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Stay ahead of the game: Future approaches to spondyloarthropathies

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Renowned Australian and European clinicians led a Novartis-sponsored symposium held during the 2019 Asia Pacific League of Associations for Rheumatology and Australian Rheumatology Association (APLAR-ARA) congress. The presentation by Professor Schett covered the latest evidence on the pathophysiology of psoriatic arthritis (PsA) and spondyloarthritis (SpA), while the presentations by Professor Brown and Professor Conaghan focussed on cutting edge methods and technologies that are changing the approach to diagnosis, investigation and management of SpA. These technologies include genome wide analysis studies (GWAS), microbial profiling and artificial intelligence (AI) and may decrease the time to diagnosis and ultimately improve patient outcomes. This review summarises each of the presentations.

About the speakers

Prof Georg Schett

Friedrich-Alexander University,
Erlangen-Nürnberg, Germany

Georg Schett is professor of Internal Medicine and since 2006, head of the Department of Medicine 3 – Rheumatology and Immunology at Universitätsklinikum Erlangen, Friedrich-Alexander University Erlangen-Nürnberg in Germany.

Before accepting his position as the chair of the Department of Medicine 3 in Erlangen, he worked as a scientist in the United States of America for one year.

Georg Schett's scientific work includes a broad spectrum of clinical and immunological issues, particularly the molecular basics of immune-inflammatory diseases. His research work led to the understanding of the phenomenon of LE-cells in 2007. He was awarded the renowned START Award in 2002 and established a research group for arthritis in Vienna. In 2008, he initiated in collaboration with colleagues the priority program IMMUNOBONE in Germany, funded by the German Research Foundation (DFG). IMMUNOBONE aims to elucidate the interactions between the skeletal and the immune systems. Since 2015, Prof. Schett has led the DFG collaborative research centre 1181 "Checkpoints for Resolution of Inflammation" in Erlangen. Additionally, he is spoekesperson of the project METARTHROS, funded by the Federal Ministry of Education and Research, which investigates the impact of the metabolism on arthritis. He has published over 650 peer-reviewed papers.

Prof Phil Conaghan

Director of the Leeds Institute of Rheumatic and Musculoskeletal Medicine/University of Leeds, UK

Philip Conaghan MBBS PhD FRACP FRCP is Professor of Musculoskeletal Medicine & Director of the Leeds Institute of Rheumatic and Musculoskeletal Medicine at the University of Leeds. He is a Rheumatologist and Deputy Director of the UK National Institute for Health Research Leeds Biomedical Research Centre for the Leeds Teaching Hospitals NHS Trust. His research spans early translational studies through large late-phase clinical trials, with major interests in understanding pathogenesis and therapeutic response for common arthritides, especially with imaging biomarkers. He is an executive member of the international outcomes group OMERACT and was inaugural Chair of the EULAR Standing Committee on Musculoskeletal Imaging. He is on a number of editorial boards, is co-editor of the most recent Oxford Textbook of Rheumatology and has authored over 500 publications as original research, reviews and book chapters.

Professor Matthew Brown

Adjunct Professor, Queensland University of Technology

Matt Brown is a clinician-scientist who trained initially as a rheumatologist before heading into a career in immunogenetics research. He has made major contributions to the development of gene-mapping approaches in human diseases. He has played a significant role in the development of genomewide association study methodology, leading to the discovery of thousands of genetic variants associated with a wide range of human diseases. His particular interest is in the disease ankylosing spondylitis, where he has helped to develop new treatments by dissecting the genetic causes of the disease. He is deeply interested in the translation of genomics into clinical applications, including in common and rare heritable diseases, and cancers. More recently, he contributed to the development of sequencing approaches to mutation mapping in unrelated cases, enabling early life or prenatal genetic diagnoses for monogenic diseases. He has led international efforts in mapping genes in rheumatic diseases (ankylosing spondylitis, rheumatoid arthritis, scleroderma), osteoporosis, neurological diseases (motor neurone disease, epilepsy), and TB, as well as contributing to efforts in many other diseases. These findings have led to major translational benefits such as the development of IL-23 pathway inhibitors for psoriasis, IBD and AS, as well as many drug development initiatives. He is expert in genomic technologies and has played a leading role in the development and introduction of next-generation sequencing for medical genomics including cancers and heritable diseases.

