NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Early Value Draft Guidance Consultation Document – Comments
Theme: Recommendations

Comment number	Name and organisation	Section number	Comment	NICE Response
1	Genedrive Diagnostics Ltd	Page 15, DAR section 1.3 and 1.4	Would the EVA recommendation be, to include testing of all babies admitted to the NICU, rather than just those babies that are suspected to be at risk of infection or sepsis who need antibiotics? Please advise?	Thank you for your comment which NICE has considered. The wording in recommendation 1.1 has now been updated to clarify that the recommendation applies to newborns who are being considered for treatment with aminoglycosides. Please note the scope of the assessment and recommendations are not limited to a neonatal intensive care unit (NICU) setting. The EAG notes that the cost-effectiveness analysis was based on the babies needing antibiotics being tested and did not explore this. They would expect the testing to be less cost-effective if administered to all babies in the NICU rather than just those that are suspected to be at risk of infection and need antibiotics. However, this scenario was not explored in the analysis. The committee noted that one of the centres in the PALOH study now routinely tests all babies on admission to the NICU. But it said that individual centres should decide which babies to test depending on local knowledge of what proportion of babies go on to receive aminoglycosides. Section 3.3 in the early value guidance document has been updated to reflect this.
2	NPPG – web comment	Recommendations – Section 1	In general, the Neonatal and Paediatric Pharmacists Group (NPPG) supports these recommendations.	Thank you for your comment which NICE has considered.

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			Members feel that this should be rolled out and tested in non-tertiary centres to see if it works and picks out babies that should be excluded from aminoglycoside therapy.	The committee said that further evidence generation should include smaller non-specialist centres and other settings outside of neonatal intensive care units where the test may be used (see section 3.12 and 4.1 of the early value guidance document). This is to ensure that the evidence generated can help assess if the time to antibiotic treatment, test failure rate and diagnostic accuracy estimates reported in the PALOH study are generalisable to other settings.

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Early Value Draft Guidance Consultation Document – Comments
Theme: Other patient groups and settings

Comment number	Name and organisation	Section number	Comment	NICE Response
3	NPPG – web comment	Recommendations – Section 1	• Are the recommendations sound, and a suitable basis for early value guidance to the NHS? This is preventative medicine in many ways and thus now that we can do this test in a non-invasive and quick turnaround, it should be available for all who need an aminoglycoside.	Thank you for your comment which NICE has considered. The scope of this assessment only includes newborn babies who need antibiotics and are being considered for treatment with aminoglycosides. NICE is unable to make any recommendations about groups that are outside the scope of the assessment. These comments will be passed to the company to consider whether further evidence generation in other groups could be considered and this may be something NICE could consider in a future evaluation if notified that evidence is available in other groups.
4	NPPG – web comment	The technology – clinical need and practice, section 2	Are there any other patient groups this could be rolled out to, e.g. Cystic Fibrosis – or do these children all have laboratory-based test assuming that at some point they are likely to need an aminoglycoside?	Thank you for your comment which NICE has considered. The scope of this assessment only includes newborn babies who need antibiotics and are being considered for treatment with aminoglycosides. NICE is unable to make any recommendations about groups that are outside the scope of the assessment. As outlined in the scope of this assessment, people with a predisposition to gram negative

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				infections, for example due to known respiratory conditions such as Cystic Fibrosis are eligible for laboratory testing. For more information please see the National genomic test directory rare and inherited disease eligibility criteria.
5	NPPG – web comment	Committee discussion, section 3	• Has all of the relevant evidence been taken into account? Yes, but the real evidence is that the system can detect the gene variant. The service evaluation research about implementation has just been done in neonates, but that has no relevance to where this could be implemented (eg PICU, PRE-Surgery etc). Thus the evaluation of use appears to not be equitable. If we looked at an Epipen in A&E we wouldn't be happy if we couldn't use it on the ward – feels similar!	Thank you for your comment which NICE has considered. The scope of this assessment only includes newborn babies who need antibiotics and are being considered for treatment with aminoglycosides. NICE is unable to make any recommendations about groups that are outside the scope of the assessment. These comments will be passed to the company to consider whether further evidence generation in other groups could be considered and this may be something NICE could consider in a future evaluation if notified that evidence is available in other groups.
6	NPPG – web comment	Evidence generation considerations, section 3.10	Usage in other settings where patients may be prescribed aminoglycosides for the first time e.g. PICU should also be included. The opportunity / need is there for a wider group of patients; the evaluation may need to be done in these areas too	Thank you for your comment which NICE has considered. The scope of this assessment only includes newborn babies who need antibiotics and are being considered for treatment with

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Comment number	Name and organisation	Section number	Comment	NICE Response
			through as the arguments about potential delays to antibiotics do become more significant when all your patients are septic vs the neonatal population. Members see a future where this test is more routine and prescribers won't want to prescribe aminoglycosides without this test first. Therefore, there are implications for changing antibiotic usage if it isn't universally available.	aminoglycosides. NICE is unable to make any recommendations about groups that are outside the scope of the assessment. These comments will be passed to the company to consider whether further evidence generation in other groups could be considered and this may be something NICE could consider in a future evaluation if notified that evidence is available in other groups.

