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# Pharmacogenetics of disease-modifying therapies in multiple sclerosis: current evidence and emerging markers

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**Background:** Multiple sclerosis (MS) is a chronic, immune-mediated neurological disorder for which a variety of disease-modifying therapies (DMTs) with distinct mechanisms of action are now available. However, interindividual variability in drug response remains a significant clinical challenge.
**Objectives:** This narrative review aims to provide a comprehensive synthesis of the current evidence on pharmacogenetic markers associated with MS treatment response and toxicity, incorporating recent pharmacogenomic literature.
**Methods:** Based on data from the ClinPGx curated database and recent pharmacogenomic literature, pharmacogenetic variants associated with altered drug response were identified and categorized by phenotype and level of evidence.
**Results:** CYP2C9 haplotypes represent the only pharmacogenetic marker with regulatory actionability, guiding siponimod dosing. Recent larger studies identified MAP3K1 (rs2053696) as a genome-wide significant predictor of glatiramer acetate response, and HLA-A*03:01 as a clinically relevant marker enabling personalized choice between glatiramer acetate and interferon-β. For interferon-β, HLA haplotypes predict formulation-specific immunogenicity with high accuracy, while SLC9A9 represents a validated efficacy predictor. For anti-CD20 therapies, FCGR3A V158F (rs396991) is emerging as a class-level pharmacogenetic determinant of B-cell depletion.
**Conclusions:** Pharmacogenetics holds real promise for personalizing DMT selection in MS. Future integration of pharmacogenetic testing into clinical practice, supported by larger and more diverse cohorts, could support more effective and safer treatment strategies for individuals with MS.

KEYWORDS
**disease-modifying therapies, multiple sclerosis, pharmacogenetics, pharmacogenomic (PGx) testing, precision medicine**

# Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated disorder of the central nervous system (CNS), arising from a complex interplay between genetic predisposition and environmental exposures (1). This interaction leads to inflammation, demyelination, and ultimately neurodegeneration involving both the brain and spinal cord (2). MS is notoriously heterogeneous in its clinical presentation (3) and can be classified into three main subtypes: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS). Descriptors of disease activity and progression applicable across all subtypes were updated in 2014 (3). This clinical diversity is paralleled by significant variability in radiological features (4), including the distribution of lesions, involvement of the cortex and spinal cord, and the severity of brain atrophy. While focal inflammatory lesions are hallmark features in early disease and RRMS, progressive forms of MS are more commonly associated with diffuse neurodegeneration and cortical damage (5). Such heterogeneity constitutes a significant challenge for therapeutic stratification, as well as for the assessment of prognosis and treatment response.

The therapeutic landscape of MS has expanded significantly over the past two decades, now including more than twenty DMTs (2). Early initiation of treatment remains a critical strategy to reduce relapse rates and to delay the accumulation of disability; furthermore, early identification of progressive forms has become essential because specific treatment options are now available for progressive MS (6). In clinical practice, the concept of NEDA-3 (No Evidence of Disease Activity-3) is currently used to evaluate the effectiveness of DMTs, through absence of clinical relapse and no worsening of MRI lesions and disability.

Interindividual variability in drug response, safety, tolerability, and pharmacokinetics is a critical determinant of clinical outcomes, shaped by multiple factors, including genetic background (7), environmental factors, and the presence of comorbidities (8). Pharmacogenetic testing identifies inherited variants that influence pharmacokinetics (PK) and pharmacodynamics (PD), enabling drug optimization tailored to the patient's genotype (9). Germline markers, particularly in ADME genes, play a key role in identifying individuals at risk of adverse effects or requiring dose adjustments (10–13).

In MS, the only DMT for which a dose adjustment is currently mandated is siponimod, an oral selective S1P1 modulator approved for SPMS. Beyond this regulatory example, a growing body of evidence highlights additional pharmacogenetic signals across multiple DMT classes — from first-line platform therapies to high-efficacy monoclonal antibodies (14, 15). This review aims to synthesize the current evidence on pharmacogenetic markers associated with MS treatment response and toxicity, integrating recent literature findings, and to discuss the potential for incorporating a pharmacogenetics approach into personalized treatment strategies.

# Methods

This narrative review was conducted to synthesize current evidence on pharmacogenetic markers associated with treatment response and toxicity in MS. The study encompassed both first-line DMTs and high-efficacy agents.

## Selection of DMTs for analysis

We considered all currently approved DMTs for MS, including first-line agents such as interferon-β, glatiramer acetate, teriflunomide, and dimethyl fumarate, and high-efficacy agents such as alemtuzumab, cladribine, fingolimod, ozanimod, ponesimod, natalizumab, ocrelizumab, ofatumumab, ublituximab, and rituximab. Siponimod was considered specifically for the treatment of secondary progressive forms.

## Identification of pharmacogenetic associations

Pharmacogenetic variants relevant to MS treatment were identified using the ClinPGx database (16), accessed in July 2026. Only associations involving currently approved DMTs for MS were considered, and only variants with ClinPGx evidence levels ranging from 1A to 3 were retained. For the purpose of this review, associations were classified into two categories: (i) MS-specific DMT associations: genetic variants linked to treatment efficacy or adverse drug reactions identified in studies conducted specifically in MS patients; (ii) cross-disease DMT associations: variants identified in non-MS diseases but involving drugs also approved for MS, in which the pharmacogenetic signal may be relevant by class effect.

