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(54) DETERMINATION OF SINGLE NUCLEOTIDE POLYMORPHISMS USEFUL TO PREDICT RESPONSE FOR GLATIRAMER ACETATE

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(57) ABSTRACT

This invention provides a method for treating a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis with a pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier, comprising the steps of:

i. identifying whether the human subject is a predicted responder to glatiramer acetate by determining the genotype of the subject at one or more single nucleotide polymorphisms (SNPs) selected from the group consisting of the SNPs in Group 1; and

ii. administering the pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier to the subject only if the subject is identified as a predicted responder to glatiramer acetate.

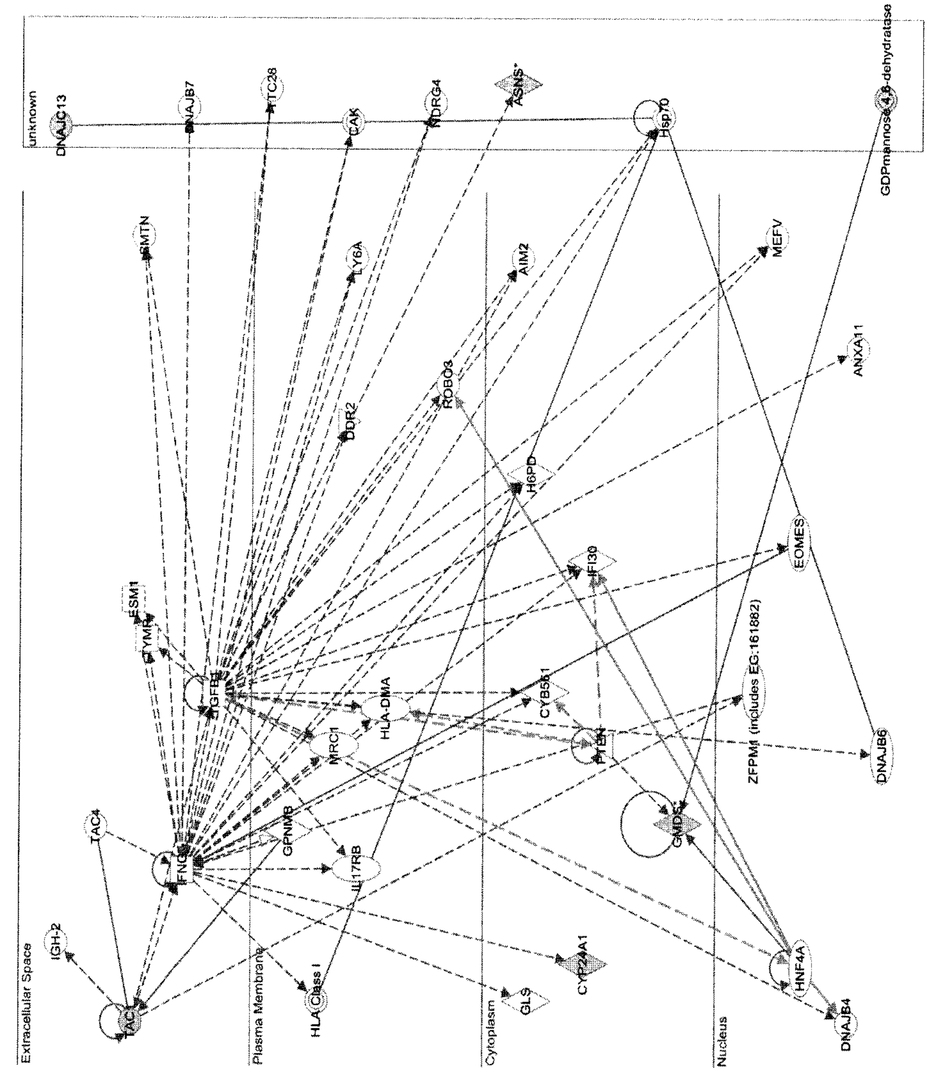
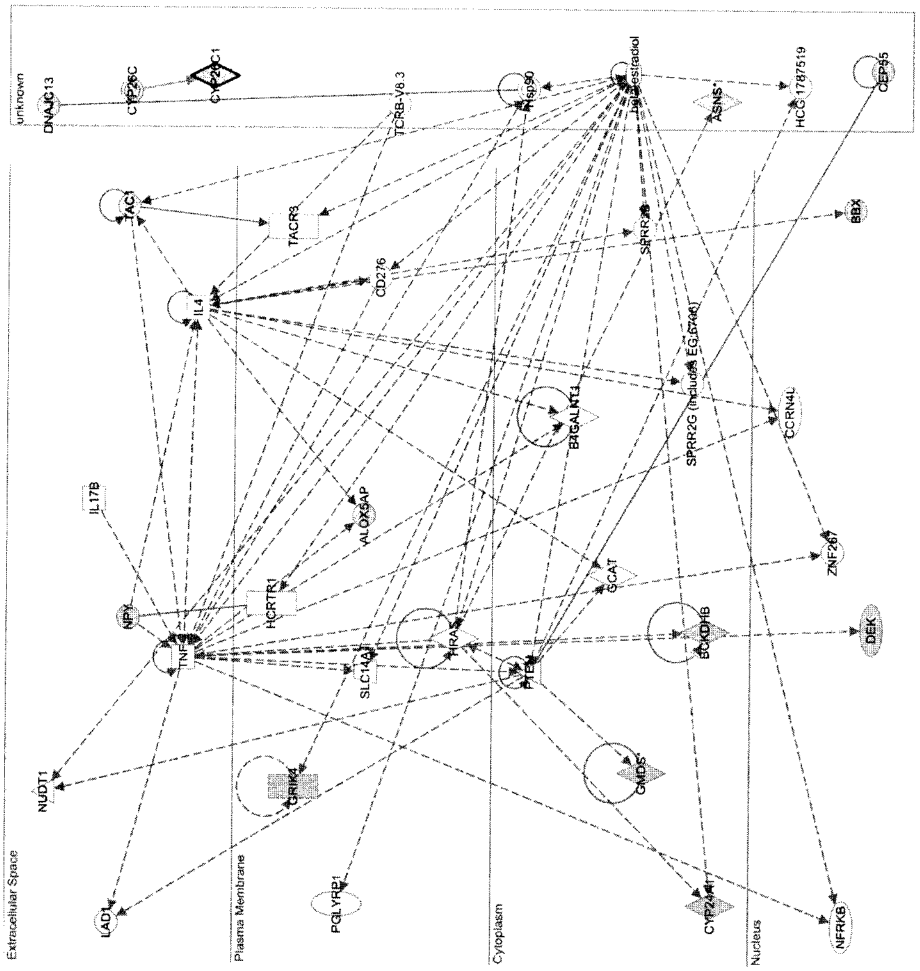


FIGURE 1

Exhibit A


Extracellular Space
Plasma Membrane
Cytoplasm
Nucleus
unknown
DNAJC13
CYP26C
CYP26C1
TCRB-V8.3
Hsp90
beta-estradiol
ASNS*
HCG1787519
CEP55
TAC1
TACR3
IL4
CD276
SPRR2B
BBX
SPRR2G (includes EG:6706)
B4GALNT1
CCRN4L
IL17B
ALOX5AP
HCRTR1
ZNF267
GCAT
NPY
TNF
BCKDHB
DEK
HRAS
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PTEN
NUDT1
GRIK4
GMDS
LAD1
PGLYRP1
CYP24A1
NFRKB

FIGURE 2

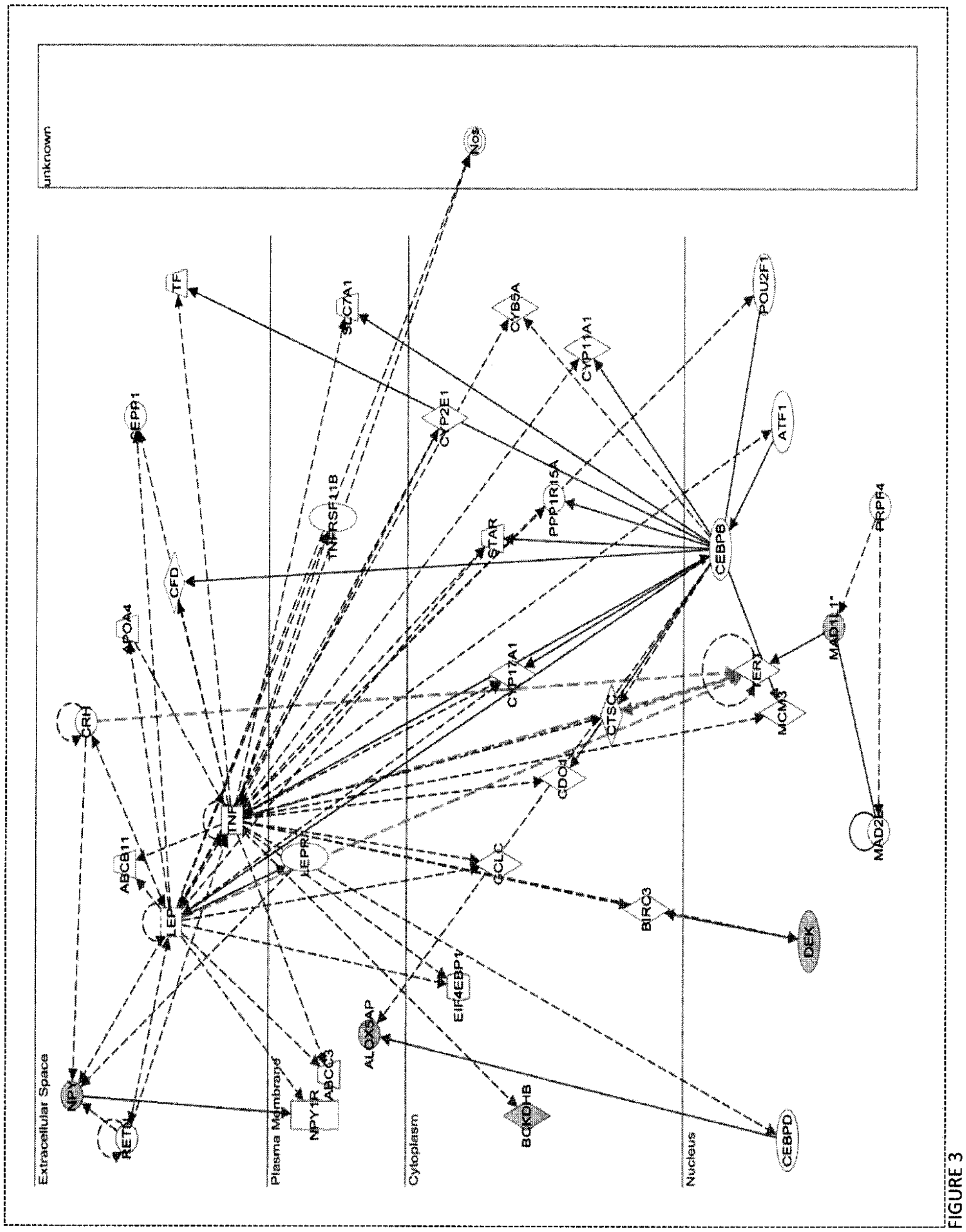
Extracellular Space
Plasma Membrane
Cytoplasm
Nucleus
unknown
NPY
RETN
CRH
ABCB11
LEP
APOA4
TNF
LEPR
CFD
SEPP1
TNFRSF11B
TF
SLC7A1
CYP2E1
CYB5A
CYP11A1
STAR
PPP1R15A
CYP17A1
CTSC
CDO1
GCLC
BIRC3
DEK
EIF4EBP1
ALOX5AP
ABCC3
NPY1R
BCKDHB
CEBPD
CEBPB
ATF1
POU2F1
TERT
MCM3
MAD1L1
MAD2L1
PRPF4
Nos

FIGURE 3

DETERMINATION OF SINGLE NUCLEOTIDE POLYMORPHISMS USEFUL TO PREDICT RESPONSE FOR GLATIRAMER ACETATE

[0001] Throughout this application various publications are referenced by their full citations in parentheses. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

BACKGROUND OF THE INVENTION

Multiple Sclerosis

[0002] Multiple sclerosis (MS) is a chronic, debilitating autoimmune disease of the central nervous system (CNS) with either relapsing-remitting (RR) or progressive course leading to neurologic deterioration and disability. At time of initial diagnosis, RRMS is the most common form of the disease (1) which is characterized by unpredictable acute episodes of neurological dysfunction (relapses), followed by variable recovery and periods of clinical stability. The vast majority of RRMS patients eventually develop secondary progressive (SP) disease with or without superimposed relapses. Around 15% of patients develop a sustained deterioration of their neurological function from the beginning; this form is called primary progressive (PP) MS. Patients who have experienced a single clinical event (Clinically Isolated Syndrome or "CIS") and who show lesion dissemination on subsequent magnetic resonance imaging (MRI) scans according to McDonald's criteria, are also considered as having relapsing MS. (2)

[0003] With a prevalence that varies considerably around the world, MS is the most common cause of chronic neurological disability in young adults. (3, 4) Anderson et al. estimated that there were about 350,000 physician-diagnosed patients with MS in the United States in 1990 (approx. 140 per 100,000 population). (5) It is estimated that about 2.5 million individuals are affected worldwide. (6) In general, there has been a trend toward an increasing prevalence and incidence of MS worldwide, but the reasons for this trend are not fully understood. (5)

[0004] Current therapeutic approaches consist of i) symptomatic treatment ii) treatment of acute relapses with corticosteroids and iii) treatment aimed to modify the course of the disease. Currently treatment aimed to modify the course of the disease. Currently approved therapies target the inflammatory processes of the disease. Most of them are considered to act as immunomodulators but their mechanisms of action have not been completely elucidated. immunosuppressants or cytotoxic agents are also used in some patients after failure of conventional therapies. Several medications have been approved and clinically ascertained as efficacious for the treatment of RR-MS; including BETASERON®, AVONEX® and REBIF®, which are derivatives of the cytokine interferon beta (IFNB), whose mechanism of action in MS is generally attributed to its immunomodulatory effects, antagonizing pro-inflammatory reactions and inducing suppressor cells. (7) Other approved drugs for the treatment of MS include Mitoxantrone and Natalizumab.

Glatiramer Acetate

[0005] Glatiramer acetate (GA) is the active substance in Copaxone®, a marketed product indicated for reduction of the frequency of relapses in patients with RRMS. Its effectiveness in reducing relapse rate and disability accumulation in RR-MS is comparable to that of other available immunomodulating treatments. (8, 9, 10) Glatiramer acetate consists of the acetate salts of synthetic polypeptides containing four naturally occurring amino acids: 1-glutamic acid, L-alanine, L-tyrosine and L-lysine. The average molecular weight of glatiramer acetate is between 5,000 and 9,000 Daltons. At a daily standard dose of 20 mg, GA is generally well tolerated, however response to the drug is variable. In various clinical trials, GA reduced relapse rates and progression of disability in patients with RR-MS. The therapeutic effect of GA is supported by the results of magnetic resonance imaging (MRI) findings from various clinical centers (11), however there are no validated predictive biomarkers of response to GA treatment.

[0006] A possible initial mode of action of GA is associated with binding to MHC molecules and consequent competition with various myelin antigens for their presentation to T cells. (12) A further aspect of its mode of action is the potent induction of T helper 2 (Th2) type cells that presumably can migrate to the brain and lead to in situ bystander suppression. (13) It has been shown that GA treatment in MS results in the induction of GA-specific T cells with predominant Th2 phenotype both in response to GA and cross-reactive myelin antigens. (13, 14) Furthermore, the ability of GA-specific infiltrating cells to express anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β) together with brain-derived neurotrophic factor (BDNF) seem to correlate with the therapeutic activity of GA in EAE. (15, 16, 17)

[0007] Clinical experience with GA consists of information obtained from completed and ongoing clinical trials and from post-marketing experience. The clinical program includes three double-blind, placebo-controlled studies in RRMS subjects treated with GA 20 mg/day. (18, 19, 20) A significant reduction in the number of relapses, compared with placebo, was seen. In the largest controlled study, the relapse rate was reduced by 32% from 1.98 under placebo to 1.34 under GA 20 mg. GA 20 mg has also demonstrated beneficial effects over placebo on MRI parameters relevant to RRMS. A significant effect in median cumulative number of Gd-enhancing lesions over 9 months of treatment (11 lesions in the 20 mg group compared to 17 lesions under placebo) was demonstrated.

[0008] The clinical program with GA also includes one double-blind study in chronic-progressive MS subjects, (21) one double-blind placebo-controlled study in primary progressive patients, (22) one double-blind placebo-controlled study in CIS patients (23) and numerous open-label and compassionate use studies, mostly in RRMS. The clinical use of GA has been extensively reviewed and published in the current literature (24, 25, 26, 27).

[0009] U.S. Pat. No. 7,855,176 discloses administering glatiramer acetate to patients afflicted with relapsing-remitting multiple sclerosis (RRMS) by subcutaneous injection of 0.5 ml of an aqueous pharmaceutical solution which contains in solution 20 mg glatiramer acetate and 20 mg mannitol (34).

[0010] U.S. Patent Application Publication No. US 2011-0046065 A1 discloses administering glatiramer acetate to patients suffering from relapsing-remitting multiple sclerosis by three subcutaneous injections of a therapeutically effective dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection (35).

Pharmacogenomics

[0011] Pharmacogenomics is the methodology which associates genetic variability with physiological responses to drug. Pharmacogenetics is a subset of pharmacogenomics and is defined as "the study of variations in DNA sequence as related to drug response" (ICH E15; http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129296.pdf. Pharmacogenetics focuses on genetic polymorphism in genes related to drug metabolism, drug mechanism of action, disease type, and side effects. Pharmacogenetics is the cornerstone of Personalized Medicine which allows the development of more individualized drug therapies to obtain more effective and safe treatment.

[0012] Pharmacogenetics has become a core component of many drug development programs, being used to explain variability in drug response among subjects in clinical trials, to address unexpected emerging clinical issues, such as adverse events, to determine eligibility for a clinical trial (pre-screening) to optimize trial yield, to develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events, to provide information in drug labels to guide physician treatment decisions, to better understand the mechanism of action or metabolism of new and existing drugs, and to provide better understanding of disease mechanisms.

[0013] Generally, Pharmacogenetics analyses are performed in either of two methodology approaches: Candidate genes research technique, and Genome Wide Association Study (GWAS). Candidate genes research technique is based on the detection of polymorphism in candidate genes preselected using the knowledge on the disease, the drug mode of action, toxicology or metabolism of drug. The Genome Wide Association Study (GWAS) enables the detection of more than 1 M (one million) polymorphisms across the genome. This approach is used when related genes are unknown. DNA arrays used for GWAS can be also analyzed per gene as in candidate gene approach.

Pharmacogenetic Studies

[0014] Various pharmacogenetic studies were done in MS patients. For example, a Genome-Wide Association study by Byun at al. (36) focused on extreme clinical phenotypes in order to maximize the ability to detect genetic differences between responders and non-responders to interferon-beta. A multianalytical approach detected significant associations between several SNPs and treatment response. Responders and nonresponders had significantly different genotype frequencies for SNPs located in many genes, including glypican 5, collagen type XXV $\alpha 1$, hyaluronan proteoglycan link protein, calpastatin, and neuronal PAS domain protein 3. Other studies used pharmacogenetic analyses in order to characterize the genomic profile and gene expression profile of IFN responders and non-responders.

[0015] Other pharmacogenetic studies analyzed the genetic background associated with response to Glatiramer Acetate. For examples, Fusco C et al (37) assessed a possible relationship between HLA alleles and response to GA (N=83 RRMS). DRB1*1501 allele frequency was increased in MS patients compared to healthy controls (10.8% vs 2.7%; p=0.001). In DRB1*1501 carriers the response rate was 81.8% compared to 39.4% in non-carriers of DRB1*1501 and to 50% in the whole study population. Grossman et al (38) genotyped HLA-DRB1*1501 and 61 SNPs within a total of 27 other candidate genes, on DNA from two clinical trial cohorts. The study revealed no association between HLA-DRB1*1501 and response to GA. The results of the study are disclosed in the international application published as 802006/116602 (39).

[0016] Pharmacogenetics is the cornerstone of personalized medicine which allows the development of more individualized drug therapies to obtain more effective and safe treatment. Multiple Sclerosis is a complex disease with clinical heterogeneity. In patients afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis, the ability to determine the likelihood of treatment success would be an important tool improving the therapeutic management of the patients. As the therapeutic options for MS and CIS increase, the importance of being able to determine who will respond favorably to therapy and specifically to GA, has become of increasing significance.

SUMMARY OF THE INVENTION

[0017] This invention provides a method for treating a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis with a pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier, comprising the steps of:

[0018] i. determining a genotype of the subject at one or more single nucleotide polymorphisms (SNPs) selected from the group consisting of: rs1007328, rs10083547, rs10136012, rs10214633, rs10277267, rs1040194, rs1041897, rs10853605, rs10931091, rs10935015, rs10935016, rs10935019, rs10950359, rs10950371, rs10988087, rs11009827, rs11009835, rs11081859, rs11599624, rs11617134, rs11618546, rs11694344, rs11709339, rs11719825, rs11761457, rs11907046, rs12055694, rs12256889, rs1229542, rs1229553, rs1229555, rs1229558, rs1229562, rs1229563, rs1229564, rs1229568, rs12340584, rs1234567, rs1234947, rs1237625, rs12488259, rs12494606, rs12496278, rs12524041, rs12529764, rs12532459, rs12540494, rs12593600, rs12633010, rs12637073, rs12639443, rs1264423, rs1282540, rs1282546, rs12968586, rs1299325, rs13021482, rs13042992, rs1320648, rs13238613, rs13245980, rs1415557, rs1538123, rs1573706, rs1591661, rs1611185, rs1683691, rs16999008, rs17007730, rs17087180, rs17104665, rs17104742, rs17134651, rs17575455, rs17588454, rs17666347, rs17771939, rs17807327, rs17807445, rs1886308, rs1892974, rs1941973, rs2033471, rs2088713, rs214526, rs2155262, rs2177073, rs2187495, rs2277431, rs2305623, rs2374730, rs2461319, rs2487889, rs2487896, rs2508806, rs2511064, rs2521643, rs2521644, rs2530121, rs2530123, rs2685484, rs2722396, rs2722398, rs28861531, rs2895215, rs2937395, rs3135391, rs35831078, rs3742228, rs401618, rs4148871, rs4255033, rs4281882, rs4289164, rs4306478, rs4343256, rs4344916, rs4369324, rs4435429, rs4445746, rs4466940, rs4468448, rs4483642, rs4565951, rs4578835, rs4634524, rs4799760, rs4809955, rs4811492, rs496486, rs552994, rs6015147, rs6025923, rs6025927, rs6091820, rs6097782, rs6097790, rs6097793, rs6097797, rs6097801, rs6123749, rs6543934, rs6558102, rs656975, rs657302, rs6584894, rs660075, rs6713772, rs6909321, rs6971202, rs702355, rs7080507, rs7086707, rs7093143, rs7178587, rs7180867, rs7232734, rs7238006, rs7244801, rs7317000, rs751370, rs752979, rs7619350, rs7633210, rs7714122, rs7789703, rs7803164, rs7806265, rs7916897, rs7955917, rs7963693, rs8099595, rs8118441, rs844602, rs844608, rs844610, rs844612, rs844626, rs860722, rs873216, rs884266, rs894857, rs913882, rs9315048, rs9332420, rs933863, rs933864, rs9378319, rs9378684, rs9392358, rs9405541, rs9405546, rs947603, rs948029, rs948032, rs949298, rs9508834, rs9944913, rs9952995, and rs998051 (hereinafter Group 1),

[0019] ii. identifying the subject as a predicted responder to glatiramer acetate if the genotype is

[0020] AA at rs10214633, rs10277267, rs10935015, rs10935019, rs10988087, rs11081859, rs11694344, rs12256889, rs12340584, rs12494606, rs1415557, rs17007730, rs17087180, rs17104665, rs17104742, rs17588454, rs17807327, rs1892974, rs2088713, rs214526, rs2374730, rs4255033, rs4306478, rs4343256, rs4344916, rs4435429, rs4578835, rs4809955, rs496486, rs6015147, rs6097790, rs6584894, rs6713772, rs6909321, rs702355, rs7086707, rs7180867, rs7317000, rs844608, rs844610, rs933863, rs9392358, rs948029, or rs9508834 (hereinafter Group 2),

[0021] AT at rs12524041 or rs7806265,

[0022] AG at rs10277267, rs10950359, rs11599624, rs13245980, rs1415557, rs2521643, rs4255033, rs6584894, rs6909321, rs702355, or rs844626,

[0023] AC at rs12256889, rs1229542, rs214526, rs6097793, rs7086707, rs7180867, rs844608, or rs844610,

[0024] TT at rs1007328, rs10931091, rs11617134, rs11709339, rs11719825, rs11761457, rs1229553, rs1234567, rs1234947, rs12532459, rs12593600, rs1264423, rs13042992, rs1320648, rs1538123, rs1591661, rs17134651, rs17666347, rs17771939, rs2461319, rs2508806, rs2722396, rs2722398, rs2895215, rs401618, rs4369324, rs4483642, rs4565951, rs4811492, rs552994, rs6025923, rs6025927, rs6097797, rs657302, rs7232734, rs751370, rs7633210, rs7714122, rs7803164, rs7806265, rs7916897, rs8118441, rs844612, rs9378319, or rs9952995 (hereinafter Group 3),

[0025] GT at rs12532459, rs2722398, rs4369324, or rs7093143,

[0026] CT at rs10950371, rs11761457, rs1229562, rs12529764, rs13021482, rs13238613, rs1538123, rs1591661, rs1611185, rs17807445, rs1941973, rs2461319, rs2685484, rs2895215, rs4634524, rs4799760, rs6097797, rs7080507, rs7238006, rs7789703, rs7803164, rs844612, or rs947603,

[0027] GG at rs10083547, rs10136012, rs10950359, rs11599624, rs12055694, rs1229558, rs1237625, rs12496278, rs12540494, rs12633010, rs12637073, rs1282540, rs1282546, rs12968586, rs1299325, rs13245980, rs16999008, rs17104665, rs17104742, rs2033471, rs2155262, rs2487889, rs2487896, rs2511064, rs2521643, rs2530121, rs2530123, rs28861531, rs3135391, rs4148871, rs4289164, rs4445746, rs6097801, rs6543934, rs6558102, rs656975, rs6971202, rs7093143, rs7244801, rs752979, rs7619350, rs7955917, rs844626, rs873216, rs894857, rs9315048, rs9332420, rs933864, rs948032, rs949298, or rs998051 (hereinafter Group 4),

[0028] CG at rs11618546 or rs860722, or

[0029] CC at rs1041897, rs10853605, rs10935016, rs10950371, rs11009827, rs11009835, rs11618546, rs11907046, rs1229542, rs1229555, rs1229562, rs1229563, rs1229564, rs1229568, rs12488259, rs12639443, rs13021482, rs13238613, rs1573706, rs1683691, rs17575455, rs17807445, rs2177073, rs2187495, rs2277431, rs2521644, rs2685484, rs2937395, rs4281882, rs4466940, rs4468448, rs4634524, rs4799760, rs6091820, rs6097782, rs6097793, rs6123749, rs660075, rs7080507, rs7789703, rs7963693, rs8099595, rs844602, rs860722, rs884266, rs913882, rs9378684, rs9405541, rs9405546, rs947603, or rs9944913 (hereinafter Group 5); and

[0030] iii. administering the pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier to the subject only if the subject is identified as a predicted responder to glatiramer acetate.

[0031] The invention also provides a method of identifying a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis as a predicted responder or as a predicted non-responder to glatiramer acetate, the method comprising determining the genotype of the subject at one or more single nucleotide polymorphisms (SNPs) selected from the group consisting of the SNPs in Group 1,

wherein the subject is identified as a predicted responder to glatiramer acetate if the genotype is

[0032] AA at one of the SNPs in Group 2,

[0033] AT at rs12524041 or rs7806265,

[0034] AG at rs10277267, rs10950359, rs11599624, rs13245980, rs1415557, rs2521643, rs4255033, rs6584894, rs6909321, rs702355, or rs844626,

[0035] AC at rs12256889, rs1229542, rs214526, rs6097793, rs7086707, rs7180867, rs844608, or rs844610,

[0036] TT at one of the SNPs in Group 3,

[0037] GT at rs12532459, rs2722398, rs4369324, or rs7093143,

[0038] CT at rs10950371, rs11761457, rs1229562, rs12529764, rs13021482, rs13238613, rs1538123, rs1591661, rs1611185, rs17807445, rs1941973, rs2461319, rs2685484, rs2895215, rs4634524, rs4799760, rs6097797, rs7080507, rs7238006, rs7789703, rs7803164, rs844612, or rs947603,

[0039] GG at one of the SNPs in Group 4,

[0040] CG at rs11618546 or rs860722, or

[0041] CC one of the SNPs in Group 5; and

[0042] wherein the subject is identified as a predicted non-responder to glatiramer acetate if the genotype is

[0043] AA at rs1040194, rs10935016, rs10950359, rs11009827, rs11599624, rs12055694, rs1229542, rs1229558, rs1237625, rs12488259, rs12540494, rs12637073, rs1282540, rs1282546, rs12968586, rs13245980, rs16999008, rs17575455, rs2177073, rs2511064, rs2521643, rs4281882, rs4289164, rs4445746, rs4811492, rs6097793, rs6097801, rs6558102, rs7244801, rs7619350, rs7806265, rs7955917, rs844626, rs873216, rs894857, rs9332420, or rs948032 (hereinafter Group 6),

[0044] AG at rs1040194, rs10935015, rs10935019, rs10988087, rs11081859, rs12055694, rs1229558, rs12340584, rs1237625, rs12494606, rs12540494, rs12637073, rs1282540, rs1282546, rs12968586, rs16999008, rs17007730, rs17087180, rs17104665, rs17104742, rs17588454, rs2374730, rs2487889, rs2487896, rs2511064, rs3135391, rs3742228, rs4148871, rs4343256, rs4445746, rs4809955, rs6097801, rs6713772, rs7244801, rs7619350, rs7955917, rs894857, rs933863, rs9392358, or rs9508834,

[0045] AC at rs10214633, rs10935016, rs11009827, rs12488259, rs2088713, rs2177073, rs4306478, rs496486, rs6097790, or rs7317000,

[0046] TT at rs10136012, rs1041897, rs10853605, rs10950371, rs11009835, rs11907046, rs1229555, rs1229562, rs1229563, rs1229564, rs1229568, rs12639443, rs13238613, rs1573706, rs1683691, rs1892974, rs2187495, rs2277431, rs2521644, rs2530121, rs2530123, rs2685484, rs2937395, rs35831078, rs4466940, rs4468448, rs4634524, rs6091820, rs6097782, rs6543934, rs660075, rs7789703, rs8099595, rs884266, rs913882, rs9378684, rs9405541, rs9405546, rs947603, rs948029, or rs9944913 (hereinafter Group 7),

[0047] GT at rs11719825, rs13042992, rs1886308, rs2305623, or rs998051,

[0048] CT at rs1041897, rs10931091, rs11009835, rs11617134, rs11709339, rs1229553, rs1229555, rs1229563, rs1229564, rs1229568, rs1234567, rs1234947, rs12593600, rs12639443, rs1320648, rs1573706, rs1683691, rs17134651, rs17666347, rs2187495, rs2277431, rs2508806, rs2937395, rs35831078, rs4466940, rs4468448, rs4483642, rs4565951, rs552994, rs6091820, rs6097782, rs657302, rs660075, rs7232734, rs7714122, rs8099595, rs9378319, rs9378684, rs9405541, rs9405546, rs9944913, or rs9952995,

[0049] GG at rs10277267, rs10935015, rs10935019, rs10988087, rs11081859, rs11618546, rs11719825, rs12340584, rs12494606, rs12532459, rs13042992, rs17007730, rs17087180, rs17588454, rs1886308, rs2305623, rs2722398, rs3742228, rs4255033, rs4343256, rs4369324, rs4435429, rs4578835, rs4809955, rs6123749, rs6584894, rs6713772, rs7916897, rs7963693, rs9392358, or rs9508834 (hereinafter Group 8),

[0050] CG at rs10083547, rs12496278, rs1299325, rs2155262, rs28861531, rs656975, rs7963693, or rs933864, or

[0051] CC at rs1007328, rs10083547, rs10214633, rs10931091, rs11617134, rs11694344, rs11709339, rs11761457, rs12256889, rs1229553, rs1234567, rs1234947, rs12496278, rs12593600, rs1299325, rs1320648, rs1538123, rs1591661, rs1611185, rs17134651, rs17666347, rs17771939, rs17807327, rs1941973, rs214526, rs2461319, rs2508806, rs2722398, rs28861531, rs2895215, rs4306478, rs4344916, rs496486, rs552994, rs6015147, rs6025923, rs6025927, rs6097790, rs6097797, rs656975, rs657302, rs7178587, rs7232734, rs7238006, rs7317000, rs751370, rs7714122, rs7803164, rs844608, rs844610, rs844612, rs9378319, or rs9952995 (hereinafter Group 9);

[0052] and thereby identifying the subject as a predicted responder or as a predicted non-responder to glatiramer acetate.

