Supplementary Tables.
Table e-1. Summary of the different diagnostic criteria evaluated in this study.

DIS criteria				
2010 McDonald[1]	≥ 2 of the following:			
	≥ 1 PV lesion	≥ 1 JC lesion	≥ 1 PF lesion	≥ 1 SC lesion
	All lesions in symptomatic regions excluded in brainstem/cerebellar and SC syndromes			
2017 McDonald[2]	≥ 2 of the following:			
	≥1 PV lesion	**≥ 1 CL/JC lesion**	≥ 1 PF lesion	≥ 1 SC lesion
	All lesions in symptomatic regions **included** in brainstem/cerebellar and SC syndromes			
2017 DIS criteria modified (3 PV)	≥ 2 of the following:			
	≥ 3 PV lesions	**≥ 1 CL/JC lesion**	≥ 1 PF lesion	≥ 1 SC lesion
	All lesions in symptomatic regions **included** in brainstem/cerebellar and SC syndromes			
DIT criteria				
2010 McDonald[1]	Simultaneous presence of Gd-enhancing and non-enhancing lesions at any time (excluding symptomatic lesions) or A new T2 and/or Gd-enhancing lesion on FU MRI irrespective of timing of baseline scan			
2017 McDonald[2]	Simultaneous presence of Gd-enhancing and non-enhancing lesions at any time **(including symptomatic lesions)** or A new T2 and/or Gd-enhancing lesion on FU MRI irrespective of timing of baseline scan or Demonstration of CSF-specific OCBs*			

*In patients with a typical CIS suggestive of MS fulfilling DIS criteria and with no better explanation for the clinical presentation, the demonstration of CSF-specific OCBs substitutes for the requirement of fulfilling DIT, thus allowing a diagnosis of MS, even if the clinical and MRI findings do not meet the criteria for DIT.
Abbreviations: CIS=clinically isolated syndrome; CL=cortical lesion; CSF=cerebrospinal fluid; DIS=dissemination in space; DIT=dissemination in time; FU=follow-up; Gd=gadolinium; JC=juxtacortical; MRI=magnetic resonance imaging; OCBs=oligoclonal bands; PF=posterior fossa; PV=periventricular; SC=spinal cord.

Table e-2. Performance of the different combined MRI criteria for DIS, DIT and DIS plus DIT also according to the evaluation of OCBs for development of CDMS in the CIS patients not receiving DMT before the second clinical event (n=550) at 36 and 60 months' follow-up.

Criteria	Timepoint	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	PPV (95% CI)	NPV (95% CI)
DIS only						
2010 McDonald[1]	M36	0.76 (0.70-0.81)	0.58 (0.51-0.65)	0.67 (0.62-0.71)	0.64 (0.58-0.7)	0.70 (0.64-0.76)
	M60	0.75 (0.70-0.80)	0.67 (0.59-0.74)	0.71 (0.66-0.75)	0.75 (0.69-0.81)	0.66 (0.59-0.73)
2017 McDonald[2]	M36	0.84 (0.79-0.88)	0.51 (0.44-0.58)	0.67 (0.63-0.71)	0.63 (0.57-0.68)	0.76 (0.69-0.82)
	M60	0.82 (0.77-0.86)	0.57 (0.48-0.65)	0.69 (0.65-0.74)	0.72 (0.66-0.77)	0.70 (0.62-0.77)
DIT only						
2010 McDonald[1]	M36	0.74 (0.69-0.79)	0.71 (0.64-0.76)	0.73 (0.68-0.76)	0.72 (0.66-0.77)	0.73 (0.68-0.79)
	M60	0.72 (0.67-0.77)	0.76 (0.68-0.82)	0.74 (0.69-0.78)	0.80 (0.74-0.85)	0.67 (0.6-0.73)
2017 McDonald[2]	M36	0.94 (0.90-0.96)	0.36 (0.29-0.44)	0.65 (0.61-0.69)	0.62 (0.57-0.67)	0.83 (0.74-0.90)
	M60	0.93 (0.89-0.95)	0.44 (0.34-0.53)	0.68 (0.63-0.73)	0.71 (0.66-0.76)	0.80 (0.70-0.87)
2017 McDonald without OCBs[2]	M36	0.74 (0.69-0.79)	0.71 (0.64-0.76)	0.73 (0.68-0.76)	0.72 (0.66-0.77)	0.73 (0.68-0.79)
	M60	0.72 (0.67-0.77)	0.76 (0.68-0.82)	0.74 (0.69-0.78)	0.80 (0.74-0.85)	0.67 (0.60-0.73)
DIS plus DIT						
2010 McDonald[1]	M36	0.63 (0.57-0.69)	0.78 (0.72-0.83)	0.71 (0.66-0.74)	0.74 (0.67-0.80)	0.68 (0.62-0.73)

