ON-LINE APPENDIX: METHODS

Data Sources and Searches

An experienced medical librarian performed comprehensive literature searches in the electronic data bases Ovid MEDLINE, Ovid Embase, and The Cochrane Library from data base inception to August 15, 2016. The first search was conducted in Ovid MEDLINE. To improve the retrieval of relevant studies and to ensure the methodologic quality of the literature search, an additional librarian peer-reviewed the primary MEDLINE search strategy. Subject headings and keywords were then adapted for the other data bases. Supplementary records were identified by using the "Cited by" and "View references" features in Scopus. Citation management and deduplication was performed in EndNote X7 (http://download.cnet.com/s/endnote-x7/).

All subject searches were conducted on August 15, 2016.

Ovid MEDLINE In-Process and Other Nonindexed Citations and Ovid MEDLINE 1946 to Present

1) exp Multiple Sclerosis/
2) (Multiple Sclerosis or MS).tw.
3) ("normal-appearing white matter" or NAWM or "white matter lesions").tw.
4) or/1–3
5) Gadolinium DTPA/
6) (Gadolinium or Gadodiamide or Gd?DTPA or gadobenate or gadopentetate or Magnograf or Magnevist or Omniscan).tw.
7) Contrast Media/
8) Imaging, Three-Dimensional/
9) exp Image Enhancement/
10) (contrast or enhance$ or 3?D or Dimension*).tw.
11) or/5–10
12) exp Magnetic Resonance Imaging/
13) (Magnetic resonance or MR or MR imaging or MRIs or MRA or MRDTI or t1 or t2).tw.
14) Image Processing, Computer-Assisted/
15) Image Interpretation, Computer-Assisted/
16) Magnetics/
17) (Magnetiz* or magnetic* or magnetism).tw.
18) or/12–17
19) (weighted or diffusion or perfusion) adj2 imag*).tw.
20) (DWI or DTI or PWI or STI or SWI).tw.
21) (quantitative or quantify or susceptibility).tw.
22) or/19–21
23) and/4,11,18,22

Embase 1974 to August 12, 2016

1) multiple sclerosis/
2) (Multiple Sclerosis or MS).tw.
3) ("normal-appearing white matter" or NAWM or "white matter lesions").tw.
4) or/1–3
5) gadolinium pentetate/
6) (Gadolinium or Gadodiamide or Gd?DTPA or gadobenate or gadopentetate or Magnograf or Magnevist or Omniscan).tw.
7) exp contrast medium/
8) three dimensional imaging/
9) image enhancement/
10) (contrast or enhance$ or 3?D or Dimension*).tw.
11) or/5–10
12) exp nuclear MR imaging/
13) (Magnetic resonance or MR or MR imaging or MRIs or MRA or MRDTI or t1 or t2).tw.
14) image processing/
15) computer assisted diagnosis/
16) magnetism/
17) (Magnetiz* or magnetic* or magnetism).tw.
18) or/12–17
19) (weighted or diffusion or perfusion) adj2 imag*).tw.
20) (DWI or DTI or PWI or STI or SWI).tw.
21) (quantitative or quantify or susceptibility).tw.
22) or/19–21
23) and/4,11,18,22

The Cochrane Library

#1 MeSH descriptor: [Multiple Sclerosis] this term only
#2 Multiple Sclerosis or MS
#3 ("normal-appearing white matter" or NAWM or "white matter lesions"):ti,ab,kw
#4 #1 or #2 or #3
#5 MeSH descriptor: [Gadolinium DTPA] this term only
#6 (Gadolinium or Gadodiamide or Gd*DTPA or gadobenate or gadopentetate or Magnograf or Magnevist or Omniscan):ti,ab,kw
#7 MeSH descriptor: [Contrast Media] this term only
#8 MeSH descriptor: [Imaging, Three-Dimensional] explode all trees
#9 MeSH descriptor: [Image Enhancement] explode all trees
#10 (contrast or enhance* or 3*D or Dimension*):ti,ab,kw
#11 #5 or #6 or #8 or #8 or #9 or #10
#12 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#13 (Magnetic resonance or MR or MR imaging or MRIs or MRA or MRDTI or t1 or t2):ti,ab,kw
#14 MeSH descriptor: [Image Processing, Computer-Assisted] this term only
#15 MeSH descriptor: [Image Interpretation, Computer-Assisted] this term only
#16 MeSH descriptor: [Magnetics] this term only
#17 (Magnetiz* or magnetic* or magnetism):ti,ab,kw
#18 #12 or #13 or #14 or #15 or #16 or #17
#19 ((weighted or diffusion or perfusion) near/two imag*):ti,ab,kw
#20 (DWI or DTI or PWI or STI or SWI):ti,ab,kw
#21 (quantitative or quantify or susceptibility):ti,ab,kw
#22 #19 or #20 or #21
#23 #four and #11 and #18 and #22

ON-LINE SUPPLEMENT REFERENCES: STUDIES INCLUDED IN SYSTEMATIC REVIEW AND META-ANALYSIS

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3. Droogan AG, Clark CA, Werring DJ, et al. **Comparison of multiple sclerosis clinical subgroups using navigated spin echo diffusion-weighted imaging.** *Magn Reson Imaging* 1999;17:653–61 CrossRef Medline
4. Faizy TD, Thaler C, Kumar D, et al. **Heterogeneity of multiple sclerosis lesions in multislice myelin water imaging.** *PLoS One* 2016;11: e0151496 CrossRef Medline
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7. Filippi M, Iannucci G, Cercignani M, et al. **A quantitative study of water diffusion in multiple sclerosis lesions and normal-appearing white matter using echo-planar imaging.** *Arch Neurol* 2000;57: 1017–21 CrossRef Medline
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11. Goodkin DE, Rooney WD, Sloan R, et al. **A serial study of new MS lesions and the white matter from which they arise.** *Neurology* 1998; 51:1689–97 CrossRef Medline
12. Hiehle JF Jr, Grossman RI, Ramer KN, et al. **Magnetization transfer effects in MR-detected multiple sclerosis lesions: comparison with gadolinium-enhanced spin-echo images and nonenhanced T1-weighted images.** *AJNR Am J Neuroradiol* 1995;16:69–77 Medline
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On-line Table 1: Study and patient characteristics[a]