For each variant, the level of evidence according to the ClinPGx classification (Levels 1A to 3) and the presence of clinical guidelines or regulatory recommendations was recorded. Each variant was assigned a phenotype category (e.g., efficacy, toxicity, or metabolism) based on the reported clinical outcome. Additionally, a targeted literature search was performed on PubMed via NCBI E-utilities (search date: 12 September 2026). For each drug, the search combined drug name synonyms AND 'multiple sclerosis' AND a pharmacogenetic terms block (pharmacogenetic*, pharmacogenomic*, polymorphism*, genotype*, allele*, SNP, HLA, 'single nucleotide', 'genetic variant*', GWAS, 'genome-wide'). For interferon-β (234 records), glatiramer acetate (95 records), and natalizumab (57 records), the full result set was retrieved and manually curated record by record; for all other drugs, retrieval was limited to the 60 most relevant records. Studies were included if they reported an association between germline host variants (SNPs, HLA alleles, polymorphisms, or GWAS loci) and drug response, efficacy, adverse events, toxicity, or immunogenicity, as well as relevant pharmacogenetic reviews. Studies were excluded if they concerned MS susceptibility only (without treatment context), reported transcriptomic or immunophenotypic data without a germline variant, used animal models (EAE), or were purely serological (e.g., anti-JCV antibody studies) without a host genetic variant.

From the ClinPGx search, 46 variants were identified in total: 31 in MS-specific studies (of which 27 reached statistical significance at $p < 0.05$) and 15 cross-disease associations. From the PubMed search (NCBI E-utilities, 12 September 2026), a total of 386 records were retrieved with full coverage for the three main drug categories

(interferon-β: 234; glatiramer acetate: 95; natalizumab: 57); for the remaining approved MS DMTs, up to 60 records per drug were retrieved, sorted by relevance. Overall, 179 records were explicitly excluded after manual screening (reasons: MS susceptibility only without treatment context; transcriptomic or immunophenotypic data without germline variant; animal models (EAE); purely serological studies without host genetic variant). After curation using a structured allow-list/exclude-list approach, at least 142 records met inclusion criteria across the three fully curated drugs (interferon-β: 88; glatiramer acetate: 29; natalizumab: approximately 25). These studies contributed 41 additional variant-phenotype associations not previously captured by ClinPGx. A PRISMA-style flow diagram summarizing the complete selection process is provided as Supplementary Figure 1.

# Results and discussion

## Summary of DMTs and pharmacogenetic markers

For each DMT, the mechanism of action, common side effects, and notable adverse events have been summarized in Table 1 (17, 18). According to the ClinPGx database, a total of 31 pharmacogenetic variants have been reported in association with response to four DMTs used in MS: siponimod, glatiramer acetate, interferon beta-1a, and interferon beta-1b. Among these, 27 associations reached statistical significance ($p < 0.05$) in various studies (Table 2). Seventy-five percent of these associations are linked to drug efficacy, 15% to drug toxicity and the remaining 10% to drug metabolism and related pharmacokinetics. Most findings in Table 2 derive from case-control studies with small sample sizes (typically <500 participants). Notable exceptions include two efficacy-related associations from a study on interferon beta-1a and beta-1b (35), and three toxicity-related associations from a large-scale study on glatiramer acetate (28). In addition, 15 variants were identified in cross-disease studies (Supplementary Table S1), primarily associated with alemtuzumab, mitoxantrone, dimethyl fumarate, and cladribine. These associations should be interpreted with caution: for example, the CXCL12 rs1801157 variant in alemtuzumab response was identified in a study with only one alemtuzumab-treated patient (39).

Among all associations, only CYP2C9 — encoding a liver enzyme responsible for siponimod metabolism — is supported by Level 1A evidence, with inclusion in international pharmacogenetic guidelines. Loss-of-function alleles CYP2C9*2 and *3 significantly affect siponimod clearance: individuals carrying the *3/*3 genotype exhibit markedly decreased enzymatic activity, leading to increased plasma drug concentrations and a substantially elevated risk of bradyarrhythmia and hepatotoxicity. As a result, both the FDA and EMA require CYP2C9 genotyping prior to treatment initiation. According to CPIC and DPWG, patients with CYP2C9 *1/*3 or *2/*3 genotypes should receive a reduced starting dose, while those with the *3/*3 genotype are contraindicated (20, 40). The remaining associations are classified as Level 3 evidence, reflecting limited or preliminary support.

For glatiramer acetate (GA), the pharmacogenetic landscape has expanded with recent larger studies. A multicenter GWAS in 679 GA-treated RRMS patients identified rs2053696A in *MAP3K1*

TABLE 1 Disease-modifying therapies for MS: mechanisms of action and adverse events.

| DMT | Mechanism of action | Common side effects | Notable adverse events | Route |
|---|---|---|---|---|
| Interferon-β | Immunomodulator: cytokine shift, T-cell inhibition | Flu-like symptoms, injection site reactions | Depression, liver enzyme elevation, thrombocytopenia, neutralizing antibodies | SC or IM injection |
| Glatiramer acetate | Antigen mimicry, Th2 shift, neuroprotection | Injection site reactions | Lipoatrophy, rare systemic reactions | SC injection |
| Dimethyl fumarate | Nrf2 activation, anti-inflammatory | Flushing, GI symptoms | Lymphopenia, PML (rare) | Oral |
| Teriflunomide | Pyrimidine synthesis inhibition | Alopecia, GI upset | Hepatotoxicity, teratogenicity | Oral |
| Fingolimod | S1P receptor modulator, lymphocyte sequestration | Bradycardia, headache, liver enzyme elevation | Bradyarrhythmia, infections, macular edema, PML (rare) | Oral |
| Siponimod | Selective S1P1/5 modulator, CNS-penetrant | Headache, liver enzyme elevation | Bradyarrhythmia, infections, macular edema | Oral |
| Ozanimod | S1P1/5 receptor modulator | Headache, liver enzyme elevation | Bradyarrhythmia, infections, macular edema | Oral |
| Natalizumab | Anti-α4 integrin mAb, blocks CNS infiltration | Fatigue, headache, infusion reactions | PML, hypersensitivity reactions | IV infusion |
| Alemtuzumab | Anti-CD52 mAb, depletes lymphocytes | Infusion reactions, infections | Secondary autoimmunity, serious infections | IV infusion |
| Ocrelizumab | Anti-CD20 mAb, B-cell depletion | Infusion reactions, infections | Infections, malignancy risk | IV infusion |
| Ofatumumab | Anti-CD20 mAb, B-cell depletion | Injection-related reactions, headache | Injection-related systemic events | SC injection |
| Ublituximab | Glycoengineered anti-CD20 mAb, enhanced ADCC | Infusion reactions | Infections | IV infusion |
| Cladribine | Purine analog, selective immune depletion | Headache, infections | Infections, malignancies | Oral |