		AUC		PPV	NPV	
	M60	0.61 (0.55-0.67)	0.83 (0.76-0.89)	0.72 (0.67-0.76)	0.83 (0.76-0.89)	0.61 (0.55-0.67)
2017 McDonald[2]	M36	0.80 (0.75-0.85)	0.62 (0.55-0.69)	0.71 (0.67-0.75)	0.68 (0.63-0.74)	0.76 (0.69-0.81)
	M60	0.78 (0.73-0.83)	0.69 (0.60-0.76)	0.73 (0.68-0.78)	0.77 (0.71-0.83)	0.70 (0.62-0.76)
2017 McDonald without OCBs[2]	M36	0.70 (0.64-0.75)	0.74 (0.68-0.80)	0.72 (0.68-0.76)	0.73 (0.67-0.79)	0.71 (0.65-0.76)
	M60	0.67 (0.62-0.73)	0.78 (0.70-0.84)	0.73 (0.68-0.77)	0.81 (0.74-0.86)	0.64 (0.57-0.70)

Abbreviations: AUC=area under the curve; CDMS=clinically definite MS; CI=confidence interval; DIS=dissemination in space; DIT=dissemination in time; DMT= disease-modifying treatment; M=month; MRI=magnetic resonance imaging; NPV=negative predictive value; OCBs=oligoclonal bands; PPV=positive predictive value.

Table e-3. Performance of the different combined MRI criteria for DIS and DIS plus DIT for development of CDMS according to the type of monofocal onset at 36 and 60 months' follow-up.

Criteria	Type of onset	Timepoint	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	PPV (95% CI)	NPV (95% CI)
DIS only							
2010 McDonald[1]	Optic neuritis	M36	0.77 (0.68-0.84)	0.47 (0.39-0.56)	0.60 (0.56-0.68)	0.51 (0.43-0.59)	0.74 (0.64-0.82)
	Brainstem / cerebellar syndrome		0.75 (0.63-0.85)	0.39 (0.29-0.50)	0.57 (0.49-0.64)	0.43 (0.34-0.53)	0.71 (0.57-0.82)
	Myelitis		0.78 (0.69-0.86)	0.29 (0.21-0.38)	0.54 (0.48-0.60)	0.48 (0.40-0.55)	0.62 (0.49-0.74)
	Optic neuritis	M60	0.74 (0.66-0.81)	0.54 (0.42-0.64)	0.64 (0.57-0.70)	0.62 (0.53-0.70)	0.67 (0.57-0.77)
	Brainstem / cerebellar syndrome		0.77 (0.66-0.86)	0.49 (0.35-0.63)	0.63 (0.54-0.71)	0.57 (0.46-0.68)	0.71 (0.57-0.82)
	Myelitis		0.80 (0.72-0.87)	0.38 (0.27-0.51)	0.59 (0.53-0.66)	0.59 (0.51-0.68)	0.64 (0.49-0.75)
2017 McDonald[2]	Optic neuritis	M36	0.78 (0.70-0.85)	0.47 (0.38-0.55)	0.62 (0.57-0.68)	0.51 (0.43-0.59)	0.75 (0.65-0.83)
	Brainstem / cerebellar syndrome		0.94 (0.85-0.98)	0.32 (0.22-0.42)	0.63 (0.57-0.68)	0.46 (0.38-0.55)	0.89 (0.74-0.97)
	Myelitis		0.87 (0.79-0.93)	0.21 (0.14-0.3)	0.54 (0.49-0.59)	0.48 (0.40-0.55)	0.67 (0.50-0.81)
	Optic neuritis	M60	0.75 (0.67-0.82)	0.53 (0.41-0.63)	0.64 (0.57-0.7)	0.61 (0.53-0.7)	0.68 (0.57-0.77)
	Brainstem / cerebellar syndrome		0.93 (0.84-0.97)	0.39 (0.26-0.53)	0.66 (0.59-0.73)	0.58 (0.48-0.67)	0.86 (0.69-0.95)
	Myelitis		0.88 (0.81-0.93)	0.26 (0.17-0.38)	0.57 (0.51-0.63)	0.57 (0.49-0.65)	0.66 (0.48-0.80)
DIS plus DIT							
2010 McDonald[1]	Optic neuritis	M36	0.63 (0.54-0.72)	0.70 (0.62-0.77)	0.67 (0.60-0.72)	0.60 (0.51-0.69)	0.73 (0.65-0.79)