Study No.	Study First Author and Year	MRI Technique	MRI Parameter	Study Design	Total No. of Subjects	Mean Age (±SD)	Women, No. (% Female)	Median Disease Duration (yr)	Median Expanded Disability Status Scale
MRI technique: DTI									
1	Tievsky et al, 1999[28]	DTI	FA	Prospective	12	33 yr (±3.9)	8 (66.7%)	3.1	NA
2	Werring et al, 1999[33]	DTI	FA + MD	Prospective	6	34.2 yr (±4.2)	5 (83.3%)	3.5	3.9
3	Bammer et al, 2000[1]	DTI	FA + MD	Prospective	14	36.2 yr (±10.1)	10 (71.4%)	NA	Range, 1–5
4	Filippi et al, 2000[7]	DTI	MD	Prospective	35	28.0 yr (±4.8)	20 (57.1%)	3.5	1.5
5	Filippi et al, 2001[6]	DTI	FA + MD	Prospective	78	41.6 yr (±9.5)	42 (53.8%)	10	5
6	Naismith et al, 2010[17]	DTI	FA + MD	Prospective	22	42.0 yr[b] (range, 33–53)	15 (68.2%)	9.1	4.4
7	Fox et al, 2011[9]	DTI	FA	Prospective	21	41.6 yr (±9.7)	15 (71.4%)	11.9[c]	NA
8	Liu et al, 2012[15]	DTI	FA + MD	Prospective	22	42 yr[b]	16 (69.6%)	6	2
9	Testaverde et al, 2012[27]	DTI	FA + MD	Prospective	14	41 yr	12 (85.7%)	NA	Range, 1–3
MRI technique: DWI									
1	Droogan et al, 1999[3]	DWI	ADC	Prospective	35	43.8 yr (±9.0)	30 (63.8%)	11.7	NA
2	Tievsky et al, 1999[28]	DWI	ADC	Prospective	12	33 yr (±3.9)	8 (66.7%)	3.1	NA
3	Nusbaum et al, 2000[18]	DWI	ADC	Prospective	16	33.4 yr (range, 16–62)	13 (81.3%)	NA	NA
4	Roychowdhury et al, 2000[25]	DWI	ADC	Retrospective	24	41 yr	17 (70.8%)	NA	NA
5	Phuttharak et al, 2006[22]	DWI	ADC	Prospective	37	38.2 yr	25 (67.6%)	NA	4.15
6	Yurtsever et al, 2008[35]	DWI	ADC	Prospective	35	35 yr (±2)	30 (85.7%)	NA	3.2[b]
7	Zivadinov et al, 2008[37]	DWI	ADC	Prospective	45	48.3 yr (±7.6)	36 (80%)	14.8	3.6
8	Michoux et al, 2015[16]	DWI	ADC	Retrospective + prospective	30 (group 1, 21; group 2, 9)	NA	NA	NA	NA
9	Sahin et al, 2015[26]	DWI	ADC	Prospective	25	NA	13 (52%)	NA	NA
MRI technique: MWI									
1	Oh et al, 2007[19]	MWI	MWF	Prospective	89	43.4 yr (±9.5)	NA	9.7	1.7
2	Levesque et al, 2010[14]	MWI	MWF	Prospective	5	42.6 yr (±10.3)	5 (100%)	NA	Range, 1–4
3	Vargas et al, 2015[31]	MWI	MWF	Prospective	23	32.8 yr (±7.9)	16 (66.7%)	5.3	1.5
4	Faizy et al, 2016[4]	MWI	MWF	Prospective	17	40.9 yr (±13.2)	10 (58.8%)	NA	2.4
MRI technique: qMRI									
1	Hiehle et al, 1995[12]	qMRI	MTR	Prospective	35	35.7 yr (±9.7)	NA	NA	NA
2	Petrella et al, 1996[21]	qMRI	MTR	Prospective	29	NA	NA	NA	NA
3	Filippi et al, 1998[8]	qMRI	MTR	Prospective	10	30.4 yr	7 (70%)	4.4[c]	2
4	Goodkin et al, 1998[11]	qMRI	MTR, PD, T1 + T2	Prospective	22	34.3 yr	11 (50%)	1[c]	1.4[bc]
5	van Waesberghe et al, 1998[30]	qMRI	MTR	Prospective	11	Range, 18–38 yr	11 (90.9%)	Range, 1–17	Range, 1–7
6	Rovira et al, 1999[24]	qMRI	MTR	Prospective	11	32 yr (range, 21–46)	11 (18.2%)	4.7[b]	2[c]
7	Pike et al, 2000[23]	qMRI	MTR	Prospective	30	41.0 yr (±7.5)	12 (36.7%)	NA	5.4[c]
8	Fazekas et al, 2002[5]	qMRI	MTR + $T1_{free}$	Prospective	12	Range, 22–37 yr	8 (66.7%)	NA	2.2
9	Papanikolaou et al, 2004[20]	qMRI	MTR + T2	Prospective	13	29.5 yr (range, 16–42)	6 (46.2%)	NA	Range, 1.5–7.5
10	Giacomini et al, 2009[10]	qMRI	MTR	Prospective	6	43.7 yr (±9.7)	6 (100%)	5.3	2.6
11	Levesque et al, 2010[14]	qMRI	$T1_{rate}$	Prospective	5	42.6 yr (±10.3)	5 (100%)	NA	Range, 1–4
12	van den Elskamp et al, 2010[29]	qMRI	MTR	Prospective	32	32.3 yr (±9.5)	20 (62.5%)	5.8[b]	2
13	Vavasour et al, 2011[32]	qMRI	MTR	Prospective	7	42 yr (range, 30–50)	4 (57.1%)	Range, 2–11	3

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On-line Table 1: Continued

Study No.	Study First Author and Year	MRI Technique	MRI Parameter	Study Design	Total No. of Subjects	Mean Age (±SD)	Women, No. (% Female)	Median Disease Duration (yr)	Median Expanded Disability Status Scale
14	Jurcoane et al, 2013[13]	qMRI	MTR, PD + $T1_{free}$	Prospective	1) RRMS: 17	27.5 yr[b] (range, 19–47)	13 (76.5%)	0.58	1
					2) PMS: 15	47 yr[a] (range, 37–68)	8 (53.3%)	14.7	6
					Total: 32	NA	21 (65.6%)	NA	NA
15	Blystad et al, 2016[2]	qMRI	R_1, R_2 + PD	Prospective	44	31 yr[b] (range, 21–62)	36 (81.8%)	NA	2
MRI technique: GRE/SWI									
1	Wiggerman et al, 2013[34]	SWI	FS	Prospective	20	40.3 yr (±9.2)	15 (75%)	6.5	2.5
2	Zhang et al, 2016[36]	SWI	QSM	Retrospective	54	34.7 yr (±8.1)	43 (80%)	5.7[c]	1.6[c]

Note:—qMRI indicates quantitative MR imaging; NA, not available; PD, proton density; PMS, progressive multiple sclerosis; FS, frequency shift; R_1, longitudinal relaxation rate; R_2, transverse relaxation rate; RRMS, relapsing-remitting multiple sclerosis; MWI, myelin water imaging; $T1_{free}$, native relaxation time; $T1_{rate}$, T1 relaxation time.

[a] Study numbers are taken from the On-line Appendix in all tables.

[b] Median values were reported instead of mean values.

[c] Mean values were reported instead of median values.

