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Imaging in rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, and osteoarthritis: An international viewpoint on the current knowledge and future research priorities

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Introduction

Increasing evidence of the impact of imaging on the management of rheumatic diseases has resulted in the publication of the first European League Against Rheumatism (EULAR) recommendations for the use of imaging in the diagnosis and management of rheumatoid arthritis (RA), spondyloarthritis (SpA), and osteoarthritis (OA) in the previous years (1-3). The widespread use of imaging in clinical practice and, more recently, clinical trials means that a review of its role is timely (4-9).

In this context, an international group of imaging experts led two annual meetings attended by imaging practitioners to discuss recent advances in imaging in rheumatology. Ultrasound (US), magnetic resonance imaging (MRI), and conventional radiography (CR) were the main imaging modalities discussed. The experts not only focused on clinical practice but also considered where imaging could enhance clinical trial development. The experts presented summaries of the key learnings for clinical practice, and in collaboration with the attending imaging practitioners, identified the possible research gaps to fulfill (what is unknown/should be known) to further inform clinical practice and future clinical trials based on what is known. The results of these discussions are summarized in this article, serving as a viewpoint for a future clinically oriented research agenda in the field of imaging in the abovementioned diseases.

Rheumatoid arthritis

What is known?

The current knowledge provides a strong rationale for the application of US and MRI to RA diagnosis and management (Table 1).

Ultrasound is more sensitive than clinical examination for identifying minimal synovitis (10, 11). Both US and MRI can detect synovitis (usually low volume), and occasionally, erosions in individuals without inflammatory arthritis or symptoms (12, 13). These findings likely represent mechanically induced problems and OA, but remind us that diagnostic tests should be used in clinical context. However, US can improve the certainty of a diagnosis of RA above the clinical criteria (14, 15), and can be used to predict the progression to
Table 1. US and MRI in RA (current knowledge)

| What is known?                                                                 |
|------------------------------------------------------------------------------|
| • US and MRI are more sensitive than clinical examination for identifying   |
| minimal synovitis and can aid diagnosis when there is diagnostic doubt.      |
| • US- and MRI-detected inflammation can predict progression to clinical RA   |
| from undifferentiated inflammatory arthritis and for ACPA-positive, non-specific symptoms. |
| • Subclinical synovitis detected by US and MRI predicts subsequent damage and |
| flare, even when clinical remission is present.                              |
| • US and MRI may be used to predict treatment response and be useful in   |
| monitoring disease activity.                                                |
| • MRI is more responsive to change in joint damage than CR and can assist in |
| monitoring of disease progression.                                          |
| • MRI is more sensitive than clinical examination and can detect bone marrow |
| edema, which is a strong predictor of subsequent radiographic progression in |
| early RA.                                                                    |

Clinical RA from undifferentiated inflammatory arthritis and for anti-citrullinated protein antibody (ACPA)-positive, non-specific symptoms (16-18), US-detected synovitis predicts subsequent damage and flare (19), and prompt treatment has been shown to reduce inflammation, thereby limiting structural damage (20, 21).

Previous studies show the discordance between clinical and US evaluation in patients in Disease Activity Score 28 joints (DAS28) remission (22, 23). US-detected synovitis and joint damage can be considered for the prediction of further joint damage (24), even when clinical remission is present, although some studies suggest that the agreement is higher when remission is assessed by the Boolean criteria (25). Moreover, US-detected synovitis may be more predictive of a therapeutic response than clinical features of disease activity (26, 27).

How US may be applied in RA clinical management was recently discussed in a consensus-based proposal from international US experts who developed five algorithms for the use of US in diagnosis, treatment monitoring, and remission (28). These five algorithms recapitulate the recent data in literature and the actual use in clinical practice. US is usually used to confirm the presence of an active synovitis, permitting for an early classification of patients with suspecting arthritis. The optimal set of joints to be scanned remains debatable, though most studies propose the inclusion of the small joints of the hands and feet as a minimum, as their responsiveness was recently demonstrated in a multicenter therapeutic trial (27, 29). Despite the amount of evidence supporting the interest to use US for guiding treatment decision and achieve clinical remission, two recent studies have questioned the added value of US in a treat-to-target approach of patients with very early RA. In these studies, both (DAS28-driven and US-driven) approaches showed the same efficacy in achieving DAS-derived remission (4, 5). The conclusions claimed the lack of utility of US; however, major methodological issues recorded in these trials have an impact on their interpretation. These methodological issues include the absence of blinding in performing US, the non-application of US to every patient but only to a selected group, and other technical issues (30).

