Systematic Review of Clinical Utility of Multimodal Imaging in Noninfectious Posterior Uveitis: MUV Project Report 3

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• TOPIC: The clinical utility of multimodal imaging for diagnosis and management of non-infectious posterior uveitis.

• RELEVANCE: Advances in multimodal imaging support amendment of the imaging strategies in the authoritative classification criteria published by the Standards of Uveitis Nomenclature II in 2021.

• METHODS: Peer-reviewed electronic search in OVID MEDLINE, Embase, Cochrane, Scopus, last accessed August 6, 2024. Medical literature published from January 1, 2018, to July 12, 2024, for the primary analysis and from 2012-2017 inclusive for the secondary analysis. Independent reviewers extracted data using the Covidence Systematic Review Tool and assessed quality and bias with the Mixed Methods Assessment Tool, followed by a consensus process. Statements of imaging findings and clinical utility were tabulated. Main outcome measures were: (1) factual imaging findings for acute posterior multifocal placoid pigment epitheliopathy (APMPPE), birdshot chorioretinitis, multifocal choroiditis, punctate inner choroidopathy, multifocal evanescent white dot syndrome (MEWDS) and serpiginous choroiditis. Imaging modalities included color fundus (CFP), autofluorescence (FAF), OCT, fluorescein angiography (FA), indocyanine green angiography (ICGA) and OCT angiography; (2) subjective or objective statements of clinical utility for diagnosis, detection of activity, monitoring, or detection of complications. The level of evidence was evaluated using the GRADE process.

• RESULTS: 70 studies from 2018-2024 met inclusion criteria and quality standards for study type. Combined with 63 foundational studies from 2012-2017, there were 292 specific imaging statements based on imaging examinations of 6537 patients in the primary analysis. There were 124 statements of clinical utility, with OCT or OCTA accounting for 66/124 (53%), plus an additional 29 statements of clinical utility for multimodal imaging (MMI). Evidence was ranked high for OCT on at least one outcome measure for each disease, followed by CFP, FAF, and FA in 4 of 5 diseases (80%), OCTA in 3 of 5 (60%), and ICGA in 1 of 5 (20%).

• CONCLUSION: Substantial information exists regarding the imaging findings in noninfectious posterior uveitis. Expert opinions generally favor the clinical utility of MMI. Additional research with efficient imaging strategies and objective outcome measures is warranted. Revision of current classification guidelines should be considered.

• OTHER: Protocol registration CRD42024576867 with PROSPERO (https://crd.york.ac.uk/prospero/).
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INTRODUCTION

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE), birdshot chorioretinitis (BSCR), multifocal choroiditis with panuveitis

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(MFC/PU), punctate inner choroiditis (MFC/PIC), and serpiginous choroiditis (SC) are collectively referred to as white dot or white spot syndromes, despite the term's original use only as the name of a specific entity, multifocal evanescent white dot syndrome (MEWDS).[1] Authoritative guidelines classify all six disorders as non-infectious posterior uveitis based on the anatomic site of greatest inflammation. Each has a distinctive appearance and clinical course.[2]

Existing classification criteria for named types of uveitis were developed by the Standards of Uveitis Nomenclature II Working Group. Between 2010 and 2016, the SUN II Working Group collected clinical data and non-standardized fundus images on thousands of cases of uveitis. Expert panels reviewed the data in 2017 to identify bona fide examples of the named entities and converted imaging data into verbal descriptions of the images. Machine learning techniques confirmed that written classification criteria could discriminate among 25 separate uveitic entities. The research group approved the criteria in 2019 and published them in 2021.[3-8] Importantly, the term "white dot syndrome" was not carried forward in the classification scheme.

The SUN II criteria describe the fundus appearance of each type of non-infectious posterior uveitis. For example, BSCR was characterized as having multifocal cream-colored or yellow-orange, oval or round choroidal lesions (birdshot spots).[4] HLA-A29 positivity was an optional criterion for BSCR, however, for the other posterior uveitis entities, ancillary testing was mentioned only to exclude infections and sarcoidosis. Some criteria specified retinal imaging. For BSCR, multifocal hypofluorescent spots on indocyanine green angiography (ICGA) were considered equivalent to visible birdshot spots on clinical examination.[4] Classification as MEWDS required specific findings on either fluorescein angiography (FA) or optical coherence tomography (OCT).[7] Either FA or fundus autofluorescence (FAF) was required by the definition of SC.[8]

The SUN II classification criteria were developed during a period of rapid technological advancement in ophthalmic imaging. Imaging of non-infectious posterior uveitis increased prior to 2018 during the early years of the SUN II project. This new information was incompletely integrated into clinical practice and, therefore, into the cases collected for SUN II. The term "multimodal imaging" (MMI) became prevalent in the literature and instructional courses, often with a recommendation to perform multimodal imaging or to use specific modalities. Spectral domain OCT and OCT angiography (OCTA) to diagnose, monitor, and detect activity and complications in multifocal choroiditis appeared in multiple studies before 2018.[9-14] BSCR studies focused on features of ICGA[15,16] and changes in retina and choroid detected on OCT and OCTA.[17-20] OCT and FAF imaging localized the principal site of injury in MEWDS to the outer retina[21,22] and to the choriocapillaris and choroid in APMPPE.[23,24] By 2024, three years after publication of the SUN II guidelines, use of MMI was widespread: a global survey revealed that nearly 90% of respondents use MMI to diagnose posterior uveitis. Over 70% of respondents supported nomenclature redefinition based on imaging findings, highlighting the need for relook at posterior uveitis.[25]

To address these developments, we conducted a systematic review and meta-analysis of literature published between 2018 and mid-2024, corresponding to the period of analysis, publication and dissemination of the SUN II classification criteria after the data collection phase. Our objective was to assess whether evidence about MMI supports modifications to the SUN II criteria. We specifically evaluated the clinical utility of MMI to diagnose and understand disease processes, assess activity, monitor course, and manage complications in six specific types of non-infectious posterior uveitis addressed by SUN II. We graded the strength of recommendations based on the quality of the published evidence. Additionally, we propose a structured algorithm to guide imaging choices for clinicians confronted with non-infectious posterior uveitis.

METHODS

Search strategy. An electronic database search strategy was developed by an academic health science librarian (JR) in consultation with the senior author (JLD.) and was reviewed by two other health science librarians using the Peer Review for Electronic Search Strategies (PRESS) tool (see acknowledgements).[26] A combination of controlled-vocabulary subject headings and title, abstract, and keywords were used for six types of uveitis, a wide range of masquerades, and ten types of imaging, along with synonyms for each. Definitions of diseases were based on the SUN II Classification of Uveitides.[2] The search was conducted in two phases, with the first including uveitis, masquerades, and imaging terms, and was limited to studies published from 2018 to mid-2024. A second search included only uveitis and imaging terms, without masquerade terms, and included studies published from 2012-2017 to capture imaging findings that may have been foundational for the later literature. The searches were conducted in the Medline (Ovid), Embase (Elsevier), Cochrane CENTRAL (Wiley), and Scopus (Elsevier) databases. The search strategy was written for Medline and translated for use in other databases using each database's appropriate syntax, subject headings, and search fields. The search strategy was adapted to run in other databases in part with the use of the Institute for Evidence Based Healthcare's Polyglot Search translator.[27] Results were limited to human studies by excluding animal research. No other validated filters were applied. Case reports and reviews were excluded by publication type. No language or other limits were applied at the search phase. No trial registries, tables of contents, or other resources were searched. No study authors were contacted for addi-

tional data. All databases were searched between July 12 and July 15, 2024, with supplemental searches done on August 6, 2024. Citations from related systematic reviews were screened separately from database records, yielding no additional studies. For full search strategies and details of databases used as well as selected systematic reviews used in citation searching, see Supplementary Material: Search Strategies**.** All database records were downloaded to EndNote 21,[28] and uploaded to Covidence web-based collaboration software platform[29] for deduplication, screening, full-text evaluation, quality assessment, and data extraction. The Retraction Watch database was checked via Endnote software for retractions of included studies.

Literature review. We used the Covidence online software to review all literature retrieved in the search. Beginning 7/17/2024, two randomly selected reviewers out of 19 independently screened the titles and abstracts of 1789 papers for inclusion or exclusion in the main data set of post-2017 literature. Either two yes or two no votes were regarded as final. Selection of the third option of "maybe" by either reviewer triggered mandatory consensus by a third independent reviewer, whose opinion was final. Accepted articles proceeded to Full Text Review to determine the final analysis set. Two independent reviewers and a consensus reviewer extracted data and assessed quality of the included articles. Reviewers indicated the reason for exclusion from a predetermined list: (1) abstract only with insufficient data (2) wrong research question (3) imaging findings not well described (4) irrelevant imaging technique (5) no clinical application (6) irrelevant diagnosis (panuveitis, infectious uveitis or other masquerade) (7) outside date window. We included studies only if subjects met the nominal inclusion and exclusion criteria of SUN II for each type of noninfectious posterior uveitis, including MFC/PIC, named punctate inner choroiditis in the SUN II nomenclature.[6] Articles published before 2018 were read by one to three independent reviewers, screened by the same criteria, and analyzed for foundational imaging findings reported prior to 2018.