[0053] The invention also provides a method for treating a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis comprising the steps of:

[0054] (i) administering to the human subject a therapeutic amount of a pharmaceutical composition comprising glatiramer and a pharmaceutically acceptable carrier;

[0055] (ii) identifying whether the human subject is a predicted responder to glatiramer acetate by determining the genotype of the subject at one or more single nucleotide polymorphisms (SNPs) selected from the group consisting of the SNPs in Group 1,

[0056] wherein the subject is identified as a predicted responder to glatiramer acetate if the genotype is

[0057] AA at one of the SNPs in Group 2,

[0058] AT at rs12524041 or rs7806265,

[0059] AG at rs10277267, rs10950359, rs11599624, rs13245980, rs1415557, rs2521643, rs4255033, rs6584894, rs6909321, rs702355, or rs844626,

[0060] AC at rs12256889, rs1229542, rs214526, rs6097793, rs7086707, rs7180867, rs844608, or rs844610,

[0061] TT one of the SNPs in Group 3,

[0062] GT at rs12532459, rs2722398, rs4369324, or rs7093143,

[0063] CT at rs10950371, rs11761457, rs1229562, rs12529764, rs13021482, rs13238613, rs1538123, rs1591661, rs1611185, rs17807445, rs1941973, rs2461319, rs2685484, rs2895215, rs4634524, rs4799760, rs6097797, rs7080507, rs7238006, rs7789703, rs7803164, rs844612, or rs947603,

[0064] GG at one of the SNPs in Group 4,

[0065] CG at rs11618546 or rs860722, or

[0066] CC at one of the SNPs in Group 5; and

[0067] (iii) continuing administration of the pharmaceutical composition if the human subject is identified as a predicted responder to glatiramer acetate, or modifying the administration of the pharmaceutical composition to the human subject if the human subject is not identified as a predicted responder to glatiramer acetate.

[0068] The invention also provides a kit for identifying a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis as a predicted responder or as a predicted non-responder to glatiramer acetate, the kit comprising

[0069] (i) at least one probe specific for a SNP selected from the group consisting of the SNPs in Group 1.

[0070] The invention also provides a kit for identifying a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis as a predicted responder or as a predicted non-responder to glatiramer acetate, the kit comprising at least one pair of PCR primers designed to amplify a DNA segment which includes a SNP selected from the group consisting of the SNPs in Group 1.

[0071] The invention also provides a PCR amplification kit comprising

[0072] (i) at least one pair of PCR primers designed to amplify a DNA segment which includes a SNP selected from the group consisting of the SNPs in Group 1, and

[0073] (ii) instructions for use of the PCR primers to amplify the segment of DNA.

[0074] The invention also provides a kit for identifying a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis as a predicted responder or as a predicted non-responder to glatiramer acetate, the kit comprising a reagent for performing a method selected from the group consisting of restriction fragment length polymorphism (RFLP) analysis, sequencing, single strand conformation polymorphism analysis (SSCP), chemical cleavage of mismatch (CCM), gene chip and denaturing high performance liquid chromatography (DHPLC) for determining the identity of at least one SNP selected from the group consisting of The SNPs in Group 1.

[0075] The invention also provides a kit for identifying a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis as a predicted responder or as a predicted non-responder to glatiramer acetate, the kit comprising reagents for TaqMan Open Array assay designed for determining the identity of at least one SNP selected from the group consisting of The SNPs in Group 1.

[0076] The invention also provides a probe for identifying the genotype of a SNP selected from the group consisting of the SNPs in Group 1.

BRIEF DESCRIPTION OF THE DRAWINGS

[0077] FIG. **1**. Merging of the two mostly enriched networks for broad phenotype definition (organized by cellular compartment). Genes with the light grey symbols are from the GWAS findings, while the others with "empty" symbols are their pathways' specific members, and have not been identified by any GWAS.

[0078] FIG. **2**. Merging of the two mostly enriched networks for narrow phenotype definition (organized by cellular compartments). Genes with the light grey symbols are from the GWAS findings, while the others with "empty" symbols are their pathways' specific members, and have not been identified by any GWAS.

[0079] FIG. **3**. Merging two networks for narrow phenotype definition (organized by cellular compartments). Genes with the light grey symbols are from the GWAS findings, while the others with "empty" symbols are their pathways' specific members, and have not been identified by any GWAS.

DETAILED DESCRIPTION OF THE INVENTION

[0080] This invention provides a method for treating a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis with a pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier, comprising the steps of:

[0081] i. determining a genotype of the subject at one or more single nucleotide polymorphisms (SNPs) selected from the group consisting of: the SNPs in Group 1,

[0082] ii. identifying the subject as a predicted responder to glatiramer acetate if the genotype is

[0083] AA at one of the SNPs in Group 2,

[0084] AT at rs12524041 or rs7806265,

[0085] AG at rs10277267, rs10950359, rs11599624, rs13245980, rs1415557, rs2521643, rs4255033, rs6584894, rs6909321, rs702355, or rs844626,

[0086] AC at rs12256889, rs1229542, rs214526, rs6097793, rs7086707, rs7180867, rs844608, or rs844610,

[0087] TT at one of the SNPs in Group 3,

[0088] GT at rs12532459, rs2722398, rs4369324, or rs7093143,

[0089] CT at rs10950371, rs11761457, rs1229562, rs12529764, rs13021482, rs13238613, rs1538123, rs1591661, rs1611185, rs17807445, rs1941973, rs2461319, rs2685484, rs2895215, rs4634524, rs4799760, rs6097797, rs7080507, rs7238006, rs7789703, rs7803164, rs844612, or rs947603,

[0090] GG at one of the SNPs in Group 4,

[0091] CG at rs11618546 or rs860722, or

[0092] CC at one of the SNPs in Group 5; and

[0093] iii. administering the pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier to the subject only if the subject is identified as a predicted responder to glatiramer acetate.

[0094] In some embodiments, administering the pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier comprises administering to the human subject three subcutaneous injections of the pharmaceutical composition over a period of seven days with at least one day between every subcutaneous injection.

[0095] In some embodiments, the pharmaceutical composition is a unit dose of a 1 ml aqueous solution comprising 40 mg of glatiramer acetate.

[0096] In some embodiments, the pharmaceutical composition is a unit dose of a 1 ml aqueous solution comprising 20 mg of glatiramer acetate.

[0097] In some embodiments, the pharmaceutical composition is a unit dose of a 0.5 ml aqueous solution comprising 20 mg of glatiramer acetate.

[0098] The invention also provides a method of identifying a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis as a predicted responder or as a predicted non-responder to glatiramer acetate, the method comprising determining the genotype of the subject at one or more single nucleotide polymorphisms (SNPs) selected from the group consisting of the SNPs in Group 1,

wherein the subject is identified as a predicted responder to glatiramer acetate if the genotype is

[0099] AA at one of the SNPs in Group 2,

[0100] AT at rs12524041 or rs7806265,

[0101] AG at rs10277267, rs10950359, rs11599624, rs13245980, rs1415557, rs2521643, rs4255033, rs6584894, rs6909321, rs702355, or rs844626,

[0102] AC at rs12256889, rs1229542, rs214526, rs6097793, rs7086707, rs7180867, rs844608, or rs844610,

[0103] TT at one of the SNPs in Group 3,

[0104] GT at rs12532459, rs2722398, rs4369324, or rs7093143,

[0105] CT at rs10950371, rs11761457, rs1229562, rs12529764, rs13021482, rs13238613, rs1538123, rs1591661, rs1611185, rs17807445, rs1941973, rs2461319, rs2685484, rs2895215, rs4634524, rs4799760, rs6097797, rs7080507, rs7238006, rs7789703, rs7803164, rs844612, or rs947603,

[0106] GG at one of the SNPs in Group 4,

[0107] CG at rs11618546 or rs860722, or

[0108] CC at one of the SNPs in Group 5; and

wherein the subject is identified as a predicted non-responder to glatiramer acetate if the genotype is

[0109] AA at one of the SNPs in Group 6,

[0110] AG at rs1040194, rs10935015, rs10935019, rs10988087, rs11081859, rs12055694, rs1229558, rs12340584, rs1237625, rs12494606, rs12540494, rs12637073, rs1282540, rs1282546, rs12968586, rs16999008, rs17007730, rs17087180, rs17104665, rs17104742, rs17588454, rs2374730, rs2487889, rs2487896, rs2511064, rs3135391, rs3742228, rs4148871, rs4343256, rs4445746, rs4809955, rs6097801, rs6713772, rs7244801, rs7619350, rs7955917, rs894857, rs933863, rs9392358, or rs9508834,

[0111] AC at rs10214633, rs10935016, rs11009827, rs12488259, rs2088713, rs2177073, rs4306478, rs496486, rs6097790, or rs7317000,

[0112] TT at one of the SNPs in Group 7,

[0113] GT at rs11719825, rs13042992, rs1886308, rs2305623, or rs998051,

[0114] CT at rs1041897, rs10931091, rs11009835, rs11617134, rs11709339, rs1229553, rs1229555, rs1229563, rs1229564, rs1229568, rs1234567, rs1234947, rs12593600, rs12639443, rs1320648, rs1573706, rs1683691, rs17134651, rs17666347, rs2187495, rs2277431, rs2508806, rs2937395, rs35831078, rs4466940, rs4468448, rs4483642, rs4565951, rs552994, rs6091820, rs6097782, rs657302, rs660075, rs7232734, rs7714122, rs8099595, rs9378319, rs9378684, rs9405541, rs9405546, rs9944913, or rs9952995,

[0115] GG at one of the SNPs in Group 8,

[0116] CG at rs10083547, rs12496278, rs1299325, rs2155262, rs28861531, rs656975, rs7963693, or rs933864, or

[0117] CC at one of the SNPs in Group 9;

[0118] and thereby identifying the subject as a predicted responder or as a predicted non-responder to glatiramer acetate.

[0119] The invention also provides a method for treating a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis comprising the steps of:

[0120] (i) administering to the human subject a therapeutic amount of a pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier;

[0121] (ii) identifying whether the human subject is a predicted responder to glatiramer acetate by determining the genotype of the subject at one or more single nucleotide polymorphisms (SNPs) selected from the group consisting of the SNPs in Group 1,

[0122] wherein the subject is identified as a predicted responder to glatiramer acetate if the genotype is

[0123] AA at one of the SNPs in Group 2,

[0124] AT at rs12524041 or rs7806265,

[0125] AG at rs10277267, rs10950359, rs11599624, rs13245980, rs1415557, rs2521643, rs4255033, rs6584894, rs6909321, rs702355, or rs844626,

[0126] AC at rs12256889, rs1229542, rs214526, rs6097793, rs7086707, rs7180867, rs844608, or rs844610,

[0127] TT at one of the SNPs in Group 3,

[0128] GT at rs12532459, rs2722398, rs4369324, or rs7093143,

[0129] CT at rs10950371, rs11761457, rs1229562, rs12529764, rs13021482, rs13238613, rs1538123, rs1591661, rs1611185, rs17807445, rs1941973, rs2461319, rs2685484, rs2895215, rs4634524, rs4799760, rs6097797, rs7080507, rs7238006, rs7789703, rs7803164, rs844612, or rs947603,

[0130] GG at one of the SNPs in Group 4,

[0131] CG at rs11618546 or rs860722, or

[0132] CC at one of the SNPs in Group 5; and

[0133] (iii) continuing administration of the pharmaceutical composition if the human subject is identified as a predicted responder to glatiramer acetate, or modifying the administration of the pharmaceutical composition to the human subject if the human subject is not identified as a predicted responder to glatiramer acetate.

[0134] In some embodiments, administering to the human subject a therapeutic amount of a pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier comprises administering to the human subject three subcutaneous injections of the pharmaceutical composition over a period of seven days with at least one day between every subcutaneous injection.

[0135] In some embodiments, the pharmaceutical composition is a unit dose of a 1 ml aqueous solution comprising 40 mg of glatiramer acetate.

[0136] In some embodiments, the pharmaceutical composition is a unit dose of a 1 ml aqueous solution comprising 20 mg of glatiramer acetate.

[0137] In some embodiments, the pharmaceutical composition is a unit dose of a 0.5 ml aqueous solution comprising 20 mg of glatiramer acetate.

[0138] In some embodiments, if the human subject is identified as a predicted responder to glatiramer acetate, the human subject is thereafter administered the pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier as monotherapy.

[0139] In some embodiments, if the human subject is identified as a predicted responder to glatiramer acetate, the human subject is thereafter administered the pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier in combination with at least one other multiple sclerosis drug.

[0140] In some embodiments, the genotype is determined at one or more single nucleotide polymorphisms (SNPs) selected from the group consisting of rs947603, rs1007328, rs1573706, rs2177073, rs2487896, rs2511064, rs2521644, rs3135391, rs4148871, rs4343256, rs4344916, rs4369324, rs4445746, rs6097801, rs9508834, rs9944913, rs10853605, rs10931091, rs10950359, rs10988087, rs11599624, rs11617134, rs12256889, rs12639443, rs13042992, rs13238613, rs17087180, rs17575455, rs17771939 and rs17807327.

[0141] In some embodiments, the genotype is determined at one or more single nucleotide polymorphisms (SNPs) selected from the group consisting of rs9508834, rs17807327, rs4344916, rs12639443, rs17087180 and rs17771939.

[0142] In some embodiments, the genotype is determined at one or more single nucleotide polymorphisms (SNPs) selected from the group consisting of rs4344916, rs12639443, rs17087180 and rs17771939.

[0143] In some embodiments, the genotype is determined at SNPs rs4344916, rs12639443, rs17087180 and rs17771939. In other embodiments the genotype is further determined at SNPs rs9508834 or rs17807327. In other embodiments the genotype is further determined at SNPs rs9508834 and rs17807327.

[0144] In some embodiments, the method comprises determining the genotype of the subject at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more of said SNPs.

[0145] In some embodiments, the method comprises determining the genotype of the subject at 4, 6, 10, 11, 12 or 13 of said SNPs.

[0146] In some embodiments, the method comprises determining the genotype of the subject at 6 or 8 of said SNPs.

[0147] In some embodiments, the method comprises determining the genotype of the subject at 6 SNPs.

[0148] In some embodiments, the genotype is determined at SNPs rs2521644, rs12256889, rs214526, rs17771939, rs496486, and rs949298.

[0149] In some embodiments, a score is assigned to each genotype of each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the scores are approximately as shown in tables 7a-f.

[0150] In some embodiments, the genotype is determined at SNPs rs2521644, rs12256889, rs214526, rs17771939, rs496486, and rs2511064.

[0151] In some embodiments, a score is assigned to each genotype of each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the scores are approximately as shown in tables 9a-f.

[0152] In some embodiments, a relative weight is assigned to each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the relative weight is approximately as shown in table 10.

[0153] In some embodiments, the genotype is determined at SNPs rs12256889, rs17771939, rs2511064, and rs2521644.

[0154] In some embodiments, a score is assigned to each genotype of each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the scores are approximately as shown in tables 9a-f.

[0155] In some embodiments, a relative weight is assigned to each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the relative weight is approximately as shown in table 11.

[0156] In some embodiments, the genotype is determined at SNPs rs11599624, rs12639443, rs13042992, rs13238613, rs17087180, rs17771939, rs17807327, rs2487896, rs3135391, rs4148871, rs4343256, rs4344916, and rs9508834.

[0157] In some embodiments, the genotype is determined at SNPs rs12256889, rs12639443, rs13238613, rs1573706, rs17087180, rs17771939, rs17807327, rs2487896, rs4343256, rs4344916, rs4369324, rs4445746, and rs9944913.

[0158] In some embodiments, the genotype is determined at SNPs rs10988087, rs12639443, rs13042992, rs13238613, rs1573706, rs17087180, rs17771939, rs17807327, rs4148871, rs4344916, rs6097801, and rs9508834.

[0159] In some embodiments, the genotype is determined at SNPs rs10988087, rs12256889, rs12639443, rs17087180, rs17771939, rs2177073, rs2521644, rs4344916, rs4369324, rs6097801, rs9508834, and rs9944913.

[0160] In some embodiments, the genotype is determined at SNPs rs10988087, rs11617134, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2487896, rs4148871, rs4344916, rs4445746, rs6097801, and rs9508834.

[0161] In some embodiments, the genotype is determined at SNPs rs10988087, rs11617134, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2487896, rs2521644, rs4148871, rs4344916, rs4445746, and rs6097801.

[0162] In some embodiments, the genotype is determined at SNPs rs10988087, rs12256889, rs12639443, rs17087180, rs17771939, rs17807327, rs2487896, rs4148871, rs4344916, rs6097801, and rs9508834.

[0163] In some embodiments, the genotype is determined at SNPs rs1007328, rs11617134, rs12639443, rs13238613, rs1573706, rs17087180, rs17771939, rs17807327, rs4343256, rs4344916, rs9508834, and rs9944913.

[0164] In some embodiments, the genotype is determined at SNPs rs12639443, rs17087180, rs17771939, rs17807327, rs2487896, rs4148871, rs4343256, rs4344916, rs4369324, rs4445746, rs6097801, rs9508834, and rs9944913.

[0165] In some embodiments, the genotype is determined at SNPs rs11617134, rs12639443, rs17087180, rs17771939, rs17807327, rs2487896, rs3135391, rs4148871, rs4344916, rs4369324, rs6097801, rs9508834, and rs9944913.

[0166] In some embodiments, the genotype is determined at SNPs rs10988087, rs12639443, rs13238613, rs17087180, rs17771939, rs2487896, rs4148871, rs4343256, rs4344916, and rs9508834.

[0167] In some embodiments, the genotype is determined at SNPs rs11617134, rs12256889, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2177073, rs2487896, rs4343256, rs4344916, rs6097801, and rs9508834.

[0168] In some embodiments, the genotype is determined at SNPs rs10950359, rs11617134, rs12639443, rs17087180, rs17771939, rs2487896, rs2511064, rs3135391, rs4148871, rs4343256, rs4344916, rs9508834, and rs9944913.

[0169] In some embodiments, the genotype is determined at SNPs rs12256889, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2487896, rs2521644, rs4344916, and rs6097801.

[0170] In some embodiments, the genotype is determined at SNPs rs10950359, rs10988087, rs11599624, rs12256889, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2521644, rs3135391, rs4344916, and rs9508834.

[0171] In some embodiments, the genotype is determined at SNPs rs1007328, rs10950359, rs12256889, rs12639443, rs13042992, rs1573706, rs17087180, rs17771939, rs17807327, rs4343256, rs4344916, rs947603, and rs9508834.

[0172] In some embodiments, the genotype is determined at SNPs rs11599624, rs12256889, rs12639443, rs1573706, rs17087180, rs17771939, rs17807327, rs2177073, rs2487896, rs4344916, rs6097801, rs9508834, and rs9944913.

[0173] In some embodiments, the method further comprises the measurement of at least one clinical variable which is indicative of response or non-response to glatiramer acetate therapy.

[0174] In some embodiments, the at least one clinical variable is selected from age of the subject and T1 brain lesion volume.

[0175] In some embodiments, the method further comprises measuring the value of a biomarker in the blood of the human subject.

[0176] In some embodiments, the biomarker is selected from the group consisting of IL-10 concentration, IL-17 concentration, IL-18 concentration, TNF-α concentration, brain-derived neurotrophic factor concentration, caspase-1 concentration, IL-10/IL-18 ratio, IL-10/IL-17 ratio, IL-2 concentration and IFN-γ concentration, or a combination thereof.

[0177] In some embodiments, the genotype is determined from a nucleic acid-containing sample that has been obtained from the subject.

[0178] In some embodiments, the genotype is determined using an array.

[0179] In some embodiments, the array is selected from the group consisting of a gene array, a gene chip, a DNA array, a DNA microarray, a TAqMan Open Array and a bead array.

[0180] In some embodiments, the array is a TaqMan Open Array.

[0181] In some embodiments, determining the genotype comprises using a method selected from the group consisting of restriction fragment length polymorphism (RFLP) analysis, sequencing, single strand conformation polymorphism analysis (SSCP), chemical cleavage of mismatch (CCM), denaturing high performance liquid chromatography (DHPLC), Polymerase Chain Reaction (PCR) and an array, or a combination thereof.

[0182] In some embodiments, the genotype is determined using at least one pair of PCR primers and at least one probe.

[0183] In some embodiments, the genotype is determined by a method selected from the group consisting of restriction fragment length polymorphism (RFLP) analysis, sequencing, single strand conformation polymorphism analysis (SSCP), chemical cleavage of mismatch (CCM), gene chip, and denaturing high performance liquid chromatography (DHPLC).

[0184] In some embodiments, determining the genotype of the subject at said one or more SNP comprises:

- **[0185]** (i) obtaining DNA from a sample that has been obtained from the subject;
- **[0186]** (ii) optionally amplifying the DNA; and
- **[0187]** (iii) contacting the DNA or the amplified DNA with an array comprising a plurality of probes suitable for determining the identity of the one or more SNPs.

[0188] In some embodiments, determining the genotype of the subject at said one or more SNPs comprises:

- **[0189]** (i) obtaining DNA from a sample that has been obtained from the subject;
- **[0190]** (ii) optionally amplifying the DNA; and
- **[0191]** (iii) subjecting the DNA or the amplified DNA to a method selected from the group consisting of restriction fragment length polymorphism (RFLP) analysis, sequencing, single strand conformation polymorphism analysis (SSCP), chemical cleavage of mismatch (CCM), gene chip, denaturing high performance liquid chromatography (DHPLC) and an array, or a combination thereof for determining the identity the one or more SNPs.

[0192] In some embodiments, the array comprises a plurality of probes suitable for determining the identity of the one or more SNPs.

[0193] In some embodiments, the human subject is a naive patient.

[0194] In some embodiments, the human subject has been previously administered glatiramer acetate.

[0195] In some embodiments, the human subject has been previously administered a multiple sclerosis drug other than glatiramer acetate.

[0196] In some embodiments, the genotype of the subject at said one or more SNPs is obtained indirectly by determining the genotype of the subject at a SNP that is in linkage disequilibrium with said one or more SNPs.

[0197] The invention also provides a kit for identifying a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis as a predicted responder or as a predicted non-responder to glatiramer acetate, the kit comprising at least one probe specific for a SNP selected from the group consisting of the SNPs in Group 1.

[0198] The invention also provides a kit for identifying a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis as a predicted responder or as a predicted non-responder to glatiramer acetate, the kit comprising at least one pair of PCR primers designed to amplify a DNA segment which includes a SNP selected from the group consisting of the SNPs in Group 1.

[0199] The invention also provides a PCR amplification kit comprising

- **[0200]** (i) at least one pair of PCR primers designed to amplify a DNA segment which includes a SNP selected from the group consisting of the SNPs in Group 1, and
- **[0201]** (ii) instructions for use of the PCR primers to amplify the segment of DNA.

[0202] The invention also provides a kit for identifying a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis as a predicted responder or as a predicted non-responder to glatiramer acetate, the kit comprising a reagent for performing a method selected from the group consisting of restriction fragment length polymorphism (RFLP) analysis, sequencing, single strand conformation polymorphism analysis (SSCP), chemical cleavage of mismatch (CCM), gene chip and denaturing high performance liquid chromatography (DHPLC) for determining the identity of at least one SNP selected from the group consisting of the SNPs of Group 1.

[0203] In some embodiments, the kit comprises

(i) at least one pair of PCR primers designed to amplify a DNA segment which includes a SNP selected from the group consisting of the SNPs of Group 1, and

(ii) at least one probe specific for a SNP selected from the group consisting of the SNPs of Group 1.

[0204] The invention also provides a kit for identifying a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis as a predicted responder or as a predicted non-responder to glatiramer acetate, the kit comprising reagents for TaqMan Open

Array assay designed for determining the identity of at least one SNP selected from the group consisting of The SNPs of Group 1.

[0205] In some embodiments the kit further comprises instructions for use of the kit for identifying a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis as a predicted responder or as a predicted non-responder to glatiramer acetate.

[0206] In some embodiments, the one or more single nucleotide polymorphisms (SNPs) is selected from the group consisting of rs947603, rs1007328, rs1573706, rs2177073, rs2487896, rs2511064, rs2521644, rs3135391, rs4148871, rs4343256, rs4344916, rs4369324, rs4445746, rs6097801, rs9508834, rs9944913, rs10853605, rs10931091, rs10950359, rs10988087, rs11599624, rs11617134, rs12256889, rs12639443, rs13042992, rs13238613, rs17087180, rs17575455, rs17771939 and rs17807327.

[0207] In some embodiments, the one or more single nucleotide polymorphisms (SNPs) is selected from the group consisting of rs9508834, rs17807327, rs4344916, rs12639443, rs17087180 and rs17771939.

[0208] In some embodiments, the one or more single nucleotide polymorphisms (SNPs) are selected from the group consisting of rs4344916, rs12639443, rs17087180 and rs17771939.

[0209] In some embodiments, the kit is designed to determine the genotype at SNPs rs9508834, rs17807327, rs4344916, rs12639443, rs17087180 and rs17771939.

[0210] In some embodiments, the kit is designed to determine the genotype at SNPs rs4344916, rs12639443, rs17087180 and rs17771939.

[0211] In some embodiments, the kit is designed to determine the genotype at SNPs rs2521644, rs12256889, rs214526, rs17771939, rs496486, and rs949298.

[0212] In some embodiments, the kit is designed to determine the genotype at SNPs rs2521644, rs12256889, rs214526, rs17771939, rs496486, and rs2511064.

[0213] In some embodiments, the kit is designed to determine the genotype at SNPs rs12256889, rs17771939, rs2511064, and rs2521644.

[0214] In some embodiments, the kit is designed to determine the genotype at SNPs rs11599624, rs12639443, rs13042992, rs13238613, rs17087180, rs17771939, rs17807327, rs2487896, rs3135391, rs4148871, rs4343256, rs4344916, and rs9508834.

[0215] In some embodiments, the kit is designed to determine the genotype at SNPs rs12256889, rs12639443, rs13238613, rs1573706, rs17087180, rs17771939, rs17807327, rs2487896, rs4343256, rs4344916, rs4369324, rs4445746, and rs9944913.

[0216] In some embodiments, the kit is designed to determine the genotype at SNPs rs10988087, rs12639443, rs13042992, rs13238613, rs1573706, rs17087180, rs17771939, rs17807327, rs4148871, rs4344916, rs6097801, and rs9508834.

[0217] In some embodiments, the kit is designed to determine the genotype at SNPs rs10988087, rs12256889, rs12639443, rs17087180, rs17771939, rs2177073, rs2521644, rs4344916, rs4369324, rs6097801, rs9508834, and rs9944913.

[0218] In some embodiments, the kit is designed to determine the genotype at SNPs rs10988087, rs11617134, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2487896, rs4148871, rs4344916, rs4445746, rs6097801, and rs9508834.

[0219] In some embodiments, the kit is designed to determine the genotype at SNPs rs10988087, rs11617134, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2487896, rs2521644, rs4148871, rs4344916, rs4445746, and rs6097801.

[0220] In some embodiments, the kit is designed to determine the genotype at SNPs rs10988087, rs12256889, rs12639443, rs17087180, rs17771939, rs17807327, rs2487896, rs4148871, rs4344916, rs6097801, and rs9508834.

[0221] In some embodiments, the kit is designed to determine the genotype at SNPs rs1007328, rs11617134, rs12639443, rs13238613, rs1573706, rs17087180, rs17771939, rs17807327, rs4343256, rs4344916, rs9508834, and rs9944913.

[0222] In some embodiments, the kit is designed to determine the genotype at SNPs rs12639443, rs17087180, rs17771939, rs17807327, rs2487896, rs4148871, rs4343256, rs4344916, rs4369324, rs4445746, rs6097801, rs9508834, and rs9944913.

[0223] In some embodiments, the kit is designed to determine the genotype at SNPs rs11617134, rs12639443, rs17087180, rs17771939, rs17807327, rs2487896, rs3135391, rs4148871, rs4344916, rs4369324, rs6097801, rs9508834, and rs9944913.

[0224] In some embodiments, the kit is designed to determine the genotype at SNPs rs10988087, rs12639443, rs13238613, rs17087180, rs17771939, rs2487896, rs4148871, rs4343256, rs4344916, and rs9508834.

[0225] In some embodiments, the kit is designed to determine the genotype at SNPs rs11617134, rs12256889, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2177073, rs2487896, rs4343256, rs4344916, rs6097801, and rs9508834.

[0226] In some embodiments, the kit is designed to determine the genotype at SNPs rs10950359, rs11617134, rs12639443, rs17087180, rs17771939, rs2487896, rs2511064, rs3135391, rs4148871, rs4343256, rs4344916, rs9508834, and rs9944913.

[0227] In some embodiments, the kit is designed to determine the genotype at SNPs rs12256889, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2487896, rs2521644, rs4344916, and rs6097801.

[0228] In some embodiments, the kit is designed to determine the genotype at SNPs rs10950359, rs10988087, rs11599624, rs12256889, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2521644, rs3135391, rs4344916, and rs9508834.

[0229] In some embodiments, the kit is designed to determine the genotype at SNPs rs1007328, rs10950359, rs12256889, rs12639443, rs13042992, rs1573706, rs17087180, rs17771939, rs17807327, rs4343256, rs4344916, rs947603, and rs9508834.

