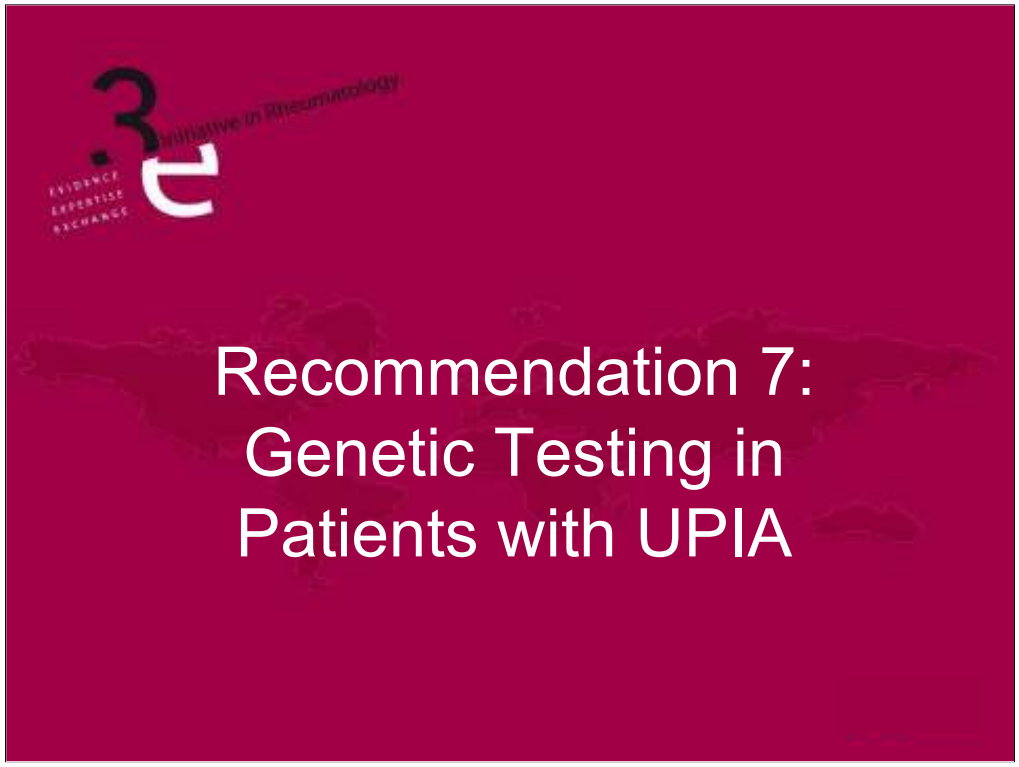
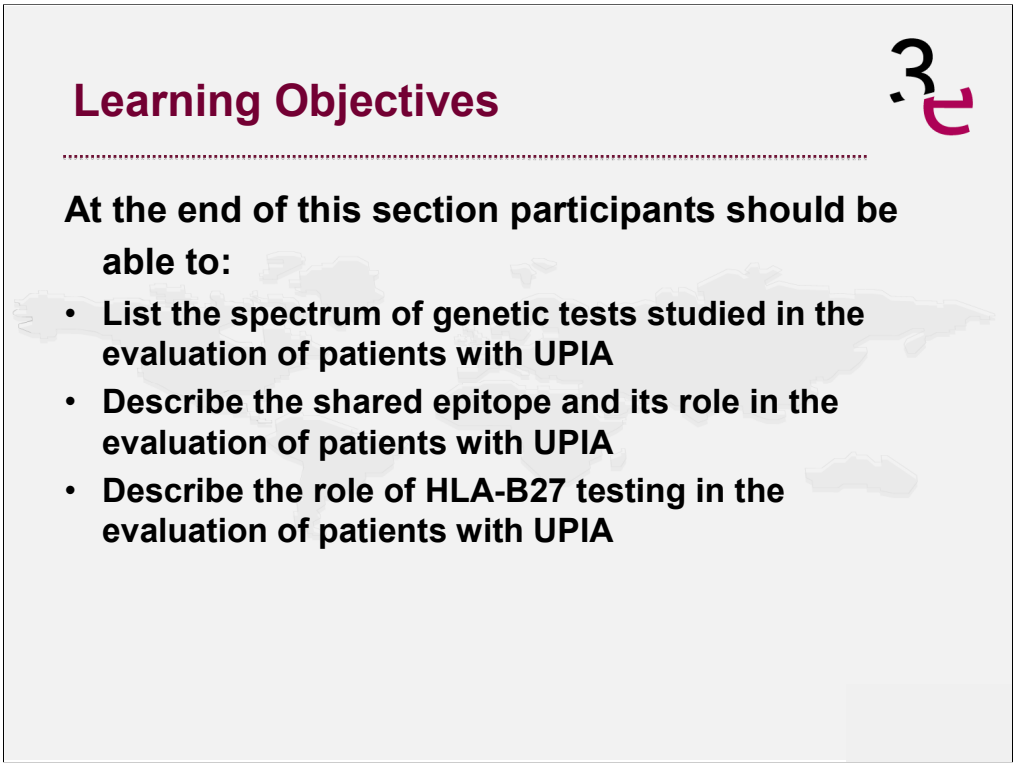


