Diagnosis

Evidence to Decision Documents (EtDs)

Features of the Evidence to Decision Document Format

- We have *italicised* the repeated sections across all EtDs: the first paragraph of the background section, as well as the Value and Equity sections.
- Where additional material is included within one of the *italicised* sections with repeated content, it is <u>underlined</u> to indicate this portion is new.
- Each EtD includes a Values section and an Equity section, which contain summaries of information from the respective core documents (see Appendices E, F and section 1.2).
- For 'Desirable' and 'Undesirable' effects, we first interpret where the point estimate lies in relation to the threshold. We then decide how certain we are in that effect, considering where the confidence interval lies in relation to the threshold. This is captured in our overall rating in the ‘Certainty of Evidence’ section. We are careful not to 'double count' the confidence interval by somehow integrating it in our description of the point estimate.
- For the ‘Balance of Effect’ section, we take into account both certainty and the point estimate.

Question 11.

Should testing for neonatal hypoglycaemia vs. not testing be used for babies at risk of neonatal hypoglycaemia ?	
POPULATION:	Babies at risk of neonatal hypoglycaemia
INTERVENTION:	testing for neonatal hypoglycaemia
COMPARISON:	not testing
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	All birth settings
PERSPECTIVE:	Clinical recommendation

BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment are recommended to reduce the risk of later developmental problems.* As neonatal hypoglycaemia is often asymptomatic unless severe, it is standard practice to screen babies considered to be at risk with repeated, painful blood tests over the first 12-24 hours after birth. There have been no studies that have compared the long-term neurodevelopmental outcomes of at-risk babies screened for neonatal hypoglycaemia and those not screened. The presumed benefit of screening babies at risk of neonatal hypoglycaemia is that treatment of hypoglycaemia may improve neurodevelopmental outcomes. However, there is currently no evidence from randomised controlled trials that treatment of neonatal hypoglycaemia improves long term outcomes, and there is recent evidence from a cohort study that babies at risk for neonatal hypoglycaemia, who were screened and found to have neonatal hypoglycaemia and received treatment to maintain a blood glucose concentration of ≥2.6 mmol/L, had worse neurodevelopmental outcomes than babies who were screened and did not have neonatal hypoglycaemia (1). It is possible that screening at-risk babies for hypoglycaemia may be harmful. Babies with hypoglycaemia who subsequently develop neurodevelopmental impairment are more likely to have had a rapid rise of their interstitial glucose concentration after hypoglycaemia, potentially due to treatment (2). Moreover, babies with risk factors for hypoglycaemia, such as babies of mothers with diabetes and preterm babies, are less likely to be exclusively breastfed on discharge.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	There have been no trials of screening for neonatal hypoglycaemia. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	The desired anticipated effects are improved neurodevelopmental outcomes. However, there is no evidence that screening for hypoglycaemia or treatment of hypoglycaemia improves outcomes.
Undesirable Effects How substantial are the undesirable anticipated effects?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	There have been no trials of screening for neonatal hypoglycaemia. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	In addition to the pain that babies experience with heel prick blood tests, observational studies show that babies who are screened for neonatal hypoglycaemia are more likely to be given formula and less likely to be exclusively breastfed, even if their blood glucose concentrations were normal (3). However, babies with risk factors for neonatal hypoglycaemia such as those whose mothers had diabetes and those born by caesarean section are at higher risk of not being breastfed, independent of hypoglycaemia (4, 5), so it is difficult to determine if this association is causal (6).
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There have been no trials of screening for neonatal hypoglycaemia. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability***	

○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	• *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	There have been no trials of screening for neonatal hypoglycaemia. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	A screening programme requires staff time, lancets and blood glucose analysers, see EtDs on timing of screening and types of analysers.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We have not systematically searched for evidence of the resources required.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There is no evidence of the cost effectiveness of screening for neonatal hypoglycaemia.	
Equity What would be the impact on health equity?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10)*. However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (11)*.* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)*(10)*.* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (11)*.* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10)*.* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** In O'Brien's (8) retrospective observational single-centre study, babies from all non-European ethnic groups were more likely to be eligible for screening compared with babies of European mothers (29.7% v 22.3%; OR, 1.47; 95% CI, 1.43-1.51; p < .001).	

	Consideration for Māori Babies of Māori wāhine were more likely to be eligible for screening for neonatal hypoglycaemia than babies of European women (26.4% v 22.3%) (8). *In the Whānau Experience study (Whānau Experiences Study Group., 2024), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (12)(13)(14). *Additionally, a systematic literature review by Graham et al.* (7) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (7). ***Consideration for Pacific*** Babies of Pacific women were more likely to be eligible for screening for neonatal hypoglycaemia than babies of European women (32.1% v 22.3%) (8). *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work (Whānau Experiences Study Group., 2024).* ***Considerations for Indian*** Babies of Indian women were more likely to be eligible for screening for neonatal hypoglycaemia than babies of European women (37.8.1% v 22.3%) (8). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (9). *Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (9)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability		

Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	This practice is in widespread use. In the Whānau Experiences study (15) of whānau/families with diverse cultural backgrounds including Māori, Pacific and Asian ethnicities (studied because these groups have a higher likelihood of having a baby born at risk of neonatal hypoglycaemia), some parents reported negative views about blood testing, including being distressed by multiple testing, seeing their small child hurt, and not being offered the chance to help. **Consideration for Māori** Whānau Māori want the very best health outcomes for their pēpi. Whānau felt empowered and disempowered by the healthcare team, and the health system, when health provision happened to them, rather than with them (e.g., testing). Whānau shared experiences of healthcare delivery that occurred without explanation, resulting in disempowerment, and others asked questions to enable enactment of mana motuhake, especially around tikanga. **Consideration for Pacific** Some Pacific mothers felt very distressed when their babies had to be tested multiple times.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	This practice is in widespread use, so it is feasible in Aotearoa New Zealand. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

SUMMARY OF JUDGEMENTS

JUDGEMENT

DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○

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Question 12.

Should expanded or restricted criteria vs. current criteria be used for screening for neonatal hypoglycaemia?	
POPULATION:	All newborn babies
INTERVENTION:	expanded or restricted criteria
COMPARISON:	current criteria
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies)

	4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment are recommended to reduce the risk of later developmental problems.* Since neonatal hypoglycaemia is often asymptomatic, it is standard procedure to screen babies deemed at risk by measuring blood glucose concentrations at intervals after birth. Although there is a lack of evidence on the long-term neurodevelopmental outcomes of at-risk babies screened for neonatal hypoglycaemia versus those not screened, the evidence suggests that screening at-risk babies and managing hypoglycaemic episodes to maintain blood glucose concentrations ≥2.6 mmol/L may help preserve cognitive function. However, given that more than a quarter of all newborn babies may be eligible for screening, it is important to identify which babies would benefit from screening (1).
CONFLICT OF INTERESTS:	CC, DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We found no evidence for any critical or important outcomes. **Risk factors for neonatal hypoglycaemia** (2)	A review of 20 local guidelines from 18 hospitals in Australia and Aotearoa New Zealand (4) found that all guidelines recommended testing the blood glucose concentrations of at-risk babies rather than testing every baby. These guidelines typically include babies born to mothers with diabetes, and most also include stressed or unwell babies, as well as those showing signs of hypoglycaemia. Other frequently mentioned risk factors were being small for gestational age (SGA, 16/18 guidelines), born preterm (16/18), and large for gestational age (LGA, 14/18). A systematic review of international guidelines on neonatal hypoglycaemia screening found that only half of them recommend screening for LGA (1). The most frequently identified risk factor reported in observational studies is babies born to mothers with diabetes, with a pooled odds ratio (derived from meta-analysis, summarises the collective findings of multiple studies to gauge the strength and direction of association between exposure or intervention and an outcome) of 4.45 (95% CI: 3.32, 5.97), followed by preterm birth at 2.82 (95% CI: 1.91, 4.15), and being small for gestational age (SGA) at 1.98 (95% CI: 1.59, 4.15). Additional risk factors were low birth weight (LBW) associated with an odds ratio of 2.21 (95% CI: 1.59, 3.08), and large for gestational age (LGA) with an odds ratio of 1.98 (95% CI: 1.59, 2.47) (2).

Risk factors	No. of studies	No. of participants	Odds ratio (OR) ranges	Pooled results OR (95%CI)
Maternal factors				
Diabetes (GDM, type 1, type 2)	53	214,766	1 – 65	4.45 (3.32, 5.97
Caesarean	5	2,195	1.18- 3.37	2.1 (1.57, 2.80)
Excess weight gain during pregnancy	3	30,004	1.12-1.83	1.36 (1.05, 1.77
Antidepressant medications used during pregnancy	2	75,219	1.37- 1.61	1.57 (1.12, 2.20
Alpha/beta blockers used during pregnancy	2	76,388	2.6-3.59	3.28 (2.47, 4.36
Obesity	3	5,971	1.2 (NS)- 5.59	2.03 (0.85, 4.89
Ritodrine used during pregnancy	2	1,073	1.58 (NS)-7.67	3.46 (0.73, 16.4
Hypertension	2	740	0.69 (NS)-1.14	0.92 (0.55, 1.56
Betamethasone	1	2,609	NA	1.69 (1.46, 1.96
Fever	1	348	NA	3.84 (1.56, 9.45
Prolonged labour	1	483	NA	9.07 (1.98, 41.5
Neonatal factors				
Preterm	19	11,234	1.33-19.32	2.82 (1.91, 4.15
SGA	13	5,623	1.32 – 23.17	1.98 (1.59, 2.47
LBW	8	4,285	1.13-6.07	2.21 (1.59, 3.08
LGA	7	2,242	1.52-34.36	2.0 (1.19, 3.36)
Macrosomia	5	6,495	1.49-6.25	2.37 (1.57, 3.57
Foetal distress	5	1,399	1.20-13.22	1.43 (1.12, 1.82
Hypothermia	3	1,098	1.50-3.40	2.09 (1.27, 3.44
Twin	3	5,412	2.0 – 13.95	3.63 (1.77, 7.44
Delayed feeding	2	5,72	1.56-2.07	1.73 (1.26, 2.37

* Abbreviations: GDM- gestational diabetes; SGA- small for gestational age; LBW: low birth weight; LGA: large for gestational age

Signs and symptoms of neonatal hypoglycaemia (2)

Signs and symptoms	No. of studies	No. of participants	Frequency ranges (among hypoglycaemia cases)
Jitteriness	15	1644	1.0% to 62.7%
Seizures/Convulsions	15	1500	0.6% to 38.9%
Poor feeding/refusal to feed	14	1315	1.1% to 90.5%
Lethargy	10	789	1.0% to 69.4%
Irritability	7	717	2.0% to 38.0%
Cyanosis	8	547	0.83% to 38.9%
Hypotonia	7	795	0.83% to 27.3%
Apnoea	6	870	0.80% to 37.88%
tachypnoea	5	569	0.45% to 29.0%
hypothermia	4	379	2.9% to 27.1%
Respiratory distress/ asphyxia	4	282	4.6% to 34.0%
Abnormal cry	3	349	0.91% to 22.3%
Pallor	3	395	0.91% to 7.0%
Vomiting	2	444	18.2% to 21.5%
Bradycardia	2	103	2.3% to 11.11%
Listlessness	1	85	69.4%
Tremor	1	22	4.55%
Tachycardia	1	30	1.0%

The most commonly reported signs of neonatal hypoglycaemia include jitteriness, with percentages ranging from 1.0% to 62.7% of all babies with hypoglycaemia across studies, followed by seizures/convulsions, ranging from 0.6% to 38.9%, poor feeding or refusal to feed at 1.1% to 90.5%, lethargy at 1.0% to 69.4%, and irritability at 2.0% to 38.0% (2).

Consideration for Māori

Babies of Māori women were more likely to be eligible for screening for neonatal hypoglycaemia than babies of European women (26.4% v 22.3%) (1).

However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%) (3*).*

Consideration for Pacific

Babies of Pacific women were more likely to be eligible for screening for neonatal hypoglycaemia than babies of European women (32.1% v 22.3%) (1).

In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%) (3*).*

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We found no evidence for any critical or important outcomes. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	There have been no studies that have compared the long-term neurodevelopmental outcomes of babies screened for neonatal hypoglycaemia and those not screened. Screening for neonatal hypoglycaemia typically involves obtaining a heel-prick capillary blood sample, and then analysing the concentration of glucose. Heel-prick tests are likely to be painful for the baby. Babies who have hypoglycaemia but are not promptly screened may experience delays in treatment, potentially leading to neurological complications, particularly in severe cases. Moreover, if testing is not consistently continued, instances of delayed, recurrent or prolonged hypoglycaemia may go undetected.
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	We found no evidence for any of the critical or important outcomes. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	The evidence comes exclusively from observational studies. We did not systematically evaluate the quality of the studies. Despite some substantial effect sizes, there is significant heterogeneity in the estimated size of effects across various studies.

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Neurodevelopmental impairment [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Considerations for Māori** Māori babies are more likely to be at risk of hypoglycaemia than New Zealand Europeans **Considerations for Pacific** Pacific babies are more likely to be at risk of hypoglycaemia than New Zealand Europeans	Panel to Consider: Expanding the screening criteria to encompass additional risk factors or symptoms is likely to increase the number of identified babies who are tested and likely receive treatment for hypoglycaemia. Consequently, initiating screening for these babies is likely to lead to the earlier detection and treatment of severe hypoglycaemia. However, some babies may receive unnecessary screening tests, and even unnecessary treatments and interventions. Restricted screening criteria may result in some babies with hypoglycaemia being incorrectly classified as not having the condition, potentially leading to delayed treatment and, in severe cases, neurological complications. Moreover, if testing is not consistently continued, instances of delayed, recurrent, or prolonged hypoglycaemia may go undetected.
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Screening with an enzymatic glucometer costs NZ $ 86.94 per baby, while using a non-enzymatic glucometer costs NZ $ 97.08 per baby (5).	

Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	We have not systematically searched for evidence of the resources required.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The cost of testing is likely to be small compared to the cost of brain injury from undetected hypoglycaemia for an individual, but the evidence that prompt detection and treatment of hypoglycaemia alter neurodevelopmental outcomes is very uncertain. Screening more babies could potentially impose a greater financial burden on the healthcare system and require additional resources, particularly staff time.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?***	In the Whānau Experiences study, (6) one Pacific mother believed that the increased testing of their baby was primarily due to their race.

○ Increased ○ Varies ○ Don't know	*There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (8)*. However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (3)*.* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (8)*.* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (3)*.* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (8)*.* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (6)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (9)(10)(11)*.*	

	Additionally, a systematic literature review by Graham et al. (12) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (12). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (6). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (7). *Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (7)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	In the Whānau Experiences study (6) of parents with diverse cultural backgrounds including Pacific, Asian, and Māori ethnicities, some parents reported negative views about blood testing, including being distressed by multiple testing, seeing their small child hurt, and not being offered the chance to help. A few Asian participants reported that the heel-prick testing felt transactional because few recalled being offered the opportunity to support their baby while being tested. **Considerations for Māori** Whānau Māori appreciated nursing staff providing additional cares during heel-pricks to provide comfort during the painful procedure.	

	Considerations for Pacific A few Pacific mothers felt deeply distressed if their babies had to be tested.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Blood glucose screening is standard practice for babies at risk in Aotearoa New Zealand. Screening for all babies is likely to be feasible if additional resources were available. A substantial increase in staffing, training and equipment would be required. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know

RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

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Question 13.

Should other timings vs. start at 1-2 hours, intervals of 3-4 hours, finish after 12 hours of glucose concentrations above the threshold be used for testing neonatal hypoglycaemia?	
POPULATION:	Babies at risk of neonatal hypoglycaemia
INTERVENTION:	other timings
COMPARISON:	start at 1-2 hours, intervals of 3-4 hours, finish after 12 hours of glucose concentrations above the threshold
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings

PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn infants over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Hypoglycaemia is commonly asymptomatic, so at-risk babies usually undergo blood testing to detect low glucose concentrations. This usually involves obtaining a heel-prick capillary blood sample, although other types of blood samples are sometimes tested. The timing of these screening tests is important, as heel-prick tests may be painful for the baby (1), distressing for their whānau, and require staff time and other resources.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are all authors of cited papers.

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We found no evidence for any of the critical or important outcomes. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Start Time A review of 20 local guidelines from 18 hospitals in Australia and Aotearoa New Zealand (11) found that the most commonly recommended start time for testing was 1-2 hours after birth (56%), including 7 guidelines from Aotearoa New Zealand (5 recommendations of 1-2 hours and 2 of 1 hour). A survey of 59 practitioners caring for babies at risk of hypoglycaemia in Aotearoa New Zealand found that 44 (75%) reported the first blood sample was taken 1-2 hours after birth, but 5 (8%) reported this was at <1 hour, 3 (5%) before 2 hours, and 4 (7%) at 2-4 hours (12). Data from three observational studies that started testing at 1-2 hours after birth in at-risk babies showed that the frequency of detected hypoglycaemia was higher at 1 hour than at 2 hours: 32% at 1h to 12% at 2h, n = 1570 (2); 6% at 1h to 3% at 2h , n = 190 (13); 10% at 1h to 2% at 2h , n = 690 (14), and decreased further thereafter. However, there are

		insufficient data to determine the timing of recurrent hypoglycaemia (since earlier detected hypoglycaemia was likely to have been treated), or the proportion of infants with hypoglycaemia on early testing who would have recovered without treatment by the next time of testing. Testing Interval In the review of 20 local guidelines, the most commonly recommended screening interval was 3-4 hourly (10 guidelines, 7 from Aotearoa New Zealand), with an additional 3 guidelines recommending 3-hourly and one recommending 4-hourly (11). Data from three observational studies (total of 417 at-risk babies) reporting regular blood glucose testing suggest that 10-17% of detected hypoglycaemia occurred between the initial test at 1-2 hours and the second test 3-4 hours later (13, 15, 16). However, there is a lack of clarity about whether the same babies were tested at every time point, and the proportion of new versus recurrent cases. There are also insufficient data to determine the proportion of cases that might occur during 3 – 4-hourly intervals between testing in older babies (3 to 4 hours). Timing in Relation to Feeds In a study of 227 babies (64 (28%) Māori) in Aotearoa New Zealand who were ≥ 35 weeks gestation and developed hypoglycaemia in the first 48 hours after birth, there was no significant change in glucose concentrations within 90 minutes after feeding by breastfeeding or mother's expressed breastmilk (whether expressed before or after the birth). However, blood glucose concentrations did increase slightly after a formula feed (mean increase 0.2mmol/L, 95% CI 0.004 to 0.04 mmol/L) (17). Another study of 62 well, term babies in Aotearoa New Zealand (2 (3%) Māori) found that there was very little change in interstitial glucose concentrations in response to breastfeeds in the first 48 hours, but the response increased after this age to 0.41-0.44 mmol/L on days 3-4 (18).

		Stop Time In the review of 20 local guidelines, six recommended screening for a minimum of 12 hours (all from Aotearoa New Zealand), three recommended 9–12 hours and one 24 hours (11). The survey of 59 practitioners caring for babies at risk of hypoglycaemia in Aotearoa New Zealand found that 41 (71%) reported that in at-risk but well babies 3 tests were taken; (3%) reported 4 tests; 4 (7%) reported 7 tests (likely to equate to 3-4 hourly testing for 24 hours); and 3 (5%) reported testing for 24 hours if the baby had a mother with diabetes, but only for 3 consecutive tests for other risk groups (12). Two studies that continued screening at-risk babies for 24 hours after birth found that relatively few new cases were identified after 12 hours (i.e., 0.3% of 1570 babies (2); and 2% of 160 babies (3)). Similarly, two studies that continued screening for 48 hours after birth found that a relatively small proportion of cases were identified after 12 hours (1.1% of 177 babies (4); 0.6% of 502 babies, (5)). However, using a testing protocol that continued for 72 hours, Kushwaha and Sahni identified 7/125 (5.6%) new cases after 24 hours and 3/125 (2.4%) after 48 hours (6). In the Sugar Babies study, Harris et al. used a testing protocol that continued for a minimum of 24 hours (1 hour after birth, then 3-4 hours for 24 hours, then 3-8 hourly for the next 24 hours) in 514 at-risk babies (150, 29% Māori, 16, 3% Pacific) in Aotearoa New Zealand, with treatment of detected hypoglycaemia intended to keep glucose concentrations >2.6 mmol/L (7). In this study, 260 babies developed hypoglycaemia, 187/390 (48%) of hypoglycaemic episodes occurred in the first 6 hours, and 315/390 (81%) in the first 24 hours, but 95/260 babies (37%) had their first episode after 3 normal blood glucose measurements, and 15 (6%) had their first episode >24 hours after birth. Of severe hypoglycaemic episodes (< 2.0 mmol/L), 106/143 (74%) occurred within 6 hours and 130/143 (90%) in the first 12 hours.

		In the hPOD trial of 2,133 at-risk babies from Aotearoa New Zealand and Australia (238 (11%) Māori, 116 (5%) Pacific) (8), hypoglycaemia occurred after 12 hours in 213/1,207 (18%) of babies with measurements after this time. In an American study of 830 at-risk babies who were tested for neonatal hypoglycaemia, it first occurred on the initial measurement for 202 babies (63.1%), the second measurement for 68 babies (21.3%), and the third measurement for 50 babies (15.6%). (9). In the babies not at risk of neonatal hypoglycaemia from the GLOW study (10), 12% had a low plasma glucose between 12-24 hours.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We found no evidence for the critical or important outcomes. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Screening for neonatal hypoglycaemia typically involves obtaining a heel-prick capillary blood sample, and then analysing the concentration of glucose. Heel-prick tests are likely to be painful for the neonate. In the Sugar Babies study of 514 at-risk babies screened for hypoglycaemia for at least 24 hours in Aotearoa New Zealand (229 (45%) Māori, 22 (4%) Pacific) (7), the median number of blood glucose measurements per baby was 9 (range 1-21). In the hPOD trial of 2,13 at-risk babies in Aotearoa New Zealand and Australia (238 (11%) Māori, 116 (5%) Pacific) (8) the mean (SD) number of glucose measurements per baby was 7.8 (4.0) in those who became hypoglycaemic and 3.8 (1.5) in those who did not.
Certainty of evidence What is the overall certainty of the evidence of effects?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	We found no evidence for the critical or important outcomes. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Estimates of frequency of hypoglycaemia at different times are very uncertain.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Starting time of 1 hour vs other times: Where data are available, it appears that the frequency of hypoglycaemia is higher at 1 hour than at 2 hours and decreases thereafter. Finishing time of 12 hours vs other times: Available data suggests that a relatively small proportion of cases of neonatal hypoglycaemia could be missed (i.e., 0.3 – 1.1%) if screening tests were to conclude at 12 hours. Intervals between tests of 3-4 hourly: There is limited evidence to suggest that a small proportion of cases or episodes (i.e., 10 – 17%) may occur between the initial test at 1–2 hours and the second test, approximately 3–4 hours later. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Panel to Consider: Start Time Earlier age at start of screening (1 hour vs 2+ hours) is likely to result in a higher proportion of babies receiving treatment for hypoglycaemia. It is uncertain what proportion of these babies would have had higher glucose concentrations later without treatment. However, earlier screening is likely to detect severe hypoglycaemia earlier and therefore allow earlier treatment. Testing Interval Approximately 10-17% of hypoglycaemia may occur between initial testing at 1-2 hours and the next test 3-4 hours later. There is no evidence about the risks and benefits of more or less frequent testing. Glucose concentrations may not change in relation to feeds in the first 48 hours. Stop Time There is wide variability in the reported incidence of later hypoglycaemia in at-risk babies, ranging from 0.3% to 18% after 12 hours and 5-6% after 24 hours.
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Each heel-prick test requires at least one heel lancet and blood collection device and approximately 5-6 minutes of staff time. The average cost of enzymatic glucometer per test is NZ $11.49. The average cost of non-enzymatic glucometer per test is NZ $4.25 (19). Cost for analysis of the sample depends on the device used (see EtD on that topic).	

Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	We have not systematically searched for evidence of the resources required.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The cost of additional testing is likely to be small compared to the cost of brain injury from undetected hypoglycaemia, but the evidence that prompt detection and treatment of hypoglycaemia alters neurodevelopmental outcome is very uncertain (see EtD on that topic).	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?***	

○ Probably increased ○ Increased ○ Varies ○ Don't know	*There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (21*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (7*).* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (21*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (7*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (21*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that***	

	inequities are reduced, if possible, and that they are not increased? ***Consideration for Māori*** *In the Whānau Experience study* (22*), participants expressed appreciation for the inclusion of prayer or tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (23, 24, 25*). Additionally, a systematic literature review by Graham et al.* (26*) provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (26*).* ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (22*).* ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (20*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (20*), 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability		

Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Number of tests In a qualitative study of 16 parents (5 Māori, 1 Pacific) interviewed 9–13 years after their baby was born at risk of hypoglycaemia, four specifically recalled blood tests for glucose measurement as stressful or traumatic and a negative aspect of participating in the follow-up study (CHYLD), even though the blood tests were part of routine care and not the research study (27). In the Whānau Experiences study (22) of whānau/families with diverse cultural backgrounds including Māori, Pacific and Asian ethnicities (studied because these groups have a higher likelihood of having a baby born at risk of neonatal hypoglycaemia), some parents reported negative views about blood testing, including being distressed by multiple testing, seeing their small child hurt, and not being offered the chance to help. Consideration for Māori Whānau Māori want the very best health outcomes for their pēpi. Whānau felt empowered and disempowered by the healthcare team, and the health system, when health provision happened to them, rather than with them (e.g., testing). Whānau shared experiences of healthcare delivery that occurred without explanation, resulting in disempowerment, and others asked questions to enable enactment of mana motuhake, especially around tikanga. Consideration for Pacific Some Pacific mothers felt very distressed when their baby had to be tested multiple times.	Start Time The protocol for the hPOD trial (8) of well, at-risk babies specified giving prophylactic dextrose or placebo gel 1 hour after birth and the first blood glucose measurement at 2 hours. There was consistent feedback from almost all of the 18 participating hospitals that at the time of administration of the gel (1 hour), many babies were receiving skin-to-skin contact and/or their first feed. Staff expressed reluctance to interrupt this time to administer other procedures.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Blood glucose screening is standard practice for babies at risk in Aotearoa New Zealand. An increase in frequency or duration of screening is likely to be feasible but would potentially require additional resources, particularly staff time, in most settings. Consideration for Māori Whānau Māori want the very best health outcomes for their pēpi. Whānau felt empowered and disempowered by the healthcare team, and the health system, when health provision happened to them, rather than with them (e.g., testing). Whānau shared experiences of healthcare delivery that occurred without explanation, resulting in disempowerment, and others asked questions to enable enactment of mana motuhake, especially around tikanga. Consideration for Pacific Some Pacific mothers felt very distressed when their baby had to be tested multiple times.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know

RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

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Question 14.