	Brainstem / cerebellar syndrome		0.66 (0.53-0.77)	0.57 (0.46-0.68)	0.62 (0.54-0.69)	0.49 (0.38-0.61)	0.73 (0.62-0.82)
	Myelitis		0.68 (0.58-0.76)	0.57 (0.47-0.66)	0.62 (0.55-0.69)	0.56 (0.47-0.65)	0.68 (0.59-0.77)
	Optic neuritis	M60	0.58 (0.49-0.67)	0.72 (0.61-0.81)	0.65 (0.58-0.71)	0.67 (0.57-0.77)	0.63 (0.54-0.71)
	Brainstem / cerebellar syndrome	M60	0.66 (0.54-0.77)	0.69 (0.55-0.80)	0.67 (0.58-0.75)	0.65 (0.52-0.77)	0.70 (0.58-0.79)
	Myelitis		0.68 (0.59-0.76)	0.62 (0.49-0.73)	0.65 (0.57-0.72)	0.66 (0.56-0.76)	0.63 (0.53-0.72)
2017 McDonald[2]	Optic neuritis	M36	0.75 (0.67-0.83)	0.53 (0.44-0.62)	0.64 (0.58-0.70)	0.54 (0.45-0.62)	0.75 (0.66-0.83)
	Brainstem / cerebellar syndrome	M36	0.89 (0.79-0.95)	0.44 (0.34-0.56)	0.67 (0.60-0.73)	0.51 (0.41-0.61)	0.86 (0.74-0.94)
	Myelitis		0.85 (0.77-0.91)	0.24 (0.17-0.33)	0.55 (0.49-0.60)	0.48 (0.41-0.56)	0.66 (0.50-0.80)
	Optic neuritis	M60	0.72 (0.64-0.80)	0.61 (0.49-0.71)	0.66 (0.59-0.73)	0.64 (0.54-0.73)	0.70 (0.60-0.78)
	Brainstem / cerebellar syndrome	M60	0.87 (0.77-0.94)	0.52 (0.38-0.67)	0.69 (0.61-0.77)	0.63 (0.52-0.73)	0.81 (0.67-0.91)
	Myelitis		0.86 (0.79-0.92)	0.32 (0.21-0.44)	0.59 (0.53-0.66)	0.59 (0.51-0.67)	0.67 (0.51-0.80)

Abbreviations: AUC=area under the curve; CDMS=clinically definite MS; CI=confidence interval; DIS=dissemination in space; DIT=dissemination in time; M=month; MRI=magnetic resonance imaging; NPV=negative predictive value; OCBs=oligoclonal bands; PPV=positive predictive value.

Table e-4. Performance of the different combined MRI criteria for DIS and DIS plus DIT for development of CDMS at 36 and 60 months' follow-up in the final cohort (n=785) and by age groups, according to the minimum number of periventricular lesions to define periventricular involvement (≥1 *vs* ≥3).

Criteria	Timepoint	Age [years]	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	PPV (95% CI)	NPV (95% CI)
DIS only							
2010 McDonald[1]	M36	**All (n=785)**	0.78 (0.73-0.82)	0.38 (0.33-0.43)	0.58 (0.55-0.62)	0.48 (0.44-0.53)	0.70 (0.64-0.76)
		<25 (n=155)	0.82 (0.72-0.89)	0.38 (0.26-0.51)	0.60 (0.52-0.67)	0.61 (0.51-0.70)	0.64 (0.47-0.77)
		25-34 (n=333)	0.73 (0.66-0.80)	0.35 (0.27-0.42)	0.54 (0.49-0.59)	0.47 (0.40-0.54)	0.62 (0.52-0.71)
		35-44 (n=210)	0.87 (0.77-0.94)	0.50 (0.41-0.60)	0.69 (0.62-0.75)	0.48 (0.39-0.57)	0.88 (0.79-0.94)
		≥45 (n=87)	0.72 (0.54-0.87)	0.23 (0.12-0.37)	0.48 (0.38-0.55)	0.34 (0.23-0.47)	0.60 (0.35-0.81)
	M60	**All (n=785)**	0.78 (0.74-0.82)	0.47 (0.40-0.53)	0.62 (0.58-0.66)	0.60 (0.55-0.65)	0.67 (0.61-0.73)
		<25 (n=155)	0.83 (0.74-0.90)	0.40 (0.30-0.65)	0.65 (0.55-0.74)	0.73 (0.62-0.82)	0.61 (0.43-0.76)
		25-34 (n=333)	0.75 (0.68-0.81)	0.41 (0.31-0.51)	0.58 (0.52-0.64)	0.59 (0.52-0.66)	0.59 (0.48-0.69)
		35-44 (n=210)	0.82 (0.70-0.90)	0.64 (0.51-0.75)	0.73 (0.65-0.80)	0.62 (0.51-0.73)	0.83 (0.71-0.90)
		≥45 (n=87)	0.75 (0.57-0.88)	0.28 (0.13-0.46)	0.51 (0.42-0.58)	0.40 (0.27-0.54)	0.63 (0.37-0.84)
2017 McDonald[2]	M36	**All (n=785)**	0.86 (0.82-0.90)	0.32 (0.28-0.37)	0.59 (0.56-0.62)	0.49 (0.44-0.53)	0.76 (0.69-0.82)
		<25 (n=155)	0.90 (0.82-0.95)	0.31 (0.20-0.44)	0.61 (0.54-0.68)	0.60 (0.51-0.69)	0.73 (0.53-0.87)
		25-34 (n=333)	0.82 (0.75-0.88)	0.32 (0.25-0.39)	0.57 (0.52-0.62)	0.49 (0.42-0.56)	0.69 (0.58-0.79)
		35-44 (n=210)	0.93 (0.84-0.97)	0.40 (0.31-0.50)	0.66 (0.60-0.72)	0.45 (0.36-0.53)	0.91 (0.81-0.97)
		≥45 (n=87)	0.79 (0.60-0.91)	0.18 (0.08-0.32)	0.49 (0.40-0.57)	0.34 (0.24-0.47)	0.61 (0.32-0.85)