TABLE 2 Pharmacogenetic variants associated with response to DMTs in MS (ClinPGx database plus recent literature).

| Drug | Variant (gene); genotype comparison | Phenotype category | Study design, cohort size and reported ancestry | Ndpoint as defined in the original study | Effect size and p-value | Replication status | MS-specific? | Evidence level (ClinPGx) | Reference (PMID) |
|---|---|---|---|---|---|---|---|---|---|
| Siponimod | *CYP2C9* *1, *2, *3; decreased/no-function alleles vs *1/*1 | Metabolism/ PK ★ | ClinPGx annotations rest on an *in vitro* and in silico study of CYP2C9-mediated metabolism (Jin et al.), a pharmacokinetic study in healthy subjects (n = 24, Gardin et al.) and a pooled analysis of published clinical trials in healthy volunteers and MS patients (n = 100, Chen et al.); ancestry not reported | Siponimod clearance and plasma exposure (AUC) by genotype — a pharmacokinetic endpoint, not a clinical outcome[b] | p = 0.0477 (Jin et al., *in vitro*/in silico); in clinical pharmacokinetic analyses *3/*3 carriers show markedly reduced clearance and increased exposure | Yes — consistent across independent pharmacokinetic studies; implemented in the FDA and EMA labels and in the DPWG guideline | Yes (siponimod PK) | 1A | 19 (Medical Genetics Summaries, NBK593688); 20[j]. Primary pharmacokinetic data: 21–23 |
| Glatiramer acetate | rs333 (*CCR5*Δ32); del vs insertion | Efficacy | Candidate-gene case–control study (9 polymorphisms), single centre (Moscow City MS Centre), Russia; European (Russian) ancestry; 285 MS patients, GA subset: 130 responders vs 84 non-responders | Responder vs non-responder on GA over ≥2 years of treatment, by clinical criteria | OR 0.065 [0.008–0.52], p = 0.013 — estimate for the allelic combination, not for the single variant[c] | None (single study, no independent cohort) | Yes | No clinical annotation (variant annotation only) | 24 |
| | rs6498169 (*CLEC16A*); A vs G | Efficacy | Candidate-gene study of 17 GWAS-identified immune loci, single centre (Pirogov RNRMU, Moscow), Russia; European (Russian) ancestry; 296 MS patients, GA subset: 133 responders vs 163 non-responders + intermediate responders | Optimal GA treatment response sustained for at least 2 years | OR 2.86 [1.42–5.75], p = 0.024; significant after correction for multiple testing | None (single study, no independent cohort) | Yes | No clinical annotation (variant annotation only) | 25 |
| | rs2371108 (*EOMES*); T vs G | Efficacy | Candidate-gene study of 17 GWAS-identified immune loci, single centre (Pirogov RNRMU, Moscow), Russia; European (Russian) ancestry; 296 MS patients, GA subset: 133 responders vs 163 non-responders + intermediate responders | Optimal GA treatment response sustained for at least 2 years | OR 2.34 [1.39–3.96], p = 0.018; significant after correction for multiple testing | None (single study, no independent cohort) | Yes | No clinical annotation (variant annotation only) | 25 |
| | HLA-DRB1*15:01 | Efficacy (reduced) | Candidate-gene case–control study (9 polymorphisms), single centre (Moscow City MS Centre), Russia; European (Russian) ancestry; 285 MS patients, GA subset: 130 responders vs 84 non-responders | Responder vs non-responder on GA over ≥2 years of treatment, by clinical criteria | OR 0.072 [0.002–0.28], p = 0.0056 — estimate for the allelic combination[c] | None (single study, no independent cohort) | Yes | No clinical annotation (variant annotation only) | 24 |
| | HLA-A*03:01 † | Efficacy (enhanced) | T-cell receptor β sequencing in 3,021 patients (discovery 1,627, of whom 204 GA-treated; validation 1,394, of whom 424 GA-treated); clinical analysis in 1,987 GA- or IFNβ-treated patients from the NationMS, ACP, EPIC, BIONAT and CombiRx cohorts; European ancestry | Relapse risk under GA compared with IFNβ in carriers vs non-carriers | OR 0.67 [0.47–0.96], p = 0.027; 33–63% relative reduction in relapse risk across cohorts | Yes — validated in an independent cohort and across five clinical trial cohorts | Yes | Not in ClinPGx (recent literature) | 26 |

