

MSAC Application 1774

**Newborn bloodspot screening for
glycogen storage disease, Type II
(Pompe disease)**

PICO Set 2

Population

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

GSD II has a recessive mode of inheritance, therefore both parents of an affected newborn with two pathogenic/likely pathogenic (P/LP) variants can be assumed to be carriers, with one in four chance that future offspring would also be affected.

When a case of infantile-onset GSD II is diagnosed, it is proposed that cascade testing is offered to parents to allow for further reproductive planning. Young siblings of the affected newborn may themselves also be affected or carriers and should also receive counselling and cascade testing.

When a case of late-onset GSD II is identified, it may be appropriate to also offer carrier testing to older members of the broader family and their children, as late-onset GSD II symptoms may not yet have been observed or diagnosed.

Cascade testing of unaffected siblings to determine carrier status may not be offered in all cases (e.g., older siblings that are asymptomatic). However, when the child reaches reproductive age, he/she may elect to undergo cascade testing, and if required, partner testing, through an appropriate clinic for family planning purposes. This would most likely occur at a cost to the sibling.

Members of the broader family (the parents' siblings and/or biological nieces and nephews) may also decide to seek carrier testing for reproductive planning purposes, at their own cost.

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 parents and older sibling(s) (born prior to the implementation of NBS for GSD II) of a newborn diagnosed with GSD II are eligible for the proposed health technology.

Provide a rationale for the specifics of the eligible population:

As an autosomal recessive condition, both parents of an affected newborn with two pathogenic variants can be assumed to be carriers, with a one in four chance that other offspring would also be affected.

Intervention

Name of the proposed health technology:

The proposed intervention is cascade testing for the biological parents (and where relevant, older sibling(s)) of babies diagnosed with GSD II as a result of NBS.

Describe the key components and clinical steps involved in delivering the proposed health technology:

The intervention for family members of a newborn identified through universal NBS with GSD II is genetic counselling and cascade testing for the specific familial variants identified in the newborn. GAA gene sequencing is likely to be the method used for cascade testing. Carrier status is determined by the presence of the familial pathogenic variant identified through screening and confirmation in the index case.

GAA gene sequencing has the potential to distinguish pseudodeficiency of alpha-glucosidase from genuine GSD II or variant of unknown significance (VUS) (Dasouki et al. 2014; Mechtler et al. 2012; Sawada, Kido & Nakamura 2020).

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 siblings, who have not been screened for the condition as part of NBS.

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:

Not applicable

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:

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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 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:

Not applicable

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? (please select your response)

- 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? (please select your response)

- Yes
 No

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

Not applicable

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 copy the below questions and complete for each comparator)

Please provide a name for your comparator:

Cascade testing offered to the family members of presenting individuals diagnosed with GSD II.

An alternative comparator, which most likely represents current clinical practice, is cascade testing as well as genetic counselling after diagnosis of a child in the public hospital system, or via private providers of genetic testing at cost to the patient.

Siblings would not necessarily be offered cascade testing to determine carrier status, depending on the type of GSD II in the index case. Future cascade testing (and if required, partner testing) would occur through an appropriate clinic for family planning purposes, at a cost to the sibling.

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

Not applicable

Please provide a rationale for why this is a comparator:

Currently, cascade testing is offered to parents 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? (please select your response)

- 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:

Parents of an affected child would be offered cascade testing following diagnosis as a result of NBS, rather than at the point of symptomatic presentation.

Outcomes

For most family members tested, the expected test results will be that they either are, or are not a carrier of, or affected by, GSD II. The major benefit of cascade testing for family members is to

inform reproductive decision-making. A small proportion of siblings who did not themselves get tested for GSD II through newborn screening (due to being born outside of Australia or born prior to the introduction of LSDs to the NBS program) may be identified as being clinically affected with GSD II (non-classic infantile-onset GSD II or late-onset GSD II) due to cascade testing. Older family members may be identified with late-onset GSD II or as a carrier of late-onset GSD II if cascade testing is offered to a broader family group following the diagnosis of a newborn with late-onset GSD II.

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 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)? (please select your response)

Superior

Non-inferior

Inferior

Please state what the overall claim is, and provide a rationale:

Cascade testing may support improved outcomes if an affected 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 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 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 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 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? (please select your response)

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 I in the absence of NBS may potentially be identified, meaning that their parents and 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: <ul style="list-style-type: none"> - individual level - interpersonal level - environmental level. 	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7784694/	December 2020

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

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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 GSD II in a child is required for the parents and siblings 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?