Magnetic resonance imaging is more sensitive than clinical examination in the detection of synovitis (1), and can uniquely detect bone marrow edema (osteoitis), which is a strong predictor of subsequent radiographic progression in early RA (31, 32). Subclinical MRI inflammation predicts clinical arthritis with subsequent erosive progression independently of other factors, such as ACPA (22, 23, 33, 34). The relevance of MRI-detected inflammation to important patient outcomes has been demonstrated in a cross-sectional study (35) involving 514 patients with early arthritis and in two longitudinal studies involving 501 patients with methotrexate naive RA, reporting that MRI-detected inflammation was associated with functional disability (36).

Thus, MRI is a tool that can improve the certainty of a diagnosis of RA (37, 38), predict progression to clinical RA from undifferentiated inflammatory arthritis (39), with evidence that it is more responsive to change in joint damage at earlier time points than CR (40), and detect inflammation that predicts subsequent joint damage (41, 42), even in the presence of clinical remission.

What is unknown/should be known?

Despite the abundance of research on the potential benefits of US and MRI in RA clinical management, many critical questions remain unanswered and should be the focus for future research (Table 2).
Table 2. Clinical practice research agenda for US and MRI in RA

What is unknown and should be known?

- What is the optimal set of joints to be scanned by US, and how frequently can clinical examination be enhanced?
- What is the optimal selection of joints and timing of MRI for the assessment of diagnosis and prognosis in RA?
- What are the thresholds of abnormality of imaging-detected inflammation to guide intervention?
- What are further data on MRI diagnostic value for patients not fulfilling the American College of Rheumatology/EULAR 2010 classification criteria?
- What is the role of MRI in predicting response to therapy and in defining remission?
- What is the cost-effectiveness of using US in diagnosis, treatment monitoring, and remission and of MRI in clinical practice?
- What is the added value of US in a tight control regimen in established RA?

Table 3. Clinical trials in RA (research agenda)

What is unknown and should be known?

- What is the value of MRI-detected damage as an endpoint in RA clinical trials?
- What is the added value of further trials based on MRI assessment of the joints other than the hand, which in most studies have been conducted?
- What cutoff values for clinical remission assessed by MRI and US (and their correlation) should be used in clinical trials?
- What is the role of MRI in predicting response to therapy and in defining remission?
- What is the cost-effectiveness of using US in diagnosis, treatment monitoring, and remission and of MRI in clinical practice?
- What is the added value of US in a tight control regimen in established RA?

The most critical research priority for imaging practitioners is how to incorporate US and MRI into routine practice to provide added value for RA management. Additionally, payers will want to know if this is cost-effective. In this context, a research agenda for clinical practice should focus on which joint sets and scoring systems are optimal to use for which purpose (diagnosis, monitoring, and remission) and which thresholds of imaging-detected inflammation, especially in low disease activity states, to guide intervention. This is a difficult task particularly considering that in many countries significant barriers to using US and MRI in practice exist (e.g., cost, time, and access/machine availability). Robust evaluations of the added value of using US for clinical management in established RA populations using a blinded study design are needed. Research needs to be tailored to better understand which subgroups/patient types can benefit most from US and MRI evaluations in a resource-limited environment.

Table 3 presents the proposal for a research agenda for future RA clinical trials. For MRI, early erosion progression has been documented as a valid measure of structural damage that could decrease sample size and study duration if it was used as an endpoint in RA clinical trials (6, 43-45), but further corroborative research is needed if MRI is to gain regulatory agencies’ acceptance.

A greater sensitivity of MRI structural outcome measures and of MRI-detected inflammation as an outcome measure relevant for the development/approval of new drugs is necessary. Magnetic resonance imaging trial outcomes will be enhanced by the advent of evolving image analysis techniques, such as those involving supervised machine learning (RAMRIQ), recently shown to be more responsive than both RAMRIS and DCMRI (46).