*(Continued)*





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TABLE 2 Continued

| Drug | Variant (gene); genotype comparison | Phenotype category | Study design, cohort size and reported ancestry | Ndpoint as defined in the original study | Effect size and p-value | Replication status | MS-specific? | Evidence level (ClinPGx) | Reference (PMID) |
|---|---|---|---|---|---|---|---|---|---|
| | rs1012335 (*IFNAR1*); G vs C | Efficacy | Candidate-gene case–control study (9 polymorphisms), single centre (Moscow City MS Centre), Russia; European (Russian) ancestry; 285 MS patients, GA subset: 130 responders vs 84 non-responders | Responder vs non-responder on GA over ≥2 years of treatment, by clinical criteria | OR 0.072 [0.02–0.28], p = 0.0056 — estimate for the allelic combination[c] | None (single study, no independent cohort) | Yes | No clinical annotation (variant annotation only) | 24 |
| | rs2114358 (*PVT1*); A vs G | Efficacy | As above (same cohort), 133 responders vs 89 non-responders | Optimal GA treatment response sustained for at least 2 years | OR 2.77 [1.33–5.77], p = 0.045; significant after correction for multiple testing | None (single study, no independent cohort) | Yes | No clinical annotation (variant annotation only) | 25 |
| | rs1800469 (*TGFB1*); A vs G | Efficacy | Candidate-gene case–control study (9 polymorphisms), single centre (Moscow City MS Centre), Russia; European (Russian) ancestry; 285 MS patients, GA subset: 130 responders vs 84 non-responders | Responder vs non-responder on GA over ≥2 years of treatment, by clinical criteria | OR 0.43 [0.23–0.81], p = 0.049 — significant only in combination with HLA-DRB1*15[c] | None (single study, no independent cohort) | Yes | No clinical annotation (variant annotation only) | 24 |
| | rs2053696 (*MAP3K1*) †; A allele | Efficacy (GWAS) | Multicentre GWAS with meta-analysis across centres; 679 GA-treated and 1,614 IFNβ-treated RRMS patients; European ancestry | Relapse count during treatment, modelled by negative binomial regression | $p = 3.97 \times 10^{-9}$ (genome-wide significant); no odds ratio reported | None reported: discovery meta-analysis without an independent replication cohort | Yes | Not in ClinPGx (recent literature) | 27 |
| | rs1056854 (*TGFB1* region); T vs G | Toxicity | Meta-analysis of coronary artery disease (CAD) GWAS datasets (CHARGE, deCODE CAD, EPIC, MORGAM and others): up to 60,801 CAD cases and 123,504 controls (ClinPGx records 82,735/199,591); ancestry not reported; no glatiramer-treated patient was studied[d] | Coronary artery disease risk, in 200-kb windows around genes reported to interact with glatiramer acetate | OR 1.06 [1.04–1.08], $p = 2.21 \times 10^{-6}$ | Signal derived within a CAD GWAS meta-analysis; never tested in GA-treated patients | No — no treated patient studied | 3 | 28 |
| | rs12459996 (*TGFB1* regulatory region); T vs G | Toxicity | Meta-analysis of coronary artery disease (CAD) GWAS datasets (CHARGE, deCODE CAD, EPIC, MORGAM and others): up to 60,801 CAD cases and 123,504 controls (ClinPGx records 82,735/199,591); ancestry not reported; no glatiramer-treated patient was studied[d] | Coronary artery disease risk, in 200-kb windows around genes reported to interact with glatiramer acetate | OR 1.09 [1.06–1.12], $p = 1.58 \times 10^{-12}$ | Signal derived within a CAD GWAS meta-analysis; never tested in GA-treated patients | No — no treated patient studied | 3 | 28 |

*(Continued)*





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TABLE 2 Continued

| Drug | Variant (gene); genotype comparison | Phenotype category | Study design, cohort size and reported ancestry | Ndpoint as defined in the original study | Effect size and p-value | Replication status | MS-specific? | Evidence level (ClinPGx) | Reference (PMID) |
|---|---|---|---|---|---|---|---|---|---|
| | rs75041078 (*TMEM91*); risk allele | Toxicity | Meta-analysis of coronary artery disease (CAD) GWAS datasets (CHARGE, deCODE CAD, EPIC, MORGAM and others): up to 60,801 CAD cases and 123,504 controls (ClinPGx records 82,735/199,591); ancestry not reported; no glatiramer-treated patient was studied[d] | Coronary artery disease risk, in 200-kb windows around genes reported to interact with glatiramer acetate | OR 1.06 [1.04–1.09], $p = 4.05 \times 10^{-10}$ | Signal derived within a CAD GWAS meta-analysis; never tested in GA-treated patients | No — no treated patient studied | 3 | 28 |
| Interferon beta-1a | rs1799752 (*ACE* I/D); del/del vs others | Efficacy | Candidate-gene study described by the authors as a preliminary report, single centre (Rijeka), Croatia; European ancestry; 275 IFNβ-treated patients (64 men, 211 women) | Negative IFNβ response by multiple forward regression analysis | p = 0.009 in men (n = 64); null in women (n = 211, p = 0.817)[e] | None (single study, no independent cohort) | Yes | No clinical annotation (variant annotation only) | 29 |
| | HLA-B*15:01 | Efficacy | Candidate HLA typing, single centre, Iran; Near Eastern (Iranian) ancestry; 231 RRMS patients (146 responders, 85 non-responders) and 180 ethnically matched controls | Responder vs non-responder to IFNβ-1a (absence of sustained progression and of relapses) | OR 0.29 [0.1–0.84], p = 0.03 | None (single study, no independent cohort) | Yes | 3 | 30 |
| | HLA-DRB1*04:01 | Efficacy | Candidate HLA typing, single centre, Iran; Near Eastern (Iranian) ancestry; 231 RRMS patients (146 responders, 85 non-responders) and 180 ethnically matched controls | Responder vs non-responder to IFNβ-1a (absence of sustained progression and of relapses) | OR 1.94 [1.19–3.17], p = 0.008 | None (single study, no independent cohort) | Yes | 3 | 30 |
| | rs4774388 (*RORA*); TT vs CC+CT | Efficacy | Candidate-gene study (2 polymorphisms), Iran; Near Eastern (Iranian) ancestry; 105 responders, 65 non-responders and 200 healthy controls | Genotype frequency in non-responders compared with healthy controls (dominant model)[f] | p = 0.03; no odds ratio reported | None (single study, no independent cohort) | Yes | 3 | 31 |
| Interferon beta-1a and -1b | rs12044852 (*CD58*); CC vs AA+AC | Efficacy | Candidate-gene study, single centre (Tehran), Iran; Near Eastern (Iranian) ancestry; 120 IFNβ-treated patients | Increase in the Multiple Sclerosis Severity Score over 2 years of follow-up | $p \leq 0.05$; no odds ratio reported | None (single study, no independent cohort) | Yes | 3 | 32 |
| | rs760316 (*FHIT*); C vs T | Efficacy | Two-stage GWAS: discovery in 151 Australian MS patients (51 responders, 24 intermediate, 76 non-responders), validation in 479 IFNβ-treated patients from Australia, Spain and Italy (273 responders, 206 non-responders); European ancestry | Responder vs non-responder to IFNβ after up to 2 years of clinical follow-up | $p = 6.74 \times 10^{-6}$; no odds ratio reported (discovery and validation combined)[g] | Partial: carried from discovery into an independent validation cohort, but no SNP reached the Bonferroni genome-wide threshold | Yes | 3 | 33 |

