NICE National Institute for Health and Care Excellence

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

Assessment Report and economic model - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
Genedrive Diagnostics Ltd	1	n/a	n/a	"Variant is rare" - is it? Overall observation - From the supplier viewpoint, we are concerned by the somewhat "non-recommendation" conclusion of the EVA report, as we don't think it will be interpreted as intended by all audiences. As a company, we have many stakeholders – clinicians being only one set – but investors and finance people as well. We endorse the concept of an EVA as a new way to highlight promising new testing that can allow the NHS to be at the forefront of innovation. By definition, topics chosen for EVA will have limited clinical data sets to support their use, so the conclusion that more clinical data is needed to make any real/full recommendation for use is not a practical or useful outcome for the supplier. The EVA's current assessment could be interpreted as "there is not sufficient evidence to support the use of this test", rather than "this is a new test at the early stage of adoption". This is a potentially damaging conclusion for a supplier if interpreted this way. It would be better to wait until more data was available before engaging NICE if "more data needed" is the result of an EVA. This of course defeats the purpose of an EVA, and the desire to have innovative new technologies used in the NHS. If an EVA review highlights that a test is not clinically effective, cannot be implemented, or is not cost effective, it may not be recommended. However, that is not the case here. As examples: • In section 7.1.1, you conclude "Overall, these results suggest that the Genedrive MT-RNR1 ID Kit has promise as an accurate point of care diagnostic test. In addition, it has potential to provide rapid identification within a time sensitive period required to impact treatment decisions of neonates with the m.1555A>G genetic variant."	We have amended the conclusion of the scientific summary to better reflect the findings of the EAG review.

NICE National Institute for Health and Care Excellence

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Assessment Report and economic model - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				• In section 7.1.2 you conclude "Overall, the base-case results from the early economic model suggest that the use of the Genedrive MTRNR1 ID Kit could potentially be cost-effective, mainly driven by the high diagnostic accuracy reported in the PALOH study, estimated relatively low cost per test and the avoidance of large future health care costs associated with the fitting of cochlear implants for those infants suffering from AIHL." **We would request a more positive summary in the opening final report summary, along the lines of 7.1.1. and 7.1.2, but acknowledging that an early stage assessment inevitably is limited in data. Most people only read the summary sections of reports and it's important for us that your positive conclusions are presented there up front at the beginning. The outcome of the EVA could also comment that "the test shows real promise and has already been effectively implemented in the NHS setting. Given the early stage of adoption, hospitals should as part of their implementation continue to collect efficacy and cost effectiveness data in their own setting, given the differing size and operational patterns of different clinical settings".**	
Genedrive Diagnostics Ltd	2	9	Plain English Summary	"*This review shows that the Genedrive MT-RNR1 ID Kit has the potential to identify the m.1555A>G variant…."* Sensitivity for the m.1555A>G variant has been shown to be 100%, with no false negatives reported to date in either pre-clinical (analytical) verification nor in the PALOH study. **We suggest revision of this to:** **"This review shows that the Genedrive MT-RNR1 ID Kit has demonstrated high accuracy to identify the m.1555A>G variant…."**	Although we agree that the study showed high accuracy of the test, the estimate of sensitivity is derived from testing three neonates only, thus we is better reflective of the evidence than 'demonstrated high accuracy'.
Genedrive Diagnostics Ltd	3	11	Results	"*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 positive cases (i.e. people with the m.1555A>G variant)*	We appreciate that the system has been updated further and potentially provides greater accuracy. However, we must base