(please select your response)

- 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:

Not applicable

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 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 siblings, and possible increase where cascade testing is offered to parents 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.

Siblings identified as being affected by GSD 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 siblings with mild / benign forms of GSD 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 light blue boxes below.

Current clinical management for infantile-onset GSD II

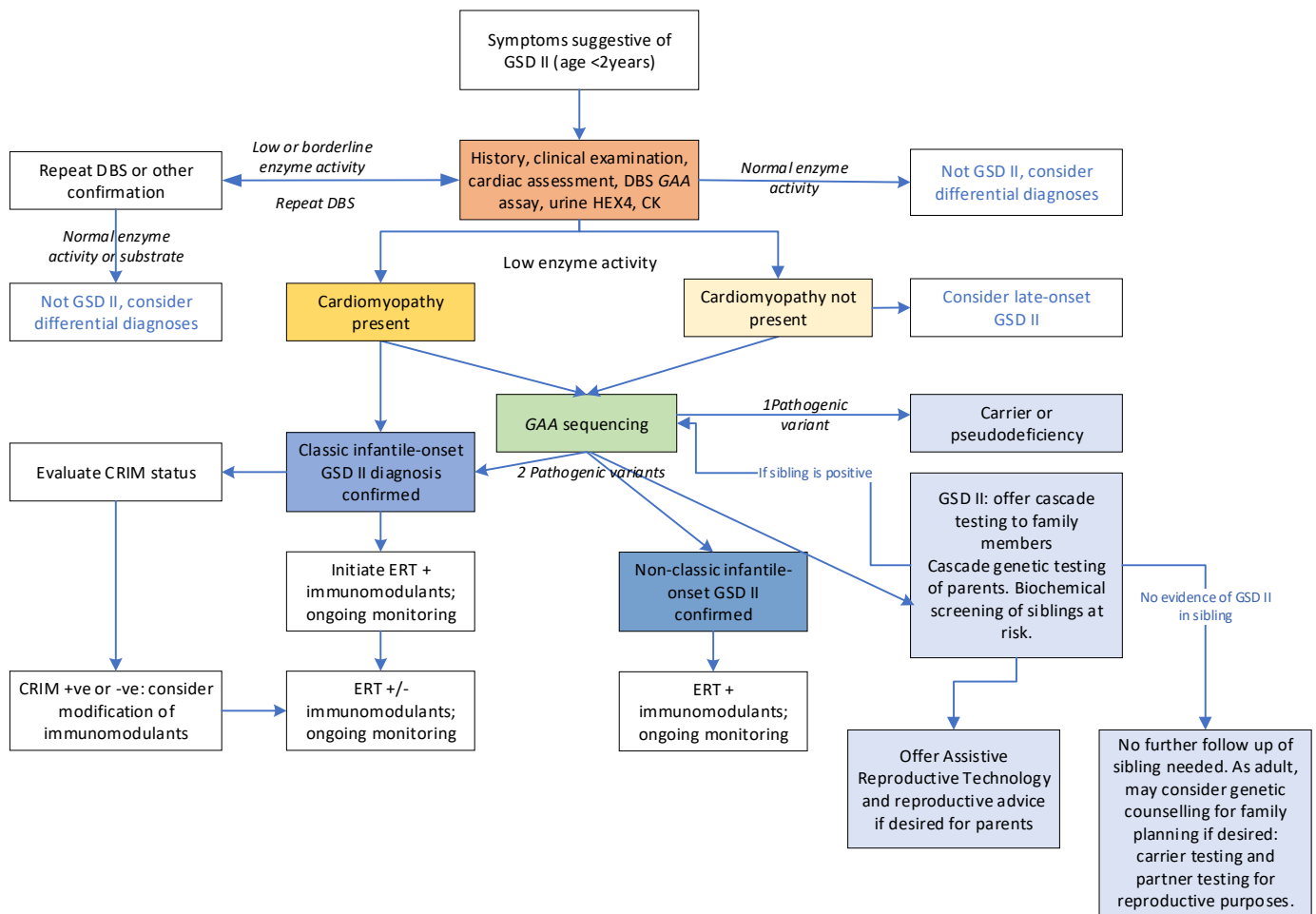


Figure 1 Current clinical management algorithm for infantile-onset GSD II

Abbreviations: CK = creatinine kinase assay; CRIM = cross-reactive immunological material; DBS = dried blood spot; ERT = enzyme replacement therapy; GAA = alpha glucosidase; GSD II = glycogen storage disease II; HEX4 = urine glucotetrasaccharides assay