Protocol registration. We registered the review with PROSPERO (https://crd.york.ac.uk/prospero/) on 8/16/2024 under the title Multimodal Imaging in Non-Infectious Posterior Uveitis (CRD42024576867). There were two review questions: What are the characteristic findings of MMI (CFP, FAF, OCT, FA, ICGA and OCTA) in non-infectious posterior uveitis? Which outcomes of MMI have clinical utility? We specified the types of non-infectious posterior uveitis as APMPPE, BSCR, MFC/PU, MFC/PIC, MEWDS, and non-infectious SC.

Data extraction began 8/22/2024. We created a custom data extraction template within the Covidence web-based software[29] to tabulate the types of imaging studies and the number of uveitis patients studied. An initial list of imaging statements based on expert opinion was compiled as part of the Multimodal Imaging in Uveitis (MUV) Project, "Evidence and Consensus based Guidelines for Imaging in Non-Infectious Posterior Uveitis – Methodology of the Multimodal Imaging in Uveitis (MUV) Project**:** Report 2"**.**[30] Two independent reviewers and a third consensus reviewer extracted both factual imaging findings and evidence-based or subjective statements that there was clinical utility of using a specific modality or combinations of modality from the primary analysis set 2018-2024. We collected only factual imaging findings from the set of papers, 2012-2017, published during the data collection phase of SUN II.

Quality assessment was performed simultaneously with the data extraction by the same reviewers. The Mixed Methods Assessment Tool Version 2018 was replicated verbatim in a Covidence Quality Assessment template (Wikitool: http://toolkit4mixedstudiesreviews.pbworks.com, accessed 8/16/2024**.)** [31]

This instrument includes quality measures for both qualitative and quantitative data. The instrument asks whether there was a clear research question with data to support it. All studies had an element of qualitative data in the form of descriptions or depictions of retinal imaging and some mixed qualitative and quantitative data such as visual outcomes and other measurements. The instrument assigns studies to 4 broad categories: qualitative only, mixed randomized controlled, mixed nonrandomized longitudinal or comparative, and mixed non-randomized cross-sectional. Studies with a mixed qualitative and quantitative component were further assessed for integration of the two types of data. Mixed-methods convergent design consisted of studies that evaluated the two types of data simultaneously, for example, measurement of choroidal thickness on qualitative OCT B scan images; sequential explanatory, for example, recording imaging findings and then reporting visual or other quantitative outcomes; or sequential exploratory, for example, recording quantitative outcomes and then explaining them based on imaging findings. We used the same method of two independent reviewers followed by a third consensus review for any items that were not identically scored. Full text articles were displayed in the same window as the data extraction and QA templates to facilitate review.

Synthesis of the data began October 7, 2024. We performed an integration at the level of extracted data, as suggested by the MMAT Wiki Tool kit. Analytic constructs focused on the clinical utility of multimodal imaging in 4 specific categories: (1) diagnosis or pathogenesis, (2) detection of activity or response to treatment, (3) longitudinal monitoring, (4) detection and monitoring of complications, including retinal atrophy or scarring, vision loss and neovascularization. We considered clinical utility for each disease we studied and each of the 6 imaging modalities.

Level of Evidence. Before making final recommendations regarding the use of MMI based on systematic review of the literature, we conducted a subjective review of the level of evidence based on study design, sample size, consistency of findings, and clinical applicability, with higher rat-

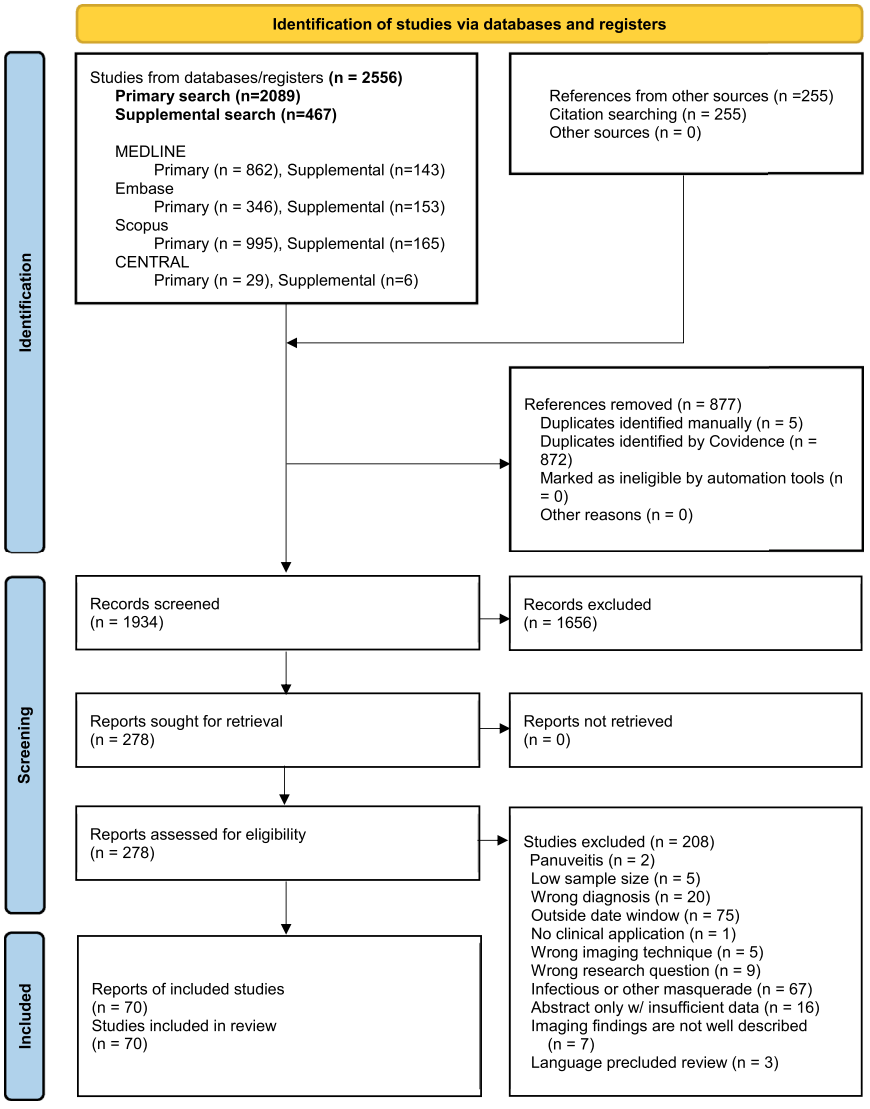

FIGURE 1. Flow chart showing the number of articles retrieved initially (2556) with subsequent removal of duplicates (877), followed by screening of titles and abstracts by 2 reviewers with a third consensus reviewer if needed resulting in exclusion of 1656. Full text review of 278 papers resulted in exclusion of 208 for various reasons listed, the most common being publication before 2018 or infectious uveitis. Five papers were excluded during full text review because they did not include at least 3 patients of at least one of the studied diagnoses. A final 70 articles were selected for data extraction and quality assessment. (Template from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71).

ings given to robust, reproducible studies. We used Grading of Recommendations, Assessment, Development and Evaluations (Grade) system[32] to score the quality of the evidence as high, moderate, low or very low for the use of multimodal imaging in the specific types of posterior uveitis we studied.

RESULTS

Figure 1 is the PRISMA diagram showing the distribution of articles after application of the inclusion and exclusion criteria. Proportionate agreement between two independent reviewers to include a study after full text review was 75.6%. Adjudication by a third reviewer in case of disagreement led to selection of 70 articles for data extraction and quality assessment.

Table 1 summarizes the number of patients examined for each modality and diagnosis in the 2018-2024 cohort. Authorship was European Union or United Kingdom for 28 articles, United States for 14 articles, and other countries for 28. The number of factual imaging statements and papers for each modality and diagnosis from 2018-2024 exceeded those prior to 2018 in almost all categories, indicating increased interest in the topic.