In addition, further evaluation of MRI-detected tenosynovitis scoring could lead the way for including this measure as a component of RAMRIS for the assessment of tenosynovitis of the hand in RA clinical trials. Trials using MRI assessment of the joints other than the hand joints are also a data gap.

In addition to these research priorities, our understanding of the development of RA pathology is being enhanced by newer imaging techniques. For example, micro-computed tomography (CT) studies have demonstrated that structural bone damage can be detected before the clinical onset of arthritis in individuals with ACPA (47). This suggests that bone damage may not be an exclusive result of synovitis.

Moreover, micro-CT imaging has revealed more profound changes in the trabecular bone architecture in seropositive RA than in seronegative RA and psoriatic arthritis (PsA) (48), suggesting that seropositive RA could be phenotypically distinct.

Conclusion

In RA clinical trials, imaging provides an objective measurement of damage and MRI and US both enable early objective detection of disease activity that will predict subsequent erosion progression. MRI with central reading is well placed to provide smaller number, shorter duration trials proving therapeutic efficacy, whereas US studies in multicenter trials are now emerging. In clinical practice, X-ray and US are usually more feasible, though US can provide assessment of inflammation and in multiple joint areas. Modern imaging should be used as an adjunct to clinical decision-making where there is uncertainty of RA diagnosis or difficulties in treatment planning. In this context, although there are limited data from studies, US, for example, may be useful in 10%-20% of patients. This may change as we move to earlier diagnosis in preclinical, autoantibody-positive patients.

Psoriatic arthritis

What is known?

The heterogeneous inflammatory involvement in PsA (intra-/extra-articular) and the resulting challenges of clinical assessment result in a need for better assessment methods.

Modern imaging may aid in the diagnosis, prognosis, and monitoring of therapeutic response in PsA by providing sensitive measures of the extent of disease (detection of subclinical synovitis and enthesitis) and for monitoring inflammation and damage. The evidence base for these roles is not nearly as extensive as for RA but is improving. Table 4 summarizes the key advances relevant to clinical practice to date.

Ultrasound can visualize the peripheral joints and entheses involved with PsA and could aid
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Table 4. US and MRI in PsA (current knowledge)

What is known?

- US visualizes the peripheral joints and entheses and is better than clinical examination in detecting entheseal abnormality.
- US studies have shown significant subclinical enthesitis and synovitis in patients with psoriasis without arthritis.
- US-detected subclinical enthesitis in psoriasis may differ from subclinical enthesitis in PsA (patients with PsA having more power Doppler).
- Baseline enthesitis and persistent synovitis or enthesitis by US after 6 months of therapy predicts subsequent structural damage.
- DAPSA and Boolean definitions of remission appear to be the best predictors of US remission.
- MRI visualizes all relevant inflammatory and structural pathologies of PsA and is more sensitive to inflammatory and destructive changes than X-ray and clinical examination.
- Whole-body MRI can assess inflammation and structural damage by detecting multisite enthesitis, peripheral synovitis, and tenosynovitis and axial involvement.

Table 5. Research agenda for US and MRI in PsA

What is unknown and should be known?

- What is the role of US- or MRI-detected subclinical enthesitis as predictor for the development of PsA in patients with psoriasis?
- What are the optimal joint sets for screening/diagnostic investigation by US/MRI?
- What is the predictive value of US monitoring compared with clinical/laboratory monitoring?
- What is the predictive capability of US-detected inflammatory patterns in PsA therapy response?
- What is the prognostic value of subclinical US/MRI abnormalities in PsA remission?
- What is the predictive value of MRI findings for therapeutic response and subsequent damage progression in PsA?
- What is the optimal MRI monitoring strategy in PsA clinical trials?
- What is the utility of novel MRI techniques (whole-body MRI, dynamic MRI, and other quantitative methods) in PsA clinical trials and practice?
- How can dactylitis and enthesitis be better defined by MRI, and how should these features be assessed in PsA clinical practice?

A recent study reported that power Doppler US-detected synovitis (PDUS) was a strong predictor of short-term flare of disease in patients with PsA in clinical remission; 65% of patients with at least one joint with PDUS synovitis at baseline had a disease flare during follow-up compared with 5.9% without baseline PDUS synovitis (relative risk = 11, 95% confidence interval 2.8-44, p < 0.001) (60).