	M60	All (n=785)	0.85 (0.81-0.88)	0.38 (0.31-0.45)	0.61 (0.58-0.65)	0.59 (0.54-0.63)	0.71 (0.64-0.78)
		<25 (n=155)	0.90 (0.82-0.95)	0.34 (0.19-0.52)	0.62 (0.54-0.72)	0.70 (0.60-0.79)	0.67 (0.43-0.84)
		25-34 (n=333)	0.82 (0.76-0.88)	0.37 (0.27-0.47)	0.60 (0.54-0.65)	0.60 (0.53-0.67)	0.65 (0.53-0.75)
		35-44 (n=210)	0.86 (0.76-0.93)	0.49 (0.36-0.62)	0.68 (0.60-0.75)	0.56 (0.45-0.65)	0.83 (0.69-0.92)
		≥45 (n=87)	0.81 (0.63-0.92)	0.21 (0.08-0.40)	0.51 (0.42-0.58)	0.39 (0.27-0.53)	0.63 (0.31-0.87)
2017 McDonald with 3 PV lesions	M36	All (n=785)	0.77 (0.73-0.82)	0.41 (0.36-0.46)	0.59 (0.56-0.63)	0.49 (0.45-0.54)	0.71 (0.65-0.76)
		<25 (n=155)	0.78 (0.68-0.86)	0.40 (0.28-0.53)	0.59 (0.51-0.67)	0.60 (0.50-0.70)	0.60 (0.45-0.74)
		25-34 (n=333)	0.75 (0.67-0.81)	0.39 (0.31-0.47)	0.57 (0.52-0.62)	0.49 (0.42-0.56)	0.66 (0.56-0.75)
		35-44 (n=210)	0.84 (0.73-0.91)	0.48 (0.38-0.57)	0.66 (0.59-0.72)	0.46 (0.36-0.55)	0.85 (0.75-0.92)
		≥45 (n=87)	0.76 (0.57-0.89)	0.32 (0.19-0.46)	0.54 (0.44-0.63)	0.38 (0.26-0.51)	0.71 (0.48-0.87)
	M60	All (n=785)	0.77 (0.72-0.81)	0.49 (0.42-0.56)	0.63 (0.59-0.67)	0.61 (0.56-0.66)	0.67 (0.61-0.73)
		<25 (n=155)	0.78 (0.68-0.85)	0.47 (0.30-0.65)	0.62 (0.53-0.72)	0.72 (0.61-0.81)	0.55 (0.38-0.70)
		25-34 (n=333)	0.75 (0.68-0.81)	0.47 (0.36-0.57)	0.61 (0.55-0.67)	0.61 (0.54-0.69)	0.62 (0.51-0.72)
		35-44 (n=210)	0.79 (0.68-0.88)	0.61 (0.47-0.72)	0.70 (0.62-0.77)	0.60 (0.48-0.70)	0.80 (0.68-0.88)
		≥45 (n=87)	0.78 (0.60-0.90)	0.34 (0.19-0.54)	0.56 (0.46-0.67)	0.43 (0.30-0.58)	0.71 (0.46-0.88)
DIS plus DIT							
2010 McDonald[1]	M36	All (n=785)	0.66 (0.61-0.71)	0.60 (0.55-0.65)	0.63 (0.59-0.67)	0.55 (0.50-0.60)	0.71 (0.66-0.75)
		<25 (n=155)	0.69 (0.58-0.79)	0.66 (0.53-0.77)	0.67 (0.59-0.75)	0.70 (0.59-0.80)	0.64 (0.52-0.75)
		25-34 (n=333)	0.65 (0.57-0.73)	0.55 (0.47-0.63)	0.60 (0.55-0.66)	0.54 (0.46-0.61)	0.67 (0.58-0.74)
		35-44	0.75	0.64	0.70	0.52	0.83