Professor Brown is a Fellow of both the Australian Academy of Sciences and the Australian Academy of Health and Medical Sciences. In 2016 Matt transitioned from The University of Queensland where he was between 2005-2016 to Queensland University of Technology as Director of Genomics where he hopes to enhance the University's genomics capabilities and continue his research with many exciting opportunities on the horizon both in Australia and internationally. In 2017 he was appointed as a 'Distinguished Professor' or Queensland University of Technology in recognition of his scientific contributions.

Pathogenesis of spondyloarthritis and treatment choice

Professor Georg Schett

Immune-mediated inflammatory diseases can be characterised by the cytokines involved, rather than the organs involved. The key cytokines in psoriatic arthritis (PsA) are IL-17, IL-23 and TNF, while spondyloarthritis (SpA) involves mainly IL-17 and TNF.

The self-limited inflammatory response is a normal response and involves the activation of inflammatory mediators in response to a trigger, such as mechanical stress, disturbed barrier function or infection, followed by resolution of inflammation and repair of any damage.[1] When resolution and repair don't occur or are interrupted, chronic inflammation occurs and can lead to diseases such as SpA, PsA and rheumatoid arthritis (**Figure 1**).[1]

In the psoriatic diseases, which are an exaggerated inflammatory response to stress, a trigger can move the patient from the "psoriatic state" to enthesitis. Enthesitis occurs prior to the manifestation of symptoms. For example patients with psoriasis but no symptoms of PsA had subclinical enthesitis, measured using the Glasgow Ultrasound Enthesitis Scoring System (GUESS), and when adjusted for BMI, the difference in GUESS in patients with psoriasis compared with healthy controls was statistically significant (7.5 vs 2.8; P<0.0001).[2] Enthesitis can be at axial or non-axial sites and is a hallmark of spondylitis, arthritis and nail disease.

Enthesitis is associated with extensive local tissue responses. It has been proposed that there are 4 steps involved in mechanoinflammation at entheseal sites:[3]

1. Mechanical injury followed by stress sensing at the bone-entheseal junction
2. Vasodilation, transcortical vessel activation and osteitis
3. Entheseal inflammation involving cell efflux through transcortical vessels and enthesitis formation
4. New bone formation as a result of mesenchymal proliferation and osteoblast differentiation.

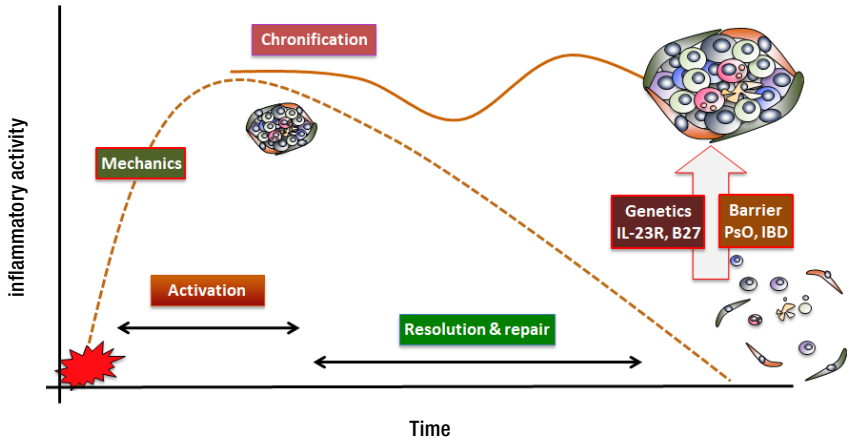


Figure 1. The spondyloarthritis inflammation concept.[1]
IBD = inflammatory bowel disease; **IL23R** = interleukin-23 receptor; **PsO** = psoriasis.

