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Association of a multi-SNP signature with response to Copaxone® (glatiramer acetate) in a subset of patients and in multiple RRMS patient cohorts.

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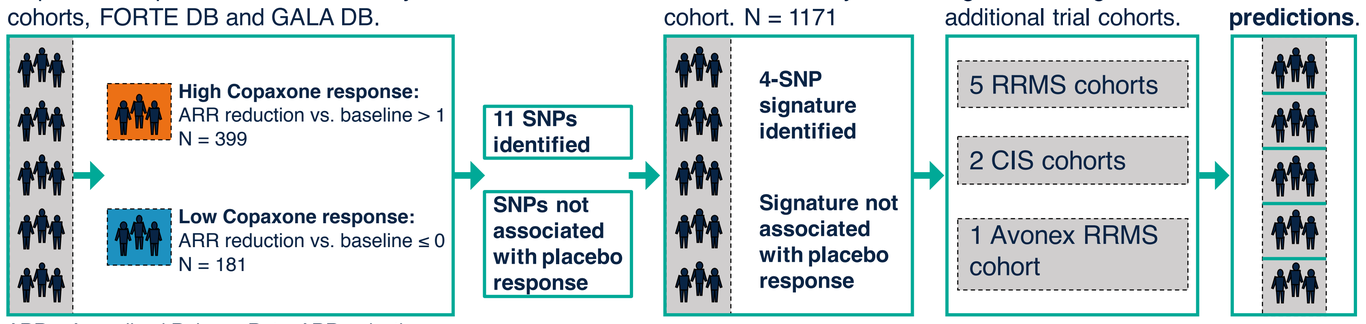
Background and Objectives

- **Copaxone** (glatiramer acetate) is an effective treatment for Multiple Sclerosis with a **safety and efficacy profile** demonstrated over **20 years of clinical use**.
- As with any treatment, **MS patients vary in their degree of responsiveness to Copaxone** at an individual level, with some achieving significantly higher response levels.
- Contribution of patient genetics to variability in Copaxone-response is supported by past studies that have shown involvement of genes with high inter-individual variability such as *HLA-DRB1*1501* in Copaxone's mechanism of action (MoA).
- Pharmacogenetic investigations of variability in response to MS drugs potentially offer a route towards tailored treatment decisions for MS patients.
- The current study aimed to **identify and independently assess a genetic signature with multiple single nucleotide polymorphisms (SNPs) associated with a response to Copaxone** based on decrease in relapses following treatment.

Study Design

Figure 1: Study design



ARR = Annualized Relapse Rate. ARR reduction vs. baseline = Individual ARR during study minus ARR for two years prior to study.

Patient cohorts

Table 1: Demographic and baseline clinical profiles

	DISCOVERY		INDEPENDENT ASSESSMENT							SPECIFICITY ASSESSMENT
Name of trial	**FORTE DB**	**GALA DB**	**GALA OL**	**GA-9001 DB**	**GA-9001 OL**	**GA-9003 DB**	**GA-9003 OL**	**PreCISe DB**	**PreCISe OL**	**BRAVO Avonex arm**
Type of MS	RRMS							CIS		RRMS
Number of patients	532	639	333	38	74	40	84	132	240	310
Age (mean ± SD)	35.91 ± 8.78	37.66 ± 9.36	37.68 ± 9.28	35.1 ± 6.16	36.16 ± 6.22	33.3 ± 7.59	33.66 ± 7.55	31.15 ± 7.02	32.24 ± 7.14	38.1 ± 9.49
Sex (% Female)	71.69%	73.31%	67.60%	73.31%	72.62%	74.90%	75.43%	66.94%	67.18%	67.45%
Caucasian (%)	100.00%	97.96%	98.41%	92.59%	92.41%	97.83%	97.83%	97.13%	97.45%	98.66%
Baseline EDSS	2.12 ± 1.12	2.77 ± 1.21	2.8 ± 1.26	2.74 ± 1.30	2.74 ± 1.56	2.39 ± 1.23	2.41 ± 1.38	0.96 ± 0.86	1.26 ± 1.11	2.64 ± 1.14
Baseline ARR (mean ± SD)	0.98 ± 0.44	0.93 ± 0.45	0.88 ± 0.50	1.49 ± 0.56	1.05 ± 0.78	1.21 ± 0.78	1.25 ± 0.78	NA	NA	0.94 ± 0.45