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

Assessment Report and economic model - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				but no false negatives were identified. However, there were some false positives (n = 5 of 8)…." We recognise the limitations to the PALOH study data and it is important to stress that the primary goal of the PALOH study was **implementation of the test** to guide antibiotic prescribing and **usability** in an emergency care setting, seeking to establish whether rapid genotype guided therapy could be implemented in practice without disrupting standard of care and time to administration of antibiotics. It was not case controlled to assess efficacy. This study was executed using an initial version of the Genedrive instrumentation hardware, test consumables and assay chemistry. These versions of the products were subsequently refined based on test performance data and extensive user feedback from the PALOH study. The new improved versions of the products exist today are the commercial products available for routine use.	our review on the available published evidence.
Genedrive Diagnostics Ltd	4	11	Results	"*This was established from 424 successful tests*…." Whilst it does not meaningfully impact sensitivity, specificity or test fail rate it is important to clarify the full cohort of individuals in the PALOH study that were genotyped. 751 patients were recruited, two being removed at the parents' request. Of the 749 patients remaining, 737 were genotyped using the Genedrive MT-RNR1 ID Kit, enabling test performance analysis. Of these 749, 526 individuals received gentamicin and enabled analysis of mean time to administration of antibiotics **Reference to the full cohort of tests performed should be cited when discussing test performance, with reference to the cohort of 526 individuals when discussing mean time to antibiotic administration.**	The text in the EAG report is based on Figure 1 (flow diagram) of the published paper which states that 424 neonates were genotyped and provided with antibiotics. We appreciate you providing further information not reported in the published paper. However since this new information does not meaningfully impact on the outcomes reported in the EAG (as acknowledged) we have not changed the text as it correctly reflects the information provided in the published paper.
Genedrive Diagnostics Ltd	5	11	Results	*"…with a test failure rate of 17.1% (90 patients). The failure rate was reduced to 5.1% in repeated testing of samples post after modifications were made to the assay buffer and the test cartridge was redesigned".*	We thank the company for providing us with further data (comment number 17). The included study suggests that a reduction in the failure rate was observed from 17.1% to

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

Assessment Report and economic model - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				As noted by the EVA panel, there have been significant post-study product enhancements to the assay and the instrument. The current versions of the Genedrive MT-RNR1 ID Kit and Genedrive System has been in routine clinical use in Manchester Royal Infirmary NICU since October 2022 and the test fail rate with clinical staff from the unit running the test is currently <2% to our understanding. Could the EVA panel please follow this up? **Updated test data could be provided to the EVA panel to enable inclusion in the final report.**	5.7%. The extra data is provided on a smaller sample and the confidence intervals are relatively wide (0.6-5.18%). While we appreciate there is an observable reduction, the confidence intervals for the new data are close to the original percentage of decreased failure rate and the confidence intervals of the two likely overlaps. We have therefore decided not to include this information.
Genedrive Diagnostics Ltd	6	11	Results	*"Uncertainties regarding 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."* We agree that sensitivity estimates will be improved with larger cohorts of individuals identified with the m.1555A>G variant. However, the practicalities of a prospective study solely aimed at this is non-viable, requiring in excess of 45,000 individuals to achieve >95% confidence assuming a frequency of 1:500 for the m.1555A>G variant. Analysis of post-neonate patients identified as m.1555G is possible, but carries the caveat that re-test is no longer under intended use setting or patient group. This approach was adopted and reported in the PALOH study for initial test verification, where the sensitivity for the variant in a larger cohort was established as 100%, with no false negatives reported. **We suggest that this should be commented on in the review. Given the above caveats, we also suggest that future analysis of improvement to sensitivity precision may best be served by ongoing frequent assessment as part of expanded routine clinical use.**	Thank you for the comment, the EAG understand the challenges of conducting research in relatively small populations such as people with the m.1555A>G variant. Therefore, nowhere in the report has it been suggested a study in excess of 45,000 individuals is required. In the EAG's view, a study including only three people with the m.1555A>G variant is insufficient to confirm the sensitivity of the test in real world settings as reflected by the 95% CI reported in the PALOH study. The report highlights that further study of the test in other real-world settings will reduce this uncertainty. The EAG are unable to comment on a programme of expanded routine clinical use- as this is largely subject to decisions that will be made by the NICE diagnostics advisory committee.