Current management for late-onset GSD II

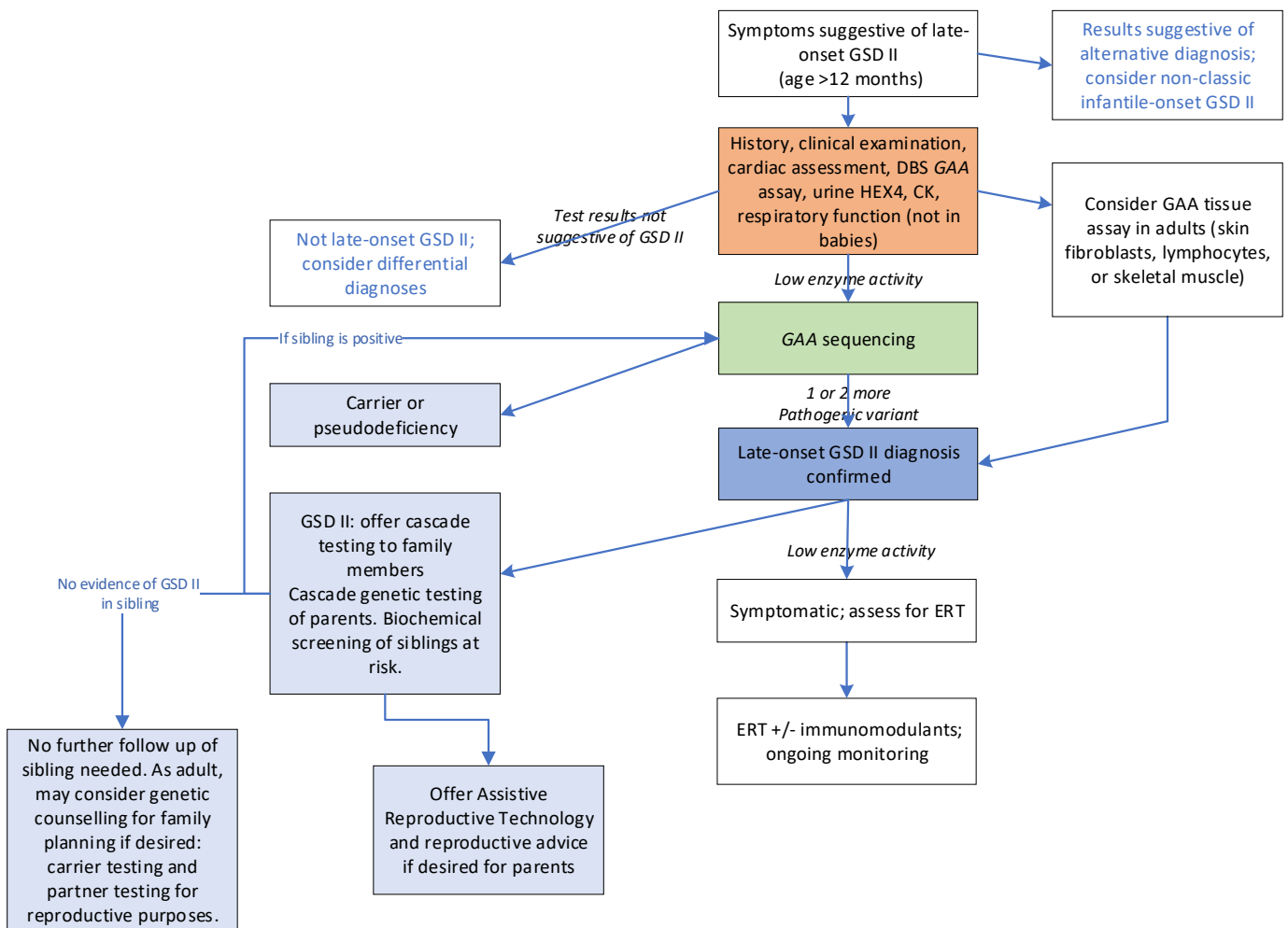


Figure 2 Current clinical management algorithm for late-onset GSD II

Abbreviations: CK = creatinine kinase assay; DBS = dried blood spot; ERT = enzyme replacement therapy; GAA = alpha glucosidase; GSD II = glycogen storage disease II; HEX4 = urine glucotetrasaccharides assay

