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### **Anti-GAGA4 IgM Antibodies (gMS<sup>®</sup>Dx test) Differentiate Newly Diagnosed Relapsing Remitting Multiple Sclerosis Patients from Other Inflammatory Demyelinating Disease Patients within One Year from Diagnosis**

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**Background:** Previous studies found that the anti-Glc( $\alpha$ -1,4)Glc( $\alpha$ ) (anti-GAGA4) IgM serum biomarker can differentiate RRMS/CIS patients from other neurological disease (OND) patients.

**Objectives:** To assess the ability of the gMS<sup>®</sup>Dx test, based on anti-GAGA4 IgM antibody detection, and additional anti-alpha-glucose IgM antibodies to differentiate newly diagnosed relapsing remitting multiple sclerosis (RRMS) patients from patients with other inflammatory demyelinating diseases (OIDD) within one year from diagnosis.

**Methods:** Cross-sectional retrospective analysis of sera with masked identity and clinical data that were collected throughout the first year after diagnosis, in five centers (n=205): USA (n=98), Denmark (n=73), Italy (n=10) and two German centers (n=24). Sixty-eight RRMS patients (35.5 $\pm$ 8.1yrs, 72.1%F) and 137 OIDD patients (optic neuritis, n=77; transverse myelitis, n=40; acute demyelinating encephalomyelitis, n=12; neuromyelitis optica, n=8; 36.4 $\pm$ 8.4yrs, 65.7%F) entered the study. Samples were tested for anti-GAGA4 IgM(EU)/TIgM(g/L)<sup>0.5</sup> (gMS<sup>®</sup>Dx), and other five anti-alpha-glucose IgM antibodies (Glycominds, Lod, Israel).

**Results:** The gMS<sup>®</sup>Dx test distinguished newly diagnosed RRMS patients from newly diagnosed OIDD patients [p=0.005, Mann-Whitney; specificity:85%; sensitivity:31%; likelihood ratio (LR)<sub>+</sub>:2.12; LR<sub>-</sub>:0.82]. Furthermore, significant differences were observed in RRMS vs. OIDD patients for other anti-alpha glucose antibodies (anti-GAGA2:p=0.003; anti-GAGA3:p=0.004; anti-GAGA6:p=0.006; anti- $\alpha$ -GlcNAc: p=0.02; anti-P63:p=0.03; Mann-Whitney). An algorithm combining several glycans, anti-GAGA4, anti-GAGA3 and anti-P63 showed that if one or more antibodies were positive, test performance remained similar to anti-GAGA4 alone (specificity:89%; sensitivity:31%; LR<sub>+</sub>:2.82; LR<sub>-</sub>:0.78), whereas if two or more antibodies were positive, the LR<sub>+</sub> increased dramatically, but sensitivity decreased (specificity:96%; sensitivity:22%; LR<sub>+</sub>:6.04; LR<sub>-</sub>:0.81).

**Conclusions:** The gMS<sup>®</sup>Dx test based on anti-GAGA4 IgM(EU)/TIgM(g/L)<sup>0.5</sup> immunoassay can differentiate RRMS patients from OIDD patients at the early diagnostic work-up. Other anti-glucose

IgM antibodies significantly differentiate RRMS patients from OIDD patients, but further studies are required to assess their potential contribution to anti-GAGA4 antibodies.