NICE National Institute for Health and Care Excellence

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

Assessment Report and economic model - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
Genedrive Diagnostics Ltd	7	12 & 14	Suggested areas for further research & 1.1.2	*"The risk and 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, primarily based on case-control studies in hearing impaired populations with the m.1555A>G variant are provided in more detail below."* *"The prevalence of nonsyndromic hearing loss in people with the m.1555A>G variant is a further uncertainty."* The review rightly points out that most studies have been done in case controlled studies, and the causative effect of the MT-RNR1 variant is virtually 100%. The literature review conducted by CPIC is quite exhaustive (CPIC: Doi:10.1002/cpt.2309 (https://cpicgx.org/guidelines) and is derived from review of 58 publications. It recommends avoidance in all cases where the MT-RNR1 mutations are found. There are a small number of studies as noted that indicate a less binary outcome to aminoglycoside exposure and subsequent hearing loss, but most of these are noted to have no follow-up post the newborn hearing screening test, and therefore most caveat their conclusions. We note that Häkli S et al. (Audiol Neurootol 2013, 18:23–30) reported that ten m.1555G carriers who had passed the newborn screening test following aminoglycoside administration all developed permanent hearing loss at a median age of 3.7 years. It could be that the newborn hearing test is not an adequate benchmark of aminoglycoside induced genetic ototoxicity. CPIC categorises m.1555A>G as having the highest (high) level of evidence, with the strongest (strong) recommendations where the evidence is high quality and desirable effects clearly outweigh the undesirable effects. Though the incomplete penetrance is accepted by CPIC, the group provided a strong recommendation that aminoglycosides should be avoided in those carrying the m.1555A>G variant because of the significantly increased risk of AIHL. **We agree that penetrance could be included to inform robustness of modelling, but question the practical relevance of it when the CPIC guidance is unequivocal on a risk basis. While penetrance is possibly a**	The EAG provide the following clarifications: 1. The CPIC recommendation cited in the comment is already discussed in the EAG report (e.g. section 1.5) 2. The EAG report provides justification for why case-control studies recruiting participants from families experiencing hearing loss means these results are subject to great uncertainty. 3. The EAG report also notes that some of these case-control studies report that nonsyndromic hearing loss may be relatively common in people with the MT-RNR1 variant. With the caveat that these studies may also reflect an overestimate of the risk. 4. The EAG report also notes the limitations of studies that seek to recruit participants not selected on the basis of experiencing hearing loss in their family (including small sample sizes, small number of studies, lack of follow up) 5. The suggested areas for further research on this matter are based on the findings of the early economic model that prevalence of nonsyndromic hearing loss in people with the MT-RNR1 variant is an important driver of cost-effectiveness. Therefore, further

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

Assessment Report and economic model - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				factor in the health economic model, it seems to be given a prominence in the review (breath of discussion and placement in the report) that is probably not proportional to its impact.	research is likely to reduce this uncertainty.
Genedrive Diagnostics Ltd	8	14	1.1.3	*"However, some mitochondrial variants are homoplasmic (when all or most copies are identical throughout mtDNA), resulting in greater penetrance of the variant. Most studies of this variant have found people are homoplasmic for the G allele (for example, Matsunaga et al). However, people with a heteroplasmic variant have been identified in several studies including in Spanish families with m.1555A>G and hearing impairment"* With respect to heteroplasmy / penetrance, as noted by CPIC[1], MT-RNR1 variants were historically described as homoplasmic variants, with latterly developed quantitative methods facilitating detection of heteroplasmy, with varying mutational load of the m.1555A>G variant from across tissues. It is a reasonable clinical question raised by the phenomenon of heteroplasmy as to the threshold of heteroplasmy at which the administration of aminoglycoside becomes acceptable, concluding that based on the literature there is no clear heteroplasmy level where aminoglycoside administration becomes safe when a high risk MT-RNR1 variant is detected. CPIC: Doi:10.1002/cpt.2309 (https://cpicgx.org/guidelines) It is important to note in this context that the Genedrive MT-RNR1 ID Kit can detect A>G heteroplasmy to the level of 10% gene variant in a background of 90% non-variant (as documented in the product IFU). **CPIC recommends that if a relevant MT-RNR1 gene variant is detected, the guidance should be followed as set out for a homoplasmic variant, irrespective of heteroplasmy status.**	This information is provided within the background section to demonstrate the maternal inheritance patterns of the variant. It is not intended as a reflection of the test ability to detect the variant given low heteroplasmy levels or as a recommendation for/against the use of aminoglycosides in these patients. You will note that the Genedrive MT-RNR1 ID Kit or other means of testing are not mentioned within this section. Therefore, we will not be incorporating further information in this regard.
Genedrive Diagnostics Ltd	9	20	3.1	The authors state that *the data was only extracted from McDermott et al 2022b[18].*	Thank you for pointing that out. We have amended the references and make sure we refer to the full study.