On-line Table 2: MRI techniques

Study No.	Study First Author and Year	Magnet Vendor and Field Strength	Contrast Agent (Dose)	Method of Characterizing Gadolinium-Enhancing Lesions	Quantitative Imaging Biomarker Compared with Gadolinium Enhancement	Quantitative Biomarker Imaging Sequence Parameters	Method of Characterizing Quantitative Imaging Biomarker	Method of Comparing Gadolinium-Enhancing Lesions with Quantitative Imaging Biomarker
MRI technique: DTI								
1	Tievsky et al, 1999[28]	1.5T	Gadopentetate (dose unspecified)	Qualitative visual assessment	FA	6 Gradient directions with b=1221 s/mm^2; TR, 6000 ms; TE, 118 ms; NEX, 3; matrix, 256 × 128; FOV, 40 × 20 cm; section thickness, 6 mm; voxel volume, 14.6 mm^3; voxel dimensions, 1.56 × 1.56 mm	Quantitative ROI assessment of lesion FA	A semiautomated program that enabled simultaneous determination of T2 signal intensity, FA, ADC, and so forth on coregistered image maps
2	Werring et al, 1999[33]	GE[a] 1.5T	Gadolinium-DTPA (0.1 mmol/kg)	Qualitative visual assessment	FA and MD	7 Noncolinear gradient directions with max b=700 s/mm^2; TR, 2 × R-R cardiac intervals; TE, 78 ms; matrix, 96 × 96; FOV, 24 × 24 cm; section thickness, 5 mm	Quantitative ROI assessment of lesion FA and MD	Quantitative FA and MD maps were interpolated up to the same matrix size as the T2WIs
3	Bammer et al, 2000[1]	Philips[b] 1.5T	Gadolinium-DTPA (0.1 mmol/kg)	Qualitative visual assessment	FA and MD	3 Gradient directions with max b=889 s/m^2; TR, 2 × R-R cardiac intervals; TE, 98 ms; matrix, 205 × 256; FOV, 184 × 230 mm; section thickness, 5 mm; section gap, 0.5 mm	Quantitative ROI assessment of lesion FA and MD	Baseline diffusion scan served as a morphologic reference on which ROIs were manually drawn and later copied onto the parameter (FA and MD) maps
4	Filippi et al, 2000[7]	1.5T	Gadolinium-DTPA (0.1 mmol/kg)	Qualitative visual assessment	MD	3 DWIs for each section with a b factor of 289 s/mm^2; interecho spacing, 0.8; TE, 160 ms; matrix, 128 × 128; FOV, 25 × 25 cm; section thickness, 5 mm	Quantitative ROI assessment of lesion MD on MD maps obtained from the average of the 3 DWIs	Lesions were outlined on PD-weighted images and were mapped onto the coregistered diffusion maps; coregistration of images was performed using a surface-matching technique
5	Filippi et al, 2001[6]	Siemens[c] 1.5T	Gadolinium-DTPA (0.1 mmol/kg)	Qualitative visual assessment	FA and MD	DWI EPI: 8 noncolinear gradient directions with duration and maximum amplitude of the diffusion gradients of 25 ms and 21 mT/m^{-1}, giving a maximum b factor of 1044 s/m^2; TE, 123 ms; interecho spacing, 0.8; matrix, 128 × 128; FOV, 25 × 25 cm; section thickness, 5 mm	FA and MD were derived for every pixel after calculating tensor values from DWI; FA and MD images were subsequently calculated, and parameters were obtained using quantitative ROI assessment of lesions	FA and MD images were coregistered on the dual-echo and T1WIs using a 3D rigid body coregistration algorithm; lesions were identified on PD-weighted and T2WIs, and ROIs were automatically transferred onto coregistered FA and MD images
6	Naismith et al, 2010[17]	Siemens 1.5T	Gadobenate dimeglumine (triple dose)	Qualitative visual assessment	FA and MD	Spin-echo EPI: 6 noncollinear directions with 2 interleaved (odd and even sections) acquisitions; TR, 6100 ms; TE, 78 ms; 2.5 × 2.5 × 2.0 mm^3 resolution; b=0 and 1000 s/mm^2; diffusion-sensitizing gradient pulses duration (δ) = 22 ms and separation (Δ) = 30 ms; DTI time, 14 min	Quantitative ROI assessment of lesion FA and MD	MR image registration was accomplished by vector gradient maximization; ROIs delineated on anatomic images (T1WI, T2WI, FLAIR) were therefore in register with the DTI data; ROIs defined on any anatomic image on any scan session were transferrable to the DTI data on any scan session
7	Fox et al, 2011[9]	Siemens 3T	Gadolinium (0.1 mmol/kg)	Qualitative visual assessment	FA	71 Noncollinear DWI gradients with b=2000 s/mm^2; 8 b=0 acquisitions; TR, 7300 ms; TE, 95 ms; matrix, 102 × 102; FOV, 256 × 256 mm; voxels, 2.5 × 2.5 × 2.5 mm; sections thickness, 2.5 mm	Quantitative ROI assessment of lesion FA	Coregistration of anatomic T1 MPRAGE images was done to follow lesions longitudinally; ROIs were inspected and drawn using AFNI[f] to confirm accuracy of coregistration
8	Liu et al, 2012[15]	Siemens 3T	Gadobenate dimeglumine (0.1 mmol/kg, up to 20 mL)	Qualitative visual assessment	FA and MD	60 Gradient directions; gradient b=2000 s/mm^2; TR, 9300 ms; TE, 104 ms, NEX, 1; matrix, 128 × 128; FOV, 204.8 × 204.8 mm^2; section thickness, 2 mm	Quantitative ROI assessment of lesion FA and MD	T2-weighted MRI images were co-registered with the DWI using FLIRT;[d] ROI delineations were transformed to diffusion image space where MD and FA were calculated
9	Testaverde et al, 2012[27]	GE 3T	Gadobutrol (0.1 mL/kg of body weight)	Qualitative visual assessment	FA and MD	25 DWI directions; TR, 13,000 ms; TE, 83 ms; FOV, 24 cm; section thickness, 2.4 mm; section spacing, 1.0 mm	Quantitative ROI assessment of lesion FA and MD	The data obtained were processed using a console for MedNRIA 1.8, which allowed coupling of DWI with the T2 FLAIR and T1 SE images
MRI technique: DWI								
1	Droogan et al, 1999[3]	GE 1.5T	Gadolinium-DTPA (0.1 mmol/kg)	Qualitative visual assessment	ADC	3 Gradient directions with optimal b-value = 738 s/mm^2; TR, 2 × R-R cardiac intervals; TE, 75 ms; NEX, 1; matrix, 128 × 256; FOV, 24 cm; section thickness, 5 mm; section gap, 1 mm	Quantitative ROI assessment of lesion ADC values	All MS lesions were identified on PD and T2WIs by a rater using a semiautomated outlining technique and were manually outlined on the b = 0 step of the DWI
2	Tievsky et al, 1999[28]	1.5T	Gadopentetate (dose unspecified)	Qualitative visual assessment	ADC	6 Gradient directions with b = 1221 s/mm^2; TR, 6000 ms; TE, 118 ms; excitations, 3; matrix, 256 × 128; FOV, 40 × 20 cm; section thickness, 6 mm; voxel volume, 14.6 mm^3; voxel dimensions, 1.56 × 1.56 mm	Quantitative ROI assessment of lesion ADC values	A semiautomated program that enabled simultaneous determination of T2 signal intensity, FA, ADC, and so forth on coregistered image maps

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On-line Table 2: Continued

Study No.	Study First Author and Year	Magnet Vendor and Field Strength	Contrast Agent (Dose)	Method of Characterizing Gadolinium-Enhancing Lesions	Quantitative Imaging Biomarker Compared with Gadolinium Enhancement	Quantitative Biomarker Imaging Sequence Parameters	Method of Characterizing Quantitative Imaging Biomarker	Method of Comparing Gadolinium-Enhancing Lesions with Quantitative Imaging Biomarker
3	Nusbaum et al, 2000[18]	GE 1.5T	Gadobenate dimeglumine (0.1 mmol/kg)	Qualitative visual assessment	ADC	EPI DWI: 3 gradient directions with $b=1000$ s/mm^2; time b/w gradients, 35 ms; pulse width, 37 ms; TR, 10,000 ms; TE, 99 ms; matrix, 128 × 128; FOV, 24 × 24 cm; section thickness, 5 mm; section gap, 2.5 mm	Quantitative ROI assessment of lesion ADC values	ROI measurements were made on the mean ADC images after being drawn on the echo-planar T2-weighted ($b=0$) images
4	Roychowdhury et al, 2000[25]	1.5T	Gadobenate dimeglumine (0.1 mmol/kg, up to 20 mL)	Qualitative visual assessment	ADC	EPI DWI: 3 gradient directions with $b=1000$ s/m^2; TR, 4000 ms; TE, 125 ms; NEX, 1; matrix, 128 × 128; FOV, 24 cm; section thickness, 5 mm	Quantitative ROI assessment of lesion ADC values	Visual comparison among the T2WI, contrast-enhanced T1WI and DWI was used to determine ROI placement on DWI; for RELs, the ROI was placed around the entire lesion, including the nonenhancing center of the lesion
5	Phuttharak et al, 2006[22]	1.5T	Gadobenate dimeglumine (0.1 mmol/kg)	Qualitative visual assessment	ADC	EPI DWI: 3 gradient directions with $b=0$, 500, 1000 s/mm^2; TR, 4521 ms; TE, 110 ms; matrix, 128 × 96; FOV, 24 × 24 cm; section thickness, 5 mm; section spacing, 1.5 mm	Quantitative ROI assessment of lesion ADC values	After lesion identification on T2-weighted and FLAIR images, the lesions were outlined on the diffusion-weighted images ($b=0$) so that the ROIs on ADC images were aligned precisely with the lesions on T2-weighted images
6	Yurtsever et al, 2008[35]	Siemens 1.5T	Not specified	Qualitative visual assessment	ADC	EPI DWI: 3 gradient directions with $b=0$ and 1000 s/mm^2; TR, 6000 ms; TE, 139 ms; excitations, 1; matrix, 96 × 200; FOV, 24 × 24 cm; section thickness, 5 mm; section gap, 0 mm	Quantitative ROI assessment of lesion ADC values	The spatial sites of MS plaques were determined on T2-weighted DWI at the same level and were obtained where ROIs were drawn
7	Zivadinov et al, 2008[37]	GE 1.5T	Gd-DTPA (0.1 mmol/kg)	Qualitative visual assessment	ADC	EPI DWI: 3 gradient directions with $b=0$ and 1000 s/mm^2; TR, 2275 ms; TE, 45 ms; matrix, 128 × 128; FOV, 36 × 27; voxel size, 2.8× 2.1 mm; section thickness, 3 mm; section gap, 0 mm	A 3D connected-components labeling algorithm was applied to create individual lesion maps	Image coregistration (FLIRT) was used to place all images, masks, and maps for each subject into the same physical space
8	Michoux et al, 2015[16]	Philips 3T	Gadobenate dimeglumine (0.1 mmol/kg)	Qualitative visual assessment	ADC	EPI DWI: TR, 4144 ms; TE, 55 ms; pulse width, 12.1 ms; time b/w gradients, 26.3 ms; $b=0/100$ s/mm^2; FOV, 230 × 230 mm; acquisition matrix, 128 × 101; section thickness, 3 mm; intersection gap, 0 mm	Quantitative ROI assessment of lesion ADC values	DWIs were registered with T2-weighted images, allowing the replication of ROIs drawn on T2-weighted images
9	Sahin et al, 2015[26]	GE 1.5T	Gadopentetate (0.1 mmol/kg)	Qualitative visual assessment	ADC	NA	Quantitative ROI assessment of lesion ADC values	NA
MRI technique: MWI								
1	Oh et al, 2007[19]	GE 3T	Gadolinium-DTPA (0.1 mmol/kg)	Semiautomated assessment	MWF	16-Section 12-echo T2 spiral prep sequence; TR, 2000 ms; TEs, 7, 17, 28, 38, 49, 60, 70, 92, 124, 177, 220, 294 ms; NEX, 6; FOV, 24 × 24 cm; matrix 128 × 128; section thickness, 5 mm; effective resolution, 2 × 2 mm^2	Quantitative assessment of lesion MWF values on a pixel-by-pixel MWF map	Masks for both T2 and CE lesions were generated first; the T1-weighted 3D IR-SPGR volume images were resampled to correspond to the PD-/T2-weighted images using nearest-neighbor interpolation; the NAWM and nonenhancing T2 and CE masks were then regridded to the lower resolution MWF map from the 12-echo data, yielding the percentage content within each pixel
2	Levesque et al, 2010[14]	Siemens 1.5T	Gadolinium-DTPA (0.2 mmol/kg)	Qualitative visual assessment	MWF	Multiecho spin-echo data were acquired using a 32-echo spin-echo sequence with nonselective 90x–180y–90x composite refocusing pulses and crusher gradient scheme to spoil stimulated echoes; a pulse TR of 2 seconds and echo spacing of TR of 10 ms were used; section thickness, 7 mm; matrix, 96 × 128; voxel size, 2 × 2 mm	Quantitative assessment of lesion MWF value using voxel-by-voxel computation of MWF	ROI labels were propagated to subsequent examination time points with software developed at the Montreal Neurological Institute; the label maps were then resampled to the lower resolution of the QMTI scans, retaining only those voxels containing >80% of each label
3	Vargas et al, 2015[31]	GE 3T	NA	Qualitative visual assessment	MWF	Whole-brain T2 prep 3D spiral gradient-echo imaging sequence, FAST T2 (1.2 × 1.2 × 5 mm^3), and a modified adiabatic T2 prep pulse were used	Spatially constrained multi-Gaussian algorithm for whole-brain WM voxel-based MWF quantification	Subjects' T1WIs were automatically processed using the longitudinal stream in FreeSurfer[e] enabling us to register all sequences and all time points together for each patient; MWF maps were registered onto the T1 FreeSurfer volume using a Boundary-Based Registration method