Magnetic resonance imaging visualizes all the relevant pathologies of PsA (inflammatory in the soft tissues and bone, as well as structural damage) and is more sensitive to inflammatory and destructive changes than X-ray and clinical examination (61). Certain findings, such as extracapsular inflammation and enthesis, are very characteristic for PsA, although not pathognomonic (62). Data on the added value of identifying peripheral PsA and the prognostic value of MRI in PsA are limited, but a preliminary study suggests a potential worth exploring.

Studies have found a higher frequency of arthritic and entheseal changes with MRI in patients with psoriasis than in healthy subjects (8, 63, 64), and a recent study showed that patients with psoriasis with tender joints and MRI inflammation had a 56% risk of PsA within 1 year compared with a 15% risk in patients with no tender joints and no MRI inflammation (65).

A relationship between MRI bone edema and subsequent CT progression has been reported (66), but overall, whether any MRI features can predict treatment response and/or subsequent joint damage in PsA remains to be determined. Moreover, there are no general rules for which joints to assess for activity and damage, due to the heterogeneous presentation of the disease. However, the most validated scoring system, Outcome Measures in Rheumatology (OMERACT) Psoriatic Arthritis Magnetic Resonance Image Score, showed good overall intrareader agreement in the hand and foot and inflammatory feature scores responsive to change (67-69).

Whole-body MRI is a novel imaging method that has been examined in small groups of patients with PsA (70, 71). Initial data suggest moderate agreement between MRI-detected enthesitis and clinical examination, raising the
possibility of a whole-body MRI enthesitis index as a potential tool for assessment of disease activity (72).

The OMERACT MRI in the Arthritis Special Interest Group has conducted a literature review and suggested consensus MRI definitions of important pathologies and a preliminary assessment system, taking the first steps toward a whole-body MRI scoring system (73).

What is unknown/should be known?
More studies are needed before modern imaging can be recommended for routine use of PsA diagnosis and assessment for imaging practitioners. The predictive value of the observation of significant subclinical enthesitis in patients with psoriasis without arthritis needs further study, and research should focus on identifying the optimal combination of joints for screening. Further research is needed to develop composite US scores for monitoring of treatment outcomes. A better understanding and definition of the different types of PsA is also needed prior to extrapolating MRI findings and “RA lessons” to PsA clinical practice. Table 5 proposes a research agenda.

In RA, micro-CT studies are illuminating our understanding of the pathology of PsA. These studies have suggested that trabecular bone mineral density and microstructure are significantly lower in patients with PsA than in patients with psoriasis where milder changes are observed. Further studies are warranted to confirm if bone loss starts early in PsA, perhaps at the stage of skin disease only, with implications for clinical practice if the concept of subclinical musculoskeletal disease in patients with psoriasis is supported (48).

Conclusion
Ultrasound is a useful bedside tool to enhance clinical assessment in PsA, from facilitating early diagnosis to improving management in established disease. MRI has a similar ability to detect and monitor peripheral soft tissue inflammation in the joints and entheses and, in addition, can provide information on peripheral bone inflammation (osteitis) and on inflammation and damage in the axial joints and entheses.

Axial spondyloarthritis
What is known?
Imaging is a useful tool in the diagnosis and prognosis (disease course and treatment response) of axial spondyloarthritis (axSpA), most experience being with X-rays and MRI, whereas more sophisticated imaging techniques are under investigation. In clinical research, imaging is the key component of the criteria for classifying axSpA based on the presence of sacroiliitis by radiography or by MRI plus at least one SpA feature. MRI has been shown to contribute to predicting a Bath Ankylosing Spondylitis Disease Activity Index 50 response in active patients treated with anti-tumor necrosis factor (TNF) agents (74).

