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Pharmacogenomics and Multiple Sclerosis: Moving Toward Individualized Medicine

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Abstract Notwithstanding the availability of disease-modifying treatments including interferon-β, glatiramer acetate, and natalizumab, a considerable proportion of multiple sclerosis (MS) patients experience continued progression of disease, clinical relapses, disease activity on MRI, and adverse effects. Application of gene expression, proteomic or genomic approaches is universally accepted as a suitable strategy toward the identification of biomarkers with predictive value for beneficial/poor clinical response to therapy and treatment risks. This review focuses on recent progress in research on the pharmacogenomics of disease-modifying therapies for MS. Although MS drug response biomarkers are not yet routinely implemented in the clinic, the diversity of reported, promising molecular markers is rapidly increasing. Even though most of these markers await further validation, given time, this research is likely to empower neurologists with an enhanced armamentarium to facilitate rational decisions on therapy and patient management.

Keywords Multiple sclerosis · Interferon-β · Glatiramer acetate · Natalizumab · Single nucleotide polymorphism · Biomarker · Genomic · Proteomic · Drug response · Pharmacogenomics · Individualized medicine

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) of unknown etiology that leads to significant neurologic disability in young adults. The disease is typified by a high degree of heterogeneity in the clinical presentation and disease course, brain lesion pathology, and response to therapy. The modern scenario of MS treatment with a rapidly increasing compendium of therapeutic strategies on offer to patients, taken together with the potential risk for treatment failure and adverse drug reactions, sets pharmacogenomics at the forefront of MS research [1]. The basic underlying thought is to establish a rational framework facilitating administration of specific treatments to those patients who will likely respond to it, while avoiding cost- and quality-of-life–related drawbacks associated with the ineffective treatment of patients who either will not respond or develop adverse effects.

Drug response includes the processes of drug absorption and disposition (pharmacokinetics), drug mechanisms of action (pharmacodynamics), drug efficacy, and adverse reactions to drugs. Response to drugs varies considerably between individuals and is, to some extent, determined by genetic factors. Genetic polymorphisms may result in altered expression or activity of proteins that regulate the

pharmacokinetic and pharmacodynamic properties of drugs [2]. In a broad sense, pharmacogenomics can be defined as the study of the variations in the DNA sequence and its products, including RNA and protein, that are related to clinical drug response. One of the main, translational objectives of pharmacogenomics is the individualization of therapy based on quantifiable individual molecular parameters. This review will focus on recent literature (published from 2010 onward) on pharmacogenomic studies carried out in the field of MS that aim to identify markers at the genetic, mRNA, or protein level associated with the response to available therapies for the disease, or with mechanisms of action potentially related to the beneficial effects conferred by these therapies.

Interferon-β (IFN-β) is a first-line disease-modifying therapy for relapsing-remitting (RR) MS that has demonstrated beneficial effects on reducing clinical and radiologic disease activity [3–5]. IFN-β is a pleiotropic cytokine that exerts its biological effects via the binding to a heterodimeric cell surface receptor complex composed of IFNAR1 and IFNAR2 subunits. This interaction activates the JAK-STAT signaling pathway, in turn leading to assembly of IFN-stimulated gene factor 3 (ISGF3) complexes that can translocate into the nucleus to activate transcription of a wide variety of genes via binding to IFN-stimulated response elements (ISREs). In addition, STAT homo- or heterodimers can be formed that bind to IFN-γ activated site (GAS) in target genes. Because many of these IFN-responsive genes are unlikely to be relevant to MS, it is hoped that current pharmacogenomics research applied to IFN-β in MS will be instrumental in discerning the indispensable effector gene sets from the superfluous ones.

Glatiramer acetate (GA) was given US Food and Drug Administration approval in 1996 for the treatment of RRMS; it is a random polymer of four amino acids enriched in myelin basic protein, with established efficacy and safety profile in RRMS [6]. The protective mechanism of action of GA involves a shift of T-cell responses to an anti-inflammatory Th2 phenotype, as well as induction of T cells to secrete brain-derived neurotrophic factor, a cytokine capable of encouraging neuronal survival, remyelination, and nerve regeneration [7]. The humanized monoclonal antibody natalizumab prevents the transmigration of activated T cells into the CNS by binding to the α4-integrin subunit of the very late activation antigen (VLA-4) expressed on leukocytes. Its administration to MS patients has been associated with important reductions in disease activity [8].

