MSAC Application 1776

Newborn bloodspot screening for mucopolysaccharidosis, Type II (MPS II)

PICO Set 2

Population

Describe the population in which the proposed health technology is intended to be used:

Biological Parents

MPS II is an X-linked recessive disorder, primarily affecting males. It is familial in most cases, although *de novo* mutations in the *IDS* gene have been identified. When MPS II is familial, the biological mother of affected male offspring with a pathogenic variant is a carrier, with a 50% chance that future male offspring would be affected. Based on this inheritance pattern, it is proposed that cascade testing of male newborns diagnosed with pathogenic or likely pathogenic variants of MPS II be offered to the mother only.

As described in the "Population" section of PICO set 1, females are rarely diagnosed with MPS II and when they are, it is usually due to abnormalities in the structure of the X-linked chromosome or the inactivation process of the X-chromosome. If a female is diagnosed with MPS II as a result of NBS, it is noted that an unaffected biological father is unlikely to carry a pathogenic variant. It is therefore proposed that genetic testing be offered to the biological mother; however, the appropriateness of offering genetic testing to the father should also be explored through the assessment.

Siblings

Older male siblings of a newborn diagnosed with MPS II with the same mother may also be affected. If born prior to the implementation of screening for MPS II as part of NBS, older male siblings may not have yet presented with symptoms and remain undetected, as the median age at symptom onset of severe disease ranges from 2 to 4 years of age. It is proposed that these individuals receive biochemical testing. If this test is positive for MPS II, the male sibling would then be offered genetic testing. If the analysis returned a negative result, genetic testing would not be offered.

Older female siblings of a newborn diagnosed with MPS II have a very low risk of being affected. There is a 50% chance that female offspring of biological mothers identified as carriers inherit the genetic variant and are themselves carriers, if the male biological parent does not have MPS II. It is proposed that genetic testing is not offered to female siblings, noting the primary purpose would be to inform future reproductive planning. In clinical practice, carrier testing is generally not offered or condoned in young people but is available once the child is old enough to engage in decision-making. The Human Genetics Society of Australasia advised in their 2022 position statement that "unless there is a direct medical benefit in the immediate future, the default position should be to postpone carrier testing until the child or young person can be supported to make an informed decision".

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

Biological mothers of a newborn diagnosed with MPS II, and older male sibling(s) (born prior to the implementation of NBS for MPS II) with the same biological mother, are eligible for cascade testing.

The appropriateness of biological fathers of females diagnosed with MPS II being made eligible for cascade testing should also be considered.

Provide a rationale for the specifics of the eligible population:
As an X-linked condition, the biological mother of an affected newborn can be assumed to be a carrier, with a 50% chance that other male offspring would also be affected.

Intervention

Name of the proposed health technology:
The proposed intervention is cascade testing for the biological mother of babies diagnosed with MPS II as a result of NBS, and older male sibling(s) with the same biological mother.

Describe the key components and clinical steps involved in delivering the proposed health technology:
The intervention for the biological mother of a newborn diagnosed with MPS II through NBS is genetic testing (for the specific familial pathogenic variants identified in the newborn) and genetic counselling for family planning. Male siblings would be offered biochemical testing (initially urine GAG analysis) if considered at risk of having MPS II. Genetic testing would only occur if the biochemical tests were positive for MPS II.

Cascade testing to determine the presence of specific pathogenic variants is usually conducted using targeted sequencing methods.

The number of individuals tested may increase slightly if MPS II is currently underdiagnosed. Additionally, there may be some initial shift towards earlier cascade testing for some families if screening for MPS II is added to NBS programs.

Identify how the proposed technology achieves the intended patient outcomes:
Cascade testing of mothers provides the value of knowing and helps to inform reproductive decision-making.

It may also support earlier diagnosis and management of disease in affected older male siblings, who have not been screened for the condition as part of NBS and have not presented clinically.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

☐ Yes
☒ No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:
N/A

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):
☐ Yes
☒ No

Provide details and explain:
N/A

If applicable, advise which health professionals will be needed to provide the proposed health technology:
Health professionals that would provide cascade testing are the same as per current practice, including genetic counsellors, clinical geneticists and laboratory scientists / geneticists.

Affected older male siblings would require referral to clinical services (see PICO set 1).

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:
N/A

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
Cascade testing would require referral from a clinician following diagnosis of the affected newborn.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

☐ Yes
☒ No

Provide details and explain:
Training and qualifications required to deliver cascade testing would be the same as current practice.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:
☒ Consulting rooms
☐ Day surgery centre
☐ Emergency Department
☒ Inpatient private hospital
☒ Inpatient public hospital
☒ Laboratory
☒ Outpatient clinic
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

Cascade testing requires oversight by relevant health professionals.