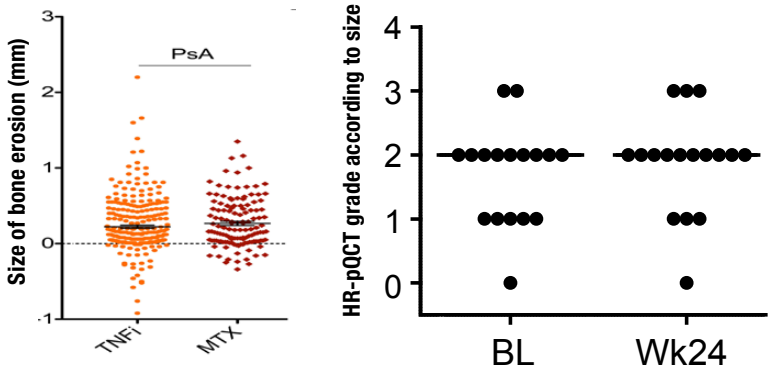


Figure 2. Enthesiophyte formation in patients with psoriatic arthritis treated with methotrexate (MTX) or TNF inhibitor after one year (left) or IL-17 inhibitor at baseline and after 24 weeks of treatment (right). Note that the graphs are from different studies and therefore direct comparisons cannot be made.[4,11]
BL = baseline; **HR-pQCT** = high-resolution peripheral quantitative computer tomography; **MTX** = methotrexate; **PsA** = psoriatic arthritis; **TNFi** = TNF inhibitor; **Wk** = week.

IL-17 is important in the development of enthesitis, and blockade of IL-17 in very early PsA patients (psoriasis plus arthralgia and subclinical inflammation or joint damage) led to improvements in pain, tender joint count, PsA magnetic resonance imaging scoring system (PsAMRIS) total score and synovitis subscore.[4] Importantly, if the development of enthesitis can be stopped early on then it is likely that damage to the joint can be prevented.

It is becoming clearer what is involved in the transition phase from psoriasis to PsA. Nail disease is a form of enthesitis and is a risk factor for the development of PsA in psoriasis patients.[5-7] Nail disease and distal interphalangeal disease are a feature of enthesitis; 100% of PsA patients with nail involvement show osteitis of the distal phalanx and 60% of PsA patients with nail involvement show distal interphalangeal arthritis.[8,9]

Enthesial disease is the primary musculoskeletal pathology in psoriasis. It can be seen at the time of the first skin lesion and prior to the first swollen joint in psoriasis patients without any symptoms of PsA.[10] This is known as the "Deep Koebner Phenomenon" at enthesial sites and is associated with new bone formation at the site.

Enthesiophyte formation is a consequence of chronic enthesitis in PsA patients.[11] Enthesiophytes do not depend on age, and the number of enthesiophytes are higher in PsA and psoriasis patients than in healthy controls.[12]

Sequential scans of the metacarpophalangeal joints of methotrexate or TNF inhibitor-treated PsA patients over one-year showed progression of enthesiophyte growth (**Figure 2**).[11] Scans in secukinumab-treated PsA patients did not show any progression over 6 months (**Figure 2**).[4]

The choice of treatment in PsA and SpA patients should take enthesitis into account and should also be based on the presentation ('gestalt') of the individual patient. Based on the mechanism of action of the available biologics for SpA, IL-17 inhibition may be considered preferable to TNF inhibition when there is skin disease and enthesitis. Conversely, TNF inhibition may be preferable to IL-17 inhibition when uveitis or inflammatory bowel disease (IBD) are present.

Take home messages

- Exaggerated mechanoinflammation is a key mechanistic factor in SpA.
- Early musculoskeletal involvement in psoriasis includes structural changes.
- IL-17 is a key mediator in enthesial inflammation.
- The pattern of organ involvement in individual patients should be a consideration in the treatment decision.

AxSpA classification and treatment options - the gut microbiome and genetics

Professor Matt Brown

Magnetic resonance imaging (MRI) scanning has greatly improved the ability to diagnose AS before radiographic change. However, at a population level it hasn't resulted in earlier diagnoses. Twenty years ago, the diagnostic delay for ankylosing spondylitis (AS) was approximately 8 years, and this delay has not improved despite the availability of MRI and the development of guidelines and recommendations for diagnosis.[13,14]

The benefits of early diagnosis to the patient are numerous and include:

- A correct diagnosis
- The avoidance of harmful or inappropriate treatments
- A potential delay to ankylosis.

An AS population screening method would therefore be valuable and could be used to diagnose cases, screen populations, predict natural history, treatment response or toxicity, classify diseases and assist with genetic counselling.