Criteria	Timepoint	Age					
		(n=210)	(0.63-0.84)	(0.55-0.73)	(0.62-0.76)	(0.42-0.62)	(0.75-0.90)
		≥45 (n=87)	0.42 (0.24-0.61)	0.61 (0.46-0.75)	0.51 (0.42-0.61)	0.37 (0.21-0.55)	0.66 (0.51-0.78)
	M60	All (n=785)	0.65 (0.59-0.69)	0.66 (0.59-0.72)	0.65 (0.61-0.69)	0.66 (0.60-0.72)	0.64 (0.59-0.69)
		<25 (n=155)	0.64 (0.53-0.73)	0.72 (0.54-0.86)	0.68 (0.57-0.76)	0.80 (0.67-0.90)	0.53 (0.39-0.66)
		25-34 (n=333)	0.66 (0.58-0.73)	0.61 (0.51-0.7)	0.63 (0.57-0.69)	0.66 (0.57-0.73)	0.61 (0.52-0.69)
		35-44 (n=210)	0.72 (0.61-0.82)	0.74 (0.62-0.84)	0.73 (0.65-0.80)	0.67 (0.54-0.78)	0.78 (0.68-0.86)
		≥45 (n=87)	0.42 (0.25-0.61)	0.59 (0.4-0.76)	0.50 (0.39-0.61)	0.39 (0.22-0.59)	0.62 (0.45-0.75)
2017 McDonald[2]	M36	All (n=785)	0.83 (0.79-0.87)	0.39 (0.34-0.44)	0.61 (0.58-0.64)	0.51 (0.46-0.55)	0.76 (0.70-0.81)
		<25 (n=155)	0.90 (0.82-0.95)	0.35 (0.23-0.49)	0.63 (0.56-0.70)	0.63 (0.53-0.72)	0.74 (0.56-0.88)
		25-34 (n=333)	0.80 (0.73-0.86)	0.35 (0.27-0.42)	0.58 (0.52-0.62)	0.50 (0.43-0.56)	0.69 (0.58-0.78)
		35-44 (n=210)	0.87 (0.77-0.93)	0.50 (0.39-0.59)	0.68 (0.61-0.74)	0.48 (0.39-0.57)	0.87 (0.78-0.94)
		≥45 (n=87)	0.72 (0.53-0.87)	0.34 (0.21-0.49)	0.53 (0.44-0.62)	0.37 (0.25-0.51)	0.69 (0.48-0.86)
	M60	All (n=785)	0.82 (0.78-0.86)	0.46 (0.40-0.53)	0.64 (0.60-0.68)	0.61 (0.56-0.66)	0.71 (0.65-0.77)
		<25 (n=155)	0.90 (0.82-0.95)	0.41 (0.24-0.60)	0.66 (0.56-0.75)	0.73 (0.62-0.82)	0.69 (0.47-0.86)
		25-34 (n=333)	0.80 (0.73-0.86)	0.41 (0.31-0.52)	0.61 (0.55-0.67)	0.60 (0.53-0.68)	0.65 (0.53-0.75)
		35-44 (n=210)	0.81 (0.71-0.9)	0.61 (0.48-0.73)	0.71 (0.63-0.79)	0.61 (0.50-0.72)	0.81 (0.70-0.90)
		≥45 (n=87)	0.70 (0.52-0.85)	0.38 (0.21-0.57)	0.54 (0.43-0.65)	0.42 (0.28-0.57)	0.67 (0.44-0.84)
2017 McDonald with 3 PV lesions	M36	All (n=785)	0.75 (0.70-0.80)	0.45 (0.40-0.50)	0.60 (0.57-0.64)	0.50 (0.46-0.55)	0.71 (0.65-0.76)
		<25 (n=155)	0.77 (0.67-0.86)	0.43 (0.30-0.56)	0.60 (0.52-0.68)	0.61 (0.51-0.71)	0.62 (0.46-0.75)
		25-34 (n=333)	0.73 (0.65-0.80)	0.41 (0.33-0.49)	0.57 (0.52-0.62)	0.50 (0.43-0.57)	0.66 (0.56-0.74)
		35-44 (n=210)	0.79 (0.69-0.88)	0.56 (0.46-0.66)	0.68 (0.6-0.74)	0.49 (0.39-0.58)	0.84 (0.75-0.91)