TABLE 1. Number of Individual Patient Examinations, Number of Reports of Specific Imaging Findings, and Number of Clinical Utility Statements for Six Commonly Used Imaging Modalities Cited in the Medical Literature 2018 to Mid-2024

	COLOR	FAF	OCT	FA	ICGA	OCTA	MMI	TOTAL
APMPPE								
Tests performed 2018-2024[a]	36	30	19	4	3	17	–	109
Imaging statements 2018-2024 (papers)[b]	4	2	4	1	1	2	–	14 (5)
Supporting statements pre-2018 (papers)[c]	5	1	5	2	2	2		17 (6)
Clinical utility statements 2018-2024[d]	1		2			2	2	7
Birdshot Chorioretinitis								
Tests performed 2018-2024	50	54	228	235	29	85	–	681
Imaging statements 2018-2024 (papers)	3	2	6	9	5	3	–	28 (12)
Supporting statements pre-2018 (papers)	3	0	2	4	4	2		15 (6)
Clinical utility statements 2018-2024	1	2	8	5	4	4	2	26
Multifocal choroiditis with panuveitis								
Tests performed 2018-2024	461	428	479	440	351	88	–	2247
Imaging statements 2018-2024 (papers)	10	12	12	11	6	8	–	59 (18)
Supporting statements pre-2018 (papers)	4	4	5	6	2	2		23 (7)
Clinical utility statements 2018-2024	4	5	9	3	2	5	8	36
Multifocal choroiditis – PIC subtype								
Tests performed 2018-2024	265	243	319	279	266	236	–	1608
Imaging statements 2018-2024 (papers)	7	5	10	6	5	6	–	39 (14)
Supporting statements pre-2018 (papers)	2	3	6	1	3	0		15 (9)
Clinical utility statements 2018-2024	1	3	7	4	0	7	5	27
MEWDS								
Tests performed 2018-2024	270	320	420	317	260	39	–	1626
Imaging statements 2018-2024 (papers)	12	9	16	11	14	1	–	63 (17)
Supporting statements pre-2018 (papers)	5	4	7	3	4	1		24 (8)
Clinical utility statements 2018-2024	4	3	11	2	4	3	9	36
Serpiginous choroiditis								
Tests performed 2018-2024	36	47	55	41	42	45	–	266
Imaging statements 2018-2024 (papers)	3	4	4	4	4	6	–	25 (7)
Supporting statements pre-2018 (papers)	1	1	1	0	0	0		3 (1)
Clinical utility statements 2018-2024	0	4	2	1	3	6	3	19
TOTAL								
Tests performed 2018-2024	1118	1122	1520	1316	951	510	–	6537
Imaging statements 2018-2024 (papers)	50	48	66	50	42	36	–	292 (64)
Supporting statements pre-2018 (papers)	20	13	26	16	15	7		97 (37)
Clinical utility statements 2018-2024	11	17	39	17	13	27	29	153 (64)

[a]Tests performed are cumulative numbers of tests based on patients, not eyes.

[b]Imaging statements 2018-2024 are the number of published imaging statements for each modality, summed in the right column, with the number of papers that included one or more imaging statements in parentheses.

[c]Supporting statements pre-2018 are the number of imaging statements that corroborated the 2018-2024 statements.

[d]Multiple clinical utility statements in a single paper for the same modality and disease were counted only once.Abbreviations: MMI indicates the number of papers reporting clinical utility specifically for multimodal imaging strategies.APMPPE = acute posterior multifocal placoid epitheliopathy; FAF = fundus autofluorescence; FA = fluorescein angiography; ICGA = indocyanine green angiography; MEWDS = multifocal evanescent white dot syndrome; OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; PIC = punctate inner choroidopathy.

The number of clinical utility statements are reported per diagnosis and modality (Table 1). In 64 individual papers, there were 124 instances of one or more clinical utility statements per paper for a specific modality for either initial diagnosis, determination of activity, monitoring of clinical course, or detection of complications, for an average of 1.9 statements per paper per modality. There were an additional 29 statements of the utility of multimodal imaging. Statements of clinical utility were the most common for the following combinations of diagnoses and modalities: APMPPE: OCTA; BSCR: all modalities; MFC/PU, MFC/PIC and MEWDS: OCT, OCTA; SC: FAF, ICGA, OCTA. Overall, 39 of 64 (60.9%) studies reported clinical utility for OCT and 27 (42.1%) studies reported clinical utility for OCTA.

Table 2 lists the reported imaging characteristics of each disorder. Only original research findings were collected, not descriptions that were referenced to other publications. Sixty-four of 70 (91.4%) papers in the principal analysis had an average of 4.6 imaging statements per paper as well as 37 of 61 (60.7%) of the 2012-2017 papers, an average 2.6 per paper, indicating a more limited and exploratory approach in the earlier literature, often focusing on a single modality. Most imaging statements appeared in both periods indicating corroboration of the earlier findings, but those in the 2018-2024 era were often either new or amplified the earlier statements, especially for OCT and OCTA. Findings occurring only in the pre-2018 APMPPE literature concerned acute hypoautofluorescence, thickened choriocapillaris, angular sign of Henle fiber layer hyperreflectivity (ASHH), bacillary detachment and choriocapillaris flow voids.[23,24,33–35] An earlier finding of increased retinal intercapillary spacing and vascular loops in MFC/PU[36] was subsequently reported only for MFC/PIC. [36] Imaging characteristics of MFC/PU and MFC/PIC were nearly identical in both data sets, with one paper stating that MMI does not distinguish two separate disorders.[37]

• QUALITY ASSESSMENT: **Study types**. Studies generally had small sample sizes with a median of 17 patients per study (minimum 3, maximum 185) reflecting the rarity of non-infectious posterior uveitis. Fifteen of 70 studies (21.4%) were pure qualitative studies that described the appearance of images without reference to quantitative data such as precise size or thickness, and/or reflectivity. Fifty-five of 70 studies (78.6%) used mixed methods with both qualitative and quantitative components. Quantitative components were present if numeric or ordinal data was analyzed in the context of descriptions or depictions of retinal images. These data might include visual acuities, frequencies, proportions, retinal or choroidal depth, topographies, dimensions or other quantification of imaging findings. Thirty-one (44.2%) were considered quantitative descriptive studies without hypothesis-testing. These were typically case series or reports with statistical analysis of numerical data. Twenty-three (32.9%) were considered quantitative non-randomized studies because they analyzed numerical data regarding the longitudinal effects of treatment or natural history, compared cases and controls, or subsets of cases. These were typically cohort studies, case-control studies and cross-sectional analytic studies. In some papers the distinction between study types was blurred or mixed within the article.

Quality measures. There was one randomized study that tested the effect of two alternative treatments on choroidal flow deficits that had poor integration of qualitative and quantitative data.[74] For each of the other 69 qualitative or non-randomized mixed studies, there were up to 22 quality questions from the MMAT for a total of 1540 questions. Two questions concerned whether there was a clear research question and whether the study was able to answer it; this was an inclusion criterion. In one case, the consensus reviewer was unable to tell if the data were adequate to address the research question, but all other papers met these two fundamental criteria for inclusion. Five questions assessed the adequacy of qualitative descriptions and interpretation of imaging studies. Ten questions assessed the quality measures of non-randomized mixed qualitative and quantitative studies, depending on study type. An additional 5 questions addressed the integration of qualitative and quantitative data. Of the 1540 possible questions, 474 were judged non-applicable due to study design (30.8%). Of the remaining 1066 datapoints, the quality measure was met in 899 (84.3%), not met in 44 (4.1%) and not discernable from the methods in 88 (8.3%). In an additional 88 measures the reviewer was unable to determine from the methods whether the quality measure had been met (8.3%). Data was missing for 30 questions (2.8%). A summary score was not generated as per the guidelines of the MMAT. *Supplementary Material: Quality Assessment* gives the results for each of the 4 study types. Two included papers did not contribute either generalizable imaging statements or clinical utility statements for the data synthesis.[120,121]

• CLINICAL UTILITY OUTCOMES: Statements regarding the clinical utility of either single or multimodal imaging techniques were recorded. There were 566 individual statements of clinical utility among the 70 studies, including multiple statements for a single modality in an article or similar statements in different articles. Overall, 64 papers mentioned utility 153 times for a modality or for MMI (Table 1). Most utiilty statements pertained to MFC/PU and MFC/PIC (246, 43.5%) and MEWDS (158, 27.9%), followed by APMPPE (34, 6%), BSCR (79, 14%), and SC (49, 8.6%). Statements were roughly distributed across four utility domains: diagnosis (174, 30.7%), disease activity (142, 25.1%), monitoring (140, 24.7%), and complications (110, 19.4%). The utility statements are summarized below.

• MMI FOR DIAGNOSIS OF NON-INFECTIOUS POSTERIOR UVEITIS: Diagnostic clinical utility was ascribed to statements that imaging discriminates features of the disease, that one modality is superior to another, that imaging characteristics correlate with visual function, or that imaging can be used to infer pathophysiology.

