

gMS[®] ProEDSS Blood Test Based on Anti-GAGA IgM Antibodies Detects Rapid Multiple Sclerosis Disability Progression

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BACKGROUND:

The clinical course of multiple sclerosis (MS) is characterized by a wide range of progression rates. Though, certain clinical and paraclinical factors modestly and variably associate with worse outcome, detailed prognosis of a given relapsing remitting MS (RRMS) patient is not possible until many years after disease onset. Prognostic factors for discerning patients who are more susceptible to breakthrough disease and deserve earlier aggressive treatment are warranted.¹

Findings from the Betaferon[®]/Betaseron[®] in newly emerging MS for initial treatment (BENEFIT) study demonstrated that clinically isolated syndrome patients positive for gMS-Classifier1 (gMS[®] ProEDSS blood test) had higher risk for faster progression in one confirmed Expanded Disability Status Scale (EDSS) point, despite Interferon beta-1b treatment, than patients negative for gMS-Classifier1.^{2,3}

OBJECTIVE:

Confirm that gMS-Classifier1, as analyzed in the BENEFIT study³, detects RRMS patients at risk for faster progression in one confirmed EDSS point.

METHODS:

Design and Setting

Retrospective analysis of serum biomarkers and longitudinal clinical data. Median follow-up time was 1015 days.

Assay and Study Population

Immunoassay Patient sera with masked identity were screened for gMS-Classifier1 IgM antibodies, anti-GAGA2, anti-GAGA3, anti-GAGA4 and anti-GAGA6 (gMS[®] ProEDSS test, Glycominds, Lod, Israel).

Eligibility Criteria 1. RRMS diagnosis, 2. Age 18 to 50 years and 3. Two EDSS evaluations separated by at least six months (Figure 1).

Time from Prior DMT Dose at Blood Withdrawal 69 (91.0%) patients less than 1 month. Five (6.6%) patients 3 or more months. Two (2.6%) patients data not recorded.

Patient Characteristics Demographic and clinical data are described (Table 1).

