# Unmet need in rheumatology: reports from the advances in targeted therapies meeting, 2022

Winthrop, K.L.; Isaacs, J.D.; Mease, P.J.; Boumpas, D.T.; Baraliakos, X.; Gottenberg, J.E.; ... ; Smolen, J.S.

# Unmet need in rheumatology: reports from the Advances in Targeted Therapies meeting, 2022

Kevin L Winthrop ,[1] John D Isaacs ,[2] Philip J Mease ,[3] Dimitrios T Boumpas ,[4] Xenofon Baraliakos ,[5] Jacques-Eric Gottenberg ,[6] Stefan Siebert ,[7] Marta Mosca,[8] Neil Basu,[7] Dana Orange,[8] R Lories,[9] Daniel Aletaha ,[10] Iain B McInnes,[7] Tom W J Huizinga ,[11] Reinhard E Voll,[12] Ellen M Gravallese,[13] Ferry C Breedveld,[14] Josef S Smolen[10]

**Handling editor** David S Pisetsky

For numbered affiliations see end of article.

**Correspondence to**
Dr Kevin L Winthrop, OHSU, Portland, Oregon, USA; winthrop@ohsu.edu

Received 28 October 2022
Accepted 3 January 2023
Published Online First 26 January 2023

## ABSTRACT

To detail the unmet clinical and scientific needs in the field of rheumatology. After a 2-year hiatus due to the SARS-CoV-2 pandemic, the 22nd annual international Advances in Targeted Therapies meeting brought together more than 100 leading basic scientists and clinical researchers in rheumatology, immunology, epidemiology, molecular biology and other specialties. Breakout sessions were convened with experts in five rheumatological disease-specific groups including: rheumatoid arthritis (RA), psoriatic arthritis, axial spondyloarthritis, systemic lupus erythematosus and connective tissue diseases (CTDs). In each group, experts were asked to identify and prioritise current unmet needs in clinical and translational research, as well as highlight recent progress in meeting formerly identified unmet needs. Clinical trial design innovation was emphasised across all disease states. Within RA, developing therapies and trials for refractory disease patients remained among the most important identified unmet needs and within lupus and spondyloarthritis the need to account for disease endotypes was highlighted. The RA group also identified the need to better understand the natural history of RA, pre-RA states and the need ultimately for precision medicine. In CTD generally, experts focused on the need to better identify molecular, cellular and clinical signals of early and undifferentiated disease in order to identify novel drug targets. There remains a strong need to develop therapies and therapeutic strategies for those with treatment-refractory disease. Increasingly it is clear that we need to better understand the natural history of these diseases, including their 'predisease' states, and identify molecular signatures, including at a tissue level, which can facilitate disease diagnosis and treatment. As these unmet needs in the field of rheumatic diseases have been identified based on consensus of expert clinicians and scientists in the field, this document may serve individual researchers, institutions and industry to help prioritise their scientific activities.

## BACKGROUND

The Advances in Targeted Therapies meeting (ATT) met annually for 21 years prior to the SARS Co-V-2 pandemic. In March 2022, we convened the 22nd meeting of clinical scientists, immunologists, epidemiologists and other experts in the field of rheumatology. As in prior years, the meeting focused on clinical and translational aspects of immune-mediated inflammatory diseases (IMIDs) with faculty delivered talks in a single room format updating participants regarding the latest insights in disease mechanism(s) and pathophysiology, and recent developments with both existing and novel targeted therapies in IMIDs. This year, unlike pre-pandemic times, a discussion around COVID-19 and relevant science around both the immune response to this infection and vaccination was included. Further, COVID-19 therapy with targeted molecules developed by the rheumatological community was highlighted, in addition to discussion around common rheumatic diseases.

## METHODS

Conference participants were divided along their subject matter expertise to take part in the following disease-specific breakout groups: rheumatoid arthritis (RA), psoriatic arthritis, axial spondyloarthritis (axSpA), systemic lupus erythematous (SLE) and other connective tissue diseases (CTDs) including vasculitis. Each group was led by a facilitator and rapporteur who guided discussion within the areas of translational science, clinical care and therapeutic development. Each group was charged with identifying and prioritising current unmet needs within these areas, as well as highlighting recent progress in meeting previously identified unmet needs.