The majority of pharmacogenomic studies published in 2010 on MS therapies have been related with IFN-β [for review of earlier studies see ref. 9]. Thus, most of this review will focus on IFN-β while touching on GA and natalizumab.

IFN-β Gene Expression and Proteomic Studies

IFN-β exerts beneficial effects in the majority of patients, but a significant proportion of patients respond poorly to this therapy. Identification of (a) powerful biomarker(s) for IFN-β treatment efficacy, preferably measurable at baseline (ie, before onset of therapy), would shortcut the long period needed to visualize treatment success based on clinical parameters only. IFN-β–induced gene or protein expression patterns that reproducibly diverge in responding versus nonresponding patients may embody the requirements of successful surrogate markers [10].

The effects of neutralizing antibodies (NAbs) formed upon administration of recombinant IFN-β have been scrutinized but are, as yet, controversial. The amount of injected bioavailable IFN-β correlates with whole-blood MX1 mRNA levels, a biomarker for quantification of the biological response to IFN-β treatment. MX1 levels are reduced once IFN-β NAbs have developed [11]. In 2009, a group of experts guided by the FP6 "Neutralizing Antibodies to Interferon-β in MS (NABINMS)" consortium concluded that sustained high titers of NAbs or lack of MX1 bioactivity are associated with frequent relapses and worse disease progression [12], and should therefore constitute inclusive criteria for managing MS treatment decisions. At any rate, most pharmacogenomics studies to date have not systematically considered the presence of NAbs, which may confound the relationship between any putative treatment efficacy markers found and success of therapy.

Three transcriptomic studies published in 2010 pursued the identification of IFN-β treatment-related biomarkers by means of DNA microarrays [13–15]. In a study by Hecker et al. [13], the authors analyzed the transcriptional profile present in peripheral blood mononuclear cells (PBMCs) from MS patients before and after 1 and 4 weeks of treatment with intramuscular IFN-β-1a (Avonex; Biogen Idec, Weston, MA). A total of 121 genes were significantly differentially expressed (up- or downregulated), mostly genes with immune-related functions, as revealed by gene ontology analysis. Binding site analysis showed enrichment for 11 transcription factors, which connected a high percentage of the total number of differentially expressed genes. Interestingly, a small subgroup of genes that were overexpressed in patients with flu-like symptoms formed a regulatory subnetwork with high representation of binding sites for nuclear factor-κB. In two similar studies by the same group [14, 15], the authors investigated the gene expression levels observed in PBMCs from MS patients at baseline and after 2 days, 1 month, and 1 year of treatment with subcutaneous IFN-β-1b (Betaferon; Bayer HealthCare Pharmaceuticals, Wayne, NJ). In the study by Goertsches et al. [14], a later time point at 24 months post-therapy was

also analyzed. In the first study [15], 15 transcripts, mostly type I IFN-responsive genes, were differentially expressed at all time points. In the second study [14], 19 genes were found to be consistently modulated by treatment throughout the analyzed time period. Interestingly, in both studies top candidate transcripts followed similar time course expression patterns, with a modest increase in the expression after 2 days of treatment, peak induction at 1 month, and later reduction in their expression at 1 and 2 years of therapy. Intersection of differentially expressed genes revealed nine type I IFN-responsive genes (*IFI44, IFI44L, IFIT1, IFIT2, IFIT3, ISG15, MX1, RSAD2, EIF2AK2*) that were consistently regulated by IFN-β-1b at all time points. These three transcriptomic studies underscore the complex and pleiotropic actions of IFN-β, a drug whose precise mechanism of action in the disease is not yet fully understood.