However, several important considerations should be kept in mind in terms of the use of imaging in clinical practice. The axial site with most bone marrow edema might not match the site with most pain (75), clinical assessment of disease activity might not correlate with MRI activity (76), MRI activity may fluctuate over time (77), and structural progression in axSpA may be independent of TNF in the short-term (78-80), but with the time-averaged disease activity leading to more structural damage in the spine over time, particularly in males (81) in both the short- and the long-term follow-up, up to 12 years. In addition, findings of sacroiliac joint (SIJ) ankylosis and fat metaplasia have been found to be associated with an increased propensity for radiographic progression in the spine (WPM 2017). A recent open-label analysis of radiographic outcomes >2 years with secukinumab showed less radiographic progression than observed in previous open-label trials of TNF inhibitor (TNFi) therapy (82). However, the study population had a shorter disease duration and lower modified Stoke Ankylosing Spondylitis Spinal Score at baseline than the trials of TNFi therapy (78-80). In addition, there were no control radiographs included so any reader bias would be to score any change conservatively because of the awareness that all patients were on active treatment.

Recent data from open-label studies on the effect of TNFi on progressive spinal damage in AS suggest that this class of drugs appears to reduce radiographic progression, especially with early initiation (83) and with longer duration of follow-up (84).

The thoracic spine is most commonly affected in axSpA and is best assessed by MRI (85), whereas SpA-related new bone formation is difficult to assess in this area with CR (86). Moreover, progression of radiographic sacroiliitis by at least one grade after 2 years occurs in only a small percentage of patients with early axSpA, with C-reactive protein (CRP) and MRI being positive predictors of progression from non-radiographic to radiographic sacroiliitis according to the modified New York criteria (87, 88).

A recent study provides an important validation of MRI structural lesions versus CT (9). It also shows that radiography is a poor indicator of structural damage when compared with MRI and raises the question as to why radiography is used as a structural damage endpoint versus MRI, especially in clinical trials.

Imaging targets should be short-term (reduction of inflammation), mid-term (avoidance of post-inflammatory lesions), and long-term (reduction/avoidance of X-ray progression) using a treat-to-target concept (89). Early assessment and treatment of patients are important considering that significant regression of spinal inflammation can occur as early as 6 weeks after TNFi treatment (90), and that mobility limitation correlates with inflammation in the spine.

Table 6. Imaging axial SpA (current knowledge)

| What is known?                                                                 |
|--------------------------------------------------------------------------------|
| • CR of the SJJs should, generally, be the first imaging method to diagnose sacroiliitis as part of axial SpA. |
| • MRI should be used if diagnosis of axial SpA cannot be established based on clinical features and CR.     |
| • CR detects new bone formation and is important for long-term monitoring of structural damage.               |
| • MRI allows early detection and monitoring of inflammation and structural damage in the sacroiliac joints and the spine. |
| • CR detects syndesmophytes, which are predictive of new development of syndesmophytes.                        |
| • MRI predicts the development of new radiographic syndesmophytes.                                             |
| • MRI-detected inflammation (bone marrow edema) is a predictor of good clinical response to anti-TNF-alpha treatment in addition to elevated CRP. |

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early phases of the disease (91). Ongoing systemic inflammation as measured by CRP values despite TNFα therapy is a factor predicting the development of radiographic progression (92), suggesting that effective suppression of inflammation, including MRI inflammation, may be important for effective disease modification. Whether an early suppression of inflammation leads to a decrease risk for new bone formation, though, remains to be demonstrated. Fat metaplasia in both the SIJs and the spine has been identified as an independent predictor of radiographic progression in the spine (93, 94). Table 6 summarizes the current knowledge regarding imaging and axial SpA in clinical practice.

What is unknown/should be known?
A significant amount of research is required to optimize the use of imaging tools, and thus, the routine clinical practice of diagnosing and treating/monitoring axial SpA. The predictive potential of various MRI lesions with respect to new bone formation is an important area of further research. Other areas relate to more advanced MRI techniques with which increased sensitivity should indicate improved prediction for prognosis and therapy decisions. Imaging modalities other than radiographs and MRI should also be evaluated in the future, such as low-dose CT that shows promise for studies of syndesmophyte development and growth (95). Table 7 proposes a research agenda for imaging in axial SpA that focuses on the priorities for imaging practitioners.