Is the proposed health technology intended to be entirely rendered inside Australia?
☒ Yes
☐ No

Please provide additional details on the proposed health technology to be rendered outside of Australia:
N/A

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

Please provide a name for your comparator:
Cascade testing offered to the family members of presenting individuals diagnosed with MPS II.

Please provide an identifying number for your comparator (if applicable):
N/A

Please provide a rationale for why this is a comparator:
Currently, cascade testing is offered to the family after diagnosis of a symptomatic child within the hospital system.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?
☐ None – used with the comparator
☐ Displaced – comparator will likely be used following the proposed technology in some patients
☐ Partial – in some cases, the proposed technology will replace the use of the comparator, but not all
☒ Full – subjects who receive the proposed intervention will not receive the comparator

Please outline and explain the extent to which the current comparator is expected to be substituted:
The biological mother and older male sibling(s) of an affected newborn would be offered cascade testing following diagnosis as a result of NBS, rather than at the point of symptomatic presentation.

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

Health benefits

- Improvement in clinical outcomes from an earlier diagnosis and intervention (for affected siblings)

Health harms

- Impact of diagnosing siblings with mild or benign forms of the condition that may not become symptomatic (overdiagnosis)

Resources

- Financial impact of cascade testing
    - Health care resources involved in testing and counselling
    - Diagnosis and management for an affected sibling
    - Total health care costs, including cost effectiveness

Other relevant considerations

- Value of knowing (for parents, siblings and broader family members, emotional benefits/harms to family, social benefits/harms to family)
- Accuracy of the test
- Ethical considerations (equity of access, notification of carrier status)

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:
Cascade testing enables the parents to undertake informed reproductive planning and may support identification of affected but undiagnosed older male siblings.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:
Cascade testing may support improved outcomes if an affected older male sibling is identified through cascade testing, but this would be limited to a small number of cases. It also supports reproductive planning for parents, who are unaffected by the condition.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
See rationale above.

Identify how the proposed technology achieves the intended patient outcomes:
Cascade testing of parents provides the value of knowing and helps to inform reproductive decision-making.

It may also support earlier diagnosis and management of affected older male siblings, who have not been screened for the condition as part of NBS.

For some people, compared with the comparator(s), does the test information result in: (please select your response for each statement)

A change in clinical management? ☒ Yes ☐ No

Affected older male siblings identified earlier would be able to receive clinical care before diagnosed clinically as a result of presenting with symptoms.

A change in health outcome? ☒ Yes ☐ No

Affected older male siblings identified earlier may receive earlier access to intervention, supporting improved health outcomes.

Other benefits? ☒ Yes ☐ No

Please provide a rationale, and information on other benefits if relevant:
The family can access support services such as genetic counselling and reproductive technologies for family planning. It may also shorten the diagnostic odyssey for affected older male siblings, who have not been screened for the condition as part of NBS.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:
Newborns with mild or benign cases who may have never been diagnosed clinically with MPS II in the absence of NBS may potentially be identified, meaning that their parents and older male siblings may receive cascade testing that would not have otherwise been offered.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Review	Cascade health service use in family members following genetic testing in children: a scoping literature review	Summarises published research on the patterns and costs of cascade health service use by relatives of children with any condition diagnosed through genetic testing. Cascade testing uptake was found to vary across diseases; from 37% in cystic fibrosis to 90% for rare monogenic conditions. Limited studies (n=2) evaluated costs.	https://www.nature.com/articles/s41431-021-00952-4	August 2021
2.	Review	Barriers and facilitators for cascade testing in genetic conditions: a systematic review	Provides the outcomes of a systematic review on the barriers and facilitators for the uptake of cascade testing by at-risk relatives, and categorised at the: - individual level - interpersonal level - environmental level.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7784694/	December 2020
3	Position statement	Human Genetics Society of Australasia Position Statement – Genetic Carrier Testing for Recessive Conditions	Provides guidance on offering cascade testing to children and young people, particularly where identifying carrier status does not have the potential for medical benefit.	Human Genetics Society of Australasia Position Statement: Genetic Carrier Testing for Recessive Conditions (hgsa.org.au)	August 2022

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).
None identified

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:
Diagnosis of MPS II in a child is required for the biological mother and older male sibling(s) to access cascade testing (see PICO set 1).

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology?
☐ Yes

☒ No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:
N/A

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:
Health professionals that would provide cascade testing are the same as per current practice, including genetic counsellors, clinical geneticists and laboratory scientists / geneticists.

Affected older male siblings would require referral to clinical services (see PICO set 1).

