The Laboratory Services Reform Programme

ADVICE NOTE

Testing for HLA B27

Version 1 Issued 31/10/2025

LS/0007/1.0/2025

Clinical Practice Guidance Document Cover Sheet

Document Type	Advice Note
Document Title	Testing for HLA B27
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National Service/Area	Office of the Chief Clinical Officer
Approved by:	Professor Martin Cormican
Unique Identifier Number(UID):	LS/0007/1.0/2025
Version Number:	1
Publication Date:	31/10/2025
Recommended Revision Date: *	31/10/2027
Electronic Location:	https://www.hse.ie/eng/about/who/cspd/lsr/resources/advice.html

Version	Revision Date	List Section Numbers Changed	Author

The Laboratory Services Reform Programme offers the following advice:

1.1 Advice for Laboratory Users

1. HLA-B27 assessment is not a test that diagnoses or excludes a condition.
2. The presence of HLA-B27 is neither necessary nor sufficient for the diagnosis of any condition.
3. A negative test for HLA-B27 does not out rule a disease
4. Testing for HLA-B27 may be useful in supporting the diagnosis and management of spondylarthropathies and other specific related immune mediated disorders (Table 1). It is typically used as part of an evaluation in a specialist setting.
5. A test for HLA-B27 should only be requested when there is a strong clinical suspicion of a relevant disease state based on clinical history, physical examination and other laboratory features.
6. Laboratory Users should be aware that HLA-B27 positivity is common in the healthy population. Approximately 6-8% of the healthy Irish population are HLA-27 positive.
7. A positive result indicates the presence of HLA B27. This can mean a greater than average risk of inflammatory diseases such as ankylosing spondylitis and/or other related disorders (Table 1). This information on HLA-B27 status in isolation is not useful.
8. The majority of unselected individuals with a positive HLA-B27 do not have an associated disease state and will not develop an associated disease. Studies suggest that 90-95% of individuals who are HLA-B27 positive will not develop a HLA-B27 associated disorder.
9. Testing for HLA-B27 in asymptomatic individuals, in patients with features not consistent with HLA-B27 associated diseases (for example non-specific back pain without inflammatory features) or in other settings with low pre-test probability of an associated inflammatory condition is not recommended.
10. Testing for HLA-B27 should never form part of a health screening approach. Testing people without relevant clinical features because they have a relative positive for HLA-B27 is not appropriate.
11. It is expected that most HLA-B27 tests will be ordered in specialist settings, such as rheumatology, ophthalmology or other specialists with appropriate experience in the diagnosis and management of HLA-B27 related disorders, as the clinical utility in a primary care setting is very limited.
12. There are a number of methods for testing for HLA-B27. Users should be aware what testing approach is being used in the laboratory they send the test to.
13. Expert users should consider this is a specialist test primarily for interpretation by them as expert users in the overall clinical context. It is generally not appropriate to delegate ordering and interpretation of HLA-B27 testing to users in non-specialist settings.
14. Ordering HLA-B27 in settings where the clinical suspicion of a related disease is low may generate a clinically irrelevant positive result. Users should avoid this situation by appropriate test requesting. If users request HLA-B27 in settings where the clinical suspicion of a related disease is low, they should ensure they have the requisite competency required to communicate the result and manage the issues that may arise without recourse to onward referral.

15. Ordering HLA-B27 tests in settings of low pre-test probability of a related inflammatory disorder with generation of unhelpful results can result in the initiation of an avoidable, inappropriate referral cascade that leads to anxiety and impacts on waiting times for patients with clinically significant findings.
16. Unnecessary testing for HLA B27 generates substantial costs, avoidable risks of needle exposure and results in clinical and laboratory waste.
17. Where there is uncertainty about test selection, users should consider discussion with the laboratory team or with the appropriate clinical specialty.