Should specific pain management strategies vs. control/ placebo/ no intervention be used for pain management during blood sampling for neonatal hypoglycaemia?	
POPULATION:	Newborn babies having blood sampling for screening for and treatment of neonatal hypoglycaemia
INTERVENTION:	specific pain management strategies
COMPARISON:	control/ placebo/ no intervention
MAIN OUTCOMES:	Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau Validated pain scores Pain reactivity Adverse effects
SETTING:	Any care settings

PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Standard clinical practice is to monitor at-risk babies to determine need for treatment to prevent long term consequences of hypoglycaemia (1). This involves collecting a blood sample to test glucose concentration, most commonly using a heel prick (1). However, blood sampling is a painful procedure (2) and pain has also been suggested to have detrimental effects on neurodevelopment in very preterm babies (3). Because using painful procedures to collect blood to test for neonatal hypoglycaemia is currently unavoidable, it is crucial to identify effective pain management strategies that can be used during blood testing. The Premature Infant Pain Profile (PIPP) is a tool designed for assessing pain in neonates, particularly preterm babies. It considers physiological and behavioural indicators, with a scale ranging from 0 to 21, with higher scores indicating more pain (4, 5). The Neonatal Infant Pain Scale (NIPS) evaluates pain based on facial expression, crying, breathing, and limb movements. Scores range from 0 to 7, with higher scores indicating more pain (6). The Douleur Aiguë Nouveau-né (DAN) scale rates acute pain in term and preterm neonates, scoring from 0 to 10. It assesses facial expressions, limb movements, and vocal expression (7). The Neonatal Facial Coding System (NFCS) assesses pain through facial expressions on a scale of 0 to 10, where 0 is no pain and 10 is the most pain (8).
CONFLICT OF INTERESTS:	CC, DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The desirable effect of different pain management methods are shown below (18): **Sucrose** (administration of oral sucrose with or without non-nutritive sucking (e.g. pacifiers) and other sweet solutions (e.g. glucose) prior to or during painful procedures) Preterm and term babies: • Reduces the Pain Profile of Premature Infants (PIPP) score at 30 seconds after heel lance (MD -1.74 (-2.11 to -1.37), 7 randomised controlled trials (RCTs), 547 babies; the mean PIPP scores at 30 seconds after heel lance ranged from 4.9 to 13.3 in the control group) (19).	

	• Reduces the Neonatal Infant Pain Scale (NIPS) score for venipuncture (MD -0.90 (-1.81 to 0.01), 1 RCT, 111 babies; the mean NIPS score was 3.8 in the control group) (20). Preterm babies: • Little to no effect on the PIPP score at 30 seconds after heel lancing (MD -1.88 (-2.32 to 1.44), 3 RCTs, 192 babies; the mean PIPP scores at 30 seconds after heel lancing ranged from 6.3 to 13.3 in the control group) (19). Term babies: • Reduces the NIPS score after heel lancing (MD -2 (-2.42 to -1.58), 1 RCT, 56 babies; the mean NIPS score immediately after heel lancing was 3 in the control group) (19). • Reduces the PIPP score at 30 seconds after heel lancing (MD -0.87 (-1.8 to 0.06), 3 RCTs, 227 babies; the mean PIPP scores at 30 seconds ranged from 4.9 to 8.5 in the control group) (19). • Uncertain effect on the Douleur Aiguë Nouveau-né behavioural pain scale (DAN) score in term babies at 30 seconds after heel lancing (MD -1.9 (-8.58 to 4.78), 1 RCT, 32 babies; the mean DAN score at 30 seconds was 9.5 in the control group) (19). • Reduces the PIPP score during venipuncture (weighted MD 2.79 (-3.76 to -1.83), 1 RCT, 213 babies; the mean PIPP scores ranged from 8.9 to 9.2 in the control group) (20). Results reported narratively Sucrose compared to water was reported to lower NIPS scores one minute after heel lance or blood sampling (21, 22) and two minutes after heel lance (22). Sucrose plus non-nutritive sucking was also reported to lower PIPP scores one minute after heel lance compared to standard care (positioning and swaddling) (24) or compared to no intervention, sucrose only or non-nutritive sucking only (9). **Skin-to-skin contact (with mothers or Whānau)** • Large reduction in PIPP at 30 seconds after heel lance (MD -3.47 (-5.55 to -1.38), 4 RCTs, 191 babies; the mean PIPP scores ranged from 10.9 to 13.2 in the control group) ((11, 12) our additional analysis). • Reduced Neonatal Facial Coding System (NFCS) score during heel lancing (MD -0.89 (-1.16 to -0.61), 2 RCTs, 362 babies; the mean NFCS score was 3 in the control group at 30 seconds after heel lancing (MD -0.78 (-0.95 to -0.60), 2 RCTs, 362 babies; the mean NFCS score was 1.78 in the control group) ((11, 12) our additional analysis).	

	• Uncertain effect on the proportion of babies with low or no pain during the procedure as measured by the Neonatal Infant Pain Scale (NIPS) score (RD -0.03 (-0.08 to 0.01), 3 RCTs, 480 babies) (11). • Reduces the proportion of infants in severe pain measured by NIPS (RD −0.23 (−0.31 to −0.15), 3 RCTs, 480 babies) and increases the proportion with no pain (0.35 (0.26 to 0.44), 3 RCTs, 480 babies) during recovery (11). Results reported narratively Skin-to-skin contact compared to control was reported to lower PIPP score at 30 seconds (14) and two minutes (15)(16) after the procedure. Skin-to-skin contact compared to control was also reported to lower NFCS score in preterm babies during heel lance and recovery (17). **Breastfeeding (23)** • Large reduction in NIPS score compared to no intervention (MD -2.53 (-3.46 to -1.60), 5 RCTs, 459 babies; the mean NIPS scores ranged from 3.45 to 6.43 in the control group). • Large reduction in NFCS score compared to no intervention (MD -4.20 (-5.14 to -3.26), 1 RCT, 60 babies; the mean NFCS score was 7.1 in the control group). • Reduction in DAN score compared to no intervention (MD -1.87 (-4.61 to 0.86), 2 RCTs, 250 babies; the mean DAN score was 5.9 in the control group). • Little to no difference in PIPP score compared to no intervention (MD -0.49 (-2.39 to 1.41), 1 RCT, 29 babies). • Large reduction in PIPP score compared to placebo (MD -5.95 (-7.42 to -4.48), 1 RCT, 29 babies; the mean PPIP score was 11.13 in the control group). • Reduction in DAN score compared to placebo (MD -6.24 (-7.38 to -5.10), 1 RCT, 89 babies; the mean DAN score was 8.49 in the control group). **Supplemental breast milk** (breast milk placed on the tongue or in the mouth) (23) • Little to no effect on the NIPS score compared to no intervention (MD -0.30 (-1.60 to 1.00), 1 RCT, 60 babies; the mean NIPS score was 5.1 in the control group). • Reduction in DAN score compared to no intervention (MD -1.00 (-2.15 to 0.15), 1 RCT, 60 babies; the mean DAN score was 6.48 in the control group). • Reduction in NFCS score at two minutes after heel lance compared to one dose of water (MD -0.84 (-1.09 to -0.59), 1 RCT, 45 babies; the mean NFCS score was 5.64 in the control group) and compared to two doses of water (MD -0.59 (-0.83 to -0.35), 1 RCT, 44 babies; the mean NFCS score was 6.23 in the control group). • Little to no effect on body pain score compared to placebo (MD 0.48 (-0.38 to 1.34)).	

	Opioids (10) This review includes babies receiving opioids for pain during procedures such as dialysis, extracorporeal membrane oxygenation treatment, before screening for retinopathy of prematurity, placement of Broviac catheter, air leak drainage, insertion of a central line, heel lance, lumbar puncture, venipuncture, arterial line placement, and any other painful procedures. • Large reduction in PIPP/PIPP-R scores during the painful procedure (MD -2.58 (95% CI -3.12 to -2.03), 3 RCTs, 199 babies; the mean PIPP/PIPP-R during the procedure ranged from 8 to 11 in the control group). • Reduction in NIPS score during the procedure (MD -1.97 (-2.46 to -1.48), 2 RCTs, 102 babies; the mean NIPS during the procedure ranged from 5 to 6 in the control group). • Little to no effect on the DAN score 1-2 hours after the procedure (MD -0.20 (-2.21 to 1.81), 1 RCT, 42 babies). **Other non-pharmacological strategies** (13) Pain reactivity: babies' response or sensitivity to painful stimuli within the first 30 seconds after the painful stimulus Pain regulation: babies' response or sensitivity to painful stimuli after the initial pain response period (i.e., after the first 30 seconds following the painful stimulus) Standard mean difference (SMD): Different measures of pain intensity (coded by either trained nurses or research staff) were converted into a standard scale to help readers interpret the findings. The standard scale ranges from 0 to 21, with 0 being no pain and 21 being very severe pain. **Non-nutritive sucking compared to control** • In preterm babies, moderate reduction in pain reactivity (SMD -0.57 (-1.03 to -0.11), 7 RCTs, 597 babies) and moderate improvement in pain regulation (SMD 0.61 (0.95 to 0.27), 6 RCTs, 379 babies). • In term babies, large reduction in pain reactivity (SMD -1.13 (-1.57 to -0.68), 8 RCTs, 545 babies), and large improvement in pain regulation (SMD -1.49 (-2.20 to -0.78), 9 RCTs, 536 babies). **Facilitated tucking** • In preterm babies, large reduction in pain reactivity (SMD -1.01 (-1.44 to -0.58), 12 RCTs, 733 babies) and moderate improvement in pain regulation (SMD -0.59 (-0.92 to -0.26), 10 RCTs, 557 babies). **Light reduction** (minimising the amount of light the baby is exposed to, either directly (e.g., covering their eyes) or indirectly (e.g., placing a blanket over the babies' incubator).	

	• In preterm babies, light reduction likely reduces pain reactivity (SMD -0.71 (-1.08 to -0.34), 2 RCTs, 125 babies) and improves immediate pain regulation compared to a no-treatment control (SMD -1.16 (-1.53 to -0.78), 2 RCTs, 125 babies). **Other methods of pain management** • In term babies, cold addition (cooling the site of the painful procedure using a non-pharmacological method, such as the application of an ice pack to the procedure site) may reduce pain reactivity compared to a no-treatment control (SMD -0.85 (-1.48 to -0.23), 2 RCTs, 142 babies). • Little to no effect of paracetamol or topical anaesthetics on pain scores. • Little to no effect of heat addition on pain reactivities. • Very uncertain effects of swaddling, swallowing water, rocking or holding, touch/massage, sound reduction, sound addition, smell addition, therapeutic touch (holding hands over the babies without direct contact), co-bedding or music on pain scores or pain reactivities. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	**Sucrose** Of several studies that reported adverse effects, none reported a difference between the sucrose and placebo groups. One study reported that there was no difference in blood glucose concentrations between the sucrose and water groups. The review authors concluded that there is a very low proportion of minor adverse events with sucrose. **Breastfeeding** One study reported that there was no difference in the number of babies with effective sucking between the breastfeeding and control groups. **Supplemental breast milk** One study found no difference in adverse events (oxygen saturation <80%, nausea, regurgitation or vomiting, heart rate <100 beats per minute) between supplemental breast milk and placebo groups. **Opioids**	Sucrose In preclinical studies, repetitive sucrose during the first week of life in mice negatively impacts the development of important brain structures (25) and did not prevent or ameliorate effects of pain (heel prick) exposure on memory in adulthood (26) Moreover, these adverse effects of sucrose in adult mice were seen regardless of whether sucrose was given for pain or not (25)(26).

	Increase in episodes of apnoea compared to placebo (RR 3.15, 95% CI 1.08 to 9.16; 3 RCTs, 199 babies; low-certainty evidence). **Non-nutritive sucking compared to control** For preterm babies, one study reported that one of the 22 participants receiving the non-nutritive sucking intervention vomited. Six studies explicitly mentioned that no adverse events occurred. For term babies, one study reported that one participant in the treatment group and two participants in the control group were desaturated during the study. The remaining eight studies did not report any adverse events. **Facilitated tucking** Of the ten studies, one reported that a participant developed septicaemia after receiving experimental care. The other nine studies did not observe any adverse effects. **Light reduction** No data **Cold addition** No data **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	The limited observational research conducted in very preterm babies suggests sucrose may not ameliorate negative long-term outcomes related to neonatal pain-related stress exposure. Studies have shown that cumulative sucrose exposure may be associated with poorer neurobehaviour at term equivalent age (27) and at 18 months corrected age (CA), perhaps more so for girls (28). Recent work by researchers in Canada demonstrated that cumulative sucrose exposure exacerbated the relationship between neonatal pain-stress (number of painful procedures) and infant cognition and language at 18 months corrected age (CA)(29). To date, no RCT has reported on long-term neurodevelopmental outcomes of repetitive sucrose for acute painful procedures (19).
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low
● Low
○ Moderate
○ High
○ No included studies

