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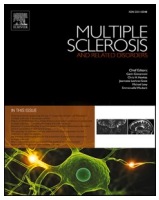

Distinct clinical, imaging, and cerebrospinal fluid profiles in people with late-onset multiple sclerosis

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ABSTRACT

Introduction: Late-onset multiple sclerosis (LOMS), defined as onset after age 50, poses unique diagnostic challenges due to clinical and radiological differences from early-onset multiple sclerosis (EOMS), which typically manifests in adults between 20 and 40 years of age. Limited research on these differences hampers accurate diagnosis of LOMS. This study aims to bridge this gap by comparing clinical presentation, imaging, and cerebrospinal fluid (CSF) findings in LOMS and EOMS patients.

Methods: We retrospectively analyzed clinical, MRI, and CSF data from 148 LOMS patients treated in the neuroimmunology outpatient clinic of a Swiss tertiary referral center between 2013 and 2023. A control group of 148 EOMS patients, matched by year of diagnosis, was included for comparison.

Results: LOMS patients, with a median onset age of 53 years (interquartile range (IQR) 51–58 years), more commonly presented with motor or multiple symptoms and a primary progressive multiple sclerosis subtype ($p < 0.001$). They were also more likely than EOMS patients (median onset age 28 years, IQR 24–33 years) to report cognitive impairment and fatigue at disease onset ($p < 0.001$). MRI analysis showed that LOMS patients had a significantly higher T2-lesion load ($p = 0.026$) but fewer Gadolinium-enhancing lesions at diagnosis ($p < 0.001$). The percentage of patients with CSF-specific oligoclonal bands was comparable between groups, whereas CSF pleocytosis was more common in EOMS patients ($p < 0.001$). Importantly, we noticed a significant delay in diagnosing multiple sclerosis in older adults likely due to misdiagnosis or difficulties in timely recognition.

Discussion: LOMS represents a subgroup of multiple sclerosis with unique clinical and radiological characteristics compared to EOMS. The higher T2-lesion burden and fewer Gadolinium-enhancing lesions in LOMS can pose diagnostic challenges. Recognizing these differences may enhance diagnostic accuracy and guide more effective management strategies for LOMS.

1. Introduction

Late-onset multiple sclerosis (LOMS), defined as disease onset after age 50, represents a challenging subset of multiple sclerosis (MS). A 2021 literature review reported that LOMS accounts for 1.1 % to 21.3 % of all people with MS (pwMS) (Naseri et al., 2021) with a trend toward increasing incidence in recent years (Capasso et al., 2023; Prosperini and Haggiag, 2024). Differentiating early-onset MS (EOMS), typically defined as onset between ages 18 and 40 or 50, from LOMS has long been regarded an important topic. Higher proportions of primary progressive MS (PPMS) subtypes were described in cohorts of LOMS (Mouresan et al., 2024). Clinically, some analyses suggest that patients with LOMS may be more prone to motor dysfunction, cerebellar symptoms and signs, fatigue, as well as sphincter disturbances, while EOMS patients are often reported to present more frequently with visual and sensory disturbances, although findings have not been consistent across all studies (Martinelli et al., 2004; Palathinkara et al., 2023). The burden of cognitive impairment seems to be higher in patients with LOMS, especially in the presence of vascular risk factors (Butler Pagnotti et al., 2022; Oliveira et al., 2024). Moreover, patients with LOMS often reach critical disability milestones, such as an Expanded Disability Status Scale (EDSS) score of six, more rapidly than EOMS patients (Andersen et al.,