*(Continued)*





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TABLE 2 Continued

| Drug | Variant (gene); genotype comparison | Phenotype category | Study design, cohort size and reported ancestry | Ndpoint as defined in the original study | Effect size and p-value | Replication status | MS-specific? | Evidence level (ClinPGx) | Reference (PMID) |
|---|---|---|---|---|---|---|---|---|---|
| | rs10760397 (*GAPVD1*); C vs T | Efficacy | Two-stage GWAS: discovery in 151 Australian MS patients (51 responders, 24 intermediate, 76 non-responders), validation in 479 IFNβ-treated patients from Australia, Spain and Italy (273 responders, 206 non-responders); European ancestry | Responder vs non-responder to IFNβ after up to 2 years of clinical follow-up | $p = 6.51 \times 10^{-5}$; no odds ratio reported (combined)[g] | Partial: carried from discovery into an independent validation cohort, but no SNP reached the Bonferroni genome-wide threshold | Yes | 3 | 33 |
| | rs9828519 (*SLC9A9*) †; G allele | Efficacy (GWAS) | GWAS in IFNβ-treated MS patients followed by validation in three independent cohorts; European ancestry | Non-response to IFNβ (persistent disease activity during treatment) | Discovery $p = 4.43 \times 10^{-8}$; replication meta-analysis $p = 7.78 \times 10^{-4}$ | Yes — confirmed in a meta-analysis across three independent replication datasets | Yes | Not in ClinPGx (recent literature) | 34 |
| | rs9272105 (*HLA-DQA1*); G vs A | Immunogenicity[h] | Genome-wide genotyping in 362 patients (178 antibody-positive, 184 antibody-negative) with validation in an independent cohort of 350 antibody-positive and 468 antibody-negative patients (combined 528/652); Germany, European ancestry | Development of (neutralizing) anti-IFNβ antibodies during therapy | $p = 3.5 \times 10^{-10}$ (combined discovery and replication) | Yes — validated in an independent cohort | Yes | 3 | 35 |
| | rs10494227 (*ZNF697*); risk allele | Efficacy | Two-stage GWAS: discovery in 151 Australian MS patients (51 responders, 24 intermediate, 76 non-responders), validation in 479 IFNβ-treated patients from Australia, Spain and Italy (273 responders, 206 non-responders); European ancestry | Responder vs non-responder to IFNβ after up to 2 years of clinical follow-up | OR 4.82 [1.98–11.7], $p = 1.96 \times 10^{-4}$ as tabulated; ClinPGx records $p = 8.15 \times 10^{-5}$[g] | Partial: carried from discovery into an independent validation cohort, but no SNP reached the Bonferroni genome-wide threshold | Yes | 3 | 33 |
| | HLA DR15-DQ6 haplotype † | Immunogenicity (IFNβ-1a sc) | GWAS on anti-drug antibodies in 2,757 genotyped and imputed patients from two cohorts (Sweden and Germany) split into discovery and replication sets; European ancestry | Binding anti-drug antibody levels (capture-ELISA) and neutralizing antibody titres (bioassay), analysed by IFNβ preparation | OR 2.88 [2.29–3.61], $p = 7.4 \times 10^{-20}$ | Yes — discovery and replication sets within the study, two countries | Yes | Not in ClinPGx (recent literature) | 36 |
| | HLA DR4-DQ3 haplotype † | Immunogenicity (IFNβ-1b sc) | GWAS on anti-drug antibodies in 2,757 genotyped and imputed patients from two cohorts (Sweden and Germany) split into discovery and replication sets; European ancestry | Binding anti-drug antibody levels (capture-ELISA) and neutralizing antibody titres (bioassay), analysed by IFNβ preparation | OR 7.35 [4.33–12.47], $p = 1.5 \times 10^{-13}$ | Yes — discovery and replication sets within the study, two countries | Yes | Not in ClinPGx (recent literature) | 36 |