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Early Value Draft Guidance Consultation Document – Comments
Theme: Evidence generation

Comment number	Name and organisation	Section number	Comment	NICE Response
7	NPPG – web comment	Evidence generation considerations, section 3.10	Further work to identify other variants associated with aminoglycoside-induced hearing loss, which may be more prevalent in different ethnic populations, should be carried out to promote equity of benefit. If identified, could the Genedrive be used to test for them?	Thank you for your comment which NICE has considered. In this early value guidance NICE has assessed the Genedrive MT RNR1 ID Kit, which currently detects only the MT-RNR1 m.1555A>G variant. The committee noted that other variants in the MT-RNR1 gene are also associated with a risk of aminoglycoside-induced hearing loss. Therefore, it considered that babies that test negative for the m.1555A>G variant but still go on to develop hearing loss should be followed up with laboratory testing to determine if they have had a false negative result. Depending on developments in laboratory testing, in the future it may also be possible to determine if they have a different MT-RNR1 variant. A clinical expert said that mitochondrial whole genome sequencing could also be considered to look for different variants where clinically indicated (see section 3.7 of the early value guidance document). These comments will be passed to the company to consider whether further variants could be considered.
8	NPPG – web comment	4 Evidence generation	How will data be collected to support section 4 evidence generation? Will there be a resource costs to units using	Thank you for your comment which NICE has considered.

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Early Value Draft Guidance Consultation Document – Comments
Theme: Evidence generation

Comment number	Name and organisation	Section number	Comment	NICE Response
		recommendations, section 4.1	the test if there is a requirement to collect data around use and resources needed to do this?	This topic is part of the pilots using NICE's new early value assessment approach. The aim of early value guidance is to provide quicker conditional recommendations from NICE on promising medical technologies while uncertainty in their evidence base is being addressed. The process, timelines and terms of the evidence generation to follow the early value guidance are currently being developed and will be discussed with the relevant stakeholders. For more information on the early value assessment process including funding of evidence generation please see our 'Early Value Assessment (EVA) for medtech' webpage.
9	NHSE		NICE has asked stakeholders to answer: 'Are the recommendations sound, and a suitable basis for early value guidance to the NHS?' **NHS England response (underlined text):** *NHS England look forward to further detail being made available regarding the evidence generation plan as outlined in the NICE publication 'Early value assessment interim statement (PMG39)'.*	Thank you for your comment which NICE has considered.
10	NHSE		Early value draft guidance states: 'Other variants in the MT-RNR1 gene are also associated with a risk of aminoglycoside-induced hearing loss. Therefore, it [the	Thank you for your comment which NICE has considered.

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Theme: Evidence generation

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			committee] considered that babies that test negative for the m.1555A>G variant but still go on to develop hearing loss should be followed up with laboratory testing to determine if they have had a false negative result, or have a different MT-RNR1 variant.' **NHS England response (underlined text):** *NHS England highlight the test available within the current version of the National Genomic Test Directory (NGTD) detects the same variant (m1555A>G) as the Genedrive MT-RNR1 ID Kit. Laboratory testing currently commissioned by the NHS in England would not detect a different MT-RNR1 variant, though this position may change in the future.*	Section 3.7 of the early value guidance document has been updated to clarify that babies that test negative for the m.1555A>G variant but still go on to develop hearing loss should be followed up with laboratory testing to determine if they have had a false negative result. Depending on developments in laboratory testing, in the future it may also be possible to determine if they have a different MT-RNR1 variant. A clinical expert said that mitochondrial whole genome sequencing could also be considered to look for different variants where clinically indicated.

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Early Value Draft Guidance Consultation Document – Comments
Theme: Implementation

Comment number	Name and organisation	Section number	Comment	NICE Response
11	NPPG – web comment	Upfront costs, section 3.8 – selected text: *However, the committee concluded that the upfront costs of implementing the Genedrive test should be carefully considered by commissioners.*	Who are the commissioners in this case? Is there going to be a choice to implement or not? Some of the phrases used in this document appear to suggest that there will be.	Thank you for your comment which NICE has considered. This topic is part of the pilots using NICE's new early value assessment approach. The aim of early value guidance is to provide quicker conditional recommendations from NICE on promising medical technologies while uncertainty in their evidence base is being addressed. NICE guidance produced by the diagnostics assessment programme does not carry a funding mandate and so centres will have a choice of whether to implement this test or not. NICE is working with NHS England on how the conditional recommendation for use resulting from an EVA could be used to support commissioning decisions in the NHS. Further detail on these plans will be released in the near future. Please refer to the NICE webpage on early value assessment for further details on the pilots.