## RESULTS

### Rheumatoid arthritis

The group highlighted the need to better understand the natural history of RA, including the evolution of 'pre-RA' to early RA and then to established disease. RA-related autoantibodies are detectable years prior to the diagnosis of RA in 49%–61%[1 2] of patients. Some individuals develop abnormalities outside the joints prior to developing RA, for example, in the lung or oral mucosa. Patients with periodontitis, but not RA, may harbour anti-CCP in their gingival crevicular fluid,[3] and anti-citrullinated protien antibody (ACPA) and airway abnormalities have been detected in the lungs of seropositive individuals without RA.[4] The group brought forward the idea of a disease progression model of checkpoints, whereby local mucosal inflammation progresses to systemic inflammation (early RA) and subsequently to established RA in patients who do not achieve early remission.

Recent studies treating patients with seropositivity and arthralgia with rituximab[5] and methotrexate[6] reported delays in the onset of diagnosis of RA, raising the question of whether the course



**To cite:** Winthrop KL, Isaacs JD, Mease PJ, *et al*. *Ann Rheum Dis* 2023;**82**:594–598.

of RA can be altered or even prevented by treatment in the pre-RA phase. However, in large population studies, 1% of unselected individuals harbour ACPA and this number decreases only slightly to 0.8% when excluding patients with a diagnosis of RA,[7] suggesting some individuals with RA-related autoantibodies will never develop RA. Similarly, some patients with early disease quickly achieve symptomatic remission with first-line therapy while others respond less well. More recently the TREAT-EARLIER trial with methotrexate initiated in those with MRI-detected subclinical joint inflammation failed to prevent the onset of clinical arthritis, but did diminish disease activity.[6] We need to better understand the molecular mechanisms that underlie these early phases of disease such that intervention could prevent either transition from pre-RA to early RA, or early RA to established disease. Ultimately, this raises the idea of precision medicine whereby molecular signatures of early disease would facilitate earlier diagnosis and identify optimal therapeutic targets[8 9] that can deliver remission or immune diversion potentially at a very early stage. This is consistent with the notion of prevention of tissue damage and long term will reduce the tissue reparative burden.

There was a parallel discussion regarding a greater need to understand refractory disease and to define and identify those individuals more clearly. Despite a plethora of successful RA therapies with different mechanisms of action, most RA patients are not in remission, 10%–15% are refractory, and there remains no cure. The group reiterated the need to carefully and safely study novel combinations of existing targeted therapies, cycling or sequencing of existing therapies, and the need for innovative therapies for such patients. While a definition of 'Difficult to Treat RA' has been proposed,[10] this is a largely clinical definition lacking an associated molecular definition of truly refractory disease. Molecular signatures of RA disease 'states' that reflect later stages of disease (ie, established RA, flare in RA, refractory RA, RA in remission) also need to be established. Single-cell RNA sequence data could be pivotal for target identification in cells, such as stromal cells, which are likely candidates for contributing to the pathology of some cases of refractory disease and for which we currently lack o specific targeted therapies.[11 12] An important caveat is that a common cause of inadequate treatment response is a lack of adherence to therapy and patient histories need to be very carefully collected in order to parse molecular signatures of primary non-response due to lack of efficacy from those of lack of adherence. The group also highlighted that clinical measures often correlate poorly with biomarkers.[13] For example, some patients report few symptoms but continue to have high C reactive protein and persistent subclinical synovitis as measured by synovial histology,[14] ultrasound and MRI,[15 16] and can even continue to develop new erosions.[17] For others, severe symptoms are accompanied by few objective findings on physical examination, synovial histology[18] or imaging. The group recognised that pain, fatigue, inflammation and joint pathology may be uncoupled and represent distinct, targetable pathways, each of which may need to be considered separately depending on the disease stage and individual patient. All of this reflects the critical unmet need for a better understanding of RA pathogenesis in its totality, including improved understanding of how patient-reported outcomes relate to molecular mechanisms, imaging and other biomarkers—ideally with a clear link between them such that symptoms clearly reflect the heterogeneous pathology. Our ultimate goal of precision medicine will be easier to achieve when we can better define RA pathobiology at different disease stages, and potentially in different organs, and have identified robust and clinically useful outcome measures that correspond to these distinct and heterogeneous states.