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On-line Table 2: Continued

Study No.	Study First Author and Year	Magnet Vendor and Field Strength	Contrast Agent (Dose)	Method of Characterizing Gadolinium-Enhancing Lesions	Quantitative Imaging Biomarker Compared with Gadolinium Enhancement	Quantitative Biomarker Imaging Sequence Parameters	Method of Characterizing Quantitative Imaging Biomarker	Method of Comparing Gadolinium-Enhancing Lesions with Quantitative Imaging Biomarker
4	Faizy et al, 2016[4]	Siemens 3T	NA	Qualitative visual assessment	MWF	MESE sequence with the following parameters: echo spacing, 8.3 ms; number of echoes, 32; maximum TE, 265 ms; TR, 3000 ms; section thickness, 4 mm; acquisition matrix, 128 × 96; NEX, 4; GRAPPA reduction factor, 2 with 24 reference lines; acquisition time, 12 min; section thickness of refocusing pulse, 12 mm; section gap, 4 mm	A multivoxel spatial regularization approach with 50 preselected different T2 times chosen over a range of 5–600 ms on a logarithmic scale	MS lesions (including CE) were identified in the group of patients with MS on T2-weighted images and linearly registered to the last echo of the corresponding acquired T2 relaxometry data
MRI technique: qMRI								
1	Hiehle et al, 1995[12]	1.5T	Gadolinium (0.1 mmol/kg, up to 20 mL)	Qualitative visual assessment	MTR	3D GRE: TR, 106 ms; TE, 5 ms; NEX, 1; flip angle, 12°; 2-kHz off-peak water resonance; average B_1 intensity, 3.67×10^{-6} T; matrix, 256 × 128; section thickness, 5 mm; images were obtained with and without saturation pulse	Quantitative ROI assessment of lesion signal intensity using saturated and unsaturated magnetization transfer images	Pixel-by-pixel MTR data points were obtained after drawing a "ray" through each WM lesion
2	Petrella et al, 1996[21]	1.5T	Gadobenate dimeglumine (0.1 mmol/kg, up to 20 mL)	Qualitative visual assessment	MTR	3D GRASS pulse sequence: TR, 100 ms; TE, 5 ms; NEX, 1; matrix, 256 × 128; section thickness, 5 mm; flip angle, 12°; the frequency offset of the pulses was 2-kHz off-peak water resonance with the average B_1 intensity, 3.67×10^{-6} T	Quantitative ROI assessment of lesion signal intensity using saturated and unsaturated magnetization transfer images	Average pixel intensity values were then obtained from ROIs drawn around the corresponding lesions on the magnetization transfer images
3	Filippi et al, 1998[8]	Siemens 1.5T	Gadolinium-DTPA (0.3 mmol/kg)	Qualitative visual assessment	MTR	2D GRE: TR, 600 ms; TE, 12 ms; flip angle, 20°; 1.5-kHz off-peak water resonance; amplitude B_1 intensity, 3.4×10^{-6} T; bandwidth, 250 Hz; FOV, 25 cm; matrix, 256 × 256; section thickness, 5 mm; images were obtained with and without saturation pulse	Quantitative ROI assessment of lesion signal intensity using saturated and unsaturated magnetization transfer images	ROI analysis of MT images were coregistrered on the enhanced images where ROI delineations were made and mapped on the corresponding MT scans
4	Goodkin et al, 1998[11]	Siemens 1.5T	Gadodiamide (0.1 mmol/kg)	Qualitative visual assessment	MTR, PD, T1, and T2 relaxation time	MTI: 3D GRE TR, 50 ms; TE, 6 ms; flip angle, 15°; matrix, 192 × 256; FOV, 18 × 24 cm; section thickness, 3 mm with no section gap; the saturation pulse was of Gaussian shape, 8 ms in duration, positioned 1.6-kHz off-resonance from the narrow proton water frequency and had a mean amplitude of 3.7 μT; PD double SE sequence; TR, 2500 ms; TE, 20 ms; T2 double SE sequence; TR: 2500 ms; TE, 80 ms; T1-TR, 600 ms; TE, 17 ms	Quantitative ROI assessment of lesion signal intensity in MT-, PD-, T1- and T2-weighted maps	All MR images were coregistered using the Woods algorithm to the PD MRI collected during the first MRI session
5	van Waesberghe et al, 1998[30]	1.5T	Gadolinium (0.1 mmol/kg)	Qualitative visual assessment	MTR	2D GRE sequences: TR, 600 ms; TE, 12 ms; NEX, 2; section thickness, 5 mm; pixel size, 1 × 1 mm; flip angle, 20°, with and without a gaussian-shaped off-resonance (21.5-kHz) presaturation pulse	Quantitative ROI assessment of lesion signal intensity with saturated and unsaturated magnetization transfer images	Size of enhancement was measured with a local seed-growing method using home-developed software, which connected all pixels with increased signal intensity on the basis of local thresholding; MTR of lesions was calculated by the mean MTR of all pixels within a lesion
6	Rovira et al, 1999[24]	1.5T	Gadolinium (0.1 mmol/kg)	Qualitative visual assessment	MTR	2D GRE sequence: TR, 714 ms; TE, 12 ms; matrix, 192 × 256; section thickness, 5 mm; intersection gap, 1 mm; flip angle, 20° with and without an off-resonance gaussian RF pulse centered 1.5 kHz below the frequency of water	Quantitative ROI assessment of lesion signal intensity using saturated and unsaturated magnetization transfer images	Pixel-by-pixel MTR maps were constructed from the 2 sets of 2D gradient-echo images; the mean values of the MTRs within selected MS lesions were obtained by averaging the pixel values in the ROIs on the MTR map; proper localization of the ROIs on the map was based on the position of the NAWM and of selected plaques on the T2-weighted images
7	Pike et al, 2000[23]	Philips 1.5T	NA	Qualitative visual assessment	MTR	Spin-echo sequence: TR, 1000 ms; TE, 20 ms; section thickness, 5 mm with 0.5-mm intersection gap; semisolid spin saturation was achieved by using 1.2-ms on-resonance 1–2-1 binomial pulses (RF field strength, 20 μT) placed just before each section-selective excitation	Quantitative ROI assessment of lesion signal intensity using saturated and unsaturated magnetization transfer images	Automated software was used to spatially coregister all data to a single time point to permit temporal tracking of voxels and differentiation between the datasets

