

# Managed Care Aspects of Managing Multiple Sclerosis

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## Abstract

Multiple sclerosis (MS) is associated with significant direct and indirect costs. Pharmacoeconomic studies of MS therapies have generally shown results which were not considered to be cost-effective when incremental cost-effectiveness ratios were analyzed for quality-adjusted life-years. When prevented relapses were considered as an end point, the cost-effectiveness results were generally more favorable, although the studies analyzed were limited by assumptions, projected outcomes, and lack of data on adverse events. Managed care professionals and clinicians can ensure maximized effectiveness of therapy by supporting adherence and by providing disease therapy management programs. Specialty pharmacies are an effective way to control costs and optimize the involvement of patients in their care.

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**M**ultiple sclerosis (MS) is a chronic immune-mediated neurologic disease that results in progressive disability over time. The goals of symptomatic and disease-modifying therapy (DMT) are to improve quality of life, reduce relapse rate, prolong remission, limit the onset of new MS lesions, and postpone the development of long-term disability. For clinicians and managed care professionals, it is imperative to be familiar with the safety and efficacy of available treatments and the pharmacoeconomic data associated with their use, and to provide access to cost-effective therapy.<sup>1-3</sup> This article evaluates the costs of MS, along with factors which influence access to medication, managed care implications to patients, and optimization of cost efficiency.

## Direct and Indirect Costs

Estimated direct medical costs of MS are more than \$47,000 annually per patient, with a single attack costing more than \$12,000. These direct medical costs may include medications, office visits, radiological imaging, laboratory evaluation, physical therapy, and inpatient treatment. The direct medical costs of MS in the United States are more than \$10 billion per year.<sup>1</sup> Indirect costs of MS are potentially even more significant, since there is a large degree of disability associated with MS. Quality of life (QOL) is impacted by problems in sensation, cognition, or motor function, and are dependent on the location of the MS lesions. Severity of fatigue, pain, urinary incontinence, bowel dysfunction, mobility problems, and depression are among the common MS-related problems which impact QOL and employability.<sup>4</sup>

