EDITORIAL OPEN ACCESS

Beyond the Lab Slip

Why Laboratory Expertise Matters in Neuronal Antibody Testing and Why Clinicians Should Care

Frank Leypoldt

Neurol Neuroimmunol Neuroinflamm 2025;12:e200425. doi:10.1212/NXI.0000000000200425

Correspondence
Dr. Leypoldt
frank.leypoldt@uksh.de

RELATED ARTICLES

Research Article
Assessing Commercial Tissue-Based Assays for Autoimmune Neurologic Disorders (I): Antibodies to Intracellular Antigens
Page e200410

Research Article
Assessing Commercial Tissue-Based Assays for Autoimmune Neurologic Disorders (II): Antibodies to Surface Antigens
Page e200406

Autoimmune encephalitis and other paraneoplastic neurologic syndromes are diagnostically challenging because of overlapping clinical features, broad differential diagnoses, and low prevalence. Early, accurate recognition is crucial: prompt immunotherapy can improve outcomes, whereas delays may result in permanent neurologic deficits.[1,2] Over the past 2 decades, an expanding repertoire of neuronal and glial autoantibodies—targeting intracellular or surface antigens—has transformed our understanding and management of these disorders. As a result, ordering autoantibody tests for suspected autoimmune encephalitis or paraneoplastic syndromes has become a common step in clinical practice.

Despite this, there remains a "world beyond the lab slip," where diagnostic accuracy depends on multiple factors: selecting the right patient for testing (increasing pretest probability), choosing appropriate assays, and interpreting results in the context of clinical presentation. Because most commercially available autoantibody tests lack perfect sensitivity and specificity, many laboratories combine different methods—historically tissue-based assays (TBAs) with confirmation by cell-based assays (CBAs) or line blots. Originally developed by academic laboratories, tissue-based immunofluorescence assays are now produced by in vitro diagnostic (IVD) companies in standardized, multiplexed, and certified formats. Their widespread availability has reduced turnaround times and improved accessibility but has also introduced pitfalls.

In this issue of *Neurology® Neuroimmunology & Neuroinflammation*, 2 companion articles evaluate common, commercially available indirect immunofluorescence tissue-based assays (IIF-TBAs) for detecting autoantibodies. One study focuses on antibodies to intracellular antigens (IC-Abs, sometimes termed onconeural or paraneoplastic antibodies such as anti-Hu or anti-Yo) (1) and the other on surface antigens (neuronal surface antibodies [NSAbs], such as NMDAR and LGI1) (2). Both ask whether these commercial IIF-TBAs can be reliably used as primary screening tools in suspected autoimmune neurologic syndromes.

In the first article, Milano et al.[3] evaluated 100 positive samples (various IC-Abs such as Hu, Yo, Ma2, and CV2) and 50 negative controls using 2 different commercial kits. Sensitivity ranged between 63% and 73%, varying markedly by antigen. While detection was good for some antibodies (e.g., anti-Yo), false-negative rates were alarmingly high for others (e.g., anti-CV2) and performance was inconsistent between suppliers (e.g., Hu and amphiphysin). Even experienced raters incorrectly classified 4%–22% of negative samples as positive (specificities 78%–96%).

In the second article, Papi et al.[4] examined NSAbs such as NMDAR, LGI1, and CASPR2 in nearly 200 patient samples (serum or CSF), plus 100 negative controls (serum or CSF). Sensitivity remained modest (76%–84%), with up to half of NMDAR-positive cases missed in some scenarios, and false positives also occurred (specificities 72%–73%).

Institute of Clinical Chemistry and Department of Neurology, University Hospital Schleswig-Holstein (UKSH) and Kiel University, Kiel, Germany.

The Article Processing Charge was funded by the authors.

Why should clinicians care? These might seem to be purely laboratory problems. Yet, the world beyond the laboratory slip directly affects patient care. Do you know which test system your local laboratory uses for "onconeural" antibodies or "autoimmune encephalitis panels"? Are IIF-TBAs used alone for screening? Are they always followed by confirmatory assays (e.g., CBAs and line blots)? Does your report explicitly state if discordant results occurred, or if certain antibody specificities have known sensitivity or specificity shortcomings?