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

Assessment Report and economic model - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				This reference is incorrect and we believe it should be 17 instead, as this is the full study publication in JAMA pediatrics, whereas 18 is only the protocol publication. The reference also appears to be incorrect. The correct reference is your reference listed as #22 which was published in the BMJ Open in 2021. McDermott JH, Mahood R, Stoddard D, et al. Pharmacogenetics to Avoid Loss of Hearing (PALOH) trial: a protocol for a prospective observational implementation trial. BMJ Open. 2021 Jun; 11(6):e044457. DOI: 10.1136/bmjopen-2020-044457. PMID: 34135034; PMCID: PMC8211036. Reference 17 (the full study publication in JAMA pediatrics) is also listed in Appendix C – A list of **excluded** records. **Please check citations.**	Reference 18 is not the protocol, but a conference abstract, so no need to action that point. We will also amend the excluded record list (it supposed to be the protocol).
Genedrive Diagnostics Ltd	10	13	1.1.1	Cohort studies in various countries suggest the variant is “rare”. From a genetics standpoint, the MT-RNR1 mutation is not considered “rare”. The NHS defines a rare disease as one effecting fewer than 1/2000 people. The UK Rare Diseases Framework - GOV.UK (www.gov.uk) Suggest just the prevalence is cited in the report (eg 1/500) Perhaps “rare” is not the right word.	We agree with this point. We’ve rephrased it.
Genedrive Diagnostics Ltd	11	10	Scientific summary and further	*there is evidence to suggest the usage of the Kit did not substantially impact on time to antibiotics* The conclusion of the study was that implementation of the test did not impact time to antibiotics (was not statistically different). It was a primary endpoint of the study, not suggested evidence.	Considering potential uncertainties regarding generalisability of the study, we think ‘suggest’ is an appropriate word to reflect this.
Genedrive Diagnostics Ltd	12	Page 11 and section	Suggested Priority for future research	The report comments that *a research priority should be to evaluate the Genedrive MT-RNR1 ID Kit in mothers.*	We appreciate this may not be a target population for Genedrive Diagnostics Ltd. However, this population was included as part of the NICE scope. Therefore, since the

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

Assessment Report and economic model - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
		7.2 and 7.3		This is not a target population for the product. The kit is intended as a rapid point of care test for use on neonates/infants in an acute setting. It may be useful to screen mothers for MT-RNR1 status, but this can be done through the NHS's pre-existing laboratory-based MT-RNR1 testing protocol – we would not advocate large scale studies on mothers, as this is not in the scope of our products intended use. Perhaps this could be looked at in future but as a minimum we would not cite this as "a priority" for this product. Overall the report comments on Mothers, but it is not a population currently within scope of the product, and perhaps not relevant with a point of care test.	EAG's rapid review did not identify any evidence for the use of Genedrive MT-RNR1 ID Kit in this population, there was judged to be high uncertainty for the use of this technology in mothers. Therefore, the EAG judged this to be a priority for further research.
Manchester Centre for Genomic Medicine	13	14	1.2	The authors note that MT-RNR1 testing is currently available for certain groups of patients, but little detail is provided on this. The "R65 Aminoglycoside exposure posing risk to hearing" test is currently available via NHS England (NHS-E) through the Nationally commissioned genomic test directory (https://www.england.nhs.uk/publication/national-genomic-test-directories/). Any individual where there is risk of significant exposure to aminoglycosides is eligible for this test. As such, m.1555A>G testing is currently available pre-emptively if a clinician feels that an adult or child is at risk of ototoxicity due to exposure to aminoglycosides. The reason this testing is not utilised in the NICU is because the turnaround timeframes for testing are too great (2-3 weeks for a standard diagnostic laboratory). If timeframes were not an issue, then NICU clinicians could make use of this current testing pathway. The authors should make note of the NHS-E genomic test directory in their guidance document and consider how any recommendation that m.1555A>G testing was not appropriate could contradict and impact upon the uptake of the existing clinical available test for the variant.	We have not made 'recommendations that m.1555A>G testing was not appropriate' – since making recommendations is not the function of an EAG report.
Manchester Centre for Genomic Medicine	14	22	3.4.2	The authors note that "12 babies did not have an index test, but no further information was provided". In the JAMA Peds paper (McDermott et al), it is stated that these babies were "missed" and "not tested by the clinical teams". Anecdotally, we can report that these were babies where the admitting clinical teams forgot to undertake the test. There was no obvious patient	Thank you for the clarification, however the EAG did not judge the statements 'missed' and 'not tested by the clinical teams' as providing sufficient information. In addition, we do not think the additional anecdotal