[0230] In some embodiments, the kit is designed to determine the genotype at SNPs rs11599624, rs12256889, rs12639443, rs1573706, rs17087180, rs17771939, rs17807327, rs2177073, rs2487896, rs4344916, rs6097801, rs9508834, and rs9944913.

[0231] In some embodiments, a score is assigned to each genotype of each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the scores are approximately as shown in tables 18a-s and 19a-h.

[0232] In some embodiments, a relative weight is assigned to each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the relative weight is approximately as shown in one of tables 20-36, wherein the table selected corresponds to the SNPs at which a genotype was determined.

[0233] As used herein, a genetic marker refers to a DNA sequence that has a known location on a chromosome. Several non-limiting examples of classes of genetic markers include SNP (single nucleotide polymorphism), STR (short tandem repeat), and SFP (single feature polymorphism). VNTR (variable number tandem repeat), microsatellite polymorphism, insertions and deletions. The genetic markers associated with the invention are SNPs.

[0234] As used herein a SNP or "single nucleotide polymorphism" refers to a specific site in the genome where there is a difference in DNA base between individuals. In some embodiments the SNP is located in a coding region of a gene. In other embodiments the SNP is located in a noncoding region of a gene. In still other embodiments the SNP is located in an intergenic region.

[0235] Several non-limiting examples of databases from which information on SNPs or genes that are associated with human disease can be retrieved include: NCBI resources, The SNP Consortium LTD, NCBI dbSNP database, International HapMap Project, 1000 Genomes Project, Glovar Variation Browser, SNPStats, PharmGKB, GEN-SniP, and SNPedia.

[0236] In some embodiments, SNPs associated with the invention comprise one or more of the SNPs listed in Tables 1-3 or table 16. In some embodiments, multiple SNPs are evaluated simultaneously while in other embodiments SNPS are evaluated separately. SNPs are identified herein using the rs identifier numbers in accordance with the NCBI dbSNP database, which is publically available at: http://www.ncbi.nlm.nih.gov/projects/SNP/.

[0237] In some embodiments, SNPs in linkage disequilibrium with the SNPs found to be associated with response or non-response to GA are useful for obtaining similar results.

[0238] As used herein, linkage disequilibrium refers to the non-random association of SNPs at one loci. Techniques for the measurement of linkage disequilibrium are known in the art. As two SNPs are in linkage disequilibrium if they are inherited together, the information they provide is correlated to a certain extent. SNPs in linkage disequilibrium with the SNPs included in the models can be obtained from databases such as HapMap or other related databases, from experimental setups run in laboratories or from computer-aided in-silico experiments.

[0239] Determining the genotype of a subject at a position of SNP as specified herein, e.g. as specified by NCBI dbSNP rs identifier, may comprise directly genotyping, e.g. by determining the identity of the nucleotide of each allele at the locus of SNP, and/or indirectly genotyping, e.g. by determining the identity of each allele at one or more loci that are in linkage disequilibrium with the SNP in question and which allow one to infer the identity of each allele at the locus of SNP in question with a substantial degree of confidence.

[0240] In some cases, indirect genotyping may comprise determining the identity of each allele at one or more loci that are in sufficiently high linkage disequilibrium with the SNP in question so as to allow one to infer the identity of each allele at the locus of SNP in question with a probability of at least 85%, at least 90% or at least 99% certainty.

[0241] A genotype at a position of SNP (genotype "at a" SNP) may be represented by a single letter which corresponds to the identity of the nucleotide at the SNP, where A represents adenine, T represents thymine, C represents cytosine, and G represents guanine. The identity of two alleles at a single SNP may be represented by a two letter combination of A, T, C, and G, where the first letter of the two letter combination represents one allele and the second letter represents the second allele, and where A represents adenine, T represents thymine, C represents cytosine, and G represents guanine. Thus, a two allele genotype at a SNP can be represented as, for example, AA, AT, AG, AC, TT, TG, TC, GG, GC, or CC. It is understood that AT, AG, AC, TG, TC, and GC are equivalent to TA, GA, CA, GT, CT, and CG, respectively.

[0242] The SNPs of the invention can be used as predictive indicators of the response to GA in subjects afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis. Aspects of the invention relate to determining the presence of SNPs through obtaining a patient DNA sample and genotyping the patient sample at one or more SNPs, or at a certain set of SNPs. It should be appreciated that a patient DNA sample can be extracted, and a SNP can be detected in the sample, through any means known to one of ordinary skill in art. Some non-limiting examples of known techniques include detection via restriction fragment length polymorphism (RFLP) analysis, microarrays including but mot limited to planar microarrays or bead arrays, gene arrays, PCR arrays including TaqMan Open Array, sequencing, single strand conformation polymorphism analysis (SSCP), chemical cleavage of mismatch (CCM), and denaturing high performance liquid chromatography (DHPLC).

[0243] In some embodiments, a SNP is detected through PCR amplification and sequencing of the DNA region comprising the SNP.

[0244] In some embodiments, a SNP is detected through PCR amplification in the presence of a probe specific for a SNP.

[0245] Probes and methods for their use in detecting SNPs are well known in the art and are described, for example, in Barnes M R. Genetic Variation: Methods and Protocols 1st ed. New York: Humana Press, 2010 and Komar, AA. Single Nucleotide Polymorphisms: Methods and Protocols 2^{nd} ed. York: Humana Press, 2009.

[0246] In some embodiments SNPs are detected using DNA microarrays including DNA CHIPs. Microarrays for detection of genetic polymorphisms, changes or mutations (in general, genetic variations) such as a SNP in a DNA sequence, comprise a solid surface, typically glass, on which a high number of genetic sequences are deposited (the probes), complementary to the genetic variations to be studied. Using standard robotic printers to apply probes to the array a high density of individual probe features can be obtained, for example probe densities of 600 features per cm^2 or more can be typically achieved. The positioning of probes on an array is precisely controlled by the printing device (robot, inkjet printer, photolithographic mask etc) and probes are aligned in a grid. The organisation of probes on the array facilitates the subsequent identification of specific probe-target interactions.

[0247] Additionally it is common, but not necessary, to divide the array features into smaller sectors, also grid-shaped, that are subsequently referred to as sub-arrays. Sub-arrays typically comprise 32 individual probe features although lower (e.g. 16) or higher (e.g. 64 or more) features can comprise each subarray.

[0248] In some embodiments, detection of genetic variation such as the presence of a SNP involves hybridization to sequences which specifically recognize the normal and the mutant allele in a fragment of DNA derived from a test sample. Typically, the fragment has been amplified, e.g. by using the polymerase chain reaction (PCR), and labelled e.g. with a fluorescent molecule. A laser can be used to detect bound labelled fragments on the chip and thus an individual who is homozygous for the normal allele can be specifically distinguished from heterozygous individuals (in the case of autosomal dominant conditions then these individuals are referred to as carriers) or those who are homozygous for the mutant allele.

[0249] In some embodiments, the amplification reaction and/or extension reaction is carried out on the microarray or bead itself. For differential hybridization based methods there are a number of methods for analysing hybridization data for genotyping: Increase in hybridization level: The hybridization levels of probes complementary to the normal and mutant alleles are compared. Decrease in hybridization level: Differences in the sequence between a control sample and a test sample can be identified by a decrease in the hybridization level of the totally complementary oligonucleotides with a reference sequence. A loss approximating 100% is produced in mutant homozygous individuals while there is only an approximately 50% loss in heterozygotes.

[0250] In Microarrays for examining all the bases of a sequence of "n" nucleotides ("oligonucleotide") of length in both strands, a minimum of "2n" oligonucleotides that overlap with the previous oligonucleotide in all the sequence except in the nucleotide are necessary. Typically the size of the oligonucleotides is about 25 nucleotides. However it should be appreciated that the oligonucleotide can be any length that is appropriate as would be understood by one of ordinary skill in the art.

[0251] The increased number of oligonucleotides used to reconstruct the sequence reduces errors derived from fluctuation of the hybridization level. However, the exact change in sequence cannot be identified with this method; in some embodiments this method is combined with sequencing to identify the mutation. Where amplification or extension is carried out on the microarray or bead itself, three methods are presented by way of example: In the Minisequencing strategy, a mutation specific primer is fixed on the slide and after an extension reaction with fluorescent dideoxynucleotides, the image of the Microarray is captured with a scanner. In the Primer extension strategy, two oligonucleotides are designed for detection of the wild type and mutant sequences respectively. The extension reaction is subsequently carried out with one fluorescently labelled nucleotide and the remaining nucleotides unlabelled. In either case the starting material can be either an RNA sample or a DNA product amplified by PCR. In the Tag arrays strategy, an extension reaction is carried out in solution with specific primers, which carry a determined 5^1 sequence or "tag". The use of Microarrays with oligonucleotides complementary to these sequences or "tags" allows the capture of the resultant products of the extension. Examples of this include the high density Microarray "Flex-flex" (Affymetrix). In the Illumina 1M Dou BeadChip array (http://www.illumina.com/products/human1m_duo_dna_analysis_beadchip_kits.ilmn), SNP genotypes are generated from fluorescent intensities using the manufacturer's default cluster settings.

[0252] In some aspects of the invention, predictive models including SNPs from tables 1-3 or table 16, are used to predict the response to GA.

[0253] In some aspects of the invention, predictive models include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more SNPs.

[0254] In some aspects of the invention, predictive models include 4, 6, 10, 11, 12, 13 or 14 SNPs.

[0255] In some aspects of the invention, a prediction model includes a specific set of SNPs constituting the model.

[0256] Some specific sets of SNPs constituting models of the invention are presented in tables 5, 8 and 17.

[0257] In some aspects of the invention, a predictive model (or "model") is used to calculate the response probability p(Response) of a patient based on the genotype of the patient at the SNPs included in the specific model.

[0258] In some aspects of the invention, patients with a p(Response) above a specific threshold ("a predictive threshold") are predicted to be responders to GA while patients with a p(Response) below the same predictive threshold are predicted to be non-responders to GA.

[0259] In other aspects of the invention, patients with a p(Response) above a first predictive threshold (for example. 0.8) are predicted to be responders to GA while patients with a p(Response) below a second predictive threshold which is lower than the first threshold (for example, 0.2) are predicted to be non-responders to GA.

[0260] In some aspects of the invention, patients with a p(Response) above 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 or 0.9 are predicted to be responders.

[0261] In some aspects of the invention, patients with a p(Response) below 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 or 0.9 are predicted to be non-responders.

[0262] In a certain aspect of the invention, the predictive threshold is 0.5, such that a patient with response probability p(Response) above 0.5 is predicted to be a responder to GA treatment and a patient with p(Response) below 0.5 is predicted to be a non-responder to GA treatment.

[0263] In another aspect of the invention, the predictive threshold is 0.8, such that a patient with response probability p(Response) above 0.8 is predicted to be a responder to GA treatment and a patient with p(Response) below 0.8 is predicted to be a non-responder to GA treatment.

[0264] In some aspects of the invention, the p(Response) is compared to a predetermined threshold or thresholds in order to decide whether to treat the patient with GA.

[0265] In certain aspects of the invention, such comparison is made by the patient and/or a caregiver including but not limited to a healthcare provider and a family member, or by a medical or a scientific entity including but not limited a hospital, a medical institute or a lab.

[0266] In other aspects of the invention, the p(Response) is used by the patient and/or a caregiver including but not limited to a healthcare provider and a family member or by a medical or a scientific entity including but not limited a hospital, a medical institute or a lab in order to decide whether to treat the patient with GA without referring to a specific/predetermined predictive threshold or thresholds.

[0267] In some aspects of the invention, the p(Response) calculation includes using a kit.

[0268] In some aspects of the invention, the use of the kit comprises genotyping of the patient.

[0269] In some aspects of the invention, the use of the kit comprises calculating the p(Response) of the patient.

[0270] In certain aspects of the invention, the use of the kit comprises an indication to the user if the patient is genetically predicted to be a responder or a non-responder to GA.

[0271] In some aspects of the invention measurement of clinical variables comprises part of the prediction model predicting response to GA along with the genetic variables. Some non-limiting examples of clinical variables are the age of the patient (in years), gender of patient, clinical manifestations and MRI parameter. "Clinical manifestations" include but are not limited to EDSS score and relapse rate. "MRI parameters" include but are not limited to the volume and/or number of T1 enhancing lesions and/or T2 enhancing lesions. In certain aspect of the invention, the clinical variables taken into account are as measured at the time of the decision about the treatment suitable for the patient, or measured at a time point which seams reasonable to the physician, researcher or other professional involved in the decision.

[0272] The identification of a patient as a responder or as a non-responder to GA based on the presence of at least one SNP from tables 1-3 or table 16 a set of SNPs from tables 1-3, 5, 8, 16 or 17, or the combination of a SNP or a set of SNPs from tables 1-3, 5, 8, 16 or 17 with one or more clinical variables described above, may be used for predicting response to GA.

[0273] Also within the scope of the invention are kits and instructions for their use.

[0274] In some embodiments of the invention the kits are diagnostic kits.

[0275] In some embodiments of the invention the kits are PCR amplification kits.

[0276] In some embodiments kits associated with the invention are kits for identifying one or more SNPs within a patient sample.

[0277] In some embodiments a kit may contain primers for amplifying a specific genetic locus.

[0278] In some embodiments, a kit may contain a probe for hybridizing to a specific SNP.

[0279] In some embodiments kits associated with the invention contain at least one pair of PCR primers designed to amplify a DNA segment which includes a SNP of the invention.

[0280] In some embodiments kits associated with the invention contain a set of pairs of PCR primers designed to amplify a specific set of SNPs constituting a model of the invention.

[0281] In some embodiments kits associated with the invention contain at least one probe specific for a SNP of the invention.

[0282] In some embodiments kits associated with the invention contain a set of probes specific for a specific set of SNPs constituting a model of the invention.

[0283] The kit of the invention can include reagents for conducting each of the following assays including but not limited to restriction fragment length polymorphism (RFLP) analysis, microarrays including but not limited to planar microarrays or bead arrays, sequencing, single strand conformation polymorphism analysis (SSCP), chemical cleavage of mismatch (CCM), and denaturing high performance liquid chromatography (DHPLC), PCR amplification and sequencing of the DNA region comprising the SNP. In some aspects of the invention, the kit comprises a TaqMan Open Array or reagents for conducting a TaqMan Open Array assay.

[0284] In some aspects of the invention, the TaqMan Open Array is designed for genotyping SNPs of the invention. In some aspects of the invention, the TaqMan Open Array is designed for genotyping a specific set of SNPs constituting a model of the invention.

[0285] A kit of the invention can include a description of use of the contents of the kit for participation in any biological or chemical mechanism disclosed herein.

[0286] A kit can include instructions for use of the kit components alone or in combination with other methods or compositions for assisting in screening or diagnosing a sample and/or determining whether a subject is predicted to be a responder or a non-responder to GA.

[0287] In some embodiments, a kit of the invention includes instructions for calculating a p(Response) of a patient based on his/her genotype in specific SNPs. In some embodiments, the instructions include a predictive threshold or predictive thresholds and instructions or recommendations of how to compare the calculated p(Response) to the threshold/s in order to predict whether the subject is a responder or non-responder to GA.

Forms of Multiple Sclerosis:

[0288] There are five distinct disease stages and/or types of MS:

[0289] 1) benign multiple sclerosis;

[0290] 2) relapsing-remitting multiple sclerosis (RRMS);

[0291] 3) secondary progressive multiple sclerosis (SPMS);

[0292] 4) progressive relapsing multiple sclerosis (PRMS); and

[0293] 5) primary progressive multiple sclerosis (PPMS).

[0294] Benign multiple sclerosis is a retrospective diagnosis which is characterized by 1-2 exacerbations with complete recovery, no lasting disability and no disease progression for 10-15 years after the initial onset. Benign multiple sclerosis may, however, progress into other forms of multiple sclerosis.

[0295] Patients suffering from RAMS experience sporadic exacerbations or relapses, as well as periods of remission. Lesions and evidence of axonal loss may or may not be visible on MRI for patients with RRMS.

[0296] SPMS may evolve from RRMS. Patients afflicted with SPMS have relapses, a diminishing degree of recovery during remissions, less frequent remissions and more pronounced neurological deficits than RRMS patients. Enlarged ventricles, which are markers for atrophy of the corpus callosum, midline center and spinal cord, are visible on MRI of patients with SPMS.

[0297] PPMS is characterized by a steady progression of increasing neurological deficits without distinct attacks or remissions. Cerebral lesions, diffuse spinal cord damage and evidence of axonal loss are evident on the MRI of patients with PPMS. PPMS has periods of acute exacerbations while proceeding along a course of increasing neurological deficits without remissions. Lesions are evident on MRI of patients suffering from PRMS. (28)

[0298] A clinically isolated syndrome (CIS) is a single monosymptomatic attack compatible with MS, such as optic neuritis, brain stem symptoms, and partial myelitis. Patients with CIS that experience a second clinical attack are generally considered to have clinically definite multiple sclerosis (CDMS). Over 80 percent of patients with a CIS and MRI lesions go on to develop MS, while approximately 20 percent have a self-limited process. (29, 30) Patients who experience a single clinical attack consistent with MS may have at least one lesion consistent with multiple sclerosis prior to the development of clinically definite multiple sclerosis.

[0299] Multiple sclerosis may present with optic neuritis, blurring of vision, diplopia, involuntary rapid eye movement, blindness, loss of balance, tremors, ataxia, vertigo, clumsiness of a limb, lack of co-ordination, weakness of one or more extremity, altered muscle tone, muscle stiffness, spasms, tingling, paraesthesia, burning sensations, muscle pains, facial pain, trigeminal neuralgia, stabbing sharp pains, burning tingling pain, slowing of speech, slurring of words, changes in rhythm of speech, dysphagia, fatigue, bladder problems (including urgency, frequency, incomplete emptying and incontinence), bowel problems (including constipation and loss of bowel control) impotence, diminished sexual arousal, loss of sensation, sensitivity to heat, loss of short term memory, loss of concentration, or loss of judgment or reasoning.

Relapsing Form of Multiple Sclerosis:

[0300] The term relapsing MS includes:

- **[0301]** 1) patients with RRMS;
- **[0302]** 2) patients with SPMS and superimposed relapses; and
- **[0303]** 3) patients with CIS who show lesion dissemination on subsequent MRI scans according to McDonald's criteria.

[0304] As used herein, relapsing forms of multiple sclerosis include: Relapsing-remitting multiple sclerosis (RAMS), characterized by unpredictable acute episodes of neurological dysfunction (relapses), followed by variable recovery and periods of clinical stability;

[0305] Secondary Progressive MS (SPMS), wherein patients having RRMS develop sustained deterioration with or without relapses superimposed; and

[0306] Primary progressive-relapsing multiple sclerosis (PPRMS) or progressive-relapsing multiple sclerosis (PRMS), an uncommon form wherein patients developing a progressive deterioration from the beginning can also develop relapses later on.

Kyrtzke Expanded Disability Status Scale (EDSS):

[0307] The Kurtzke Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis. The EDSS replaced the previous Disability Status Scales which used to bunch people with MS in the lower brackets. The EDSS quantifies disability in eight Functional Systems (FS) and allows neurologists to assign a Functional System Score (FSS) in each of these. The Functional Systems are: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual & cerebral (according to www.mult-sclerosis.org/expandeddisabil itystatusscale).

Clinical Relapse:

[0308] A clinical relapse, which may also be used herein as "relapse," "confirmed relapse," or "clinically defined relapse," is defined as the appearance of one or more new neurological abnormalities or the reappearance of one or more previously observed neurological abnormalities.

[0309] This change in clinical state must last at least 48 hours and be immediately preceded by a relatively stable or improving neurological state of at least 30 days. This criterion is different from the clinical definition of exacerbation "at least 24 hours duration of symptoms," (31) as detailed in the section "relapse evaluation."

[0310] An event is counted as a relapse only when the subject's symptoms are accompanied by observed objective neurological changes, consistent with:

a) an increase of at least 0.5 in the EDSS score or one grade in the score of two or more of the seven FS (32); or,

b) two grades in the score of one of FS as compared to the previous evaluation.

[0311] The subject must not be undergoing any acute metabolic changes such as fever or other medical abnormality. A change in bowel/bladder function or in cognitive function must not be entirely responsible for the changes in EDSS or FS scores.

[0312] As used herein "a predicted responder/a genetically predicted responder to glatiramer acetate" is a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis that is predicted to be a responder to glatiramer acetate based on his/her genotype at SNPs, sets of SNPs or models of the invention. Similarly, a subject or patient which is predicted to be a non-responder to glatiramer acetate treatment based on his/her genotype is called "a predicted non-responder/genetically predicted non-responder to glatiramer acetate".

[0313] As used herein, a "multiple sclerosis drug" is a drug or an agent intended to treat clinically defined MS, CIS, any form of neurodegenerative or demyelinating diseases, or symptoms of any of the above mentioned diseases. "Multiple sclerosis drugs" may include but are not limited to antibodies, immunosuppressants, anti-inflammatory agents, immunomodulators, cytokines, cytotoxic agents and steroids and may include approved drugs, drugs in clinical trial, or alternative treatments, intended to treat clinically defined MS, CIS or any form of neurodegenerative or demyelinating diseases. "multiple sclerosis drugs" include but are not limited to Interferon and its derivatives (including BETASERON®, AVONEX® and REBIF®), Mitoxantrone and Natalizumab. Agents approved or in-trial for the treatment of other autoimmune diseases, but used in a MS or CIS patient to treat MS or CIS are also defined as multiple sclerosis drugs.

[0314] As used herein, a "naïve patient" is a subject that has not been treated with any multiple sclerosis drugs as defined in the former paragraph.

[0315] The administration of glatiramer acetate may be oral, nasal, pulmonary, parenteral, intravenous, intra-articular, transdermal, intradermal, subcutaneous, topical, intramuscular, rectal, intrathecal, intraocular, buccal or by gavage.

EXPERIMENTAL DETAILS

Examples

Analysis of DNA Sequence Polymorphism in Patients Classified as Responders or Non-Responders to GA

Methods

Subjects:

[0316] Relapsing-remitting multiple sclerosis patients were treated with either 20 mg GA or 40 mg GA daily in the Teva FORTE clinical trial www.medicalnewstoday.com/articles/48863.php). Blood samples were drawn from each subject that signed an informed consent for the pharmacogenetic study and analyzed as described below.

[0317] The incidence of clinical relapses, and MRI data after 12 months treatment (T1 and T2 enhancing lesions) were used to define patients as responders or non-responders, according to two definitions: A "broad definition" or A "narrow definition" described herein below. In a first analysis, the subjects were binomially classified as "responders" (R) or "non-responders" (NR) according to a definition herein below defined as "broad". A further analysis was then conducted using a narrower definition, excluding some of the patients formerly classified as responders and leading to a much smaller sample. In addition, a third analysis used a continuous measure of response to GA, which was calculated based on the patients' clinical data and MRI parameters as described herein below ("A continuous measure").

Response Definitions

[0318] A "broad definition" or "broad phenotype": Responders according to the broad definition were defined as patients in the treatment group which had no relapse during the 12 months treatment period, and no T1 enhancing lesions and no new T2 enhancing lesions were observed at 12 months (end of 12 month treatment). Non responders were defined as patients having at least one relapse during the 12 months treatment period, and more than one new T2 enhancing lesion at 12 months.

[0319] A "narrow definition" or "narrow phenotype": Responders according to the narrow definition, were defined as patients in the treatment group which had no relapse during the 12 months treatment period, and no T1 enhancing lesions and no new T2 enhancing lesions at 12 months, as in the "broad" definition. In addition, patients in which no T1 enhancing lesion were observed at the time of recruitment and subjects in which the volume of T2 lesions significantly increased by 1000 mm^3) during the experiment were not defined as responders. The definition of Non-responders was the same as in the "broad" definition.

[0320] A "Composite measure", "composite phenotype" or "continuous measure" is calculated based on the clinical and MRI parameters (relapse rate during the 12 months treatment and T1 and T2 enhancing lesions at 12 months). This measure which is a continuous measure (in contrast to the "responder/non-responder" Binomial measure) was used in quantitative GWAS looking for SNPs associated with GA R/NR.

Relapse Evaluation

[0321] A clinical relapse was defined as the appearance of one or more new neurological abnormalities or the reappearance of one or more previously observed neurological abnormalities.

[0322] This change in clinical state lasted at least 48 hours and was immediately preceded by a relatively stable or improving neurological state of at least 30 days. The criterion used in the study was different from the clinical definition of exacerbation "at least 24 hours duration of symptoms". (31) Since "in study" exacerbation definition must be supported by an objective neurological evaluation (see next paragraph), a neurological deficit must sustain long enough to eliminate pseudo exacerbations.

[0323] An event was counted as a relapse only when the subject's symptoms were accompanied by observed objective neurological changes, consistent with:

a) an increase of at least 0.5 in the EDSS score or one grade in the score of two or more of the seven FS (32); or,

b) two grades in the score of one of FS as compared to the previous evaluation.

[0324] The subject was not undergoing any acute metabolic changes such as fever or other medical abnormality. A change in bowel/bladder function or in cognitive function was not entirely responsible for the changes in EDSS or FS scores.

Subject Evaluation by the Examining Neurologist

[0325] A complete neurological assessment was performed at months −1 (screening), 0 (baseline), 3, 6, 9, 12 (end of double-blind phase), 18 and 24 (termination/early discontinuation).

Relapse Determination by the Treating Neurologist

[0326] The decision as to whether the neurological change was considered a confirmed relapse was made by the Treating Physician, based on EDSS/FS actual (not converted) scores assessed by the Examining Neurologist.

[0327] Follow-up visits to monitor the course of the relapse were made at the Treating Physician's discretion, in addition to the assessment at the next scheduled visit, but the neurological assessments were performed by the Examining Neurologist.

Relapse Evaluation Procedures

[0328] Subjects were instructed to telephone their study site within 48 hours should any symptoms suggestive of a relapse appear.

[0329] The Examining Neurologist evaluated the subject within 7 days of symptoms onset, conditional upon a symptomatic period of $\geqq$48 hours. The Treating Neurologist/Physician evaluated the subject once any symptom suggestive of a relapse occurred.

[0330] In case of a suggestive relapse during a scheduled or unscheduled visit, the Treating Neurologist/Physician referred the subject to the Examining eurologist/Physician.

Analysis

[0331] The DNA chip selected for the GWAS was Illumina 1M Dou BeadChip(http://www.illumina.com/products/human1m_duo_dna_analysis_beadchip_kits.ilmn). Normalized bead intensity data obtained for each sample were analyzed with the Illumina Genome Studio v1.0.2 software, which generated SNP genotypes (including the different homozygotes and heterozygotes), from fluorescent intensities using the manufacturer's default cluster settings. Quality Controls (QC) included evaluation of call rate, check of SNPs with (1) no calls, (2) with MAF less than 0.05 and (3) with genotyping rate less than 0.9. SNPs that did not match these criteria were removed from further analyses. Data from individuals with missing genotyping >10% were also excluded from analyses. An additional quality control step was performed to exclude individuals and/or markers based on Mendelian error rate (PLINK; 56) version 1.04). SNPs with more than 10% and families with more than 5% Mendelian errors were discarded. Additionally, SNPs that showed a significant deviation from Hardy-Weinberg Equilibrium (HWE—$p<0.00001$) were flagged for evaluation before excluding them from further analyses.

[0332] GWAS analyses have been performed with the PLINK software (http://pngu.mgh.harvard.edu/-purcell/

plink/), using the appropriate subroutines to analyze binomial or continuous measures. Results have not been corrected for multiple testing. SNPs with a p value of 10^{-4} or lower from the three analyses are considered as having a predictive ability of GA response. For the binomial measures (broad and narrow definitions), a marker was selected if the distribution of genotypes were significantly different in responders than in non responders.

Predictive Modeling

[0333] To find genotypic profiles that discriminate responders (R) from the non-responders (NR) to the treatment, we used a backward stepwise logistic regression procedure on the SNPs that emerged significant using the narrow definition (e.g., at p-value=10^{-4} or lower). Other models were generated based on combinatorial optimization heuristics. Once a pool of models was created, selected models were chosen based on the low value of Akaike's Information Criterion (AIC) and low number SNPs in the model. The model chosen in the previous step went through "Leave one out" cross validation, searching for high values of the Area Under the ROC curve.

[0334] The response probability p(Response) of a specific patient was calculated according to the tables and formulas indicated for each specific model.

[0335] The SNPs were further genotypes by the TaqMan open array assay and the predictive value in the FORTE cohort and other cohorts was evaluated. Some of the predictive models were also evaluated in the same cohorts.

Results

[0336] GWAS Using the Three R/NR Phenotypes Found 86 SNPs having a Predictive Value for the Response to Treatment with GA

[0337] As described in the "methods" section, SNPs with a p value of 10^{-4} or lower from the three analyses were considered as having a predictive ability of GA response.

[0338] When we conducted the GWAS analysis based on the broad definition, 17 SNPs having p value of 10^{-4} or lower were round These SNPs are presented in table 1.

[0339] A second analysis was performed which included responders and non-responders according to the narrow definition. Using this definition, 31 SNPs having p value of 10^{-4} or lower were found. These SNPs are presented in table 2.

[0340] Performing the analysis using the composite phenotype, Genome-Wide (GW) significance was found for 38 SNPs having p value of 10^{-4} or lower, which are presented in table 3.

TABLE 1

Annotated SNPs with p-val < or = 1*10E−05 from the GWAS of the broad phenotype. Seventeen (17) SNPs have been genotyped with the Human1M Illumina chip and 110 additional SNPs are uniquely tagged by the genotyped SNPs. Among these 110 tagged SNPs, 11 are cross-represented within the list of the 17 "taggers", ultimately leading to 99 tagged SNPs that are not present, on the Human 1M chip.

SNP	rank	P	chrom	coordinates	closest gene	type	distance to gene	Tagged_SNP	Tagged_SNP_r2	Tagged_SNP_P
rs17771939	1	3.05E−07	8	94259105	AC011118.2	INTERGENIC	99590			
rs6097801	2	9.87E−07	20	52767434	CYP24A1	DOWNSTREAM	2554			
rs6097797	3	1.60E−06	20	52763331	CYP24A1	INTERGENIC	6657			
								rs4811492	1	—
								rs1886308	1	—
								rs6097782	1	—
								rs6091820	1	—
								rs11907046	1	—
								rs16999008	1	—
								rs873216	1	—
								rs6097790	1	—
								rs6097793	1	—
								rs4809955	1	1.83E−06
								rs8118441	1	—
								rs6097801	1	9.87E−07
rs4809955	4	1.83E−06	20	52765349	CYP24A1	DOWNSTREAM	4639			
rs1229553	5	2.53E−06	7	97432533	; ASNS	INTERGENIC	48907			
								rs1234567	1	—
								rs1229568	1	3.76E−06
								rs1234947	1	—
								rs1237625	1	—
								rs1229564	1	3.76E−06
								rs1229563	1	—
								rs1229562	1	—
								rs1229559	1	—
								rs1229558	1	—
								rs1229557	1	—
								rs1229555	1	—
								rs2530123	0.93	—
								rs2530121	0.93	—
rs1229542	6	3.76E−06	7	97422926	TAC1	INTERGENIC	53048			

TABLE 1-continued

Annotated SNPs with p-val < or = 1*10E−05 from the GWAS of the broad phenotype. Seventeen (17) SNPs have been genotyped with the Human1M Illumina chip and 110 additional SNPs are uniquely tagged by the genotyped SNPs. Among these 110 tagged SNPs, 11 are cross-represented within the list of the 17 "taggers", ultimately leading to 99 tagged SNPs that are not present, on the Human 1M chip.