Recommendation 7



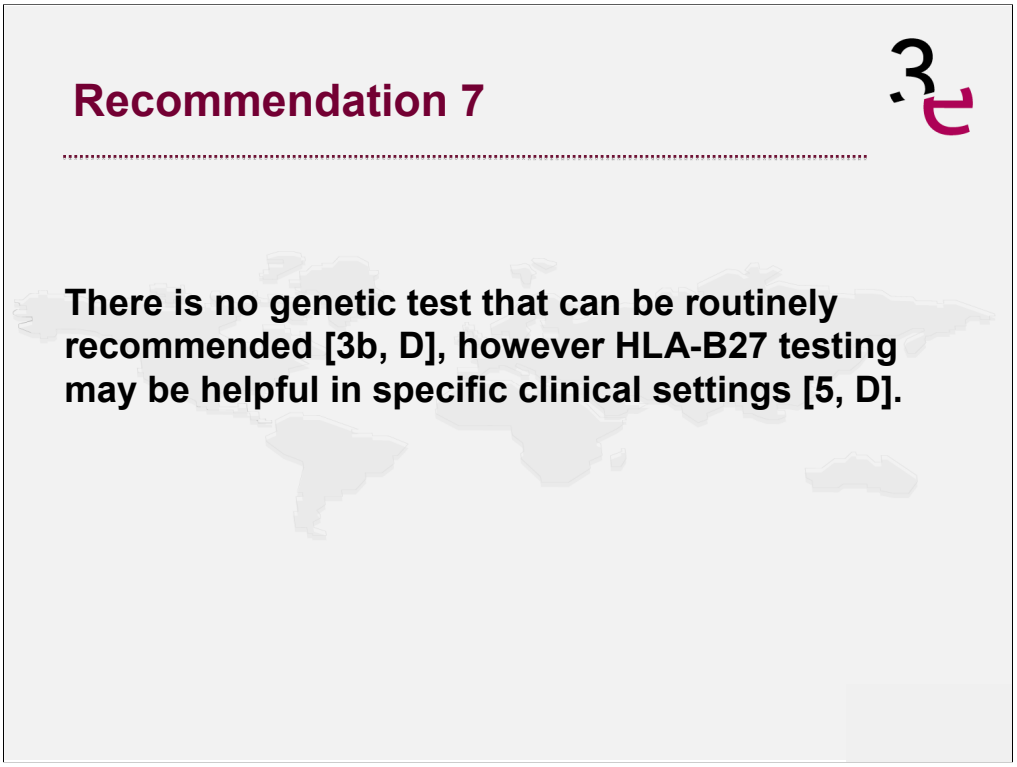
Learning Objectives

At the end of this section participants should be able to:

•List the spectrum of genetic tests studied in the evaluation of patients with UPIA

•Describe the shared epitope and its role in the evaluation of patients with UPIA

•Describe the role of HLA-B27 testing in the evaluation of patients with UPIA



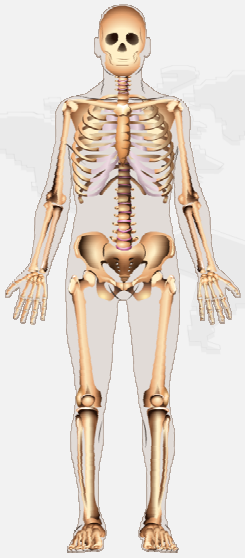
Recommendation 7

There is no genetic test that can be routinely recommended [3b, D], however HLA-B27 testing may be helpful in specific clinical settings [5, D].

This recommendation had a strong agreement of 8.8/10.

93% of rheumatologists felt that this recommendation was already implemented in their practice.