Proposed management of infantile-onset and late-onset GSD II

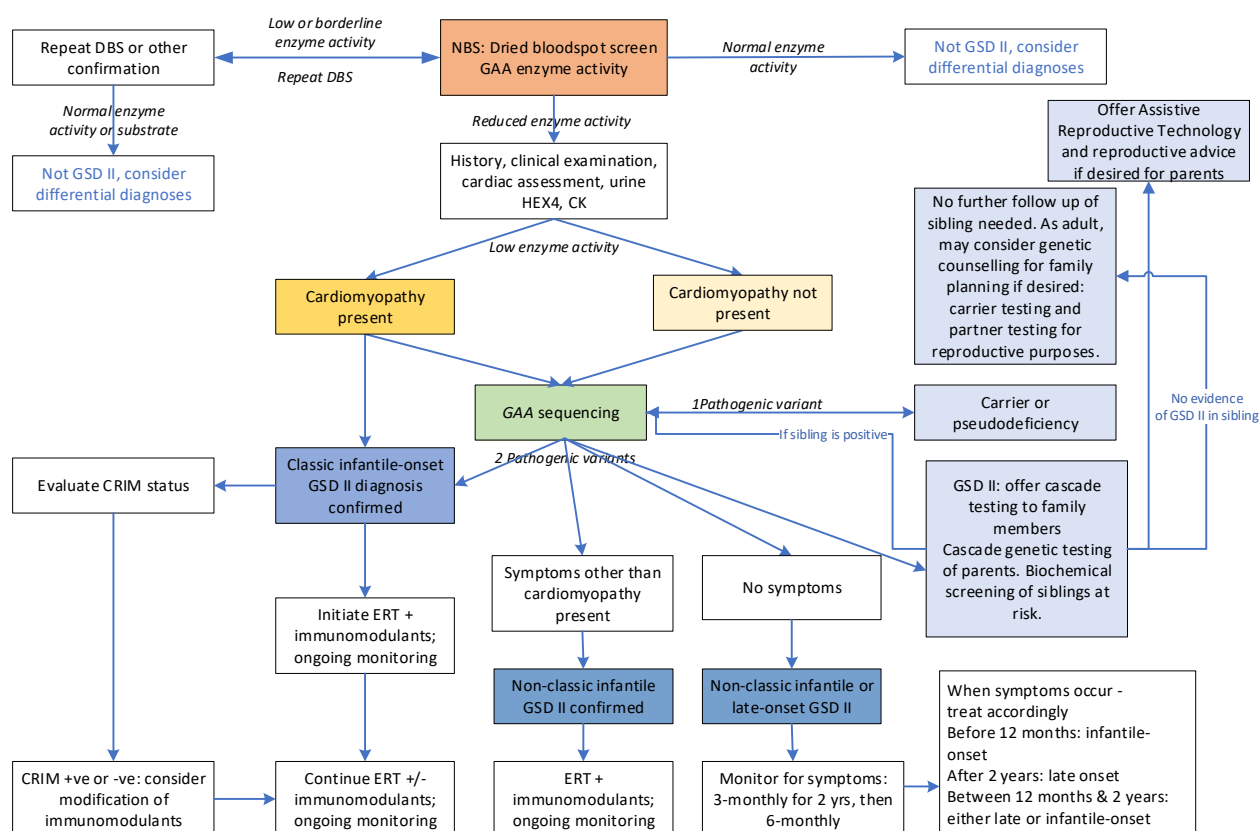


Figure 3 Proposed clinical management algorithm for infantile-onset and late-onset GSD II

Abbreviations: CK = creatinine kinase assay; CRIM = cross-reactive immunological material; DBS = dried blood spot; ERT = enzyme replacement therapy; GAA = alpha glucosidase; GSD II = glycogen storage disease II; HEX4 = urine glucotetrasaccharides assay