Genome-wide association studies (GWAS) can identify genes involved in disease and have less variance than other gene mapping and heritability techniques. The method is based on searching the genome for small variations known as single nucleotide polymorphisms (SNPs) that occur more frequently in people with a particular disease than in people without the disease. The power in this method is that hundreds or thousands of SNPs can be analysed simultaneously to identify genes that may contribute to a person's risk of developing a certain disease. While using more markers captures more heritability and increases the performance of the method, it also increases the number of false positives.[15]

There are already large databases containing GWAS SNP microarray data. For example, approximately 120 million people have deposited their data in the NHGBRI-EBI GWAS catalogue.[16] In the US, 12 million people have had their GWAS analysed and more than 1 million have deposited their data in the public repository, GEDmatch.[17] The NHS in the UK has announced whole genome sequencing will be completed for 5 million people by 2024.[18]

GWAS has already identified SNPs related to several complex conditions including diabetes, heart abnormalities and Parkinson's disease and could help to identify genetic variations that affect treatment response.

In the field of AS, polygenic risk scores have been developed. For example, Li et al performed GWAS using thousands of SNPs in a dataset containing approximately 37000 samples from AS patients and healthy controls in Europe and East Asia.[19] Receiver Operating Characteristic (ROC) analysis was used to assess polygenic risk scores, where an area under the curve (AUC) of 0.7 to 0.8 is considered useful (**Figure 3**). For the European AS subset, the polygenic risk score AUC was 0.92 (83% sensitivity, 92% specificity). Using imputed HLA-B27 status alone gives an AUC of 0.87 (**Figure 3**).[19] The European AS polygenic risk score compared well with MRI-based prediction which is estimated to have an AUC of 0.89.[20]

An investigation of the predictive ability of the AS polygenic risk score and B27 status was undertaken.[19] The prevalence of AS in the general population is approximately 0.5%. Using a polygenic risk score, the top 15-20% patients will have more than a 10% chance of developing AS. Using B27, 8% of the population carry B27 and of those, the risk of getting AS is 5%. This means it provides a positive predictive value of 5% which is relevant to only 8% of the community. Therefore, the AS polygenic risk score performs much better. In terms of negative predictive value of the polygenic risk score, 91% of the population have a less than 21% chance of developing AS, is better than based on B27 status.

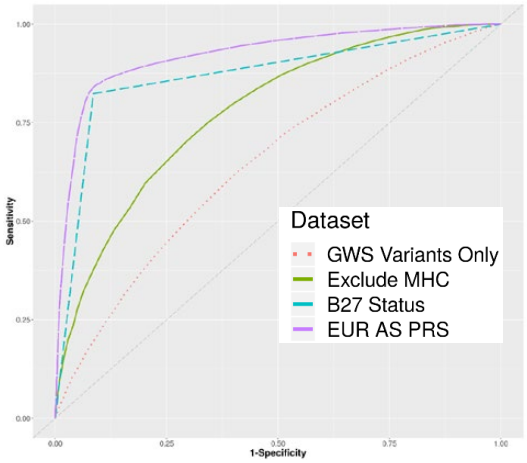
Although AS can be a genetic condition, it is not entirely heritable, and the environment plays an important role. Microbial profiling is a method that can predict AS based on the fact that the gut microbiome in AS patients is different to that in healthy controls.[21,22] For example AS patients have a higher abundance of Lachnospiraceae (P=0.001) Ruminococcaceae (P=0.012), Rikenellaceae (P=0.004), Porphyromonadaceae (P=0.001), and Bacteroidaceae (P=0.001) compared to healthy controls, and a decreased abundance of Veillonellaceae (P=0.01) and Prevotellaceae (P=0.004).[23]

In terms of treatment response, there have been studies demonstrating that clinical response to treatment is influenced by the gut microbiome. In patients with solid tumours treated with PD-1 and PD-L1 inhibitors, non-responders were more likely to have been treated with antibiotics within 2 months before, or 1 month after, the first administration of PD-1/PD-L1 and had a less diverse microbiome.[24] Transfer of the non-responder and responder microbiome to PDX mice led to concordant differences in survival.[25] Microbiome changes associated with response may be related to changes in tumour infiltrating lymphocyte and Th17 lymphocyte activity.