Undifferentiated Arthritis



Undifferentiated Arthritis

- **Early stage of classifiable disease**
- **Part of an overlap of disease**
- **Partial form of a defined disease**
- **Disease of unknown origin**

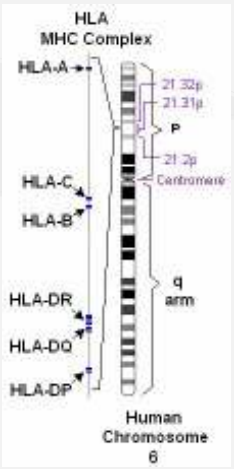
UA envelops a heterogeneous group of recent onset arthritides that are not classifiable within established criteria sets such as those of the American College of Rheumatology (ACR) and The European League Against Rheumatism (EULAR).

UA may represent an early stage of a classified form of arthritis that will eventually be definable; an overlap of more than one disease; a partial form of a defined disease; or a disease of unknown origin. UA overall has a better prognosis than RA as it encompasses a spectrum of self-limited disorders. As compared to RA, a patient with UA usually presents with fewer affected joints, less radiographic erosions, better functional ability, and a greater likelihood of being seronegative. Patients with UA are also less likely than patients with RA to require treatment that involves the use of corticosteroids (such as Prednisone) or DMARDs and a substantial proportion of UA patients remit spontaneously.

Hitchon CA, Peschken CA, Shaikh S, El-Gabalawy HS. Early undifferentiated arthritis. *Rheum Dis Clin N Am*. 2005;31:605-626.

The Superlocus HLA

- **HLA class I: A, B & C**
  - **present peptides from inside the cell (including viral peptides if present)**
  - **Eg: HLA-B27**
- **HLA class II: DR, DP, & DQ**
  - **present antigens from outside of the cell to T-lymphocytes**
  - **Eg: Shared epitope**



The Superlocus HLA

HLA class I: A, B & C

present peptides from inside the cell (including viral peptides if present)

Eg: HLA-B27

HLA class II: DR, DP, & DQ

present antigens from outside of the cell to T-lymphocytes

Eg: Shared epitope

The HLA system is a superlocus, as it contains a large number of genes related to immune system function in humans. This group of genes resides on chromosome 6, and encode cell-surface antigen-presenting proteins and many other genes.

-HLA-B27 is a well known example of an HLA Class I antigen

-The shared epitope in RA is an example of a Class II antigen

Shared Epitope

The Shared Epitope is a short sequence of 5 amino acids which is shared amongst the different HLA-DRB1 alleles which have been associated with rheumatoid arthritis.

Shared Epitope

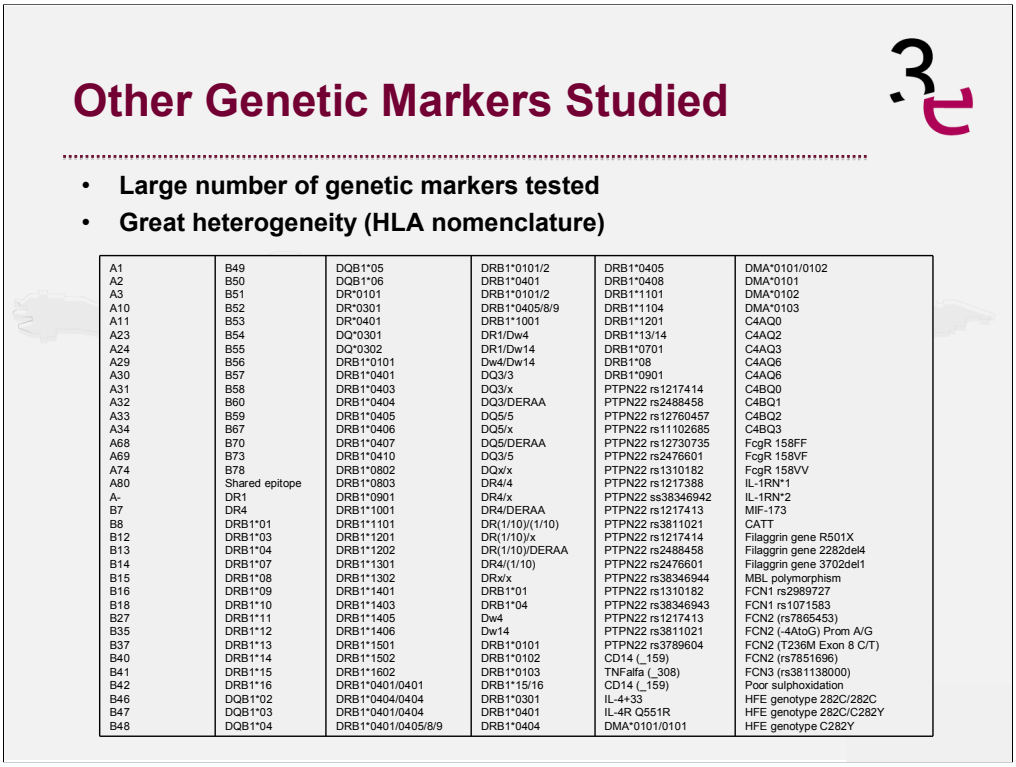
- **The evidence for SE diagnostic utility in UPIA, however, was poor. Only in one study the positive likelihood ratio for RA was relevant, but this result came from the study with the poorest quality and smallest sample size (1)**
- **SE was slightly associated with a poor prognosis of arthritis in terms of development of erosions, mortality, disability and persistent synovitis (2-6)**