Explain what other healthcare resources are used in conjunction with the comparator health technology:
Health professionals that provide cascade testing include genetic counsellors, clinical geneticists and laboratory scientists / geneticists.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:
There may be an increase in healthcare resource use associated with the earlier diagnosis of affected older male siblings, and possible increase where cascade testing is offered to the biological mother of newborns with mild / benign forms of the condition that would otherwise not be detected.

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:
Parents would access any services associated with counselling and family planning following the provision of cascade testing.

Older male siblings identified as being affected by MPS II would receive clinical care, as per the services outlined in PICO set 1.

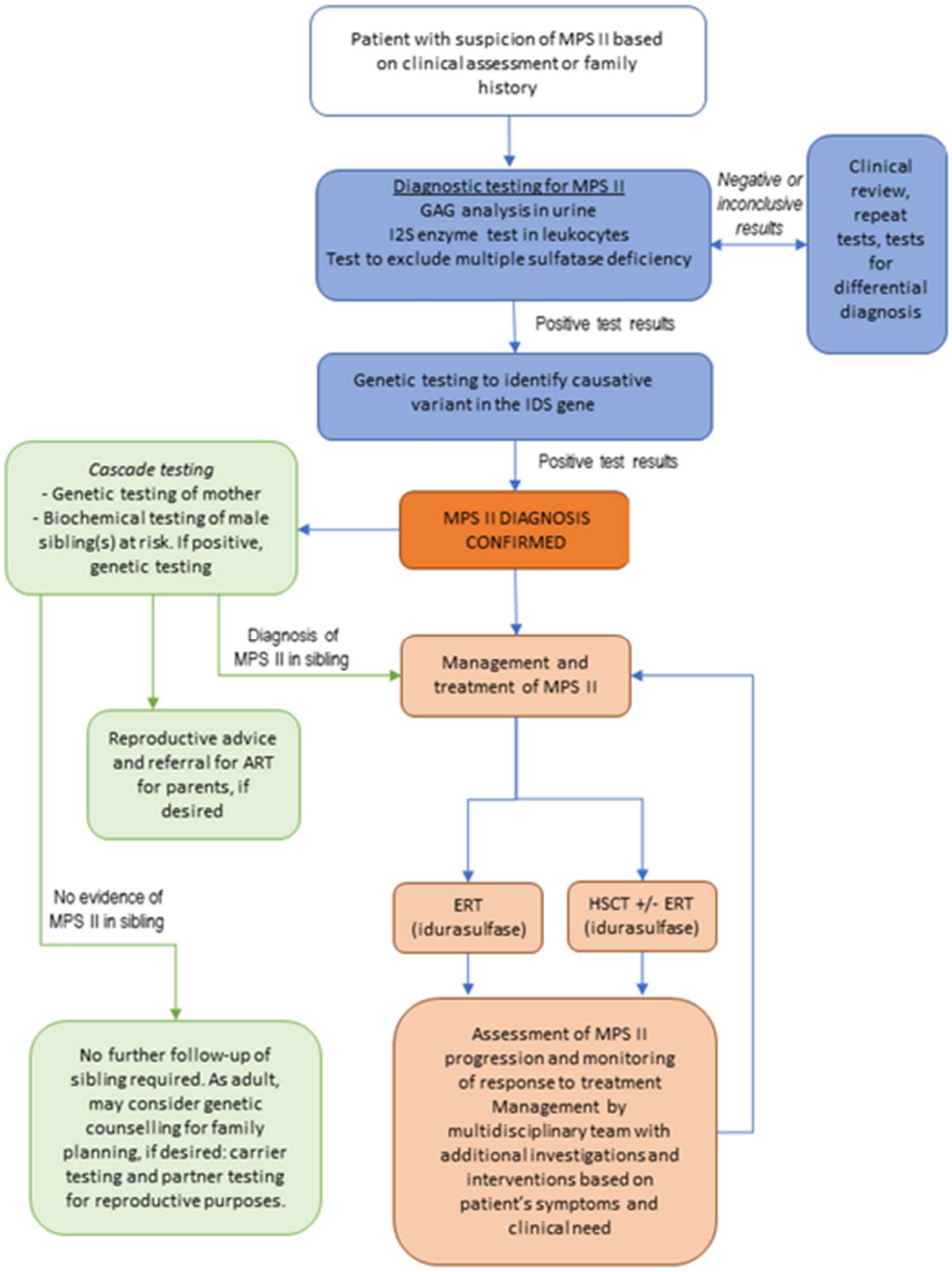
Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:
Parents would access any services associated with counselling and family planning following the provision of cascade testing.

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:
Resource use may be associated with the diagnosis and surveillance of older male siblings with mild / benign forms of MPS II identified as a result of cascade testing, who may not otherwise have been detected.

Algorithms

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:
Please see PICO set 1 for further details on these algorithms. Cascade testing components are indicated in the green boxes.