Outcomes	Certainty of Evidence
Sucrose	
PIPP scores at 30 seconds after heel lance in preterm and term infants	Moderate
NIPS score for venipuncture in preterm and term infants	Moderate
PIPP scores at 30 seconds after heel lancing in preterm infants	Low
NIPS score after heel lancing in term infants	Moderate
PIPP scores at 30 second after lancing in term infants	Low
DAN scores at 30 seconds after heel lancing in term infants	Very low
NIPS score immediately after heel lance in term infants	Moderate
PIPP score during venipuncture in term infants	High
Adverse event – not estimated	Very low
Skin-to-skin contact	
PIPP during heel prick compared to control	High
NFCS during heel lance and recovery	Moderate
proportion of infants in low or no pain during the procedure	Very low
proportion of infants in severe pain measured by NIPS and proportion in no pain	Moderate
Adverse event – not reported	-
Breastfeeding	
Compared to no intervention: NIPS score	Moderate
Compared to no intervention: NFCS score	Low
Compared to no intervention: DAN score	Low
Compared to no intervention: PIPP score	Low
Compared to placebo: PIPP score	Low
Compared to placebo DAN score	Low
Adverse event – not estimated	Very low
Supplemental breastmilk	
Compared to no intervention: NIPS score	Low
Compared to no intervention: DAN score	Low
Compared to one dose of water: NFCS score at two minutes after heel lance	Low
Compared to two doses of water: NFCS score at two minutes after heel lance	Low
body pain score compared to placebo	Low
Adverse event – not estimated	Very low
Opioids	
PIPP/PIPP-R scores during the painful procedure	Moderate
NIPS score during the procedure	Low
DAN score 1-2 hours after the procedure	Low
Adverse event – not estimated	Very low
Non-nutritive sucking compared to control	
pain reactivity and pain regulation in preterm and term infants	Very low
Adverse events in preterm and term infants	Very low
Facilitated tucking	
Pain reactivity and pain regulation in preterm infants	Very low
Adverse events in preterm infants	Very low
Light reduction	
Pain reactivity and pain regulation in preterm infants	Moderate
Adverse events – not reported	-
Cold addition	
Pain reactivity in term infants	Low
Adverse events – not reported	-

	Considerations for Māori No additional data available **Considerations for Pacific** No additional data available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In the Whānau Experiences study (30) of whānau/families with diverse cultural backgrounds, including Māori, Pacific, and Asian ethnicities (studied because these groups have a higher likelihood of having a baby born at risk of neonatal hypoglycaemia), some parents reported negative views about blood testing, including being distressed by multiple tests, seeing their small child hurt, and not being offered the chance to help. *Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Desirable effects • Sucrose compared to control probably results in a reduction of pain after single heel lances. • Skin-to-skin contact, breastfeeding or supplemental breast milk, opiods, light reduction, or cold addition may reduce pain in babies undergoing painful procedures. • Non-nutritive sucking or facilitated tucking may reduce pain in babies, but the evidence is very uncertain. Undesirable effects • Very uncertain undesirable effects for sucrose, breastfeeding, supplemental breastmilk, non-nutritive sucking, or facilitated tucking. • Opioids may result in an increase in episodes of apnoea. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Sucrose cost NZ$13.91 per 25 ml (Biomed, NZ) Skin-to-skin contact, breastfeeding, supplemental breastmilk, non-nutritive sucking, facilitated tucking, light reduction or cold addition do not have a per unit cost, but time must be spent training health professionals and their supporting the interventions and educating parents. These non-pharmacological methods require minimal financial resources but necessitate dedicated time and effort for training and education.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ○ Low ○ Moderate ○ High ● No included studies	We are reasonably certain of the cost of sucrose, but uncertain about the cost of staff time and training.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No evidence on the cost-effectiveness. As the comparator of standard care or no intervention does not have a cost, cost-effectiveness is likely to favour the comparator. However, since pain has been suggested to have detrimental effects on neurodevelopment in very preterm babies (3), adequately treating pain in the NICU may have beneficial effects on later neurodevelopment, which have not yet been quantified.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social*	It is important that education for parents around pain management strategies occurs consistently, as a Finnish study of 178 NICU parents found that the non-pharmacological strategies used by parents varied in different hospitals (38). The authors suggested this may be due to

	determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions. ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (32). *However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (33). *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (32). *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* ((33). *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (32). ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** Whānau Māori are highly tuned to notice when healthcare professionals appear to be both desensitised to providing care versus caring for their pēpi. Whānau noticed when staff provided comfort and care for painful procedures, which made them feel like the staff cared for their pēpi. In some situations, this was their pēpi first experience of pain. When staff had made a connection with the whānau through whanaungatanga, whānau had an opportunity to establish a relationship, which enabled the opportunity to ask questions, and be fully informed about the painful procedure. *In the Whānau Experience study* (30)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (34)(35)(36)*. Additionally, a systematic literature review by Graham et al.* (37) *provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance,*	differing levels of family-centred care practised between the hospitals. Providing a range of different pain strategies will help ensure sufficient pain management is available to all babies, including those whose parents face barriers to being present for all painful procedures. These barriers may be present for a variety of reasons including continued need to work, living further from the hospital or having other young children.

	perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming" (37). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (30) ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (31)*. Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (31)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A study of smell addition with mother's breastmilk to manage pain during heel pricks found this intervention acceptable for more than 80% of mothers (n=11) and nurses (n=20) (39). In a questionnaire completed by 81 parents in a surgical NICU in Australia, most parents used non-nutritive sucking and strategies involving touch nearly always or always during painful procedures (including touching, holding, positioning, swaddling, and facilitated tucking), suggesting that these strategies are acceptable to parents and clinicians (40). Breastfeeding, breastmilk scent, sucrose, skin-to-skin and music were not as frequently used, with 12%, 22%, 33%, 34% and 40% of parents using these nearly always or always during painful procedures. This study also reported that 80% of parents wanted to be present during painful procedures (40). Researchers who interviewed 12 parents suggested that pain management strategies involving parents decreased parental stress by providing a way for parents to contribute to reducing their babies' pain (41). However, this is not true for all parents, with some preferring to leave the room during painful procedures to avoid seeing their baby in pain (42). Because parental presence is necessary for some pain management strategies like skin-to-skin and	

	breastfeeding, it is important to offer a range of strategies so parents can decide what is best for their whānau. **Considerations for Māori** In the whānau experience study (30), Whānau Māori valued being offered skin to skin and then supported to breastfeed their pēpi during testing. **Considerations for Pacific** In the whānau experience study (30), 50% of Pacific women were offered skin-to-skin contact during hypoglycaemia testing. All the women who were offered this, expressed they believe skin-to-skin contact is very important for the care of their baby. One woman interviewed said that in a case where a mother cannot provide skin-to-skin contact, a father should. **Consideration for Asian** In the whānau experience study (30), few Asian participants remembered being offered the opportunity to provide skin-to-skin contact. A few participants expressed that they would have appreciated being offered the choice.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	By 2007, sucrose was already used in most Aotearoa New Zealand neonatal units, indicating feasibility in the Aotearoa New Zealand context (43). It is recommended for consideration in the Starship guidelines for neonates and babies undergoing painful procedures, alongside ensuring the babies is "calm, relaxed, warm and fed" (44). Sucrose is feasible as it provides pain relief only 1-2 minutes after administration, meaning it can be applied immediately before a painful procedure. Although the Australian study above (40) noted that breastfeeding and skin-to-skin contact were used by some parents during painful procedures, these interventions do pose logistical challenges as the breastfeeding parent or another caregiver needs to be present at the time of the painful procedure (45). Breastfeeding is also not as feasible for some babies who have difficulty sucking (45). The need for different strategies to suit different situations was highlighted in a study of 178 parents in NICUs across Finland (38). They found that the non-pharmacological interventions used by parents were related to the gestational and postnatal age of babies, their length of hospitalisation, condition, and pain intensity. For example, babies with a lower gestational age	

	were more likely to receive comforting touch methods, including kangaroo care, whilst those with a higher gestational age were more likely to receive sucrose or breastfeeding. Lack of information about feasibility in relation to other methods not currently used (i.e. facilitated tucking). **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

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Question 15.

Should a point-of-care testing method be used to diagnose hypoglycaemia in neonates ?	
POPULATION:	Neonates
INTERVENTION:	a point-of-care testing method

PURPOSE OF THE TEST:	Screening for neonatal hypoglycaemia
LINKED TREATMENTS:	Milk feedings (either breastmilk or breastmilk substitute); buccal dextrose gel; glucagon; intravenous glucose
ANTICIPATED OUTCOMES:	Critical outcomes True positive True negative False positive False negative
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendations
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* The difficulty with detecting hypoglycaemic episodes is that they are usually asymptomatic or babies may have non-specific signs, so regular blood testing to measure glucose concentrations is recommended, particularly for at-risk babies. While laboratory methods are the diagnostic standard and have a high degree of accuracy, the requirement to send blood to the lab and wait for the results means that there can be delays in providing timely treatment for low blood glucose concentrations. Point-of-care (also called cot-side) testing methods allow for rapid results and immediate management decisions, but concerns have been raised about their inaccuracies, leading to missed cases where hypoglycaemia remains undetected, or unnecessary treatment of those with normal blood glucose concentrations (1). There are a number of different types of point-of-care devices and they use several different methods for detecting glucose concentrations. We have grouped studies together based on the modality of each device (reaction enzyme used, photometric or electrochemical measurement). These are (the devices currently used in Aotearoa New Zealand are bolded): Enzymatic (glucose oxidase, GO) + photometry: Reflotest, BM-Reflolux, Reflolux II, Accu-chek III, One Touch II, Ames Glucometer, SureStep, **Dextrostix** Enzymatic (glucose dehydrogenase, GDH) + photometry: **HemoCue; Accu-chek Active** Enzymatic (GO) + electrochemistry: **Elite XL** , Precision PCx , ABL 735, EasyGluco, GlucoTest Plus, StatStrip, **iSTAT, Freestyle NeoH** Enzymatic (GDH) + electrochemistry: Advantage Boeh , Accu-chek Advantage, Accu-chek Inform, Precision Xceed, Precision Xceed Pro, Optium Xceed, Contour, Accu-chek Aviva Nano, Accu-chek Performa Enzymatic (hexokinase): Encore QA+, **ABL 800**

	These are metrics commonly used in medical diagnostics and binary classification tasks to evaluate the performance of a model or a test. 1. Sensitivity (True Positive Rate): Sensitivity measures the proportion of actual positive cases that are correctly identified by a diagnostic test or a model. Sensitivity = True Positives / (True Positives + False Negatives) 2. Specificity (True Negative Rate): Specificity measures the proportion of actual negative cases that are correctly identified by a diagnostic test or a model. Specificity = True Negatives / (True Negatives + False Positives) 3. Positive Predictive Value (PPV): PPV measures the probability that subjects with a positive test result truly have the disease. PPV = True Positives / (True Positives + False Positive) 4. Negative Predictive Value (NPV): NPV measures the probability that subjects with a negative test result truly don't have the disease. NPV = True Negatives / (True Negatives + False Negatives) 5. Accuracy: Accuracy measures the overall correctness of the diagnostic test or model across all classes. Accuracy = (True Positives + True Negatives) / (True Positives + True Negatives + False Positives + False Negatives)
CONFLICT OF INTERESTS:	CC, DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Test accuracy How accurate is the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ○ Varies ○ Don't know	Different point-of-care testing methods have different sensitivities and specificities for detecting hypoglycaemia in at-risk babies (2). **Enzymatic (GO) + photometry (Dextrostix)** Low sensitivity:0.72 (95% CI: 0.64 to 0.76)| High specificity:0.95 (95% CI: 0.87 to 0.98) **Enzymatic (GDH) + photometry (HemoCue, Accu-chek Active)** Low sensitivity:0.64 (95% CI: 0.13 to 0.95)| High specificity:0.99 (95% CI: 0.88 to 1.00) **Enzymatic (GO) + electrochemistry (Elite XL, iSTAT, Freestyle NeoH)** Moderate to high sensitivity:0.82 (95% CI: 0.70 to 0.89)| High specificity:0.94 (95% CI: 0.83 to 0.98) **Enzymatic (GDH) + electrochemistry (Optium Xceed, Accu-chek Advantage)**	Threshold (mmol/L) to classify positive or negative results: **Enzymatic (GO) + photometry:** 7 studies used 2.2, 1 study used 2.1, 1 study 2.0 and 1 study used 1.9 **Enzymatic (GDH) + photometry:** 4 studies used 2.5/2.6, 2 studies used 2.2, and 1 study used 2.0 **Enzymatic (GO) + electrochemistry:**

	Moderate to high sensitivity: 0.81 (95% CI: 0.62 to 0.91)| High specificity:0.96 (95% CI: 0.88 to 0.99) **Enzymatic (hexokinase) (ABL 800)** Moderate to high sensitivity: 0.84 (95% CI: 0.73 to 0.91) | High specificity: 0.93 (95% CI: 0.88 to 0.96) **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	8 studies used 2.5/2.6, 4 studies used 2.2/2.1, and 1 study used 2.0 **Enzymatic (GDH) + electrochemistry:** 10 studies used 2.5/2.6, 2 studies used 2.2 **Enzymatic (hexokinase):** 2 studies used 2.6
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We assumed a pre-test probability (prevalence) of 50% in at-risk babies (4). Among 1000 at-risk babies, of whom 500 babies (50%) will develop hypoglycaemia and 500 will not, using the following point-of-care testing methods: **Enzymatic (GO) + photometry (Dextrostix)** 360 (320 to 380) babies with hypoglycaemia will be correctly identified; 475 (435 to 490) babies without hypoglycaemia will be correctly identified. **Enzymatic (GDH) + photometry (HemoCue, Accu-chek Active)** 320 (65 to 475) babies with hypoglycaemia will be correctly identified; 495 (440 to 500) babies without hypoglycaemia will be correctly identified. **Enzymatic (GO) + electrochemistry (Elite XL, iSTAT, Freestyle NeoH)** 410 (350 to 445) babies with hypoglycaemia will be correctly identified; 470 (415 to 490) babies without hypoglycaemia will be correctly identified. **Enzymatic (GDH) + electrochemistry (Optium Xceed, Accu-chek Advantage)** 405 (310 to 455) babies with hypoglycaemia will be correctly identified; 480 (440 to 495) babies without hypoglycaemia will be correctly identified. **Enzymatic (hexokinase) (ABL 800)** 420 (365 to 455) babies with hypoglycaemia will be correctly identified; 465 (440 to 480) babies without hypoglycaemia will be correctly identified. **Considerations for Māori** No additional evidence available	Babies with positive results will usually be treated and undergo further testing. For babies with negative results, testing may cease, alleviating any burden for the baby and whānau/family and reducing the use of resources (3).