		≥45 (n=87)	0.69 (0.50-0.84)	0.39 (0.25-0.53)	0.54 (0.44-0.63)	0.38 (0.25-0.52)	0.70 (0.50-0.85)
	M60	All (n=785)	0.74 (0.70-0.79)	0.54 (0.48-0.61)	0.64 (0.60-0.68)	0.63 (0.58-0.68)	0.67 (0.61-0.73)
		<25 (n=155)	0.77 (0.68-0.85)	0.53 (0.35-0.71)	0.65 (0.55-0.75)	0.75 (0.63-0.84)	0.57 (0.41-0.72)
		25-34 (n=333)	0.74 (0.66-0.80)	0.49 (0.39-0.60)	0.61 (0.55-0.68)	0.62 (0.54-0.70)	0.62 (0.52-0.71)
		35-44 (n=210)	0.76 (0.65-0.85)	0.70 (0.57-0.81)	0.73 (0.65-0.80)	0.65 (0.53-0.76)	0.79 (0.69-0.87)
		≥45 (n=87)	0.67 (0.49-0.83)	0.38 (0.21-0.57)	0.53 (0.41-0.64)	0.41 (0.27-0.56)	0.65 (0.42-0.82)

Abbreviations: AUC=area under the curve; CDMS=clinically definite MS; CI=confidence interval; CIS=clinically isolated syndrome; DIS=dissemination in space; DIT=dissemination in time; M=month; MRI=magnetic resonance imaging; NPV=negative predictive value; OCBs=oligoclonal bands; PPV=positive predictive value.

Table e-5. Adjusted hazard ratios (aHRs) with their corresponding 95% confidence intervals (CI). aHRs were obtained from extended Cox regression models using time to clinically definite multiple sclerosis (CDMS) as the outcomes in the final cohort (n=785).

Criteria	aHR* (95% CI)	p value	Interaction with treatment			Interaction with type of onset		
			aHR (95% CI)	p value	p value heterogeneity	aHR with type of onset (95% CI)	p value	p value heterogeneity
DIS only								
2010 McDonald[1]	2.45 (1.91-3.15)	<0.001	Without treatment 2.79 (2.14-3.64)	<0.001	0.004	Optic neuritis 2.73 (1.88-3.97)	<0.001	0.76
						Brainstem / cerebellar syndrome 2.46 (1.44-4.21)	0.001	
			Under treatment 0.86 (0.46-1.59)	0.63		Myelitis 2.00 (1.29-3.10)	0.002	
2017 McDonald[2]	3.25 (2.43-4.34)	<0.001	Without treatment 3.48 (2.57-4.70)	<0.001	0.009	Optic neuritis 2.87 (1.97-4.20)	<0.001	0.26
						Brainstem / cerebellar syndrome 7.42 (2.98-18.49)	<0.001	
			Under treatment 1.26 (0.51-3.11)	0.62		Myelitis 2.70 (1.55-4.70)	<0.001	
DIS plus DIT								
2010 McDonald[1]	2.68 (2.15-3.35)	<0.001	Without treatment 3.11 (2.44-3.96)	<0.001	<0.001	Optic neuritis 2.91 (2.08-4.06)	<0.001	0.36
						Brainstem / cerebellar syndrome 2.98 (1.84-4.82)	<0.001	
			Under treatment 1.29 (0.80-2.10)	0.30		Myelitis 2.63 (1.79-3.87)	<0.001	
2017 McDonald[2]	3.59	<0.001	Without treatment	<0.001	0.002	Optic neuritis	<0.001	0.30

	(2.71-4.76)		3.78 (2.83-5.06)			3.23 (2.21-4.73)		
						Brainstem / cerebellar syndrome 6.42 (3.17-13.00)	<0.001	
			Under treatment 1.75 (0.71-4.35)	0.23		Myelitis 2.86 (1.69-4.84)	<0.001	
2017 McDonald without OCBs[2]	3.22 (2.54-4.09)	<0.001	Without treatment 3.47 (2.69-4.46)	<0.001	<0.001	Optic neuritis 3.01 (2.16-4.21)	<0.001	0.19
						Brainstem / cerebellar syndrome 5.06 (2.88-8.89)	<0.001	
			Under treatment 1.89 (1.03-3.47)	0.04		Myelitis 3.17 (2.04-4.95)	<0.001	

Abbreviations: aHR=adjusted hazard ratios; CI=confidence interval; DIS=dissemination in space; DIT=dissemination in time; EDSS=Expanded Disability Status Scale; OCBs=oligoclonal bands.
*=adjusted for age, sex, centre, treatment, and type of onset.

Table e-6. Adjusted hazard ratios (aHRs) with their corresponding 95% confidence intervals (CI). aHRs were obtained from extended Cox regression models using time to EDSS$\geq$3.0 as the outcomes in the final cohort (n=785).