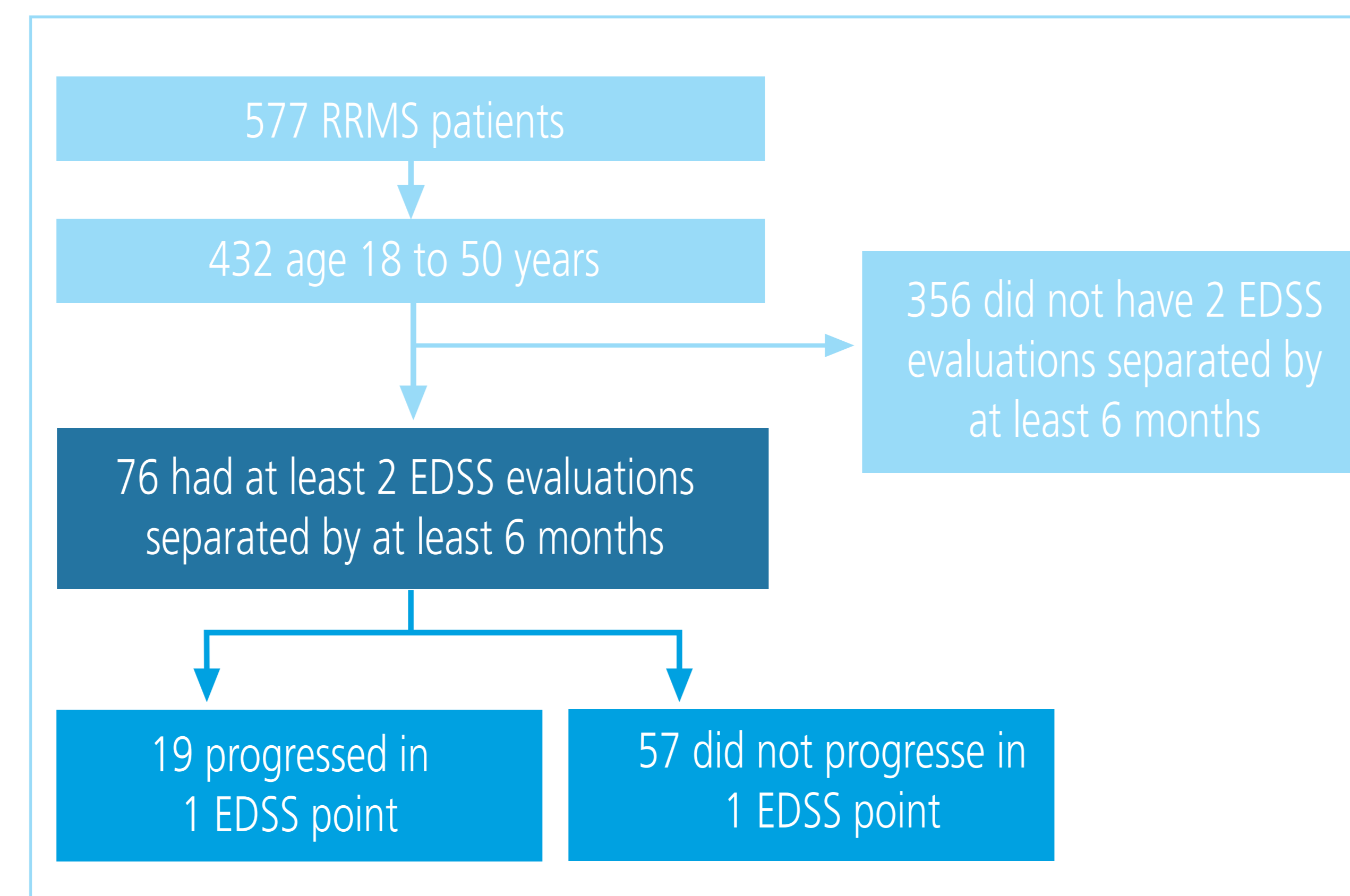


Figure 1. Patient flow diagram for gMS-Classifier1 study.

Table 1: Patients Demographic and Clinical Characteristics at Blood Draw

Variable at Blood Collection	Total patients (n=76)	Advanced One EDSS Point (n=19)	Did not Advance in One EDSS Point (n=57)
Mean Age, years (SD)	39.8 (7.4)	38.3 (8.4)	40.2 (7.0)
Female (%)	69.7	71.9	63.2
Median Time from First Symptom, years (P25,P75)	8 (4.5, 15.5)	8 (4.0, 14.8)	8.0 (5.0, 16.0)
Median Time from Last Treatment of DMT, days (P25,P75) n=74	2 (1.0, 5.0)	2 (1.0, 4.8)	2 (1.0, 5.0)
Mean Time to Second EDSS Evaluation (SD)	306.8 (599.4)	281.9 (480.6)	315.0 (637.8)
Median First EDSS Evaluation (P25,P75)*	2.5 (1.5, 3.0)	1.5 (1.5, 2.9)*	2.5 (2.0, 3.0)
Median Second EDSS Evaluation (P25,P75)**	2.5 (2.0, 3.3)	4.0 (2.5, 5.6)**	2.0 (1.5, 3.0)

Mean values are shown for normally distributed data and were compared by independent samples T-test. Median values are shown for data that are not normally distributed and were compared by Mann-Whitney. P25,P75 is interquartile range. Patients that advance by at least one EDSS point vs. those that did not advance* p-value=0.018; **p-value<0.0001.

RESULTS:

gMS-Classifier1 and EDSS Progression Patients positive for gMSClassifier1 (n=7, Median Survival 1157 days) increased by at least one EDSS point faster (p-value=0.0004) than patients negative (Figure 2) for gMS-Classifier1 (n=69, Median Survival 2705 days).

Adjustment for Confounding Factors gMS-Classifier1 can independently predict EDSS progression (Table 2).

Rate of EDSS Advancement In order to compensate potential influence for the difference in follow-up time of the patients, the yearly rate of EDSS change (EDSS/Year) was assessed (Figure 3). Patients positive for gMS-Classifier1 had a higher yearly rate, median (P25,P75) of 0.57(0.13, 0.97) EDSS/Years than patients negative for the test (p-value=0.02) 0.0 P25,P75) EDSS/Years.

Table 2: Association of Time to Progression in One EDSS Point to gMS-Classifier1 Status and Additional Confounding Factors, Cox Proportional Hazards Regression

Factor	Univariate		Covariate with gMS-Classifier1	
	HR (95%CI)	P-value	HR (95%CI)	P-value
gMS-Classifier1 Status (positive or negative)	6.9 (2.0-23.5)	0.002	7.7 (2.2-27.3) ^a / 5.9 (1.7-20.3) ^b	0.002 ^a / 0.005 ^b
Age (years)	---	NS	---	NS
Sex	---	NS	---	NS
Time from First Symptom to BC (years)	0.85 (0.77-0.94)	0.002	0.85 (0.77-0.94)	0.002
Time from BC to Second EDSS Evaluation (days)	---	NS	---	NS
Time from BC to Prior DMT Dose (days)	---	NS	---	NS
First EDSS Evaluation (quartile score)	0.56 (0.33-0.93)	0.02	0.58 (0.35-0.98)	0.04
Second EDSS Evaluation (quartile score)	1.6 (1.1-2.4)	0.02	---	NS