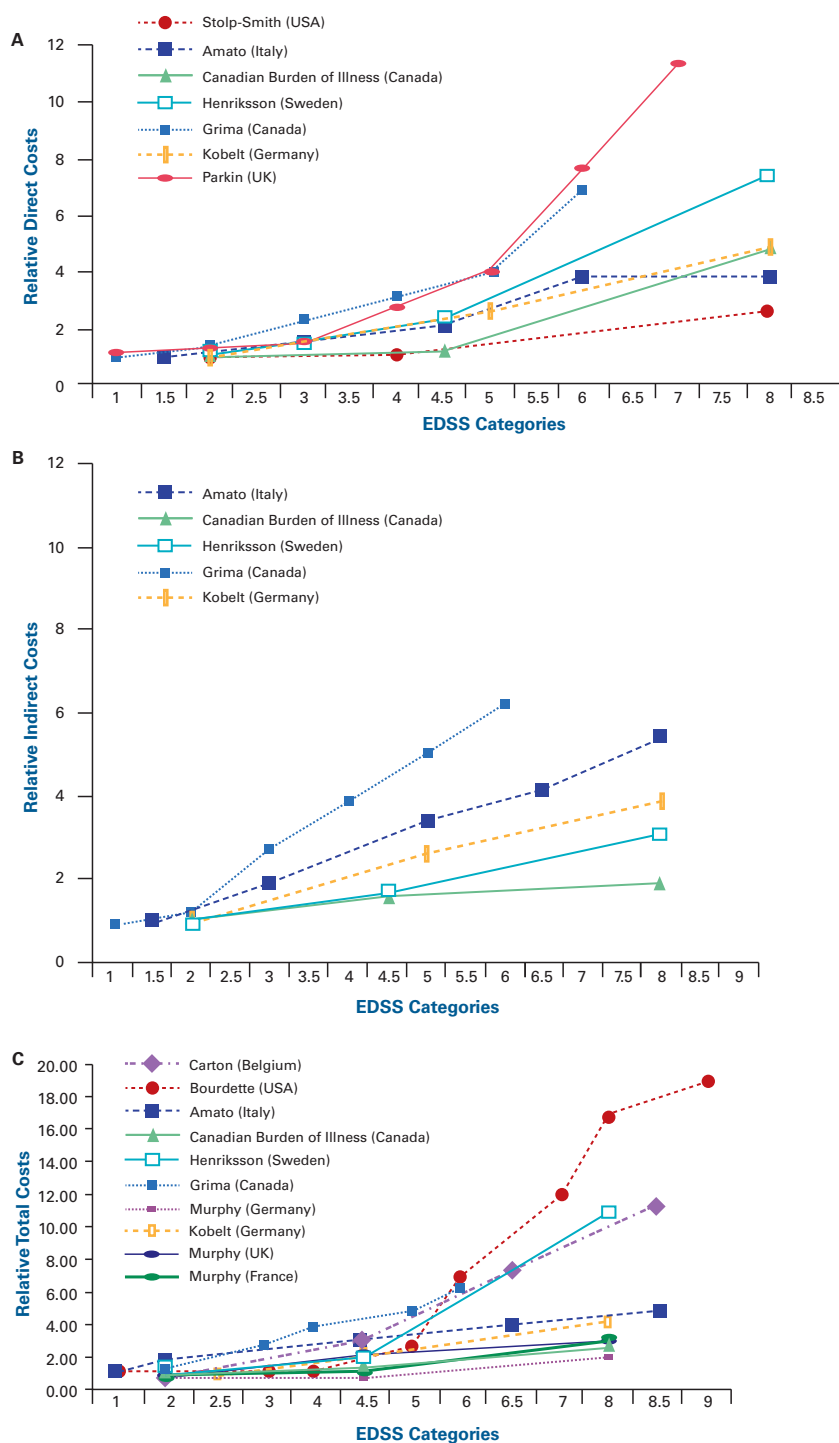
In 1 study, employees with MS were more likely to have short-term or long-term disability than employee controls without MS (21.4% vs 5.2%, respectively;  $P < .0001$ ), resulting in a higher mean disability days per year (29.8 vs 4.5;  $P < .0001$ ). Employees with MS also had a higher rate of medically related absenteeism and absenteeism days than employee controls. In 2006, average annual costs for disability were significantly higher for employees with MS (\$3868) than employee controls (\$414;  $P < .0001$ ), and annual medically related absenteeism costs were also higher for employees with MS than for controls (\$1901 vs \$1003, respectively;  $P < .0001$ ). Total average annual indirect costs for employees with MS were \$5769 compared

with \$1417 for controls ( $P < .0001$ ).<sup>5</sup> In addition to productivity losses, there are costs associated with assistive equipment, disability-related home modifications, paid or unpaid personal care, early retirement, and death.<sup>5</sup> There appears to be a relationship between the level of disability and the cost of MS. As demonstrated in the Figure, the direct, indirect, and total costs of MS increased as the Expanded Disability Status Scale (EDSS) increased.<sup>6</sup>

Cost-effectiveness analyses of platform DMTs (eg, interferon, glatiramer) for relapsing-remitting MS (RRMS) have been largely disappointing.<sup>7-10</sup> In 1 study, interferon beta-1a, interferon beta-1b, and glatiramer acetate were compared with respect to incremental cost-effectiveness ratio (ICER), based on quality-adjusted life-years (QALYs) over 10 years (1999 US dollars). Compared with no treatment, interferon beta-1a provided more health benefits and was more costly, based on a 0.03 QALY improvement in women and a 0.036 QALY improvement in men. Interferon beta-1b was less effective, based on subtracted QALYs for treatment-adverse events, and more costly, and thus was dominated by no treatment. Glatiramer acetate had a higher ICER, but lower cost than interferon beta-1b, so it was also dominated, meaning the most cost-effective therapy was interferon beta-1a, which had an ICER per QALY of \$1,838,000 in men and \$2,218,000 in women.<sup>7</sup> Usual willingness to pay is up to \$100,000 ICER per QALY, so this demonstrated that platform therapies were not cost-effective. Values improved as the length of time studied increased, but remained above the threshold of cost-effectiveness.<sup>7</sup>

A second 10-year study determined ICERs per QALY were €322,510 for glatiramer acetate, €329,595 for intramuscular (IM) interferon beta-1a, €333,925 for subcutaneous (SC) interferon beta-1b,

**Figure.** Expanded Disability Status Scale Score Versus Direct (A), Indirect (B), and Total (C) Costs of MS<sup>6</sup>



EDSS indicates Expanded Disability Status Scale; MS, multiple sclerosis. Reprinted with permission from Patwardhan MB, Matchar DB, Samsa GP, et al. *Mult Scler*. 2005;11(2):232-239.