1.2 Advice for Laboratories and Users

1. Indications for testing for HLA-B27 include features not explained by another cause, detailed below. Test orders should detail one or more of these features

    A) Suspected ankylosing spondylitis / axial spondyloarthritis
        - Chronic (more than 3 months duration) back pain with onset before the age of 45 years and inflammatory features
        - Features suggestive of inflammatory back pain
            - Morning stiffness lasting more than 30 minutes
            - Improvement of pain and stiffness with exercise
            - Night pain
        - Imaging findings suggestive of sacroiliitis or spinal inflammation
        - Known family history of spondylarthritis or other HLA-B27 associated disease in setting of a compatible clinical picture

    B) Peripheral features of spondyloarthritis
        - Enthesitis – inflammation of tendons or ligaments
        - Dactylitis
        - Oligoarthritis in young adults

    C) Recurrent acute anterior uveitis

    D) Suspected inflammatory arthritis in specific disease settings
        - Psoriasis with symptoms suggestive of axial involvement
        - Inflammatory bowel disease with symptoms suggestive of axial involvement or atypical peripheral arthritis
        - Reactive arthritis especially with a recurrent or chronic course

2. Testing for HLA-B27 is not indicated in settings such as non-specific back pain where there are none of the features outlined in Section 1.2.1. Where appropriate clinical details are absent. laboratories and users should be aware that positive results may be misleading.
3. Repeat testing for HLA-27 is not required.

1.3 Advice for Laboratories

1. Laboratories should communicate to laboratory users the indications to test for HLA-B27.
2. Testing for HLA-B27 should be performed when relevant and legible clinical details and requestor information are provided on the request (electronic or paper) accompanying the sample and where the sample received is suitable for analysis.

3. To the greatest extent that is practical, requests for HLA-B27 testing that do not meet these requirements, or where the information received is inadequate should not be processed.
4. If samples are not processed, a report should issue to the effect that testing for HLA-27 testing was not performed because testing criteria were not met. Individual laboratories may wish to develop a process to store samples for a defined period of time, to allow users to update a request with appropriate information.
5. Laboratories should communicate to laboratory users the main testing modality employed for the assessment of HLA-B27. Laboratories should consider including this information on results.
6. Where laboratories use a secondary testing modality or send samples to a referral laboratory, for confirmation of equivocal results, this should be made clear in the laboratory user guide.
7. Laboratories should consider engaging with key user groups, such as rheumatologists, to refine testing algorithms and to identify and engage with inappropriate practice
8. Laboratories should consider developing educational strategies to help users optimise use test selection and interpretation within their own clinical practice.

2 Background

HLA-B27 (Human Leucocyte Antigen) is a class I major histocompatibility complex surface antigen. It is encoded in the HLA-B locus on chromosome 6. Class I MHC antigens expressed on somatic cells present processed peptides in the context of a binding cleft to CD8+ T cells. Allelic variation resulting in amino acid changes in the binding pocket are thought to result in differences in antigen presentation that contribute to the development of HLA-B27 associated diseases (Table 1). Alterations in protein folding resulting in the presentation of 'arithrogenic' peptides are thought to be important. The association of HLA-B27 with reactive arthritis related to exposure to intracellular bacteria has led to speculation about the role of such pathogens as triggers of other associated disease states. However, much uncertainty remains.

The prevalence of HLA-B27 varies widely between geographic areas and ethnic groups. 8-10% of Caucasians are thought to be HLA-B27 positive. Some studies suggest the prevalence within the Irish population is slightly lower, around 6-8%. HLA-B27 is itself highly polymorphic with 105 known subtypes. Individual allelic differences contribute to disease pathology but assessment in diagnostic laboratories is not routine.

HLA-B27 is associated with several systemic inflammatory diseases. The main associated conditions are grouped together as seronegative spondlyarthropathies with seronegativity referring to the absence of rheumatoid factor. The strongest disease association is with ankylosing spondylitis (AS). More than 90% of AS patients will express HLA-B27. Importantly, absence of HLA-B27 does not exclude the disease. The expression of HLA-B27 increases the relative risk of developing ankylosing spondylitis 50-100 fold. Although it is a marker of risk most (90-95%) of HLA-B27 positive individuals do not develop HLA-B27 related disorders. This very obviously limits the utility of testing HLA-B27 status outwith specific high pre-test probability clinical scenarios and as part of the comprehensive assessment typical in specialist care.

In summary, HLA-B27 positivity is a risk factor for seronegative spondylarthropathies. It is not a standalone diagnostic test, but can be useful as part of the assessment of patients with features suggestive of these disorders, typically within a specialist setting.

Table 1. Disorders associated with HLA-B27

Ankylosing spondylitis / Axial Spondylarthropathy
Reactive arthritis
Psoriatic arthritis
Enteropathy associated arthritis – related to inflammatory bowel disease
Acute anterior uveitis – especially recurrent forms
Juvenile idiopathic arthritis – Enthesitis related subtype

References

1.

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