SNP	rank	P	chrom	coordinates	closest gene	type	distance to gene	Tagged_SNP	Tagged_SNP_r2	Tagged_SNP_P
rs1229568	7	3.76E−06	7	97425721	ASNS	INTERGENIC	55719			
								rs1234567	1	—
								rs1234947	1	—
								rs1237625	1	—
								rs1229564	1	3.76E−06
								rs1229563	1	—
								rs1229562	1	—
								rs1229559	1	—
								rs1229558	1	—
								rs1229557	1	—
								rs1229555	1	—
								rs1229553	1	2.53E−06
								rs2530123	0.93	—
								rs2530121	0.93	—
rs1229564	8	3.76E−06	7	97428673	ASNS	INTERGENIC	52767			
								rs1234567	1	—
								rs1229568	1	3.76E−06
								rs1234947	1	—
								rs1237625	1	—
								rs1229563	1	—
								rs1229562	1	—
								rs1229559	1	—
								rs1229558	1	—
								rs1229557	1	—
								rs1229555	1	—
								rs1229553	1	2.53E−06
								rs2530123	0.93	—
								rs2530121	0.93	—
rs4344916	9	3.84E−06	2	35597319	AC083939.1	INTERGENIC	−99352			
								rs4670454	0.84	—
								rs1439859	0.88	0.0008
								rs7570329	0.88	—
								rs1439850	0.38	—
								rs10208122	0.88	—
								rs7587522	0.88	—
								rs4670460	0.88	—
								rs12477791	0.88	—
								rs17327405	0.88	0.004
								rs7419474	0.88	—
								rs2371748	0.88	—
								rs11124426	0.88	—
								rs7608244	0.88	—
								rs13424077	0.92	2.33E−05
								rs13398774	0.96	—
								rs13429141	0.88	—
								rs4233912	0.92	—
								rs10168563	0.92	—
								rs4643516	0.88	—
								rs7579183	0.88	0.0002
								rs10174888	0.92	—
								rs10184819	0.88	—
								rs4371344	0.88	0.0004
								rs10195590	0.88	—
								rs7584849	0.88	—
								rs6543931	0.87	0.0015
								rs4533454	0.92	—
								rs7603696	0.92	0.0003
								rs7584898	0.96	—
								rs11680546	0.96	—
								rs6739671	0.96	—
								rs9332420	0.96	1.13E−05
								rs7556865	0.96	—
								rs7599336	0.96	—
								rs13021482	0.96	1.48E−05
								rs6726189	0.96	—
								rs6741426	0.96	—
								rs11674793	0.96	—

TABLE 1-continued

Annotated SNPs with p-val < or = 1*10E−05 from the GWAS of the broad phenotype. Seventeen (17) SNPs have been genotyped with the Human1M Illumina chip and 110 additional SNPs are uniquely tagged by the genotyped SNPs. Among these 110 tagged SNPs, 11 are cross-represented within the list of the 17 "taggers", ultimately leading to 99 tagged SNPs that are not present, on the Human 1M chip.

SNP	rank	P	chrom	coordinates	closest gene	type	distance to gene	Tagged_SNP	Tagged_SNP_r2	Tagged_SNP_P
								rs7560990	0.96	—
								rs6543934	0.96	1.48E−05
								rs11694344	0.96	1.82E−05
								rs6543935	0.96	—
								rs4578835	1	—
								rs4281882	1	—
								rs4289164	1	6.43E−06
								rs4435429	1	—
								rs11124430	0.88	0.0005
rs2487896	10	5.51E−06	10	100802380	HPSE2	INTRONIC	0			
								rs2487889	0.93	2.86E−05
rs5908518	11	6.09E−06	X	142128422	SPANXN4	INTERGENIC	5934			
rs4289164	12	6.43E−06	2	35594631	AC083939.1	INTERGENIC	−102040			
								rs4670454	0.84	—
								rs1439859	0.88	0.0008
								rs7570329	0.88	—
								rs1439850	0.88	—
								rs10208122	0.88	—
								rs7587522	0.88	—
								rs4670460	0.88	—
								rs12477791	0.88	—
								rs17327405	0.88	0.004
								rs7419474	0.88	—
								rs2371748	0.88	—
								rs11124426	0.88	—
								rs7608244	0.88	—
								rs13424077	0.92	2.33E−05
								rs13398774	0.96	—
								rs13429141	0.88	—
								rs4233912	0.92	—
								rs10168563	0.92	—
								rs4643516	0.88	—
								rs7579183	0.88	0.0002
								rs10174888	0.92	—
								rs10184819	0.88	—
								rs4371344	0.88	0.0004
								rs10195590	0.88	—
								rs7584849	0.88	—
								rs6543931	0.87	0.0015
								rs4533454	0.92	—
								rs7603696	0.92	0.0003
								rs7584898	0.96	—
								rs11680546	0.96	—
								rs6739671	0.96	—
								rs9332420	0.96	1.13E−05
								rs7556865	0.96	—
								rs7599336	0.96	—
								rs13021482	0.96	1.48E−05
								rs6726189	0.96	—
								rs6741426	0.96	—
								rs11674793	0.96	—
								rs7560990	0.96	—
								rs6543934	0.96	1.48E−05
								rs11694344	0.96	1.82E−05
								rs6543935	0.96	—
								rs4578835	1	—
								rs4281882	1	—
								rs4344916	1	3.84E−06
								rs4435429	1	—
								rs11124430	0.88	0.0005
rs9405541	13	6.55E−06	6	2052811	GMDS	INTRONIC	0			
								rs9392358	1	—
								rs9378319	1	—
								rs12055694	1	6.55E−06
								rs17134651	1	—
								rs9405546	1	—

TABLE 1-continued

Annotated SNPs with p-val < or = 1*10E−05 from the GWAS of the broad phenotype. Seventeen (17) SNPs have been genotyped with the Human1M Illumina chip and 110 additional SNPs are uniquely tagged by the genotyped SNPs. Among these 110 tagged SNPs, 11 are cross-represented within the list of the 17 “taggers”, ultimately leading to 99 tagged SNPs that are not present, on the Human 1M chip.

SNP	rank	P	chrom	coordinates	closest gene	type	distance to gene	Tagged_SNP	Tagged_SNP_r2	Tagged_SNP_P
								rs9378684	1	—
rs12055694	14	6.55E−06	6	2072157	GMDS	INTRONIC	0			
								rs9405541	1	6.55E−06
								rs9392358	1	—
								rs9378319	1	—
								rs17134651	1	—
								rs9405546	1	—
								rs9378684	1	—
rs11009827	15	7.76E−06	10	19710332	C10orf112	INTRONIC	0			
								rs11009812	1	—
								rs11009826	1	—
								rs7912880	0.82	—
								rs11009835	1	7.76E−06
								rs11009843	1	—
rs11009835	16	7.76E−06	10	19712714	C10orf112	INTRONIC	0			
								rs11009812	1	—
								rs11009826	1	—
								rs11009827	1	7.76E−06
								rs7912880	0.86	—
								rs11009843	1	—
								rs10508584	0.8	—
rs12637073	17	9.79E−06	3	132183561	DNAJC13	INTRONIC	0			
								rs12639443	1	—
								rs11709339	1	—
								rs12633010	1	—
								rs10935015	1	—
								rs12496278	1	—
								rs10935016	1	—
								rs7619350	1	1.53E−05
								rs7633210	0.93	—
								rs12494606	0.93	4.90E−05
								rs12488259	0.86	4.90E−05
								rs10935019	0.93	4.90E−05
								rs2088713	0.93	4.90E−05
								rs11719825	0.93	4.90E−05
								rs10804610	0.93	0.0008
								rs6779298	0.86	0.0008
								rs2305623	0.93	0.0002
								rs11719902	0.93	0.0002
								rs10935023	0.93	0.0001
								rs12491543	0.93	—
								rs10512873	0.93	—
								rs2168435	0.93	0.0006

TABLE 2

Annotated SNPs with p-val < or = 5 * 10E−05 from the GWAS of the narrow phenotype. Thirtyone (31) SNPs have been genotyped with the Human1M Illumina chip and 82 additional SNPs are uniquely tagged by the genotyped SNPs. Among these 82 tagged SNPs, 6 are cross-represented within the list of the 31 “taggers”, ultimately leading to 76 tagged SNPs that are not present on the Human 1M chip.

SNP	rank	P	chrom	coordinates	type	closest gene
rs10277267	1	4.03E−06	7	1809120	INTERGENIC	AC074389.1
rs10950359	2	4.89E−06	7	1800967	INTRONIC	AC074389.1
rs2521644	3	6.48E−06	7	24427969	INTERGENIC	NPY
rs35603463	4	9.28E−06	6	32531745	UPSTREAM	AL713966.2
rs13245980	5	9.64E−06	7	1813198	INTERGENIC	AC074389.1
rs10270654	6	9.64E−06	7	1815851	INTERGENIC	AC074389.1
rs1538123	7	1.48E−05	10	110513959	WITHIN__NON__CODING__GENE	RP11-655H13.2
rs4369324	8	1.48E−05	10	110530574	WITHIN__NON__CODING__GENE	;RP11-655H13.2
rs2895215	9	1.81E−05	7	1837636	INTERGENIC	MAD1L1
rs10950371	10	1.95E−05	7	1825304	INTERGENIC	AC074389.1

TABLE 2-continued

Annotated SNPs with p-val < or = 5 * 10E−05 from the GWAS of the narrow phenotype.
Thirtyone (31) SNPs have been genotyped with the Human1M Illumina chip and 82 additional SNPs are uniquely tagged by the genotyped SNPs. Among these 82 tagged SNPs, 6 are cross-represented within the list of the 31 "taggers", ultimately leading to 76 tagged SNPs that are not present on the Human 1M chip.

rs7916897	11	2.39E−05	10	9061104	INTERGENIC	RP11-428L9.2
rs17807445	12	2.54E−05	6	80804273	INTERGENIC	BCKDHB
rs17771939	13	2.62E−05	8	94259105	INTERGENIC	AC011118.2
rs6584894	14	2.90E−05	10	110518607	WITHIN_NON_CODING_GENE	RP11-655H13.2
rs496486	15	3.18E−05	3	107225936	INTERGENIC	BBX
rs949298	16	3.29E−05	11	120608085	INTRONIC	GRIK4
rs948032	17	3.29E−05	11	120608661	INTRONIC	GRIK4
rs7803164	18	3.41E−05	7	1829835	INTERGENIC	MAD1L1
rs7093143	19	3.65E−05	10	110478002	WITHIN_NON_CODING_GENE	RP11-655H13.2
rs1415557	20	3.65E−05	10	110504802	WITHIN_NON_CODING_GENE	RP11-655H13.2
rs7086707	21	3.65E−05	10	110573667	WITHIN_NON_CODING_GENE	RP11-655H13.2
rs1007328	22	3.71E−05	15	96703373	INTERGENIC	AC012409.1
rs12256889	23	4.34E−05	10	94827183	INTRONIC	CYP26C1
rs214526	24	4.35E−05	6	18248916	INTRONIC	DEK
rs9315048	25	4.38E−05	13	31327840	INTRONIC	ALOX5AP
rs4445746	26	4.38E−05	13	31341435	DOWNSTREAM	RP11-469L23.2
rs11599624	27	4.64E−05	10	110606763	UPSTREAM	RP11-655H13.1
rs2155262	28	4.65E−05	11	120610692	INTRONIC	GRIK4
rs10056549	29	4.73E−05	5	114329175	INTERGENIC	RP11-438C19.2
rs844626	30	4.85E−05	6	147898558	WITHIN_NON_CODING_GENE	AL034350.1
rs947603	31	4.87E−05	10	95249605	INTERGENIC	CEP55

SNP	rank	distance to gene	Tagged_SNP	Tagged_SNP_r2	Tagged_SNP_P
rs10277267	1	−7016			
			rs2222813	0.91	—
rs10950359	2	0			
rs2521644	3	96485			
			rs6971202	0.87	—
			rs2722398	0.83	—
			rs2521643	0.84	—
			rs2722396	0.88	0.0016
rs35603463	4	−3946			
rs13245980	5	−11094			
rs10270654	6	−13747			
			rs4634524	1	—
			rs4255033	1	—
			rs12532459	1	—
			rs12540494	1	—
			rs13231999	1	—
			rs10280601	1	—
			rs13245980	1	9.64E−06
			rs10235174	1	—
			rs10238227	1	—
			rs10225815	1	—
			rs10228960	1	—
			rs6955820	1	—
			rs10950368	1	—
			rs10270415	1	—
			rs10270538	1	—
			rs12539381	1	—
			rs10271168	1	—
			rs4436012	1	—
			rs10259574	1	—
			rs10259592	1	—
			rs10259699	1	—
			rs10275253	1	—
			rs10278438	1	—
			rs1881858	0.87	—
			rs11766215	0.85	—
			rs10950371	0.86	1.95E−05
rs1538123	7	0			
			rs7080507	0.95	6.97E−05
			rs1591661	0.95	—
			rs2685484	0.95	—
			rs2461319	0.86	—
rs4369324	8	0			
			rs7080507	0.95	6.97E−05
			rs1591661	0.95	—
			rs2685484	0.95	—
			rs2461319	0.86	—

TABLE 2-continued

Annotated SNPs with p-val < or = 5 * 10E−05 from the GWAS of the narrow phenotype. Thirtyone (31) SNPs have been genotyped with the Human1M Illumina chip and 82 additional SNPs are uniquely tagged by the genotyped SNPs. Among these 82 tagged SNPs, 6 are cross-represented within the list of the 31 "taggers", ultimately leading to 76 tagged SNPs that are not present on the Human 1M chip.

rs2895215	9	17747			
rs10950371	10	−23200			
rs7916897	11	45673			
			rs1031161	0.96	—
rs17807445	12	−12091			
			rs12524041	0.87	—
			rs12529764	0.87	0.0002
			rs17807327	1	—
rs17771939	13	99590			
rs6584894	14	0			
rs496486	15	−15847			
			rs1282534	1	—
			rs1282540	1	7.04E−05
			rs1299325	1	—
			rs1040194	1	—
			rs1282546	0.91	—
			rs552994	1	—
			rs657302	1	—
			rs577189	1	—
			rs660075	1	7.04E−05
			rs656975	1	—
			rs860722	1	—
			rs618213	1	—
			rs565614	0.85	—
			rs2937395	1	—
rs949298	16	0			
rs948032	17	0			
			rs1320648	1	—
			rs752979	1	—
rs7803164	18	25548			
			rs1881858	0.82	—
			rs11766215	0.85	—
			rs10950371	0.9	1.95E−05
			rs13238613	0.95	—
			rs11761457	0.86	—
			rs7789703	0.86	9.91E−05
			rs7806265	0.95	—
			rs2895215	0.86	1.81E−05
rs7093143	19	0			
			rs7080507	0.95	6.97E−05
			rs1591661	0.95	—
			rs2685484	0.95	—
			rs2461319	0.9	—
rs1415557	20	0			
			rs7080507	0.95	6.97E−05
			rs1591661	0.95	—
			rs2685484	0.95	—
			rs2461319	0.86	—
rs7086707	21	0			
rs1007328	22	108628			
rs12256889	23	0			
rs214526	24	0			
rs9315048	25	0			
			rs4468448	0.95	0.0014
			rs12019512	0.9	0.0002
			rs4466940	0.9	—
			rs4445746	1	4.38E−05
rs4445746	26	−35908			
			rs9315048	1	4.38E−05
			rs4468448	0.95	0.0014
			rs12019512	0.9	0.0002
			rs4466940	0.9	—
rs11599624	27	−1181			
rs2155262	28	0			
			rs2852230	1	—
			rs949298	1	3.29E−05
			rs752979	0.81	—
			rs751370	0.83	—
			rs751369	0.87	—
			rs2187495	1	—

TABLE 2-continued

Annotated SNPs with p-val < or = 5 * 10E−05 from the GWAS of the narrow phenotype.
Thirtyone (31) SNPs have been genotyped with the Human1M Illumina chip and 82 additional SNPs are uniquely tagged by the genotyped SNPs. Among these 82 tagged SNPs, 6 are cross-represented within the list of the 31 "taggers", ultimately leading to 76 tagged SNPs that are not present on the Human 1M chip.

			rs2511064	1	—
			rs2508806	1	—
			rs1892974	1	—
			rs948029	1	—
rs10056549	29	−37795			
rs844626	30	0			
			rs844612	1	—
			rs844610	1	0.0002
			rs844609	1	—
			rs844608	1	—
			rs702355	1	—
			rs844603	1	—
			rs844602	1	—
rs947603	31	−6764			

TABLE 3

Annotated SNPs with p-val < or = 5 * 10E−05 from the GWAS of the composite phenotype
Thirty-eight (38) SNPs have been genotyped with the Human1M Illumina chip and 89 additional SNPs are uniquely tagged by the genotyped SNPs. Among these 89 tagged SNPs, 20 are cross-represented within the list of the 38 "taggers", ultimately leading to 69 tagged SNPs that are not present on the Human 1M chip.

SNP	rank	P	chr	coordinate	type	closest gene
rs11617134	1	2.29E−08	13	30590793	INTERGENIC	RP11-629E24.2
rs17588454	2	3.92E−08	13	30580656	INTERGENIC	RP11-629E24.2
rs9944913	3	1.41E−07	18	31926438	INTERGENIC	NOL4
rs2177073	4	1.84E−07	18	32054724	INTERGENIC	DTNA
rs913882	5	6.90E−07	20	56521654	INTERGENIC	RP13-379L11.2
rs10136012	6	1.29E−06	14	93505960	INTRONIC	ITPK1
rs6025927	7	1.35E−06	20	56523799	INTERGENIC	RP13-379L11.2
rs884266	8	1.60E−06	20	56520904	INTERGENIC	RP13-379L11.2
rs9405541	9	2.38E−06	6	2052811	INTRONIC	GMDS
rs869106	10	2.38E−06	9	2421273	DOWNSTREAM	RP11-125B21.2
rs12055694	11	2.77E−06	6	2072157	INTRONIC	GMDS
rs28861531	12	3.22E−06	Y	1324728	INTERGENIC	N/A
rs10988087	13	3.35E−06	9	131443671	UPSTREAM	SET
rs11618546	14	3.50E−06	13	58874752	INTERGENIC	RP11-538C21.1
rs894857	15	3.55E−06	1	211901341	UPSTREAM	RP11-122M14.3
rs12340584	16	4.00E−06	9	14210653	INTRONIC	NFIB
rs6682365	17	4.01E−06	1	233718651	INTERGENIC	KCNK1
rs1573706	18	4.04E−06	20	40921149	INTRONIC	PTPRT
rs12968586	19	4.59E−06	18	31909968	INTERGENIC	NOL4
rs11081859	20	4.73E−06	18	31926289	INTERGENIC	NOL4
rs17104742	21	4.86E−06	5	145895558	NON_SYNONYMOUS_CODING	GPR151
rs10214633	22	5.54E−06	6	147989996	WITHIN_NON_CODING_GENE	RP11-307P5.1
rs1041897	23	5.62E−06	20	46561222	INTERGENIC	RP11-347D21.1
rs7955917	24	5.82E−06	12	128860496	INTERGENIC	AC023595.1
rs6713772	25	5.95E−06	2	123216847	INTERGENIC	N/A
rs17575455	26	6.00E−06	2	76624220	INTERGENIC	AC078940.2
rs1802027	27	6.79E−06	5	145890228	3PRIME_UTR	TCERG1
rs998051	28	6.83E−06	5	145875259	INTRONIC	TCERG1
rs7714122	29	6.87E−06	5	96255017	3PRIME_UTR	ERAP2
rs3742228	30	7.00E−06	13	113459221	INTRONIC	ATP11A
rs4483642	31	7.19E−06	12	108308740	INTERGENIC	ASCL4
rs12439713	32	7.27E−06	15	91200733	UPSTREAM	AC021422.1
rs13042992	33	7.79E−06	20	14737843	INTRONIC	MACROD2
rs17007730	34	7.89E−06	2	123192216	INTERGENIC	N/A
rs2277431	35	9.19E−06	13	113473375	INTRONIC	ATP11A
rs10931091	36	9.53E−06	2	184533968	INTERGENIC	AC074182.1
rs6558102	37	9.69E−06	8	29096853	INTRONIC	KIF13B
rs4343256	38	1.01E−05	15	91198415	INTERGENIC	AC021422.1

TABLE 3-continued

Annotated SNPs with p-val < or = 5 * 10E−05 from the GWAS of the composite phenotype
Thirty-eight (38) SNPs have been genotyped with the Human1M Illumina chip and 89 additional SNPs are uniquely tagged by the genotyped SNPs. Among these 89 tagged SNPs, 20 are cross-represented within the list of the 38 "taggers", ultimately leading to 69 tagged SNPs that are not present on the Human 1M chip.

SNP	rank	distance to gene	Tagged_SNP	Tagged_SNP_r2	Tagged_SNP_P
rs11617134	1	5365			
			rs35831078	0.82	—
			rs35831078	0.82	—
			rs17588454	0.82	3.92E−08
			rs17588454	0.82	3.92E−08
			rs7317000	1	—
			rs7317000	1	—
rs17588454	2	15502			
			rs35831078	1	—
			rs7317000	0.83	—
			rs11617134	0.82	2.29E−08
rs9944913	3	−122923			
			rs7238006	1	—
			rs17666347	1	0.0004
rs2177073	4	−18530			
rs913882	5	10528			
			rs6025914	0.95	—
			rs6025917	0.94	—
			rs12480795	0.95	—
			rs6015147	1	—
			rs6025921	0.95	—
			rs6025923	1	—
			rs884266	0.95	1.60E−06
			rs884265	1	—
			rs6123749	1	—
			rs6123750	1	—
			rs6025924	1	—
			rs6025926	1	—
			rs6025927	1	1.35E−06
rs10136012	6	0			
rs6025927	7	8383			
			rs6025914	0.96	—
			rs6025917	0.95	—
			rs12480795	1	—
			rs6015147	1	—
			rs6025921	0.83	—
			rs6025923	1	—
			rs884266	0.96	1.60E−06
			rs884265	0.96	—
			rs913882	1	6.90E−07
			rs6123749	1	—
			rs6123750	1	—
			rs6025924	1	—
			rs6025926	1	—
rs884266	8	11278			
			rs6025914	0.92	—
			rs6025917	0.91	—
			rs12480795	0.92	—
			rs6015147	0.96	—
			rs6025921	0.8	—
			rs6025923	0.96	—
			rs884265	0.92	—
			rs913882	0.95	6.90E−07
			rs6123749	0.96	—
			rs6123750	0.96	—
			rs6025924	0.96	—
			rs6025926	0.96	—
			rs6025927	0.96	1.35E−06
rs9405541	9	0			
			rs9392358	1	—
			rs9378319	1	—
			rs12055694	1	2.77E−06
			rs17134651	1	—
			rs9405546	1	—
			rs9378684	1	—
rs869106	10	1429			
			rs7033436	1	—
			rs7042088	0.93	—

TABLE 3-continued

Annotated SNPs with p-val < or = 5 * 10E−05 from the GWAS of the composite phenotype
Thirty-eight (38) SNPs have been genotyped with the Human1M Illumina chip and 89 additional SNPs are uniquely tagged by the genotyped SNPs. Among these 89 tagged SNPs, 20 are cross-represented within the list of the 38 “taggers”, ultimately leading to 69 tagged SNPs that are not present on the Human 1M chip.

			rs16906059	1	—
			rs869105	0.92	—
			rs9696012	0.83	—
rs12055694	11	0			
			rs9405541	1	2.38E−06
			rs9392358	1	—
			rs9378319	1	—
			rs17134651	1	—
			rs9405546	1	—
			rs9378684	1	—
rs28861531	12	−9			
rs10988087	13	−2032			
rs11618546	14	67501			
rs894857	15	−2597			
rs12340584	16	0			
rs6682365	17	−31099			
			rs11800854	1	—
rs1573706	18	0			
rs12968586	19	−106453			
			rs7232734	1	—
			rs8099595	1	—
			rs9952995	0.83	—
			rs7244801	1	—
rs11081859	20	−122774			
			rs4799760	0.92	—
rs17104742	21	0			
			rs17104665	1	—
			rs998051	1	6.83E−06
			rs2033471	1	—
			rs1802027	1	6.79E−06
rs10214633	22	0			
rs1041897	23	−18321			
rs7955917	24	−22481			
			rs1905942	0.83	0.0064
			rs1112925	0.83	0.0076
			rs7963693	1	—
			rs1683691	1	—
			rs1713615	1	—
			rs1713618	0.91	—
			rs7979791	0.9	—
			rs4882750	0.81	—
			rs4882751	0.92	—
rs6713772	25	−9			
			rs10864878	0.93	—
			rs17007730	1	7.89E−06
			rs10207898	1	—
			rs11687082	1	—
			rs13412899	1	—
			rs10170186	1	—
			rs10170543	0.93	—
			rs6742690	1	—
			rs13419434	1	—
			rs11674429	1	—
rs17575455	26	47985			
			rs17575434	0.92	0.0003
rs1802027	27	0			
			rs17104665	1	—
			rs998051	1	6.83E−06
			rs2033471	1	—
			rs17104742	1	4.86E−06
rs998051	28	0			
			rs17104665	1	—
			rs2033471	1	—
			rs1802027	1	6.79E−06
			rs17104742	1	4.86E−06
rs7714122	29	0			
			rs17087180	1	—
rs3742228	30	0			
rs4483642	31	138319			
			rs2374730	0.91	—
			rs4565951	1	—

TABLE 3-continued

Annotated SNPs with p-val < or = 5 * 10E−05 from the GWAS of the composite phenotype
Thirty-eight (38) SNPs have been genotyped with the Human1M Illumina chip and 89 additional SNPs are uniquely tagged by the genotyped SNPs. Among these 89 tagged SNPs, 20 are cross-represented within the list of the 38 "taggers", ultimately leading to 69 tagged SNPs that are not present on the Human 1M chip.

			rs933863	1	—
			rs933864	1	—
rs12439713	32	−2732			
			rs7175350	1	—
			rs7180867	1	0.0004
			rs8035793	1	—
			rs10520693	1	—
			rs7183485	1	—
			rs11633340	1	—
			rs11638226	1	—
			rs6416556	1	—
			rs7178587	1	0.0001
			rs6496716	1	—
			rs17180345	1	—
			rs4506872	1	—
			rs4343256	1	1.01E−05
			rs12593600	1	—
			rs10083547	1	—
			rs4306478	1	—
			rs11855570	1	—
rs13042992	33	0			
rs17007730	34	−9			
			rs10864878	0.92	—
			rs10207898	1	—
			rs11687082	1	—
			rs13412899	1	—
			rs10170186	1	—
			rs10170543	0.92	—
			rs6742690	1	—
			rs13419434	1	—
			rs11674429	1	—
			rs6713772	1	5.95E−06
rs2277431	35	0			
rs10931091	36	−61118			
			rs10931090	1	—
			rs11899025	0.81	—
			rs11884398	0.81	0.0037
rs6558102	37	0			
rs4343256	38	−5050			

[0341] Tables 1-3 also include the identity of the closest genes to the SNPs identified as having a predictive value for the response to GA (GWAS significant SNPs), and "tagged SNPs" (SNPs which are in linkage disequilibrium with the GWAS significant SNPs). SNPs which are in linkage disequilibrium with the GWAS significant SNPs and/or reside in the closest genes may also serve to predict whether the subject is a responder or non-responder to GA.

[0342] We then compared the p values of the SNPs we found using the broad definition to results from the analysis of the narrow definition. This comparison confirmed that the same SNPs had a significant association with response to GA in both analyses, as presented in table 4.

TABLE 4

results of GWAS using a narrow definition of the R/NR phenotype, with corresponding p values also for the broad phenotype

SNP	chromosome	Closest gene	Narrow Phenotype	Broad Phenotype
rs2521644	7	NPY; OTTHUMG00000022973	6.48E−06	0.0003
rs35603463	6	AL713966.1	9.28E−06	0.0002
rs4369324	10	OTTHUMG00000019024; RP11-655H13.1	1.48E−05	9.45E−05
rs1538123	10	OTTHUMG00000019024; RP11-655H13.1	1.48E−05	0.0001
rs17807445	6	OTTHUMG00000016430; BCKDHB	2.54E−05	0.0004
rs17771939	8	AC011118.1	2.62E−05	3.05E−07
rs6584894	10	OTTHUMG00000019024; RP11-655H13.1	2.90E−05	0.0003
rs496486	3	OTTHUMG00000150360; BBX	3.18E−05	6.86E−05
rs949298	11	GRIK4; OTTHUMG00000048255	3.29E−05	3.38E−05
rs948032	11	GRIK4; OTTHUMG00000048255	3.29E−05	3.38E−05
rs7086707	10	OTTHUMG00000019024; RP11-655H13.1	3.65E−05	0.0001

TABLE 4-continued

results of GWAS using a narrow definition of the R/NR phenotype, with corresponding p values also for the broad phenotype

SNP	chromosome	Closest gene	Narrow Phenotype	Broad Phenotype
rs7093143	10	OTTHUMG00000019024; RP11-655H13.1	3.65E−05	0.0003
rs1415557	10	OTTHUMG00000019024; RP11-655H13.1	3.65E−05	0.0003
rs1007328	15	AC012409.1	3.71E−05	0.0007
rs12256889	10	CYP26C1; OTTHUMG00000018766	4.34E−05	0.0008
rs214526	6	OTTHUMG00000014319; DEK	4.35E−05	0.0018
rs9315048	13	ALOX5AP; OTTHUMG00000016677	4.38E−05	0.0008
rs4445746	13	ALOX5AP; OTTHUMG00000016677	4.38E−05	0.0015
rs2155262	11	GRIK4; OTTHUMG00000048255	4.65E−05	2.93E−05
rs844626	6	SAMD5; OTTHUMG00000015767	4.85E−05	0.0014
rs947603	10	CEP55; OTTHUMG00000018774	4.87E−05	0.0037

A Predictive Model Based on the SNPs Having a Predictive Value for the Response for GA Treatment

[0343] A predictive model using the SNPs from table 2 was created in order to improve the predictive value by certain combinations of SNPs with certain genotypes. It should be emphasized that this specific model is created by a specific backward stepwise procedure, and is therefore intended to illustrate certain preferred embodiments of the invention and is not limiting in nature. It would be appreciated by those of skill in the art that other sets of SNPs and combinations of certain SNPs with certain clinical variables may be obtained by methods known to the person skilled in the art, which would demonstrate a predictive value for the response to GA. Other predictive models created from SNPs from tables 1-3 and table 16 are presented in tables 17-36.