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2021; D'Amico et al., 2018). However, they are less likely to be treated with high-efficacy disease modifying drugs (Knowles et al., 2024). Magnetic resonance imaging (MRI) has been used to explore potential distinctions between the two groups: patients with LOMS may have a higher incidence of spinal lesions, while EOMS patients are more likely to exhibit contrast-enhancing brain lesions (Kis et al., 2008; Palathinkara et al., 2023). Diagnosing LOMS is complicated by a higher frequency of nonspecific or vascular white matter changes on brain MRI, as well as a greater likelihood of differential diagnoses that can mimic MS in this age group. These factors may lead to diagnostic delay and false diagnoses (de Seze et al., 2005; Kis et al., 2008; Martinelli et al., 2004; Polliack et al., 2001). Consequently, incorporating cerebrospinal fluid (CSF) analysis, especially the detection of CSF-specific oligoclonal bands and other markers of inflammatory processes, is of particular importance for confirming MS diagnoses in older patients. Despite previous studies investigating clinical and imaging characteristics in LOMS and EOMS, comprehensive data on differences, particularly regarding CSF profiles and other disease features, remain limited. To address this gap, we conducted a retrospective analysis comparing the clinical, radiological, and CSF characteristics of 148 LOMS patients with 148 EOMS patients from our MS cohort.

2. Methods

2.1. Study design

We retrospectively reviewed the clinical records of all patients treated at the neuroimmunology outpatient clinic of the University Hospital Zurich, Switzerland, between January 2013 and June 2023. The University Hospital Zurich is a tertiary referral center serving a population of approximately 2 million inhabitants. The diagnosis of MS and classification of initial disease course were based on the 2017 McDonald Criteria (Thompson et al., 2018). We reapplied the 2017 McDonald Criteria also for patients who were diagnosed with MS or a clinically isolated syndrome (CIS) before 2017. We defined late-onset MS (LOMS) as symptom onset at the age of 50 years or later. All patients with available clinical data at the time of MS diagnosis were included. Only patients who declined the use of their data for research purposes were excluded. To form a comparison group, we randomly selected an equal number of early-onset MS (EOMS) patients, defined as having disease onset between the ages of 18 and 40 years, from the same cohort. The LOMS and EOMS groups were then matched by year of diagnosis, ensuring equal distribution across the following time periods: before 2006, 2006–2010, 2011–2015, 2016–2020, and after 2020.

2.2. Variables

Clinical data extracted included symptoms and signs at disease onset, categorized as visual, motor, sensory, cerebellar, brainstem (e.g., internuclear ophthalmoplegia, trigeminal neuropathy), urinary or multifocal symptoms. We also recorded self-reported fatigue and cognitive symptoms and collected the Expanded Disability Status Scale (EDSS) score at diagnosis. Secondary diagnoses including cardiovascular diseases, diabetes, other neurological disorders, malignancies, other autoimmune diseases and mood disorders were evaluated. All clinical data was assessed at the point of diagnosis, before a disease-modifying treatment was started. CSF data extracted included the presence of CSF pleocytosis (defined as a total CSF cell count >4 cells/μL), blood-brain barrier dysfunction (defined as an elevated serum/CSF albumin quotient, corrected for age), CSF-specific oligoclonal bands, and, when available, the "measles, rubella, zoster" (MRZ) reaction. The MRZ reaction was defined as the intrathecal synthesis of antibodies against measles, rubella, and varicella-zoster virus, with a positive result indicated by an antibody index >1.5 for at least two of the three tested antibodies. CSF analysis was generally conducted after MRI acquisition. It was performed at the University Hospital Zurich in 64 % of LOMS and 63 % of EOMS patients, and in other hospitals in 29 % of LOMS and 36 % of EOMS patients.

MRI data extracted from initial brain MRI included total T2-lesion load, categorized as low (three or fewer T2-lesions), medium (four to nine T2-lesions), or high (ten or more T2-lesions). We also recorded the presence of contrast-enhancing lesions in brain and spinal MRI, and the distribution of lesions in periventricular, juxtacortical, infratentorial, and spinal regions, as well as the presence of black holes. Only lesions with a minimum diameter of three millimeters were considered. Where available, MRI data were extracted from the original neuroradiology report. If certain parameters were not mentioned (e.g., T2-lesion load on brain MRI), LS and NN assessed the missing data from the MR images using standard image evaluation methods, without automated image analysis programs. This assessment was done unblinded to patient group. MRI scans were primarily acquired at the Department of Neuroradiology of the University Hospital of Zurich or at associated neuroradiological institutions. For patients diagnosed after 2015, most MRI protocols followed the 2015 MAGNIMS recommendations (Rovira et al., 2015), and from 2021 onward, the MAGNIMS-CMSC-NAIMS recommendations (Wattjes et al., 2021). More information about specific MRI parameters is provided in the supplementary material (supplementary file 1).