HR=Hazard Ratio, NS=non-significant, BC= Blood Collection, DMT=disease modifying therapy
^agMS-Classifier1 with Time from first symptom; ^bgMS-Classifier1 with First EDSS Evaluation

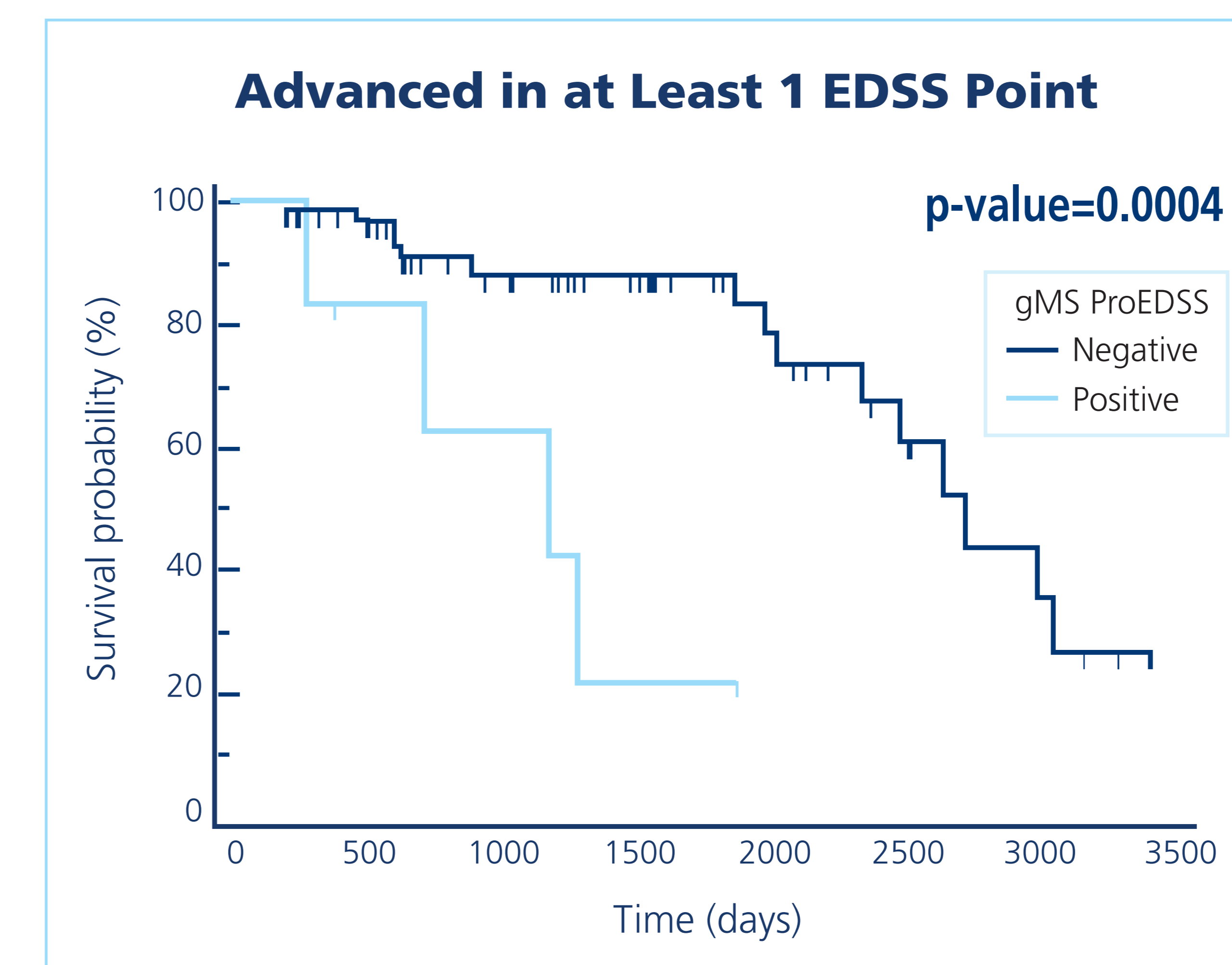


Figure 2. Kaplan-Meier survival plot for time to EDSS progression in one point. The dark blue line represents patients negative for gMS-Classifier1 (n=69, Median Survival 2705 days), the light blue line represents patients positive for gMS-Classifier1 (n=7, Median Survival 1157 days).