## Psoriatic arthritis

Given the clinical heterogeneity of psoriatic arthritis (PsA), that is, differing phenotypic expression of articular, entheseal, axial and skin domains, there is a need to base disease diagnosis, classification and management on the immunophenotypic basis of clinical domains, rather than clinical manifestations alone. Such an approach has potential for greater accuracy and success in treating an appropriate target domain, that is, 'precision medicine'. This requires a better understanding of disease processes at a tissue level. In the investigation of domains where tissue biopsy is not straightforward to obtain (eg, entheses or spine), then 'molecular imaging' (eg, advanced PET) with granular probes for specific cell types could help contextualise disease endotypes. Furthermore, there is a need to more fully understand how specific cells behave in the context of the tissue milieu and compartment in which they reside.

One specific clinical phenotype requiring further clinical definition to facilitate more detailed study is axial PsA (axPsA). It appears that the clinical, imaging, genetic and possibly immunophenotypic expression of axPsA differs enough from axSpA to yield differences in response to certain classes of therapy. To increase our understanding of axPsA, both the Group for Research and Assessment of Psoriasis and the Assessment of SpondyloArthritis international Society are collaborating in the AXIS study to develop classification criteria for axPsA.[19 20] Equally important in light of differences in genetic contributions to the different clinical manifestations of PsA[21] is a need to understand the cellular and molecular mechanisms that lead to the different clinical subtypes. Which mechanisms distinguish the polyarticular form with involvement of metacarpo-phalangeal and proximal phalangeal joints from the oligoarticular form with involvement of distal interphalangeal joints? Which mechanisms drive enthesitis and what common and disparate grounds exist compared with those that lead to joint or skin disease?

Outcomes and clinical measures were identified as areas of unmet need by the group. The inadequacies and limitations of existing clinical measures for disease subtypes are clearly evident within clinical practice as well as clinical trial design. The ACR response measure, commonly employed as the primary endpoint of phase II/III randomised clinical trials (RCTs), is not a reliable outcome measure for oligoarticular, entheseal or axial predominant patients, nor does it holistically assess the non-articular aspects of PsA.[22] Although the varied clinical domains of PsA, (eg, enthesitis, dactylitis, spondylitis) can show response to treatment, only a subset of patients demonstrate these domains in RCTs and thus the measured response may not achieve statistical significance if the subset is too small. Enthesitis measures lack objectivity and should be accompanied by advanced imaging techniques. Further codification and validation of imaging approaches to categorise and classify enthesitis and axPsA are needed.

There is a need for clinicians and trialists to consider contextual factors, which influence disease activity measurements including sex, obesity, smoking and central pain sensitisation/fibromyalgia. The diagnosis and definition of 'early PsA' or 'pre-PsA' should be pursued, in order to facilitate treatment trials designed with the goal of preventing or early eradication of disease. More consideration should be given to nesting substudies including tissue sampling, biomarker evaluation and advanced imaging assessment,

**Table 1** Identified unmet research needs of high priority within RA, PsA, AxSpA, SLE and other systemic autoimmune rheumatic diseases

| | |
|---|---|
| RA | The need to molecularly define different states of disease (eg, 'pre-RA'). |
| | The need to better define treatment-refractory patients, and to develop novel therapeutics and treatment strategies for such individuals |
| PsA | The need for a diagnosis and definition of 'early' or 'pre-PsA' should be pursued, and treatment trials designed with the goal of early disease eradication or prevention |
| | The need to develop classification criteria for axial PsA |
| AxSpA | Understanding the role of the microbiome in disease pathogenesis and potential therapy |
| | Understanding disease pathology specifically with regard to why Il-23 inhibition does not improve the disease. |
| SLE | The further development of patient-focused outcome measures, and the development of new ways to measure disease activity. |
| | The need to understand the molecular and cellular basis of flares in order to better identify treatment targets |
| Other systemic autoimmune rheumatic diseases | A new taxonomy in the description of diseases within the CTD label that is biologically based (endotypes). |

axSpA, axial spondyloarthritis; CTD, connective tissue disease; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematous.

within phase II/III RCTs to inform basic immunobiology questions and better understand the biology of treatment response and non-response. Lastly, a major area of unmet need in PsA is the management of truly treatment-refractory patients who have ongoing inflammatory disease despite having 'tried everything'. Emergence of new approved therapies will partially address this need, as would rational and carefully designed 'combination' or 'sequential' treatment studies. The possibility exists that higher and more sustained response can be achieved by combining medications with different mechanism of action. Much like the treatment of refractory RA, clinical trials of biological combinations and of novel biologic/targeted synthetic disease modifying antirheumatic drugs (DMARDs) should be pursued.