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On-line Table 2: Continued

Study No.	Study First Author and Year	Magnet Vendor and Field Strength	Contrast Agent (Dose)	Method of Characterizing Gadolinium-Enhancing Lesions	Quantitative Imaging Biomarker Compared with Gadolinium Enhancement	Quantitative Biomarker Imaging Sequence Parameters	Method of Characterizing Quantitative Imaging Biomarker	Method of Comparing Gadolinium-Enhancing Lesions with Quantitative Imaging Biomarker
8	Fazekas et al, 2002[5]	Philips 1.5T	Gadolinium-DTPA (0.1 mmol/kg)	Qualitative visual assessment	MTR and T1 relaxation time	TR, 640 ms; TE, 20 ms; field strength, $b = 21 \times 10^{-6}$ T; FOV, 25 cm; matrix, 128 × 128; section thickness, 6 mm; images were obtained with and without saturation pulse	Quantitative ROI assessment of lesion signal intensity using saturated and unsaturated magnetization transfer images	All scans were coregistered; ROI analysis was done on the PD weight (with enhanced scans as reference); the ROIs were stored as a mask, which was transferred onto coregistered MT maps
9	Papanikolaou et al, 2004[20]	Siemens 1.5T	NA	Qualitative visual assessment	MTR and T2 relaxation time	MTR: 3D FLASH sequence with TR, 25 ms; TE, 5 ms; flip angle, 8°; with and without an off-resonance synchronized Gaussian-shaped pulse located 1.5 kHz away from the water frequency; the duration of the MT pulse was 5125 ms, while the equivalent flip angle was 500°; T2: a multiecho CPMG sequence with alternating 180° pulses (PHAPS) and 16 equidistant echoes starting from 22.5 ms were applied in the axial plane to measure the T2 relaxation time	Quantitative ROI assessment of lesion signal intensity in MT and T2-weighted maps	NA
10	Giacomini et al, 2009[10]	Siemens 1.5T	Gadolinium (0.2 mL/kg)	Qualitative visual assessment	MTR	NA	Quantitative ROI assessment of lesion signal intensity using saturated and unsaturated magnetization transfer images	The gadolinium-enhancing voxels were manually segmented on the high-resolution anatomic scans, and labels corresponding to the initial gadolinium-enhancing lesion voxels were propagated to subsequent points using software
11	Levesque et al, 2010[14]	Siemens 1.5T	Gadolinium-DTPA (0.2 mmol/kg)	Qualitative visual assessment	T1 relaxation time	Oblique 7-mm section, with 2 × 2 mm in-plane voxel size and a rectangular 96 × 128 matrix	Quantitative ROI assessment of lesion signal intensity in T1-weighted maps	ROI labels were propagated to subsequent examination time points using software developed at the Montreal Neurological Institute; the label maps were then resampled to the lower resolution of the QMTI scans, retaining only those voxels containing >80% of each label
12	van den Elskamp et al, 2010[29]	Philips 1.5T + Siemens 1.5T	Gadolinium-DTPA (0.1 mmol/kg)	Qualitative visual assessment	MTR	2D GRE: TR, 23 ms; TE, 4 ms; flip angle, 20°; pixel size, 1 mm × 1 mm; section thickness, 5 mm with and without a gaussian MT prepulse; duration, 7.68 ms; offset, 1500 Hz; equivalent flip angle, 500°; both on- and offsets were then coregistered	Quantitative ROI assessment of lesion signal intensity using saturated and unsaturated magnetization transfer images	All scans from months 1–6 were coregistered to the baseline scan using a rigid body registration method; the transformation matrices were used to coregister the MTR scans and ROIs, allowing accurate determination of MTR values in the designated ROIs before and after Gd enhancement
13	Vavasour et al, 2011[32]	GE 1.5T	Gadolinium-DTPA (0.2 mL/kg)	Qualitative visual assessment	MTR	3D GRE: TR, 106 ms; TE, 5 ms; flip angle, 12°; matrix, 256 × 128; total sections, 28; with and without a sinc-shaped off-resonance preparation pulse; duration, 19 ms; maximum amplitude, 6.4×10^{-6} T, frequency offset, 2000 Hz	Quantitative ROI assessment of lesion signal intensity with saturated and unsaturated magnetization transfer images	MT images were registered to the PD volume using a rigid body, voxel-similarity registration technique with sinc interpolation; ROIs were outlined on the PD images by a trained observer; ROIs were then mapped onto the registered T1, T2, and MT images
14	Jurcoane et al, 2013[13]	Siemens 3T	Gadolinium (0.1 mmol/kg)	Adjudicated by comparing local values of relative T1 shortening on contrast administration with the respective average value for NAWM	MTR, PD and T1 relaxation time	MTR: 3D GRE; TR, 25 ms; TE, 4.08 ms; flip angle, 15°; frequency offset of MT pulse, 1500 Hz; amplitude B_1, 14.16×10^{-6} T; bandwidth, 200 Hz; matrix, 176 × 256 × 44; T1 and PD 3D GRE; TR, 16.4 ms; TE, 6.7 ms; flip angles, 4° and 24°; bandwidth, 222; matrix, 256 × 224 × 160; spatial resolution, 1 mm^3	Quantitative ROI assessment of lesion signal intensity in MT, PD, and T1-weighted maps	Lesion ROI delineations were performed manually on 3D-FLAIR images; analysis of each parameter was made possible by image coregistration of all quantitative maps
15	Blystad et al, 2016[2]	Philips 1.5T	Gadobenate dimeglumine (0.1 mmol/kg)	Qualitative visual assessment	Longitudinal relaxation rate, transverse relaxation rate, and PD	qMRI: axial; TR, 4244 ms; TE, 14, 28, 42, 56, 70 ms; T1, 0.0974, 0.5846, 1.8511, 4.0919 seconds; flip angle, 120°; FOV, 230 × 182; voxel size, 1.5 × 1.5 mm; section thickness, 3 mm	Quantitative ROI assessment of lesion signal intensity in the synthetic image scans	ROI analysis of synthetic MR images within MS lesions; synthetic T2-weighted, T2-FLAIR, T1-weighted, and T1-weighted Gd images were created using quantitative maps of R_1, R_2, and PD

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On-line Table 2: Continued

Study No.	Study First Author and Year	Magnet Vendor and Field Strength	Contrast Agent (Dose)	Method of Characterizing Gadolinium-Enhancing Lesions	Quantitative Imaging Biomarker Compared with Gadolinium Enhancement	Quantitative Biomarker Imaging Sequence Parameters	Method of Characterizing Quantitative Imaging Biomarker	Method of Comparing Gadolinium-Enhancing Lesions with Quantitative Imaging Biomarker
MRI technique: GRE/SWI								
1	Wiggerman et al, 2013[34]	Philips 3T	Gadolinium (0.1 mmol/kg body weight)	Qualitative visual assessment	Frequency shifts on SWI frequency maps	3D GRE: TR, 40 ms; TE, 20 ms; flip angle, 19°; section-oversampling factor, 1.28; acquisition time, 4.55 min; matrix, 480 × 231 × 32; FOV, 240 × 166 × 64 mm^3; voxel size, 0.5 × 0.7 × 2 mm^3; section thickness, 5 mm	Quantitative ROI assessment of average frequency shifts of the lesions	All phase, FLAIR, and Gd-DTPA–enhanced T1-weighted images were registered to the venogram images of the phase scan of the first acquisition using the FLIRT tool; ROIs encompassing enhancing MS lesions were defined manually on 1 frequency map calculated from the last serial scan, and the ROIs were projected onto all other months
	Zhang et al, 2016[36]	GE 3T	Not specified	Qualitative visual assessment	QSM	TR, 57 ms; number of echoes, 11; first TE, 4.3 ms; TE spacing, 4.8 ms; flip angle, 20°; bandwidth, 244 kHz; FOV, 24 cm; matrix, 416 × 320; section thickness, 2 mm	Qualitative and quantitaive ROI assessment of QSM lesion intensity	ROI analysis of QSM images overlaid on T1WI and T2WI sequences