Copaxone doses: Forte DB: Both 20mg/mL and 40mg/mL a day arms were included. GALA DB 40mg/mL thrice-a-week. GALA OL: 40mg/mL a day. GA-9001, GA-9003 and PreCISe: 20 mg/ML a day. RRMS: Relapsing Remitting type of MS. CIS: Clinically isolated syndrome. OL: Open-label. Avonex: Interferon β-1a. EDSS: Kurtzke Expanded Disability Status Scale. Baseline ARR: Individual ARR for two years prior to study. Patients who gave their informed consent to being genotyped were included in the study. Genotyped patients were representative of the study population in the parent trial.

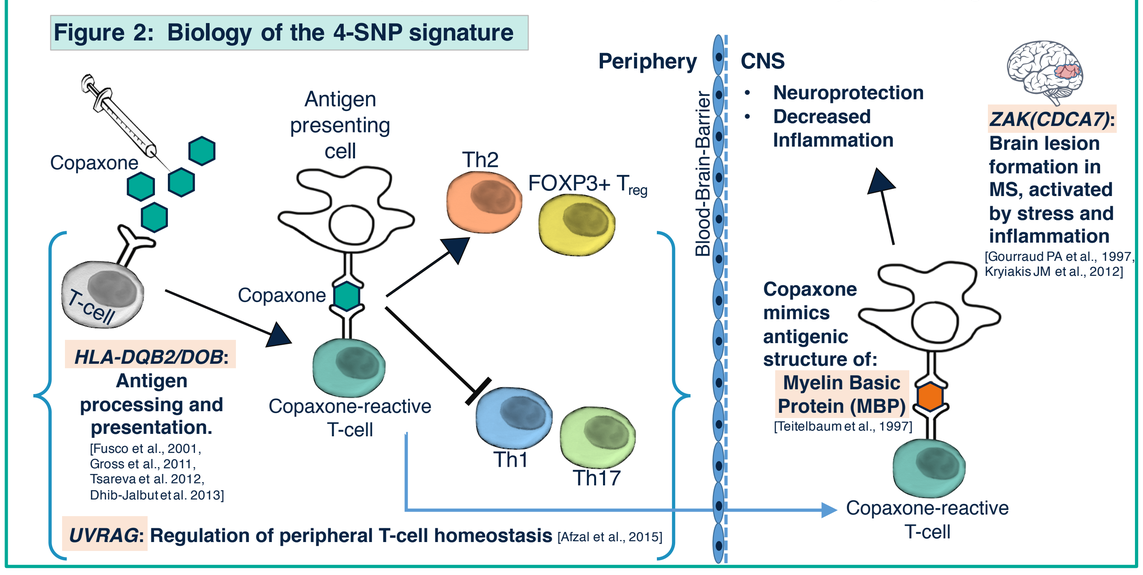
I. Association analysis in genome-wide SNP data

- A five-step SNP-by-SNP association analysis incorporating prior literature evidence was conducted on genome-wide SNP data on high and low Copaxone responders in FORTE DB and GALA DB.
- The identified SNPs were also assessed in the GALA DB placebo cohort.
- **11 SNPs** were identified as associated with response **in both FORTE DB and GALA DB Copaxone-treated patients** and **not in placebo patients.**
- The 11 SNPs comprised variants from the following gene-regions: *HLA-DRB1*1501, HLA-DQB2/DOB, HLA-DOB/TAP2, MBP, PTPRT, ALOX5AP, MAGI2, ZAK(CDCA7), SLC5A4(RFPL3), UVRAG and SLC1A4* [Ross et al., 2014].

II. Bayesian predictive modeling

- To develop a multi-SNP model for predicting Copaxone response, a multivariable logistic regression model was estimated on 1171 patients in the discovery cohorts.
  - Using Bayesian model averaging with a sparse prior enabled the model to capture the expectation that only a subset of the 11 identified SNPs would accurately predict the response.
- A relapse-free definition was used, such that patients with no relapses within 1 year of starting treatment were considered relapse-free or responders. Patients with relapses within a year of starting treatment were considered relapsing or non-responders.
- The threshold for being predicted as a responder or a non-responder was optimized for maximum sensitivity and specificity (the "top-left" threshold).
- A **4-SNP signature of Copaxone-response** was identified. The signature was not associated with response to placebo. The signature comprised SNPs in the gene-regions of ***HLA-DQB2/DOB, MBP, UVRAG and ZAK(CDCA7)***. Each of these gene-regions has been linked with either the MoA of Copaxone or disease processes underlying MS (Figure 2).