In diagnosis, gut microbial profiling can distinguish cases from controls in many diseases, and it may be possible for a single test to assist in the diagnosis of multiple conditions. Microbial profiling will also provide additive information that can be used in conjunction with genetic tests and polygenic risk scores. The utility of microbial profiling prior to and at different stages of diseases, and in relation to ethnicity, diet and environment still needs to be assessed.

Take home messages

- Both genetics and microbiome profiling have a clinically significant discriminatory capacity for SpA.
- These tests could soon be a cost-effective option for population screening and early disease diagnosis in the clinic.
- Large well-characterised datasets will be required to test the utility of genetics and microbiome profiling in other applications, such as predicting treatment response.



Cohort	Sensitivity	Specificity	AUC
GWS Signal Only	62.7%	58.9%	0.65
European-noMHC	59.7%	79.8%	0.78
European-B27	82.4%	91.5%	0.87
European AS PRS	83.0%	92.3%	0.92
MRI[1]	85.0%	92.0%	0.89
CRP[2]	50.0%	80%	0.70

1.Diekhoff et. al ARD 2017
2.Rudwaleit et. al ARD 2014

Figure 3. Comparison of AS prediction performance using GWAS, MRI and C-Reactive Protein[19,20]

AS PRS = ankylosing spondylitis polygenic risk score; **AUC** = area under the curve; **CRP** = C-reactive protein; **EUR** = European; **GWS** = genome-wide significance; **MHC** = major histocompatibility complex; **MRI** = magnetic resonance imaging

How you will be able to leverage artificial intelligence for faster MRI interpretation and data-led diagnosis, prognosis and treatment choice direction

Professor Philip Conaghan

There are a range of imaging technologies that are currently used in patients with PsA and rheumatoid arthritis. These methods can detect osteitis, enthesitis and subclinical disease, and are facilitating the understanding of the pathogenesis of the diseases with the aim of being able to detect the diseases earlier. MRI can also be quantitative and can help to measure the response to treatment.

Despite the availability of sensitive imaging technology, patients with axial spondyloarthritis (axSpA) are not being diagnosed any quicker. And even though MRI can be quantitative and can detect osteitis and subclinical disease, it does have issues including difficulty distinguishing between PsA and osteoarthritis.

While whole body MRI can help to distinguish between SpA and PsA based on the distributions of inflammatory and structural lesions, it is not routinely used in clinical practice due to a fairly low resolution and the longtime requirements for patients.[26]

The studies and investigations that have been conducted in rheumatoid arthritis, SpA and osteoarthritis patients have led to the development of disease-specific recommendations for the use of imaging in the diagnosis and clinical management of each of the conditions.[27-29]

There is potential to better use the information contained in digital images for the diagnosis and treatment of diseases. Digital images contain information that is not perceptible by human observers, and hundreds of parameters can be extracted using computational methods. This information can then be used to determine how the different parameters relate to each other temporally and spatially and how the parameters manifest in the disease process leading to the identification of biomarkers.

Artificial intelligence (AI) is the development of computer systems that can perform tasks that would normally require human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages. It is a broad area that encompasses knowledge, robotics, perception processing and machine learning among other things.

Machine learning is a subset of artificial intelligence and provides the computer the ability to self-learn without being explicitly programmed. There are 3 types of machine learning:

1. Supervised – task driven where the computer learns to predict the next value
2. Unsupervised – unlabelled data trains the algorithm and the computer learns to identify clusters
3. Reinforcement – where the computer learns from mistakes.

Deep learning is a subset of machine learning that can discover intricate structures in large data sets using specific algorithms based on processing layers. This type of machine learning has brought about breakthroughs in processing images, video, speech and audio.

There are several challenges in the use of machine learning for human disease. These include patient consent and confidentiality, adequate datasets (size and heterogeneity of disease), robust testing of diagnostic ability, and patient and clinician concerns about the technology.[31]

Despite these challenges, machine learning applications are currently being developed in several diseases. Supervised machine learning has been used to interpret X-rays in tuberculosis patients and diagnose retinopathy from optical coherence tomography (OCT) scans, and unsupervised learning has been used to identify and label transcription start sites in genetic sequences.[31-33]

In the area of bone imaging, statistical shape modelling using radiographs with multiple points defined by a human reader in two dimensions has found a relationship between the shape of the distal femur and proximal tibia and knee osteoarthritis.[34] Likewise, in a study of hips, statistical shape modelling from radiographs found an association between hip shape and radiographic osteoarthritis, total hip replacement, hip pain, effusion-synovitis, bone marrow lesions, muscle strength, and hip structural changes.[35]

The application of machine learning to 3D bone shape is also possible and the AAM model has been used to determine the undulating 3D surfaces of bone from 3D MRI scans. In these scans, computers were taught to recognise edges, and 100,000 consistent landmarks were used to define and quantify the 3D bone shape of the femur, tibia and patella in large cohorts.