For **APMPPE**, OCTA outperformed ICGA in delineating lesions and identifying choriocapillaris hypoperfusion.[38] MMI with CFP, FAF and OCTA showed hypochromic, hyperautofluorescent lesions that were hyperreflective on OCT, with flow signal deficits in the choriocapillaris on OCTA, providing insight into the pathophysiology.[39] The deep retinal capillary plexus may also be hypoperfused.[38] Number, size and location of lesions is predictive of visual outcome.[38]

In BSCR, CFP documents the pathognomonic choroidal birdshot lesions,[41] ICGA is superior to CFP or FA in de-

TABLE 2. Factual Statements About Imaging Findings for Each Disease and Each Modality Preceding and Following the Completion of SUN II Data Collection and Analysis

Imaging Statement	Pre-2018	2018-2024
APMPPE - Color Fundus Photography		
A.1.1. Lesions are typically bilateral and multifocal or paucifocal.	24,34	38,39,40
A.1.2. Lesions appear white or yellow on color imaging.	24	38,39,41,40
A.1.3. Lesions are deep, with overlying retinal vessels visible.	24,34	38,39
A.1.4. RPE mottling may be seen in later stages.		38,40
APMPPE - Autofluorescence		
A.2.1. Hypoautofluorescence is seen in the acute phase due to masking.	24	
A.2.2. Hyperautofluorescence in the convalescent phase may reflect RPE damage or lipofuscin accumulation.		40
A.2.3 Hypoautofluorescence in the convalescent phase may indicate RPE atrophy or loss.	24	40
A.2.4. Lesions in different stages of activity may coexist within the same eye.		38,42
APMPPE - OCT		
A.3.1. Active lesions show focal hyperreflectivity involving the ellipsoid zone, external limiting membrane, and outer nuclear layer.	23,33,34,43	39,40,42
A.3.2. Thickening of the choriocapillaris may be seen beneath hyperreflective lesions.	33	
A.3.3. The angular sign of hyperreflectivity (ASHH) may be observed in outer nuclear layer lesions.	24,33,34	
A.3.4. RPE atrophy may follow disruption of the RPE and the development of drusenoid changes.	34	38,40
A.3.5. Bacillary detachment may occur in active disease.	23,33,34	
A.3.6. Irregularity or loss of the ellipsoid zone line and outer retinal architecture is common.		40,42
APMPPE - Fluorescein Angiography		
A.4.1. Active lesions are hypofluorescent in early phases of FA.	24,34	38
A.4.2. Late-phase FA shows hyperfluorescence of active lesions due to staining.	24,34	38
APMPPE - Indocyanine Green Angiography		
A.5.1. Active lesions appear hypofluorescent in both early and late ICGA frames; some may be more clearly seen in early phases.	24,34	38
APMPPE - OCT Angiography		
A.6.1. Flow deficits are observed in the choriocapillaris slab on OCTA.	34	38,39
A.6.2. The area of flow deficit often exceeds the zone of outer retinal hyperreflectivity.	35	
A.6.3. Choriocapillaris flow voids may appear hypo-intense, surrounded by iso- or hyper-intense background signal.	35	
BIRDSHOT CHORIORETINITIS - Color Fundus Photography		
B.1.1. Lesions are located within the choroidal layer, typically oval in shape and aligned with the course of choroidal vessels, most commonly observed in the nasal and inferonasal regions.	17	44,45
B.1.2. Lesions are multifocal.	17	44,45
B.1.3. Lesions appear lighter than the surrounding choroidal background.	17,19	45,46
B.1.4. Posterior lesions typically measure 250–500 microns.	19	
B.1.5. Peripheral lesions may appear confluent.	17	
B.1.6. Lesions can evolve into areas of retinal pigment epithelium (RPE) atrophy.	19	45
B.1.7 Lesions may not be clinically visible in all cases.	47	
BIRDSHOT CHORIORETINITIS - Autofluorescence		
B.2.1. Both hyper- and hypoautofluorescent lesions may be present.		48
B.2.2. Early hyperautofluorescence may reflect active outer retinal disease.		49
BIRDSHOT CHORIORETINITIS - OCT		
B.3.1. OCT does not show disease-specific features but can support monitoring.	19	
B.3.2. Outer retinal hyperreflectivity and elevation may occur, sometimes with RPE elevation and disruption of the external limiting membrane and EZ.	50	51,49,48

(*continued on next page*)

TABLE 2. (*continued*)

Imaging Statement	Pre-2018	2018-2024
B.3.3. Perivascular thickening may indicate inflammatory activity.		52
B.3.4. Early active disease can show a thicker choroid with loss of visible choroidal vasculature. Inactive disease or late-stage disease may show a thinner choroid compared with controls.		52,45,53
B.3.5. Retinal maps may show thickening in active disease, particularly inferonasal, and thinning in inactive or treated cases.		45,53
BIRDSHOT CHORIORETINITIS - Fluorescein Angiography		
B.4.1. Retinal vascular leakage may be present, typically involving the large posterior retinal veins and capillaries, with irregular venous caliber	15,17,19	51,52,54,44,45,46,55,56
B.4.2. Macular edema can occur.	17	45,46,55,56
B.4.3. Birdshot lesions may stain in late phases of FA.		54,56
B.4.4. Early and late hyperfluorescent window defects can be seen.		49
B.4.5. Peripheral capillary non-perfusion, telangiectasias, and microaneurysms may be present.		56
B.4.6. Neovascular complications may occur (e.g., macular neovascularization, neovascularization of the disc or elsewhere).	17	
B.4.7. Optic nerve head leakage is a recognized feature.	16,17	55
BIRDSHOT CHORIORETINITIS - Indocyanine Green Angiography		
B.5.1. Active lesions show early and mid-phase hypofluorescence on ICGA.	15-17,19	49,45,46,55
B.5.2. Inactive lesions show early hypofluorescence with iso- or hyperfluorescence in mid-to-late phases.	15	51
BIRDSHOT CHORIORETINITIS - OCT Angiography		
B.6.1. Macular neovascularization may be present.	17	
B.6.2. Flow deficits can be seen in both the superficial and deep capillary plexuses.	17,19	51,53
B.6.3. Vascular telangiectasias and macular loops may be observed in the superficial plexus.	17,19	51,45,53
MULTIFOCAL CHOROIDITIS WITH PANUVEITIS - Color Fundus Photography		
C.1.1. Lesions are multifocal, discrete, vary in size, and involve the choroid or retina.	11,12,36,57	37,58,59,60,61,62,63,64
C.1.2. Active lesions appear cream-colored.	36,57	58,65
C.1.3. Inactive lesions are depigmented or hyperpigmented.	11,12,36,57	59,60,62,66,64
C.1.4. MFC/PIC lesions may evolve into patterns resembling myopic patchy or linear atrophy.		59,61
MULTIFOCAL CHOROIDITIS WITH PANUVEITIS - Autofluorescence		
C.2.1. Inactive lesions are typically hypoautofluorescent.	11,12,36	37,59,60,61,65,67,63,64
C.2.2. Active and inactive lesions may have hyperautofluorescent borders.	12,36,68	69,58,59,60,61,65–67
C.2.3. New lesions may appear hyperautofluorescent.	11,36	58,62,66
C.2.4. Persistent hyperautofluorescence may be seen in association with subretinal fluid, CNV, or outer retinal disruption.	36	58,60,66
C.2.5. Chrysanthemum lesions are characteristically hypoautofluorescent.		60
MULTIFOCAL CHOROIDITIS WITH PANUVEITIS - OCT		
C.3.1. Active lesions may show subretinal hyperreflective material overlying disrupted RPE.	11,14,36,57,70	37,69,58,59,60,61,62,65,67,71,64
C.3.2. The choroidal layer may be thickened and disrupted in active disease on EDI-OCT.	11,14,70	37,69,60,62,72
C.3.3. Inactive lesions are punched out with loss of the ellipsoid zone and RPE.	12,14,36,57	37,69,58,59,60,61,65,67,64
C.3.4. Some inactive lesions may appear as choroidal excavations.	14	58,60,61,71
C.3.5. Chrysanthemum lesions show downward deflection of Bruch's membrane.		60

(*continued on next page*)

TABLE 2. (*continued*)