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and €348,208 for SC interferon beta-1a (1 € ≈ 1.29 US dollars).<sup>8</sup> In another study, ICERs per QALY over the lifetime of the patient, in 2005 US dollars, were \$258,465 for glatiramer acetate, \$303,968 for IM interferon beta-1a, \$416,301 for SC interferon beta-1a, and \$310,691 for SC interferon beta-1b.<sup>9</sup> These results confirmed that extension of the length of assessment improves the value of these agents, but they still do not reach conventional thresholds of cost-effectiveness. It also highlights that MS is a lifetime disease, that treatment is expensive, and the measurement of QALYs may not be a viable metric in MS because outcomes are based more on disability than life expectancy.

A separate study took a different approach and evaluated the cost-effectiveness ratio (CER) per relapse avoided over 2 years based on clinical trial data. The CER per relapse avoided was \$80,589 for SC interferon beta-1a, \$87,061 for interferon SC beta-1b, \$88,310 for glatiramer acetate, and \$141,721 for IM interferon beta-1a (2008 US dollars).<sup>10</sup>

Fingolimod has been found to be more effective than interferon beta-1a, but the acquisition cost is higher.<sup>3,11-13</sup> Consequently, the ICER per QALY was compared relative to interferon beta-1a over a 10-year time horizon, extrapolated from a 1-year study. The ICER estimate was \$73,975 for fingolimod relative to only interferon beta-1a, with 35% of 10,000 Monte Carlo simulations demonstrating cost-effectiveness at a willingness-to-pay of \$50,000 per QALY and 70% demonstrating cost-effectiveness at a threshold of \$100,000.<sup>13</sup>

Fingolimod was compared with natalizumab in another study with respect to direct medical costs over a 10-year horizon, and fingolimod was found to reduce total medical costs by €28,287 over 10 years. Natalizumab costs were sensitive to the costs of infusion and sterile preparation.<sup>14</sup> However, another 2-year study demonstrated that natalizumab was less costly (\$86,461) than fingolimod (\$98,748), and more effective in mean relapses avoided per 2 years (0.74 vs 0.59, respectively), and hence dominated fingolimod.<sup>15</sup> This demonstrates the impact of assumptions used in pharmacoeconomic studies. The cost conclusions can vary depending on the items assessed.

A separate study compared natalizumab with IM interferon beta-1a, SC interferon beta-1a, SC interferon beta-1b, and glatiramer acetate with regard to 2-year cost-effectiveness. Acquisition cost was \$72,120 for natalizumab, \$56,790 for IM interferon beta-1a, \$58,538 for SC interferon beta-1a, \$56,773 for interferon beta-1b, and \$57,180 for glatiramer acetate. However, cost per relapse avoided was \$56,594 for natalizumab, \$93,306 for IM interferon beta-1a, \$96,178 for SC interferon beta-1a, \$87,791 for interferon beta-1b, and

\$103,665 for glatiramer acetate. Relative ICERs per QALY for natalizumab were \$23,029 for IM interferon beta-1a, \$20,403 for SC interferon beta-1a, \$24,452 for interferon beta-1b, and \$20,671 for glatiramer acetate. Thus, natalizumab was the most cost-effective agent compared with platform therapies for total cost per relapse avoided, but it also had a higher cost compared with platform therapies.<sup>16</sup> Major limitations of most of these studies were that the outcomes were often extrapolated, 100% adherence to therapy was assumed, and many did not capture adverse event data.