[0344] An analysis was performed which included responders and non-responders according to the narrow definition. Data from 33 patients classified as responders according to the narrow definition and from 41 patients classified as non-responders were obtained, which included genotypes of all 31 SNPs. Patients which were included in the following prediction model consisting of 6 SNPs were 51 patients classified as responders, and 61 classified as non-responders, out of 599 patients in the FORTE cohort.

[0345] A backward stepwise logistic regression procedure led to the following predictive model which includes a set of 6 SNPs. The 6 SNPs and predictive values are presented in table 5. This model is also called FM1.

TABLE 5

results from a logistic regression analysis of R/NR to Copaxone with best resulting SNPs from the GWAS. The model has been performed with a backward stepwise procedure (probability of removal if $p < 0.05$) and lead to a pattern composed by 6 SNPs,.

resp1__amir	Odds Ratio	Std. Err.	z	P > |z|	[95% Conf.	Interval]
rs2521644__g	15.58231	14.09115	3.04	0.002	2.647807	91.70168
rs12256889__a	11.63899	11.44968	2.49	0.013	1.692618	80.03346
rs214526__a	10.38811	9.471729	2.57	0.010	1.739496	62.03686
rs17771939__g	.0332771	.0338315	−3.35	0.001	.0045369	.2440786
rs496486__c	.0205013	.0344571	−2.31	0.021	.0007606	.5526131
rs949298__a	.1027731	.0902505	−2.59	0.010	.0183821	.5745987

[0346] In addition, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were analyzed to determine the usefulness of the predictive model to predict the response to GA treatment. The sensitivity of the test is defined as the proportion of clinical responders who are correctly identified as such. The specificity on the other hand measures the proportion of negatives which are correctly identified. The PPV of a test is defined as the proportion of patients with positive test results who are correctly identified, whereas the NPV of a test is the proportion of patients with negative test results who are correctly identified.

[0347] The predictive values derived from the logistic regression in table 5 are presented in table 6.

TABLE 6

Classification table from the logistic regression as in Table 7

	True		
Classified	R	NR	Total
(R)	29	3	32
(NR)	4	38	42
Total	33	41	74

TABLE 6-continued

Classification table from the logistic regression as in Table 7

Classified + if predicted Pr(R) >= .5
True R defined as resp1_amir != 0

Sensitivity	Pr(+|R)	87.88%
Specificity	Pr(−|NR)	92.68%
Positive predictive value	Pr(R|+)	90.62%
Negative predictive value	Pr(NR|−)	90.48%
False + rate for true ~D	Pr(+|NR)	7.32%
False − rate for true D	Pr(−|R)	12.12%
False + rate for classified +	Pr(NR|+)	9.38%
False − rate for classified −	Pr(R|−)	9.52%
Correctly classified		90.54%

[0348] Based on this model, it can be concluded that the specific set of SNPs presented in table 5 can be used to determine whether the patient is responder to GA.

[0349] The response probability of a specific patient was calculated according to the model. Following the genotyping of the patient at the relevant SNPs, the values of the 6 SNPs were recoded to numeric values as described in the following tables (7a-f):

TABLE 7a

rs2521644	rs2521644_g
TT	0
CT	1
CC	2

TABLE 7b

rs12256889	rs12256889_a
CC	0
AC	1
AA	2

TABLE 7c

rs214526	rs214526_a
CC	0
AC	1
AA	2

TABLE 7d

rs17771939	rs17771939_g
TT	0
CT	1
CC	2

TABLE 7e

rs496486	rs496486_c
AA	0
AC	1
CC	2

TABLE 7f

rs949298	rs949298_a
GG	0
AG	1
AA	2

Then, βX was calculated according to the following formula:

$$\beta X - -1.6546 + 2.7614 \cdot rs2521644_g + 3.0106 \cdot rs12256889_a + 2.4996 \cdot rs214526_a - 2.6679 \cdot rs17771939_g - 3.6010 \cdot rs496436_c - 2.1277 \cdot rs949298\_a$$

and the response probability p(Response) was calculated using the formula:

$$P(\text{Response}) = \frac{e^{\beta X}}{1 + e^{\beta X}}$$

Patients with p(Response) above 0.5 were predicted to be responders and patients with p(Response) below 0.5 were predicted to be non-responders. When the model was retrospectively applied to the full cohort of 599 FORTE patients, we observed that the annualized relapse rate (ARR) in patients genetically predicted as responders was reduced by 62% compared to all patients, and by 76% compared to non-responders ($p<0.0001$). When we applied the model retrospectively to a second independent cohort of 79 patients, the model could identify subpopulations genetically predicted to be responders and non-responders with respectively lower (for responders) and higher (for non-responders) relapse rate. In the placebo-treated arm no specific pattern could be observed. This may suggest that this genetic model is specific to response to GA and not to the MS disease natural course.

Two other variations of the model presented in table 5 were further created, as presented in table 8:

TABLE 8

Model	SNPs in model
FM1a	rs12256889 rs17771939 rs214526 rs2521644 rs496486 rs2511064
FM2	rs12256889 rs17771939 rs2511064 rs2521644

The response probability of a specific patient was calculated according to each model. Following the genotyping of the patient at the relevant SNPs, the values of the SNPs were recoded to numeric values as described in the following tables (9a-f):

TABLE 9a

rs12256889	Recoded value
AA	2
AC	1
CC	0

TABLE 9b

rs17771939	Recoded value
CC	2
CT	1
TT	0

TABLE 9c

rs2511064	Recoded value
AA	0
AG	1
GG	2

TABLE 9d

rs2521644	Recoded value
TT	0
CT	1
CC	2

TABLE 9e

rs496486	Recoded value
AA	0
AC	1
CC	2

TABLE 9f

rs214526	Recoded value
AA	2
AC	1
CC	0

Then, βX was calculated by multiplying the recoded value of each of the defined numeric variables by the coefficient in the table (Table 10 for the FM1 model, table 11 for the FM2 model):

TABLE 10

FM1a model parameter	Coefficient
Intercept	−5.0447
rs12256889	2.8853
rs17771939	−1.9024
rs214526	3.2451
rs2521644	1.9614
rs496486	−2.2393
rs2511064	1.7477

TABLE 11

FM2 model parameter	Coefficient
Intercept	−2.8016
rs12256889	1.5847
rs17771939	−0.9850
rs2521644	1.1482
rs2511064	1.1486

and the response probability p(Response) was calculated using the formula:

$$P(\text{Response}) = \frac{e^{\beta X}}{1 + e^{\beta X}}$$

[0350] GWAS Using a Composite/Continuous Measure

A composite measure has been created using a multivariate algorithm that considers diverse measures (Number of Relapses, Number of new T2 lesions and number of T1 lesions) in a unique quantitative measure of Response to Copaxone. Then, we performed a quantitative GWAS looking for SNPs that may distinguish R from NR patients. As described above, analysis using the composite measure led to the identification of 38 SNPs having p value of 10^{-4} or lower, which are presented in table 3.

Pathway Analyses

[0351] We created a list of genes identified via SNPs by the GWAS analyses for the broad and narrow phenotypes. The two lists are presented in Table 12. Based on these genes, we identified several canonical pathways which are significantly enriched using the broad or the narrow definitions. Beginning with the list of "genes" presented in table 12, we could initially find out which canonical pathways are significantly enriched using the broad (Table 13) or the narrow (Table 14) phenotype.

TABLE 12

List of genes identified via SNPs from the GWAS analyses

BROAD PHENO	NARROW PHENO
AC016885.1	AC011118.1
CYP24A1	CYP24A1
ASNS	ASNS
TAC1	TAC1
ASNS	ASNS
AC083939.1	SPANXN4
HPSE2	GMDS
SPANXN4	C10orf112
AC083939.1	DNAJC13
GMDS	NPY
C10orf112	AL713966.1
C10orf112	BCKDHB
DNAJC13	RP11-655H13.1
	BBX
	GRIK4
	AC012409.1
	CYP26C1
	DEK
	ALOX5AP
	SAMD5
	CEP55
	AC093762.1
	AL138825.1

TABLE 13

Canonical pathways significantly enriched by top SNPs in broad definition

Pathway	P-value	Genes
Stilbene, Coumarine and Lignin Biosynthesis	1.28E−02	CYP24A1
Ascorbate and Aldarate Metabolism	1.16E−02	CYP24A1
Biosynthesis of Steroids	7.81E−03	CYP24A1
Neuroprotective Role of THOP1 in Alzheimer's Disease	1.85E−02	TAC1
Alanine and Aspartate Metabolism	1.14E−02	ASNS
Nitrogen Metabolism	7.52E−03	ASNS
Fructose and Mannose Metabolism	6.90E−03	GMDS
VDR/RXR Activation	1.25E−02	CYP24A1
Sphingolipid Metabolism	8.62E−03	CYP24A1
Neuropathic Pain Signaling In Dorsal Horn Neurons	9.71E−03	TAC1
NRF2-mediated Oxidative Stress Response	5.46E−03	DNAJC13

TABLE 14

Canonical pathways significantly enriched by top SNPs in narrow definition

Pathway	P-value	Genes
Stilbene, Coumarine and Lignin Biosynthesis	2.56E−02	CYP24A1, BCKDHB
Ascorbate and Aldarate Metabolism	2.33E−02	CYP24A1, BCKDHB
Aminophosphonate Metabolism	1.54E−02	BCKDHB
Biosynthesis of Steroids	7.81E−03	CYP24A1
Pentose Phosphate Pathway	1.12E−02	BCKDHB
Neuroprotective Role of THOP1 in Alzheimer's Disease	1.85E−02	TAC1
Alanine and Aspartate Metabolism	1.14E−02	ASNS
Nitrogen Metabolism	7.52E−03	ASNS
Pentose and Glucuronate Interconversions	6.67E−03	BCKDHB
Glutamate Receptor Signaling	1.43E−02	GRIK4
Fructose and Mannose Metabolism	6.90E−03	GMDS
Eicosanoid Signaling	1.20E−02	ALOX5AP
Valine, Leucine and Isoleucine Degradation	9.01E−03	BCKDHB
Leptin Signaling in Obesity	1.22E−02	NPY
Ubiquinone Biosynthesis	8.40E−03	BCKDHB
VDR/RXR Activation	1.25E−02	CYP24A1
Tyrosine Metabolism	4.95E−03	BCKDHB
Arginine and Proline Metabolism	5.46E−03	BCKDHB
Pyruvate Metabolism	6.71E−03	BCKDHB
Sphingolipid Metabolism	8.62E−03	CYP24A1
Amyotrophic Lateral Sclerosis Signaling	8.93E−03	GRIK4
Neuropathic Pain Signaling In Dorsal Horn Neurons	9.71E−03	TAC1
Tryptophan Metabolism	3.95E−03	BCKDHB
CREB Signaling in Neurons	5.10E−03	GRIK4
NRF2-mediated Oxidative Stress Response	5.46E−03	DNAJC13
Purine Metabolism	2.28E−03	BCKDHB

With the same enrichment strategy, we can generate various pathways that our current findings suggest, and that are related to disorder-related pathways, Molecular and cellular functions and Physiological system development and functions. Table 15 (a and b) shows a summary of the pathways findings.

TABLE 15a-15b

15.a BROAD PHENOTYPE
TOP BIO FUNCTIONS

Disease and disorders	P-value	Genes
Neurological Disease	1.66E-03-3.68E-02	GMDS, TAC1, HPSE2, ASNS, C10ORF112
Cancer	1.9E-03-1.9E-03	CYP24A1
Endocrine System Disorders	1.9E-03-2.73E-02	CYP24A1, GMDS, HPSE2, C10ORF112
Connective Tissue Disorders	4.22E-02-4.22E-02	GMDS, TAC1, HPSE2
Genetic Disorder	1.9E-03-3.68E-02	CYP24A1, GMDS, TAC1, HPSE2, ASNS, C10ORF112
Psychological Disorders	1.98E-03-3.37E-02	GMDS, TAC1, HPSE2, C10ORF112
	P-value	P-value
Molecular and cellular functions		
Amino Acid Metabolism	4.76E-04-1.93E-02	TAC1
Cell Cycle	4.76E-04-5.69E-03	TAC1
Cell Signaling	4.76E-04-2.63E-02	TAC1
Drug Metabolism	4.76E-04-3.37E-02	CYP24A1, TAC1
Lipid Metabolism	4.76E-04-3.74E-02	CYP24A1, TAC1
Physiological System Development and Functions		
Connective Tissue Development and Function	4.76E-04-2.85E-03	TAC1
Digestive System Development and Function	4.76E-04-2.45E-02	TAC1
Organ Morphology	4.76E-04-2.38E-03	TAC1
Skeletal and Muscular System Development and Function	4.76E-04-8.53E-03	CYP24A1, TAC1
Tissue Morphology	4.76E-04-1.93E-02	TAC1

TABLE 15a-15b-continued

15.b NARROW PHENOTYPE
TOP BIO FUNCTIONS

Disease and disorders	P-value	Genes
Connective Tissue Disorders	2.93E−04-2.72E−02	NPY, DEK, GMDS, GRIK4, SAMD5, ALOX5AP, TAC1, BCKDHB
Inflammatory Disease	2.93E−04-2.72E−02	NPY, DEK, GMDS, GRIK4, SAMD5, ALOX5AP, TAC1, C10OR F112, BCKDHB
Skeletal and Muscular Disorders	2.93E−04-2.72E−02	NPY, DEK, GMDS, GRIK4, SAMD5, ALOX5AP, TAC1, ASNS, BCKDHB
Hypersensitivity Response	1.02E−03-7.11E−03	NPY, TAC1
Inflammatory Response	1.02E−03-4E−02	NPY, DEK, ALOX5AP, TAC1
	P-value	P-value
Molecular and cellular functions		
Cell Morphology	1.84E−05-2.82E−02	NPY, GRIK4, TAC1
Amino Acid Metabolism	7.77E−04-2.52E−02	NPY, TAC1, BCKDHS
Molecular Transport	7.77E−04-3.63E−02	NPY, CYP24A1, GRIK4, ALOX5AP, TAC1
Small Molecule Biochemistry	7.77E−04-3.71E−02	NPY, CYP24A1, GMDS, CYP26C1, ALOX5AP, TAC1, BCKDHB
Cell Cycle	1.02E−03-4.98E−02	DEK, TAC1, ASNS, CEP55
Physiological System Development and Functions		
Behavior	5.99E−04-4.88E−02	NPY, TAC1
Nervous System Development and Function	2.1E−03-4.67E−02	NPY, GRIK4, TAC1
Connective Tissue Development and Function	1.02E−03-2.62E−02	NPY, TAC1
Digestive System Development and Function	1.02E−03-4.59E−02	NPY, TAC1
Organ Morphology	1.02E−03-5.09E−03	TAC1, ALOX5AP

As examples, FIGS. **1-2** were created using the Ingenuity Systems Pathway Analysis software, show how a set of genes from some of the enriched pathways reported in Table 15 can be arranged within the blueprint of a cellular layout, to suggest possible functional hypotheses of how genes indirectly related to Response to Copaxone by proxy SNPs may act.

FIG. **1** relates to the broad phenotype findings, points to genes related to Inflammatory Response, Cell-To-Cell Signaling and Interaction and Hematological System Development and Function (AIM2, ANXA11, ASNS, CAR, CYB561, CYP24A1, DDR2, DNAJB4, DNAJB6, DNAJB7, DNAJC13, EOMES, ESM1, GDPmannose 4,6-dehydratase, GLS, GMDS, GPNMB, H6PD, HLA Class I, HLA-DMA, HNF4A, Hsp70, IFI30, IFNG, IGH-2, IL17RB, LY6A, MEFV, MRC1, NDRG4, PTEN, ROBO3, SMTN, TAC1, TAC4, TGFB1, TTC28, TYMP, ZFPM1)

[0352] FIG. **2**, relates to the narrow phenotype findings, points to pathways relating to Cell Death; Cell-To-Cell Signaling and Interaction; Cellular Development via another set of genes that are again identified by the resulting significant SNPs from the GWAS on narrow phenotype (ALOX5AP, ASNS, B4GALNT1, BBX, BCKDHB, beta-estradiol, CCRN4L, CD276, CEP55, CYP24A1, CYP26C, CYP26C1, DEK, DNAJC13, GCAT, GMDS, GRIK4, HCG 1787519, HCRTR1, HRAS, Hsp90, IL17B, IL4, LAD1, NFRRB, NPY, NUDT1, PGLYRP1, PTEN, SLC14A1, SPRR2B, SPRR2G (includes EG:6706), TAC1, TACR3, TCRB-V8.3, TNF, ZNF267).

We have further repeated the analysis using the Ingenuity Systems Pathway Analysis software and created a modified pathway analysis.

FIG. **3**, relates to the narrow phenotype findings, points to pathways relating to connective Tissue Disorders, Metabolic Disease, Lipid Metabolism via another set of genes that are relating to Cell Cycle, DNA Replication, Recombination, and Repair, Cellular Growth and Proliferation. The two networks are functionally related to each other and together make a single large Gene Regulatory Network orchestrated by TNFα and CEBPB. A third, independent pathway is related to GRIK4 (Glutamatergic transmission).

Prediction Using the Broad, Narrow, and Composite Definitions of R/NR

[0353] We tested 81 GWAS significant SNPs from tables 1-3 and SNPs which are in linkage disequilibrium with those SNPS ("tagged SNPs") in a confirmation study. The SNPs were genotypes by the TaqMan Open Array assay and the predictive value in the FORTE cohort was evaluated. Table 16 suggests an interpretation of genotype data to Response/Non-Response prediction according to the narrow definition. For the SNPs and tagged SNPs originating in the broad and narrow phenotypes, PPV, NPV, specificity and sensitivity values are given. For SNPs and tagged SNPs originating in the composite phenotype, R square is given. When tested in non-treated patients (from the CORAL study), none of the SNPs that were found highly associated with response in the FORTE study were found associated with response. Table 16a presents data for the broad phenotype, Table 16b presents data for the narrow and composite phenotypes.

TABLE 16a

Broad Phenotype (pages 73-81).

SNP ID	R Allele	NR Allele	analysis according to phenotype:	response definition	P-value	specificity	sensitivity	positive predicting value	negative predicting value
rs1007328	TT	CC	broad/narrow	broad	0.00125	37.50%	97.70%	85.80%	80.80%
rs10083547	GG	CC, CG	composite/broad	broad	0.04799	35.60%	97.20%	84.70%	77.80%
rs10136012	GG	TT	composite/broad	broad	0.08301	32.20%	97.20%	84.10%	76.00%
rs10214633	—	—	composite/narrow	broad	0.36439	34.50%	96.90%	85.00%	74.10%
rs10277267	AA, AG	GG	broad/narrow	broad	0.25544	35.60%	96.80%	84.60%	75.00%
rs1040194	GG	AA, AG	broad/narrow	broad	0.00787	35.60%	96.80%	84.80%	75.00%
rs1041897	CC	CT, TT	composite	broad	0.58427	31.00%	96.30%	84.10%	69.20%
rs10853605	CC	TT	broad/narrow/composite	broad	0.00033	42.40%	97.30%	86.30%	80.60%
rs10931091	TT	CC, CT	composite	broad	0.92888	30.50%	96.30%	83.50%	69.20%
rs10935015	AA	AG, GG	broad/narrow/composite	broad	0.03250	39.00%	96.80%	85.40%	76.70%
rs10935016	CC	AA, AC	broad/narrow/composite	broad	0.02452	39.70%	96.40%	85.90%	74.20%
rs10935019	AA	AG, GG	broad/narrow/composite	broad	0.07243	37.30%	96.80%	85.10%	75.90%
rs10950359	AG, GG	AA	narrow	broad	0.10917	35.00%	96.70%	84.20%	75.00%
rs10950371	CC, CT	TT	broad/narrow	broad	0.03299	36.70%	97.30%	85.10%	78.60%
rs10988087	AA	AG, GG	composite	broad	0.97429	34.50%	96.80%	84.70%	74.10%
rs11009827	CC	AA, AC	broad	broad	0.03226	36.20%	97.30%	85.20%	77.80%
rs11009835	CC	CT, TT	broad	broad	0.06069	34.50%	97.30%	84.90%	76.90%
rs11081859	AA	AG, GG	composite	broad	0.31158	32.20%	96.70%	83.70%	73.10%
rs11599624	AG, GG	AA	broad/narrow/composite	broad	0.00254	41.40%	96.20%	85.50%	75.00%
rs11617134	TT	CC, CT	composite/broad	broad	0.00609	42.40%	96.80%	86.20%	78.10%
rs11618546	CC, CG	GG	composite	broad	0.78326	31.70%	96.40%	84.00%	70.40%
rs11694344	AA	CC	broad/narrow/composite	broad	0.00449	39.00%	97.20%	85.50%	79.30%
rs11709339	TT	CC, CT	broad/narrow/composite	broad	0.02699	39.70%	97.30%	85.90%	79.30%
rs11719825	TT	GG, GT	broad/narrow/composite	broad	0.04708	35.10%	97.20%	84.70%	76.90%
rs11761457	TT, CT	CC	broad/narrow	broad	0.05228	35.60%	97.30%	84.90%	77.80%
rs11907046	CC	TT	broad/narrow	broad	0.00115	43.30%	95.90%	86.20%	74.30%
rs12055694	GG	AA, AG	broad/narrow/composite	broad	0.00789	39.00%	96.80%	85.40%	76.70%
rs12256889	AA, AC	CC	broad/narrow/composite	broad	0.01840	37.30%	96.80%	85.10%	75.90%
rs1229542	CC, CA	AA	broad	broad	0.03832	31.00%	96.40%	84.30%	69.20%
rs1229553	TT	CC, CT	composite/broad	broad	0.02602	35.00%	96.40%	84.70%	72.40%
rs1229555	CC	CT, TT	composite/broad	broad	0.02523	36.20%	96.90%	85.40%	75.00%
rs1229558	GG	AA, AG	composite	broad	0.34952	33.90%	97.70%	85.40%	79.20%
rs1229562	CC, CT	TT	composite/broad	broad	0.02149	35.60%	96.70%	84.50%	75.00%
rs1229563	CC	CT, TT	composite/broad	broad	0.02734	35.60%	96.80%	84.80%	75.00%
rs1229564	CC	CT, TT	composite/broad	broad	0.02309	35.60%	96.80%	84.90%	75.00%
rs1229568	CC	CT, TT	composite/broad	broad	0.02316	35.60%	96.70%	84.60%	75.00%
rs12340584	AA	AG, GG	composite	broad	0.57078	35.00%	97.30%	84.80%	77.80%
rs1234567	TT	CC, CT	composite/broad	broad	0.02755	35.00%	96.40%	84.70%	72.40%
rs1234947	TT	CC, CT	composite/broad	broad	0.02605	35.00%	96.40%	84.60%	72.40%
rs1237625	GG	AA, AG	composite/broad	broad	0.02189	35.60%	96.80%	84.80%	75.00%
rs12488259	CC	AA, AC	broad/narrow/composite	broad	0.02922	33.90%	96.80%	84.50%	74.10%
rs12494606	AA	AG, GG	broad/narrow/composite	broad	0.06989	37.30%	96.80%	85.00%	75.90%
rs12496278	GG	CC, CG	broad/narrow/composite	broad	0.01703	38.30%	96.40%	85.10%	74.20%
rs12524041	AT		broad/narrow	broad	0.01216	32.20%	96.40%	84.10%	70.40%
rs12529764	CT		broad/narrow	broad	0.01478	32.80%	96.30%	84.10%	70.40%
rs12532459	GT, TT	GG	narrow	broad	0.20971	37.30%	96.70%	84.90%	75.90%
rs12540494	GG	AA, AG	narrow	broad	0.14854	37.30%	96.80%	85.10%	75.90%
rs12593600	TT	CC, CT	broad/narrow/composite	broad	0.03049	36.20%	97.30%	85.20%	77.80%
rs12633010	GG	GT	broad/narrow	broad	0.04672	38.60%	97.30%	86.20%	78.60%
rs12637073	GG	AA, AG	broad/narrow/composite	broad	0.01574	40.00%	95.90%	85.40%	72.70%
rs12639443	CC	CT, TT	broad/narrow/composite	broad	0.01513	39.00%	95.90%	85.50%	71.90%
rs1264423	TT		broad/narrow	broad	0.04086	37.30%	96.80%	85.10%	75.90%
rs1282540	GG	AA, AG	broad/narrow	broad	0.01061	33.30%	96.80%	84.60%	73.10%
rs1282546	GG	AA, AG	broad/narrow	broad	0.00800	35.60%	96.80%	84.70%	75.00%
rs12968586	GG	AA, AG	composite	broad	0.74958	31.70%	96.40%	83.90%	70.40%
rs1299325	GG	CC, CG	broad/narrow	broad	0.00972	35.60%	96.80%	84.70%	75.00%
rs13021482	CC, CT		broad	broad	0.01565	36.50%	96.90%	85.10%	76.00%
rs13042992	TT	GG, GT	composite/broad	broad	0.02245	34.50%	96.70%	84.50%	74.10%
rs1320648	TT	CC, CT	broad/narrow	broad	0.00037	36.20%	95.90%	85.10%	70.00%
rs13238613	CC, CT	TT	broad/narrow	broad	0.04644	35.60%	97.30%	84.90%	77.80%
rs13245980	AG, GG	AA	narrow	broad	0.16285	37.30%	96.80%	85.20%	75.90%
rs1415557	AA, AG		broad/narrow	broad	0.01902	33.90%	96.80%	84.30%	74.10%
rs1538123	CT, TT	CC	broad/narrow	broad	0.00422	39.00%	96.80%	85.50%	76.70%
rs1573706	CC	CT, TT	broad/narrow/composite	broad	0.00645	44.10%	97.20%	86.50%	81.30%
rs1591661	CT, TT	CC	broad/narrow	broad	0.00665	39.00%	96.80%	85.30%	76.70%
rs1611185	CT	CC	broad/narrow/composite	broad	0.00162	38.90%	97.60%	86.10%	80.80%
rs1683691	CC	CT, TT	composite	broad	0.20336	37.30%	96.80%	85.10%	75.90%
rs16999008	GG	AA, AG	broad/narrow	broad	0.00079	44.10%	96.00%	86.60%	74.30%
rs17007730	AA	AG, GG	composite	broad	0.28369	31.00%	97.70%	84.20%	78.30%
rs17087180	AA	AG, GG	composite	broad	0.44158	29.80%	97.20%	83.90%	73.90%
rs17104665	AA, GG	AG	composite	broad	0.89875	31.00%	96.70%	83.80%	72.00%

TABLE 16a-continued

Broad Phenotype (pages 73-81).

SNP ID	R Allele	NR Allele	analysis according to phenotype:	response definition	P-value	specificity	sensitivity	positive predicting value	negative predicting value
rs17104742	AA, GG	AG	composite	broad	0.84851	31.60%	96.80%	84.50%	72.00%
rs17134651	TT	CC, TT	broad/narrow/composite	broad	0.00970	39.00%	96.80%	85.50%	76.70%
rs17575455	CC	AA	composite	broad	0.10700	37.30%	96.40%	85.10%	73.30%
rs17588454	AA	AG, GG	broad/narrow/composite	broad	0.00670	40.70%	96.80%	85.80%	77.40%
rs17666347	TT	CC, CT	composite	broad	0.72869	33.90%	96.30%	84.30%	71.40%
rs17771939	TT	CC	broad/narrow	broad	0.00006	47.50%	95.00%	87.00%	71.80%
rs17807327	AA, AC		broad/narrow	broad	0.01086	32.20%	96.30%	84.10%	70.40%
rs17807445	CC, CT		broad/narrow	broad	0.01540	33.30%	96.40%	84.30%	71.40%
rs1886308		GG, GT	broad/narrow	broad	0.00115	43.30%	96.00%	86.30%	74.30%
rs1892974	AA	TT	broad/narrow	broad	0.00006	37.30%	94.60%	85.10%	64.70%
rs1941973	CT	CC, TT	composite	broad	0.71879	30.00%	96.80%	83.50%	72.00%
rs2033471	GG	CG	composite	broad	0.99912	32.20%	96.90%	84.40%	73.10%
rs2088713	AA	AC	broad/narrow/composite	broad	0.01689	40.40%	96.30%	85.80%	74.20%
rs214526	AA, AC	CC	narrow	broad	0.18675	34.50%	97.30%	84.90%	76.90%
rs2155262	GG	GG, CG	broad/narrow	broad	0.00006	39.00%	95.00%	85.20%	67.60%
rs2177073	CC	AA, AC	composite/broad	broad	0.02974	35.00%	95.90%	84.50%	70.00%
rs2187495	CC	CT, TT	broad/narrow	broad	0.00007	38.30%	95.10%	85.10%	67.60%
rs2277431	CC	CT, TT	composite	broad	0.96105	33.30%	96.40%	84.30%	71.40%
rs2305623		GG, GT	narrow	broad	0.17456	33.90%	96.80%	84.50%	74.10%
rs2374730	AA	AG	composite	broad	0.70015	35.00%	96.90%	84.80%	75.00%
rs2461319	TT, CT	CC	narrow	broad	0.17373	32.20%	97.30%	84.20%	76.00%
rs2487889	GG	AG	broad/narrow	broad	0.00113	39.00%	97.30%	85.50%	79.30%
rs2487896	GG	AG	broad/narrow	broad	0.00094	41.70%	96.90%	86.10%	78.10%
rs2508806	TT	CC, CT	broad/narrow	broad	0.00007	38.20%	95.80%	85.70%	70.00%
rs2511064	GG	AA, AG	broad/narrow	broad	0.00007	42.40%	94.60%	86.10%	67.60%
rs2521643	GG, AG	AA	broad/narrow	broad	0.01564	38.30%	97.30%	85.40%	79.30%
rs2521644	CC	TT	broad/narrow	broad	0.00918	39.70%	97.30%	85.90%	79.30%
rs2530121	GG	TT	composite/broad	broad	0.02672	36.20%	96.80%	85.00%	75.00%
rs2530123	GG	TT	composite/broad	broad	0.02099	40.40%	96.70%	85.90%	76.70%
rs2685484	CC, CT	TT	broad/narrow	broad	0.00334	41.70%	96.80%	85.90%	78.10%
rs2722396	TT	CC	broad/narrow	broad	0.06130	33.90%	97.30%	84.80%	76.90%
rs2722398	TT, CT	CC	broad/narrow	broad	0.01847	38.30%	97.30%	85.40%	79.30%
rs28861531	GG	CC, CG	composite	broad	0.80326	32.20%	96.80%	84.30%	73.10%
rs2895215	TT, CT	CC	broad/narrow	broad	0.06951	37.90%	97.60%	85.20%	81.50%
rs2937395	CC	TT, CT	broad/narrow	broad	0.00775	35.60%	96.80%	84.80%	75.00%
rs3135391	GG	AG	broad/narrow	broad	0.00031	44.80%	95.80%	86.60%	74.30%
rs35831078		TT, CT	broad/narrow/composite	broad	0.00412	42.40%	96.40%	86.30%	75.80%
rs3742228		GG, AG	composite	broad	0.42320	33.90%	96.80%	84.60%	74.10%
rs3778630	—	—	broad/narrow	broad	0.04590	35.00%	96.80%	84.60%	75.00%
rs401618	—	TT, CT	broad/narrow	broad	0.00439	37.30%	97.70%	85.40%	81.50%
rs4148871	GG	AG	narrow	broad	0.32856	31.00%	97.20%	83.70%	75.00%
rs4255033	AA, AG	GG	narrow	broad	0.16036	35.60%	96.80%	84.60%	75.00%
rs4281882	CC	AA	broad/narrow/composite	broad	0.00315	36.80%	97.20%	85.10%	77.80%
rs4289164	GG	AA	broad/narrow/composite	broad	0.00467	39.00%	96.70%	85.00%	76.70%
rs4306478	AA	AC, CC	composite/broad	broad	0.08034	37.30%	97.20%	85.00%	78.60%
rs4343256	AA	AG, GG	composite/broad	broad	0.06024	35.60%	97.30%	84.90%	77.80%
rs4344916	AA	CC	broad/narrow/composite	broad	0.00375	40.00%	97.30%	85.70%	80.00%
rs4369324	TT	GG, GT	broad/narrow	broad	0.00588	40.70%	96.80%	85.70%	77.40%
rs4435429	AA	GG	broad/narrow/composite	broad	0.00412	36.80%	97.30%	85.60%	77.80%
rs4445746	GG	AA, AG	broad/narrow/composite	broad	0.00687	37.90%	96.80%	85.50%	75.90%
rs4466940	CC	TT, CT	broad/narrow/composite	broad	0.01163	39.00%	96.20%	85.10%	74.20%
rs4468448	CC	TT, CT	broad	broad	0.08451	37.30%	96.80%	85.10%	75.90%
rs4483642	TT	CT	composite	broad	0.71368	33.90%	96.80%	84.60%	74.10%
rs4565951	TT	CT	composite	broad	0.67826	36.70%	96.30%	84.70%	73.30%
rs4578835	AA	GG	broad/narrow/composite	broad	0.00489	37.90%	96.80%	85.40%	75.90%
rs4634524	CC, CT	TT	narrow	broad	0.23175	47.10%	96.80%	87.00%	80.00%
rs4799760	CC, CT	—	composite	broad	0.30448	32.20%	96.80%	84.20%	73.10%
rs4809955	AA	GG, AG	broad/narrow	broad	0.00180	41.40%	96.30%	86.10%	75.00%
rs4811492	TT	AA	broad/narrow	broad	0.03358	40.40%	97.20%	86.00%	79.30%
rs496486	AA	CC, AC	broad/narrow	broad	0.00754	35.60%	96.80%	84.90%	75.00%
rs552994	TT	CC, CT	broad/narrow	broad	0.00597	37.30%	96.80%	85.20%	75.90%
rs6015147	AA	CC	composite	broad	0.31168	37.90%	96.30%	85.20%	73.30%
rs6025923	TT	CC	composite	broad	0.47714	26.50%	96.60%	84.80%	65.00%
rs6025927	TT	CC	composite	broad	0.16216	32.70%	96.60%	84.30%	72.00%
rs6091820	CC	TT, CT	broad/narrow	broad	0.00357	44.80%	97.30%	87.00%	81.30%
rs6097782	CC	TT, CT	broad/narrow	broad	0.00164	42.40%	97.30%	86.50%	80.60%
rs6097790	AA	CC, AC	broad/narrow	broad	0.00252	42.40%	96.30%	86.10%	75.80%
rs6097793	CC, AC	AA	broad/narrow	broad	0.00265	42.40%	95.90%	86.00%	73.50%
rs6097797	TT, CT	CC	broad/narrow	broad	0.00354	42.10%	95.80%	86.30%	72.70%
rs6097801	GG, AG	AA	broad/narrow	broad	0.00086	45.00%	95.90%	86.60%	75.00%
rs6123749	CC	GG	composite	broad	0.19902	35.60%	96.30%	84.60%	72.40%

TABLE 16a-continued

Broad Phenotype (pages 73-81).