	Considerations for Pacific No additional evidence available	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We assumed a pre-test probability (prevalence) of 50% in at-risk babies (4), among 1000 at-risk babies, of whom 500 babies (50%) will develop hypoglycaemia and 500 will not, using the following point-of-care testing methods: **Enzymatic (GO) + photometry (Dextrostix)** 140 (120 to 180) babies with hypoglycaemia will be incorrectly classified as not having hypoglycaemia; 25 (10 to 65) babies without hypoglycaemia will be incorrectly classified as having hypoglycaemia . **Enzymatic (GDH) + photometry (HemoCue, Accu-chek Active)** 320 (65 to 475) babies with hypoglycaemia will be incorrectly classified as not having hypoglycaemia; 5 (0 to 60) babies without hypoglycaemia will be incorrectly classified as having hypoglycaemia. **Enzymatic (GO) + electrochemistry (Elite XL, iSTAT, Freestyle NeoH)** 90 (55 to 145) babies with hypoglycaemia will be incorrectly classified as not having hypoglycaemia; 25 (10 to 85) babies without hypoglycaemia will be incorrectly classified as having hypoglycaemia. **Enzymatic (GDH) + electrochemistry (Optium Xceed, Accu-chek Advantage)** 90 (55 to 150) babies with hypoglycaemia will be incorrectly classified as not having hypoglycaemia; 30 (10 to 85) babies without hypoglycaemia will be incorrectly classified as having hypoglycaemia. **Enzymatic (hexokinase) (ABL 800)** 80 (45 to 135) babies with hypoglycaemia will be incorrectly classified as not having hypoglycaemia; 35 (20 to 60) babies without hypoglycaemia will be incorrectly classified as having hypoglycaemia.	Babies incorrectly classified as having hypoglycaemia will potentially undergo unnecessary treatment and additional testing. This places an unnecessary burden on the whānau/family in terms of both time and anxiety. Moreover, it entails the wasteful expenditure of time and resources. Babies with hypoglycaemia incorrectly classified as not having hypoglycaemia may not be treated promptly, and in severe cases this may result in neurological complications (5). Testing may not be continued so that delayed or prolonged hypoglycaemia may not be detected.

	Considerations for Māori No additional evidence available **Considerations for Pacific** No additional evidence available	
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of test accuracy?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low
○ Low
○ Moderate
○ High
○ No included studies

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence50%		
Enzymatic (GO) + photometry: Pooled sensitivity:0.72 (95% CI: 0.64 to 0.76)| **Pooled specificity**:0.95 (95% CI: 0.87 to 0.98)			
True positives	**360** (320 to 380)	3614 (10)	⊕⊕⊕◯ Moderate[a]
False negatives	**140** (120 to 180)		
True negatives	**475** (435 to 490)	3614 (10)	⊕⊕◯◯ Low[a,b]
False positives	**25** (10 to 65)		
Enzymatic (GDH) + photometry: Pooled sensitivity:0.64 (95% CI: 0.13 to 0.95)| **Pooled specificity**:0.99 (95% CI: 0.88 to 1.00)			
True positives	**320** (65 to 475)	952 (6)	⊕◯◯◯ Very low[b,c]
False negatives	**180** (25 to 435)		
True negatives	**495** (440 to 500)	952 (6)	⊕⊕⊕⊕ High
False positives	**5** (0 to 60)		
Enzymatic (GO) + electrochemistry: Pooled sensitivity:0.82 (95% CI: 0.70 to 0.89)|**Pooled specificity**:0.94 (95% CI: 0.83 to 0.98)			
True positives	**410** (350 to 445)	5791 (14)	⊕⊕⊕◯ Moderate[b]
False negatives	**90** (55 to 150)		
True negatives	**470** (415 to 490)	5791 (14)	⊕⊕⊕◯ Moderate[b]
False positives	**30** (10 to 85)		
Enzymatic (GDH) + electrochemistry: Pooled sensitivity:0.81 (95% CI: 0.62 to 0.91)|**Pooled specificity**:0.96 (95% CI: 0.88 to 0.99)			
True positives	**405** (310 to 455)	3862 (12)	⊕◯◯◯ Very low[a,b,d]
False negatives	**95** (45 to 190)		
True negatives	**480** (440 to 495)	3862 (12)	⊕⊕◯◯ Low[a,b]
False positives	**20** (5 to 60)		
Enzymatic (hexokinase): Pooled sensitivity: 0.84 (95% CI: 0.73 to 0.91) |**Pooled specificity**: 0.93 (95% CI: 0.88 to 0.96)			
True positives	420 (365 to 455)	201 (2)	⊕⊕⊕◯ Moderate[a]
False negatives	80 (45 to 135)		
True negatives	465 (440 to 480)	201 (2)	⊕⊕⊕◯ Moderate[a]
False positives	35 (20 to 60)		

CI: confidence interval. ***Explanations:*** a. Downgraded one level of risk of bias due to overall unclear risk of bias. b. Downgraded one

	Considerations for Māori No additional evidence available **Considerations for Pacific** No additional evidence available	

Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	We did not find any research evaluating the direct impact of tests on outcomes for babies.	The mean number of blood glucose tests was 6.0 in at-risk babies who did not have hypoglycaemia, 7.0 in babies with an initial measurement below the threshold, and 11.1 in babies whose first measurement was above the threshold but who had a subsequent measurement below the threshold (3). Inaccurate measurement was cited as a contributing factor in almost all cases of litigation related to neonatal hypoglycaemia in the UK (6).

Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No direct evidence was found.	In otherwise healthy newborn babies with asymptomatic moderate hypoglycaemia, using a lower glucose treatment threshold (1.9 mmol/L) was found to be as effective as a conventional threshold (2.6mmol/L) in terms of psychomotor development at 18 months (7).

Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No direct evidence was found.	
Certainty of effects What is the overall certainty of the evidence of effects of the test?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	We are reasonably confident about the effects of the test, as these are routine practices throughout Aotearoa New Zealand. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty	Increased accuracy is associated with a decreased number of tests because if testing methods are known to be inaccurate, it is usual to recommend that any positive test (i.e. blood glucose concentration measured below the threshold) is repeated using a more accurate laboratory method (3). In the Whānau Experiences study (8) of whānau/families with diverse cultural backgrounds including Māori, Pacific and Asian ethnicities (studied because these groups have a higher likelihood of having a baby born at risk of neonatal hypoglycaemia), some parents reported	

or variability	negative views about blood testing, including being distressed by multiple testing, seeing their small child hurt, and not being offered the chance to help. *Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention	A guideline panel needs to evaluate whether the benefits of a correct classification (True Positive and True Negative) outweigh the potential harms of an incorrect classification (False Positive and False Negative). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

○ Varies ○ Don't know		
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost usually includes cost of inital device, supplies and staff timing. Cost data were available from a study of babies at risk of hypoglycaemia who had blood glucose concentrations measured 1 hour after birth, then every 3–4 hours before feeds for the first 24 hours, and every 6–8 hours for the subsequent 24 hours. The authors reported that screening using an enzymatic + electrochemical glucometer (i-STAT) cost NZ$86.94, whereas using a photometric glucometer (Accu-CHEK, HemoCue) with positive tests repeated cost NZ$97.08 per baby in 2016/2017 (3).	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	High certainty about the cost of enzymatic + electrochemical glucometer (i-STAT) and a photometric glucometer (Accu-CHEK, HemoCue).	
Cost effectiveness		

Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The cost-effectiveness analyses showed that using an enzymatic + electrochemical glucometer is cost-saving with wide variations in staff time and costs, irrespective of the false-positive level of photometric glucometers, and where ≥78% of low values are laboratory confirmed. Where photometric glucometers may be less costly (e.g., a false-negative rate exceeding 15%), instances of hypoglycaemia will be missed (3).	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?***	

	Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%) (10*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (4*).* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (4*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (8*), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (11, 12, 13). *Additionally, a systematic literature review by Graham et al.* (14*) provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (14*).* ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (8*).* ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (9*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist*	

	services. In the 2014 Maternity Consumer Survey, (9)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	A national survey (15) of directors/managers of neonatal units, midwives, registered nurses, and neonatal/paediatric consultants (n=84) spanned all district health boards (DHBs) in Aotearoa New Zealand except Te Whatu Ora Whanganui. Respondents were asked which device they preferred for neonatal blood glucose testing. The majority of midwives preferred iStat (7/24), Blood gas analsyer (5/24) and Accuchek (4/24). The majority of doctors preferred blood gas analyser (8/16) followed by iSTAT (5/16). Managers of care units preferred iStat (6/19), blood gas analyser (5/19) and Accuchek (5/19). Lead maternity carer (LMC) midwives mainly preferred iSTAT (4/8). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Point-of-care devices are readily accessible throughout Aotearoa New Zealand. A national survey in Aotearoa New Zealand (15), encompassing directors/managers of neonatal units, midwives, registered nurses, and neonatal/paediatric consultants (n=84), spanned all DHBs except Te Whatu Ora Whanganui. Nearly all respondents (69 out of 70) indicated that capillary heel-prick blood sampling was their preferred method for screening neonates for hypoglycaemia. The technique for analysing capillary blood samples were blood gas analyser (19/59), Accu-chek (10/59), i-STAT (9/58), HemoCue (10/59), FreeStyle NeoH (3/59), Dextrostix (1/59), lab analysis (unknown instrument) (4/59)	

	Considerations for Māori No additional evidence available **Considerations for Pacific** No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	Low	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	Low	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			No included studies
CERTAINTY OF EFFECTS	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know

RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

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Question 16.

Should higher or lower blood glucose concentrations vs. blood glucose concentration of 2.6 mmol/L be used for defining of neonatal hypoglycaemia?	
POPULATION:	Newborn babies
INTERVENTION:	higher or lower blood glucose concentrations
COMPARISON:	blood glucose concentration of 2.6 mmol/L
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia

	5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* However, the definition of neonatal hypoglycaemia remains controversial and has changed over time (1). Recommended thresholds for defining hypoglycaemia in published guidance vary between 2.0 and 4.0 mmol/L. The most common threshold in primary studies was 2.6 mmol/L (2).
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are all authors of cited papers.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Lower threshold** Would result in fewer babies being identified as having hypoglycaemia and therefore being treated and having further testing. This would potentially: • reduce testing • avoid overtreatment, including NICU admission [critical] • increase breastfeeding [critical] In a single randomised controlled trial (RCT) conducted in the Netherlands (3), 689 at-risk babies ≥35 weeks' gestation with asymptomatic moderate hypoglycaemia (blood glucose 1.9 to <2.6 mmol/L) at 3–24 hours of age were randomised to treatment to maintain glucose concentrations of ≥2.0 mmol/L (intervention group) or ≥2.6 mmol/L. They found little to no difference in: • Neurodevelopmental impairment at ≥18 months of age [critical] • Bayley cognitive or motor scores at ≥18 months of age	**Reasons for threshold of 2.6mmol/L:** There are at least three methods for determining an appropriate threshold for identifying neonatal hypoglycaemia. One is the statistical approach, which defines hypoglycaemia as a blood or plasma glucose level that is more than two standard deviations below the mean in healthy low-risk babies, i.e., below the 95th centile. In the GLOW study, a prospective observational study of healthy-term appropriate-for-gestational age babies, the mean glucose concentrations rose throughout the first 18 hours, remained stable to 48 hours (3.3 ± 0.6 mmol/L), and then rose to a new plateau after 72 hours (4.6 ± 0.7

- Duration of initial hospital stay [important]
- Cost [important]

There were no data for admission to special care nursery or neonatal intensive care nursery, fully breastfeeding at hospital discharge, separation from the mother for treatment of hypoglycaemia before discharge home, hypoglycaemic injury on brain imaging, time to blood glucose normalisation after intervention, receipt of treatment for hypoglycaemia during initial hospital stay, number of episodes of hypoglycaemia, breastmilk feeding exclusively from birth to hospital discharge, or duration of treatment.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 2.6 mmol/L blood glucose concentrations	Risk difference with lower blood glucose concentrations
Neurodevelopment impairment at ≥18 months	582 (1 RCT)	⨁⨁◯◯ Low[a,b]	-	No differences between groups of the neurodevelopment impairment at ≥18 months measured by either Bayley cognitive scores or motors < -2 standard deviation.	
Admission to special care nursery or neonatal intensive care nursery - not measured	-	-	-	-	-
Fully breastfeeding at hospital discharge - not measured	-	-	-	-	-
Separation from the mother for treatment of hypoglycaemia before discharge home - not measured	-	-	-	-	-

mmol/L). In this study, a blood glucose concentration <2.6 mmol/L was approximately the 10th percentile from 2 hours to 48 hours of age (8).

The second approach to defining neonatal hypoglycaemia is to consider the glucose concentration at which there is evidence of triggering counter-regulatory mechanisms or the neurophysiological definition.

Koh 1988 measured evoked potentials (electrical potentials produced after stimulation of specific neural tracts) during hypoglycaemia in 17 babies (only 5 were neonates) and found that abnormal sensory evoked potentials occurred only in those with blood glucose concentrations <2.6 mmol/L, although this did not occur in all babies. Importantly, recovery of evoked potentials took up to 24 hours in the neonates (9).

Pryds 1990 found that when blood glucose concentrations were <1.7 to 2.5 mmol/L in babies <34 weeks of gestational age (n = 25, mean gestational age 30.4 weeks), cerebral blood flow and plasma epinephrine concentrations increased (10).