Criteria	aHR*	95% CI	p value
DIS only			
2010 McDonald[1]	2.04	1.20-3.48	0.008
2017 McDonald[2]	2.34	1.27-4.28	0.006
DIT only			
2010 McDonald[1]	2.26	1.37-3.74	0.001
2017 McDonald[2]	3.42	1.21-9.68	0.02
2017 McDonald without OCBs[2]	1.92	1.16-3.19	0.01
DIS plus DIT			
2010 McDonald[1]	2.00	1.28-3.14	0.002
2017 McDonald[2]	2.52	1.41-4.52	0.002
2017 McDonald without OCBs[2]	1.98	1.23-3.18	0.005

Abbreviations: aHR=adjusted hazard ratios; CI=confidence interval; DIS=dissemination in space; DIT=dissemination in time; EDSS=Expanded Disability Status Scale; OCBs=oligoclonal bands.
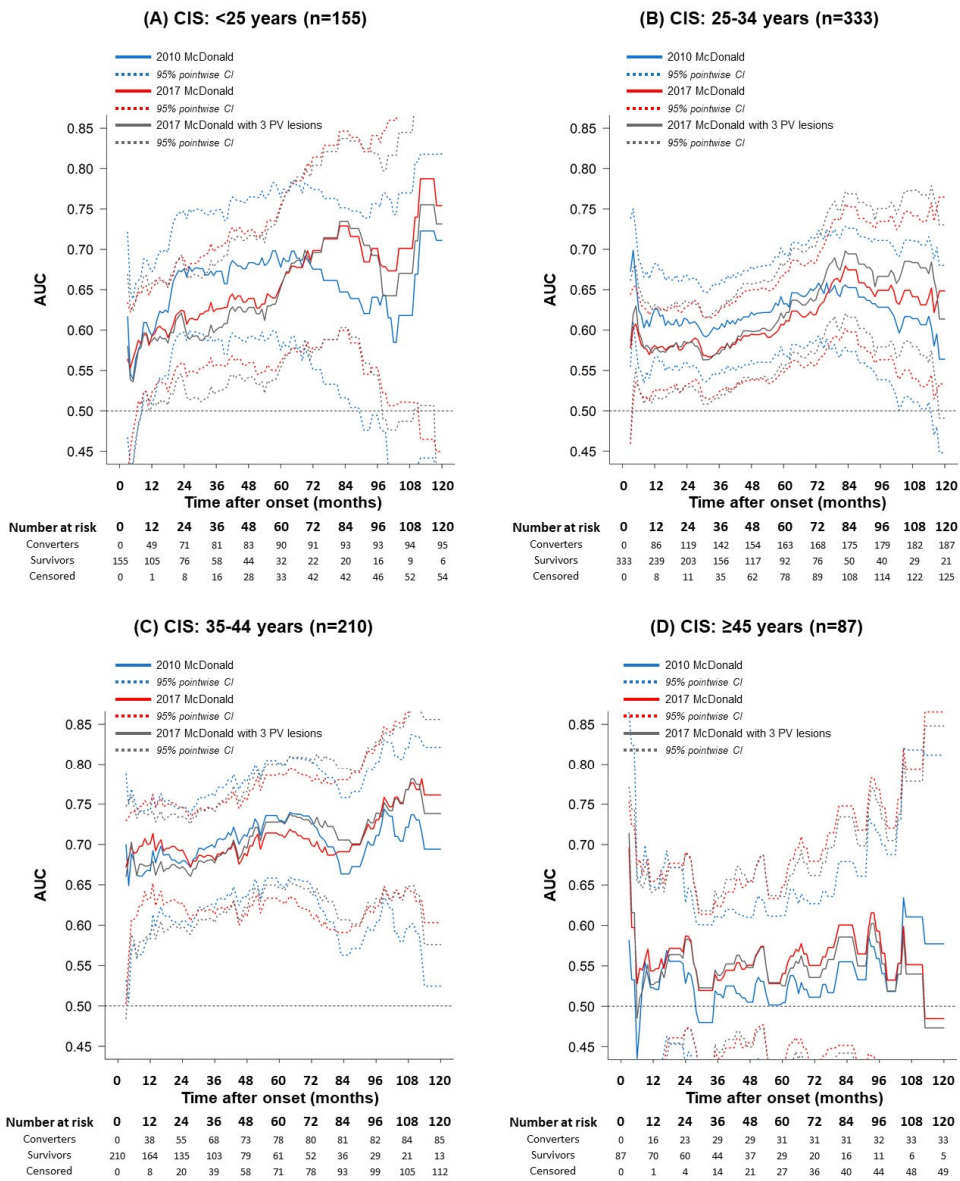*=adjusted for age, sex, centre, treatment, and type of onset.

Figure e-1. Overall accuracy over time of DIS plus DIT criteria according to age at onset and to 3 instead of 1 periventricular lesions.