## Axial spondyloarthritis

In 2022, the spondyloarthritis discussion group identified a variety of unmet needs which included: understanding the relationship of peripheral disease to axial disease; early recognition and diagnosis of disease; understanding the causes/relationship of extramusculoskeletal manifestations including bowel and eye disease to the joint disease; improved imaging technologies and interpretation; development of biomarkers for prognosis and choice of therapy; a wider choice of biological therapies; an ability to improve prognosis (disease modifying treatment); direct comparison among TNF inhibitors with regard to efficacy and safety; more frequent disease remission; improved referral to a rheumatologist and international collaboration.[23] Although this list is comprehensive, additional themes were identified of importance. First, the need to better understand the role of the microbiome is paramount. While it is likely that the gut microbiome is contributing to disease, we do not know which bacteria are most important, which portion of the bowel is most important, the mechanism by which bacteria affect the disease, the role of non-gut microbiota, the role of non-bacterial microbiota or how best to therapeutically alter the gut microbiome as by diet or faecal transplant. The technologies to study the microbiome are relatively young and further methodological progress appears to be required to obtain directly clinically meaningful insights into the disease pathogenesis. Second, the failure to establish IL-23 as an effective therapeutic target in axSpA, as opposed to targeting IL-17A, suggests the need to better understand the IL-23/IL-17 axis and the role of IL-23 in the pathogenesis of this disease.[24–27] We also need a better understanding as to how the disease results in both new bone formation and osteoporosis with increasing evidence that sustained disease control has a beneficial effect on structural disease progression.[26]

## Systemic lupus erythematosus

A number of recent advances were highlighted including the approvals of anifrolumab and voclosporin.[28–30] Highly prioritised unmet needs include particularly the need to better categorise and endotype patients. Better endotyping would allow for optimally directed therapy and improve the probability of detecting clinical benefit in trials. There has been progress on this front, as a recent transcriptomic analysis has revealed novel molecular endotypes with discrete molecular biological signatures including interferon, neutrophil, B cell, plasmablast, metabolic and autophagy.[31–38] The high interferon stimulated gene expression signature is derived from a small number of transcriptionally defined subpopulations within major cell types, including monocytes, $CD4^+$ and $CD8^+$ T cells, natural killer cells, conventional and plasmacytoid dendritic cells, and B cells, especially plasma cells. Analysis of tubular cells from patients with proliferative, membranous and mixed lupus nephritis (LN) highlight pathways relevant to inflammation and fibrosis. Type I interferon (IFN)-response signatures are present in tubular cells and keratinocytes and distinguish patients with LN from healthy control subjects, and a high IFN-response signature and fibrotic signature in tubular cells is associated with failure to respond to treatment.[39–41] Which cellular and molecular mechanisms induce the different organ manifestations of the disease? Why, for example, do some patients have severe renal but no or minimal skin lesions and others the reverse?

Further, with regard to clinical trials, it is imperative to educate regulatory agencies and increase cross-Atlantic cooperation for changes in clinical trial design. Adaptive designs or drug withdrawal designs could be pursued,[42] and better understanding of how to study novel therapies in the context of background therapies must be explored. Currently, there is little agreement on standardised background therapies, making trial design and analysis more complex. It was agreed that the need to limit heterogeneity in trial inclusion would also improve the likelihood of measuring efficacy of specific study drugs, such as limited trial inclusion to those with single organ disease or those with certain severity of disease. Outcome measures were also discussed including the need for patient-focused outcomes and new ways to measure disease activity including the SLE-DAS and the Lupus Low Disease Activity State.[43 44] New frontiers in research were discussed particularly within childhood SLE.