Shared Epitope

- The evidence for SE diagnostic utility in UPIA, however, was poor. Only in one study the positive likelihood ratio for RA was relevant, but this result came from the study with the poorest quality and smallest sample size (1)
- SE was slightly associated with a poor prognosis of arthritis in terms of development of erosions, mortality, disability and persistent synovitis (2-6)

While the shared epitope is clearly implicated in the genetics of RA, it's role in the evaluation of patients with UPIA is less clear.

1. Morel J, Legouffe MC, Bozonat MC, Sany J, Eliaou JF, Daures JP, et al. Outcomes in patients with incipient undifferentiated arthritis. Joint Bone Spine. 2000 Jan; 67(1):49-53.
2. 2. El-Gabalawy HS, Goldbach-Mansky R, Smith D, 2nd, Arayssi T, Bale S, Gulko P, et al. Association of HLA alleles and clinical features in patients with synovitis of recent onset. Arthritis Rheum. 1999 Aug; 42(8):1696-1705.
3. Farragher TM, Goodson NJ, Naseem H, Silman AJ, Thomson W, Symmons D, et al. Association of the HLA-DRB1 gene with premature death, particularly from cardiovascular disease, in patients with rheumatoid arthritis and inflammatory polyarthritis. Arthritis Rheum. 2008 Feb; 58(2):359-369.
4. Gough A, Faint J, Salmon M, Hassell A, Wordsworth P, Pilling D, et al. Genetic typing of patients with inflammatory arthritis at presentation can be used to predict outcome. Arthritis Rheum. 1994 Aug; 37(8):1166-1170.
5. Emery P, Salmon M, Bradley H, Wordsworth P, Tunn E, Bacon PA, et al. Genetically determined factors as predictors of radiological change in patients with early symmetrical arthritis. Bmj. 1992 Dec 5; 305(6866):1387-1389.
6. Harrison B, Thomson W, Symmons D, Ollier B, Wiles N, Payton T, et al. The influence of HLA-DRB1 alleles and rheumatoid factor on disease outcome in an inception cohort of patients with early inflammatory arthritis. Arthritis Rheum. 1999 Oct; 42(10):2174-2183.



Other Genetic Markers Studied

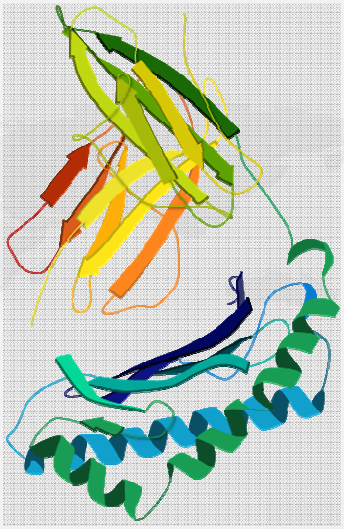
•Large number of genetic markers tested

•Great heterogeneity (HLA nomenclature)

The range of genetic markers tested was very wide and there was great heterogeneity in the association measures used.

HLA-B27

- **Current lack of evidence for the practical utility of genetics in UPIA is acknowledged**
- **HLA-B27 may be helpful in the appropriate clinical setting, namely when spondyloarthritis is suspected**



HLA-B27

The experts acknowledged the current lack of evidence for the practical utility of genetics in UPIA. However, based on their clinical experience, they chose to highlight that HLA-B27 may be helpful in the appropriate clinical setting, namely when spondyloarthritis is suspected.

Summary

- **A wide number of genetic tests have been studied in rheumatoid arthritis**
- **There is some evidence for the shared epitope in predicting a diagnosis of RA or a particular prognosis, but its value in the evaluation of patients with UPIA is less clear**
- **HLA-B27 may have a role in the evaluation of patients with UPIA in particular circumstances**

Summary

•A wide number of genetic tests have been studied in rheumatoid arthritis

•There is some evidence for the shared epitope in predicting a diagnosis of RA or a particular prognosis, but its value in the evaluation of patients with UPIA is less clear

•HLA-B27 may have a role in the evaluation of patients with UPIA in particular circumstances

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