Imaging Statement	Pre-2018	2018-2024
MULTIFOCAL CHOROIDITIS WITH PANUVEITIS - Fluorescein Angiography		
C.4.1. Choroidal neovascular membranes appear as early and late hyperfluorescence.	11,14,36,57,70	69,58,59,60,62,65,63,71–73
C.4.2. Inactive lesions appear as window defects.	11,12,14,36,57	58,59,60,61,65,64
C.4.3. Chrysanthemum lesions show early and late hyperfluorescence.		60
MULTIFOCAL CHOROIDITIS WITH PANUVEITIS - Indocyanine Green Angiography		
C.5.1. Both active and inactive lesions are hypofluorescent on ICGA.	12,36	69,59,60,61,64
C.5.2. Late-phase ICGA may reveal lesions not visible on color or FA or autofluorescence.	12,36	69,59,60,62
C.5.3. ICGA often detects more lesions than color imaging or autofluorescence.	12,36	
MULTIFOCAL CHOROIDITIS WITH PANUVEITIS - OCT Angiography		
C.6.1. OCTA can demonstrate vascular flow within choroidal neovascular membranes.	36,70	69,59,60,65,72,73
C.6.2. Active lesions may show flow voids in the outer retina or choriocapillaris.	36	74,69,60,62,73
C.6.3. Inactive lesions may also present with persistent flow deficits.		60
C.6.4. Increased intercapillary spacing and vascular loops may be seen.	36	
MULTIFOCAL CHOROIDITIS - PUNCTATE INNER CHOROIDOPATHY Color Fundus Photography		
C.1.1. Lesions are multifocal and discrete and may vary in size.	10,75	76,77,78
C.1.2. Active lesions appear cream-colored.	75	76,77,79,80,81,78,82
C.1.3. Inactive lesions may appear depigmented or hyperpigmented.		82
C.1.4. Lesions are choroidal or chorioretinal in location.	10	77
C.1.5. In MFC/PIC, active lesions may have indistinct borders with surrounding edema.	10	
MULTIFOCAL CHOROIDITIS - PUNCTATE INNER CHOROIDOPATHY Autofluorescence		
C.2.1. Inactive lesions are hypoautofluorescent.	83,84	76
C.2.2. Active and inactive lesions may have hyperautofluorescent borders.	36	77,78
C.2.3. New lesions may initially appear hyperautofluorescent		85
C.2.4. Persistent hyperautofluorescence may occur in the presence of subretinal fluid, choroidal neovascular membrane, or outer retinal disruption.		81
MULTIFOCAL CHOROIDITIS - PUNCTATE INNER CHOROIDOPATHY OCT		
C.3.1. Active lesions may show subretinal homogenous hyperreflective material (SHRM) typically overlying disrupted ellipsoid zone and RPE	57	37,41,77,79,80,86,81,82,87,88
C.3.2. Choroidal thickening and disruption may be seen on enhanced depth imaging OCT in active lesions.	75,89	80,81,82
C.3.3. Inactive lesions are punched out with loss of the ellipsoid zone and RPE and may show focal choroidal excavation	90	79
C.3.4. RPE elevation with sub-Bruch's hyporeflective space may be observed.	10,57,90	80,81,87,88
MULTIFOCAL CHOROIDITIS - PUNCTATE INNER CHOROIDOPATHY Fluorescein Angiography		
C.4.1. Active lesions may show hyperfluorescence due to leakage or staining of window defects.	75	76,52,77,79,81
MULTIFOCAL CHOROIDITIS - PUNCTATE INNER CHOROIDOPATHY Indocyanine Green Angiography		
C.5.1. Both active and inactive lesions appear hypofluorescent on ICGA.	36,75,83	77,80,81,85,78
C.5.2. Late ICGA frames may reveal active lesions not visible on color fundus photography or FA.	83	80
C.5.3. ICGA detects more active lesions than color or autofluorescence imaging.	83	80

(*continued on next page*)

TABLE 2. (*continued*)

Imaging Statement	Pre-2018	2018-2024
MULTIFOCAL CHOROIDITIS - PUNCTATE INNER CHOROIDOPATHY OCT Angiography		
C.6.1. OCTA can show vascular detail and flow in choroidal neovascular membranes.		80,82
C.6.2. Flow voids may be seen in active lesions.		76,79,80,86,78,82
C.6.3. Increased intercapillary spacing and vascular loops may be observed.		76
MEWDS - Color Fundus Photography		
D.1.1 Lesions are pale, located in the deep retina, approximately 50-150 microns, and clustered around the optic disc, macular, and vascular arcades	21,91,92	93–95,96,97,62,98,99,100,101
D.1.2. Distribution may extend from the posterior pole to the mid-periphery or beyond.	21	62,102
D.1.3. The fundus may appear relatively bland despite the presence of lesions.	21	95,96,62
D.1.4. Lesions typically resolve spontaneously.	21,92,103	95,96,97,98,102,101
D.1.5. A granular fovea may be seen on high-resolution color imaging.	21,103,104	95,96,97,98,105
D.1.6. Optic disc margins may appear blurred.	92,103	94,97,105
D.1.7. Well-defined lesions suggest an alternative diagnosis and are an exclusion criterion.		95
MEWDS - Autofluorescence		
D.2.1. Lesions are hyperautofluorescent and easier to see than on colors	21,22,91,103	93,95,96,62,98
D.2.2. Hyperautofluorescent lesions may present as wreath-like spots with overlying dots and do not typically follow retinal or choroidal vascular patterns	21	93,94,96,97,62,98,106
MEWDS - OCT		
D.3.1. Multifocal hyporeflectivity (attenuation) is seen in the interdigitation and ellipsoid zones.	21,22,91,92,104,107	93–95,96,97,62,98,105,108, 109,110,106,102,101
D.3.2. The external limiting membrane may remain intact.	21	93,98,105,106
D.3.3. Hyperreflective material may extend from the ellipsoid zone into the outer and inner retina.	91,92,104	93,94,96,97,108,110,101
D.3.4. The RPE and choriocapillaris typically remain intact.	91,111	93,97,62,98,108,100
D.3.5. Increased signal transmission is seen beneath active lesions.		108
D.3.6. Vertical hyperreflective lines may cross the outer retina.	103	95,112
D.3.7. Hyperreflective dots may be seen in the inner choroid.		106
MEWDS - Fluorescein Angiography		
D.4.1. Wreath-like lesions appear in mid-phase FA with hypofluorescent centers, hyperfluorescent borders, and late leakage.	91,103,104	94,96,97,98,105,108,110
D.4.2. Optic disc staining may be present.	103	93,97,98
D.4.3. Focal or segmental venous wall leakage may occur.	103	94,97,105,106
D.4.4. Late-phase foveal alterations may appear as hypofluorescent areas.		95
MEWDS - Indocyanine Green Angiography		
D.5.1. Lesions are absent in early ICGA frames and spread centrifugally in later phases.	91,104	93,95,96,62,99,105,108
D.5.2. Lesions appear hypofluorescent from mid-phase to late-phase.	92,104	93,95,96,97,62,99,105,108, 100,106,109,110,102
D.5.3. Hypofluorescent dots may overlay areas of broader hypofluorescence.	91,92,103,104	93,96
MEWDS - OCT Angiography		
D.6.1. *En face* imaging shows round, wreath-like hyporeflective lesions in the ellipsoid zone, often with central dots.	91	
D.6.2. OCTA shows mild flow voids at the level of the choriocapillaris.		100
SERPIGINOUS CHOROIDITIS - Color Fundus Photography		
E.1.1. Lesions originate in the choroid, may be unifocal or multifocal and are typically larger than 125 microns.	113	114
E.1.2. Lesions appear gray, white, or yellow.	113	115
E.1.3. Lesions may follow a helicoid pattern and coalesce over time.	113	114
E.1.4. Lesions are most commonly located in the posterior pole, peripapillary area, and mid-periphery.	113	114,115

(*continued on next page*)

TABLE 2. (*continued*)

Imaging Statement	Pre-2018	2018-2024
E.1.5. Healed lesions show variable pigmentation.		39,115
SERPIGINOUS CHOROIDITIS - Autofluorescence		
E.2.1. Active lesion borders are hyperautofluorescent, while inactive borders are hypoautofluorescent.	113	39,116,114,117
SERPIGINOUS CHOROIDITIS - OCT		
E.3.1. OCT shows outer retinal hyperreflectivity and disruption of photoreceptors and RPE	113	39,114,118,115
E.3.2. The choriocapillaris may appear thickened beneath active lesions.		118
E.3.5. OCT may show clumping or atrophy of the outer retina and RPE in healed lesions.	113	39,114
SERPIGINOUS CHOROIDITIS - Fluorescein Angiography		
E.4.1. Lesions exhibit early diffuse hypofluorescence.		116,114,117,115
E.4.3. Active lesions may show late hyperfluorescence at the borders.		114,117,115
SERPIGINOUS CHOROIDITIS - Indocyanine Green Angiography		
E.5.1. Active lesions are hypofluorescent on ICGA, except for large choroidal vessels.		116,114,117,115
SERPIGINOUS CHOROIDITIS - OCT Angiography		
E.6.1. Active lesions show confluent flow deficits in the choriocapillaris.		116,114,119,117,115
E.6.2. OCTA reveals vascular detail and flow within choroidal neovascular membranes.		114

tecting the birdshot lesions.[54] FA shows a distinctive pattern of perineural leakage along the major arcade vessels that is not seen in non-BSCR patients.[54] This is noninvasively replicated on *en face* OCT as moderate to severe thickening along the major arcade vessels.[52] OCT may detect suprachoroidal fluid in the absence of retinal inflammation on FA indicating that retinal and choroidal inflammation may occur independently.[51] Active, early-onset BSCR may present with severe outer retinal dysfunction characterized by a triad of hyperautofluorescence, loss of ellipsoid zone (EZ) and RPE on OCT, and hypofluorescent spots in the late ICGA.[49] Diffuse, transient hyperautofluorescence at presentation was associated with worse visual acuity.[49] On OCTA, reduced foveal choroidal vascular density is also correlated with worse vision.[122]