A third approach to defining neonatal hypoglycaemia is to determine the glucose concentration below which there is evidence of brain injury.

Lucas 1988 studied 661 preterm babies <1850g birthweight and examined the relationship between developmental scores at 18 months and the number of days on which blood glucose was measured below concentrations varying from 0.4 to 4 mmol/L. They reported that the strongest association was seen using a cut-off of <2.5 mmol/L, i.e., babies who had blood glucose

Hypoglycaemic injury on brain imaging - not measured	-	-	-	-	-
Breastmilk feeding exclusively from birth to hospital discharge - not measured	-	-	-	-	-
Duration of initial hospital stay	686 (1 RCT)	⊕⊕◯◯ Low[a,b]	-	The mean duration of initial hospital stay was **4.7** days	MD **0.1 days lower** (0.6 lower to 0.4 higher)
Cost	686 (1 RCT)	⊕⊕◯◯ Low[a,b]	-	No differences between groups on the cost of hospital stay for the babies and the costs after the neonatal period.	

a.Downgraded one level for serious risk of bias due to lack of blinding.
b.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
*Absolute effects were calculated based on the control group risk

A retrospective cohort study conducted in Ottawa, Canada including 10,965 babies consistently observed decreases in the initial rate of exclusive breastfeeding with hypoglycaemia screening (4).
Using data from the Sugar Babies study (5), which focused on babies at risk of hypoglycaemia, it was estimated that reducing the blood glucose concentration threshold to 1.94 mmol/L would decrease the incidence of hypoglycaemia from 52% to 13% and the cost of screening using a non-enzymatic glucometer from NZ $97.08 to NZ $47.71 (6).

Higher threshold
Would result in more babies being identified as having hypoglycaemia and therefore being treated and having further testing. This would potentially lead to:

concentrations <2.5 mmol/L on more days had lower developmental scores. Abnormalities in arithmetic and motor scores persisted at 8 years (11).
An Aotearoa New Zealand prospective cohort study (CHYLD) of children at risk of hypoglycaemia found that children who had experienced blood glucose concentrations <2.6 mmol/L (n = 477, 38% Māori, 4% Pacific) had poorer scores on executive function and visual-motor function at 4.5 years (12), but not 2 years, with worse scores if the hypoglycaemia was recurrent or severe (<2.0 mmol/L) (13). There were no differences in school achievement between those who did and did not have glucose concentrations <2.6 mmol/L at 9–10 years (n = 480, 31% Māori, 2% Pacific) (14), but there were small differences in specific aspects of executive function, behaviour and brain imaging (15)(16).
All babies were screened and treated with the intention of maintaining blood glucose concentrations >2.6 mmol/L.
Lower Threshold
In the RCT of lower versus higher thresholds (3), babies randomised to the lower threshold group experienced a large decrease in receipt of IV dextrose: 21/348 (6%) vs. 70/341 (21%), mean difference -14.5% (-19.5 to -9.5) (146 fewer per 1,000), and a large decrease in supplemental oral feeding, although the rate of supplemental feeding was high in both groups: 275/348 (79%) vs. 332/341 (97%), mean difference -18.3% (-23.1 to -13.8) (185 per 1000). The number of babies who needed to be treated to prevent one instance of intravenous glucose administration was 7, to prevent one instance of tube feeding

	• fewer recurrent and severe episodes of hypoglycaemia • better long-term neurological outcomes for some babies [critical] **Consideration for Māori** Using a threshold of 2.6 mmol/L for neonatal hypoglycaemia, the Sugar Babies study (7) reported that the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%). **Consideration for Pacific** Using a threshold of 2.6 mmol/L for neonatal hypoglycaemia, the Sugar Babies study (7) reported that the proportion of babies who developed hypoglycaemia was similar in Pacific babies (6/16, 38%) to that in the whole cohort (260/514, 51%).	was 12, and to prevent one instance of supplemental oral feeding was 5. The duration of breastfeeding was similar in both groups. Babies randomised to the lower threshold group also had a small decrease in the number of glucose measurements, mean 6.4 (SE 0.1), n = 345 vs. 7.0 (0.2), n = 337, mean difference -0.7 (-1.0 to -0.3). These numbers are similar to those found in a single study conducted in Aotearoa New Zealand (n = 481, 31% Māori), where the mean number of blood glucose tests was 6.0 in at-risk babies who did not have hypoglycaemia, 7.0 in babies with an initial measurement below the threshold, and 11.1 in babies whose first measurement was above the threshold but who had a subsequent measurement below the threshold (6). **Higher Threshold** No additional studies
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Lower Threshold** May result in: • Some at-risk babies not being identified • Delayed diagnosis and treatment • More recurrent or severe episodes of hypoglycaemia • Increased risk of neurological complications [critical] In the RCT (3) there were two serious adverse effects [critical]; one convulsions and one death, both in the lower threshold group and considered not likely related to treatment. Severity of hypoglycaemia [less important]—more in lower threshold group Lower threshold results in:	**Lower Threshold** In the RCT (3) the low threshold group had a large increase in episodes of hypoglycaemia (<2.6 mmol/L) (57% vs. 47%, mean difference 10%, 95% CI 2-17) (225 more per 1,000) . **Higher Threshold** No additional studies

- Large increase in moderate hypoglycaemia (104 more per 1,000) [critical]
- Moderate increase in severe hypoglycaemia (46 more per 1,000) [critical]
- Uncertain effect on serious adverse effects [critical]; both in the lower threshold group (1 convulsions and 1 death) and considered not likely related to treatment.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with blood glucose concentration of 2.6 mmol/L	Risk difference with lower blood glucose concentrations
Adverse effects-serious	689 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 4.93** (0.24 to 103.02)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Adverse effects - severe hypoglycaemia (< 2.0 mmol/L)	689 (1 RCT)	⨁⨁⨁◯ Moderate[a]	**RR 1.88** (1.04 to 3.41)	Study population	
				53 per 1,000	**46 more per 1,000** (2 more to 127 more)
Adverse effect-moderate hypoglycaemia (2.0-2.6mmol/L)	689 (1 RCT)	⨁⨁◯◯ Low[a,c]	**RR 1.25** (0.92 to 1.69)	Study population	
				416 per 1,000	**104 more per 1,000** (33 fewer to 287 more)

a.Downgraded one level for serious risk of bias due to lack of blinding.
b.Downgraded two levels for serious imprecision due to wide confidence intervals and zero events in the control group.
c.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
*Absolute effects were calculated based on the control group risk

Higher Threshold

	Would result in more babies being identified as having hypoglycaemia and therefore being treated and having further testing. This would potentially lead to: • increased testing • increased treatment • more NICU admission, formula use • decrease in the initial rate of exclusive breastfeeding **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence is mostly based on observational studies and expert opinions. While there was one high-quality randomised trial examining different treatment thresholds (3), the developmental outcomes in this study were assessed at 18 months of age. However, cognitive and social functioning problems that have been associated with neonatal hypoglycaemia typically emerge in later developmental stages than this age. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]*	In the Whānau Experiences study (17) of whānau/families with diverse cultural backgrounds including Māori, Pacific and Asian

or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	• *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	ethnicities (studied because these groups have a higher likelihood of having a baby born at risk of neonatal hypoglycaemia), some parents reported negative views about blood testing, including being distressed by multiple testing, seeing their small child hurt, and not being offered the chance to help. **Consideration for Māori** Whānau Māori want the very best health outcomes for their pēpi. Whānau felt empowered and disempowered by the healthcare team, and the health system, when health provision happened to them, rather than with them (e.g., testing). Whānau shared experiences of healthcare delivery that occurred without explanation, resulting in disempowerment, and others asked questions to enable enactment of mana motuhake, especially around tikanga. **Consideration for Pacific** Some Pacific mothers also felt very distressed when their baby had to be tested multiple times.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Lower threshold** compared to 2.6 mmol/L: Very low certainty evidence showed: • Little to no effect on neurodevelopmental impairment at ≥18 months of age [critical], duration of initial hospital stay [important], cost [important]. • Large increase in moderate hypoglycaemia • Moderate increase in severe hypoglycaemia • Uncertain effect on serious adverse effects [critical] **Higher threshold** compared to 2.6 mmol/L: No additional studies. **Considerations for Māori** Limited evidence suggests that the effects are similar for Māori babies. **Considerations or Pacific** No specific evidence about the effects on Pacific babies, but the baseline risk is likely to be similar to other babies studied.	**Lower threshold** compared to 2.6 mmol/L: May result in • a large decrease in receipt of IV dextrose • a large decrease in supplemental oral feeding, although the rate of supplemental feeding was high in both groups • small decrease in the number of glucose measurements Operational thresholds should be set at a level that is intended to achieve the best balance of benefits for the least harm for all babies, even if only a proportion of them would be at risk below this level, since it is currently not possible to identify individual risk. In addition, operational thresholds need to include a "margin of safety", to allow for intervention to prevent glucose concentrations falling to a potentially brain-threatening level. The need for this margin of safety was demonstrated in data from the CHYLD study (13). Despite all babies being screened and treated to maintain blood glucose concentrations ≥2.6 mmol/L, 24% had glucose concentrations below this level that were not detected by routine blood glucose measurements, and 25% of those treated for hypoglycaemia had glucose concentrations <2.6 mmol/L for >5 hours in the first 48 hours.
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	Cost: Screening using an enzymatic glucometer cost NZ$86.94 (US $63.47) (6). Costs of treatment for a baby with hypoglycaemia estimated at NZ $7-8,000 Time: Staff time for testing with an enzymatic glucometer is around 6 to 8 minutes. Additional time is needed for informing the family, preparing the meter, and documenting the results. **Lower Threshold:** In the randomised trial, reducing the intervention threshold to 2.0 mmol/L meant the number of newborns that needed to be treated to prevent one instance of intravenous glucose administration was 7, and the number needing to be treated to prevent one instance of tube feeding was 12 (3). Reducing the blood glucose concentration threshold to 1.94 mmol/L was estimated to decrease the incidence of hypoglycaemia from 52% to 13%. Additionally, the cost of screening decreased from NZ $87-97 to NZ $48-87 per baby (6). These are likely to result in substantial cost savings.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not do a systematic search for evidence about resource requirements.	
Cost effectiveness		

Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	We did not do a systematic search for evidence about cost-effectiveness.	
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	A consistent definition of neonatal hypoglycaemia can improve equity by ensuring fair and equal access to diagnosis, treatment, and care for all babies. This consistency helps to minimise potential biases or disparities that may arise from different interpretations or thresholds used by different healthcare professionals or institutions. ***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism,*	

	income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions. ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (19*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (7*).* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (19*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (7*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (19*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (17*), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (20, 21, 22). *Additionally, a systematic literature review by Graham et al.* (23*) provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (23). ***Consideration for Pacific***	

	Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work (17). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (18*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (18*), 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We found no evidence about acceptability to whānau/families. A survey conducted within Australia and Aotearoa New Zealand Neonatal Network in 2014 showed that doctors were consistent about the definition of neonatal hypoglycaemia and would treat babies with a blood glucose level <2.6 mmol/L (24). A more recent review of guidelines for the management of neonatal hypoglycaemia in 9 Aotearoa New Zealand and 9 Australian hospitals from 2015–19 reported that 11 of the 12 Aotearoa New Zealand guidelines used a definition of <2.6 mmol/L, as did 4 of the 7 Australian guidelines. The other 4 guidelines used <2.0 mmol/L (2 guidelines), <2.1 mmol/L (1 guideline), and <2.2 mmol/L (1 guideline) (25). Thus, a threshold of 2.6 mmol/L or lower is likely to be acceptable to practitioners. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Since 11 out of the 12 Aotearoa New Zealand guidelines employed a definition of <2.6 mmol/L, it is feasible to use this definition (25). Considerations for Māori No additional evidence available Considerations for Pacific No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**

COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

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Question 17.

Should clinical observations vs. other/no clinical observations be used for monitoring babies with neonatal hypoglycaemia?	
POPULATION:	Babies with neonatal hypoglycaemia
INTERVENTION:	clinical observations
COMPARISON:	other/no clinical observations
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **Less important for decision making:**

	1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in babies over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* There are no evidence-based recommendations regarding whether clinical observations should be used for monitoring babies with neonatal hypoglycaemia.
CONFLICT OF INTERESTS:	JA, DH, JH, JR and LL are authors of a cited paper.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Symptomatic neonatal hypoglycaemia was associated with poorer neurodevelopmental outcomes compared to asymptomatic hypoglycaemia in a study of 110 hypoglycaemic neonates (1). At follow up when infants were at least 6 months of age, symptomatic infants were more likely to have cerebral palsy or cerebral palsy and epilepsy, compared to asymptomatic infants (21/42, 50% and 29/68, 42.5% respectively, p <0.05). Similarly, a study of 70 hypoglycaemic neonates found increased rates of neurological problems in those with symptomatic hypoglycaemia compared to those who were asymptomatic (2) followed up for a mean of 8.3 months.	According to Rozance and Hay, the signs and symptoms of neonatal hypoglycaemia are abnormal cry, poor feeding, hypothermia, diaphoresis, tremors and jitteriness, hypotonia, irritability, lethargy, seizures, cyanosis, pallor, tachypnoea, apnoea and cardiac arrest (5). However, these are non-specific and not present in all babies with hypoglycaemia, even when hypoglycaemia is severe (6).