2.3. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 29.0. We employed Pearson's chi-square test for categorical variables, the Mann-Whitney U test for ordinal variables, and the *t*-test for normally distributed variables. A p-value of <0.05 was considered statistically significant.

2.4. Ethics

This study was approved by the Ethics Board of the Canton of Zurich (KEK-ZH—Nr. 2024–00,239).

3. Results

3.1. Baseline characteristics and clinical data

We identified 148 patients with LOMS with a median age at disease onset of 53 years (range: 50 to 78 years) and a median age at diagnosis of 57 years (range: 50 to 79 years). The control group consisted of 148 EOMS patients, with a median age at disease onset of 28 years (range: 18 to 40 years) and a median age at diagnosis of 29 years (range: 18 to 61 years). Female patients made up 58.8 % of the LOMS group, a proportion not significantly different from the EOMS group, in which 66.2 % were female (Table 1). The disease duration at the time of MS diagnosis was significantly longer in LOMS (median one year, interquartile range (IQR) zero to three years) than in EOMS (median zero years, IQR zero to one year; $p < 0.001$), indicating a significant diagnostic delay in LOMS.

Patients with LOMS more frequently presented with motor or multiple symptoms, whereas EOMS patients more often experienced visual, brainstem, or sensory symptoms ($p < 0.001$). The EDSS at diagnosis was significantly higher in the LOMS group ($p < 0.001$). Additionally, the proportion of patients with primary progressive MS (PPMS) was higher in the LOMS group ($p < 0.001$, Table 1). Patients with LOMS reported suffering from fatigue and cognitive impairment significantly more often than patients with EOMS ($p < 0.001$).

A significantly higher proportion of LOMS patients (33.8 %) had at least one comorbid condition compared to EOMS patients (18.2 %, $p = 0.002$). This difference was primarily driven by a higher prevalence of cardiovascular diseases in LOMS (14.2 % vs. 2.7 %, $p < 0.001$). No significant differences were found for diabetes, other neurological disorders, neoplastic disorders, mood disorders, or other autoimmune diseases.

Table 1
Clinical data of LOMS and EOMS patients.

	LOMS (N = 148)	EOMS (N = 148)	p-value
Sex			0.187[a]
Male	61 (41.2 %)	50 (33.8 %)	
Female	87 (58.8 %)	98 (66.2 %)	
Age at disease onset			n/a
Mean (SD)	55.2 (5.4)	28.3 (6.0)	
Median (range)	53 (50–78)	28 (18–40)	
Age at diagnosis			n/a
Mean (SD)	57.4 (6.1)	29.7 (6.9)	
Median (range)	57 (50–79)	29 (18–61)	
Subtype			**<0.001**[a]
RRMS	90 (62.1 %)	144 (97.3 %)	
PPMS	55 (37.9 %)	4 (2.7 %)	
Symptoms at onset			**<0.001**[a]
Visual	23 (15.5 %)	49 (33.1 %)	
Motor	20 (13.5 %)	5 (3.4 %)	
Sensory	25 (16.9 %)	33 (22.3 %)	
Brain stem	20 (13.5 %)	35 (23.6 %)	
Cerebellar	3 (2 %)	2 (1.4 %)	
Urinary	1 (0.7 %)	0 (0 %)	
Multiple	54 (36.5 %)	23 (15.5 %)	
Other	2 (1.4 %)	1 (0.7 %	
Fatigue at onset			**<0.001**[a]
Present	49 (45.4 %)	29 (23.6 %)	
Absent	59 (54.6 %)	94 (76.4 %)	
Missing data	40	25	
Cognitive symptoms at onset			**<0.001**[a]
Present	28 (26.4 %)	7 (5.7 %)	
Absent	78 (73.6 %)	115 (94.3 %)	
Missing Data	42	26	
EDSS at diagnosis			**<0.001**[b]
Median (IQR)	2 (1.375–3)	1 (0–2)	

[a] CHI-Square-Test.
[b] Mann-Whitney-U-Test. SD = standard deviation. LOMS = late-onset multiple sclerosis. EOMS = early-onset multiple sclerosis. EDSS = expanded disability status scale. IQR = interquartile range.