Note:—NAWM indicates normal-appearing WM; b/w, between; FAST, Fast Acquisition with Spiral Trajectory and T2prep; MESE, multi echo spin echo; GRAPPA, generalized autocalibrating partially parallel acquisition; GRASS, gradient-recalled acquisition in steady state; SE, spin-echo; RF, radiofrequeny; CPMG, Carr-Purcell-Meiboom-Gill; PHAPS, properties of the phase-alternating phase-shift; MT, magnetization transfer; REL, ring enhancing lesion; CE, contrast-enhanced; IR-SPGR, inversion recovery echo-spoiled gradient echo; MTI, magnetization transfer imaging; QMTI, quantitative magnetization transfer imaging; Gd, gadolinium, Max, maximum; qMRI, quantitative MR imaging; NA, not available; PD, proton density; R-R, interval between 2 ventricular contractions; FS, frequency shift; R1, longitudinal relaxation rate; R2, transverse relaxation rate; MWI, myelin water imaging.

[a] GE Healthcare, Milwaukee, Wisconsin.

[b] Philips Healthcare, Best, the Netherlands.

[c] Siemens, Erlangen, Germany.

[d] FMRIB Linear Image Registration Tool (FLIRT; http://www.fmrib.ox.ac.uk).

[e] FreeSurfer (http://surfer.nmr.mgh.harvard.edu).

[f] Analysis of Functional Neuro Images (AFNI; http://afni.nimh.nih.gov/afni/).

On-line Table 3: MRI testing results

Study No.	Study First Author and Year	MRI Technique	MRI Parameter	No. of Gadolinium-Enhancing Lesions Studied	No. of Nonenhancing Lesions Studied	Mean Value of Biomarker in Gadolinium-Enhancing Lesions	Mean Value of Biomarker in Non-enhancing Lesions	*P* Value Comparison between Enhancing and Nonenhancing Lesion Values	Optimal Threshold to Distinguish Enhancing and Nonenhancing Lesions	Sensitivity	Specificity	Area Under the Curve
MRI technique: DTI												
1	Tievsky et al, 1999[28]	DTI	FA	9	64	0.189 (±0.0096)	0.289 (±0.079)	<.01	NA	NA	NA	NA
2	Werring et al, 1999[33]	DTI	FA	25	245	0.38 (±0.09)	0.51 (±0.12)	<.001	NA	NA	NA	NA
			MD	25	245	$(1.16 \pm 0.17) \times 10^{-3}$ mm^2/s	$(1.10 \pm 0.22) \times 10^{-3}$ mm^2/s	.03	NA	NA	NA	NA
3	Bammer et al, 2000[1]	DTI	FA	15	121[b]	0.44 (±0.119)	0.32 (±0.085)[b]	.069	NA	NA	NA	NA
					48[c]		0.43 (±0.228)[c]	<.005				
			MD	15	121[b]	$(0.885 \pm 0.124) \times 10^{-3}$ mm^2/s	$(1.198 \pm 0.248) \times 10^{-3}$ mm^2/s[b]	NA	NA	NA	NA	NA
					48[c]		$(1.006 \pm 0.248) \times 10^{-3}$ mm^2/s[c]	NA				
4	Filippi et al, 2000[7]	DTI	MD	22	151	$(1.039 \pm 0.17) \times 10^{-3}$ mm^2/s	$(1.040 \pm 0.14) \times 10^{-3}$ mm^2/s	NS	NA	NA	NA	NA
5	Filippi et al, 2001[6]	DTI	FA	128	4718	0.21 (±0.07)	0.26 (±0.09)	<.001	NA	NA	NA	NA
			MD	128	4718	$(1.09 \pm 0.18) \times 10^{-3}$ mm^2/s	$(1.06 \pm 0.23) \times 10^{-3}$ mm^2/s	NS	NA	NA	NA	NA
6	Naismith et al, 2010[17]	DTI	FA	95	95	0.668 (95% CI, 0.628–0.712)	0.780 (95% CI, 0.730–0.832)[d]	<.05	NA	NA	NA	NA
			MD	95	95	1.196 (95% CI, 1.152–1.240)	1.164 (95% CI, 1.120–1.204)[d]	<.05	NA	NA	NA	NA
7	Fox et al, 2011[9]	DTI	FA	60	NA	0.277 (±0.012)	NA	NA	NA	NA	NA	NA
8	Liu et al, 2012[15]	DTI	FA	13	NA	0.25 (±0.08)	NA	NA	NA	NA	NA	NA
			MD	13	NA	0.79 (±0.11)	NA	NA	NA	NA	NA	NA
9	Testaverde et al, 2012[27]	DTI	FA	7	14	0.348 (±0.100)	0.311 (±0.0744)	<.05	NA	NA	NA	NA
			MD	7	14	2.806 (±0.3944) mm^2/s	3.178 (±0.4018) mm^2/s	NS	NA	NA	NA	NA
MRI technique: DWI												
1	Droogan et al, 1999[3]	DWI	ADC	31	180	1.15×10^{-3} mm^2/s[e]	1.11×10^{-3} mm^2/s[e]	.01	NA	NA	NA	NA
2	Tievsky et al, 1999[28]	DWI	ADC	9	64	$(1.59 \pm 0.62) \times 10^{-3}$ mm^2/s	$(1.08 \pm 0.22) \times 10^{-3}$ mm^2/s	<.05	NA	NA	NA	NA
3	Nusbaum et al, 2000[18]	DWI	ADC	26[b]	39[b]	$(1.078 \pm 0.212) \times 10^{-3}$ mm^2/s[b]	$(1.316 \pm 0.229) \times 10^{-3}$ mm^2/s[b]	NS	NA	NA	NA	NA
				6[c]	29[c]	$(0.823 \pm 0.203) \times 10^{-3}$ mm^2/s[c]	$(1.075 \pm 0.210) \times 10^{-3}$ mm^2/s[c]	<.05	NA	NA	NA	NA
4	Roychowdhury et al, 2000[25]	DWI	ADC	28[h]	57	$(0.77 \pm 0.14) \times 10^{-3}$ mm^2/s	$(1.25 \pm 0.35) \times 10^{-3}$ mm^2/s	<.0001	NA	NA	NA	NA
5	Phuttharak et al, 2006[22]	DWI	ADC	16[b]	191[b]	$(1.314 \pm 0.0129) \times 10^{-3}$ mm^2/s	$(1.413 \pm 0.0233) \times 10^{-3}$ mm^2/s	NA	NA	NA	NA	NA
				4[c]	59[c]	$(1.011 \pm 0.00961) \times 10^{-3}$ mm^2/s	$(1.024 \pm 0.00647) \times 10^{-3}$ mm^2/s					
6	Yurtsever et al, 2008[35]	DWI	ADC	63	NA	$(1.42 \pm 0.08) \times 10^{-3}$ mm^2/s	NA	NA	NA	NA	NA	NA
7	Zivadinov et al, 2008[37]	DWI	ADC	33	998	$(0.954 \pm 0.256) \times 1 \times 10^{-3}$ mm^2/s	$(0.937 \pm 0.339) \times 10^{-3}$ mm^2/s	NS	NA	NA	NA	NA
8	Michoux et al, 2015[16]	DWI	ADC	44	37	$(1.014 \pm 0.2278) \times 10^{-3}$ mm^2/s	$(1.046 \pm 0.1684) \times 10^{-3}$ mm^2/s	.2061	937	0.512	0.784	0.583
9	Sahin et al, 2015[26]	DWI	ADC	23	73	$(1.53 \pm 0.49) \times 10^{-3}$ mm^2/s	$(1.40 \pm 0.35) \times 10^{-3}$ mm^2/s	Significant, but no *P* value was reported	NA	NA	NA	NA
MRI technique: MWI												
1	Oh et al, 2007[19]	MWI	MWF	13	88	0.084 (±0.004)	0.08 (±0.003)	NA	NA	NA	NA	NA
2	Levesque et al, 2010[14]	MWI	MWF	6	6	0.063 (±0.007[f])	0.076 (±0.015[f])[d]	NS	NA	NA	NA	NA
3	Vargas et al, 2015[31]	MWI	MWF	38	25	0.052 (±0.028)	0.081 (±0.033)	<.001	NA	NA	NA	NA
4	Faizy et al, 2016[4]	MWI	MWF	NA	NA	0.044 (±0.031)	T2 lesions: 0.033 (±0.018)[g]	T2 lesions: .02[g]	NA	NA	NA	NA
					NA		Black holes: 0.016 (±0.015)	Black holes: .02				
MRI Technique: qMRI												
1	Hiehle et al, 1995[12a]	qMRI	MTR	Group 1: 22[h]	57	30.2% (±3.3%)	27.5% (±5.3%)	NS	NA	NA	NA	NA
				Group 2: 10[h]	117	27.1% (±3.7%)	29.8% (±4.7%)	NS	NA	NA	NA	NA
2	Petrella et al, 1996[21]	qMRI	MTR	14[h]	19	32.2% (±3.4%)	29.4% (±4.3%)	NS	NA	NA	NA	NA
3	Filippi et al, 1998[8]	qMRI	MTR	48	NA	33.1% (±8.4%)	NA	NA	NA	NA	NA	NA
4	Goodkin et al, 1998[11]	qMRI	MTR	11	5 (minimum)	32.1%[e] (95% CI, 30.9–33.1%)	35.8%[e] (95% CI, 35.3–37.4%)[d]	NA	NA	NA	NA	NA
			PD	10	5 (minimum)	1.566[e] (95% CI, 1.541–1.596)	1.518[e] (95% CI, 1.496–1.539)[d]	NA	NA	NA	NA	NA
			T1	11	5 (minimum)	0.315[e](95% CI, 0.311–0.323)	0.348[e] (95% CI, 0.324–0.360)[d]	NA	NA	NA	NA	NA
			T2	11	5 (minimum)	88.0[e] ms (95% CI, 84.4–90.0)	73.5[e] ms (95% CI, 68.0–77.9)[d]	NA	NA	NA	NA	NA
5	van Waesberghe et al, 1998[30]	qMRI	MTR	101[b]	NA	38% (34%–41%)[b]	NA	NA	NA	NA	NA	NA
				25[c]		43% (41%–45%)[c]			NA	NA	NA	NA
6	Rovira et al, 1999[24]	qMRI	MTR	8	22	32.6% (±5.1%)	26.3% (±6.2%)	<.05	NA	NA	NA	NA
7	Pike et al, 2000[23]	qMRI	MTR	44	~44	30.1% (±2.3%)	26.9% (±2.6%)[d]	NA	NA	NA	NA	NA
8	Fazekas et al, 2002[5]	qMRI	MTR	44	10	39.5% (±4.3%)	45.0% (±5.1%)	<.001	NA	NA	NA	NA
			$T1_{free}$	44	10	1015 ± 217 ms	890 ± 96 ms	<.01	NA	NA	NA	NA