### Influencing Access to Medication and Adherence

First-line therapies for MS are very expensive, ranging from about \$37,000 to \$57,000 per year.<sup>3</sup> The efficacy of an agent is greatly influenced by treatment adherence, and adherence is further influenced by the amount of cost-sharing a patient has to bear. A recent study indicated that for patients with MS, out-of-pocket (OOP) expenses of more than \$200 for MS medications dramatically increased prescription abandonment rate. Abandonment was 5.7% for OOP expenses of \$0 to \$100, 5.3% for \$101 to \$150, 10.6% for \$151 to \$200, and 25.8% to 28.5% for \$251 to \$500 ( $P < .001$  vs \$0-\$100).<sup>17</sup>

Beyond filling a prescription, there are a number of factors that influence whether a patient is adherent to therapy. In 1 US administrative claims study, 57% of patients with an index diagnosis were not treated with a DMT over  $35.7 \pm 17.5$  months. Among the 43% who started treatment, 27.7% discontinued therapy after an average of  $17.6 \pm 14.6$  months, and 16.5% had gaps in treatment lasting more than 60 days.<sup>18</sup>

Because MS is associated with a low QOL, it is unclear why patients do not take their medication.<sup>19</sup> Patients adherent to DMTs have been documented to have fewer MS relapses than those who are not adherent to therapy (odds ratio [OR], 0.71; 95% confidence interval [CI], 0.59-0.85), lower inpatient costs (OR, 0.63; 95% CI, 0.47-0.83), and fewer medical costs (\$3380 [95% CI, \$3046-\$3750] vs \$4348 [95% CI, \$3828-\$4940];  $P = .003$ ). The authors suggested that medications that are given less frequently may benefit patients who have trouble adhering to their therapy.<sup>20</sup>

The impact of dosing frequency on treatment adherence was investigated in a recent study of patients with chronic disease.<sup>21</sup> This study demonstrated the benefit of treatment adherence in terms of improving costs and relapse rates in chronic disease, although the exact reasons why patients failed to take their medication remained unclear. Pharmacists should educate patients on the relative value of adherence to the successful treatment of the disease. Managed care professionals should be aware of the impact of adherence on overall

**Table. Consensus Panel Recommendations<sup>23</sup>**

Topic	Recommendations
Initiating disease-modifying therapy	<ol style="list-style-type: none"> <li>1. The decision to start patients with CIS on disease-modifying therapy should be left up to the provider.</li> <li>2. Most patients with CDMS should be treated with a disease-modifying therapy.</li> </ol>
Platform therapies: IFN beta-1a IM; IFN beta-1b SC; IFN beta-1a SC; glatiramer acetate	<ol style="list-style-type: none"> <li>3. Both glatiramer acetate and a preferred IFN should be on a health plan's formulary.</li> <li>4. Patients with MS should have preferred access to platform therapies, including glatiramer acetate and at least 1 IFN.</li> <li>5. Glatiramer acetate should be a preferred agent on a health plan's formulary.</li> <li>6. Access to nonpreferred IFNs should be restricted by step therapy or use of a preferred agent first.</li> <li>7. Health plans should have a preferred high-dose/high-frequency IFN on formulary.<sup>a</sup></li> <li>8. Health plans should take efficacy, safety, cost, and contracting into consideration when selecting the preferred high-dose/high-frequency IFN for formulary.</li> </ol>
Natalizumab	<ol style="list-style-type: none"> <li>9. Health plans should manage patient access to natalizumab with a PA or by requiring patients to fail an IFN or glatiramer acetate first.</li> <li>10. Formulary restrictions should be in place to limit natalizumab use to the FDA-approved indication.</li> <li>11. Formulary restrictions should be in place to limit natalizumab use/reimbursement to once every 28 days.</li> <li>12. Step therapy should be in place to help manage the safety concerns associated with natalizumab.</li> <li>13. The TOUCH Prescribing Program should not be utilized in place of a PA.</li> <li>14. Safety is a factor in the use of a PA for natalizumab.</li> <li>15. Clinical efficacy, safety, and cost data should be considered when reviewing natalizumab for formulary placement.</li> </ol>
Fingolimod	<ol style="list-style-type: none"> <li>16. PAs should be utilized by health plans to manage patient access to fingolimod.</li> <li>17. Formulary restrictions should be put in place to limit the use of fingolimod to neurologists.</li> <li>18. Access to combination therapy with fingolimod and an injectable disease-modifying therapy should be restricted until safety and efficacy data are available.</li> </ol>
Dalfampridine	<ol style="list-style-type: none"> <li>19. Dalfampridine is a symptom-management agent.</li> <li>20. Patient access to dalfampridine should be managed by a PA according to the FDA-approved labeled indication.</li> <li>21. Dalfampridine should be limited to patients who are also receiving a disease-modifying therapy.<sup>b</sup></li> <li>22. Efficacy, safety, and cost should be taken into consideration when reviewing dalfampridine for formulary placement.</li> </ol>
Patient considerations	<ol style="list-style-type: none"> <li>23. Compliance and persistence to MS therapies is very important.</li> <li>24. MS patients need educational support/assistance.</li> <li>25. Some MS patients need financial support/assistance.</li> </ol>