Three studies focused on the changes induced by IFN-β either in the levels of candidate immune biomarkers [16, 17] or in the expansion of specific T-cell populations [18]. In a longitudinal study on MS patients receiving treatment with subcutaneous IFN-β-1b (Betaferon), Alexander et al. [16] analyzed the effects of treatment on serum levels of a panel of matrix metalloproteinases (MMP-8, MMP-9, and tissue inhibitor of metalloproteinase-1 [TIMP-1]) and proinflammatory cytokines (interleukin [IL]-12 p40, IL-17, and IL-23). Whereas no significant changes were observed for TIMP-1 and IL-17, treatment with IFN-β was associated with a reduction in the levels of MMP-8, MMP-9, IL-12 p40, and IL-23 at 6 and 12 months post-therapy. Tran et al. [17] reported specific induction of the negative regulator of G-protein signaling RGS1 by IFN-β. Of note, this finding has not been reported previously and suggests an attractive link between type I IFNs and chemokine signaling. Finally, Namdar et al. [18] observed a significant increase in the frequency and suppressive activity of $CD4^+CD25^+Foxp3^+$ regulatory T cells in MS patients treated with IFN-β for 6 months, likely associated with the beneficial effect of the drug.

Balashov et al. [19] proposed a novel mechanism of action of IFN-β, which extends the long list of pleiotropic actions reported for this cytokine. These authors isolated plasmacytoid dendritic cells (pDCs) from PBMCs of untreated and IFN-β–treated MS patients and controls to investigate the effect of IFN-β on the expression of Toll-like receptor 9 (TLR9). Whereas expression levels of the full-length unprocessed TLR9 were similar in pDCs from untreated and treated patients, expression of the processed and functionally active TLR9 C-terminal form was found to be significantly decreased by IFN-β treatment.

Finally, two studies proposed IL-17 and IgM oligoclonal bands as biomarkers of response to IFN-β [20•, 21]. Axtell et al. [20•] identified a subgroup of IFN-β nonresponders (defined by the relapse rate and steroid usage) characterized by the presence of high serum levels of IL-17 F and IFN-β before treatment. These findings are in agreement with a previous study showing baseline overexpression of type I IFN-responsive genes in nonresponders to IFN-β [22•, 23]. In a prospective study, Bosca et al. [21] determined lipid-specific IgM oligoclonal bands in cerebrospinal fluid (CSF) samples from patients with RRMS before initiating treatment with IFN-β. Interestingly, during treatment, patients with lipid-specific IgM oligoclonal bands had a lower reduction in the relapse rate, shorter time to a first relapse, and had a lower percentage of relapse-free patients compared to treated patients without CSF lipid-specific IgM oligoclonal bands.

Use of proteinaceous biomarkers of clinical utility found in the serum or plasma of treated patients may overcome some of the technical difficulties related to gene expression markers. By means of two-dimensional difference gel electrophoresis coupled to a proteomics approach, Gandhi et al. [24] identified biomarkers associated with the response to IFN-β treatment. Three proteins were significantly more abundant in plasma samples from clinical responders to IFN-β compared with nonresponders: α2 macroglobulin, apolipoprotein A1, and fibrinogen B. Fibrinogen B has not previously been reported to be associated with either IFN-β treatment or MS. In the same study, a nonsignificant trend toward elevated serum IL-6 levels was observed in clinical responders, in support of earlier findings [9].

The above studies describe a number of genes of which the products show previously unrecognized modified and/or time-dependent regulation by IFN-β in MS patients, or tend to segregate with response to therapy. When added to those identified in earlier studies [9] as well as to putative markers of disease progression, the challenge is to characterize the regulatory cascades and functional mechanisms by which these markers are implicated in IFN-β treatment efficacy or disease pathogenesis. Multi-analytical approaches such as systems biology that integrate genomic and clinical data have been proposed as key tools for this endeavor to be ultimately successful [14, 25].

Single Nucleotide Polymorphisms as Determinants of IFN-β or GA Response

In contrast to gene or protein expression profiles, single nucleotide polymorphisms (SNPs) are mostly bi-allelic nucleotide variants embedded in the genome that, depending on their location, may affect transcription, stability, splicing of mRNA, or activity of encoded proteins. When occurring within specific DNA sequences (eg, ISREs, GAS, mRNA stabilizing elements, etc.), they may alter various aspects of gene regulation by type I IFN. If the concerned

gene is involved in the control of disease progression in MS, such SNPs may ultimately (co-)determine treatment success in MS. Compared with gene or protein expression biomarkers, the potential for routine implementation of response-predictive SNPs in the clinic is more appealing for a variety of reasons including stability of DNA, lack of marker fluctuation over time and according to cell type, and cost-effectiveness of genotyping, as well as limited invasiveness to patients, given that DNA can easily be recovered via a mouth swab [26]. Studies identifying SNPs in pharmacogenomics studies on IFN-β in MS published prior to 2010 have been reviewed recently [27].