SNP ID	R Allele	NR Allele	analysis according to phenotype:	response definition	P-value	specificity	sensitivity	positive predicting value	negative predicting value
rs6543934	GG	TT	broad/narrow/composite	broad	0.00389	39.00%	96.80%	85.40%	76.70%
rs6558102	AA	GG	composite	broad	0.85966	31.00%	96.30%	84.00%	69.20%
rs656975	GG	CC, CG	broad/narrow	broad	0.00805	35.60%	96.80%	84.90%	75.00%
rs657302	TT	CC, CT	broad/narrow	broad	0.01109	32.80%	96.80%	84.30%	73.10%
rs6584894	AA, AG	GG	broad/narrow	broad	0.00822	40.00%	97.00%	85.70%	78.60%
rs660075	CC	TT, CT	broad/narrow	broad	0.00805	35.60%	96.80%	84.90%	75.00%
rs6713772	AA	GG, AG	composite	broad	0.49662	30.50%	97.30%	83.90%	75.00%
rs6909321	AA, AG	—	narrow	broad	0.13191	32.20%	97.30%	84.30%	76.00%
rs6971202	GG	—	broad/narrow	broad	0.06288	35.60%	97.30%	84.90%	77.80%
rs702355	AA, AG		narrow	broad	0.12523	34.50%	96.80%	84.60%	74.10%
rs7080507	CC, CT	—	broad/narrow	broad	0.01211	36.20%	96.70%	84.90%	75.00%
rs7086707	AA, AC	—	broad/narrow	broad	0.00572	39.00%	96.80%	85.40%	76.70%
rs7093143	GG, GT	—	broad/narrow	broad	0.00990	35.60%	96.80%	84.70%	75.00%
rs7178587	—	CC	broad/narrow/composite	broad	0.00158	33.90%	97.20%	84.80%	76.00%
rs7180867	AA, AC	—	broad	broad	0.09670	34.50%	96.30%	84.70%	71.40%
rs7232734	TT	CC, CT	composite	broad	0.77696	32.20%	96.40%	84.10%	70.40%
rs7238006	CT	CC	composite	broad	0.98175	28.60%	96.80%	84.10%	69.60%
rs7244801	GG	AA, AG	composite	broad	0.74039	33.30%	96.40%	84.80%	70.40%
rs7317000	AA	CC, AC	composite/broad	broad	0.01775	41.40%	96.70%	85.80%	77.40%
rs751370	—	CC	broad/narrow/composite	broad	0.00182	37.90%	96.80%	85.40%	75.90%
rs752979	GG	—	broad/narrow	broad	0.00011	39.00%	94.60%	85.40%	65.70%
rs7619350	GG	AA, AG	broad/narrow/composite	broad	0.03076	39.70%	97.20%	85.80%	79.30%
rs7633210	TT	—	broad/narrow	broad	0.07574	35.70%	97.60%	85.10%	80.00%
rs7714122	TT	CC, CT	composite	broad	0.46907	32.80%	96.80%	84.50%	73.10%
rs7789703	CC, CT	TT	narrow	broad	0.17605	33.90%	97.70%	85.00%	79.20%
rs7803164	TT, CT	CC	broad/narrow	broad	0.04543	38.60%	97.20%	85.80%	78.60%
rs7806265	TT, AT	AA	broad/narrow	broad	0.05396	35.60%	97.20%	84.80%	77.80%
rs7916897	TT	GG	narrow	broad	0.60788	48.10%	97.40%	87.60%	83.30%
rs7955917	GG	AA, AG	composite	broad	0.10317	37.30%	96.80%	85.30%	75.90%
rs7963693	CC	GG, CG	composite	broad	0.13295	37.90%	96.30%	85.40%	73.30%
rs8099595	CC	TT, CT	composite	broad	0.76429	31.00%	96.80%	84.10%	72.00%
rs8118441	TT	—	broad/narrow	broad	0.00186	42.40%	95.90%	86.10%	73.50%
rs844602	CC	—	composite	broad	0.95421	38.60%	97.10%	85.30%	78.60%
rs844608	AA, AC	CC	composite	broad	0.99091	36.80%	97.30%	85.60%	77.80%
rs844610	AA, AC	CC	composite	broad	0.99078	37.30%	97.30%	85.30%	78.60%
rs844612	TT, CT	CC	broad/narrow	broad	0.08601	35.60%	97.20%	84.80%	77.80%
rs844626	GG, AG	AA	broad/narrow/composite	broad	0.06588	36.20%	97.30%	85.20%	77.80%
rs860722	CC, CG	—	broad	broad	0.02761	35.60%	96.40%	84.80%	72.40%
rs873216	GG	AA	broad/narrow	broad	0.00074	44.10%	96.40%	86.70%	76.50%
rs884266	CC	TT	composite	broad	0.51236	30.40%	96.40%	84.60%	68.00%
rs894857	GG	AA, AG	composite	broad	0.93523	31.00%	96.80%	84.30%	72.00%
rs913882	CC	TT	composite	broad	0.14380	37.30%	96.40%	85.10%	73.30%
rs9315048	GG	—	broad/narrow	broad	0.00848	35.30%	98.10%	86.40%	81.80%
rs9332420	GG	AA	broad/narrow/composite	broad	0.00460	39.00%	96.80%	85.50%	76.70%
rs933863	AA	AG	composite	broad	0.64163	37.30%	96.40%	85.20%	73.30%
rs933864	GG	CG	composite	broad	0.88068	34.50%	96.80%	84.60%	74.10%
rs9378319	TT	CC, CT	broad/narrow/composite	broad	0.00955	39.00%	96.80%	85.60%	76.70%
rs9378684	CC	TT, CT	broad/narrow/composite	broad	0.00897	40.70%	96.40%	85.80%	75.00%
rs9392358	AA	GG, AG	broad/narrow/composite	broad	0.01177	39.70%	97.30%	85.90%	79.30%
rs9405541	CC	TT, CT	broad/narrow/composite	broad	0.00787	41.40%	96.80%	86.20%	77.40%
rs9405546	CC	TT, CT	broad/narrow/composite	broad	0.00765	41.40%	96.80%	86.10%	77.40%
rs947603	CC, CT	TT	broad/narrow	broad	0.03909	33.90%	96.80%	84.30%	74.10%
rs948029	AA	TT	broad/narrow	broad	0.00007	40.70%	94.50%	85.60%	66.70%
rs948032	GG	AA	broad/narrow	broad	0.00011	39.00%	94.60%	85.50%	65.70%
rs949298	GG	—	broad/narrow	broad	0.02138	39.30%	97.70%	86.30%	81.50%
rs9508834	AA	GG, AG	broad/narrow/composite	broad	0.00409	40.70%	96.40%	85.90%	75.00%
rs9944913	CC	TT, CT	composite	broad	0.99956	30.50%	96.80%	83.70%	72.00%
rs9952995	TT	CC, CT	composite	broad	0.98014	29.30%	96.80%	83.90%	70.80%
rs998051	GG	GT	composite	broad	0.65018	32.80%	96.70%	84.20%	73.10%

TABLE 16b

Narrow and Composite Phenotypes (pages 82-90).

SNP ID	response definition	P-value	specificity	sensitivity	positive predicting value	negative predicting value	response definition	P-value	R Square
rs1007328	narrow	0.00408	67.90%	71.90%	69.50%	70.40%	composite	0.2050811449	0.250
rs10083547	narrow	0.10505	64.40%	71.40%	65.60%	70.40%	composite	0.0001776096	0.269
rs10136012	narrow	0.22150	67.80%	58.90%	63.50%	63.50%	composite	0.0000000122	0.293
rs10214633	narrow	0.09531	60.30%	68.40%	62.90%	66.00%	composite	0.0016635019	0.269
rs10277267	narrow	0.01876	74.60%	63.00%	69.40%	68.80%	composite	0.1624935610	0.253
rs1040194	narrow	0.07052	66.10%	73.20%	67.20%	72.20%	composite	0.8333666744	0.246
rs1041897	narrow	0.23820	63.80%	61.40%	62.50%	62.70%	composite	0.0000000016	0.297
rs10853605	narrow	0.00184	71.20%	73.20%	70.70%	73.70%	composite	0.0192031795	0.257
rs10931091	narrow	0.63575	69.50%	60.00%	64.70%	65.10%	composite	0.0002547344	0.267
rs10935015	narrow	0.06898	61.00%	71.40%	63.50%	69.20%	composite	0.0348126442	0.253
rs10935016	narrow	0.05887	63.80%	71.90%	66.10%	69.80%	composite	0.0870671686	0.252
rs10935019	narrow	0.08402	59.30%	73.20%	63.10%	70.00%	composite	0.0707246889	0.253
rs10950359	narrow	0.00292	76.70%	67.30%	72.50%	71.90%	composite	0.2165718898	0.236
rs10950371	narrow	0.00602	73.30%	71.90%	71.90%	73.30%	composite	0.1803959905	0.252
rs10988087	narrow	0.71678	63.80%	67.90%	64.40%	67.30%	composite	0.0000000031	0.305
rs11009827	narrow	0.13412	63.80%	69.60%	65.00%	68.50%	composite	0.1112191369	0.250
rs11009835	narrow	0.17860	62.10%	67.90%	63.30%	66.70%	composite	0.1131736185	0.250
rs11081859	narrow	0.80646	66.10%	56.40%	60.80%	61.90%	composite	0.0006049647	0.266
rs11599624	narrow	0.00049	77.60%	70.90%	75.00%	73.80%	composite	0.0695370150	0.240
rs11617134	narrow	0.11844	61.00%	69.60%	62.90%	67.90%	composite	0.0000183303	0.273
rs11618546	narrow	0.73048	65.00%	59.60%	61.80%	62.90%	composite	0.0000000276	0.290
rs11694344	narrow	0.07036	72.90%	67.90%	70.40%	70.50%	composite	0.0676961332	0.251
rs11709339	narrow	0.06063	60.30%	71.40%	63.50%	68.60%	composite	0.0748133928	0.252
rs11719825	narrow	0.05582	61.40%	75.50%	64.50%	72.90%	composite	0.0278392113	0.257
rs11761457	narrow	0.01490	69.50%	71.40%	69.00%	71.90%	composite	0.2595068530	0.250
rs11907046	narrow	0.01512	61.70%	71.90%	64.10%	69.80%	composite	0.6134026928	0.246
rs12055694	narrow	0.05185	64.40%	70.90%	65.00%	70.40%	composite	0.0006868573	0.276
rs12256889	narrow	0.00223	71.20%	70.20%	70.20%	71.20%	composite	0.0048849245	0.261
rs1229542	narrow	0.22302	60.30%	70.20%	63.50%	67.30%	composite	0.3948082568	0.256
rs1229553	narrow	0.14140	60.00%	66.70%	61.30%	65.50%	composite	0.0011542566	0.264
rs1229555	narrow	0.14151	62.10%	66.70%	63.30%	65.50%	composite	0.0006891767	0.270
rs1229558	narrow	0.35801	60.70%	69.60%	63.90%	66.70%	composite	0.0004112907	0.276
rs1229562	narrow	0.10238	61.00%	71.40%	63.50%	69.20%	composite	0.0013755214	0.263
rs1229563	narrow	0.14702	61.00%	69.60%	62.90%	67.90%	composite	0.0016266164	0.266
rs1229564	narrow	0.10238	61.00%	71.40%	63.50%	69.20%	composite	0.0011739273	0.263
rs1229568	narrow	0.11245	62.70%	69.10%	63.30%	68.50%	composite	0.0015575098	0.262
rs12340584	narrow	0.70311	63.30%	53.60%	57.70%	59.40%	composite	0.0000498360	0.271
rs1234567	narrow	0.14140	60.00%	66.70%	61.30%	65.50%	composite	0.0014524348	0.262
rs1234947	narrow	0.14140	60.00%	66.70%	61.30%	65.50%	composite	0.0013208828	0.262
rs1237625	narrow	0.10238	61.00%	71.40%	63.50%	69.20%	composite	0.0010132650	0.263
rs12488259	narrow	0.05733	59.30%	75.00%	63.60%	71.40%	composite	0.0677945040	0.263
rs12494606	narrow	0.08402	59.30%	73.20%	63.10%	70.00%	composite	0.0649695076	0.251
rs12496278	narrow	0.05483	63.30%	71.40%	64.50%	70.40%	composite	0.0901845657	0.252
rs12524041	narrow	0.00842	71.20%	64.30%	67.90%	67.70%	composite	0.3664238633	0.247
rs12529764	narrow	0.01003	72.40%	66.10%	69.80%	68.90%	composite	0.1210653349	0.250
rs12532459	narrow	0.02232	78.00%	69.60%	75.00%	73.00%	composite	0.3350822048	0.254
rs12540494	narrow	0.01891	78.00%	70.90%	75.00%	74.20%	composite	0.1669469791	0.257
rs12593600	narrow	0.09698	58.60%	71.40%	62.50%	68.00%	composite	0.0001262140	0.270
rs12633010	narrow	0.05946	61.40%	73.70%	65.60%	70.00%	composite	0.1145268012	0.261
rs12637073	narrow	0.05223	63.30%	71.90%	65.10%	70.40%	composite	0.0967951660	0.252
rs12639443	narrow	0.01681	66.10%	71.90%	67.20%	70.90%	composite	0.0664176972	0.252
rs1264423	narrow	0.02012	71.20%	62.50%	67.30%	66.70%	composite	0.1631840283	0.249
rs1282540	narrow	0.07052	66.70%	73.20%	68.30%	71.70%	composite	0.6472043851	0.248
rs1282546	narrow	0.07052	66.10%	73.20%	67.20%	72.20%	composite	0.7524765779	0.245
rs12968586	narrow	0.94218	63.30%	58.90%	60.00%	62.30%	composite	0.0004984226	0.265
rs1299325	narrow	0.07052	66.10%	73.20%	67.20%	72.20%	composite	0.6954314594	0.247
rs13021482	narrow	0.21323	67.30%	64.60%	64.60%	67.30%	composite	0.1249466723	0.270
rs13042992	narrow	0.60485	63.80%	65.50%	63.20%	66.10%	composite	0.0000481220	0.271
rs1320648	narrow	0.00068	63.80%	76.80%	67.20%	74.00%	composite	0.7343494667	0.248
rs13238613	narrow	0.00756	74.60%	71.40%	72.70%	73.30%	composite	0.1828487368	0.251
rs13245980	narrow	0.02028	79.70%	64.80%	74.50%	71.20%	composite	0.3356975007	0.254
rs1415557	narrow	0.01107	74.60%	69.60%	72.20%	72.10%	composite	0.9001338769	0.246
rs1538123	narrow	0.00308	76.30%	69.60%	73.60%	72.60%	composite	0.9139002586	0.245
rs1573706	narrow	0.01127	71.20%	73.20%	70.70%	73.70%	composite	0.0013465086	0.262
rs1591661	narrow	0.00222	76.30%	69.60%	73.60%	72.60%	composite	0.8782253468	0.252
rs1611185	narrow	0.01980	66.70%	69.60%	68.40%	67.90%	composite	0.0722742172	0.181
rs1683691	narrow	0.43495	61.00%	66.10%	61.70%	65.50%	composite	0.0019111927	0.263
rs16999008	narrow	0.01200	62.70%	73.70%	65.60%	71.20%	composite	0.6105720761	0.246
rs17007730	narrow	0.58028	63.80%	60.00%	61.10%	62.70%	composite	0.0000223406	0.272
rs17087180	narrow	0.18731	63.20%	69.60%	65.00%	67.90%	composite	0.0000000001	0.304
rs17104665	narrow	0.86999	63.80%	58.20%	60.40%	61.70%	composite	0.0000160623	0.276

TABLE 16b-continued

Narrow and Composite Phenotypes (pages 82-90).

SNP ID	response definition	P-value	specificity	sensitivity	positive predicting value	negative predicting value	response definition	P-value	R Square
rs17104742	narrow	0.86754	64.90%	64.30%	64.30%	64.90%	composite	0.0000104133	0.281
rs17134651	narrow	0.05573	62.70%	71.40%	64.50%	69.80%	composite	0.0008626073	0.265
rs17575455	narrow	0.10819	67.80%	67.90%	66.70%	69.00%	composite	0.0000053597	0.277
rs17588454	narrow	0.07799	62.70%	73.20%	65.10%	71.20%	composite	0.0000204321	0.274
rs17666347	narrow	0.97881	69.50%	56.40%	63.30%	63.10%	composite	0.0000458865	0.271
rs17771939	narrow	0.00387	67.80%	73.20%	68.30%	72.70%	composite	0.8848357851	0.248
rs17807327	narrow	0.00749	76.30%	61.80%	70.80%	68.20%	composite	0.4731278635	0.248
rs17807445	narrow	0.02258	71.70%	62.50%	67.30%	67.20%	composite	0.1064680457	0.251
rs1886308	narrow	0.01502	61.70%	68.40%	62.90%	67.30%	composite	0.5133224539	0.247
rs1892974	narrow	0.00024	69.50%	77.20%	71.00%	75.90%	composite	0.6406540443	0.248
rs1941973	narrow	0.49180	60.00%	60.70%	58.60%	62.10%	composite	0.0000547438	0.271
rs2033471	narrow	0.84659	62.70%	61.40%	61.40%	62.70%	composite	0.0000256482	0.273
rs2088713	narrow	0.04883	63.20%	69.80%	63.80%	69.20%	composite	0.0893788014	0.243
rs214526	narrow	0.02901	69.00%	64.30%	66.70%	66.70%	composite	0.3079668681	0.248
rs2155262	narrow	0.00031	67.80%	78.60%	69.80%	76.90%	composite	0.5761110166	0.251
rs2177073	narrow	0.98321	66.70%	64.90%	64.90%	66.70%	composite	0.0000025098	0.278
rs2187495	narrow	0.00015	68.30%	76.80%	69.40%	75.90%	composite	0.6545016897	0.248
rs2277431	narrow	0.44554	65.00%	56.40%	59.60%	61.90%	composite	0.0000450193	0.272
rs2305623	narrow	0.07317	59.30%	72.70%	62.50%	70.00%	composite	0.1998120292	0.250
rs2374730	narrow	0.16022	63.30%	59.60%	60.70%	62.30%	composite	0.0000019327	0.279
rs2461319	narrow	0.09884	72.90%	66.10%	69.80%	69.40%	composite	0.9302610439	0.245
rs2487889	narrow	0.02308	61.00%	66.10%	61.70%	65.50%	composite	0.4149154853	0.247
rs2487896	narrow	0.04167	63.30%	68.40%	63.90%	67.90%	composite	0.4363548670	0.247
rs2508806	narrow	0.00301	65.50%	76.80%	69.40%	73.50%	composite	0.6790301896	0.245
rs2511064	narrow	0.00577	66.10%	76.80%	68.30%	75.00%	composite	0.6854191571	0.247
rs2521643	narrow	0.00682	73.30%	66.70%	70.40%	69.80%	composite	0.8397645047	0.258
rs2521644	narrow	0.00303	77.60%	63.20%	73.50%	68.20%	composite	0.7274741771	0.252
rs2530121	narrow	0.19485	60.30%	66.70%	62.30%	64.80%	composite	0.0157723654	0.256
rs2530123	narrow	0.12073	59.60%	69.10%	62.30%	66.70%	composite	0.0169136879	0.188
rs2685484	narrow	0.00273	76.70%	70.90%	73.60%	74.20%	composite	0.8157058663	0.245
rs2722396	narrow	0.00818	72.90%	61.40%	68.60%	66.20%	composite	0.6811200337	0.247
rs2722398	narrow	0.00682	73.30%	66.70%	70.40%	69.80%	composite	0.7767461226	0.246
rs28861531	narrow	0.95650	61.00%	58.90%	58.90%	61.00%	composite	0.0000000623	0.293
rs2895215	narrow	0.01525	74.10%	70.40%	71.70%	72.90%	composite	0.1030119635	0.252
rs2937395	narrow	0.07058	66.10%	73.20%	67.20%	72.20%	composite	0.7574277637	0.245
rs3135391	narrow	0.00362	67.20%	72.70%	67.80%	72.20%	composite	0.7886848031	0.248
rs35831078	narrow	0.04785	62.70%	75.40%	66.20%	72.50%	composite	0.0000393384	0.277
rs3742228	narrow	0.93310	59.30%	57.90%	57.90%	59.30%	composite	0.0000001929	0.285
rs3778630	narrow	0.08732	70.00%	58.90%	64.70%	64.60%	composite	0.1201100770	0.248
rs401618	narrow	0.01912	66.10%	64.90%	64.90%	66.10%	composite	0.2527657227	0.255
rs4148871	narrow	0.00638	62.10%	76.80%	66.20%	73.50%	composite	0.2213169699	0.254
rs4255033	narrow	0.02413	78.00%	66.10%	74.00%	70.80%	composite	0.2641530455	0.248
rs4281882	narrow	0.02853	70.20%	70.90%	69.60%	71.40%	composite	0.0055073684	0.260
rs4289164	narrow	0.05358	72.90%	67.90%	70.40%	70.50%	composite	0.0284597023	0.262
rs4306478	narrow	0.32247	67.80%	67.30%	66.10%	69.00%	composite	0.0001910761	0.270
rs4343256	narrow	0.18768	62.70%	66.10%	62.70%	66.10%	composite	0.0001403301	0.268
rs4344916	narrow	0.04203	75.00%	67.90%	71.70%	71.40%	composite	0.0109294485	0.257
rs4369324	narrow	0.00308	76.30%	69.60%	73.60%	72.60%	composite	0.9220257544	0.247
rs4435429	narrow	0.02361	71.90%	71.90%	71.90%	71.90%	composite	0.0049301543	0.245
rs4445746	narrow	0.00937	63.80%	80.40%	68.20%	77.10%	composite	0.0853642663	0.252
rs4466940	narrow	0.02967	64.40%	75.00%	66.70%	73.10%	composite	0.0124998039	0.259
rs4468448	narrow	0.11642	62.70%	73.20%	65.10%	71.20%	composite	0.1384180377	0.250
rs4483642	narrow	0.29453	62.70%	59.60%	60.70%	61.70%	composite	0.0000146605	0.280
rs4565951	narrow	0.48217	65.00%	57.10%	60.40%	61.90%	composite	0.0001718130	0.256
rs4578835	narrow	0.04990	72.40%	67.90%	70.40%	70.00%	composite	0.0116559644	0.262
rs4634524	narrow	0.03289	80.40%	68.90%	75.60%	74.50%	composite	0.3275992309	0.265
rs4799760	narrow	0.72214	64.40%	64.30%	63.20%	65.50%	composite	0.0003882703	0.265
rs4809955	narrow	0.01531	60.30%	71.40%	63.50%	68.60%	composite	0.6111078532	0.175
rs4811492	narrow	0.03685	64.90%	75.00%	67.70%	72.50%	composite	0.4190188183	0.251
rs496486	narrow	0.07058	66.10%	73.20%	67.20%	72.20%	composite	0.7537962256	0.246
rs552994	narrow	0.07052	66.10%	73.20%	67.20%	72.20%	composite	0.7714754149	0.246
rs6015147	narrow	0.95445	69.00%	63.00%	65.40%	66.70%	composite	0.0000005811	0.222
rs6025923	narrow	0.74123	61.20%	66.70%	65.50%	62.50%	composite	0.0000238011	0.277
rs6025927	narrow	0.99741	63.60%	66.70%	64.30%	66.00%	composite	0.0001156133	0.176
rs6091820	narrow	0.03230	60.30%	71.90%	64.10%	68.60%	composite	0.7102878021	0.248
rs6097782	narrow	0.01874	61.00%	71.90%	64.10%	69.20%	composite	0.6232805036	0.246
rs6097790	narrow	0.02179	62.70%	69.60%	63.90%	68.50%	composite	0.5460615394	0.246
rs6097793	narrow	0.02179	62.70%	69.60%	63.90%	68.50%	composite	0.5534389737	0.246
rs6097797	narrow	0.01685	63.20%	71.40%	65.60%	69.20%	composite	0.6656843066	0.251
rs6097801	narrow	0.01512	61.70%	71.90%	64.10%	69.80%	composite	0.7551179553	0.247
rs6123749	narrow	0.90554	66.10%	64.30%	64.30%	66.10%	composite	0.0000013456	0.280

TABLE 16b-continued

Narrow and Composite Phenotypes (pages 82-90).