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

Assessment Report and economic model - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				variable which predicted this oversight. It is inevitable in acute clinical scenarios that a small number of tests will not be undertaken - training and incorporation into standard pathways will minimise any such omissions.	information meaningfully adds to what has already been discussed in the report.
Manchester Centre for Genomic Medicine	15	24	3.6.2	Patient Experience – The authors state that the study did not report on this outcome. Please note that since this literature search was undertaken, a paper has been publishing describing the PPIE work which underpinned the PALOH study. PMID: 36573267	Thank you for informing us about this study. However, there is insufficient time to include this information in our report (as mentioned in the protocol).
Manchester Centre for Genomic Medicine	16	41	5.5.2.2	The early economic model assumes that the test will require 30 minutes of nursing time to implement each diagnostic test. Even allowing for variation in practice across other (some smaller) centres, this is highly likely to represent a significant overestimate. Based on extensive consultation with NICU nursing colleagues who use the genedrive RNR1 platform, we are aware that the system has a “hands on” time of approximately 3-4 minutes. The nurse is not required to remain with the system whilst it is in operation and returns for 1-2 minutes once the results are available. The genedrive platform has been designed as a near patient system with a small footprint, so it can be accommodated in clinical settings. Importantly, no additional staff were rostered on the NICU during the PALOH study. Despite this, the key clinical measure - time to antibiotic administration (within 1 hour) - was not altered and so the impact on nursing time is minimised by this point of care approach. Furthermore, there were no reports of the clinical teams being unable to complete other aspects of the babies’ care when the test was administered.	Variations in the cost of staff time have been explored within the sensitivity analysis. The sensitivity analysis has shown that there is virtually no impact on overall costs and cost-effectiveness. We do not consider this point to be a key issue and have not updated the document.