*(Continued)*





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TABLE 2 Continued

| Drug | Variant (gene); genotype comparison | Phenotype category | Study design, cohort size and reported ancestry | Ndpoint as defined in the original study | Effect size and p-value | Replication status | MS-specific? | Evidence level (ClinPGx) | Reference (PMID) |
|---|---|---|---|---|---|---|---|---|---|
| | rs2205986 (*IRF6*); G vs A | Toxicity (liver) | Two-stage GWAS; combined analysis of 56 cases and 126 controls, plus an independent cohort identified through electronic medical records; Canada, European ancestry | IFNβ-induced liver injury; in the independent cohort, peak aspartate aminotransferase and alkaline phosphatase levels | OR 8.3 [3.6–19.2], $p = 2.3 \times 10^{-8}$ (genome-wide significant in the combined two-stage analysis) | Yes — genome-wide significant across two stages and supported in an independent EMR-based cohort (AST $p = 7.6 \times 10^{-5}$; ALP $p = 4.9 \times 10^{-4}$) | Yes | 3 | 37 |
| | rs738409 (*PNPLA3*) †; C>G | Toxicity (liver) | Retrospective multicentre candidate-gene study (5 polymorphisms in hepatic lipid-metabolism genes), Italy; European ancestry; 113 MS patients, 29 with liver toxicity | Occurrence of IFNβ-induced liver toxicity | Significant in logistic regression ($p < 0.05$); no odds ratio reported in the abstract | None described by the authors as an exploratory study | Yes | Not in ClinPGx (recent literature) | 38 |

★ Level 1A evidence (regulatory guideline); †New findings from recent literature (not in original ClinPGx search).

For every association the table reports the study design, cohort size and reported ancestry, the endpoint as defined in the original publication, the effect estimate with its p-value, the replication status, whether the finding was obtained in multiple sclerosis patients, the ClinPGx level of evidence and the primary publication with its PMID. Data were retrieved from ClinPGx (https://clinpgx.org, accessed 16 October 2026) and each entry was checked against the primary publication.

ADA, anti-drug antibodies; ALP, alkaline phosphatase; AST, aspartate aminotransferase; AUC, area under the concentration–time curve; CAD, coronary artery disease; CI, confidence interval; DMT, disease-modifying therapy; DPWG, Dutch Pharmacogenetics Working Group; EMR, electronic medical records; GA, glatiramer acetate; GWAS, genome-wide association study; IFNβ, interferon-β; MS, multiple sclerosis; OR, odds ratio; PK, pharmacokinetics; RRMS, relapsing-remitting multiple sclerosis; sc, subcutaneous.

at genome-wide significance ($p = 3.97 \times 10^{-9}$), implicating MAPK-mediated signaling in GA responsiveness (27). A key advance from a retrospective analysis across five MS cohorts (n = 3,021 patients) revealed that HLA-A*03:01 carriers specifically benefit from GA versus interferon-β, showing a 33–63% relative reduction in relapse risk (OR/HR 0.37–0.67; 26, 27). This HLA-based stratification could enable a personalized choice between two first-line platform therapies. The HLA-DRB1*15:01 allele — a major MS-risk allele — paradoxically reduces GA efficacy, reinforcing the interplay between disease susceptibility genetics and treatment outcomes. Additional loci including CLEC16A (rs6498169) and IFNAR1 (rs1012335) are under investigation for their role in modulating GA responsiveness.

For interferon-β (IFNβ), beyond the efficacy and toxicity associations in Table 2, a clinically relevant dimension concerns immunogenicity: up to 40% of patients develop neutralizing antibodies (NAbs) that impair drug efficacy. A large GWAS of 2,757 IFNβ-treated MS patients (36) demonstrated that NAb risk is both strongly HLA-dependent and preparation-specific: the HLA DR15-DQ6 haplotype confers risk for IFNβ-1a subcutaneous (OR = 2.88; $p = 7.4 \times 10^{-20}$), while HLA DR4-DQ3 is the major risk haplotype for IFNβ-1b subcutaneous (OR = 7.35; $p = 1.5 \times 10^{-13}$). Genetic prediction models for NAb development achieved AUC of 0.83–0.91, suggesting real clinical potential for pre-treatment genotyping. Additionally, the intronic *SLC9A9* variant rs9828519 — identified by GWAS and replicated in three independent cohorts — is associated with IFNβ non-response and appears to influence T-cell differentiation toward a proinflammatory phenotype (34). Furthermore, the CTLA-4 + 49 A/G polymorphism predicts favorable IFNβ response specifically in female patients, with the AA genotype combined with CCR5Δ32 wt/wt providing additive predictive value (41). For IFNβ-associated liver toxicity, *PNPLA3* rs738409 has been identified as an independent predictor of hepatotoxicity, complementing the IRF6 rs2205986 signal reported in Table 2 (38).

## Clinical relevance of pharmacogenetic findings

The identification of pharmacogenetic variants with potential impact on treatment efficacy, toxicity, or metabolism represents a promising step toward personalized care in MS. Although only CYP2C9 haplotypes influencing siponimod metabolism currently meet high-confidence criteria (ClinPGx Level 1A evidence) and is supported by regulatory guidelines for clinical genotyping, numerous additional variants show preliminary yet biologically plausible associations with drug response.