Continued on next page

On-line Table 3: Continued

Study No.	Study First Author and Year	MRI Technique	MRI Parameter	No. of Gadolinium-Enhancing Lesions Studied	No. of Non-enhancing Lesions Studied	Mean Value of Biomarker in Gadolinium-Enhancing Lesions	Mean Value of Biomarker in Nonenhancing Lesions	*P* Value Comparison between Enhancing and Nonenhancing Lesion Values	Optimal Threshold to Distinguish Enhancing and Nonenhancing Lesions	Sensitivity	Specificity	Area Under the Curve
9	Papanikolaou et al, 2004[20]	qMRI	MTR	10	105	37.63% (±3.3%)	34.66% (±5.5%)	.132	NA	NA	NA	NA
			T2	10	105	113.26 ± 8.9 ms	128.87 ± 30.6 ms	.09	NA	NA	NA	NA
10	Giacomini et al, 2009[10]	qMRI	MTR	6	5	0.75 (±0.05)	0.86 (±0.07)[d]	<.001	NA	NA	NA	NA
11	Levesque et al, 2010[14]	qMRI	$T1_{rate}$	6	6	0.96 (±0.06[f]) s^{-1}	1.11 (±0.09[f]) s^{-1}[d]	<.05	NA	NA	NA	NA
12	van den Elskamp et al, 2010[29]	qMRI	MTR	349	101	25.2% (±5.4%)	27.0% (±5.6%)[d]	NA	NA	NA	NA	NA
13	Vavasour et al, 2011[32]	qMRI	MTR	7	30	24.7% (±3.03%)	24.4% (±3.53%)	NA	NA	NA	NA	NA
14	Jurcoane et al, 2013[13]	qMRI	MTR	RRMS: 13	RRMS: 13	RRMS: 23% (±3%)	RRMS: 28% (±2%)	<.01	NA	NA	NA	NA
				PMS: 12	PMS: 12	PMS: 19% (±3%)	PMS: 26% (±2%)	<.01	NA	NA	NA	NA
			PD	RRMS: 14	RRMS: 14	RRMS: 83% (±3%)	RRMS: 75% (±2%)	<.01	NA	NA	NA	NA
				PMS: 13	PMS: 13	PMS: 87% (±4%)	PMS: 78% (±3%)	<.01	NA	NA	NA	NA
			T1	RRMS: 14	RRMS: 14	RRMS: 1696 ± 199 ms	RRMS: 1168 ± 102 ms	<.01	NA	NA	NA	NA
				PMS: 13	PMS: 13	PMS: 2206 ± 280 ms	PMS: 1259 ± 142 ms	<.01	NA	NA	NA	NA
15	Blystad et al, 2016[9]	qMRI	$T1_{rate}$	43	622	1.22 (±0.36)	0.89 (±0.24)	<.001	3.93	NA	NA	0.832
			$T2_{rate}$	43	622	9.8 (±2.6)	7.4 (±1.9)	<.001	0.21	NA	NA	0.832
			PD	43	622	77.0 (±11.2)	89.8 (±8.4)	<.001	0.194	NA	NA	0.832
MRI technique: GRE/SWI												
1	Wiggerman et al, 2013[34]	SWI	FS	36	3–5 per subject	1.3 ± 0.25 ppb	2.3 ± 0.2 ppb[d]	<.0001	NA	NA	NA	NA
2	Zhang et al, 2016[36]	SWI	QSM	86	47	Relative susceptibility value: 2.49 ± 6.39 ppb	Relative susceptibility value: 20.26 ± 7.55 ppb	<.0001	Relative susceptibility value: 11.2 ppb	0.884	0.915	0.95

Note:—NS indicates nonsignificant; ppb, parts per billion; qMRI, quantitative MR imaging; NA, not available; PD, proton density; R-R, interval between 2 ventricular contractions; FS, frequency shift; MWI, myelin water imaging; $T1_{free}$, native relaxation time; $T1_{rate}$, T1 relaxation rate; $T2_{rate}$, T2 relaxation rate; RRMS, relapsing-remitting multiple sclerosis; PMS, progressive multiple sclerosis.

[a] The study was conducted in 2 phases. The first phase focused on comparing the MTR ratio to gadolinium enhancement on postcontrast T1 images, while the second phase analyzed the relationship of the MTR ratio and signal intensity on precontrast T1-weighted images. Both phases of the study included lesions that are enhancing and nonenhancing; thus, both groups were relevant to our analysis.

[b] The numbers shown are pertaining nonenhancing lesions that appear T1-hypointense on non-contrast-enhancing T1 sequences.

[c] The numbers shown are pertaining nonenhancing lesions that appear T1-isointense on non-contrast-enhancing T1 sequences.