Using retrospectively assembled data sets of GA- or IFN-β–treated patients, Gross et al. [28•] showed that the hazard rate of an event in either treatment group (defined as either clinical relapse, change in T2 hyperintense lesion burden or presence of gadolinium-enhancing lesion on MRI, or increase of Expanded Disability Status Scale [EDSS] by 1 point sustained over 6 months) is not constant but appeared to decrease over the first years of treatment. This was interpreted so as to be indicative for the presence of distinct subsets in the treated patient groups that vary in probability of contracting early inflammatory events. These authors investigated whether allelic variants in two genes, *HLA-DRB1*1501* (rs3135388, proxy) and *IRF8* (rs17445836), modulated the duration of event-free interval. Although both these genes are genetic risk loci for MS, HLA class II gene products are purported to play a central role in the mechanism of action of GA [28•], and *IRF8* rs17445836 is associated with increased mRNA transcription of type I IFN response genes in peripheral blood [29]. In the GA-treated group, homozygotes for the A allele of rs3135388 experienced a significantly longer event-free survival than AG heterozygotes (hazard ratio $(HR)_{AG/AA}$=2.7) or GG homozygotes ($HR_{GG/AA}$=2.2), whereas no such effect was seen in the IFN-β–treated group. Vice versa, homozygotes for the A allele of *IRF8* rs17445836 treated with IFN-β displayed a significantly shorter time to event than carriers of the other genotypes ($HR_{AG/AA}$=0.45; $HR_{GG/AA}$=0.53), and this effect was not present in the GA-treated group. The association of *HLA-DRB1*1501* with better response to GA is in line with a previous report [30], even though a more recent study could not replicate this association in a larger GA-treated MS cohort [31]. The association of *IRF8* rs17445836 could not be replicated in a second, independent cohort of IFN-β–treated patients negative for neutralizing anti-IFN-β antibodies for which only clinical relapse was implemented as measure of event [28•]. However, the variability in the replication of these markers does not necessarily invalidate the existence of true response-modifying effects mediated by *HLA-DRB1*1501* and *IRF8* rs1744583 in GA- and IFN-β–treated MS patients, respectively, but may point to a polygenic effector mechanism jeopardizing penetration of modest single-gene effects in small study data sets and therefore requiring large cohort sizes for robust validation.

IRF5 is a transcription factor that regulates expression of a wide variety of genes through binding to ISREs. Like *IRF8* [29], the *IRF5* gene locus has recently been identified and validated as an MS risk factor [32, 33•]. Two independent studies have assessed association of *IRF5* with clinical response to IFN-β treatment in MS [33•, 34•]. In the first study, two MS-associated SNPs, rs4728142 and rs3807306, were analyzed in two independent cohorts of IFN-β response-stratified MS patients [33•]. Response was defined by lack of clinical relapse or of increases in EDSS monitored over a 2-year period following onset of therapy. The MS-predisposing T allele of rs3807306 was reproducibly although not significantly increased in two cohorts of responders to therapy compared with nonresponders (P=0.09; odds ratio [OR]=1.39) and was, in addition, significantly associated with human herpesvirus 6 (HHV-6)-positive status (P=0.05; OR=1.56). In the second study, treatment response to IFN-β was quantified by absence or appearance of new T2 lesions on MRI, as well as by time to first relapse during IFN-β treatment [34•]. A poor pharmacologic response to IFN-β was found to be associated with the *IRF5* rs2004640 TT (P=0.0006) and rs4728142 AA (P=0.002) genotypes compared with carriers of the G alleles. Homozygotes for the T allele of rs2004640 developed a significantly higher number of annualized T2 lesions during IFN-β treatment (P=0.003) [34•]. The rs2004640 TT genotype was associated with shorter time to first relapse in an independent cohort (P=0.037).