Variants affecting immune function and antigen presentation, such as HLA-DRB1*15:01, HLA-DRB1*04:01, and IFNAR1 (rs1012335), have been associated with differential responses to IFNβ and glatiramer acetate. These associations, while not yet implemented in clinical practice, suggest the possibility of genotype-driven stratification for first-line therapy. The emerging evidence for HLA-A*03:01 as a predictor of GA response over IFNβ is particularly noteworthy, as it is derived from large independent cohorts and reflects a biologically coherent mechanism through

CD8+ T-cell receptor repertoire selection (26). Similarly, MAP3K1 represents the first genome-wide significant pharmacogenetic locus for GA, highlighting the role of MAPK signaling in treatment response.

Toxicity-related variants highlight the role of pharmacogenetics in preventing adverse effects. TGFB1 regulatory polymorphisms (rs1056854, rs12459996) show strong statistical associations with increased toxicity risk in glatiramer acetate-treated patients. For IFNβ-treated patients, both IRF6 (rs2205986, genome-wide significant) and PNPLA3 (rs738409) predict liver injury risk. These markers could aid in identifying individuals at higher risk for drug-related hepatotoxicity before treatment initiation.

Importantly, many identified variants map to genes involved in immune regulation (e.g., CLEC16A, EOMES, RORA) or signal transduction, offering biologically credible links to MS pathophysiology and treatment mechanisms. While most findings are supported by Level 3 evidence from small or single-cohort studies, they offer valuable hypotheses for validation in larger, well-powered clinical trials. Beyond MS-specific data, variants from other disease contexts suggest additional candidate markers for high-efficacy therapies such as cladribine, alemtuzumab, and dimethyl fumarate.

## High-efficacy disease-modifying therapies

High-efficacy DMTs (HE-DMTs) reduce inflammatory activity and disease progression in MS (42). Among these, natalizumab stands out for its high efficacy, although this is offset by the risk of progressive multifocal leukoencephalopathy (PML) in JC virus-positive individuals. While JCV antibody status — which is itself under host genetic control, being strongly associated with HLA class II variants (43) — remains the primary tool for PML risk stratification, emerging germline data suggest that rare variants in immune function genes (e.g., *C8B*, *LY9*, *FCN2*) may identify individuals at substantially higher risk for PML when drug-exposed (OR = 8.7; 44). Regarding pharmacodynamic response to natalizumab, FcγR polymorphisms are emerging as predictors: FCGR2A AG and FCGR3A AC genotypes were associated with a significantly lower odds of therapeutic failure (OR = 0.044 and 0.077, respectively) in a cohort of 116 natalizumab-treated MS patients (45).

For anti-CD20 therapies — ocrelizumab, ofatumumab, and ublituximab — a class-level pharmacogenetic signal has been identified in *FCGR3A*, building on earlier evidence from rituximab pharmacogenetics in oncology (46). The V158F polymorphism (rs396991) influences FcγRIIIa binding affinity, directly affecting antibody-dependent cell-mediated cytotoxicity (ADCC), the primary mechanism of B-cell depletion. In MS patients treated with ocrelizumab, FCGR3A F-carrier status significantly modifies B-cell repopulation kinetics: F-carriers show a significantly higher odds of B-cell repopulation with longer infusion intervals (OR = 3.67; $p = 0.00023$), while VV individuals do not (47). This effect is mechanistically supported by ex vivo evidence of reduced ocrelizumab binding to NK cells from FCGR3A-FF donors ($p = 4.34 \times 10^{-4}$). Importantly, ublituximab is glycoengineered with reduced fucosylation, enhancing FcγRIIIa affinity and partially overcoming the V158F polymorphism effect — a rare example of a drug specifically designed to mitigate a pharmacogenetic limitation (48, 49). While current data are insufficient for clinical genotyping recommendations for anti-CD20 therapies, FCGR3A represents the most biologically compelling candidate pharmacogenetic marker for this drug class.

For fingolimod, exploratory evidence suggests that variants in CYP4F2 and CYP2C9 may influence drug metabolism and plasma levels, with potential implications for safety and tolerability including bradycardia risk, though these associations await independent replication. Computational analyses of S1PR1 coding variants suggest potential modulation of pharmacodynamic response (50). Cladribine's pharmacogenetic profile remains under investigation, with interindividual differences in deoxycytidine kinase (DCK) and 5'-nucleotidase (NT5C1A) activity potentially influencing drug activation (51). Alemtuzumab is associated with secondary autoimmunity in a significant subset of patients; IL-21 polymorphisms may contribute to this susceptibility, though no validated predictive markers exist (52). Finally, azathioprine — used off-label in MS particularly in resource-limited settings — is associated with well-characterized pharmacogenetic risk through TPMT and NUDT15 variants, which predict myelosuppression risk and are covered by CPIC/DPWG actionable guidelines in other settings, though MS-specific validation data remain limited.

Collectively, these examples highlight the emerging relevance of integrating genetic profiling into therapeutic decision-making, particularly when balancing early efficacy against long-term safety risks.

## Opportunities for implementation in clinical practice

The implementation of pharmacogenetic testing in MS care holds great promise, but its current application remains limited. Specifically, genotyping for CYP2C9 variants is required to identify individuals with reduced metabolic capacity, for whom dose adjustment of siponimod — or treatment exclusion in the case of poor metabolizers — is necessary. This example illustrates the potential of pharmacogenetics to enhance treatment safety and efficacy when strong evidence supports a clear genotype-phenotype relationship.