3.2. Radiological findings

For patients diagnosed after 2014, complete MRI protocols were available for 70 LOMS (47 %) and 62 EOMS patients (42 %). For patients diagnosed in 2014 or earlier, MRI protocols with a 1.5 Tesla field strength, including at least FLAIR- and/or T2-sequences and T1-sequences before and after Gadolinium contrast in at least two planes, were available for 42 LOMS (28 %) and 53 EOMS patients (36 %). Incomplete MRI protocols were found in 14 % of LOMS and 20 % of EOMS patients, while MR images were unavailable for 10 % and 2 %, respectively. Whole spinal cord MRI was available for 86 % of LOMS and 94 % of EOMS patients. LOMS patients had a significantly higher T2-lesion load on their initial cerebral MRI ($p = 0.026$), whereas EOMS patients were significantly more likely to have contrast-enhancing lesions on their initial cerebral and/or spinal MRI ($p < 0.001$, Table 2). Aside from a higher proportion of juxtacortical lesions in the EOMS group, no significant differences were observed between LOMS and EOMS patients regarding the presence of lesions in other regions or the presence of black holes.

3.3. CSF data

A full CSF analysis (excluding MRZ reaction) was available for 85 % of LOMS and 92 % of EOMS patients. Partial CSF analysis was available for 7 % of both groups, while no CSF analysis was available for 7 % of LOMS and 1 % of EOMS patients. CSF pleocytosis was significantly less frequent in LOMS patients ($p < 0.001$), and CSF cell numbers were higher in EOMS patients ($p < 0.001$; Table 3). We observed no significant differences between LOMS and EOMS patients regarding the presence or absence of CSF barrier dysfunction, CSF-specific oligoclonal bands, or the MRZ reaction.

Table 2
MRI data of LOMS and EOMS patients.

	LOMS (N = 148)	EOMS (N = 148)	p-value
MRI lesion count			**0.026**[b]
Low (<4 lesions)	9 (7 %)	19 (13.3 %)	
Intermediate (4–9 lesions)	31 (24 %)	43 (30.1 %)	
High (>9 lesions)	89 (69 %)	81 (56.6 %)	
Contrast enhancing lesions			**<0.001**[a]
Present	64 (48.1 %)	101 (71.6 %)	
Absent	69 (51.9 %)	40 (28.4 %)	
Periventricular lesions			0.638[a]
Present	128 (96.2 %)	141 (97.2 %)	
Absent	5 (3.8 %)	4 (2.8 %)	
Juxtacortical lesions			**0.004**[a]
Present	71 (53.4 %)	102 (70.3 %)	
Absent	62 (46.6 %)	43 (29.7 %)	
Infratentorial lesions			0.438[a]
Present	84 (63.2 %)	98 (67.6 %)	
Absent	49 (36.8 %)	47 (32.4 %)	
Black holes			0.557[a]
Present	110 (85.9 %)	115 (83.3 %)	
Absent	18 (14.1 %)	23 (16.7 %)	
Spinal lesions			0.9[a]
Present	103 (80.5 %)	111 (79.9 %)	
Absent	25 (19.5 %)	28 (20.1 %)	

[a] CHI-Square-Test.
[b] Mann-Whitney-U-Test. LOMS = late-onset multiple sclerosis. EOMS = early-onset multiple sclerosis.

Table 3
CSF data of LOMS and EOMS patients.