SNP ID	response definition	P-value	specificity	sensitivity	positive predicting value	negative predicting value	response definition	P-value	R Square
rs6543934	narrow	0.06219	72.90%	65.50%	69.20%	69.40%	composite	0.0600136502	0.253
rs6558102	narrow	0.64731	63.80%	67.90%	64.40%	67.30%	composite	0.0000008558	0.283
rs656975	narrow	0.07052	66.10%	73.20%	67.20%	72.20%	composite	0.7480314538	0.246
rs657302	narrow	0.08729	67.20%	74.50%	68.30%	73.60%	composite	0.7230354724	0.246
rs6584894	narrow	0.01294	78.20%	67.30%	73.30%	72.90%	composite	0.6868242683	0.232
rs660075	narrow	0.07058	66.10%	73.20%	67.20%	72.20%	composite	0.7494347642	0.246
rs6713772	narrow	0.71395	62.70%	60.70%	60.70%	62.70%	composite	0.0000002337	0.284
rs6909321	narrow	0.06543	71.20%	62.50%	67.30%	66.70%	composite	0.1096157565	0.251
rs6971202	narrow	0.00663	76.30%	61.80%	70.80%	68.20%	composite	0.6839825085	0.246
rs702355	narrow	0.06082	75.90%	60.00%	70.20%	66.70%	composite	0.1579609518	0.250
rs7080507	narrow	0.00600	75.90%	73.20%	74.50%	74.60%	composite	0.8019114252	0.247
rs7086707	narrow	0.00500	74.60%	69.60%	72.20%	72.10%	composite	0.9233502939	0.246
rs7093143	narrow	0.00961	74.60%	68.50%	71.20%	72.10%	composite	0.8860702002	0.246
rs7178587	narrow	0.03385	62.50%	67.30%	63.80%	66.00%	composite	0.0678997453	0.242
rs7180867	narrow	0.16354	65.50%	66.10%	64.90%	66.70%	composite	0.1819945701	0.254
rs7232734	narrow	0.90058	66.10%	58.90%	62.30%	62.90%	composite	0.0002842721	0.272
rs7238006	narrow	0.52288	67.90%	66.10%	67.30%	66.70%	composite	0.0079837106	0.257
rs7244801	narrow	0.84726	61.40%	69.60%	63.90%	67.30%	composite	0.0002560514	0.273
rs7317000	narrow	0.21018	56.90%	71.90%	62.10%	67.30%	composite	0.0001141326	0.269
rs751370	narrow	0.00859	67.20%	70.40%	66.70%	70.90%	composite	0.0185234836	0.265
rs752979	narrow	0.00046	64.40%	77.20%	67.70%	74.50%	composite	0.7360004970	0.252
rs7619350	narrow	0.06063	60.30%	71.40%	63.50%	68.60%	composite	0.0851490259	0.251
rs7633210	narrow	0.05618	67.90%	71.70%	67.90%	71.70%	composite	0.5617924237	0.260
rs7714122	narrow	0.20804	65.50%	67.30%	64.90%	67.90%	composite	0.0027785239	0.279
rs7789703	narrow	0.07183	66.10%	65.40%	64.20%	67.30%	composite	0.3143051576	0.247
rs7803164	narrow	0.01264	71.90%	69.60%	70.90%	70.70%	composite	0.2698212215	0.254
rs7806265	narrow	0.00718	74.60%	71.90%	73.20%	73.30%	composite	0.1586648076	0.184
rs7916897	narrow	0.05231	76.90%	76.00%	76.00%	76.90%	composite	0.1481399148	0.261
rs7955917	narrow	0.29246	55.90%	66.10%	58.70%	63.50%	composite	0.0002623828	0.270
rs7963693	narrow	0.39632	55.20%	66.70%	59.40%	62.70%	composite	0.0001330852	0.275
rs8099595	narrow	0.90747	63.80%	62.50%	62.50%	63.80%	composite	0.0003997105	0.265
rs8118441	narrow	0.02179	62.70%	69.60%	63.90%	68.50%	composite	0.5282969814	0.246
rs844602	narrow	0.96474	75.40%	59.30%	69.60%	66.20%	composite	0.0172114588	0.260
rs844608	narrow	0.99421	75.40%	58.90%	70.20%	65.20%	composite	0.0505344333	0.260
rs844610	narrow	0.99419	74.60%	59.60%	69.40%	65.70%	composite	0.0385055827	0.260
rs844612	narrow	0.03225	74.60%	60.00%	68.80%	66.70%	composite	0.1289376035	0.251
rs844626	narrow	0.02163	77.60%	59.30%	71.10%	67.20%	composite	0.0447630201	0.262
rs860722	narrow	0.19021	67.80%	69.60%	67.20%	70.20%	composite	0.5902077325	0.254
rs873216	narrow	0.01102	62.70%	71.90%	65.10%	69.80%	composite	0.5672550674	0.253
rs884266	narrow	0.97903	58.90%	63.20%	61.00%	61.10%	composite	0.0004725485	0.269
rs894857	narrow	0.82796	62.10%	66.70%	63.30%	65.50%	composite	0.0000000002	0.308
rs913882	narrow	0.93461	66.10%	64.30%	64.30%	66.10%	composite	0.0000000055	0.294
rs9315048	narrow	0.00172	64.70%	82.10%	71.90%	76.70%	composite	0.3705256604	0.233
rs9332420	narrow	0.05980	71.20%	66.10%	68.50%	68.90%	composite	0.0331420821	0.255
rs933863	narrow	0.26426	62.70%	59.60%	60.70%	61.70%	composite	0.0000047280	0.283
rs933864	narrow	0.69839	62.10%	64.30%	62.10%	64.30%	composite	0.0956803375	0.186
rs9378319	narrow	0.05573	62.70%	71.40%	64.50%	69.80%	composite	0.0008169610	0.265
rs9378684	narrow	0.03293	64.40%	69.60%	65.00%	69.10%	composite	0.0013903659	0.262
rs9392358	narrow	0.08140	62.10%	72.70%	64.50%	70.60%	composite	0.0006766609	0.265
rs9405541	narrow	0.04542	65.50%	71.40%	66.70%	70.40%	composite	0.0003778692	0.271
rs9405546	narrow	0.05023	65.50%	70.90%	66.10%	70.40%	composite	0.0003198511	0.272
rs947603	narrow	0.00687	74.60%	69.60%	72.20%	72.10%	composite	0.2358314299	0.255
rs948029	narrow	0.00046	64.40%	77.20%	67.70%	74.50%	composite	0.7136661558	0.252
rs948032	narrow	0.00046	64.40%	77.20%	67.70%	74.50%	composite	0.7162224264	0.254
rs949298	narrow	0.01576	62.50%	78.90%	68.20%	74.50%	composite	0.6959498100	0.252
rs9508834	narrow	0.00833	66.10%	76.80%	68.30%	75.00%	composite	0.0072643808	0.280
rs9944913	narrow	0.86061	69.50%	60.70%	65.40%	65.10%	composite	0.0000151282	0.284
rs9952995	narrow	0.77141	65.50%	69.60%	66.10%	69.10%	composite	0.0001815576	0.273
rs998051	narrow	0.65765	65.50%	61.80%	63.00%	64.40%	composite	0.0000059311	0.283

Prediction Models Using GWAS Significant SNPs and Tagged SNPs

[0354] Additional models were established based on 30 SNPs that were chosen out of the 201 SNPs listed in table 16, based on having low p-values. The 30 SNPs chosen were rs947603, rs1007328, rs1573706, rs2177073, rs2487896, rs2511064, rs2521644, rs3135391, rs4148871, rs4343256, rs4344916, rs4369324, rs4445746, rs6097801, rs9508834, rs9944913, rs10853605, rs10931091, rs10950359, rs10988087, rs11599624, rs11617134, rs12256889, rs12639443, rs13042992, rs13238613, rs17087180, rs17575455, rs17771939 and rs17807327.

A pool of model candidates was generated based on combinatorial optimization heuristics. Selected models were chosen based on low value of Akaike's Information Criterion (AIC) and low number of SNPs. The model chosen in the previous step went through "Leave one out" cross validation—searching for high values of the Area Under the ROC curve.

TABLE 17

Model	SNPs in model
GM1003	rs11599624 rs12639443 rs13042992 rs13238613 rs17087180 rs17771939 rs17807327 rs2487896 rs3135391 rs4148871 rs4343256 rs4344916 rs9508834
GM1006	rs12256889 rs12639443 rs13238613 rs1573706 rs17087180 rs17771939 rs17807327 rs2487896 rs4343256 rs4344916 rs4369324 rs4445746 rs9944913
GM1011	rs10988087 rs12639443 rs13042992 rs13238613 rs1573706 rs17087180 rs17771939 rs17807327 rs4148871 rs4344916 rs6097801 rs9508834
GM1012	rs10988087 rs12256889 rs12639443 rs17087180 rs17771939 rs2177073 rs2521644 rs4344916 rs4369324 rs6097801 rs9508834 rs9944913
GM2004	rs10988087 rs11617134 rs12639443 rs13042992 rs17087180 rs17771939 rs17807327 rs2487896 rs4148871 rs4344916 rs4445746 rs6097801 rs9508834
GM2014	rs10988087 rs11617134 rs12639443 rs13042992 rs17087180 rs17771939 rs17807327 rs2487896 rs2521644 rs4148871 rs4344916 rs4445746 rs6097801
GM2022	rs10988087 rs12256889 rs12639443 rs17087180 rs17771939 rs17807327 rs2487896 rs4148871 rs4344916 rs6097801 rs9508834
GM2027	rs1007328 rs11617134 rs12639443 rs13238613 rs1573706 rs17087180 rs17771939 rs17807327 rs4343256 rs4344916 rs9508834 rs9944913
GM2043	rs12639443 rs17087180 rs17771939 rs17807327 rs2487896 rs4148871 rs4343256 rs4344916 rs4369324 rs4445746 rs6097801 rs9508834 rs9944913
GM2068	rs11617134 rs12639443 rs17087180 rs17771939 rs17807327 rs2487896 rs3135391 rs4148871 rs4344916 rs4369324 rs6097801 rs9508834 rs9944913
GM2090	rs10988087 rs12639443 rs13238613 rs17087180 rs17771939 rs2487896 rs4148871 rs4343256 rs4344916 rs9508834
GM2094	rs11617134 rs12256889 rs12639443 rs13042992 rs17087180 rs17771939 rs17807327 rs2177073 rs2487896 rs4343256 rs4344916 rs6097801 rs9508834
GM2277	rs10950359 rs11617134 rs12639443 rs17087180 rs17771939 rs2487896 rs2511064 rs3135391 rs4148871 rs4343256 rs4344916 rs9508834 rs9944913
GM2338	rs12256889 rs12639443 rs13042992 rs17087180 rs17771939 rs17807327 rs2487896 rs2521644 rs4344916 rs6097801
GM3102	rs10950359 rs10988087 rs11599624 rs12256889 rs12639443 rs13042992 rs17087180 rs17771939 rs17807327 rs2521644 rs3135391 rs4344916 rs9508834
GM3150	rs1007328 rs10950359 rs12256889 rs12639443 rs13042992 rs1573706 rs17087180 rs17771939 rs17807327 rs4343256 rs4344916 rs947603 rs9508834
GM3332	rs11599624 rs12256889 rs12639443 rs1573706 rs17087180 rs17771939 rs17807327 rs2177073 rs2487896 rs4344916 rs6097801 rs9508834 rs9944913

The response probability of a specific patient was calculated according to each model. Following the genotyping of the patient at the relevant SNPs, the values of the SNPs were recoded to numeric values as described in the following tables (18a-s)

TABLE 18a

rs1007328	Recoded value
CC	0
CT	1
TT	2

TABLE 18b

rs10950359	Recoded value
AA	0
AG	1
GG	2

TABLE 18c

rs10988087	Recoded value
AA	0
AG	1
GG	1

TABLE 18d

rs11617134	Recoded value
CC	0
CT	1
TT	2

TABLE 18e

rs1225689	Recoded value
AA	0
AC	1
CC	2

TABLE 18f

rs13042992	Recoded value
TT	0
GG	1
GT	1

TABLE 18g

rs13238613	Recoded value
CC	0
CT	1
TT	2

TABLE 18h

rs17087180	Recoded value
AA	0
AG	1
GG	2

TABLE 18i

rs2177073	Recoded value
CC	0
AA	1
AC	1

TABLE 18j

rs2511064	Recoded value
AA	0
AG	1
GG	2

TABLE 18k

rs2521644	Recoded value
CC	0
CT	1
TT	2

TABLE 18l

rs4343256	Recoded value
AA	0
AG	1
GG	2

TABLE 18m

rs4344916	Recoded value
AA	0
AC	1
CC	2

TABLE 18n

rs4369324	Recoded value
GG	0
GT	1
TT	2

TABLE 18o

rs4445746	Recoded value
AA	0
AG	1
GG	2

TABLE 18p

rs6097801	Recoded value
AA	0
AG	1
GG	2

TABLE 18q

rs947603	Recoded value
CC	0
CT	1
TT	2

TABLE 18r

rs9508834	Recoded value
AA	0
AG	1
GG	2

TABLE 18s

rs9944913	Recoded value
CC	0
CT	1
TT	1

For each of the following SNPs define two new numeric variables as described in the following tables (19a-h):

TABLE 19a

rs11599624	rs11599624__AA	rs11599624__AG
AA	1	0
AG	0	1
GG	−1	−1

TABLE 19b

rs12639443	rs12639443__CC	rs12639443__CT
CC	1	0
CT	0	1
TT	−1	−1

TABLE 19c

rs1573706	rs1573706__CC	rs1573706__CT
CC	1	0
CT	0	1
TT	−1	−1

TABLE 19d

rs17771939	rs17771939__CC	rs17771939__CT
CC	1	0
CT	0	1
TT	−1	−1

TABLE 19e

rs17807327	rs17807327__AA	rs17807327__AC
AA	1	0
AC	0	1
CC	−1	−1

TABLE 19f

rs2487896	rs2487896__AA	rs2487896__AG
AA	1	0
AG	0	1
GG	−1	−1

TABLE 19g

rs3135391	rs3135391__AA	rs3135391__AG
AA	1	0
AG	0	1
GG	−1	−1

TABLE 19h

rs4148871	rs4148871__AA	rs4148871__AG
AA	1	0
AG	0	1
GG	−1	−1

βX was calculated by multiplying the recoded value of each of the defined numeric variables by the coefficient in the table (each table defines a model):

TABLE 20

GM1003 model parameterization	
Variable	coefficient
Intercept	9.3288
rs11599624__AA	−0.6054
rs11599624__AG	1.8340
rs12639443__CC	1.6819
rs12639443__CT	−5.2952
rs13042992	−2.1062
rs13238613	−1.6323
rs17087180	−5.6010
rs17771939__CC	−8.0785
rs17771939__CT	2.0671
rs17807327__AA	−4.1034
rs17807327__AC	7.1312
rs2487896__AA	3.4005
rs2487896__AG	−4.5188
rs3135391__AA	1.1864
rs3135391__AG	0.4869
rs4148871__AA	−3.8189
rs4148871__AG	2.5264
rs4343256	−6.9897
rs4344916	−4.3873
rs9508834	−4.0794

TABLE 21

GM1006 model parameterization	
variable	coefficient
Intercept	0.8934
rs12256889	−0.3642
rs12639443__CC	0.3262
rs12639443__CT	−2.8743
rs13238613	−1.2795
rs1573706__CC	0.2463
rs1573706__CT	−1.3858
rs17087180	−1.3097
rs17771939__CC	−3.1145
rs17771939__CT	0.5409
rs17807327__AA	−3.2420
rs17807327__AC	4.8105
rs2487896__AA	−1.4076
rs2487896__AG	−1.0467
rs4343256	−4.0890
rs4344916	−2.4887
rs4369324	1.7375
rs4445746	2.8535
rs9944913	−1.8489

TABLE 22

GM1011 model parameterization

variable	coefficient
Intercept	6.2733
rs10988087	−1.6114
rs12639443__CC	1.3759
rs12639443__CT	−1.4160
rs13042992	−1.9210
rs13238613	−2.9116
rs1573706__CC	1.2609
rs1573706__CT	−0.7329
rs17087180	−5.9857
rs17771939__CC	−3.3508
rs17771939__CT	1.2529
rs17807327__AA	−3.0312
rs17807327__AC	1.9158
rs4148871__AA	−0.5022
rs4148871__AG	0.4602
rs4344916	−2.3358
rs6097801	1.3835
rs9508834	−2.8596

TABLE 23

GM1012 model parameterization

variable	coefficient
Intercept	4.8013
rs10988087	−1.3216
rs12256889	−1.4875
rs12639443__CC	0.8026
rs12639443__CT	−2.1054
rs17087180	−0.9015
rs17771939__CC	−4.1661
rs17771939__CT	1.2859
rs2177073	0.7441
rs2521644	−1.6096
rs4344916	−2.1699
rs4369324	1.5320
rs6097801	0.4036
rs9508834	−2.7916
rs9944913	−2.3396

TABLE 24

GM2004 model parameterization

variable	coefficient
Intercept	−2.4137
rs10988087	−3.2236
rs11617134	3.2842
rs12639443__CC	2.5129
rs12639443__CT	−5.6785
rs13042992	−2.2749
rs17087180	−7.7618
rs17771939__CC	−7.4691
rs17771939__CT	1.7498
rs17807327__AA	−3.8468
rs17807327__AC	6.1901
rs2487896__AA	3.2967
rs2487896__AG	−5.6031
rs4148871__AA	−3.4591
rs4148871__AG	2.3145
rs4344916	−4.3650
rs4445746	−0.7965
rs6097801	1.5690
rs9508834	−5.2894

TABLE 25

GM2014 model parameterization

variable	coefficient
Intercept	−7.8077
rs10988087	−2.6273
rs11617134	2.8140
rs12639443__CC	2.6274
rs12639443__CT	−5.5577
rs13042992	−2.6555
rs17087180	−8.5303
rs17771939__CC	−7.6788
rs17771939__CT	2.1630
rs17807327__AA	−3.9942
rs17807327__AC	5.4647
rs2487896__AA	2.5228
rs2487896__AG	−5.2338
rs2521644	−1.0118
rs4148871__AA	−2.9546
rs4148871__AG	1.6983
rs4344916	−4.6078
rs4445746	3.3039
rs6097801	0.9950

TABLE 26

GM2022 model parameterization

variable	coefficient
Intercept	0.7315
rs10988087	−2.7341
rs12256889	−0.6341
rs12639443__CC	2.2261
rs12639443__CT	−3.7174
rs17087180	−3.8342
rs17771939__CC	−4.7874
rs17771939__CT	0.9707
rs17807327__AA	−2.3173
rs17807327__AC	4.6672
rs2487896__AA	1.4718
rs2487896__AG	−3.3924
rs4148871__AA	−2.0086
rs4148871__AG	0.8390
rs4344916	−3.3546
rs6097801	1.6744
rs9508834	−3.6073

TABLE 27

GM2027 model parameterization

variable	coefficient
Intercept	6.1931
rs1007328	1.0823
rs11617134	1.0945
rs12639443__CC	0.5046
rs12639443__CT	−2.5608
rs13238613	−2.2037
rs1573706__CC	0.4573
rs1573706__CT	−1.0221
rs17087180	−6.2114
rs17771939__CC	−2.8678
rs17771939__CT	1.0193
rs17807327__AA	−3.6846
rs17807327__AC	1.0093
rs4343256	−4.1274
rs4344916	−1.7464
rs9508834	−3.2225
rs9944913	−1.0139

TABLE 28

GM2043 model parameterization

variable	coefficient
Intercept	0.9415
rs12639443__CC	0.5518
rs12639443__CT	−4.7541
rs17087180	−4.2930
rs17771939__CC	−5.9952
rs17771939__CT	1.4480
rs17807327__AA	−3.7064
rs17807327__AC	4.9288
rs2487896__AA	1.3741
rs2487896__AG	−3.4768
rs4148871__AA	−2.5161
rs4148871__AG	1.7311
rs4343256	−4.8515
rs4344916	−3.2447
rs4369324	1.6196
rs4445746	0.3546
rs6097801	1.7405
rs9508834	−3.8363
rs9944913	−2.3385

TABLE 29

GM2068 model parameterization

variable	coefficient
Intercept	−10.0845
rs11617134	4.5538
rs12639443__CC	2.7799
rs12639443__CT	−5.9539
rs17087180	−3.3532
rs17771939__CC	−8.8437
rs17771939__CT	1.4087
rs17807327__AA	−3.3124
rs17807327__AC	7.3851
rs2487896__AA	1.8417
rs2487896__AG	−5.5723
rs3135391__AA	2.6828
rs3135391__AG	−0.4052
rs4148871__AA	−4.3161
rs4148871__AG	2.2073
rs4344916	−4.6260
rs4369324	2.0398
rs6097801	2.3816
rs9508834	−5.9421
rs9944913	−2.3240

TABLE 30

GM2090 model parameterization

variable	coefficient
Intercept	4.0746
rs10988087	−2.0102
rs12639443__CC	1.6253
rs12639443__CT	−3.1638
rs13238613	−1.6126
rs17087180	−2.6288
rs17771939__CC	−4.5000
rs17771939__CT	0.9317
rs2487896__AA	1.0289
rs2487896__AG	−2.7833
rs4148871__AA	−1.7042
rs4148871__AG	0.4143
rs4343256	−1.5111
rs4344916	−3.9136
rs9508834	−3.2171

TABLE 31

GM2094 model parameterization

variable	coefficient
Intercept	−0.5847
rs11617134	2.6429
rs12256889	−0.6230
rs12639443__CC	0.9349
rs12639443__CT	−3.4318
rs13042992	−1.1986
rs17087180	−3.1618
rs17771939__CC	−4.0279
rs17771939__CT	0.7481
rs17807327__AA	−2.9966
rs17807327__AC	3.5249
rs2177073	−1.0156
rs2487896__AA	0.6515
rs2487896__AG	−2.4396
rs4343256	−3.2118
rs4344916	−2.6570
rs6097801	0.7221
rs9508834	−3.3025

TABLE 32

GM2277 model parameterization

variable	coefficient
Intercept	−8.0820
rs10950359	0.6756
rs11617134	3.0151
rs12639443__CC	1.8613
rs12639443__CT	−4.7429
rs17087180	−3.0913
rs17771939__CC	−5.5319
rs17771939__CT	1.5306
rs2487896__AA	1.9046
rs2487896__AG	−4.3657
rs2511064	2.0087
rs3135391__AA	1.3667
rs3135391__AG	0.1182
rs4148871__AA	−3.7287
rs4148871__AG	0.7481
rs4343256	−1.2743
rs4344916	−4.1012
rs9508834	−2.9978
rs9944913	−2.3903

TABLE 33

GM2338 model parameterization

variable	coefficient
Intercept	4.9303
rs12256889	−1.1920
rs12639443__CC	1.6753
rs12639443__CT	−2.6864
rs13042992	−2.9155
rs17087180	−1.7977
rs17771939__CC	−4.7042
rs17771939__CT	1.4442
rs17807327__AA	−2.2426
rs17807327__AC	3.9474
rs2487896__AA	−0.0709
rs2487896__AG	−2.2441
rs2521644	−1.8304
rs4344916	−2.8265
rs6097801	0.4595

TABLE 34

GM3102 model parameterization

variable	coefficient
Intercept	5.5127
rs10950359	1.4764
rs10988087	−2.9752
rs11599624_AA	−0.6179
rs11599624_AG	2.8171
rs12256889	−1.1438
rs12639443_CC	2.0266
rs12639443_CT	−2.4140
rs13042992	−1.3091
rs17087180	−4.0442
rs17771939_CC	−3.7615
rs17771939_CT	1.0481
rs17807327_AA	−1.3721
rs17807327_AC	2.5104
rs2521644	−1.6019
rs3135391_AA	−1.4040
rs3135391_AG	0.7262
rs4344916	−2.4904
rs9508834	−2.7692

TABLE 35

GM3150 model parameterization

variable	coefficient
Intercept	4.7936
rs1007328	1.5777
rs10950359	1.7864
rs12256889	−0.4262
rs12639443_CC	1.5767
rs12639443_CT	−2.3687
rs13042992	−1.5894
rs1573706_CC	0.4357
rs1573706_CT	−1.4587
rs17087180	−3.4853
rs17771939_CC	−2.4489
rs17771939_CT	0.5208
rs17807327_AA	−3.1700
rs17807327_AC	2.8718
rs4343256	−2.7644
rs4344916	−2.0371
rs947603	−1.0418
rs9508834	−3.1861

TABLE 36

GM3332 model parameterization

variable	coefficient
Intercept	3.9516
rs11599624_AA	−1.1461
rs11599624_AG	2.2491
rs12256889	−0.7295
rs12639443_CC	0.6782
rs12639443_CT	−2.7278
rs1573706_CC	1.1868
rs1573706_CT	−1.4399
rs17087180	−1.5211
rs17771939_CC	−3.5821
rs17771939_CT	0.5404
rs17807327_AA	−2.0945
rs17807327_AC	4.1007
rs2177073	−1.0741
rs2487896_AA	−0.1642
rs2487896_AG	−1.8886
rs4344916	−2.5787
rs6097801	0.4844
rs9508834	−3.0143
rs9944913	−1.5636

The response probability was calculated using the formula:

$$P(\text{Response}) = \frac{e^{\beta X}}{1 + e^{\beta X}}$$

We have noticed that the following four SNPs were common to all models: rs4344916, rs12639443, rs17087180 and rs17771939. Two additional SNPs were common to at least 25/30 models containing the four SNPs described above: rs9508834 and rs17807327. Therefore, it would be appreciated by a person skilled in the art that sets of SNPs comprising rs4344916, rs12639443, rs17087180 and rs17771939 are expected to constitute models which are effective in predicting response to GA. The models may include other SNPs in addition to rs4344916, rs12639443, rs17087180 and rs17771939, including rs9508834, rs17807327, both, or other SNPs.

[0355] The models were retrospectively applied to the full cohort of 599 FORTE patients using different predictive thresholds. The ratios between the Annualized Relapse Rate (ARR) of genetically predicted responder patients (R) compared to the average ARR in genetically predicted non-responder patients (NR), and the ratios between the average ARR observed in the genetically predicted responder patients (R) compared to average ARR in the whole study population (All), according to each predictive threshold or two predictive thresholds, are presented in table 37. Table 37a shows data for models FM1, FM2, FM1a and GM1003, table 37b shows data for models GM1006, GM1011, GM1012 and GM2004, table 37c shows data for models GM2014, GM2022, GM2027 and 2043, table 37d shows data for models GM2068, GM2090, GM2094 and GM2277, and table 37e shows data for models GM2338, GM3102, GM3150 and GM3332.

[0356] Applying the 0.8 threshold for the FM1 model (presented in tables 5-7) in the FORTE cohort as well as two other cohorts (European/Canadian study and CORAL), we found that the average ARR in the GA-treated patients that were genetically predicted as responders in the FORTE and in the European/Canadian study was 76% and 81% lower, respectively, than in patients predicted as NR and 64% and 77% lower, respectively, than in the whole study population. In comparison, the average ARR in either placebo-treated patients or non treated patients (from European/Canadian study and CORAL, respectively) genetically predicted as responders was −7% and 26% lower, respectively, than in patients predicted as Non-Responders and 10% and 11% lower than in the whole study population. The reduction in average ARR by GA over placebo-treated patients in the responders population in the European/Canadian study was 79%.

TABLE 37

The Annualized Relapse Rate (ARR) average in all subjects of the FORTE trial compared to ARR average in genetically predicted responders (R) and non-responders (NR). UD = undefined

ARR -	Annual Relapse Rate average as calculated for each genetically defined sub-population
Risk Ratio	The ratio between ARR observed in the genetically predicted responders (R) compared to the ARR in genetically predicted non-responders (NR)

TABLE 37-continued

The Annualized Relapse Rate (ARR) average in all subjects of the FORTE trial compared to ARR average in genetically predicted responders (R) and non-responders (NR). UD = undefined

ARR Vs all	The ratio between ARR observed in the genetically predicted super responders (R) compared to ARR in the whole study population (All)

TABLE 37a

Models FM1, FM2, FM1a and GM1003 (pages 106-111)

		Model:											
		FM1			FM2			FM1a			GM1003		
threshold	response prediction	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all
NA	All	0.241		100%	0.245		100%	0.245		100%	0.26		100%
0-0.1	NR	0.482	35%	200%	0.531	41%	217%	0.419	50%	171%	0.502	35%	193%
0.1-1	R	0.167		69%	0.217		89%	0.211		86%	1.176		67%
0-0.2	NR	0.423	37%	176%	0.533	37%	218%	0.433	43%	177%	0.509	31%	195%
0.2-1	R	0.157		65%	0.195		80%	0.185		75%	0.16		61%
0-0.3	NR	0.427	32%	177%	0.485	37%	198%	0.415	44%	169%	0.51	29%	196%
0.3-1	R	0.135		56%	0.178		73%	0.182		74%	0.146		56%
0-0.4	NR	0.424	32%	176%	0.37	48%	151%	0.412	40%	168%	0.504	29%	193%
0.4-1	R	0.134		55%	0.178		73%	0.164		67%	0.145		56%
0-0.5	NR	0.423	32%	175%	0.344	51%	141%	0.343	46%	140%	0.491	29%	189%
0.5-1	R	0.134		56%	0.174		71%	0.159		65%	0.14		54%
0-0.6	NR	0.412	33%	171%	0.349	46%	143%	0.334	46%	136%	0.475	28%	182%
0.6-1	R	0.136		56%	0.16		65%	0.154		63%	0.132		51%
0-0.7	NR	0.383	34%	159%	0.332	37%	135%	0.333	40%	136%	0.468	28%	180%
0.7-1	R	0.132		55%	0.122		50%	0.138		54%	0.131		50%
0-0.8	NR	0.361	24%	150%	0.289	44%	118%	0.322	40%	131%	0.457	27%	175%
0.8-1	R	0.088		36%	0.126		52%	0.129		53%	0.125		48%
0-0.9	NR	0.318	31%	132%	0.259	49%	106%	0.302	36%	123%	0.438	28%	168%
0.9-1	R	0.098		41%	0.127		52%	0.11		45%	1.123		47%
0-0.1	NR	0.481	33%	200%	0.53	37%	217%	0.42	44%	171%	0.5	32%	192%
0.2-1	R	0.157		65%	0.195		80%	0.185		75%	0.16		61%
0.1-0.2	UD	0.252		105%	0.538		220%	0.463		189%	0.592		227%
0-0.1	NR	0.481	28%	200%	0.533	33%	218%	0.42	43%	171%	0.501	29%	193%
0.3-1	R	0.135		56%	0.178		73%	0.182		74%	0.146		56%
0.1-0.3	UD	0.326		135%	0.453		185%	0.408		166%	0.549		211%
0-0.1	NR	0.483	28%	200%	0.533	33%	218%	0.421	39%	171%	0.501	29%	193%
0.4-1	R	0.134		56%	0.178		73%	0.164		67%	0.145		56%
0.1-0.4	UD	0.322		134%	0.315		129%	0.404		165%	0.513		197%
0-0.1	NR	0.482	28%	200%	0.533	33%	217%	0.42	38%	171%	0.501	28%	192%
0.5-1	R	0.134		56%	0.174		71%	0.16		65%	0.14		54%
0.1-0.5	UD	0.319		132%	0.293		120%	0.299		122%	0.462		177%
0-0.1	NR	0.482	28%	200%	0.533	30%	218%	0.419	37%	171%	0.503	26%	193%
0.6-1	R	0.136		56%	0.16		65%	0.154		63%	0.132		51%
0.1-0.6	UD	0.299		124%	0.304		124%	0.291		119%	0.412		158%
0-0.1	NR	0.483	27%	200%	0.531	23%	217%	0.418	32%	170%	0.502	26%	193%
0.7-1	R	0.132		55%	0.122		50%	0.134		54%	0.131		50%
0.1-0.7	UD	0.265		110%	0.296		121%	0.297		121%	0.395		152%
0-0.1	NR	0.483	18%	201%	0.53	24%	217%	0.418	31%	170%	0.505	25%	194%
0.8-1	R	0.088		36%	0.127		52%	0.129		53%	0.125		48%
0.1-0.8	UD	0.273		113%	0.256		105%	0.284		116%	0.373		143%
0-0.1	NR	0.481	20%	200%	0.531	24%	217%	0.42	26%	171%	0.503	24%	193%
0.9-1	R	0.098		41%	0.127		52%	0.11		45%	0.123		47%
0.1-0.9	UD	0.225		93%	0.229		94%	0.265		108%	0.342		132%
0-0.2	NR	0.424	32%	176%	0.535	33%	218%	0.433	42%	177%	0.51	29%	196%
0.3-1	R	0.135		56%	0.178		73%	0.182		74%	0.146		56%
0.2-0.3	UD	0.445		185%	0.385		157%	0.254		104%	0.508		195%
0-0.2	NR	0.425	32%	176%	0.534	33%	218%	0.434	38%	177%	0.509	28%	196%
0.4-1	R	0.134		55%	0.178		73%	0.164		67%	0.145		56%
0.2-0.4	UD	0.419		174%	0.252		103%	0.349		142%	0.454		174%
0-0.2	NR	0.425	32%	176%	0.534	33%	218%	0.434	37%	177%	0.509	28%	195%
−10.5	R	0.134		56%	0.174		71%	0.16		65%	0.14		54%
0.2-0.5	UD	0.409		170%	0.242		99%	0.243		99%	0.398		153%
0-0.2	NR	0.424	32%	176%	0.535	30%	219%	0.434	35%	177%	0.51	26%	196%

TABLE 37a-continued

Models FM1, FM2, FM1a and GM1003 (pages 106-111)

		Model:											
		FM1			FM2			FM1a			GM1003		
threshold	response prediction	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all
0.6-1	R	0.136		56%	0.16		65%	0.154		63%	0.132		51%
0.2-0.6	UD	0.353		146%	0.26		106%	0.241		98%	0.357		137%
0-0.2	NR	0.424	31%	176%	0.534	23%	218%	0.433	31%	176%	0.51	26%	196%
0.7-1	R	0.132		55%	0.122		50%	0.134		55%	0.131		50%
0.2-0.7	UD	0.272		113%	0.264		108%	0.255		104%	0.342		131%
0-0.2	NR	0.425	21%	176%	0.533	24%	218%	0.432	30%	176%	0.512	24%	197%
0.8-1	R	0.088		36%	0.127		52%	0.13		53%	0.125		48%
0.2-0.8	UD	0.279		116%	0.228		93%	0.246		100%	0.326		125%
0-0.2	NR	0.423	23%	176%	0.533	24%	218%	0.434	25%	177%	0.51	24%	196%
0.9-1	R	0.098		41%	0.126		52%	0.11		45%	0.123		47%
0.2-0.9	UD	0.218		91%	0.206		84%	0.232		94%	0.298		115%
0-0.3	NR	0.427	31%	177%	0.485	37%	198%	0.416	39%	170%	0.51	28%	196%
0.4-1	R	0.134		55%	0.178		73%	0.164		67%	0.145		56%
0.3-0.4	UD	0.236		98%	0.18		73%	0.394		161%	0.259		99%
0-0.3	NR	0.427	31%	177%	0.485	36%	198%	0.415	39%	169%	0.509	28%	196%
0.5-1	R	0.134		55%	0.175		71%	0.16		65%	0.14		54%
0.3-0.5	UD	0.201		84%	0.189		77%	0.241		98%	0.29		111%
0-0.3	NR	0.427	32%	177%	0.486	33%	198%	0.415	37%	169%	0.51	26%	196%
0.6-1	R	0.136		56%	0.16		65%	0.154		63%	0.132		51%
0.3-0.6	UD	0.101		42%	0.221		90%	0.239		97%	0.29		111%
0-0.3	NR	0.427	31%	177%	0.485	25%	198%	0.415	32%	169%	0.51	26%	196%
0.7-1	R	0.132		55%	0.122		50%	0.134		55%	0.131		50%
0.3-0.7	UD	0.153		63%	0.241		98%	0.255		104%	0.278		107%
0-0.3	NR	0.428	21%	178%	0.485	26%	198%	0.414	31%	169%	0.511	24%	196%
0.8-1	R	0.088		36%	0.127		52%	0.13		53%	0.125		48%
0.3-0.8	UD	0.238		99%	0.206		84%	0.245		100%	0.276		106%
0-0.3	NR	0.427	23%	177%	0.485	26%	198%	0.416	26%	169%	0.51	24%	196%
0.9-1	R	0.098		41%	0.127		52%	0.11		45%	0.123		47%
0.3-0.9	UD	0.179		74%	0.187		76%	0.23		94%	0.253		97%
0-0.3	NR	0.424	32%	176%	0.37	47%	151%	0.412	39%	168%	0.503	28%	193%
0.5-1	R	0.134		56%	0.174		71%	0.16		65%	0.14		54%
0.4-0.5	UD	0		0%	0.21		86%	0.178		72%	0.302		116%
0-0.4	NR	0.425	32%	176%	0.37	43%	151%	0.412	37%	168%	0.504	26%	194%
0.6-1	R	0.136		56%	0.16		65%	0.154		63%	0.132		51%
0.4-0.6	UD	0		0%	0.276		113%	0.189		77%	0.294		113%
0-0.4	NR	0.424	31%	176%	0.369	33%	151%	0.412	33%	168%	0.504	26%	194%
0.7-1	R	0.133		55%	0.122		50%	0.134		55%	0.131		50%
0.4-0.7	UD	0.143		59%	0.276		113%	0.22		90%	0.28		108%
0-0.4	NR	0.425		176%	0.37		151%	0.412		168%	0.505		194%
0-0.7	NR	0.384	23%	159%	0.332	38%	135%	0.333	39%	136%	0.469	26%	180%
0.8-1	R	0.088		36%	0.127		52%	0.129		53%	0.124		48%
0.7-0.8	UD	0.284		118%	0.112		46%	0.172		70%	0.27		104%
0-0.7	NR	0.383	26%	159%	0.332	38%	135%	0.333	33%	136%	0.468	26%	180%
0.9-1	R	0.098		41%	0.127		52%	0.11		45%	0.123		47%
0.7-0.9	UD	0.188		78%	0.12		49%	0.18		73%	0.219		84%
0-0.8	NR	0.362	27%	150%	0.289	44%	118%	0.322	34%	131%	0.457	27%	175%
0.9-1	R	0.098		41%	0.127		52%	0.11		45%	0.123		47%
0.8-0.9	UD	0.043		18%	0.126		51%	0.182		74%	0.16		61%

TABLE 37b

Models GM1006, GM1011, GM1012 and GM2004 (pages 111-116).