These considerations are particularly relevant for the aging MS population. While MS onset typically occurs in young adulthood, patients increasingly age with their disease; SPMS — the progressive subtype for which siponimod is specifically approved — disproportionately affects older individuals. In this population, age-related declines in hepatic and renal function can alter drug pharmacokinetics and amplify the clinical impact of pharmacogenetic variants on drug exposure and toxicity risk. Furthermore, aging patients with MS more frequently present comorbidities requiring polypharmacy, raising the potential for pharmacokinetic drug–drug interactions mediated through shared metabolic pathways — most notably CYP2C9 and CYP3A4. Emerging pharmacogenetic markers for anti-CD20 therapies (FCGR3A V158F) and for IFNβ immunogenicity (HLA haplotypes) are also gaining relevance in older patients increasingly exposed to these drugs. Pharmacogenetic profiling may therefore provide additive clinical value in aging MS patients beyond standard clinical assessment, supporting safer and more individualized treatment decisions in this growing subgroup.

However, no other DMT currently benefits from clinically actionable pharmacogenetic guidelines, despite the identification

of numerous genetic associations with drug efficacy or toxicity. Most of these associations remain at an early stage of evidence (ClinPGx Level 3). As such, there is a pressing need for larger, well-designed studies specifically focused on pharmacogenetic predictors of MS treatment response. The recent multicenter GWAS for GA response (26, 27) and the large GWAS on IFNβ immunogenicity (36) exemplify the kind of evidence needed to move from exploratory findings to clinically actionable markers.

In this context, real-world data (RWD) represents a valuable, yet underutilized, resource. Ongoing pharmacovigilance initiatives, post-marketing surveillance studies, and clinical registries collect vast amounts of data on treatment outcomes, adverse events, and patient-reported efficacy under routine care conditions. By integrating pharmacogenetic data with longitudinal clinical outcomes, the goal should be to identify clinically meaningful predictors of treatment response or intolerance. Furthermore, pharmacogenetic testing across different DMT classes and patient subgroups, including underrepresented populations, is crucial.

To translate pharmacogenetic discoveries into clinical practice, several steps are needed: (1) validation of promising variants in independent, well-characterized MS cohorts; (2) standardization of genotyping protocols and reporting; (3) development of decision-support tools to guide treatment selection based on genetic profiles; and (4) incorporation of pharmacogenetics into national and international MS management guidelines.

## Limitations

Several methodological limitations of the reviewed evidence deserve systematic consideration. First, the vast majority of pharmacogenetic associations identified in this review lack independent replication: most findings derive from single-cohort or case-control studies with small sample sizes (typically fewer than 500 participants), limiting their clinical reproducibility. Second, population stratification is a critical concern, as most studies were conducted in predominantly European ancestry cohorts, restricting the generalizability of identified markers to non-European populations in whom allele frequencies and linkage disequilibrium patterns may differ substantially. Third, the heterogeneity of outcome definitions across studies — including relapse rate, NEDA-3 status, MRI lesion counts, EDSS progression, and surrogate markers such as neutralizing antibody titres — makes cross-study comparisons unreliable and hampers meaningful evidence synthesis. Fourth, variability in treatment exposure, including differences in follow-up duration, dosing regimens, and prior treatment history, further complicates the interpretation of pharmacogenetic signals. Finally, the cross-disease associations reported in Supplementary Table S1 were derived from non-MS populations and involve drugs whose pharmacological context and patient characteristics may differ meaningfully from the MS setting, as explicitly noted for the alemtuzumab/CXCL12 example. These limitations collectively underscore the preliminary nature of most reported associations and highlight the current scarcity of pharmacogenetic markers that are ready for clinical implementation in MS.

## Conclusions and future perspectives

This review provides an updated overview of pharmacogenetic variants relevant to MS treatment, highlighting both opportunities and current limitations. Unfortunately, most reported associations are supported by low-level evidence, often derived from small, single-cohort studies which lack replication, restricting their utility for clinical applicability. This underscores the need for further pharmacogenetic studies to clarify the potential utility of these findings.

Notable progress has been made in several areas. For glatiramer acetate, HLA-A*03:01 offers a biologically grounded rationale for personalized choice between platform therapies, while MAP3K1 represents the first genome-wide significant pharmacogenetic locus for this drug. For interferon-β, HLA-based prediction of immunogenicity achieves clinically meaningful accuracy (AUC 0.83–0.91), potentially enabling pre-treatment risk stratification for NAb development. For anti-CD20 therapies, FCGR3A V158F is emerging as a class-level pharmacogenetic signal with therapeutic design implications, as exemplified by the development of ublituximab to overcome this polymorphism. These findings, if replicated and validated, could substantially advance precision medicine in MS.

The complexity of defining and measuring treatment response in MS, along with heterogeneity in therapeutic mechanisms and patient profiles, poses additional challenges. Current reliance on endpoints such as NEDA or relapse rates may not fully reflect the variability of treatment effects or subclinical disease progression. Overall, these limitations underscore the need for standardized response criteria, longitudinal evaluation frameworks, and integration of multimodal outcome measures encompassing clinical, imaging, and biological data.

Future efforts should focus on large-scale, well-powered pharmacogenetic studies in MS patients, covering diverse therapeutic classes and clinical phenotypes. These studies should aim not only to identify predictive variants but also to validate their clinical utility through prospective, genotype-guided trials. Multidisciplinary frameworks incorporating pharmacogenomics, pharmacokinetics, clinical pharmacology, and real-world data analytics are key to bridging the gap between research and practice. Coordinated efforts among researchers, clinicians, regulatory authorities, and patient organizations, alongside clinical decision-support tools, will be critical to realizing personalized medicine goals for MS patients.

## Author contributions

MF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. EZ: Data curation, Software, Writing – review & editing. GF: Methodology, Writing – review & editing. MI: Conceptualization, Writing – review & editing. SM: Investigation, Writing – review & editing. DB: Methodology, Writing – original draft, Writing – review & editing. LL: Conceptualization, Writing – original draft, Writing – review & editing.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2026.2006956/full#supplementary-material

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