The SNPs arising from both *IRF5* studies as more strongly associated markers with clinical response to IFN-β (ie, rs3807306 and rs2004640) are both located in the first intron of *IRF5* separated by an interval of 2.38 kb, and occur in strong linkage disequilibrium (r^2=0.73, D'=0.96; SNAP 1000 Genomes Pilot 1 SNP Dataset). Although rs2004640 alters a consensus splice donor site facilitating expression of *IRF5* isoforms carrying the alternative exon 1B, fine-mapping in larger cohorts of the *IRF5* locus for additional functional allelic variants including an exon-6 30-bp in-frame indel variant and a 3'UTR SNP that alters the polyadenylation signal and affects length and stability of the mRNA, is warranted to fully validate the genetic and mechanistic contribution of *IRF5* to response modification in IFN-β therapy [35]. A putative relationship between *IRF5*, IFN-β response, and HHV-6 infection status in MS has been suggested [33•]. The recent finding that IRF5 contributes to the plasticity of macrophage polarization via induction or repression of phenotypic markers of M1 and M2 macrophages, respectively, hints to a novel, intriguing mechanism by which functional *IRF5* allelic variants might affect response to IFN-β by modifying direction of T-helper type (Th1/Th17 vs Th2) development [36]. Furthermore, a

baseline type I IFN gene expression signature is associated with poor clinical response to IFN-β [22•]. Whether the phenotypic manifestation of this profile is driven by "hardwired" allelic variations in genes of IFN pathway transcription factors is currently not known. From the *IRF5* and *IRF8* studies cited above emerge two excellent candidates for testing this hypothesis, and if successful, this would provide a regulatory framework for integration of phenotypic (mRNA levels of type I IFN genes) and genotypic (genomic DNA variants in master regulators) biomarker data. Although presence of a baseline type I IFN pathway gene expression profile may constitute in itself a useful IFN-β nonresponse biomarker, as discussed above, DNA-based polymorphic variations may be preferable as a response-predictive surrogate marker due to ease of implementation in a clinical setting.

Although apolipoprotein E (*APOE*) has been linked to neuronal plasticity, CNS inflammation, and myelin repair, the *APOE* epsilon (ε) genotype is unlikely to contribute to MS risk, disease course, or severity as concluded from a meta-analysis of 22 published studies [37]. Two recent studies have assessed the influence of *APOE* gene polymorphisms on IFN-β treatment response [38, 39]. In the first study, the *APOE* ε2 or ε4 alleles were not significantly associated with clinical response at 2 years after onset of IFN-β therapy measured by presence of relapses, increase of disability, or both [38]. In the second study, the ε2 allele was found to be associated with increased time to moderate disability, whereas the ε4 allele was not associated with any of the clinical response variables measured [39]. Ascertainment of *APOE* in larger data sets is warranted to reject or confirm its prognostic value as an IFN-β clinical response marker. In addition, recently, IFN-β treatment was found to exert dose-dependent cognitive benefits in MS patients [40]. However, although the *APOE* ε4 allele has been proposed as a genetic determinant of cognitive outcome in MS [41], in two independent studies, *APOE* ε4 was found not to be associated with cognitive impairment [42, 43].

A series of haplotype-tagging SNPs covering the gene for inhibitory complement receptor CD46 were analyzed as potential markers of clinical response, defined as the absence of relapses and disease progression after 1 year of IFN-β treatment [44•]. Genotype distribution of a single intronic SNP, rs2724385, was significantly different between responders and nonresponders to treatment. A potential functional repercussion of this finding is the observation that nonresponders were significantly more often found among treated MS patients with increased CD46 mRNA levels, whereas patients with decreased CD46 mRNA were more likely to be responders. The same group also reported a potential association between the C allele of rs4774 in *MHC2TA* (*CIITA*) in MS patients with active HHV-6A infection and IFN-β treatment response—in that this subset of patients is more likely to constitute clinical nonresponders compared with MS patients not carrying the C allele and without HHV-6A infection [45]. When considered irrespective of HHV-6 infection status, the C allele remained significantly associated with poor clinical response to IFN-β treatment [45].

Enevold et al. [46•] analyzed 42 SNPs in genes coding for selected pattern recognition receptors in a prospective study recruiting more than 550 MS patients treated with IFN-β. Outcome parameters included formation of IFN-β NAbs, and clinical response based on number of relapses or disease progression after 2 years of treatment. Although several promising associations were uncovered, the strongest association was found between a nonsynonymous SNP in *TLR6*, rs5743810, and development of IFN-β NAbs in the male subset of patients [46•]. This association was entirely absent in female patients, and hints toward gender as an additional variable to include in IFN-β pharmacogenomics studies.

