used unnecessarily.

Diagnostic accuracy

Further evidence on the diagnostic accuracy of the Genedrive MT-RNR1 ID Kit is needed to reduce the uncertainty about the current test, which was changed during development.

Use in smaller non-specialist centres

Using the Genedrive MT-RNR1 ID Kit outside of neonatal intensive care is essential to check whether the time to antibiotic treatment, test failure rate and diagnostic accuracy estimates reported in PALOH are generalisable to other settings. It will also show how the test affects antibiotic prescribing decisions in different centres.

2.2 Evidence that is important and may have a substantial role in committee decision making

Use in centres with babies from diverse ethnic backgrounds

For equality, it is important to collect data on the ethnicity of babies who have the Genedrive MT-RNR1 test because the prevalence of the m.1555A>G variant varies.

PharmGKB's allele frequency table includes frequencies of the m.1555A>G variant by ethnicity. These are 0.11% (Central or South Asian), 1.81% (East Asian), 0.11% (European), 0.14% (Near Eastern) and 0.3% (Sub-Saharan African).

2.3 Evidence that may support committee decision making

Use in a wide range of geographical regions

Implementing the Genedrive MT-RNR1 ID Kit in a wide range of geographical regions would support babies from different socioeconomic groups having access to the test. It would also generate evidence for services with differences in practice.

3 Approach to evidence generation

The proposed approach to addressing the evidence gaps for the Genedrive MT-RNR1 ID Kit is real-world data collection within the evidence generation period. How this approach will address the evidence gaps is considered, and any strengths and weaknesses highlighted.

3.1 Ongoing post-market performance follow up

The technology developer is doing the RNR-01 usability study. This is collecting information on the total number of Genedrive MT-RNR1 tests, the number of positive results (followed up with a confirmatory laboratory test) and the test failure rate. It is also collecting general feedback from the users.

This data will provide additional information about using the Genedrive MT-RNR1 ID Kit in neonatal intensive care, by staff experienced in doing the test. Confirmatory laboratory testing of positive results will help to address the uncertainty around the Genedrive System's diagnostic accuracy (positive predictive value). But it would not allow estimation of other aspects of diagnostic accuracy (sensitivity, specificity, and negative predictive value). The data would also not address the other evidence gaps, including time to antibiotic treatment in non-specialist centres, information on antibiotic prescribing decisions, or the ethnicity of babies having the test.

3.2 Data collection

Centres using the Genedrive MT-RNR1 ID Kit, particularly non-specialist centres outside of neonatal intensive care, could collect data on newborns needing antibiotics for whom aminoglycoside treatment is being considered.

This should include:

- demographics, including age, sex and ethnicity
- type of maternity unit and location
- time from diagnosing suspected sepsis to administering antibiotics

- test result (positive or negative or failed, and whether first or second result)
- person doing the test (for example, staff nurse)
- type of antibiotic given (name and class)
- laboratory confirmation of a positive Genedrive MT-RNR1 test result (whether the confirmation result is positive or negative).

An audit of time to antibiotic treatment before implementation starts (for example, for 2 weeks) is suggested. This could be followed by a short period of implementation, and a period of data collection while the Genedrive test is being used (for example, for 8 weeks).

Collecting this data would provide information on time to antibiotic treatment in settings other than neonatal intensive care, and address how using the Genedrive MT-RNR1 ID Kit affects antibiotic prescribing decisions. It would also provide more information on failure rate and diagnostic accuracy (positive predictive value) of the test.

Data collection should follow a predefined protocol, and quality assurance processes should be put in place to ensure the integrity and consistency of data collection. See NICE's real-world evidence framework, which provides guidance on the planning, conduct, and reporting of real-world evidence studies.

3.3 Evidence generation period

This will be 3 years to allow for setting up, implementing the test, data collection, analysis and reporting.

4 Safety and monitoring

4.1 Safety

NICE's patient safety oversight group has recommended additional data collection to monitor the safety of the Genedrive MT-RNR1 ID Kit on:

- false positive results leading to use of antibiotic regimes that might drive cephalosporin resistance
- delay in use of antibiotics while waiting for results.

The group should be notified of any data collected that could indicate a safety concern, and the proposed response.

4.2 Monitoring

The technology developer must contact NICE:

- within 6 months of evidence generation plan publication to confirm agreements are in place to generate the evidence
- annually to confirm that the data is being collected and analysed as planned.

Technology developers should tell NICE as soon as possible of anything that may affect ongoing evidence generation, including:

- any substantial risk that the evidence will not be collected as planned
- new safety concerns
- the technology significantly changing in a way that affects the evidence generation process.

If data collection is expected to end later than planned, the technology developers should contact NICE to arrange an extension to the evidence generation period. NICE reserves the right to withdraw the guidance if data collection is delayed, or if it is unlikely to resolve the evidence gaps.

5 Implementation considerations

The following considerations around implementing the evidence generation process have been identified through working with system partners.

- Developers should provide training for staff in using the Genedrive MT-RNR1 ID Kit.
- Potential barriers to implementation include:
  - the availability of research funds for data collection, analysis and reporting
  - lack of expertise and staff to collect data
  - differences in practice between large tertiary referral centres and smaller hospitals
  - burden on clinical staff; the need to have a pre-study audit, collect data and do follow up; in small units this has a greater impact on staff time than in larger units.
- Because of the urgency of the setting, the test will be done without prospective consent. This may result in uncertainty about how much information to give parents or carers, and materials may need to be developed to help with this. Presumed consent was implemented in PALOH, and was acceptable to the Health Research Authority.
- There would be quality control costs. The technology developer recommends running a positive control and negative control every month or in line with local quality control policy.
- Some follow-up laboratory confirmation of positive tests could be done using the nationally commissioned R65 test if the commissioning criteria are met. This is usually organised through the local Genomic Medicine Service (after a referral) and a clinical geneticist or genetic counsellor can arrange confirmatory testing. They can also arrange cascade testing, that is, offering genetic testing to relatives of a baby who has the genetic mutation, although this is not currently commissioned.

- Follow-up laboratory testing for babies who have a negative Genedrive MT-RNR1 test result but develop hearing loss later would potentially provide more information on the false negative rate. But it would give a biased estimate of sensitivity. Also, true false negative results may not be known for many years. Collecting this information is not considered practical as part of data collection. In clinical practice there is routine follow up of any baby with hearing loss. Testing for the genetic variant m.1555A>G would be part of this assessment, and results could be checked against hospital records.
- There are feasibility concerns with recording ethnicity accurately. Ensuring that babies from diverse ethnic backgrounds are included would need ongoing monitoring to check this is being achieved.

Update information

Minor changes since publication

October 2023: We made the wording clearer around laboratory confirmation of positive Genedrive MT-RNR1 test results in sections 3.2 and 5.

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