	LOMS (N = 148)	EOMS (N = 148)	p-value
CSF pleocytosis			**<0.001**[a]
Present	37 (28.5 %)	86 (61.9 %)	
Absent	93 (71.5 %)	53 (38.1 %)	
CSF cell count (cells/ μL)			**<0.001**[b]
Mean (SD)	4.4 (5.7)	8.9 (10.1)	
CSF barrier dysfunction			0.053[a]
Present	28 (22.2 %)	18 (13.1 %)	
Absent	98 (77.8 %)	119 (86.9 %)	
CSF-specific oligoclonal bands			0.407[a]
Present	124 (90.5 %)	137 (93.2 %)	
Absent	13 (9.5 %)	10 (6.8 %)	
MRZ-reaction			0.181[a]
Positive	10 (50.0 %)	9 (31.0 %)	
Negative	10 (50.0 %)	20 (69.0 %)	

[a] CHI-Square-Test.
[b] T-Test. CSF = cerebrospinal fluid. LOMS = Late-onset multiple sclerosis. EOMS = early-onset multiple sclerosis. MRZ reaction = "measles, rubella, zoster-reaction". SD = standard deviation.

4. Discussion

The diagnosis of MS in patients aged 50 and older, along with determining optimal treatment strategies for this population, remains a clinical challenge. Our study provides valuable insights into distinct features of LOMS compared to EOMS. While relapsing-remitting MS (RRMS) remains the most common disease course in both groups, the proportion of patients with a primary progressive course (PPMS) is significantly higher in LOMS (Table 1). This finding aligns with those of a recent meta-analysis, which reported that around 59 % of LOMS cases have a RRMS phenotype when using a cut-off of 50 years for disease onset (Naseri et al., 2021). The predominance of PPMS in LOMS patients is reflected in our cohort, where motor symptoms and multiple symptom presentations were more frequent in LOMS patients compared to EOMS patients. These findings align with the higher incidence of progressive sensorimotor spinal syndromes and ataxia in PPMS (Kis et al., 2008; Knowles et al., 2024; Noseworthy et al., 1983).

LOMS patients significantly more often reported fatigue and

cognitive symptoms at diagnosis than EOMS patients. This finding aligns with prior studies indicating a higher prevalence of self-reported fatigue in LOMS patients (Palathinkara et al., 2023). Moreover, neuropsychological testing has revealed greater cognitive impairments in visual learning and memory, as well as auditory working memory, in LOMS compared to EOMS patients (Butler Pagnotti et al., 2022). A study using standardized neuropsychological tests found that LOMS patients performed worse than EOMS patients in both classical and social cognitive domains when matched for disease duration and age at assessment (Oliveira et al., 2024). While both studies assessed patients later in the disease course, our findings suggest that cognitive symptoms and fatigue are already prominent at LOMS diagnosis. Although these findings are based on self-reported data, the consistent association of these symptoms with LOMS onset suggests they may form part of its early clinical presentation, distinct from EOMS. This observation underscores the need for heightened clinical awareness of fatigue and cognitive symptoms in older adults presenting with potential MS, which could facilitate earlier and more accurate diagnosis of LOMS, ultimately improving patient outcomes.

As expected, LOMS patients more frequently had age-related comorbidities, primarily cardiovascular disorders. This may partly explain the higher prevalence of fatigue and subjective cognitive deficits in LOMS, as cardiovascular risk factors have been shown to negatively impact cognitive performance in both LOMS and EOMS patients (Oliveira et al., 2024). However, the difference in comorbidities was substantially smaller than the observed differences in fatigue and cognitive symptoms.

A key finding of our study is the difference in contrast-enhancing lesions between LOMS and EOMS patients. LOMS patients were significantly less likely to present with gadolinium-enhancing lesions (Nasiri et al., 2023). Gadolinium enhancement on MRI is known to correlate inversely with age in pwMS (Koch et al., 2020), suggesting that older patients tend to have less active inflammation. This observation is supported by neuropathological studies indicating that older MS patients exhibit fewer actively demyelinating lesions and more neurodegenerative changes, such as neuron loss in the gray matter (Knowles et al., 2024). Thus, the lack of gadolinium-enhancing lesions in LOMS patients may reflect the age-related decline in inflammatory activity. In our cohort, LOMS patients had a significantly higher total T2-lesion load on initial brain MRI, with over two-thirds presenting with more than nine T2 lesions compared to only 56.6 % in EOMS patients (Table 2). Similar observations were reported in previous studies, albeit with small sample sizes (Arias et al., 2011; de Seze et al., 2005). While this higher lesion load could be attributed to a longer subclinical phase of MS in LOMS patients, potentially leading to an accumulation of lesions before clinical onset, it may also reflect the presence of non-specific or microvascular lesions, which are more common in older patients.