Overall accuracy of the 2010 McDonald (blue line), 2017 McDonald criteria, with 1 (red line) or 3 (gray line) periventricular lesions, determined by the AUC over time, up to 10 years, from disease onset, to the development of CDMS, considering DIS only in CIS patients aged (A) <25 years, (B) 25-34 years, (C) 35-44 years or ≥45 years at onset.

See text for further details.

Abbreviations: AUC=area under the curve; CDMS=clinically definite MS; CI=confidence interval; DIS=dissemination in space ; DIT=dissemination in time.

2017 McDonald and 2010 McDonald

Survival probability estimates of not reaching EDSS ≥ 3.0
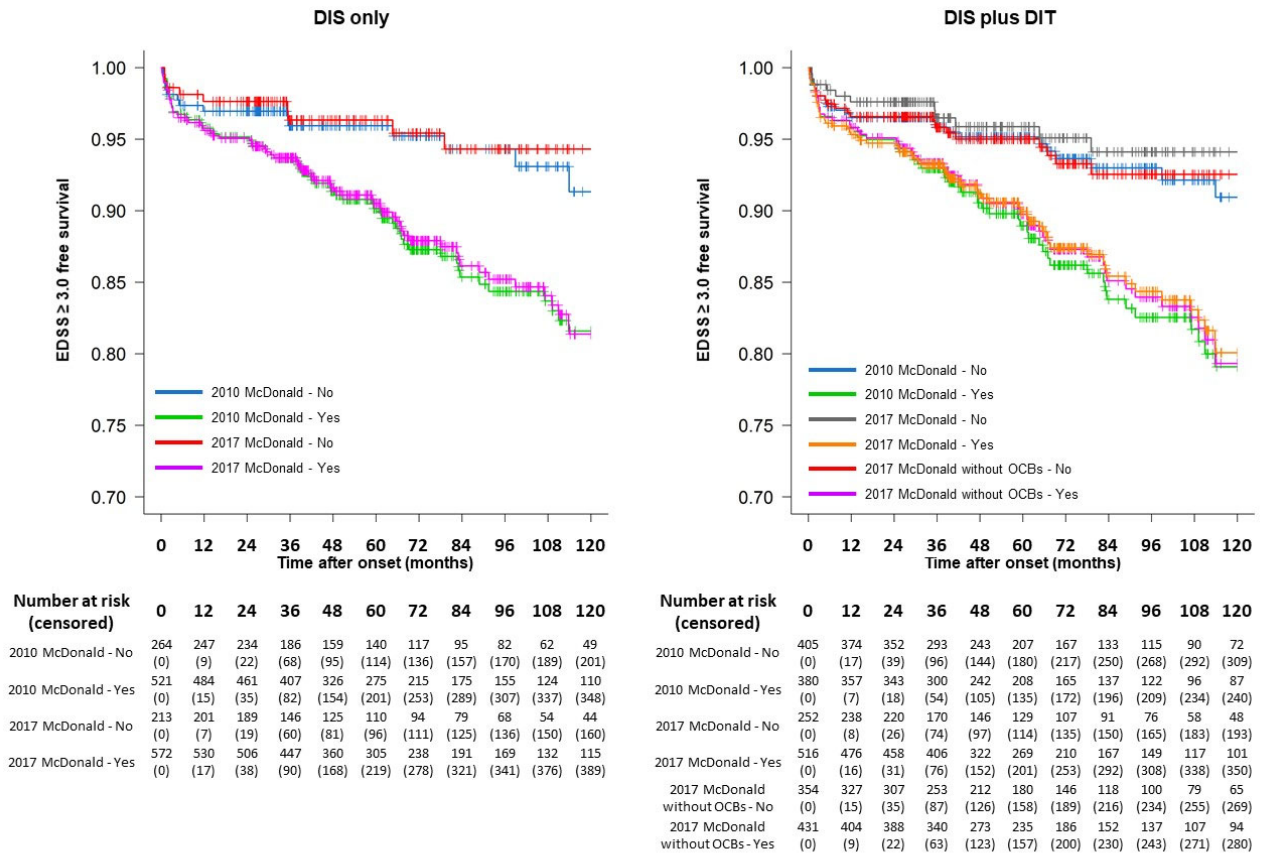

Figure e-2. Survival probability estimates of not reaching an EDSS score ≥3.0 according to the different sets of criteria investigated.
Kaplan-Meier curves showing the survival probability estimates of not reaching an EDSS score ≥3.0 up to 10 years from disease onset considering DIS only or DIS plus DIT according to the 2010 McDonald 2010 and 2017 McDonald criteria, also without OCBs assessment. See text for further details. Abbreviations: DIS=dissemination in space; DIT=dissemination in time; EDSS=Expanded Disability Status Scale; OCBs=oligoclonal bands.

References

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2.   Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology 2018;17:162-173.