### Osteoarthritis

#### What is known?
The application of MRI and US has completely changed our understanding of the complex, multi-tissue processes underpinning the OA phenotype. They have demonstrated that multiple tissue pathologies are highly prevalent in individuals aged >50 years even with normal X-rays (with and without symptoms) (96). Imaging continues to inform us about the pathological processes. For example, the commonly seen bone marrow lesions (BMLs) associated with both pain and structural progression) likely represent a response to adjacent cartilage loss (97). Though this increased understanding of OA pathology has not yet resulted in new therapies, it has led to therapies using novel imaging inclusion criteria, such as a trial of zoledronic acid in patients with positive BML (98), and the use of a biomechanically modifying device has been reported to reduce the size of BMLs, and the use of a device-modifying biomechanics has been reported to reduce the size of BMLs in patellofemoral OA (99).

The first EULAR recommendations on the use of imaging in OA clinical practice were recently published (3). Imaging is recommended to aid confirm the diagnosis of OA only in atypical presentations and only in follow-up if there is an unexpected rapid progression of symptoms or a change in clinical characteristics. CR should generally be used before other modalities. US, MRI, and CT are recommended to make additional diagnoses involving soft tissues/bone. Imaging is also recommended for guiding injections in difficult to access joints, such as the hip.

#### What is unknown/should be known?
The EULAR recommendations identified significant gaps in evidence pertaining to routine use, particularly the use of imaging in identifying therapeutic targets and a lack of data for the added value of imaging above clinical evaluation alone.

A research agenda was consequently developed (3). Until these knowledge gaps are filled, regular use of imaging cannot be recommended for diagnosis, follow-up, or predicting outcome of non-pharmacological treatments of OA.

Magnetic resonance imaging provides a more complete assessment of the joint and could play a diagnostic role in patients whose symptoms are not explained by radiographic change. Although OA desperately lacks a licensed disease-modifying therapy, MRI currently plays a pivotal role in sensitively quantifying structural change in intervention studies and providing the novel tools required by the industry and academia to develop such therapies. Stratification for the presence/severity of imaging-detected pathologies may be one route to successful therapy development (100, 101). Table 8 proposes topics for a research agenda in imaging of OA based on the current expert opinion.

### Table 7. Imaging axial SpA (research agenda)

| What is unknown/should be known? |
|----------------------------------|
| • What is the potential role of very early intervention, prediction, and identification of patients likely to progress early? |
| • What is the significance of fat metaplasia as a lead indicator of radiographic progression? |
| • What is the role of MRI in defining remission in treat-to-target strategies, and is subclinical inflammation on MRI of prognostic significance? |
| • What is the predictive potential of MRI lesions with respect to new bone formation? |
| • What is the validation of MRI lesions as lead indicators of radiographic progression in the spine? |
| • What is the interaction of different types of inflammatory and structural lesions detected by MRI and CR to predict disease progression? |
| • What are more rational clinical trial study designs for disease modification (disease duration <10 years, patients selected for disease progression, positive CRP, presence of MRI inflammation, and baseline presence of definite syndesmophyte)? |

### Table 8. Imaging OA (research agenda)

| What is unknown/should be known? |
|----------------------------------|
| • What is the added value of imaging (any modality) to clinical or differential diagnosis? |
| • What is the cost-effectiveness of imaging in OA clinical practice? |
| • Can imaging identify subgroups/phenotypes to enable targeted treatment? |
| • Is the use of imaging to measure therapy response of clinical benefit? |
| • Can imaging features predict therapy response to specific therapies? |
| • What are the benefits of imaging in less studied OA sites, such as the foot and shoulder? |
| • What is the added value of weight-bearing versus non-weight-bearing X-rays? |
| • Can imaging guidance be developed to improve the efficacy of treatments? |
Conclusion
In clinical trials, although X-rays are the current regulatory standard, MRI offers a tool to sensitively and directly quantify the cartilage, thereby vastly reducing the participant numbers required in trials. It also demonstrates multiple OA pathologies and supports studies of structure modification and symptom–structure associations. In clinical practice, there is little use for imaging in the diagnosis of typical clinical presentations, though imaging will aid with the differential diagnosis, or occasionally, with guiding therapy.

Overarching conclusion
Magnetic resonance imaging and US are crucial tools for the sensitive and accurate diagnosis and management of RA, PsA, axial SpA, and OA in routine clinical practice. Despite the fact that the utility of these modalities has been documented in many studies, some areas are unexplored. Further research is necessary to clarify the optimal role of modern imaging.

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