In the CSF analysis, we found no significant differences in the presence of CSF-specific oligoclonal bands (OCB) between LOMS and EOMS patients. However, LOMS patients were significantly less likely to exhibit CSF pleocytosis and had a lower absolute CSF cell count (Table 3). Previous findings from a small study showed similar trends with lower cell counts in LOMS patients (Konen et al., 2022). Another study compared 14 LOMS patients with 28 EOMS patients and found a significantly lower rate of CSF pleocytosis in the LOMS cohort, though no differences were observed in the presence of CSF-specific OCB (Huhn et al., 2016). The lower rate of CSF pleocytosis in LOMS may reflect age-related reductions in inflammatory disease activity, which parallels the lower number of gadolinium-enhancing lesions seen in these patients. Since CSF-specific OCB are part of the diagnostic criteria for MS, assessing their prevalence across different MS cohorts is inherently biased. Patients without CSF-specific OCB are more likely to be misdiagnosed, potentially inflating OCB prevalence rates. However, this bias would equally affect findings in both LOMS and EOMS patients.

Importantly, we identified a significant delay in diagnosing LOMS, likely due to misdiagnosis or recognition challenges. This delay may contribute to the higher lesion load on initial MRI, the greater prevalence of fatigue and subjective cognitive deficits, and the higher EDSS at diagnosis in LOMS. Matching for disease duration instead of the year of diagnosis could have mitigated the influence of longer disease duration on these differences. However, as disease-modifying treatment (DMT) is typically initiated soon after diagnosis, we prioritized matching by diagnosis year to avoid confounding from a higher proportion of EOMS patients already receiving DMT. The observed diagnostic delay suggests that subclinical MS or misdiagnosis may play a critical role in LOMS and warrants further investigation. Additionally, a potentially longer subclinical phase in patients with older age at MS onset may also account for the substantially higher proportion of LOMS patients experiencing fatigue and cognitive impairment at disease onset. This aligns with evidence that subtle cognitive impairments are characteristic of the prodromal phase of MS (Makhani and Tremlett, 2021). Recognizing this prolonged subclinical phase could improve diagnostic accuracy and allow earlier intervention in LOMS patients, ultimately mitigating disease burden.

The results of this study should be interpreted in the context of its acknowledged limitations. The retrospective design of our analysis resulted in incomplete data for some patients, and the inclusion of patients diagnosed over an extended period, during which diagnostic criteria and imaging techniques evolved, introduces potential bias, particularly in MRI findings. However, the matching of LOMS and EOMS patients by the year of diagnosis helps to mitigate these concerns. Fatigue and cognitive deficits were assessed through self-reported symptoms, as standardized questionnaires or test methods were unavailable for most patients, introducing potential bias. Additionally, these symptoms at first presentation may be overestimated, potentially influenced by recent relapse activity and steroid treatment.

In conclusion, our study provides new insights into the clinical, radiological, and CSF characteristics of LOMS patients. LOMS patients are more likely to present with motor symptoms, fatigue, and cognitive impairment at disease onset, and have a higher total lesion load on MRI compared to EOMS patients. However, they are less likely to show gadolinium-enhancing lesions or CSF pleocytosis, which may reflect either a decline in inflammatory activity with age or a more advanced stage of the disease. Our findings underscore the importance of CSF analysis in diagnosing LOMS, particularly in the absence of contrast-enhancing lesions. These results contribute to a better understanding of LOMS, highlighting key differences from EOMS and providing evidence for the importance of early recognition and diagnosis of MS in older adults.

