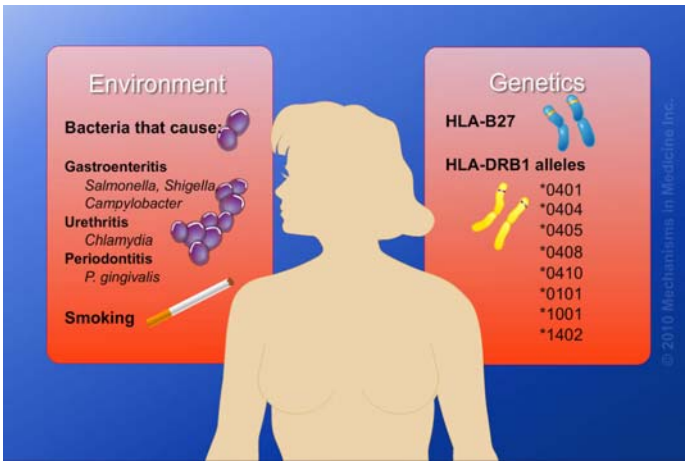
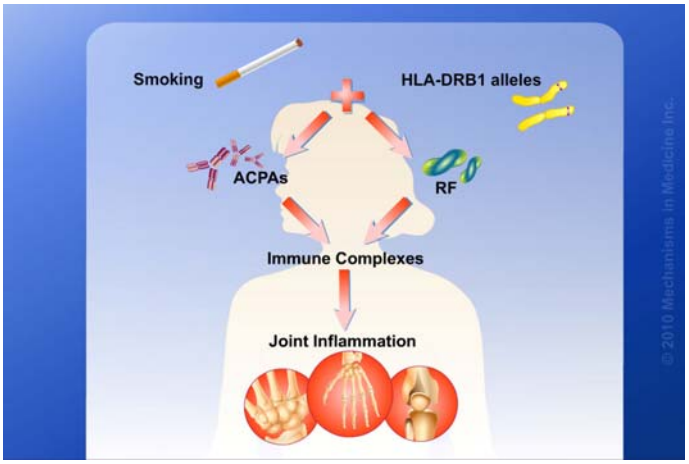
3e Recommendations in Rheumatology
Animation 1: The Role of Environment and Genetics in the Development of Undifferentiated Arthritis



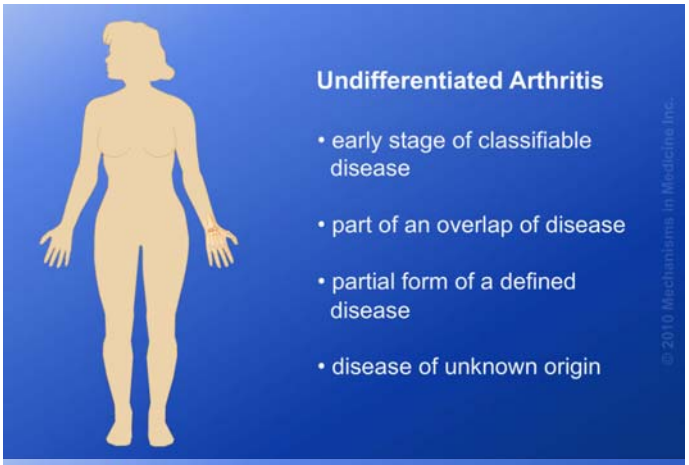
Scene 1 Notes:
Environment and Genetics: Contributors to Undifferentiated Arthritis (UA)

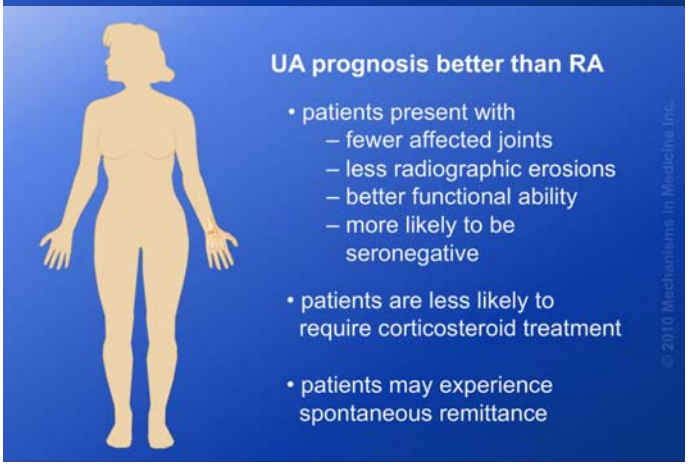
Genetic and environmental risk factors for undifferentiated arthritis (UA) converge to initiate inflammatory joint disease. Environmental risk factors for UA include the bacteria responsible for diseases such as: gastroenteritis, urethritis, and periodontitis.[1(p52)] Cigarette smoking is also an environmental risk factor.[1(p49,52)] Genetic contributors include the HLA-B27 allele, found in 16% of early UA patients,[2(p614)] and the HLA-DRB1 alleles, known as the "shared epitope".[1(p51)] The "shared epitope" has been found in up to 32% of patients with UA.[2(p614)]