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Early Value Draft Guidance Consultation Document – Comments
Theme: Test costs and cost effectiveness

Comment number	Name and organisation	Section number	Comment	NICE Response
12	NPPG – web comment	Cost effectiveness, section 3.7	Some members have asked for clarification on the cost per test	Thank you for your comment which NICE has considered. The list price of the Genedrive MT-RNR1 ID kit and the cost per test as used in the economic model have now been added to section 2.4 of the early value guidance document. Further details on the list price of the Genedrive machine are in section 3.8. The external assessment group (EAG) said that as part of the economic analysis, it estimated the cost per test to the NHS, to help estimate whether the implementation of the Genedrive test is likely to be cost effective over the patient lifetime. The cost per test uses estimates of staff costs, capital costs and other costs of implementing the test. It assumed that 3 tests were done per day. The total estimated cost per test to the NHS was £130. Full details of the EAG estimates can be found in the 'diagnostics assessment report'.
13	NPPG – web comment	Cost effectiveness, section 3.7	Members have commented that the cost per test is far too high and should be negotiated down.	Thank you for your comment which NICE has considered. The committee concluded that the upfront costs of implementing the Genedrive test should be carefully considered by commissioners. It noted

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Comment number	Name and organisation	Section number	Comment	NICE Response
				that purchase options not associated with large capital investment costs should be explored for the conditional recommendations and real-world data collection. See section 3.8 of the early value guidance document.
14	NPPG – web comment	Upfront costs – section 3.7	Has there been any discussion around the cost of the equipment potentially being less if this is rolled out to many units? Have costs included been based on what it has cost Manchester and would this be reduced if more centres implement?	Thank you for your comment which NICE has considered. The EAG said that costs of the equipment were calculated using the information provided by the company at the time of writing and estimates of resource usage are partially based on the PALOH study.
15	NPPG – web comment	Cost effectiveness, section 3.9	One of the benefits that has not been mentioned is the fact that some babies may be picked up on this newborn screen that may in future be treated with aminoglycosides, hence we could avoid exposure in the neonatal and future episodes of care. Hence there may be a further cost benefit.	Thank you for your comment which NICE has considered. The committee also considered the potential additional benefits of avoiding aminoglycoside exposure in the future but noted that these were not included in the cost-effectiveness analysis. These considerations have now been added to section 3.10 of the early value guidance document.

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Early Value Draft Guidance Consultation Document – Comments
Theme: Editorial

Comment number	Name and organisation	Section number	Comment	NICE Response
16	NHSE		Early value draft guidance states: 'There is currently no test available in the NHS that gives results quickly enough to inform decisions on antibiotic prescribing' & 'Currently available laboratory testing for m.1555A>G cannot provide results quickly enough to inform antibiotic prescribing in babies with suspected infection or sepsis that need to be treated within 1 hour.' The following test is already available and carried out in laboratory setting: R65 - Aminoglycoside exposure posing risk to hearing – Targeted mutation testing for: MT-RNR1 1555A>G NHS England response (underlined text): NHS England suggest amended wording to: 'results quickly enough to inform decisions on ACUTE antibiotic prescribing.'	Thank you for your comment which NICE has considered. The 'potential benefits of early access' section of the early value guidance document has now been updated to incorporate this suggestion. See page 2 of the early value guidance document.

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Early Value Draft Guidance Consultation Document – Comments
Theme: Comments in support of guidance

Comment number	Name and organisation	Section number	Comment	NICE Response
17	RNID – web comment		The Royal National Institute for Deaf People (RNID) is the leading charity supporting the 12 million people in the UK who are deaf, have hearing loss or tinnitus. We campaign to end the discrimination faced by our communities, help people to hear better now and fund world-class research to restore hearing and silence tinnitus. RNID funded a pilot grant at the University of Manchester in 2016 to support the development of a prototype of the Genedrive MT-RNR1 ID Kit and to provide a proof of concept that the kit could correctly and accurately identify babies with this genetic variant (and therefore at higher risk of hearing loss if treated with aminoglycosides) within a one-hour timeframe. We are pleased that the researchers have been able to generate further support to refine and improve the kit and that it has been tested successfully in a clinical setting. We hope that it can be implemented more widely in the future following implementation of the early value guidance, which will generate more evidence to improve confidence in the test and its ability to correctly identify babies at risk of hearing loss within the necessary timeframe. As far as we are aware, all the relevant evidence has been considered by the committee in drafting their early value guidance.	Thank you for your comment which NICE has considered.

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			The summaries of the clinical and cost effectiveness are reasonable interpretations of the evidence, and the recommendations that have been made around collecting further data in smaller non-specialist centres and outside of neonatal intensive care units, including in centres where babies will come from different patient demographics (such as different ethnicities and socio-economic backgrounds), improving confidence in the test's performance in terms of accuracy and failure rate, and studying how the test results affect antibiotic prescribing decisions, are all reasonable and appropriate recommendations from our perspective. They will provide valuable data that will help to strengthen confidence in the clinical and cost-effectiveness of the test. Overall, we are supportive of the draft guidance and the recommendations made and hope that the kit can be used more widely to help prevent hearing loss.	