NICE National Institute for Health and Care Excellence

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

Assessment Report and economic model - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
Manchester Centre for Genomic Medicine	17	62	7.1.1	Failure Rate - The genedrive MT-RNR1 platform has been used at the Manchester University NHS Foundation Trust since October 2022 in babies admitted to NICU. We are able to update the authors on the current performance of the system. As of 16th December 2022, 166 tests had been performed with 1 confirmed "positive" detected. There were 162 "negative" results and 3 "fails". This provides an updated failure rate (95% CI) of 1.81% (0.6-5.18). Further details can be provided on request if the panel would like more information on the current implementation.	See our response to comment 5 where a very similar comment was made.
Manchester Centre for Genomic Medicine	18	64	7.2.1	Throughout the assessment the authors note that testing mothers may be an alternative option. This is something which was discussed extensively by the PALOH authors during the design of the study. A response to a letter in JAMA Pediatrics, published in June 2022, discusses this alternative scenario. The major barriers to the implementation of m.1555A>G testing in mothers is outlined, which may be of interest to the committee. (PMID 35727572)	The EAG report makes clear: -there is currently no evidence on testing mothers -this is a population included in the NICE scope
Manchester Centre for Genomic Medicine	19		8.2	In the "suggested research priorities", the authors outline a theoretical cohort study (or meta-analysis of multiple future cohort studies) to better quantify the risk of AIHL in individuals with the m.1555A>G variant exposed to aminoglycoside antibiotics. We have concerns regarding the 1) feasibility and 2) ethics of this approach. Firstly, with regard to feasibility, the authors note that to derive accurate point estimates for penetrance, a future study would need to be extremely large. These studies would need to undertake longitudinal audiological assessments and have robust mechanisms for monitoring aminoglycoside exposure. Achieving such uniformity across multiple cohort studies is highly unlikely and the financial cost of running these studies would be onerous. Secondly, the ethics of undertaking such a cohort study are questionable. If the data is collected prospectively, then there is potential that individuals who	Thank you for the comment, however we think you are misunderstanding the suggested research priorities. 1. The report focuses on existing cohorts that are already following neonates longitudinally. 2. You will notice that no requirement for uniformity across these cohort studies has been stated. We agree heterogeneity is expected when combining data across cohort studies– hence the need for meta-analysis to quantify this heterogeneity. We consider further

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

Assessment Report and economic model - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				are known to have the m.1555A>G variant would be knowingly exposed to aminoglycosides. Since the publication of the 2022 CPIC guidance (PMID: 34032273) for the use of aminoglycosides based on MT-RNR1 genotype, the clinical equipoise has shifted. As such, undertaking a prospective cohort study to assess the question of penetrance would be challenged by any research ethics committee. Given the points discussed above, we would suggest that the recommendation that a cohort study is undertaken should be removed or heavily caveated. Rather, one might consider a staged implementation process (in tandem with 8.2.2) where real world impact of implementation is monitored closely over time, assessing, for example, reduction in cases of AIHL or the need for cochlear implantation.	information, albeit with limitations, to be more likely to reduce uncertainty than no further information. 3. As above, the proposed study nowhere requires individuals known to have the m.1555A>G variant to be knowingly exposed to aminoglycosides. The proposed study or studies are based on existing cohorts that are already being followed up longitudinally.
United Kingdom Clinical Pharmacy Association	20	13	1.1 1.1.2	Rarer mtRNR1 variants obviously outside scope of report/test, but given there is CPIC guidance for 1095T>c and 1494C>T, there should be acknowledgement of the small risk of AIHL due to other mt RNR1 variants, despite a normal genedrive MT-RNR1 test result	Thank you for the comment, we have now included this information.
United Kingdom Clinical Pharmacy Association	21	23	3.4.10	Data on usability ideally would be available given high numbers of staff who will require training to use this	The EAG agree that this would be useful, however we do not have access to this data. Also, as stated in the report, staff training costs are very unlikely to make any material difference to the results from the cost effectiveness analysis.
United Kingdom Clinical	22	41	5.5.2.2	Staff time estimates do not explicitly state time to upload into patient's electronic health record. Risk of POC test result never making it into patient records and implications of this for future treatment episodes not	As the stakeholder points out, the staff time estimates did not consider the time taken to upload the results into a patient's electronic