Scene 2 Notes:
Gene-Environment Interaction Preceding RA Onset

A close association has been found to exist between HLA-DRB1 alleles and cigarette smoking. This association is hypothesized to lead to an increased expression of anti-citrullinated protein antibodies (ACPAs).[1(p52)] ACPAs are likely the first autoantibodies to develop in patients with UA; followed by the formation of rheumatoid factors (RFs).[1(p55)] The exact gene-environment interaction responsible for the development of RF remains unclear. However, it is recognized that an individual who develops both RFs and ACPAs has the highest risk of developing arthritis in the future through the formation of immune complexes.[1(p55)]

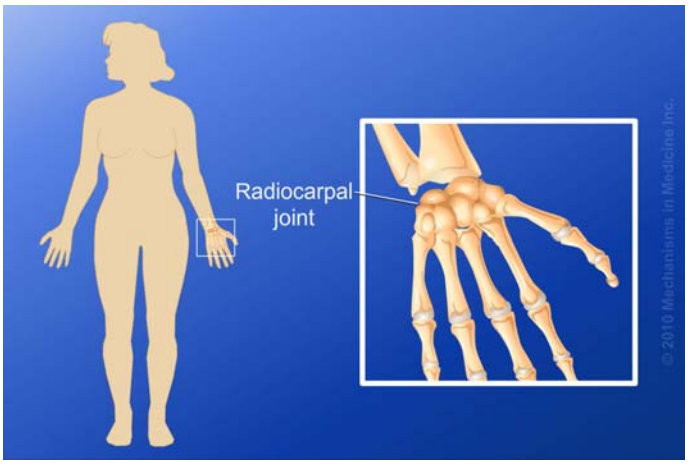




Scene 3 Notes:
Focusing on UA

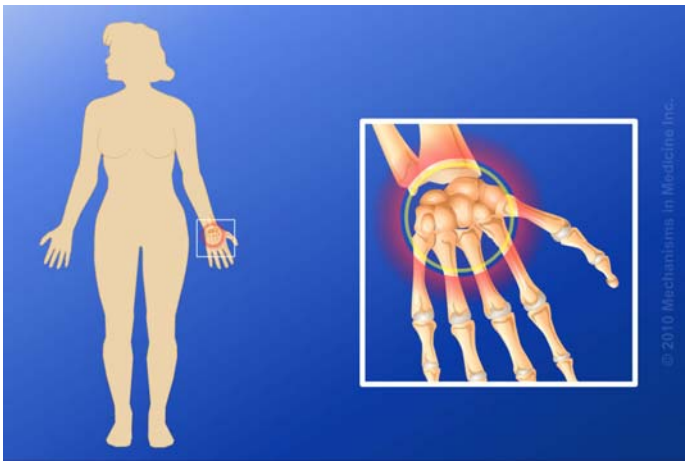
UA envelops a heterogeneous group of recent onset arthritides that are not classifiable within established criteria sets such as those of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).[2(p605)] UA may represent either an early stage of a classified form of arthritis that will eventually be definable; part of an overlap of more than one disease; a partial form of a defined disease; or a disease of unknown origin.[2(p605)]

Overall, UA has a better prognosis than rheumatoid arthritis (RA).[2(p621)] As compared to RA, patients with UA generally present with fewer affected joints, less radiographic erosions, better functional ability, and a greater likelihood of being seronegative.[2(p621)] Patients with UA are also less likely than those with RA to require treatment involving the use of corticosteroids (such as prednisone) or disease modifying antirheumatic drugs (DMARDs). As well, a substantial proportion of patients with UA experience spontaneous remittance.[2(p621)]



Scene 4 Notes:
The Onset of Synovial Inflammation in ACPA/RF Positive RA and UA

In many cases, RFs and ACPAs are serologically detectable in patients prior to the development of RA.[1(p49)]



Scene 5 Notes:
Focus and Zoom-in on the Radio-Carpal Joint

RFs readily form immune complexes with ACPAs. This interaction is a key step in allowing pathogenic autoantibodies, such as ACPA, access to the joint for involvement in the synovial inflammatory process.[1(p55)]

References:

1. El-Gabalawy H. The preclinical stages of RA: Lessons from human studies and animal models. *Best Practice & Research Clinical Rheumatology*. 2009;23:49-58.

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