Lastly, the need to understand the molecular basis of flares and the cell types that drive flares would lead to the identification of therapeutic interventions to prevent flares.

### Other CTDs

The expert group initially outlined the need for a new taxonomy in the description of diseases within the rather broad CTD group of conditions. The existing phenotypical-based classifications do not adequately differentiate between these conditions. While such taxonomy should be biologically based (endotypes), it is crucial that they are framed by clinical descriptors given the relatively significant levels of clinical heterogeneity. Such a taxonomy should also integrate specific organ involvement which can vary within individuals and not necessarily correlate with patterns of systemic biological dysfunction. Ultimately, such a taxonomy should be the basis of innovative experimental medicine and clinical trial designs (eg, basket trials).

Outcome measures were also discussed at length. There is a need for developing composite outcome measures which incorporate objective markers which align with evaluated/prescribed targeted interventions but also subjective markers which adequately capture patient priorities. Such tools should be able to parse out those elements considered responsive to a particular intervention from those which are disconnected and worthy of a distinct therapeutic strategy. For example, objective measures of prevailing symptoms such as persisting pain and fatigue would enable a more stratified approach to management. In parallel, we need to learn whether or not persistent pain and fatigue are related to residual disease activity or are a consequence of damage, or are due to comorbid conditions dependent or independent of the underlying disease.

There is a need to better understand on a biological and clinical level early, typically undifferentiated disease. Cellular and molecular signatures which may identify novel drug targets are needed, but also predictors of disease trajectory (which are highly variable). Moreover, extending inspection into the preclinical phase may facilitate studies of prevention.

Lastly, establishing and investigating the burden of comorbidities, such as cardiovascular disease, which impede treatment response and outcomes including quality of life, is needed, considering lifestyle as well as pharmacological approaches. Minimising glucocorticoid exposure should be a goal. Glucocorticoids are routinely used in excess, often without sufficient efficacy and invariably associated with dose-related comorbidities and adverse events. A combination of education and development of steroid-sparing interventions and regimens are required. Finally, 'Long-Covid' was discussed and it is currently unclear how best to define this syndrome, or whether it is a collection of syndromes and if autoimmunity is involved in its pathogenesis.

## SUMMARY

The convening of the 22nd ATT afforded the possibility to discuss and articulate major unmet needs in the field of rheumatology, at the interface with other IMIDs, and across domains there were several overarching perceived unmet needs (table 1). As in prior years, there remains a strong need to develop therapies and therapeutic strategies for those with treatment-refractory disease. There is need to better understand the natural history of these diseases and 'pre-disease' states, such that molecular signatures can facilitate disease diagnosis, treatment targeting and the evolution of precision medicine.

**Author affiliations**
[1]Department of Medicine, Oregon Health and Sciences University (OHSU), Portland, Oregon, USA
[2]Department of Clinical Rheumatology, Newcastle University, Newcastle upon Tyne, UK
[3]Swedish Medical Center; University of Washington, Seattle, Washington, USA
[4]4th Department of Internal Medicine, Rheumatology and Clinical Immunology Unit, National and Kapodistrian University of Athens, Athens, Greece
[5]Ruhr-University Bochum, Rheumazentrum Ruhrgebiet Herne, Herne, Germany
[6]Centre National de Référence des Maladies Autolmmunes Systémiques Rares CHU Strasbourg-Hautepierre, Strasbourg, France
[7]College of Medical, Veterinary & Life Sciences; University of Glasgow, Glasgow, UK
[8]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[9]Division of Rheumatology Hospital for Special Surgery, New York, NY, USA
[10]Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Wien, Austria
[11]Division of Rheumatology, University of Leuven, Leuven, The Netherlands
[12]Department of Rheumatology and Clinical Immunology, University of Freiburg, Freiburg, Germany
[13]Brigham and Women''s Hospital, Harvard University, Boston, Massachusetts, USA
[14]Department of Rheumatology, University of Leiden, Leiden, The Netherlands

**Correction notice** This article has been corrected since it published Online First. Author affiliations have been corrected.