These 2 reports emphasize 5 central lessons:

1. IC-Abs: Commercial IIF-TBAs alone are inadequate as a screening strategy. They must be combined with antigen-specific tests (e.g., line blots[5,6]), along with careful clinical correlation. Labs should highlight relevant strengths or limitations in their reports and suggest retesting when suspicion remains high despite negative results.
2. NSAbs: Commercial IIF-TBAs for NSAbs are frequently misleading—both false negatives and false positives. They should not be used as standalone screening or confirmatory assays and ideally should not be marketed as such. Presently, commercially available CBAs[7,8] are a better (although still imperfect) option, using both CSF and serum testing.[8,9]
3. Expertise: Skilled interpretation matters. Experienced personnel, rigorous quality controls, interlaboratory comparisons, and continuous training help maximize accuracy in clinical neuroimmunology labs.
4. Interdisciplinary communication: These syndromes are rare, which lowers pretest probability; thus, proactive dialogue among neurologists, immunologists, and laboratory staff is essential for matching tests to clinical suspicion. In uncertain cases, reference centers can provide retesting with specialized platforms.
5. Multimodal testing: A comprehensive, research-based or reference laboratory approach remains the gold standard. When IIF-TBA and commercial CBA fail to explain a high clinical suspicion, further investigations, including advanced or in-house assays, are warranted.

Altogether, these companion studies illustrate the promise and pitfalls of commercial tissue-based assays for diagnosing autoimmune encephalitis and paraneoplastic neurologic syndromes. They reinforce a straightforward principle: relying on any single test—even one sanctioned by regulatory authorities—can lead to both false reassurance and unnecessary interventions, a risk heightened when uncommon diseases are tested indiscriminately. Ongoing efforts—similar to these systematic evaluations—and consensus statements on autoantibody test accuracy are vital to ensuring that clinicians can trust and optimally interpret the data that guide therapeutic decisions.

Study Funding

The author reports no targeted funding.

Disclosure

F. Leypoldt is supported by E-Rare Joint Transnational research support (ERA-Net, LE3064/2-1) ERA-NET NEURON_BB-148 MICE-AE, Stiftung Pathobiochemie of the German Society for Laboratory Medicine and HORIZON MSCA 2022 Doctoral Network 101119457 - IgG4-TREAT and discloses speaker honoraria from Grifols, Teva, Biogen, Bayer, Roche, Novartis, Fresenius, travel funding from Merck, Grifols and Bayer and serving on advisory boards for Roche, Biogen and Alexion. He works in an academic institution offering commercial antibody testing. Go to Neurology.org/NN for full disclosures.

Publication History

Received by *Neurology® Neuroimmunology & Neuroinflammation* March 24, 2025. Accepted in final form April 4, 2025.

References

1. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol*.2016;15(4):391-404. doi:10.1016/S1474-4422(15)00401-9
2. Graus F, Vogrig A, Muñiz-Castrillo S, et al. Updated diagnostic criteria for paraneoplastic neurologic syndromes. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(4):e1014. doi:10.1212/nxi.0000000000001014
3. Milano C, Businaro P, Papi C, et al. Assessing commercial tissue-based assays for autoimmune neurological disorders (I): antibodies to intracellular antigens. *Neurol Neuroimmunol Neuroinflamm*. 2025;12(4):e200410. doi:10.1212/NXI.0000000000200410.
4. Papi C, Milano C, Arlettaz L, et al. Assessing commercial tissue-based assays for autoimmune neurological disorders (II): antibodies to surface antigens. *Neurol Neuroimmunol Neuroinflamm*. 2025;12(4):e200406. doi:10.1212/NXI.0000000000200406.
5. Déchelotte B, Muñiz-Castrillo S, Joubert B, et al. Diagnostic yield of commercial immunodots to diagnose paraneoplastic neurologic syndromes. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(3):e701. doi:10.1212/nxi.0000000000000701
6. Ruiz-García R, Martínez-Hernández E, Saiz A, Dalmau J, Graus F. The diagnostic value of onconeural antibodies depends on how they are tested. *Front Immunol*. 2020;11:1482. doi:10.3389/fimmu.2020.01482
7. Ruiz-García R, Muñoz-Sánchez G, Naranjo L, et al. Limitations of a commercial assay as diagnostic test of autoimmune encephalitis. *Front Immunol*. 2021;12:691536. doi:10.3389/fimmu.2021.691536
8. Muñoz-Sánchez G, Planagumà J, Naranjo L, et al. The diagnosis of anti-LGI1 encephalitis varies with the type of immunodetection assay and sample examined. *Front Immunol*. 2022;13:1069368. doi:10.3389/fimmu.2022.1069368
9. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol*, 2014;13(2):167-177. doi:10.1016/S1474-4422(13)70282-5