Figure 2: Biology of the 4-SNP signature



III. Independent Assessment

- Signature-positive patients in **all Copaxone-treated RRMS independent cohorts demonstrated lower ARR (13% to 53% reductions)** compared to signature-negative patients.
- CIS cohorts were inconclusive, with DB cohort showing 5% lower ARR in signature-positive patients and OL cohort showing 10% higher ARR compared to signature-negative.
- In the Avonex-treated RRMS cohort, signature-positive patients showed an ARR *increase* of 10%, which was in the opposite direction to the ARR change in Copaxone-treated RRMS patients, **demonstrating specificity of the 4-SNP signature to Copaxone**.
- **AUC in independent cohorts,** reflecting the discriminatory power of the signature, ranged from **0.45 to 0.67**.

IV. Profiling model predictions

- To identify patient groups with better signature performance**, patients in the discovery cohort were split into 5 similar-sized bins** based on predicted probabilities from the 4-SNP model [Kent et al., 2010].
- Each bin was characterized for multiple clinical parameters, including percentage of relapse-free patients, change in ARR, time to first relapse and percentage of patients who achieved NEDA4 (Figure 3 and Table 2).

Figure 3: Percentage of responders and non-responders in each bin.

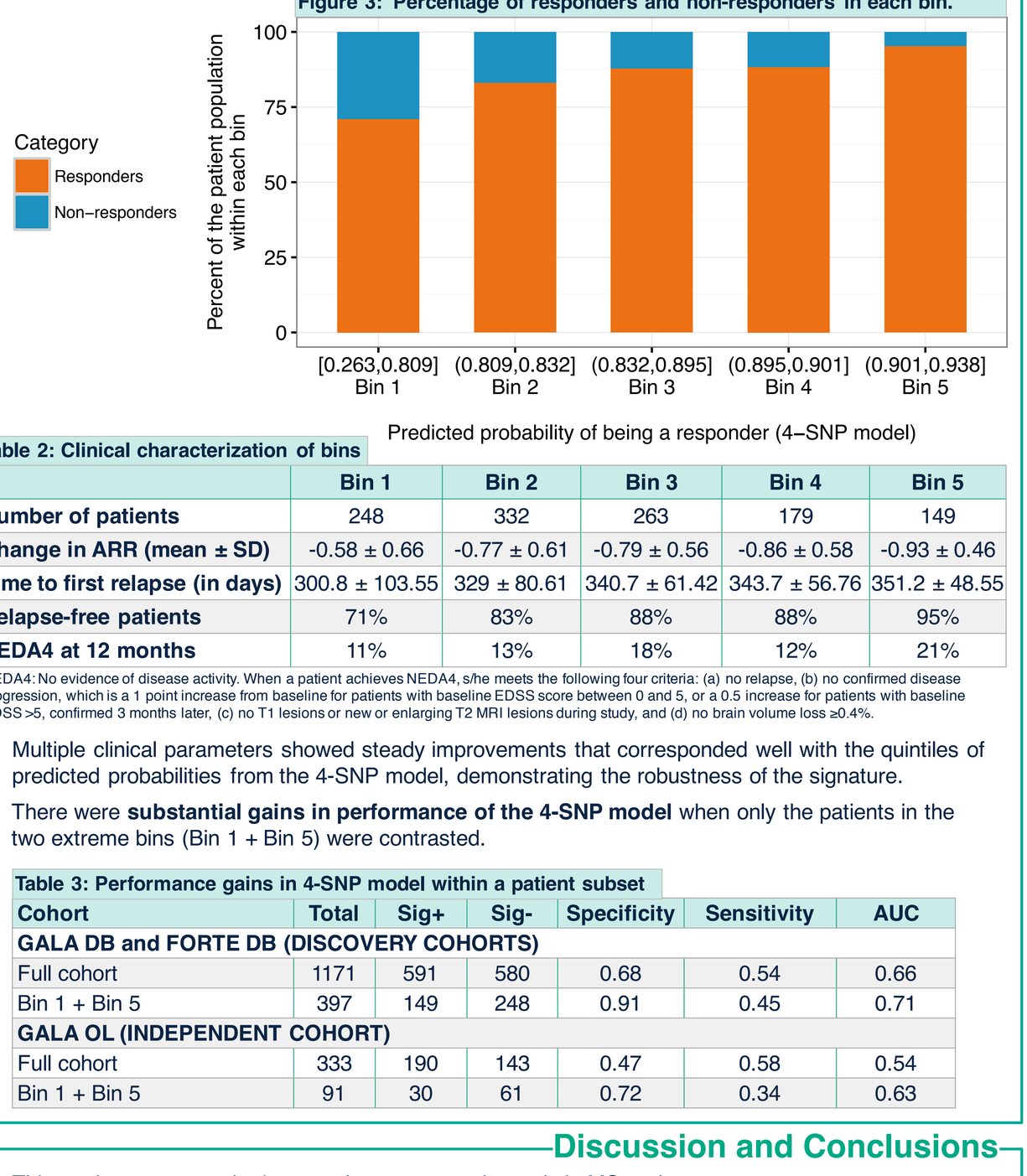


Table 2: Clinical characterization of bins

	Bin 1	Bin 2	Bin 3	Bin 4	Bin 5
Number of patients	248	332	263	179	149
Change in ARR (mean ± SD)	-0.58 ± 0.66	-0.77 ± 0.61	-0.79 ± 0.56	-0.86 ± 0.58	-0.93 ± 0.46
Time to first relapse (in days)	300.8 ± 103.55	329 ± 80.61	340.7 ± 61.42	343.7 ± 56.76	351.2 ± 48.55
Relapse-free patients	71%	83%	88%	88%	95%
NEDA4 at 12 months	11%	13%	18%	12%	21%

NEDA4: No evidence of disease activity. When a patient achieves NEDA4, s/he meets the following four criteria: (a) no relapse, (b) no confirmed disease progression, which is a 1 point increase from baseline for patients with baseline EDSS score between 0 and 5, or a 0.5 increase for patients with baseline EDSS >5, confirmed 3 months later, (c) no T1 lesions or new or enlarging T2 MRI lesions during study, and (d) no brain volume loss ≥0.4%.