[d] Values marked were obtained from post-gadolinium-enhancement intervals.

[e] Median of the marked values was reported instead of mean.

[f] Variability is reported in standard error of mean.

[g] T2 lesions were regarded as T2 hyperintense lesions that were non-contrast-enhancing lesions and non-black-hole lesions.

[h] Only homogeneously enhancing lesions were included in this analysis.

On-line Table 4: Risk of bias question results regarding DTI[a]

Question	Tievsky et al, 1999[35]	Werring et al, 1999[33]	Bammer et al, 2000[3]	Filippi et al, 2000[7]	Filippi et al, 2001[6]	Naismith et al, 2010[17]	Fox et al, 2011[9]	Liu et al, 2012[15]	Testaverde et al, 2012[27]
Was the study prospective in nature?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the study clearly define inclusion and exclusion criteria?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the index test (MRI quantitative biomarker) results interpreted without knowledge of the results of the reference standard (gadolinium enhancement)?	Yes	No	No	Yes	Yes	Yes	No	No	Yes
Were the MRI quantitative biomarker analysis techniques reproducible as described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did more than one investigator analyze the MRI quantitative biomarker imaging data? If so, was there an evaluation of interrater reliability?	No	No	Yes/No	No	No	No	No	No	No
Was the definition of lesion enhancement adequately described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the presence of gadolinium enhancement defined without knowledge of the results of the index test (MRI quantitative biomarker)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[a] If data are not provided or not specified, the answer is recorded as no (−).

On-line Table 5: Risk of bias question results regarding DWI[a]

Question	Droogan et al, 1999[3]	Tievsky et al, 1999[35]	Nusbaum et al, 2000[18]	Roychowdhury et al, 2000[25]	Phuttharak et al, 2006[22]	Yurtsever et al, 2008[35]	Zivadinov et al, 2008[37]	Michoux et al, 2015[16]	Sahin et al, 2015[26]
Was the study prospective in nature?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes (Partially)	Yes
Did the study clearly define inclusion and exclusion criteria?	Yes	No	Yes	No	No	No	Yes	Yes	Yes
Were the index test (MRI quantitative biomarker) results interpreted without knowledge of the results of the reference standard (gadolinium enhancement)?	Yes	Yes	Yes	No	No	No	Yes	No	No
Were the MRI quantitative biomarker analysis techniques reproducible as described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Did more than one investigator analyze the MRI quantitative biomarker imaging data? If so, was there an evaluation of interrater reliability?	No	No	No	No	Yes/yes	No	No	Yes/no	No
Was the definition of lesion enhancement adequately described?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the presence of gadolinium enhancement defined without knowledge of the results of the index test (MRI quantitative biomarker)?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

[a] If data are not provided or not specified, the answer is recorded as no (−).

On-line Table 6: Risk of bias question results regarding MWI[a]

Question	Oh et al, 2007[19]	Levesque et al, 2010[14]	Vargas et al, 2015[31]	Faizy et al, 2016[4]
Was the study prospective in nature?	Yes	Yes	Yes	Yes
Did the study clearly define inclusion and exclusion criteria?	No	Yes	Yes	Yes
Were the index test (MRI quantitative biomarker) results interpreted without knowledge of the results of the reference standard (gadolinium enhancement)?	No	No	No	No
Were the MRI quantitative biomarker analysis techniques reproducible as described?	Yes	Yes	Yes	Yes
Did more than one investigator analyze the MRI quantitative biomarker imaging data? If so, was there an evaluation of interrater reliability?	No	No	No	No
Was the definition of lesion enhancement adequately described?	Yes	Yes	Yes	Yes
Was the presence of gadolinium enhancement defined without knowledge of the results of the index test (MRI quantitative biomarker)?	Yes	Yes	Yes	Yes

[a] If data are not provided or not specified, the answer is recorded as no (−).

On-line Table 7: Risk of bias question results regarding qMRI[a]

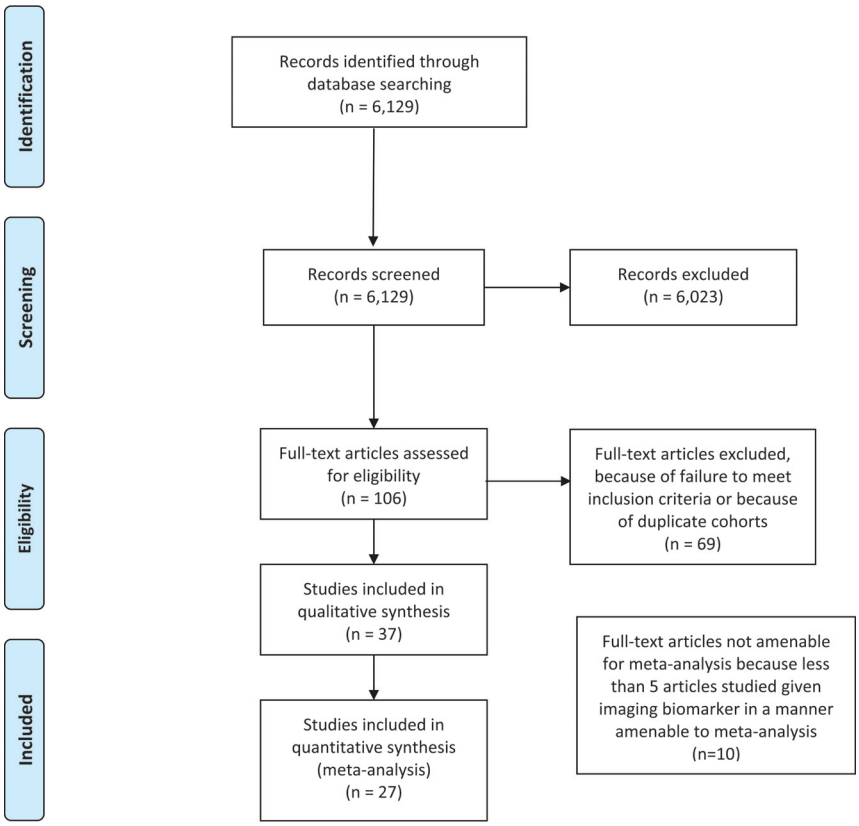
Question	Hiehle et al, 1995[12]	Petrella et al, 1996[21]	Filippi et al, 1998[8]	Goodkin et al, 1998[11]	van Waesberghe et al, 1998[30]	Rovira et al, 1999[24]	Pike et al, 2000[23]	Fazekas et al, 2002[5]	Papanikolaou et al, 2004[20]	Giacomini et al, 2009[10]	Levesque et al, 2010[14]	van den Elskamp et al, 2010[29]	Vavasour et al, 2011[32]	Jurcoane et al, 2013[13]	Blystad et al, 2016[9]
Was the study prospective in nature?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the study clearly define inclusion and exclusion criteria?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the index test (MRI quantitative biomarker) results interpreted without knowledge of the results of the reference standard (gadolinium enhancement)?	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No
Were the MRI quantitative biomarker analysis techniques reproducible as described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did more than one investigator analyze the MRI quantitative biomarker imaging data? If so, was there an evaluation of interrater reliability?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Was the definition of lesion enhancement adequately described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the presence of gadolinium enhancement defined without knowledge of the results of the index test (MRI quantitative biomarker)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[a] If data are not provided or not specified, the answer is recorded as no (−).

On-line Table 8: Risk of bias question result regarding SWI[a]

Question	Wiggerman et al, 2013[34]	Zhang et al, 2016[36]
Was the study prospective in nature?	Yes	No
Did the study clearly define inclusion and exclusion criteria?	Yes	Yes
Were the index test (MRI quantitative biomarker) results interpreted without knowledge of the results of the reference standard (gadolinium enhancement)?	No	Yes
Were the MRI quantitative biomarker analysis techniques reproducible as described?	Yes	Yes
Did more than one investigator analyze the MRI quantitative biomarker imaging data? If so, was there an evaluation of interrater reliability?	No	Yes/yes
Was the definition of lesion enhancement adequately described?	Yes	Yes
Was the presence of gadolinium enhancement defined without knowledge of the results of the index test (MRI quantitative biomarker)?	Yes	Yes

[a] If data are not provided or not specified, the answer is recorded as no (−).



ON-LINE FIGURE. Study selection flow diagram.