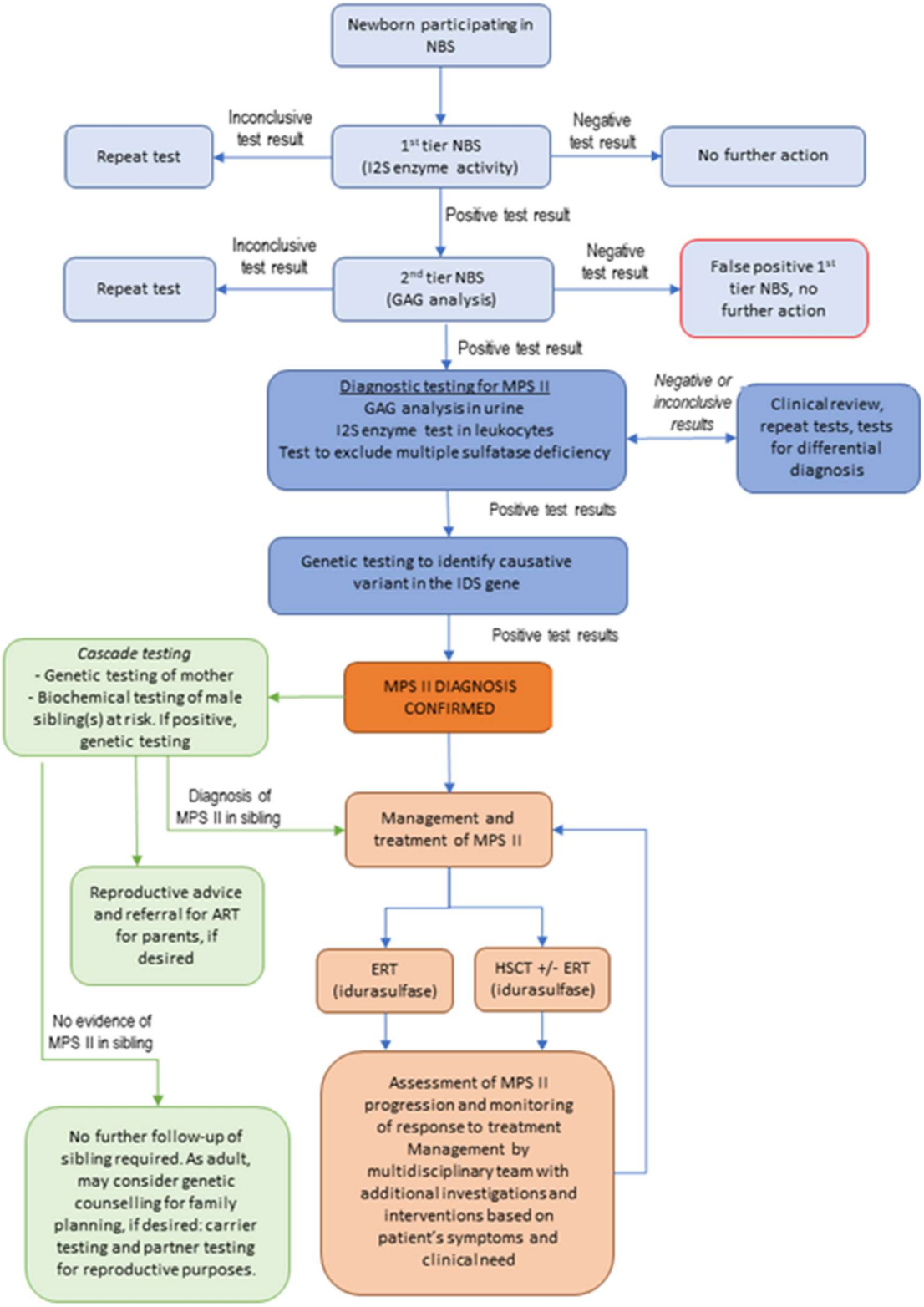
Current clinical management algorithm



ART = assisted reproductive technology; ERT = enzyme replacement therapy; GAG = glycosaminoglycans; HSCT = haematopoietic stem cell transplant; I2S = iduronate-2-sulfatase; *IDS* = iduronate-2-sulfatase gene; MPS = mucopolysaccharidosis.

Adapted from (Burton & Giugliani 2012; Scarpa et al. 2011)

Proposed clinical management algorithm



ART = assisted reproductive technology; ERT = enzyme replacement therapy; GAG = glycosaminoglycans; HSCT = haematopoietic stem cell transplant; I2S = iduronate-2-sulfatase; *IDS* = iduronate-2-sulfatase gene; MPS = mucopolysaccharidosis; NBS = Newborn bloodspot screening. Adapted from (Arunkumar et al. 2020; Burton & Giugliani 2012; Scarpa et al. 2011)