The ability to identify and quantitate bone shape and to identify image-based parameters that predict the risk of developing a certain condition is now possible. For example, change in medial femur area was shown to be more sensitive in predicting osteoarthritis than cartilage thickness of the JSM.[36] Bone change followed a characteristic spatial pattern, involving both addition of bone around the cartilage plate, and an overall widening and spreading of all bones in the knee, particularly on the medial side.[36] In another study, the whole joint (tibia, femur, and patella) 3D bone shape vector had the strongest magnitude of effect in determining which knees would develop radiographic osteoarthritis 12 months later, and bone shape at baseline, often several years before incidence, predicted later osteoarthritis.[37]

The power of AI technology is in the automation, where the computer can extract and interpret the digital information, thereby decreasing the manual labour required. This makes the technology much more suitable for biomarker detection and therefore earlier diagnosis and assessing response to treatment.

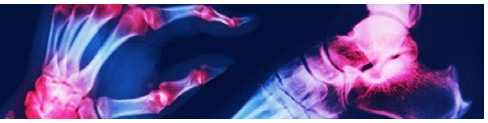
In addition to applications in clinical trials and clinical practice, efforts are underway to use machine-learning in areas such as telerheumatology, where the patient uses a device (for example a pocket-sized ultrasound, a smartphone App or a wearable device) and the data is transferred to a remote expert or non-expert with AI capabilities for the analysis and interpretation.[38]

Take home messages

- Increasingly powerful image analysis is possible.
- Advances in imaging technology and the application of machine learning can help improve phenotypes and identify biomarkers.
- Machine learning will have increased applications in research and may have future clinical applications in telemedicine in conjunction with mobile phones, wearable sensors, and virtual reality.

References

1. Schett G and Neurath MF. Resolution of chronic inflammatory disease: Universal and tissue-specific concepts. Nat Commun. 2018; 9:3261.
2. Gisondi P, et al. Lower limb enthesopathy in patients with psoriasis without clinical signs of arthropathy: a hospital-based case-control study. Ann Rheum Dis. 2008;67:26–30.
3. Schett G, et al. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol. 2017;13:731–41.
4. Kampylafka E, et al. Resolution of synovitis and arrest of catabolic and anabolic bone changes in patients with psoriatic arthritis by IL-17A blockade with secukinumab: results from the prospective PSARTROS study. Arthritis Res Ther. 2018;20(1):153.
5. Eder L, et al. The incidence and risk factors for psoriatic arthritis in patients with psoriasis: A prospective cohort study. Arthritis Rheumatol. 2016;68(4):915-23.
6. Wilson FC, et al. Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. Arthritis Rheumatol. 2009;61:233–9.
7. Soltani-Arabshahi R, et al. Obesity in early adulthood as a risk factor for psoriatic arthritis. Arch Dermatol. 2010;146:721–6.