MMI does not show distinctive features that discriminate MFC/PU from MFC/PIC, suggesting that the two diagnoses share a common pathophysiology.[37,77,69] Similarly, the MMI characteristics of solitary punctate chorioretinitis resemble those of MFC/PIC except in number of lesions.[79] MMI provides comprehensive lesion detection of the characteristic posterior or peripheral punched out chorioretinal lesions.[58] Although they are visible on CFP and FAF, all lesions are better detected on wide field FA and ICGA.[59] FA is more effective in detecting small punctate lesions in MFC/PIC than color photography alone.[80] MMI also reveals a diagnostic feature of chrysanthemum lesions, which are hypoautofluorescent, uniformly hyperfluorescent grey-yellow cores surrounded by satellite dots that demonstrate early and late hypofluorescence on ICGA.[58,60] Linear streaks are another characteristic feature of MFC/PU; in the posterior pole MMI discriminates linear, atrophic lesions from the lacquer cracks of myopic maculopathy.[61] On OCTA, areas of RPE elevation and subretinal hyperreflectivity co-localize with demarcated flow voids in the choriocapillaris, which is helpful in hypothesis generation about pathophysiology.[86]

MEWDS generated many clinical utility statements for initial diagnosis.[93–95,112] CFP is better at displaying larger lesions (spots) of 200 microns or greater rather than smaller lesions.[96] There is often a characteristic foveal granularity on CFP that persists after fading of the white dots.[95,97] Superior diagnostic MMI combinations are FAF and OCT[96,123] and ICGA compared to other modalities.[95,62,98,105] MMI findings support RPE dysfunction rather than choroidal pathology as the primary source of the photoreceptor and vision abnormalities. This is evident in the structural alignment of inflammatory lesions with hyperautofluorescence on FAF, hyperreflective material over the RPE with hypertransmission on OCT, FA hyperfluorescence with preserved retinal capillary plexuses on OCTA, and hypofluorescence on ICGA in the absence of choriocapillaris flow voids.[97,98,108] Visual function on microperimetry correlates with foveal granularity and photoreceptor hyperreflectivity.[112] MMI is useful in distinguishing primary from secondary MEWDS. Secondary MEWDS has fewer lesions than primary MEWDS on FAF and the lesions associate with the choroidal disorder rather than a typical perineural and posterior distribution of primary MEWDS.[99]

In SC, OCTA is more sensitive in detecting the early choriocapillaris hypoperfusion of new lesions than

other modalities.[39,116,114] OCT identifies anatomic differences between serpiginous choroiditis and tuberculous serpiginous-like choroiditis with the latter more frequently showing features such as vitreous hyperreflective spots, intraretinal edema, sub-RPE drusenoid deposits, and choroidal granulomas.[118]

• **MMI FOR ACTIVITY OF NON-INFECTIOUS POSTERIOR UVEITIS:** Clinical utility to determine disease activity was ascribed to statements that contrasted active and inactive lesions in cross-sectional or longitudinal studies or demonstrated superiority of a modality in detecting activity.

In APMPPE, OCTA offers superior differentiation, compared to ICGA, between active hypoperfusion and inhomogeneity of the choriocapillaris and inactive atrophy.[38,119] The co-localization of early, active hypofluorescent lesions on FA with hypoperfusion on OCTA is also more precise than with ICGA.[38] On FAF, subacute lesions display central hyperautofluorescence, while inactive lesions display alternating hypo- and hyperautofluorescence patterns.[40] The transition between active and inactive lesions is seen in multiple modalities, for example, the hypochromic, hyperautofluorescent lesions regress over time,[39] EZ disruption improves on OCT,[42] and choriocapillaris nonperfusion improves on OCTA.[39]

BSCR typically has a chronic course rather than a remitting or recurrent course. Signs of persistent activity are therefore largely the same as those used for diagnosis with the added significance of whether treatment is effective. Active BSCR has retinal thickening on OCT[52] and retinal leakage on FA[44] as well as thickened choroid on OCT.[44] In active disease, an increased proportion of the choroidal volume is occupied by choroidal vessels on OCTA, giving an appearance of choroidal hyporeflectivity.[124] Vascular loops in the perifoveal retinal capillary plexus on OCTA are also indicators of disease activity.[45] ICGA provides additional findings of fuzzy choroidal vessels and hypofluorescent dark dots.[49,46] A specific early-onset pattern of active disease may occur with hyperautofluorescence and outer retinal disruption on OCT and has a poor prognosis for visual acuity outcomes.[49]

In MFC/PU and MFC/PIC, active focal lesions are typically yellowish with irregular borders due to retinal edema and are hypoautofluorescent centrally with hyperautofluorescent margins or diffusely hyperautofluorescent.[58,61,65–67,81] Small active MFC/PIC lesions are more readily detected with FAF than CFP.[77,85] Active lesions are hyperfluorescent and leaking in the later phases of FA,[65,78] whereas active lesions are hypofluorescent on ICGA, with an increase in lesion area compared to the inactive stage.[69] The area of hypofluorescence on ICGA often correlates with FAF findings and reflects the extent of choroidal involvement.[69] On OCT, active lesions present iso- or hyperreflective material between Bruchs membrane and RPE and hypertransmission of signal to the choroid.[60,61,67,82,63] Outer retinal infiltration and disruption of the EZ may occur.[69,65] Choroidal thickness on OCT increases during activity and decreases after treatment.[37] OCTA choriocapillaris flow voids and the corresponding hypofluorescence on ICGA also increase during activity.[69,86]

The short time course of MEWDS also results in overlap of diagnostic and activity markers. MMI provides insights about the effects of active disease on the retina. In the acute stages of MEWDS, foveal granularity is present on CFP.[97] OCT shows outer retinal disruption[95,109] and increased choroidal thickness and vascularity in active lesions. [109,100] Discrete hyperreflective dots may be present in the inner choroid.[112,110] Active lesions are hyperautofluorescent,[106] hyperfluorescent on FA in late stages, and hypofluorescent on ICGA in late stages.[97,106] EZ disruption and RPE irregularities on OCT are associated with increased transmission beneath active inflammatory foci.[108] Each of these markers of activity resolves completely over time.[95] Because no single modality fully captures disease activity or resolution, MMI is preferred.[105] Additionally, OCT B scans reveal vertical hyperreflective lines and hyperreflective dots, which were proposed as indirect markers of Müller cell activation.[112]

New activity during the persistent, recurrent course of SC is well defined by MMI. OCTA is the most sensitive modality for detecting active lesions, which appear as expanding areas of choriocapillaris flow deficits that shrink following corticosteroid treatment.[39,116,114,117,115] Active lesions show an area of complete lack of a decorrelation signal (flow) from the choroid as well as the choriocapillaris slab whereas inactive lesions are hyperintense due to exposure of the large choroidal vessels.[125] FAF changes lag behind OCTA flow deficits, suggesting delayed RPE response to choriocapillaris ischemia. As lesions heal, overlying RPE becomes hyperautofluorescent (a typical border change) or hypoautofluorescent (scarred), indicating secondary RPE and outer retinal damage from ischemia.[116] ICGA has characteristic blurred margins during activity and sharp margins after healing.[117] FA also shows blurred margins for active lesions and well-defined margins that stain with fluorescein when inactive.[117] ICGA is superior to FA because it shows more lesions.[114]

• **MMI FOR MONITORING OF NONINFECTIOUS POSTERIOR UVEITIS:** Clinical utility of MMI for monitoring was interpreted as a meaningful correlation between imaging findings and the clinical course and outcomes of the uveitis.

