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Review article

# Approach to JCV testing with natalizumab biosimilar: a UK consensus statement

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ABSTRACT

Biosimilars have an important role to play in healthcare, with the potential to reduce costs and widen access to treatment. We welcome the use of biosimilars in the treatment of multiple sclerosis. Serological testing for JC virus is mandated as part of safety monitoring in those treated with natalizumab. All PML risk stratification data to date has come from the use of the "Stratify" JC virus (JCV) serostatus test.

The "Immunowell" test used to define JCV serostatus (used with Tyruko) does not always give equivalent results to the Stratify test (used with Tysabri), particularly around thresholds used to define risk of progressive multifocal leukoencephalopathy (PML). In comparison to the Stratify test, Immunowell appears more likely to report a positive JCV index. However, negative results using Immunowell show a high rate of agreement with Stratify, which allows for a rational safety strategy. There remains a real risk that a proportion of patients will be inappropriately classified as being at higher risk of PML, and therefore denied the option of natalizumab, a highly effective therapy, or undergo unnecessarily burdensome monitoring, with resultant cost to the NHS and anxiety.

We provide guidance for patients with discordant results between assays, aiming to balance the need for rigorous safety monitoring with patient access to highly effective therapy and unnecessary monitoring burden on healthcare services.

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## 1. Background

Natalizumab is a highly effective treatment for multiple sclerosis. It is currently used across the NHS for people with rapidly evolving severe (RES) MS. It has a shorter therapeutic lag than other DMTs, (Roos et al., 2020) and has been shown to have superior efficacy in network meta-analysis. (Gonzalez-Lorenzo et al., 2024) Based on pre-clinical data and a phase III clinical trial demonstrating comparable efficacy to originator natalizumab (Tysabri), biosimilar natalizumab (Tyruko) has been approved for use by the EMA and MHRA, and is subsequently being rolled out across the UK. (Shirley, 2024) This biosimilar switch is driven by the important aim to ensure maximum value and widest possible treatment access across the NHS.

Serological testing for JCV, the virus associated with progressive multifocal leukoencephalopathy (PML), is mandated as part of safety monitoring for patients receiving natalizumab (TYSABRI, n.d.; Tyruko, n.d.). To date, Biogen have provided this, using the StratifyJCV assay. A range of PML risk calculators to aid clinical decision-making and patient communication have been developed to support natalizumab use, based on evidence from large cohorts utilising the Stratify-JCV assay. (Dsilva et al., 2023) In those patients who switch to biosimilar natalizumab, JCV serological testing is provided using the Immunowell assay, supported by Sandoz. An unintended consequence of the biosimilar switch has been apparent discrepancies in the JCV index in individual patients, related to different assays. (Inojosa et al., 2024; Gelissen et al., 2025)

The Immunowell assay has been licensed as a medical device following comparison studies across 328 patients, with subsequent validation in 888 samples. However, early experience in natalizumab treated cohorts who tend to be seronegative, or seropositive at low indices, has demonstrated that results do not always agree with those provided by the Stratify test, particularly across thresholds used to define clinical risk categories. (Inojosa et al., 2024; Gelissen et al., 2025) This poor agreement leads to poor specificity (50 - 52 %) and positive predictive values (PPV) (38 - 67 %) of the Immunowell test compared with Stratify test, with overall 41 % (147/361) patients reclassified from negative to positive across the two assays in population-based studies (Vukusic *in press MSJ;* Varley *in press MSJ*). This reclassification exceeds the expected 3–6 % reclassification rate per year previously demonstrated using the Stratify test. (Hegen et al., 2017; Hegen et al., 2018; Gaughan et al., 2022; Dwyer et al., 2021) This discrepancy in serostatus and its impact on risk stratification can potentially reduce clinician and patient confidence in estimating and mitigating PML risk using Tyruko. Unfortunately, the Stratify test is unavailable for patients on, or considering, Tyruko.

In comparison to the Stratify test, Immunowell appears more likely to report a positive JCV index. However, negative results using Immunowell show a high rate of agreement with Stratify, which allows for a rational safety strategy when using Tyruko. A management strategy must be developed until more definite risk stratification related to Immunowell is available. There is a real risk that a proportion of patients will be inappropriately identified as being at high risk of PML and therefore discount the option of a highly effective therapy or undergo unnecessarily burdensome monitoring and anxiety.

Our opinion is that it is reasonable to use Tyruko and associated Immunowell assay, despite concerns regarding risk stratification given the preserved sensitivity and negative predictive value. We recommend that clinicians consider the following principles when starting biosimilar product or switching between originator and biosimilar product.

## 2. Guidance

*In patients with RES-MS who have not previously received Tysabri who are considering treatment with natalizumab*

- Patients with negative JCV index measured using the Immunowell test can be reassured and monitored as per standard protocols
- Patients with positive Immunowell tests can be reassured that the risk of PML in JCV positive individuals remains low for the first two years of natalizumab treatment. They should be offered treatment, usually for a time limited period, with a clear plan to switch/derisk, typically after 12–24 months of natalizumab therapy, based on individual risk-benefit discussion with their treating team.
- A switch may consist of moving to another disease modifying therapy with lower PML risk. Risk mitigation may consist of increased MRI monitoring. Consideration may also be given to extending the dosing interval to 6 weekly, however available evidence around the benefits and risks of this approach is limited. (Cutter, 2025)

*In patients with negative/very low JCV index (<0.9) established on Tysabri who are switching to biosimilar natalizumab (Tyruko)*