<sup>a</sup>Discussed by the panelists in the context of the availability of 3 high-dose/high-frequency IFNs.

<sup>b</sup>Discussed in the context of patients with relapsing-remitting multiple sclerosis. However, concomitant disease-modifying therapy is not a requirement for use of dalfampridine. Dalfampridine is indicated for all MS patients with walking disability, including patients with RRMS, secondary-progressive MS, and primary-progressive MS. Source: Ampyra (dalfampridine) Extended Release Tablets [prescribing information]. Ardsley, NY: Acorda Therapeutics, Inc; January 2010.

CDMS indicates clinically definite MS; CIS, clinically isolated syndrome; FDA, US Food and Drug Administration; IFN, interferon; IM, intramuscular; MS, multiple sclerosis; PA, prior authorization; SC, subcutaneous; TOUCH, Tysabri Outreach: Unified Commitment to Health. Reprinted with permission from Miller RM, Happe LE, Meyer KL, Spear RJ. *J Manag Care Pharm.* 2012;18(1):54-62.

costs and the potential impact on cost-effectiveness. These data also suggest that methods to improve affordability may help to ensure that patients have access to their prescription.

### Reimbursement Tier Decisions and Insurance Barriers

The National Multiple Sclerosis Society recommends that treatment with interferon beta or glatiramer acetate be considered as soon as possible following a definite diagnosis of MS with active, relapsing disease. Further, they

state that a patient's access to medication should not be limited by the frequency of relapses, age, or level of disability, and that treatment should not be stopped while insurers evaluate for continuing coverage of treatment, as lapses in therapy may lead to recurrent disease activity. The consensus statement indicates that therapy should be continued indefinitely, and that all therapies approved by the US Food and Drug Administration should be on formularies and covered by third-party payers, although

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medications should not be changed except for medically appropriate reasons.<sup>22</sup>

A more recent consensus document from US managed care pharmacists and physicians is also available (Table).<sup>23</sup> This document also recommended initiation of a DMT for definite MS, and that glatiramer acetate and an interferon product should be preferred on the health plan formulary. In addition, other interferons (non-preferred) should be accessible through step therapy after the use of a preferred agent. Health plans should take efficacy, safety, cost, and contracting into consideration when selecting the preferred high-dose/high-frequency interferon for formulary. According to the consensus document, natalizumab should be restricted to patients with a prior authorization, or after failure of a first-line therapy. Fingolimod should be restricted to prior authorization. Teriflunomide and mitoxantrone were not addressed. The consensus panel did agree that compliance and persistence was very important, and that patients with MS need educational support and assistance, and some may need financial support and assistance.<sup>23</sup> Tiered approaches to MS therapy may be necessary because the medications are not available in generic form. Prior authorization and tiered access benefits, however, are restrictive and may limit access to medications.<sup>24</sup>

Due to these barriers and patient cost sharing, patients may not fill or delay filling medications. Pharmacists need to educate patients about the importance of these medications, despite the potential financial difficulties encountered, and try to reduce barriers. In addition, patients with MS need to be identified, because care is more expensive than for those without MS; an adjusted capitated payment, or diagnostic risk adjustment, would prevent some of the disincentive to take on and manage patients with MS.<sup>24</sup>

### Disparities Between Patients From Clinical Trials and Those in the Real World

The MS research agenda has 5 priorities: experimental models, identification and validation of therapeutic targets, strategies for proof-of-concept clinical trials, clinical outcome measures, and symptom management and rehabilitation.<sup>25</sup>