APMPPE presents a complex disease course of variable length. Monitoring with MMI allows documentation of healing as flare ups rarely occur. The acute hypochromic and hyperautofluorescent lesions gradually regress. [39] OCTA can show either persistent closure of the choriocapillaris or near complete recovery. [38] Hyperautofluorescence partially resolves.[39] Quantitative evaluation of the EZ is recommended for tracking anatomic recovery.[42]

For BSCR long-term immunosuppressive therapy necessitates continued monitoring for the response to ther-

apy. Both FA and ICGA display fewer inflammatory signs during treatment.[44] Choroidal lesions regress on ICGA.[46] OCT-derived choroidal vascularity index measurements and OCTA retinal vascular imaging are proposed to detect subclinical activity.[124,45,53] Outer retinal lesions and EZ disruption on OCT correlate with vision loss even in the absence of CME.[48] Choroidal thinning and suprachoroidal fluid during follow up may indicate progressive choroidal degeneration.[55]

MMI confirms lesion healing and absence of new lesions in treated or observed patients with MFC/PU and MFC/PIC. As lesions heal, they become flat and sharply margined with variable atrophy.[69,61] Despite healing, atrophic scars may enlarge centrifugally, [63] increasing the risk of recurrence.[67] Persistent hyperautofluorescence around inactive lesions [66] and atrophic scar enlargement are associated with poorer visual function.[63] In either MFC/PU or MFC/PIC, OCT shows resolution of the sub-RPE material with healing; disrupted RPE and EZ loss may persist.[69,61,81] Reconstitution of the EZ correlates with vision improvement. In MFC/PIC hyperautofluorescence decreases with EZ reconstitution but may persist despite lesion healing, [66,85] or recur.[77,85] Patchy hyperautofluorescence at onset is associated with increased risk of new lesions.[77] On OCTA choriocapillaris flow deficits improve with treatment, [74,86] a change that is also seen in solitary punctate chorioretinitis.[79]

For **MEWDS,** MMI effectively tracks disease resolution. All modalities appear to be useful in documenting resolution of the disease. Color fundus photography shows visible reduction in spots and foveal granularity.[110] There is progressive restoration of isoreflectivity on OCT.[96,97,98,108,100,106,110,102] Concomitant with resolution of the EZ disruption on OCT, hyperautofluorescence becomes isoautofluorescence.[98] Similarly, lesions become isofluorescent on ICG and undetectable on FA.[97,108] The initial thickening and increased vascularity of the choroid subsides during follow up.[97,109,102] Flow voids on OCTA improve [100] while on OCT there is reduction in the number of choroidal hyperreflective dots.[112] The combination of OCT and autofluorescence imaging is especially recommended for monitoring.[95,96]

Monitoring serpiginous choroiditis with MMI can confirm that treatment is effective and detect recurrences before they are clinically evident. OCTA quantifies a decrease in vascular density in newly affected areas that improves after treatment.[117] OCTA findings correlate with OCT, which shows decreasing choroidal thickness and hyperreflectivity during treatment.[115] In pre-2018 literature [113] and in SUN II, [8] autofluorescence was the main modality used for monitoring, however, the hyperautofluorescence of new lesions may lag the acute changes in choriocapillaris flow seen on OCTA.[39,116]

• **MMI FOR COMPLICATIONS OF NON-INFECTIOUS POSTERIOR UVEITIS:** Macular neovascularization (MNV), often referred to as choroidal neovascularization (CNVM) in this dataset, is the primary target of MMI in non-infectious posterior uveitis. CNVM can lead to scarring and progressive vision loss but is treatable if detected early. Non-exudative outer retinal atrophy is another significant complication that can result in irreversible visual impairment.

In APMPPE, OCTA is superior to ICGA in delineating hypoperfused areas that, if unresolved, may lead to RPE and outer retina damage.[38] The integrity of the outer retinal layers on OCT correlates with visual acuity outcomes.[40] In addition to detecting hypoperfusion, OCTA aids in the diagnosis of CNVM.[39]

In BSCR, wide-angle fluorescein angiography reveals peripheral retinal ischemic changes in some patients.[56] The complication of cystoid macular edema is relatively specific for BSCR among the other types of posterior uveitis. OCT detects macular edema and loss of the EZ, both contributing to decreased visual acuity.[45,48] OCTA detects microvascular changes in the retinal capillary beds and absent flow in the choriocapillaris.[51] Choroidal thinning during follow up is interpreted as a degenerative process.[55]

MFC lesions usually heal with retinal atrophy or scarring.[60,61,63] Hady et al. reported that 80.4% of the active MFC/PIC lesions progress to punched out atrophic scars.[61] Less autofluorescence on FAF indicates that linear scars from MFC/PU are more atrophic than myopic lacquer cracks.[59] Characteristics of CNVM on OCTA are similar in both MFC/PU and MFC/PIC.[36,49,83,84,99] OCT findings help differentiate CNVM from inflammatory lesions. CNVM is associated with hypotransmission of the OCT signal to the choroid (shadowing), whereas hypertransmission may precede CNVM development.[69,88] CNVM appears as a hyperautofluorescent lesion with variable hypo- or hyperautofluorescent ring.[58] Increased choroidal thickness is often present in active CNVM.[72,71] A "pitchfork" sign on OCT with vertical, hyperreflective lines extending above the outer nuclear layer also indicates CNVM is present.[71] FA distinguishes active CNVM, which leaks, from inactive CNVM, which stains.[58] Both FA and OCTA aid in CNVM diagnosis, [65,78,73] with OCTA particularly effective in differentiating CNVM from inflammatory lesions based on vascular flow characteristics.[69,65,72]

MEWDS is short-lived and complications are infrequent. Persistent hyperfluorescence of the optic nerve on FA may indicate incomplete resolution.[105]

In SC, OCT shows diffuse outer retinal and RPE atrophy that colocalizes to absent choriocapillaris on OCTA.[115] Early lesions that show only decrease in choriocapillaris flow with intact outer nuclear layer structures and without hypoautofluorescence may resolve without scarring.[116] OCTA is predicted to be similarly effective in detecting CNVM as in other types of posterior uveitis.

• **GRADE EVALUATION:** The systematic review was used to estimate the effect of performing vs. not performing a specific test. Diagnosis is a critical outcome for all diseases, as is

TABLE 3. Summary of Findings: Recommendation to Use Imaging Modalities for Specific Outcomes of Diagnosis, Activity, Monitoring and Complications in Non-Infectious Posterior Uveitis

Modality (overall rank)	Clinical Utility Domain	APMPPE	BSCR	MFC/PU or MFC/PIC	MEWDS	SC
COLOR	Diagnosis	++++	+++	++++	++++	++++
	Activity			+	+	+
	Monitoring	++++		++++	++++	+++
	Complications					
FAF	Diagnosis	++++	++	++++	++++	++++
	Activity	++++		++++	++++	++++
	Monitoring	++++		+++	++++	++++
	Complications					
FA	Diagnosis	+++	++++	++++	+++	++++
	Activity		++++	++++		+++
	Monitoring		++++	+++		++
	Complications	++++	++	++++	+++	++++
ICG	Diagnosis		++++	+++		+++
	Activity		++++	++	++	+++
	Monitoring		++++	++		++
	Complications	+++	+++	+++		+++
OCT	Diagnosis	++++	++	++++	++++	++++
	Activity	++++	+++	++++	++++	++++
	Monitoring	+++	++++	++++	++++	++++
	Complications	++++	++++	++++	++	++++
OCTA	Diagnosis		+			
	Activity	+++	+++	++	+++	++++
	Monitoring		++			+++
	Complications	+++	++++	++++	+++	++++

Strength of recommendation to use: ++++ = high. +++ = moderate. ++ = low. + = very low. Blank = not graded due to insufficient information.

the assessment of complications. Activity and monitoring are critically important in patients in whom activity can be intermittent (MFC/PU and MFC/PIC, SC), or in whom healing is expected after a time limited course (MEWDS, APMPPE). Activity and monitoring are also critically important in MFC/PU, BSCR and SC, in which immunosuppressive therapy is often used.[126] Complications such as macular neovascularization or retinal atrophy are especially important in uveitis prone to MNV, such as MFC/PU and MFC/PIC, or retinal atrophy, such as SC.

The assumption was that each study provided at least low-level evidence for a positive effect on outcomes because it met the traditional quality criteria for papers on retinal imaging in uveitis. The strength of the recommendation was thereafter upgraded or downgraded based on various considerations.[127] Case series were not *a priori* considered as very low evidence because often no higher level of evidence exists due to the rarity of posterior uveitis.[128] Cohort and case-control studies were assessed as having less risk of bias than cross-sectional case series.[129] In addition, the rating was upgraded if there were consistent conclusions among multiple papers and larger numbers of patients as noted in Table 1 or if there were compatible consensus guidelines in SUN II.[3,4,7,8] The frequency of clinical utility statements relative to the number of studies was also a factor (Table 1).

Qualitative precision was met for any digital color photograph other than multi-color, any digital autofluorescence, any SS-OCT or SD-OCT, any digital angiography, any SS-OCTA or SW-OCTA. Quantitative precision for OCT and OCTA was met if there were multiple independent measures.[130] Results were considered only if they pertained directly to utility in non-infectious posterior uveitis rather than appearing as an incidental factor in a study that did not focus on imaging.[131] Due to the similarity of imaging findings in MFC/PU and MFC/PIC, they were grouped for this analysis.

The GRADE evidence levels were ranked as high, moderate, low or very low (Table 3).