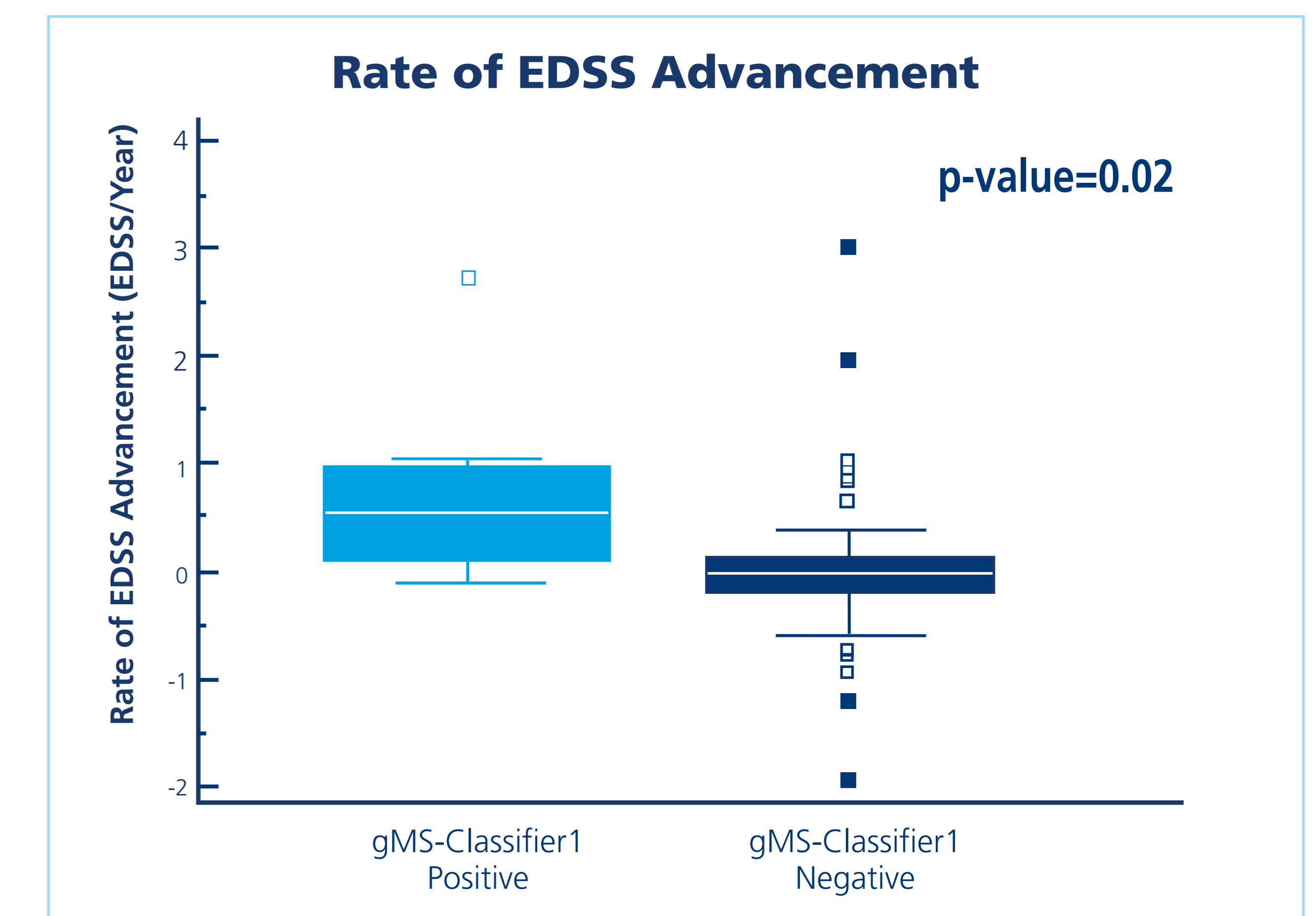


Figure 3. Box plots of rate of EDSS advancement (ΔEDSS/Year) median values and 25% / 75% quartiles. Outliers are smaller or larger than the upper quartile plus 1.5 times the interquartile range (empty squares). Far outliers (filled squares) are larger or smaller than the upper quartile plus 3 times the interquartile range. Patients positive for gMS-Classifier1 had a higher yearly rate of EDSS advancement than patients negative for gMS-Classifier1.

CONCLUSIONS:

Results here support the BENEFIT study findings, demonstrating that gMS-Classifier1 (gMS[®] ProEDSS blood test) may be a useful tool to detect breakthrough RRMS patients at risk for fast disability progression despite DMT treatment.

ACKNOWLEDGMENTS:

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DISCLOSURES:

Study Supported by: Glycominds Ltd., Israel