- Patients who remain JCV negative or with very low JCV index on Immunowell can be reassured and monitored as per standard local protocols.
- Where patients have a negative JCV index on Stratify but are low positive on Immunowell, the biological factor being measured is likely stable, whilst the assay results differ. This cohort of patients should thus be counselled that their absolute risk of PML has likely not changed significantly in the short term. However, 3–6 % of patients per year move across risk stratification boundaries, (Hegen et al., 2017; Hegen et al., 2018; Gaughan et al., 2022; Dwyer et al., 2021) thus longer-term risk should be considered. Patients should be advised that treatment switching/ derisking should be considered, typically 12–24 months after the first positive test should their JCV index remain positive or increase on repeat testing at 6 months. This should be based on individual risk-benefit discussion with their treating team, considering prior MS disease activity, clinical and radiological response to natalizumab, prior treatment exposure and monitoring burden. Once the overall treatment duration exceeds 24 months, regular MRI monitoring should be performed according to local protocols as part of risk mitigation for patients with positive JCV index and treatment duration >24 months.
- Where patients have negative or very low JCV index (<0.9) results on Stratify but high positive on Immunowell, they should be advised that their absolute risk of PML may have increased. However, given the lack of longitudinal data with Immunowell and PML risk this is currently an area of clinical uncertainty. As a result, treatment switching/derisking should be considered, typically 12–24 months after the first positive test, dependent on the duration of prior natalizumab therapy. Once overall treatment duration exceeds 24 months, they should have regular MRI monitoring according to local protocols for patients with high JCV index and treatment duration >24 months.

In JCV positive patients established on Tysabri who develop high titre index on Immunowell

- Where patients are known to be JCV positive with low-moderate JCV index (0.4–1.5) and subsequently test high positive on Immunowell, they should be counselled that their overall risk may have increased, and they should consider treatment switching/derisking. If and when they exceed 24 months treatment duration, then they should undergo frequent MRI monitoring according to local protocols. This advice is based on reasonable agreement between assays towards the middle and upper ranges of the testable range.

## 3. Next steps

Our recommendations are a temporary solution to an unfortunate situation where a new tool to inform risk prediction (i.e. new JCV assay) has been introduced without the evidence needed to enable its interpretation. PML risk is a real concern for many receiving natalizumab;

whilst it is thankfully rare, it is associated with significant morbidity and mortality, and risk monitoring is mandated by regulatory authorities.

To maintain trust and confidence in treatment decisions, shared decision making is essential, including openly discussing both the benefits and risks of therapy. Collaboration within the MS community is also critical in this process. Ideally, new risk models need to be developed and validated using Immunowell assay data. However, given the low rates of PML with current clinical approaches, these will take many years to build, even with novel study design and statistical methodology. These challenges around robust data generation affect both risk stratification and risk mitigation strategies such as extended dose intervals. Until such a time as these are available, applying Stratify-based risk tools to data generated via the Immunowell assay may lead to misleading conclusions, potentially overestimating PML risk.

A publicly developed, standardised JCV assay would ensure uniform, reliable results across biosimilar preparations. Current challenges have highlighted the importance of decoupling "wrap around" services from pharmaceutical companies, particularly where these are crucial for safe and effective treatment delivery. Biosimilars offer an opportunity for more cost effective health services, however their rollout has the potential to highlight vulnerabilities in service delivery models. Until a definitive solution is found, it is incumbent on regulators, pharmaceutical companies, clinical teams, and commissioning bodies to work together to understand how best to gather longitudinal data, counsel patients, and ensure ongoing access to a highly effective therapy.

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## CRediT authorship contribution statement

**Ruth Dobson:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. **Tarunya Arun:** Writing – review & editing, Conceptualization. **James Varley:** Writing – review & editing, Conceptualization. **Jeremy Chataway:** Writing – review & editing, Conceptualization. **Wallace Brownlee:** Writing – review & editing, Conceptualization. **Paul Gallagher:** Writing – review & editing, Conceptualization. **Gavin Giovannoni:** Writing – review & editing, Conceptualization. **Orla Gray:** Writing – review & editing, Conceptualization. **Gillian Ingram:** Writing – review & editing, Conceptualization. **Niall MacDougall:** Writing – review & editing, Conceptualization. **Paolo A Muraro:** Writing – review & editing, Conceptualization. **Katy Murray:** Writing – review & editing, Conceptualization. **David Paling:** Writing – review & editing, Conceptualization. **Kate Petheram:** Writing – review & editing, Conceptualization. **Waqar Rashid:** Writing – review & editing, Conceptualization. **Emma Tallantyre:** Writing – review & editing, Conceptualization. **S Anand Trip:** Writing – review & editing, Conceptualization. **Alasdair Coles:** Writing – review & editing, Conceptualization.

## Declaration of competing interest

RD has received honoraria for speaking and/or travelling from Biogen, Esai, Merck, Roche, Teva, Janssen and Sanofi. She served on the advisory boards for Roche, Biogen, Janssen, Sandoz and Merck. All honoraria were paid into an institutional account and used to support research and educational activities. She has received grant support from Biogen, Merck, Celgene.

TA has received honoraria or consulting fees for participating in advisory boards related to trial steering committees and data and safety monitoring committees, speaker fees & research grants from Janssen, Merck, Novartis, Roche and Sanofi-Genzyme

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GG in the last 2 years, GG has received compensation for serving as a consultant or speaker for, or has received research support from: AbbVie, Aslan, Atara Bio, Biogen, BMS-Celgene, GlaxoSmithKline, Janssen/J&J, Japanese Tobacco, Jazz Pharmaceuticals, LifNano, Merck & Co., Merck KGaA/EMD Serono, Moderna, Novartis, Sanofi, and Roche/Genentech

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