8. Scarpa R, et al. Nail and distal interphalangeal joint in psoriatic arthritis. J Rheumatol. 2006;33:1315–9.
9. McGonagle D, et al. The nail as a musculoskeletal appendage--implications for an improved understanding of the link between psoriasis and arthritis. Dermatology. 2009;218:97-102.
10. Simon D, et al. Analysis of periarticular bone changes in patients with cutaneous psoriasis without associated psoriatic arthritis. Ann Rheum. 2016;75:660-6.
11. Finzel S, et al. Bone anabolic changes progress in psoriatic arthritis patients despite treatment with methotrexate or tumour necrosis factor inhibitors. Ann Rheum Dis. 2013;72(7):1176-81.
12. Simon D, et al. Simultaneous quantification of bone erosions and enthesiophytes in the joints of patients with psoriasis or psoriatic arthritis - effects of age and disease duration. Arthritis Res Ther. 2018;20(1):203.
13. Feldtkeller E, et al. Scientific contributions of ankylosing spondylitis patient advocacy groups. Curr Opin Rheumatol. 2000;12(4):239-47.
14. Sykes MP et al. Delay to diagnosis in axial spondyloarthritis: are we improving in the UK? Rheumatol. 2015;54(12):2283-4.
15. Lall K, et al. Personalized risk prediction for type 2 diabetes: the potential of genetic risk scores. Genet Med. 2017;19:322–9.
16. GWAS Catalogue. Available at www.ebi.ac.uk/gwas. Accessed May 2019.
17. The Database Geek. Database sizes - September 2018 Update. Available at https://thednageek.com/database-sizes-september-2018-update/. Accessed May 2019.
18. Genomics England. Secretary of State for Health and Social Care announces ambition to sequence 5 million genomes within five years. Available at https://www.genomicsengland.co.uk/matt-hancock-announces-5-million-genomes-within-five-years/. Accessed May 2019.
19. Li Z, et al. Genetic risk score prediction in ankylosing spondylitis. Arthritis Rheumatol. 2018;70(suppl 10).
20. Diekhoff T, et al. Comparison of MRI with radiography for detecting structural lesions of the sacroiliac joint using CT as standard of reference: results from the SIMACT study. Ann Rheum Dis. 2017;76(9):1502-8.
21. Costello ME, et al. Brief Report: Intestinal dysbiosis in ankylosing spondylitis. Arthritis Rheumatol. 2015;67(3):686-91.
22. Yin J, et al. Shotgun metagenomics reveals an enrichment of potentially cross-reactive bacterial epitopes in ankylosing spondylitis patients, as well as the effects of TNFi therapy and the host's genotype upon microbiome composition. BiorXiv. 2019;
23. Thomas GP, et al. Genetic diagnostic profiling in axial spondyloarthritis: a real world study. Clin Exp Rheumatol. 2017;35(2):229-33.
24. Routy B, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 2018;359(6371):91-7.
25. Gopalakrishnan V, et al. Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. Science. 2018;359(6371):97-103.
26. Poggenborg R, et al. Magnetic resonance imaging for diagnosing, monitoring and prognostication in psoriatic arthritis. Exp Rheumatol. 2015;33(Suppl. 93):S66-9.
27. Colebatch AN, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. Ann Rheum Dis. 2013;72(6):804-14.
28. Mandl P, et al. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. Ann Rheum Dis. 2015;74(7):1327-39.
29. Sakellariou G, et al. EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis. Ann Rheum Dis. 2017;76(9):1484-94.
30. Ting DSW, et al. Artificial intelligence and deep learning in ophthalmology. Br J Opthalmol. 2019;103(2):167-75.
31. Towards Data Science. Machine Learning For Beginners. Available at: https://towardsdatascience.com/machine-learning-for-beginners-d247a9420dab. Accessed November 2019
32. Lakhani P, Sundaram B. Deep learning at chest radiography: Automated classification of pulmonary tuberculosis by using convolutional neural networks. Radiology. 2017;284(2):574-82.
33. Qu Z, et al. Visual analytics of genomic and cancer data: A systematic review. Cancer Inform. 2019;18:1176935119835546.
34. Wise BL, et al. Bone shape mediates the relationship between sex and incident knee osteoarthritis. BMC Musculoskelet Disord. 2018;19:331.
35. Ahedi HG, et al. Hip shape as a predictor of osteoarthritis progression in a prospective population cohort. Arthritis Care Res. 2017; 69(10):1566-73.
36. Bowes MA, et al. Osteoarthritic bone marrow lesions almost exclusively colocate with denuded cartilage: a 3D study using data from the Osteoarthritis Initiative. Ann Rheum Dis. 2015; 75(10):1852-7.
37. Neogi T, et al. Magnetic resonance imaging-based three-dimensional bone shape of the knee predicts onset of knee osteoarthritis: data from the osteoarthritis initiative. Arthritis Rheumatol. 2013;65(8):2048-58.
38. Seetharam K, et al. Application of mobile health, telemedicine and artificial intelligence to echocardiography. Echo Res Prac. 2019; doi:10.1530/ERP-18-0081.

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