- Multiple clinical parameters showed steady improvements that corresponded well with the quintiles of predicted probabilities from the 4-SNP model, demonstrating the robustness of the signature.
- There were **substantial gains in performance of the 4-SNP model** when only the patients in the two extreme bins (Bin 1 + Bin 5) were contrasted.

Table 3: Performance gains in 4-SNP model within a patient subset

Cohort	Total	Sig+	Sig-	Specificity	Sensitivity	AUC
GALA DB and FORTE DB (DISCOVERY COHORTS)						
Full cohort	1171	591	580	0.68	0.54	0.66
Bin 1 + Bin 5	397	149	248	0.91	0.45	0.71
GALA OL (INDEPENDENT COHORT)						
Full cohort	333	190	143	0.47	0.58	0.54
Bin 1 + Bin 5	91	30	61	0.72	0.34	0.63

Discussion and Conclusions

- This study represents the largest pharmacogenetic study in MS to date.
- A multi-SNP signature associated specifically with Copaxone response was identified.
- Each of the four SNPs in the signature has been either associated with Copaxone's immunomodulatory effects or specifically implicated in MS disease processes.
- Signature-positive RRMS patients demonstrate higher response compared to signature-negative patients in multiple clinical endpoints, including relapse rate, time to first relapse, and MRI parameters as well as the aggregate NEDA4 definition, supporting the potential clinical utility of the signature.
- The signature's performance is most pronounced in a small subset of patients (~10%), consistent with the complex, multifactorial nature of Copaxone's mechanism of action, which is yet to be fully elucidated [Hasson et al., 2016].

ePoster: EP1421. **Contact: Daphna Laifenfeld (Daphna.Laifenfeld@teva.co.il)**. Colin Ross, Fadi Towfic and Jyoti Shankar contributed equally to the work described in this poster. Support for this study was provided by Teva Pharmaceutical Industries, Ltd. All authors indicated as [2,3] above, are employees and/or stockholders of Teva or Immuneering (51% owned by Teva). Presented at the ECTRIMS Meeting, September, 2016, London, England.