The above SNP studies propose a few new promising markers for GA or IFN-β treatment success to be added to those that emerged from two recent whole-genome association scans [47, 48] and additional candidate gene studies [49] on response to IFN-β in MS. Although there is no doubt that these SNP profiling efforts show tremendous potential for future management of MS treatments and patients, validation of reported hits is required to identify SNP sets that reproducibly and accurately predict clinical response.

Natalizumab Markers

Current treatments for MS also include the monoclonal antibody natalizumab, which is indicated for the treatment of RRMS with lack of response to first-line therapies such as IFN-β or GA. The search of biomarkers related with natalizumab will be instrumental toward identification of responders and nonresponders to this drug and, more importantly, to identify patients at risk for serious adverse effects including progressive multifocal leukoencephalopathy, opportunistic infections, melanoma, and hepatotoxicity [50, 51].

A couple of studies evaluated the effect of natalizumab on levels of immune markers in MS patients. Millonig et al. [52] investigated the effect of treatment on serum levels of the soluble vascular cell adhesion molecule-1 (sVCAM-1) and expression of VLA-4 (CD49d) by peripheral blood cells. Natalizumab treatment was associated with reductions in the levels of both markers compared with untreated and IFN-β–treated MS patients, and healthy controls. Interestingly, serum sVCAM-1 levels were higher in patients who developed NAbs against natalizumab compared to those

who remained NAb-negative. Mellergård et al. [53] evaluated changes in both plasma and CSF levels of a large panel of cytokines and chemokines induced by natalizumab. Compared with baseline levels, natalizumab treatment maintained for 1 year was associated with a pronounced decrease in CSF levels of proinflammatory cytokines such as IL-1β, IL-6, and IL-8, as well as Th1 and Th2 chemokines including CXCL9, CXCL10, CXCL11, and CCL22. Of note, natalizumab-induced CSF changes were not paralleled by an increase in levels of immune markers in peripheral blood. Much to the contrary, plasma levels of granulocyte-macrophage CSF, IL-6, IL-10, and tumor necrosis factor-α (TNF-α) were significantly reduced by natalizumab. However, these results are in disagreement with a previous study showing increased mRNA expression levels of proinflammatory cytokines such as IFN-γ and TNF-α in peripheral blood cells [54]. Natalizumab was also found to reduce the extent of axonal loss, thought to be a key process in the accumulation of neurologic disability. Specifically, CSF levels of neurofilament light (NFL) showed a threefold reduction in a prospective study on MS patients treated for 12 months with natalizumab [55]. These decreased NFL levels were not significantly different from those seen in healthy control subjects [55]. Thus, NFL may constitute a promising biomarker for monitoring the inhibition of nerve injury upon application of disease-modifying treatments in MS.

Conclusions

Research into the pharmacogenomics of MS therapies is currently yielding an abundancy of potential markers of various outcomes of drug response. However, this data will only be implementable in clinical practice following robust validation of the most encouraging markers in large cohorts of carefully classified responders and nonresponders. For the near future, therefore, personalized treatment decisions will continue to rely predominantly on clinical parameters and MRI scans, and for IFN-β, measurement of drug efficacy via NAb or MX1 assays [56]. In-depth decipherment of the mechanistic relationship between validated response-modifying genes and clinical response is needed, and this may yield further targets for therapeutic intervention [9, 25].

Clinical response to IFN-β, GA, and natalizumab is likely governed by sets of multiple genes. Thus, development of models estimating aggregate effects of multiple allelic variants on drug treatment response will be mandatory in view of our current understanding that common allelic variants with (very) strong effect on treatment response are unlikely to exist [28•]. Model-independent whole-genome SNP, transcriptome, exome, or metabolome screens, rather than candidate gene studies that are per definition limited in design and coverage, constitute beyond question the most cost-effective and rapid approach for detection of response-associated variants with enhanced resolution. To date, two whole-genome association screens for identification of SNPs associated with IFN-β treatment success have been completed [47, 48]. Further screens will need to be performed in well-powered cohorts including controls to limit confounding effects of natural disease history [1]. For now, ongoing progress into the pharmacogenomics of MS therapies foretells the arrival in the not-too-distant future of a paradigm shift by which availability of panels of powerful, predictive markers will inform treatment selection in MS likely in conjunction with clinical and MRI measures.

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