DISCUSSION

This systematic review assesses the role of MMI in the diagnosis and clinical management of non-infectious poste-

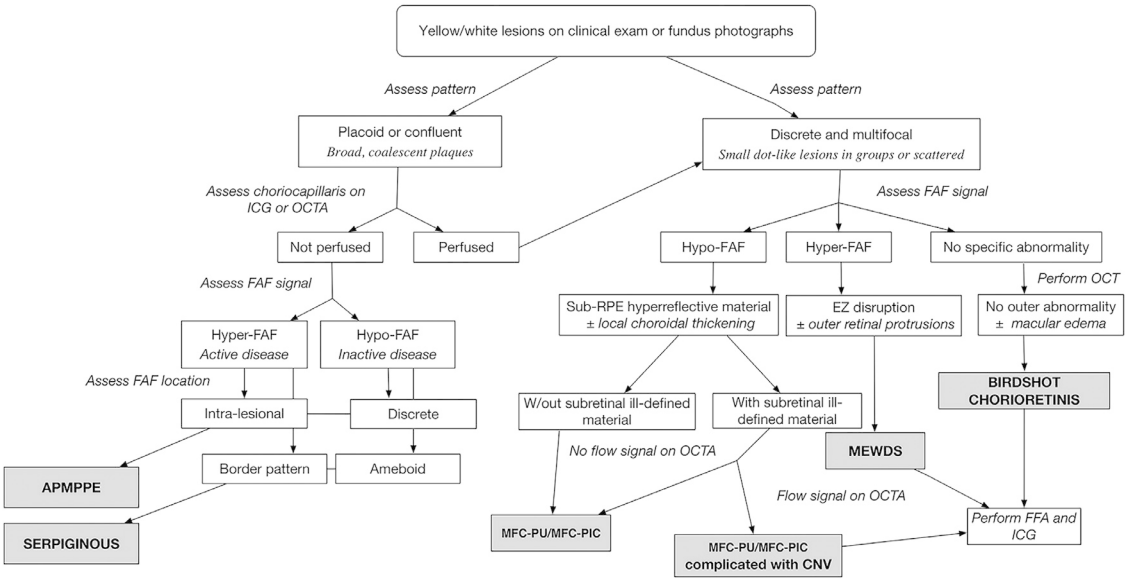

FIGURE 2. Algorithmic approach to diagnostic multimodal imaging in patients presenting with outer retinal or subretinal lesions consistent with non-infectious posterior uveitis of the types studied in this review. After pattern assessment, preferably including wide-angle color fundus photography, non-invasive imaging is performed first. For placoid and coalescing lesions, OCTA is performed to detect either A) choriocapillaris non-perfusion or B) *en face* hyporeflectivity at the outer retina/RPE junction. For choriocapillaris non-perfusion, perform autofluorescence (FAF) to discriminate between APMPPE and serpiginous choroiditis. Fluorescein and indocyanine green angiography (FA/ICG) are also recommended for initial diagnosis. En face outer retinal hyporeflectivity also requires FAF but is interpreted according to the algorithm for discrete and multifocal lesions. Hyperautofluorescence (hyper-FAF) with ellipsoid zone (EZ) disruption on OCT is highly suggestive of multifocal evanescent white dot syndrome (MEWDS). Discrete hypoautofluorescent (hypo-FAF) lesions between Bruchs and RPE are compatible with inactive multifocal choroiditis with panuveitis (MFC-PU) and punctate inner choroidopathy (MFC-PIC). Either hypo-FAF or hyper-FAF is compatible with active MFC-PU or MFC-PIC. Subretinal ill-defined material on OCT prompts OCTA or dye-based angiography. Presence of OCTA flow signal in this material is interpreted as choroidal neovascularization. Autofluorescence and OCT may be unremarkable in birdshot chorioretinopathy (BSCR), therefore, wide-angle dye-based FA/ICG is the preferred modality to detect typical fluorescein leakage of large retinal veins and absent indocyanine green staining in the birdshot lesions. Dye-based angiography should also be performed if algorithmic testing does not result in a diagnosis or when non-invasive imaging tools are not available or inadequate to visualize peripheral lesions.

rior uveitis. The review contributes new information to the SUN II classification criteria that were based primarily on clinical features and fundus appearance. In SUN II, imaging was incorporated into criteria sparingly. The results of this review suggest that imaging currently plays a broader role in diagnosis and management than reflected in SUN II classification criteria. Publication of MMI findings has increased since the data collection and analysis phase of SUN II prior to 2018. It is now common to include statements of the clinical utility of imaging findings. Although each of the diseases studied are rare, necessitating reliance on case series for analysis, the methods employed in the published work mirror those used in clinical settings in which technologically advanced imaging studies are now common.

The utility of MMI for posterior uveitis seems intuitive. The outer retinal, RPE-Bruch's and inner choroid complex in the posterior pole is critical for visual function. Imaging provides a level of cellular and subcellular detail of this region that surpasses clinical examination, allowing for earlier detection of pathological changes. The benefits of MMI are particularly important in monitoring the course of diseases with slow resolution (APMPPE), chronic course (BSCR), or sporadic reactivations that are potential sight-threatening and require urgent management (MFC/PU, MFC/PIC and SC). In active BSCR, early identification of inflammatory photoreceptor involvement on OCT can prompt timely intervention, potentially preventing irreversible retinal damage and vision loss.[49,48] In chronically treated BSCR, MMI provides objective measures of ICGA for choroidal inflammation and OCT for outer retinal integrity that enable clinicians to assess the adequacy of treatment. OCTA, with its ability to noninvasively identify and characterize pathological vascular networks, is particularly effective in distinguishing CNVM from inflammatory lesions, ensuring appropriate therapeutic decisions. In SC, OCTA can detect clinically inapparent choriocapillaris closure in the early stages of activity when intervention may yet preserve function by reopening ischemic areas.

FAF and OCT effectively track the initial expansion and ultimate resolution of MEWDS. FAF and OCT changes are also closely associated with visual prognosis in each of these disorders. MMI is also critical in differentiating between APMPPE and SC, and important in recognizing that MFC/PU and MFC/PIC are likely the same pathogenically with differences mainly in location and size of lesions but not in imaging characteristics, suggesting that future consensus diagnostic guidelines incorporating MMI may refine disease classification, supplementing the primarily clinical framework of SUN II.

Several limitations of this review must be acknowledged. It focuses on specific forms of non-infectious uveitis, and the findings of clinical utility may not translate to other inflammatory, infectious, neoplastic, vascular, or degenerative disorders that affect the outer retinal complex. The decision to image or not to image is often before a diagnosis is reached and alternative diagnoses such as masquerades or infections will usually require ancillary testing beyond imaging and have important outcomes other than those studied here. Grouping MFC/PU and MFC/PIC may be controversial. Additionally, other SUN II uveitis types with some imaging as part of the classification criteria were not addressed. This is a worthwhile future project.

Most studies included in this review derive from real-world clinical practice and unsponsored clinical research and therefore reflect typical diagnostic and management strategies. Imaging availability varies across practice settings, and some clinicians may opt for less imaging due to preference or resource limitations. The outcomes reported in the literature may not apply to settings where imaging is not routinely performed. The clinical utility of MMI in the reviewed studies supports and refines clinical impressions and practice while offering deeper insight into disease mechanisms at the tissue level. The accuracy of imaging-based conclusions remains contingent on correct clinical diagnosis, as no definitive gold standard test exists for these diseases. Future prospective studies with standardized imaging protocols may help refine the classification of non-infectious posterior uveitis based on objective imaging criteria.

The use of GRADE methodology in this study provides an evidence-based framework for evaluating the certainty of imaging recommendations. Consistent findings across many observational studies strengthens the case for incorporating advanced imaging into practice and into guidelines. The assessment that case series provide at least low-level evidence is justified by the absence of higher-tier studies, a limitation inherent to rare disease research. Translation of GRADE recommendations to actual practice may vary. To enhance the clinical applicability of this review, a simplified algorithm has been developed to identify efficient imaging choices based on the initial clinical presentation of presumed non-infectious posterior uveitis (Figure 2). Some tests may be performed simultaneously or in different orders depending on physician preference and local resources. Imaging of some eyes may require modification due to media clarity, either cataract or vitreous haze. Exceptions for other types of uveitis and uveitis masquerades are acknowledged. Reference to the SUN II classification criteria and other clinical references is advised before reaching a final diagnosis.

During the time period covered by this systematic review, OCT resolution improved, wide-angle dye-based angiography expanded visualization of the fundus, and greater utilization of noninvasive imaging techniques such as OCTA and en face OCT enhanced the ability to diagnose complications and hypothesize disease pathophysiology through better lesion definition. Further advancements in imaging technology will likely refine disease classification, monitoring, and management strategies. Machine learning techniques such as were used in SUN II have the potential to enhance the diagnostic and prognostic value of imaging, offering automated pattern recognition and predictive analytics for retinal inflammatory disease. The effective application of machine learning will depend on higher-resolution imaging, standardized acquisition protocols, and uniform specifications for screen resolution and color calibration in image grading.

Additional emerging modalities, such as quantitative autofluorescence and adaptive optics, were not represented in this review but may hold promise for refining characterization of posterior uveitis and detecting subtle disease changes. As imaging continues to evolve, its integration into routine clinical care will likely increase, providing greater precision in diagnosis, disease activity assessment, and therapeutic response monitoring. Standardization of imaging protocols and improved multimodal analysis will be key to optimizing the clinical application of these technologies in NIPU management and future classification frameworks.

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APPENDIX

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