	Seizures during symptomatic neonatal hypoglycaemia have been associated with poorer clinical outcomes at 5-7 years, although in this study only 8 hypoglycaemic infants had seizures (3). Another study found convulsions during neonatal hypoglycaemia were associated with poorer neurodevelopmental outcomes at 1-4 years, but the 8 babies who had convulsions were also diagnosed and treated later which may also contribute to poor neurodevelopmental outcomes (4). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	A study of 220 babies (32 hypoglycaemic) examined all the above signs and symptoms except for diaphoresis, lethargy, cyanosis, and cardiac arrest (7). They found that only jitteriness and tachypnoea were predictive of low blood glucose levels within 2 hours of birth. A study of 190 babies in rural India found that, of those with neonatal hypoglycaemia, only 5% of had seizures, 35% were jittery, 30% had poor activity, 10% poor sucking and 15% poor crying (8). Another Indian study of 100 hypoglycaemic babies found that jitteriness, lethargy and cyanosis were the most common clinical signs (38%, 35%, 23% respectively) (9). Fewer than 10% of hypoglycaemic babies demonstrated hypotonia, apnoea, seizures or tachypnoea (9). In Aotearoa New Zealand, of 514 babies at risk of neonatal hypoglycaemia (150 Māori, 16 Pacific), 79% of those who developed hypoglycaemia had no clinical signs, 15% were too sleepy to feed and 7% were jittery (10). Of all hypoglycaemic episodes in this group, 81% occurred within the first 24 hours, with episodes continuing to at least 48 hours. This suggests that the first 48 hours may be an important window for monitoring babies for hypoglycaemia.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	The studies identified did not report on undesirable effects of monitoring infants for symptoms or seizures. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence is very low as it comes from observational studies with small sample sizes. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]*	

	• *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	Clinical observations to identify signs of hypoglycaemia may aid in detection and treatment, including in babies who are not considered at risk, and this may improve neurodevelopmental outcomes. There is no information about undesirable effects. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	Clinical observations require staff time, depending on the specific observations and their frequency.	

Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not do a systematic search for evidence about resource requirements.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	Clinical observation of babies with neonatal hypoglycaemia will increase costs. However, recognising which babies have hypoglycaemia, and particularly severe hypoglycaemia, may allow treatment and improve neurodevelopmental outcomes and result in substantial cost savings. We found no evidence assessing this.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?***	

○ Probably increased ○ Increased ○ Varies ○ Don't know	*There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (13)*. However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (10)*.* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (13)*.* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (10)*.* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (13)*.* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (11)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions. Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (14)(15)(16)*. Additionally, a systematic literature review by Graham et al.* (17) *provides a summary of 20 years of data from Whānau Māori experiences in the*	

	public health and/or hospital system. A key barrier included perception of racism or discrimination amongst Whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming" (17). Whānau Māori requested that they be fully informed of what to expect following hypoglycaemia testing, and what follow-up they should receive, when they should receive follow up, and what both the short-term, medium-term, and long-term best practice monitoring plan is. Whānau Māori thought about the future, and any involvement in providing feedback was seen in a service mindset. ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (11). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (12). *Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (12*), 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	A systematic search was not carried out for evidence investigating acceptability of clinical observations for babies with hypoglycaemia. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Regular clinical observation of newborn babies is recommended standard practice and therefore likely to be feasible in all newborn care settings, although increased frequency may require additional staffing resources. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	In Aotearoa New Zealand, the Newborn Observation Chart is used in many facilities to assess babies >35 weeks of gestational age in the first two hours and at 24 hours (18). It involves observing respiratory rate, work of breathing, temperature, heart rate, colour, behaviour and feeding. Monitoring for babies at risk of hypoglycaemia will involve making the same observations, but specifically looking for abnormal cries, tremors, jitteriness, hypotonia, irritability, lethargy and seizures when assessing behaviour. However, monitoring for hypoglycaemia would need to be done regularly over the first 24-48 hours, which would require increased staffing resources and is impossible in the home birth setting.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			

BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

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Question 18.

Should continuous glucose monitoring vs. intermittent blood glucose testing be used for babies at risk of or diagnosed with neonatal hypoglycaemia?	
POPULATION:	Babies at risk of or diagnosed with neonatal hypoglycaemia
INTERVENTION:	continuous glucose monitoring
COMPARISON:	intermittent blood glucose testing
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment at ≥18 months of age (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies)

	2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	All birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn infants over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Diagnosis and monitoring or treatment of neonatal hypoglycaemia routinely involve intermittent measurement of blood or plasma glucose concentrations. However, this is invasive, and the likelihood of detecting changes in glucose concentrations depends on the frequency of measurement, so rapid changes may be missed with infrequent testing. For adults and children, particularly those with diabetes, there are a range of continuous interstitial glucose monitoring devices available. These comprise of a filament sensor placed under the skin, which generates a small electric current by oxidation of glucose in the interstitial fluid when a voltage is applied. The current is recorded by a transmitter device on the skin and converted to a glucose concentration using the algorithm built into each device. The glucose concentration is then displayed in real time on a nearby monitor. Measurements are usually averaged every 5 minutes to give 12 “continuous” readings each hour, or 288 each day. The devices can be set to trigger an alarm when the measured glucose concentration is outside the target range set. The sensors can remain in place for 5–14 days, depending on the device, but most need calibration with blood glucose measurements every 12 hours. No commercially available devices have regulatory approval for children younger than two years.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are all authors of cited papers.

ASSESSMENT

Desirable Effects

How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	We found no studies of the use of continuous glucose monitoring (CGM) in babies already diagnosed with hypoglycaemia. Continuous glucose monitoring compared to intermittent blood glucose testing in very preterm or very low birthweight (VLBW) babies results in (1) • Little to no effect on hypoglycaemia episodes [critical] and duration of initial hospital stay [important] • No studies reported on the other critical or important outcomes.	In one of the RCTs contributing to this review (2), there were fewer hypoglycaemic events in the CGM group (1.4 ±2 vs 4.7 ± 6.2 events per subject, P = .01, MD −3.30, 95% CI −5.85 to −0.75; 1 study, 50 participants). In the other RCT in this review (3) there were fewer events in the control group (MD 0.80, 95% CI 0.62 to 0.98; 1 study, 48 participants). In an RCT (2) of 50 preterm babies (<= 32 weeks or <1500g), babies randomised to CGM compared to those randomised to blinded CGM (not available to clinicians) spent more time in the euglycaemic range (4–8 mmol/L) (median 84% vs 68%, *P* <.001) and less time in the "severe" (<2.6 mmol/L) hypoglycaemia range (0.6% (95% CI, 0.3 to 1.4) vs 2.2% (95% CI, 1.4 to 3.3), P = .007) and with severe hyperglycaemia (>10 mmol/L, 0.0% (IQR 0.0 to 0.3) vs 0.3% (IQR 0.0 to 1.6), P =.14). The CGM group also had decreased glycaemic variability (SD: 1.2 ± 0.3 vs 1.5 ± 0.4 mmol/L, *P* =.01; coefficient of variation: 22.8% ± 4.2% vs 27.9% ± 5.0%; *P* <.001). In an RCT (3) of 43 very low birth weight preterm babies (<=1500g), the number

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with intermittent blood glucose testing	Risk difference with continuous glucose monitoring
Hypoglycaemia episode [critical]	200 (2 RCTs)	⊕⊕◯◯ Low[a,b]	**RR 1.02** (0.49 to 2.12)	Study population	
				124 per 1,000	**2 more per 1,000** (63 fewer to 139 more)
Neurodevelopmental impairment [critical] - not measured	-	-	-	-	-
Admission to special care nursery or neonatal intensive care nursery [critical] - not measured	-	-	-	-	-
Fully breastfeeding at hospital discharge [critical] - not measured	-	-	-	-	-
Separation from the mother for treatment of	-	-	-	-	-

hypoglycaemia before discharge home [important] - not measured						
Hypoglycaemic injury on brain imaging [important] - not measured	-	-	-	-	-	
Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	-	-	-	-	-	
Duration of initial hospital stay	50 (1 RCT)	⨁◯◯◯ Very low[a,c]	-	The median duration was 46 days (interquartile range 40 to 74) in the CGM group and 51 days (37 to 63) in the control group (P = 0.59).		
Cost - not measured	-	-	-	-	-	

a.Downgraded one level for serious risk of bias due to moderate to low quality of the included studies (study).
b.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
c.Downgraded two levels for very serious imprecision due to small sample size.

Considerations for Māori
No additional evidence available
Considerations for Pacific
No additional evidence available

of blood samples per baby was lower in the CGM group (16.9 ± 1.0 vs 21.9 ± 1.0, P <0.001).

One study reported on pain scores during CGM device insertion and blood sampling for glucose monitoring (4). Median Premature Infant Pain Profile (PIPP) was 5 (interquartile range 4 to 6) in the CGM group and 8 (7 to 9) in the heel prick control group (P <0.001).

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Studies of CGM use in babies reported no adverse effects over seven days in 188 VLBW babies (5) and in 102 babies ≥ 32 weeks at risk of hypoglycaemia (6). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	One study reported detachment of the device more than once in 2/50 VLBW babies (2). One study reported failure of the device in 4/48 babies due to technical problems with insertion (3). No study reported skin problems with CGM. Characteristics of current CGM devices include a relatively long initial stabilisation period (usually 1-2 hours) before a reading is available, and a lag between any change in glucose concentration and a change in the reading (likely to be up to 30 minutes). They are also susceptible to drift between calibrations, and will usually report a low glucose concentration as <2.2 mmol/L without giving the actual value (7). This combination of drift, physiological lag and the inherent noise of the sensor results in poor point accuracy, with 95% limits of agreement of at least ± 1 mmol/L (6, 8). CGM also detects many episodes of low glucose concentrations that are not detected clinically using intermittent blood sampling. In one study of 102 babies (ethnicity not reported) ≥32 weeks at risk of hypoglycaemia , low glucose concentrations (<2.6mmol/L) were detected in 32 babies with blood sampling and 45 babies with CGM (6). Of 265 episodes of low glucose concentrations on CGM, 215 (81%) were not detected with blood glucose

		concentrations (6). In normal term babies not considered at risk of hypoglycaemia, CGM detected low glucose concentrations in 30/41 (73%) compared to 26/67 (39%) using blood glucose concentrations (9).

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		The certainty of the evidence was very low due to the overall limited number of studies, with few babies enrolled (2).

Outcomes	Importance	Certainty of the evidence (GRADE)
Hypoglycaemia episode [critical]	CRITICAL	⊕⊕◯◯ Low[a,b]
Neurodevelopmental impairment [critical] - not measured	CRITICAL	-
Admission to special care nursery or neonatal intensive care nursery [critical] - not measured	CRITICAL	-
Adverse effects [critical]	CRITICAL	⊕◯◯◯ Very low[c]
Fully breastfeeding at hospital discharge [critical] - not measured	CRITICAL	-
Separation from the mother for treatment of hypoglycaemia before discharge home [important] - not measured	IMPORTANT	-
Hypoglycaemic injury on brain imaging [important] - not measured	IMPORTANT	-

Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	IMPORTANT	-
Duration of initial hospital stay	IMPORTANT	⊕◯◯◯ Very low[a,d]
Cost - not measured	IMPORTANT	-

a.Downgraded one level for serious risk of bias due to moderate to low quality of the included studies (study).
b.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
c.Downgraded two levels for very serious imprecision due to small sample size and zero event.
d.Downgraded two levels for very serious imprecision due to small sample size.

Considerations for Māori
No additional evidence available
Considerations for Pacific
No additional evidence available

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]*	

	• *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Continuous glucose monitoring compared to intermittent blood glucose testing Very low certainty evidence showed • Little to no effect on hypoglycaemic episode [critical] • Uncertain effect on adverse effect [critical] • Uncertain effect on duration of initial hospital stay [important] **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Use of CGM may reduce the number of hypoglycaemic events in VLBW babies, reduce the number of heel-prick blood tests, and reduce pain, but the evidence is very uncertain. Further, point glucose measurements on CGM are very inaccurate, potentially leading to over- and under-detection and therefore potential mistreatment of hypoglycaemia. CGM also detects many episodes of low interstitial glucose concentrations that are not detected using intermittent blood sampling, including in well term babies not considered at risk of neonatal hypoglycaemia, and it is uncertain what these episodes mean and whether they should be treated.
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The costs of the devices vary widely but are likely to be several thousand NZD. The cost of the sensor and transmitter, whether supplied separately or as a single unit, is $1–200 per patient (for up to 7-10 days). Sensor insertion takes a few minutes. Connection of the device and regular calibration also take a few minutes. Training is required to place and connect the sensors, and to troubleshoot the resulting signal on the monitor.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The cost estimates are from recent use in research settings in Aotearoa New Zealand, but specific quotes have not been obtained. The costs of staff training and time have not been estimated. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention	Given that most CGM devices necessitate intermittent blood tests for calibration, it is improbable that the intervention would be cost-effective over the relatively brief monitoring period typically needed for most babies with hypoglycaemia. However, for babies experiencing prolonged or severe hypoglycaemia, or those requiring extended monitoring such as low birth weight babies, CGM may approach cost-effectiveness.	

○ Varies ○ No included studies		
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (11*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (12*).*	

	Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%) (11*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (12*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (11*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study (*(13*), participants expressed appreciation for the inclusion of prayer or tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (14, 15, 16*).* *Additionally, a systematic literature review by Graham et al.* (17*) provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (17*).* ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work (*(13*).* ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (10*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (10*), 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Harris et al reported that parents of 102 babies at risk of hypoglycaemia at ≥32 weeks tolerated CGM well and that nursing staff found the CGM easy to use (6). In another study of 67 (9 (14%) Māori) well term babies, no parents reported that they disliked the CGM device (18). Both studies were undertaken in Aotearoa New Zealand but Māori data were not reported separately. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The devices are widely used in older children and adults so are potentially available in secondary and tertiary care settings, as is the expertise needed to use them. However, they have rarely been used outside a research setting for babies in Aotearoa New Zealand. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies

VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

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Question 19.