**Twitter** John D Isaacs @ProfJohnIsaacs, Dimitrios T Boumpas @none and Stefan Siebert @StefanSiebert1

**Acknowledgements** Gloria Rhyne for assistance with manuscript submission.

**Contributors** All authors contributed to the study design, data collection, discussion and critical revision of the manuscript.

**Funding** Funding for this meeting was provided by AbbVie, Chugai Pharmaceutical, Eli Lilly, Galapagos, Mitsubishi Tanabe, Novartis, Pfizer, BMS

**Competing interests** KLW has received research grants and/or consulting honoraria from Janssen Pfizer, AbbVie, Union Chimique Belge (UCB), Eli Lilly & Company, Galapagos, GlaxoSmithKline (GSK), Roche, Gilead, BMS, Regeneron, Sanofi, AstraZeneca, Novartis; JDI has received grants and/or consulting honoraria from Janssen, Pfizer, AbbVie, BMS, Gilead, Roche, UCB, Eli Lilly; PJM has received grants and/or consulting honoraria from AbbVie, Acelyrin, Aclaris, Amgen, Boehringer Ingelheim, BMS, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Inmagene, Janssen, Moonlake, Novartis, Pfizer, Sun Pharma, UCB; DTB has received grants/or consulting honoraria from AstraZeneca, Abbvie, Pfiser, GSK and Lilly; XB has received grants and/or consulting honoraria from AbbVie, BMS, MSD, Celgene, Chugai, Merck, Novartis, Pfizer, Sandoz, and UCB; J-EG has received grants and/or consulting honoraria from Abbvie, BMS, Gilead, Galapagos, Lilly, MSD, Novartis, Pfizer, Roche Chugai, Sanofi; SS has received grants and/or consulting honoraria from Amgen, AbbVie, Biogen, Eli Lilly, GSK, Janssen, UCB, Pfizer, Boehringer Ingelheim and Novartis; MM has received grants and/or consulting honoraria from Lilly, GSK, Astra Zeneca, UCB, Janssen, Abbvie and Pfizer; NB has received grants and/or consulting honoraria from Roche, MSD, Pfizer, GSK, Galapagos, Vifor and Lilly; RL has received grants and/or consulting honoraria from Abbvie, Boehringer-Ingelheim, Celgene, Eli-Lilly, Galapagos, Janssen, MSD, Novartis, Pfizer, Sandoz, Kabi-Fresenius, Biosplice (formerly Samumed) and UCB; DA has received grants and/or consulting honoraria from Abbvie, Amgen, Galapagos, Lilly, Janssen, Merck, Novartis, Pfizer, Sandoz and Sanofi; IBM has received grants and/or consulting honoraria from AbbVie, Amgen, BMS, Causeway Therapeutics, Cabaletta, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, Sanofi, UCB, Evelo, Compugen, AstraZeneca, Moonlake and serves as a NHS GGC board member, Evelo Board of Directors, Versus Arthritis Trustee Status; REV has received grants and/or consulting honoraria from AbbVie, Amgen, Boehringer Ingelheim, BMS, Janssen-Cilag, GSK, Hexal, Neutrolis, Novartis and Pfizer; EMG: serves as an associate editor at the New England Journal of Medicine; JSS has received research grants and/or consulting honoraria from AbbVie, Amgen, AstraZeneca, Astro, Bristol-Myers Squibb, Chugai, Janssen, Lilly, Merck Sharp & Dohme, Novartis-Sandoz, Pfizer, R-Pharma, Roche, Samsung and UCB serves as the editor of Annals of Rheumatic Diseases but was not involved in the handling or review of this manuscript.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**ORCID iDs**
Kevin L Winthrop http://orcid.org/0000-0002-3892-6947
John D Isaacs http://orcid.org/0000-0002-6103-7056
Philip J Mease http://orcid.org/0000-0002-6620-0457
Dimitrios T Boumpas http://orcid.org/0000-0002-9812-4671
Xenofon Baraliakos http://orcid.org/0000-0002-9475-9362

Jacques-Eric Gottenberg http://orcid.org/0000-0002-9469-946X
Stefan Siebert http://orcid.org/0000-0002-1802-7311
Daniel Aletaha http://orcid.org/0000-0003-2108-0030
Tom W J Huizinga http://orcid.org/0000-0001-7033-7520

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