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CRediT authorship contribution statement

Lukas Steinegger: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Veronika Kana:** Writing – review & editing. **Nathalie Nierobisch:** Writing – review & editing. **Adham Elshahabi:** Writing – review & editing. **Michael Weller:** Writing – review & editing. **Marina Herwerth:** Writing – review & editing. **Patrick Roth:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Veronika Kana reports a relationship with Biogen that includes: consulting or advisory, speaking and lecture fees, and travel

reimbursement. Veronika Kana reports a relationship with Novartis that includes: consulting or advisory and speaking and lecture fees. Veronika Kana reports a relationship with Merck that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Veronika Kana reports a relationship with Roche that includes: consulting or advisory, funding grants, speaking and lecture fees, and travel reimbursement. Veronika Kana reports a relationship with Teva that includes: consulting or advisory and speaking and lecture fees. Michael Weller reports a relationship with Novartis that includes: consulting or advisory, funding grants, and speaking and lecture fees. Michael Weller reports a relationship with Quercis that includes: funding grants. Michael Weller reports a relationship with Versameb that includes: funding grants. Michael Weller reports a relationship with Anheart that includes: consulting or advisory and speaking and lecture fees. Michael Weller reports a relationship with Bayer that includes: consulting or advisory and speaking and lecture fees. Michael Weller reports a relationship with Curevac that includes: consulting or advisory and speaking and lecture fees. Michael Weller reports a relationship with Medac that includes: consulting or advisory and speaking and lecture fees. Michael Weller reports a relationship with Neurosense that includes: consulting or advisory and speaking and lecture fees. Michael Weller reports a relationship with Novocure that includes: consulting or advisory and speaking and lecture fees. Michael Weller reports a relationship with Orbus that includes: consulting or advisory and speaking and lecture fees. Michael Weller reports a relationship with Pfizer that includes: consulting or advisory and speaking and lecture fees. Michael Weller reports a relationship with Philogen that includes: consulting or advisory and speaking and lecture fees. Michael Weller reports a relationship with Roche that includes: consulting or advisory and speaking and lecture fees. Michael Weller reports a relationship with Servier that includes: consulting or advisory and speaking and lecture fees. Marina Herwerth reports a relationship with Biogen that includes: consulting or advisory. Marina Herwerth reports a relationship with Merck Serono that includes: consulting or advisory. Marina Herwerth reports a relationship with Alexion that includes: consulting or advisory. Marina Herwerth reports a relationship with Horizon Therapeutics (Amgen) that includes: consulting or advisory. Marina Herwerth reports a relationship with Biogen that includes: speaking and lecture fees. Marina Herwerth reports a relationship with Roche that includes: funding grants and travel reimbursement. Patrick Roth reports a relationship with Alexion that includes: consulting or advisory and speaking and lecture fees. Patrick Roth reports a relationship with Bristol Myers Squibb that includes: consulting or advisory and speaking and lecture fees. Patrick Roth reports a relationship with Boehringer Ingelheim that includes: consulting or advisory and speaking and lecture fees. Patrick Roth reports a relationship with Debiopharm that includes: consulting or advisory and speaking and lecture fees. Patrick Roth reports a relationship with Galapagos that includes: consulting or advisory and speaking and lecture fees. Patrick Roth reports a relationship with Merck Sharp and Dohme that includes: consulting or advisory, funding grants, and speaking and lecture fees. Patrick Roth reports a relationship with Laminar that includes: consulting or advisory and speaking and lecture fees. Patrick Roth reports a relationship with Midatech Pharma that includes: consulting or advisory and speaking and lecture fees. Patrick Roth reports a relationship with Novocure that includes: consulting or advisory and speaking and lecture fees. Patrick Roth reports a relationship with QED that includes: consulting or advisory and speaking and lecture fees. Patrick Roth reports a relationship with Roche that includes: consulting or advisory and speaking and lecture fees. Patrick Roth reports a relationship with Sanofi that includes: consulting or advisory and speaking and lecture fees. Patrick Roth reports a relationship with Servier that includes: consulting or advisory and speaking and lecture fees. Patrick Roth reports a relationship with TME Pharma that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2025.106399.

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