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

Assessment Report and economic model - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
Pharmacy Association				mentioned. Educational needs of HCP in wider system being aware of and acting on test result throughout patient's lifetime could also be considered	health record. However, it is very unlikely that the costs of uploading the results would make any material difference to the results from the cost effectiveness analysis.
United Kingdom Clinical Pharmacy Association	23	30 & 68	5.2.2.2 (fig 5) & 8.2.2	Criteria for proposed maternal testing not entirely clear. Flow charts state 'mothers with risk factors' indicating that this relates to the likelihood of the mother receiving aminoglycosides and suggestions for further research (8.2.2) specify mothers with 'risk factors for sepsis'. Unclear whether this relates solely to risk of intrauterine exposure to aminoglycosides or risk to mother? Would first choice antibiotics include an aminoglycoside for sepsis in pregnancy? Elsewhere in report, maternal testing seems to focus solely on inherited maternal risk to neonate.	The aim of this research recommendation was to avoid being too prescriptive. Our rapid review identified this has not yet been studied therefore there is substantial uncertainty. Further research will help to reduce uncertainty on the viability of this approach.
United Kingdom Clinical Pharmacy Association	24	41	5.5.2.2	CPIC guidelines mention 'advice from a clinical genetics service can be sought' to help with cascading information to family - obviously a loose recommendation and unclear whether this would happen in all cases, but cost not considered in modelling	As the stakeholder points out, the recommendation is loose and unclear. Therefore, this was not considered in the economic modelling. However, it is unlikely that the costs of accessing a clinical genetics service would make any material difference to the results from the cost effectiveness analysis.
United Kingdom Clinical Pharmacy Association	25	47 & 65	5.6 & 7.2.2	If default position is to administer alternative antibiotics for all cases where there is test failure (around 5%, based on limited data with revised test), then there is a possibility that issues of resistance to alternative antibiotics would increase. It would also be helpful to see figures on treatment failure for alternative antibiotics in treating sepsis vs benzyl penicillin & gentamicin	The EAG agree that antimicrobial resistance is a significant issue. However, this was not included in the early economic model, and it is also unclear how exactly it could be captured in a definitive model. We assumed equal effectiveness (in line with clinical opinion), a pragmatic decision made for an early economic model. This

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

Assessment Report and economic model - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
					could potentially be considered in a full economic model.

Section B: Comments on the economic model (please add further rows as required)

Stakeholder	Issue	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG Response
Genedrive Diagnostics Ltd	1	The assumption of the addition of 30 minutes of staff costs per test to implement the test used in the early economic model is incorrect. According to the report this time was based on the Health Economics Utility Paper that we provided, which in section 4.1 states 'The average analysis time from sample collection to result is 30 minutes' which includes the 26 minutes taken to run the test plus the 4 minutes of nurse time to prepare the test prior to starting the test run on the instrument.	In the PALOH publication the median time to obtain a sample for testing was 6 minutes, as quoted in sections 3.4.6 and 7.1.1 of the EVA report. Therefore this data point should be used for the economic modelling analyses for the staff costs per test calculation instead of 30 minutes.	We have not re-run the model. We would expect this cost to be significantly reduced.	Variations in the cost of staff time have been explored within the sensitivity analysis. This sensitivity analysis has shown that there is virtually no impact on overall costs and cost-effectiveness. The EAG do not consider this point to be a key issue and have not amended the document.
Manchester Centre for Genomic Medicine	2	The early economic model assumes that the test will require 30 minutes of nursing time to implement each diagnostic test. This is costed at £28 with a sensitivity analysis (low-high) of £15-40. Even allowing for variation in practice across other (some smaller) centres, this is highly likely to represent a significant overestimate. Based on extensive consultation with NICU nursing colleagues who use the genedrive RNR1 platform in clinical practice, we are aware that the system has a "hands on" time of approximately 3-4 minutes. The nurse is not required to remain with the system whilst it is in operation and returns for 1-2	We would suggest lowering the base-case value to 6 minutes with a correspondingly adjusted sensitivity analysis.	This is unlikely to significantly impact the result of the ICER and the test will remain dominant. However, it will likely mean that the Ten-Year Time Horizon ICER becomes dominant. [We did not re-run the model]	Variations in the cost of staff time have been explored within the sensitivity analysis. The sensitivity analysis has shown that there is virtually no impact on overall costs and cost-effectiveness over the lifetime. The stakeholder is correct in stating that the point estimate of cost at 10 years of the Genedrive RNR1 platform would be less than

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

Assessment Report and economic model - Comments

Stakeholder	Issue	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG Response
		minutes once the results are available. The genedrive platform has been designed as a near patient system with a small footprint, so it can be accommodated in clinical settings.			standard care, but this of course does not reflect some of the other considerable uncertainty that exists. The EAG do not consider this point to be a key issue and have not amended the document.