Genedrive kit for detecting single nucleotide polymorphism m.1555A>G in neonates and their mothers: a systematic review and cost-effectiveness analysis

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Scientific summary

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Background

Sepsis and bacterial infections are a significant cause of mortality and morbidity in neonates (up to and including a corrected gestational age of 28 days). Expert opinion suggests that the incidence of culture-confirmed neonatal infection is around 1 in 2000 deliveries. But a larger proportion of babies will go on to receive precautionary antibiotic treatment for suspected infection [e.g. 30–60 in 1000 for those admitted to neonatal intensive care units (NICUs)]. Treatment for suspected infection or sepsis is commonly conducted using gentamicin, an antibiotic of the aminoglycoside family. This antibiotic is associated with a high risk of ototoxicity in those with a genetic variation of the mitochondrial *MT-RNR1* gene, specifically m.1555A>G. The purpose of this assessment was to investigate the use of the Genedrive MT-RNR1 ID Kit for identifying the m.1555A>G variant in neonates with suspected infection or sepsis. This technology has the potential to identify those at most risk of ototoxicity from aminoglycoside antibiotics and inform treatment decisions within the time frame recommended by National Institute for Health and Care Excellence (NICE) guidance.

Aim

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

Methods

A rapid review methodology was used to identify eligible studies for clinical effectiveness and cost-effectiveness. Databases searches were conducted on MEDLINE, EMBASE and CINAHL (Cumulative Index to Nursing and Allied Health Literature) for both aspects of the review; additionally, the cost-effectiveness review searched Cochrane and RePEc-IDEAS from 2010 to November 2022. Search results were screened by two independent reviewers. Only one study met the inclusion criteria for the clinical effectiveness rapid review, and no studies met the eligibility criteria for the cost-effectiveness rapid review. Data extraction and quality appraisal of the clinical effectiveness study were completed by one reviewer and checked for accuracy by another. Quality appraisal was conducted per outcome, the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool was used to assess diagnostic test accuracy outcomes, and the ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions) tool was used for all other outcomes. Meta-analyses were not possible as only one study was included in the clinical effectiveness rapid review.

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

Results

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

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

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

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

No relevant economic evaluations were identified. From the conceptual economic model, key evidence gaps were identified. These include the sensitivity of the Genedrive MT-RNR1 ID Kit for identifying the m.1555A>G gene variant in neonates, the magnitude of risk for aminoglycoside-induced hearing loss (AIHL) in neonates and mothers with m.1555A>G, and the prevalence of the gene m.1555A>G variant. Other potential important gaps include how data regarding maternal inheritance may potentially be used in the clinical pathway. The early health economic model focused on some of those parameters where, on consideration of the available data, the estimates of cost-effectiveness would be most sensitive to changes. The results of this model showed that the use of the Genedrive MT-RNR1 ID Kit for identification of the m.1555A>G genetic variant could potentially be cost-effective, with lower costs (£58.48) and higher effectiveness in terms of QALYs (0.01) over the patient lifetime. In a deterministic sensitivity analysis, the results were shown to be most sensitive to changes in the time horizon, the sensitivity of the Genedrive MT-RNR1 ID Kit system, the proportion of neonates with m.1555A>G variant suffering from AIHL after being exposed to aminoglycosides and the prevalence of the m.1555A>G variant in the UK population.

Conclusions

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

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

Suggested priorities for further research

This report identifies two key priorities for research required to reduce the uncertainty around this early value assessment and to provide the additional data needed to inform a full diagnostic assessment, including cost-effectiveness modelling.

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

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

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

Study registration

This study is registered as PROSPERO (CRD42022364770).

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This article

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