In Europe, special training is being offered to nurses through funded initiatives.<sup>25</sup> This type of training is both warranted and laudable, and serves as a crossover scenario between clinical trials and the real world, and it was developed and rolled out in a standardized fashion across numerous countries. However, this type of program can be expensive and is not the only disparity between clinical trials and the real world.<sup>25</sup> Another gap is in the duration of clinical trials, which tend to be short. Although they can be used to

predict outcomes, concrete results may take 30 or 40 years to accrue.<sup>26</sup>

Although long-term benefits are difficult to predict, the data demonstrate that earlier initiation of therapy can reduce relapses and decrease costs related to hospitalizations.<sup>26,27</sup> In 1 study, adjusted annual per-patient cost (including OOP expenses) were \$28,280 versus \$29,102 for early and delayed initiation of therapy, respectively. Respective costs were lower excluding DMT (\$15,214 vs \$17,630;  $P < .01$ ) and cost for MS-related management (\$9365 vs \$13,661;  $P < .01$ ), and hospitalizations were reduced (10.1% vs 16.5%; OR, 0.51; 95% CI, 0.32-0.81).<sup>27</sup>

Another important difference between clinical trials and the real world is the time pattern of the annual relapse rate (ARR).<sup>28</sup> Trials assume a constant rate for the ARR, but the ARR is higher in the first year than the second year of clinical trials in both the placebo and active treatment groups, so a 2-year follow-up average may not properly estimate the true ARR.<sup>28</sup> Also, patients from clinical trials may differ from those in the real world in other areas, such as the QOL and productivity measures. Also, the structured approach to care may be lacking in real-world situations.<sup>29</sup> In addition, adherence rates appear to be higher in clinical trials than in real-world settings, which speaks to the potential of a formalized approach to care and the impact of patients' motivation to adhere to therapy.<sup>20</sup>

### Optimizing Patient Outcomes and Cost Efficiency With Disease Management Programs

Disease therapy management (DTM) programs provided by specialty pharmacies or managed care organizations can improve adherence and persistence, and decrease relapses.<sup>24,30</sup> However, the value to QOL or work productivity is less clear. One study evaluated a DTM program with a regular retail pharmacy and found that scores from the Short Form 12-item Health Survey and Work Productivity Activity Impairment questionnaire were not changed from months 0 to 6; however, 97% of patients at month 6 reported that the DTM program was somewhat helpful or very helpful in enabling them to better manage their health. Results from 1 study indicate that 80% of patients are compliant with injectable therapy 80% of the time for the first 6 months, but adherence drops off to about 60% by 2 to 5 years.<sup>24</sup> Programs aimed at improving QOL, through exercise training, nurse visits, or nurse-based clinics, have been modestly effective.<sup>31-33</sup> Newer technology, such as telemedicine and Internet-based self management (personal electronic health records), have been assessed to improve symptoms or QOL metrics.<sup>34,35</sup> It appears that the most successful programs are those that target relapses, as QOL changes appear to be small.<sup>36</sup>



### Rational Clinical Pathways and Cost Control

Use of first-line therapies, glatiramer acetate, or an interferon beta agent based on formulary availability is a reasonable starting place for relapsing forms of MS. Because up to 22% of the population has a fear of needles, fingolimod may be considered for DMT in place of an interferon or glatiramer acetate. Although fingolimod appears to be more effective, it is more expensive than the other platform therapies. Adverse effects or treatment failure may also be reason for switching to a different agent.<sup>24</sup>

Starting therapy earlier and targeting prevention of relapses appear to optimize cost-effectiveness.<sup>26,27</sup> Relapses may cost more than \$12,000 per episode.<sup>24</sup> Ensuring adherence and thereby obtaining the full potential of the medication is another way to improve cost-effectiveness.<sup>20</sup> From a managed care perspective, moving from a buy-and-bill approach to a specialty pharmacy benefit can reduce overall costs. Specialty pharmacy involvement can provide oversight of distribution, management, and reimbursement, particularly when case management services are provided.<sup>24</sup>

### Conclusion

MS is associated with significant direct and indirect costs. Most pharmacoeconomic studies suggest that cost-effectiveness can be optimized by starting therapy early in the disease state, focusing on preventing relapses, and improving adherence. Managed care organizations should try to limit barriers to medication use by limiting copays and managing costs by using specialty pharmacies and DTM programs.

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