Should measurement of other metabolites in addition to glucose vs. measurement of glucose alone be used for diagnosing and monitoring of neonatal hypoglycaemia?	
POPULATION:	Babies at risk of or diagnosed with neonatal hypoglycaemia
INTERVENTION:	measurement of other metabolites in addition to glucose
COMPARISON:	measurement of glucose alone
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies)

	Important but not critical: 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any settings where newborn babies are tested
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment are recommended to reduce the risk of later developmental problems.* Glucose is the primary fuel for the brain. Alternative brain fuels include lactate, ketones (beta-hydroxybutyrate, acetoacetate), and some amino acids, with lactate and ketones being the most substantive. Lactate is continually produced by many tissues including the brain, but increased production and therefore blood concentrations occurs particularly when oxygen supply is limited. Ketones are produced in the liver by breakdown of fatty acids in response to insufficient glucose supply, usually caused by fasting. The brain availability and utilisation of both ketones (1) and lactate (2) is related to the blood concentrations. The newborn brain is able to extract and utilise ketones for brain fuel at a rate 4 to 5-fold greater than that of an adult (1). The availability of these alternative fuels to sustain brain metabolism has long been proposed as an important mechanism to prevent injury when glucose availability is reduced (3)(4)(5). Thus, it has been proposed that measuring these fuels in addition to glucose might help identify which babies are at risk of brain injury, and which might not be and thus not need treatment to increase glucose concentrations. In older babies and children, measuring alternative fuels as well as glucose can also help to identify the likely cause of the hypoglycaemia, but it is not clear if these tests are helpful in newborn babies, and if so, when they should be done.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	We found no evidence for any of the critical or important outcomes. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	Although most neonatal hypoglycaemia occurs in the first few days after birth due to delayed transition from continuous glucose supply from the mother to intermittent feeding, a small proportion can be due to serious and potentially life-threatening conditions such as genetic causes, congenital anomalies and excessive insulin production (hyperinsulinaemia). These babies may be at particularly high risk of hypoglycaemic brain injury (8) and early diagnosis and treatment may therefore be particularly important in these babies. Measurement of lactate and beta-hydroxybutyrate, along with glucose and insulin, may help detect these rarer causes of hypoglycaemia. Blood lactate concentrations are variable in well term newborns and fall quickly after the first day (9)(10). There is minimal synthesis of ketones (ketogenesis) in the first 6 to 12 hours after birth, even in healthy babies (11)(12). Ketone concentrations are low on the first day, and rise slowly over the next 2-4 days (13). The GLOW study showed in 67 healthy breastfed newborns in Aotearoa New Zealand (2 (3%) Māori) glucose provided 72-84% of estimated potential brain fuels in the first 5 days, with lactate providing a maximum of 25% on day 1 and beta-hydroxybutyrate up to 7% on days 2-3. However, when blood glucose concentrations were low (below the median of 3.7 mmol/L, over the first 5 days) an increase in beta-hydroxybutyrate concentrations was slow and only seen

		after the first postnatal day. The blood lactate concentration did not increase when the blood glucose concentrations were low (11). Babies with hypoglycaemia (< 2.6 mmol/L) in the first 2-3 days have very low blood ketone concentrations during hypoglycaemic episodes (9) (13)(14). Data from the GLOW study suggests that there are two phases of low glucose concentrations in healthy newborns: an initial phase in which ketone concentrations are low; and a second phase in which low glucose concentrations are accompanied by elevated ketone concentrations (11)(6). Preliminary findings suggest that it may be useful to measure the combination of blood glucose and BHB concentrations after 72 hours to help distinguish between those babies with congenital hyperinsulinemia and those who remain hypoglycaemic for other reasons, such as failure to establish breastfeeding (fasting) (7). Preliminary evidence suggests that measuring ketones at approximately 72 hours may help distinguish the cause of the hypoglycaemia (8). **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	We found no evidence for any of the critical or important outcomes. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	Additional measurements incur additional costs and require additional blood, sometimes resulting in more than one heel prick per measurement. One study reviewing case records of babies born at Auckland and Middlemore hospitals over five years (67,965 babies) identified 39 babies (7 (18%) Māori, 19 (49%) Pacific) ≥36 week's gestation with prolonged (>72 hours) hypoglycaemia, or approximately 5.7 per 10,000 births (15). An additional two babies with prolonged hypoglycaemia due to congenital hyperinsulinism were identified. This suggests that approximately 4 per 1,000 babies would be potentially eligible for additional testing if this occurred at or after 72 hours of age.
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	We found no evidence for any of the critical or important outcomes.	Additional evidence is very uncertain.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]*	

○ Probably no important uncertainty or variability ○ No important uncertainty or variability	***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	We found no evidence about the balance of desirable and undesirable effects for the outcomes of interest. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	Additional measurements, particularly of lactate, ketones and insulin in addition to glucose, may help identify more serious causes of hypoglycaemia. However, these are very uncommon.
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Costs of measuring (LabPlus NZ) lactate NZ $18.69 ketones NZ $18.81 insulin NZ $29.43 Blood volume needed lactate 0.5 mL ketones 0.5 mL insulin 0.5 mL Additional cost of staff time and storage of sample.	While reliable point-of-care analysers are available, the analysis of the alternative brain fuels often requires a separate analyser and may necessitate a second heel prick.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	We are confident in our estimates for the cost of measuring test and blood volume, but uncertain about the additional costs related to staff time or storage.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	We did not conduct a systematic cost-effectiveness analysis. The laboratory cost for measuring glucose is NZ$3.19 (Labplus, NZ).	
Equity		

What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing)) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (18). *However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (19). *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (18). *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (19). *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (18).	

	Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased? ***Consideration for Māori*** *In the Whānau Experience study* (16)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (20)(21)(22). *Additionally, a systematic literature review by Graham et al.* (23) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (23). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (16) ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (17)*. Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (18)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability		

Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	We found no evidence about the acceptability of measuring other metabolites for diagnosing or monitoring neonatal hypoglycaemia. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Most clinical laboratories can analyse lactate and ketone concentrations, but some may only be able to do this on relatively large volumes of blood, and require samples to be transported on ice. Many birthing units have access to point-of-care lactate analysers (used for measuring fetal scalp samples) but few, if any, have point-of-care ketone analysers. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies

VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

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Question 20.

Should neurological monitoring/ imaging vs. no neurological monitoring/ imaging be used for monitoring babies with neonatal hypoglycaemia?	
POPULATION:	Babies with neonatal hypoglycaemia
INTERVENTION:	neurological monitoring/ imaging
COMPARISON:	no neurological monitoring/ imaging
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies)

	2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn infants over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* It is unclear which, if any, neurological monitoring or imaging techniques should be recommended for monitoring of babies with neonatal hypoglycaemia.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are authors of cited paper.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	A study of 264 term babies (35 cases with symptomatic hypoglycaemia, 229 controls) was conducted, excluding babies with hypoxic-ischemic encephalopathy, major congenital malformations, multiple dysmorphic features, congenital infections and chromosomal abnormalities (1). Using T1- weighted transverse and sagittal MRI and T2 weighted transverse MRI before six weeks' postnatal age was found to be moderately predictive for abnormal neurodevelopmental outcomes at a minimum of 18 months of age (positive predictive value (PPV) for any white matter injury predicting any abnormal neurodevelopmental outcome = 26/33, 79%, PPV for severe injury predicting any abnormal neurodevelopmental outcome = 13/15, 87%). In a study of 45 late preterm or term babies with neonatal hypoglycaemia, including babies with comorbid conditions (44% had hypoxic-ischaemic-encephalopathy) (2), MRI scanning within six days of the onset of neonatal hypoglycaemia allowed diffusion restriction to be visualised. At follow-up when babies were 4-8 months, low mesial occipital apparent diffusion coefficient was associated with cortical visual defects, but this was based on only two participants with cortical visual loss i.e., a PPV of 2/6, 33% and did not reach statistical significance (p=0.1). Participants with cortical visual loss had significantly lower occipital diffusion coefficients than gestational-age matched control subjects, whilst those without cortical visual loss did not have significantly different occipital diffusion compared to gestational-age matched controls. In a study of 86 late preterm or term babies with hypoglycaemic brain injury (not due to asphyxia, infection or congenital disease) (3), using conventional and diffusion-weighted MRI imaging within 23 days of the onset of neonatal hypoglycaemia, extensive brain injury was found to be moderately predictive of death and any neurodevelopmental impairment (PPV = 10/14, 71%). This rate was higher than for participants with focal injury on MRI (35/62, 56%). A study of 75 term babies with hypoglycaemic encephalopathy, excluding babies with congenital dysplasia of the brain, bilirubin encephalopathy, hypoxic-ischemic encephalopathy, intracranial infection and septicaemia or poor MRI quality (4) undertook T1, T2 and diffusion-weighted imaging at a mean of 6 days of age. 40 participants had normal neurodevelopment or mild developmental disability and 35 had severe developmental disability at 9-12 months. Increased T1 and T2 values of the occipital lobe, T1 value of the corpus callosum or T1 value of the thalamus predicted increased risk of severe developmental disability with a sensitivity and specificity of above 75%. A combination of these parameters with clinical features (duration of hypoglycaemia and neonatal behavioural neurological assessment) had the highest sensitivity and specificity (89.1% and 90.6% respectively). In 24 babies without major congenital abnormalities who were moderate preterm, late preterm or term, changes in amplitude-integrated EEG were not found to be associated with hypoglycaemic	

	episodes (5). The authors concluded there was no clinical utility of cot-side amplitude-integrated EEG for monitoring brain function in relation to hypoglycaemia. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	No undesirable effects were explored in the studies found. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence is all from observational studies, meaning that the certainty of evidence is low or very low. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not conduct a systematic search to assess how people value the main outcomes, but caregivers may have different perspectives as to whether they want to know the neurodevelopmental prognosis of their baby. For example, parents of an extremely preterm baby who received a routine MRI before discharge described receiving an abnormal result as traumatic (6). They found no changes to their follow-up care based on the MRI and the prognosis provided was not in line with their toddler's neurodevelopmental trajectory. They state in retrospect, if they had the opportunity to make a fully informed choice, they would not have agreed to the MRI. However, in a qualitative study of caregivers of moderate to late preterm babies who were taking part in an MRI study in Aotearoa New Zealand (n = 12, 1 Māori) 7/12 reported initial anxiety due to abnormal findings, but all 12 expressed a preference for early detection of potential developmental risks, all reported reassurance from study participation, and none voiced any safety concerns for MRI (7). *Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know	MRI is moderately predictive of neurodevelopmental outcome in some groups of babies, particularly those with severe hypoglycaemia. Amplitude-integrated EEG does not appear to have any desirable effects. There is no information about other kinds of neurological monitoring, or about undesirable effects. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not conduct a systematic search to evaluate the resources required. An economic analysis of the installation and use of a specialised MRI machine in the neonatal intensive care unit was conducted in the UK in 2003 (8). The cost of each scan was estimated at £60 and the cost of the machine and set up £150,000. The time taken per scan was 30-40 minutes. However, this study did not specifically include infants with neonatal hypoglycaemia and only involved T1 and T2 weighted imaging, not diffusion weighted imaging. In a research study of babies in Auckland, New Zealand, using MRI sequences that would be suitable for studying babies with hypoglycaemia, each MRI costs approximately NZ$900, excluding staffing and transport costs. Costs for MRI for clinical purposes are likely to be higher. No information could be found about the cost of EEG monitoring.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ● Low ○ Moderate ○ High ○ No included studies	The resources required for MRI scanning are uncertain. The resources required for EEG monitoring are very uncertain. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	The cost of MRI scans mean that cost-effectiveness is unlikely to favour the intervention. However, it is unclear whether resources may be saved from potential earlier diagnosis of neurodevelopmental impairment when MRI scans are used to indicate prognosis. It is unclear whether resource requirements favour the intervention or comparison for EEG as no information has been found regarding costs.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?***	

	There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions. ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (11*).* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (11*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (12*), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (13, 14, 15*).* *Additionally, a systematic literature review by Graham et al.* (16*) provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (16*).* ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (12*).* ***Other considerations***	

	The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities (9)*. Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (9)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	We did not do a systematic search for evidence on acceptability and could not find any evidence on the acceptability of using MRI or EEG on babies for caregivers or clinicians. However, a study investigating the use of MRI for preterm babies at term equivalent age found that MRI reduced maternal anxiety, suggesting it is likely acceptable to caregivers (17). Recruitment of moderate-to-late preterm babies to an MRI study (MoPED) suggests that MRI is acceptable to a proportion of parents in Aotearoa New Zealand, but this is very variable. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	MRI imaging of babies with hypoglycaemia may be feasible to help predict later outcomes as MRI is currently used to assess babies with encephalopathy in Aotearoa New Zealand to provide diagnostic and prognostic information (18). However, a survey of neonatologists in New Zealand and Australia identified that resource limitations and logistics would prevent 17/95 (18%) of clinicians from conducting an MRI scan in a term infant with encephalopathy (18).	

	The use of amplitude-integrated EEG monitoring may be feasible in an Aotearoa New Zealand context as it was used in the study discussed above conducted in Waikato Hospital (5). According to Starship Guidelines, video amplitude-integrated EEG brain monitoring should be considered for infants with perinatal asphyxia, further suggesting feasibility in infants with hypoglycaemia in Aotearoa (19). For some secondary and all primary services, babies would need to be transported to another centre to access MRI and EEG facilities. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies

COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

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