		Model:											
		GM1006			GM1011			GM1012			GM2004		
threshold	response prediction	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all
NA	All	0.253		100%	0.256		100%	0.251		100%	0.255		100%
0-0.1	NR	0.597	26%	235%	0.621	26%	242%	0.58	29%	231%	0.511	31%	200%
0.1-1	R	0.157		62%	0.16		63%	0.169		67%	0.157		62%
0-0.2	NR	0.55	26%	217%	0.578	25%	225%	0.528	30%	210%	0.513	27%	201%

TABLE 37b-continued

Models GM1006, GM1011, GM1012 and GM2004 (pages 111-116).

		Model:											
		GM1006			GM1011			GM1012			GM2004		
threshold	response prediction	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all
0.2-1	R	0.143		56%	0.142		55%	0.157		62%	0.139		54%
0-0.3	NR	0.51	27%	201%	0.549	25%	214%	0.514	27%	205%	0.505	27%	198%
0.3-1	R	0.139		55%	0.135		53%	0.138		55%	0.134		52%
0-0.4	NR	0.491	28%	194%	0.495	28%	193%	0.498	28%	198%	0.493	27%	194%
0.4-1	R	0.137		54%	0.137		53%	0.137		54%	0.131		51%
0-0.5	NR	0.463	30%	183%	0.48	27%	187%	0.479	27%	191%	0.488	27%	191%
0.5-1	R	0.138		55%	0.13		51%	0.129		51%	0.13		51%
0-0.6	NR	0.452	29%	178%	0.451	27%	176%	0.442	28%	176%	0.494	24%	194%
0.6-1	R	0.129		51%	0.12		47%	0.123		49%	0.118		46%
0-0.7	NR	0.424	30%	167%	0.422	29%	165%	0.416	30%	166%	0.484	23%	190%
0.7-1	R	0.126		50%	0.121		47%	0.124		49%	0.11		43%
0-0.8	NR	0.397	32%	157%	0.41	29%	160%	0.386	32%	154%	0.447	25%	175%
0.8-1	R	0.128		50%	0.118		46%	0.125		50%	0.113		44%
0-0.9	NR	0.377	33%	149%	0.381	31%	149%	0.358	33%	143%	0.417	27%	163%
0.9-1	R	0.123		48%	0.119		46%	0.118		47%	0.114		45%
0-0.1	NR	0.597	24%	236%	0.622	23%	242%	0.581	27%	231%	0.512	27%	201%
0.2-1	R	0.143		57%	0.142		55%	0.157		62%	0.139		54%
0.1-0.2	UD	0.348		137%	0.409		160%	0.332		132%	0.517		203%
0-0.1	NR	0.595	23%	235%	0.623	22%	243%	0.584	24%	232%	0.513	26%	201%
0.3-1	R	0.139		55%	0.135		53%	0.138		55%	0.134		52%
0.1-0.3	UD	0.296		117%	0.366		143%	0.376		150%	0.463		181%
0-0.1	NR	0.595	23%	235%	0.624	22%	243%	0.584	23%	233%	0.512	26%	201%
0.4-1	R	0.138		54%	0.136		53%	0.136		54%	0.131		51%
0.1-0.4	UD	0.279		110%	0.282		110%	0.351		140%	0.414		162%
0-0.1	NR	0.595	24%	235%	0.624	21%	243%	0.585	22%	233%	0.513	25%	201%
0.5-1	R	0.14		55%	0.13		51%	0.128		51%	0.13		51%
0.1-0.5	UD	0.241		95%	0.284		111%	0.338		134%	0.392		154%
0-0.1	NR	0.593	22%	234%	0.622	19%	243%	0.584	21%	232%	0.512	23%	201%
0.6-1	R	0.131		52%	0.12		47%	0.123		49%	0.118		46%
0.1-0.6	UD	0.256		101%	0.275		107%	0.301		120%	0.434		170%
0-0.1	NR	0.593	22%	234%	0.621	19%	242%	0.583	21%	232%	0.513	21%	201%
0.7-1	R	0.128		51%	0.121		47%	0.124		49%	0.11		43%
0.1-0.7	UD	0.24		95%	0.249		97%	0.274		109%	0.413		162%
0-0.1	NR	0.594	22%	234%	0.621	19%	242%	0.583	21%	232%	0.512	22%	201%
0.8-1	R	0.13		51%	0.119		46%	0.125		50%	0.113		44%
0.1-0.8	UD	0.218		86%	0.242		95%	0.247		98%	0.326		128%
0-0.1	NR	0.595	21%	235%	0.621	19%	242%	0.582	20%	232%	0.512	22%	201%
0.9-1	R	0.125		49%	0.12		47%	0.118		47%	0.114		45%
0.1-0.9	UD	0.212		84%	0.221		86%	0.231		92%	0.277		108%
0-0.2	NR	0.549	25%	217%	0.579	23%	226%	0.531	26%	211%	0.513	26%	201%
0.3-1	R	0.139		55%	0.135		53%	0.138		55%	0.134		52%
0.2-0.3	UD	0.218		86%	0.289		113%	0.422		168%	0.34		134%
0-0.2	NR	0.549	25%	217%	0.579	23%	226%	0.531	26%	211%	0.513	26%	201%
0.4-1	R	0.138		54%	0.136		53%	0.137		54%	0.131		51%
0.2-0.4	UD	0.211		83%	0.191		74%	0.364		145%	0.297		116%
0-0.2	NR	0.55	25%	217%	0.58	22%	226%	0.531	24%	211%	0.513	25%	201%
-10.5	R	0.14		55%	0.13		51%	0.129		51%	0.13		51%
0.2-0.5	UD	0.168		66%	0.216		84%	0.339		135%	0.28		110%
0-0.2	NR	0.548	24%	216%	0.579	21%	226%	0.53	23%	211%	0.513	23%	201%
0.6-1	R	0.131		52%	0.121		47%	0.123		49%	0.118		46%
0.2-0.6	UD	0.211		83%	0.225		88%	0.288		115%	0.379		149%
0-0.2	NR	0.548	23%	216%	0.578	21%	225%	0.53	23%	211%	0.514	21%	201%
0.7-1	R	0.128		50%	0.121		47%	0.124		49%	0.11		43%
0.2-0.7	UD	0.201		79%	0.202		79%	0.256		102%	0.364		143%
0-0.2	NR	0.549	24%	217%	0.578	21%	225%	0.53	24%	211%	0.513	22%	201%
0.8-1	R	0.13		51%	0.119		47%	0.125		50%	0.113		44%
0.2-0.8	UD	0.18		71%	0.198		77%	0.226		90%	0.266		104%
0-0.2	NR	0.549	23%	217%	0.578	21%	225%	0.529	22%	211%	0.513	22%	201%
0.9-1	R	0.125		49%	0.12		47%	0.118		47%	0.115		45%
0.2-0.9	UD	0.181		72%	0.182		71%	0.213		85%	0.221		86%
0-0.3	NR	0.51	27%	201%	0.549	25%	214%	0.514	27%	205%	0.505	26%	198%
0.4-1	R	0.137		54%	0.136		53%	0.137		54%	0.131		51%
0.3-0.4	UD	0.2		79%	0.122		47%	0.207		83%	0.25		98%
0-0.3	NR	0.51	27%	201%	0.549	24%	214%	0.515	25%	205%	0.505	26%	198%
0.5-1	R	0.139		55%	0.13		51%	0.129		51%	0.13		51%
0.3-0.5	UD	0.13		51%	0.184		72%	0.259		103%	0.238		93%
0-0.3	NR	0.509	26%	201%	0.549	22%	214%	0.515	24%	205%	0.505	23%	198%
0.6-1	R	0.13		51%	0.121		47%	0.124		49%	0.118		46%

TABLE 37b-continued

Models GM1006, GM1011, GM1012 and GM2004 (pages 111-116).

		Model:											
		GM1006			GM1011			GM1012			GM2004		
threshold	response prediction	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all
0.3-0.6	UD	0.208		82%	0.208		81%	0.224		89%	0.396		155%
0-0.3	NR	0.509	25%	201%	0.549	22%	214%	0.515	24%	205%	0.505	22%	198%
0.7-1	R	0.127		50%	0.122		47%	0.124		49%	0.11		43%
0.3-0.7	UD	0.196		77%	0.184		72%	0.196		78%	0.37		145%
0-0.3	NR	0.51	25%	201%	0.549	22%	214%	0.515	24%	205%	0.505	22%	198%
0.8-1	R	0.129		51%	0.12		47%	0.125		50%	0.113		44%
0.3-0.8	UD	0.172		68%	0.182		71%	0.175		70%	0.253		99%
0-0.3	NR	0.51	24%	201%	0.549	22%	214%	0.514	23%	205%	0.505	23%	198%
0.9-1	R	0.124		49%	0.12		47%	0.118		47%	0.115		45%
0.3-0.9	UD	0.175		69%	0.166		65%	0.173		69%	0.206		81%
0-0.3	NR	0.492	28%	194%	0.495	26%	193%	0.498	26%	198%	0.494	26%	194%
0.5-1	R	0.139		55%	0.13		51%	0.129		51%	0.13		51%
0.4-0.5	UD	0.076		30%	0.295		115%	0.288		115%	0.216		85%
0-0.4	NR	0.491	26%	194%	0.494	24%	192%	0.498	25%	198%	0.494	24%	194%
0.6-1	R	0.13		51%	0.121		47%	0.124		49%	0.118		46%
0.4-0.6	UD	0.211		83%	0.264		103%	0.228		91%	0.492		193%
0-0.4	NR	0.491	26%	194%	0.494	25%	193%	0.498	25%	198%	0.494	22%	194%
0.7-1	R	0.127		50%	0.122		47%	0.124		49%	0.11		43%
0.4-0.7	UD	0.195		77%	0.211		82%	0.195		77%	0.409		160%
0-0.4	NR	0.491	26%	194%	0.494	24%	193%	0.498	25%	198%	0.494	23%	194%
0.8-1	R	0.129		51%	0.12		47%	0.125		50%	0.113		44%
0.4-0.8	UD	0.168		66%	0.204		80%	0.171		68%	0.253		99%
0-0.4	NR	0.491	25%	194%	0.495	24%	193%	0.498	24%	198%	0.494	23%	194%
0.9-1	R	0.123		49%	0.121		47%	0.118		47%	0.115		45%
0.4-0.9	UD	0.172		68%	0.178		70%	0.17		68%	0.201		79%
0-0.5	NR	0.462	28%	182%	0.479	25%	187%	0.479	26%	191%	0.486	24%	191%
0.6-1	R	0.129		51%	0.121		47%	0.124		49%	0.118		46%
0.5-0.6	UD	0.326		129%	0.246		96%	0.188		75%	0.656		257%
0-0.5	NR	0.462	27%	182%	0.479	25%	187%	0.479	26%	191%	0.487	23%	191%
0.7-1	R	0.126		50%	0.122		47%	0.124		49%	0.11		43%
0.5-0.7	UD	0.236		93%	0.185		72%	0.158		63%	0.452		177%
0-0.5	NR	0.462	28%	182%	0.479	25%	187%	0.479	26%	191%	0.487	23%	191%
0.8-1	R	0.128		51%	0.119		47%	0.125		50%	0.113		44%
0.5-0.8	UD	0.187		74%	0.182		71%	0.142		57%	0.258		101%
0-0.5	NR	0.462	27%	182%	0.48	25%	187%	0.479	25%	191%	0.488	24%	191%
0.9-1	R	0.123		48%	0.12		47%	0.118		47%	0.115		45%
0.5-0.9	UD	0.186		73%	0.159		62%	0.151		60%	0.2		78%
0-0.6	NR	0.451	28%	178%	0.451	27%	176%	0.442	28%	176%	0.494	22%	194%
0.7-1	R	0.126		50%	0.121		47%	0.124		49%	0.11		43%
0.6-0.7	UD	0.175		69%	0.105		41%	0.112		45%	0.325		128%
0-0.6	NR	0.452	28%	178%	0.451	26%	176%	0.442	28%	176%	0.494	23%	194%
0.8-1	R	0.128		51%	0.119		46%	0.125		50%	0.113		44%
0.6-0.8	UD	0.138		54%	0.13		51%	0.114		45%	0.16		83%
0-0.6	NR	0.452	27%	178%	0.451	27%	176%	0.442	27%	176%	0.494	23%	194%
0.9-1	R	0.123		48%	0.12		47%	0.118		47%	0.115		45%
0.6-0.9	UD	0.155		61%	0.121		47%	0.138		55%	0.133		52%
0-0.7	NR	0.424	30%	167%	0.422	28%	165%	0.416	30%	165%	0.484	23%	190%
0.8-1	R	0.128		50%	0.118		46%	0.125		50%	0.113		44%
0.7-0.8	UD	0.097		38%	0.17		66%	0.115		46%	0.053		21%
0-0.7	NR	0.424	29%	167%	0.422	28%	165%	0.416	28%	166%	0.484	24%	190%
0.9-1	R	0.122		48%	0.119		46%	0.118		47%	0.115		45%
0.7-0.9	UD	0.145		57%	0.129		50%	0.146		58%	0.075		29%
0-0.8	NR	0.398	31%	157%	0.41	29%	160%	0.386	31%	154%	0.447	26%	175%
0.9-1	R	0.122		48%	0.119		46%	0.118		47%	0.115		45%
0.8-0.9	UD	0.181		71%	0.111		43%	0.168		67%	0.093		37%

TABLE 37c

Models GM2014, GM2022, GM2027 and 2043 (pages 116-121).

Model:		GM2014			GM2022			GM2027			GM2043		
threshold	response prediction	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all
NA	All	0.255		100%	0.253		100%	0.253		100%	0.258		100%
0-0.1	NR	0.528		207%	0.551		218%	0.558		221%	0.511		198%
0.1-1	R	0.153	29%	60%	0.162	29%	64%	0.159	28%	63%	0.16	31%	62%
0-0.2	NR	0.517		203%	0.535		211%	0.489		193%	0.501		194%
0.2-1	R	0.143	28%	56%	0.148	28%	58%	0.153	31%	60%	0.153	31%	59%
0-0.3	NR	0.503		198%	0.519		205%	0.47		186%	0.483		187%
0.3-1	R	0.13	26%	51%	0.144	28%	57%	0.145	31%	57%	0.144	30%	56%
0-0.4	NR	0.497		195%	0.498		197%	0.446		176%	0.47		182%
0.4-1	R	0.128	26%	50%	0.138	28%	55%	0.143	32%	57%	0.146	31%	56%
0-0.5	NR	0.482		189%	0.504		199%	0.431		170%	0.472		183%
0.5-1	R	0.122	25%	48%	0.117	23%	46%	0.138	32%	54%	0.128	27%	49%
0-0.6	NR	0.465		183%	0.482		190%	0.425		168%	0.466		180%
0.6-1	R	0.123	26%	48%	0.115	24%	45%	0.121	28%	48%	0.124	27%	48%
0-0.7	NR	0.461		181%	0.442		175%	0.403		159%	0.451		174%
0.7-1	R	0.118	26%	46%	0.121	27%	48%	0.119	30%	47%	0.12	27%	46%
0-0.8	NR	0.443		174%	0.419		165%	0.377		149%	0.423		163%
0.8-1	R	0.112	25%	44%	0.119	28%	47%	0.124	33%	49%	0.12	28%	47%
0-0.9	NR	0.416		163%	0.404		160%	0.357		141%	0.396		153%
0.9-1	R	0.107	26%	42%	0.115	28%	45%	0.111	31%	44%	0.117	30%	45%
0-0.1	NR	0.526		207%	0.552		218%	0.558		221%	0.51		197%
0.2-1	R	0.143	27%	56%	0.148	27%	58%	0.153	27%	60%	0.153	30%	59%
0.1-0.2	UD	0.425		167%	0.432		171%	0.231		91%	0.383		148%
0-0.1	NR	0.526		206%	0.552		218%	0.559		221%	0.509		197%
0.3-1	R	0.13	25%	51%	0.144	26%	57%	0.145	26%	57%	0.144	28%	56%
0.1-0.3	UD	0.408		160%	0.384		152%	0.257		102%	0.347		134%
0-0.1	NR	0.526		207%	0.551		218%	0.559		221%	0.509		197%
0.4-1	R	0.129	25%	51%	0.138	25%	55%	0.143	26%	56%	0.146	29%	57%
0.1-0.4	UD	0.385		151%	0.352		139%	0.24		95%	0.297		115%
0-0.1	NR	0.527		207%	0.552		218%	0.559		221%	0.511		198%
0.5-1	R	0.122	23%	48%	0.117	21%	46%	0.138	25%	54%	0.128	25%	49%
0.1-0.5	UD	0.356		140%	0.408		161%	0.241		95%	0.361		140%
0-0.1	NR	0.529		208%	0.551		218%	0.559		221%	0.511		198%
0.6-1	R	0.123	23%	48%	0.115	21%	45%	0.121	22%	48%	0.124	24%	48%
0.1-0.6	UD	0.315		124%	0.368		146%	0.266		105%	0.353		137%
0-0.1	NR	0.528		208%	0.551		218%	0.559		221%	0.51		197%
0.7-1	R	0.119	23%	47%	0.121	22%	48%	0.119	21%	47%	0.12	24%	46%
0.1-0.7	UD	0.317		125%	0.298		118%	0.248		98%	0.228		127%
0-0.1	NR	0.529		208%	0.552		218%	0.558		221%	0.51		197%
0.8-1	R	0.112	21%	44%	0.12	22%	47%	0.124	22%	49%	0.121	24%	47%
0.1-0.8	UD	0.298		117%	0.272		108%	0.221		87%	0.282		109%
0-0.1	NR	0.529		208%	0.551		218%	0.558		220%	0.51		197%
0.9-1	R	0.108	20%	42%	0.115	21%	46%	0.112	20%	44%	0.118	23%	46%
0.1-0.9	UD	0.268		105%	0.263		104%	0.218		86%	0.253		98%
0-0.2	NR	0.516		203%	0.535		212%	0.489		194%	0.501		194%
0.3-1	R	0.13	25%	51%	0.144	27%	57%	0.145	30%	57%	0.144	29%	56%
0.2-0.3	UD	0.394		155%	0.288		114%	0.303		120%	0.327		126%
0-0.2	NR	0.517		203%	0.535		211%	0.49		194%	0.501		194%
0.4-1	R	0.128	25%	50%	0.139	26%	55%	0.143	29%	56%	0.146	29%	57%
0.2-0.4	UD	0.36		141%	0.284		112%	0.248		98%	0.258		100%
0-0.2	NR	0.517		203%	0.536		212%	0.489		194%	0.502		194%
-10.5	R	0.122	24%	48%	0.117	22%	46%	0.138	28%	54%	0.128	25%	49%
0.2-0.5	UD	0.329		129%	0.396		156%	0.248		98%	0.355		137%
0-0.2	NR	0.518		203%	0.534		211%	0.49		194%	0.502		194%
0.6-1	R	0.123	24%	48%	0.115	22%	45%	0.121	25%	48%	0.124	25%	48%
0.2-0.6	UD	0.28		110%	0.344		136%	0.283		112%	0.347		134%
0-0.2	NR	0.518		203%	0.534		211%	0.49		194%	0.502		194%
0.7-1	R	0.119	23%	47%	0.122	23%	48%	0.119	24%	47%	0.12	24%	46%
0.2-0.7	UD	0.287		113%	0.261		103%	0.254		100%	0.318		123%
0-0.2	NR	0.518		204%	0.535		212%	0.489		193%	0.501		194%
0.8-1	R	0.112	22%	44%	0.12	22%	47%	0.124	25%	49%	0.121	24%	47%
0.2-0.8	UD	0.271		106%	0.237		94%	0.218		86%	0.269		104%
0-0.2	NR	0.518		203%	0.535		211%	0.489		193%	0.501		194%
0.9-1	R	0.108	21%	42%	0.116	22%	46%	0.112	23%	44%	0.118	24%	46%
0.2-0.9	UD	0.244		96%	0.23		91%	0.215		85%	0.24		93%
0-0.3	NR	0.503		198%	0.518		205%	0.47		186%	0.483		187%
0.4-1	R	0.128	25%	50%	0.138	27%	55%	0.143	30%	57%	0.146	30%	56%
0.3-0.4	UD	0.221		87%	0.281		111%	0.182		72%	0		0%
0-0.3	NR	0.504		198%	0.519		205%	0.47		186%	0.484		187%
0.5-1	R	0.122	24%	48%	0.117	23%	46%	0.138	29%	54%	0.128	26%	49%
0.3-0.5	UD	0.265		104%	0.43		170%	0.215		85%	0.376		146%

TABLE 37c-continued

Models GM2014, GM2022, GM2027 and 2043 (pages 116-121).

Model:		GM2014			GM2022			GM2027			GM2043		
threshold	response prediction	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all
0-0.3	NR	0.504		198%	0.518		205%	0.471		186%	0.484		187%
0.6-1	R	0.123	24%	48%	0.115	22%	45%	0.121	26%	48%	0.124	26%	48%
0.3-0.6	UD	0.207		81%	0.357		141%	0.276		109%	0.358		139%
0-0.3	NR	0.504		198%	0.518		205%	0.47		186%	0.483		187%
0.7-1	R	0.118	23%	47%	0.122	24%	48%	0.119	25%	47%	0.12	25%	46%
0.3-0.7	UD	0.23		90%	0.256		101%	0.241		95%	0.314		121%
0-0.3	NR	0.505		198%	0.519		205%	0.47		186%	0.482		187%
0.8-1	R	0.112	22%	44%	0.12	23%	47%	0.125	27%	49%	0.12	25%	47%
0.3-0.8	UD	0.228		90%	0.23		91%	0.201		80%	0.252		97%
0-0.3	NR	0.504		198%	0.519		205%	0.47		186%	0.483		187%
0.9-1	R	0.107	21%	42%	0.116	22%	46%	0.112	24%	44%	0.117	24%	45%
0.3-09	UD	0.208		82%	0.224		89%	0.202		80%	0.222		86%
0-0.3	NR	0.498		195%	0.5		197%	0.446		176%	0.472		183%
0.5-1	R	0.122	24%	48%	0.117	23%	46%	0.138	31%	54%	0.128	27%	49%
0.4-0.5	UD	0.279		110%	0.545		216%	0.248		98%	0.475		184%
0-0.4	NR	0.498		195%	0.498		197%	0.446		177%	0.471		182%
0.6-1	R	0.123	25%	48%	0.115	23%	45%	0.121	27%	48%	0.124	26%	48%
0.4-0.6	UD	0.205		81%	0.392		155%	0.316		125%	0.427		165%
0-0.4	NR	0.498		196%	0.498		197%	0.446		176%	0.471		182%
0.7-1	R	0.118	24%	47%	0.121	24%	48%	0.119	27%	47%	0.12	25%	46%
0.4-0.7	UD	0.232		91%	0.248		98%	0.258		102%	0.353		136%
0-0.4	NR	0.498		196%	0.498		197%	0.446		176%	0.47		182%
0.8-1	R	0.112	22%	44%	0.119	24%	47%	0.125	28%	49%	0.12	26%	47%
0.4-0.8	UD	0.229		90%	0.219		87%	0.204		81%	0.272		105%
0-0.4	NR	0.498		196%	0.498		197%	0.446		176%	0.47		182%
0.9-1	R	0.107	21%	42%	0.115	23%	46%	0.112	25%	44%	0.117	25%	45%
0.4-0.9	UD	0.207		81%	0.214		85%	0.204		81%	0.234		91%
0-0.5	NR	0.482		189%	0.504		199%	0.432		171%	0.472		183%
0.6-1	R	0.122	25%	48%	0.115	23%	46%	0.121	28%	48%	0.124	26%	48%
0.5-0.6	UD	0.1		39%	0.165		65%	0.365		144%	0.297		115%
0-0.5	NR	0.482		190%	0.504		199%	0.431		170%	0.472		183%
0.7-1	R	0.118	24%	46%	0.122	24%	48%	0.119	28%	47%	0.12	25%	46%
0.5-0.7	UD	0.19		74%	0.067		27%	0.261		103%	0.244		94%
0-0.5	NR	0.483		190%	0.504		199%	0.431		170%	0.472		183%
0.8-1	R	0.112	23%	44%	0.12	24%	47%	0.124	29%	49%	0.121	26%	47%
0.5-0.8	UD	0.208		82%	0.101		40%	0.193		76%	0.178		69%
0-0.5	NR	0.483		190%	0.504		199%	0.431		170%	0.472		183%
0.9-1	R	0.107	22%	42%	0.116	23%	46%	0.112	26%	44%	0.118	25%	46%
0.5-0.9	UD	0.19		74%	0.122		48%	0.198		78%	0.167		65%
0-0.6	NR	0.465		183%	0.482		191%	0.425		168%	0.466		180%
0.7-1	R	0.118	25%	46%	0.121	25%	48%	0.119	28%	47%	0.12	26%	46%
0.6-0.7	UD	0.341		134%	0		0%	0.15		59%	0.217		84%
0-0.6	NR	0.465		183%	0.482		190%	0.425		168%	0.466		180%
0.8-1	R	0.112	24%	44%	0.119	25%	47%	0.125	29%	49%	0.121	26%	47%
0.6-0.8	UD	0.253		99%	0.079		31%	0.101		40%	0.153		59%
0-0.6	NR	0.465		183%	0.482		190%	0.425		168%	0.466		180%
0.9-1	R	0.107	23%	42%	0.115	24%	46%	0.112	26%	44%	0.118	25%	46%
0.6-0.9	UD	0.208		82%	0.112		44%	0.149		59%	0.152		59%
0-0.7	NR	0.462		181%	0.442		175%	0.403		159%	0.451		174%
0.8-1	R	0.112	24%	44%	0.119	27%	47%	0.124	31%	49%	0.121	27%	47%
0.7-0.8	UD	0.223		88%	0.148		59%	0.051		20%	0.106		41%
0-0.7	NR	0.461		181%	0.442		175%	0.403		159%	0.451		174%
0.9-1	R	0.107	23%	42%	0.115	26%	45%	0.112	28%	44%	0.118	26%	46%
0.7-0.9	UD	0.19		74%	0.167		66%	0.149		59%	0.132		51%
0-0.8	NR	0.443		174%	0.418		165%	0.377		149%	0.423		163%
0.9-1	R	0.107	24%	42%	0.115	28%	45%	0.112	30%	44%	0.117	28%	45%
0.8-0.9	UD	0.165		65%	0.192		76%	0.205		81%	0.15		58%

TABLE 37d

Models GM2068, GM2090, GM2094 and GM2277 (pages 121-126).

		Model:											
		GM2068			GM2090			GM2094			GM2277		
threshold	response prediction	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all
NA	All	0.256		100%	0.254		100%	0.251		100%	0.258		100%
0-0.1	NR	0.486	34%	190%	0.514	33%	203%	0.537	32%	214%	0.487	34%	189%
0.1-1	R	0.165		64%	0.172		68%	0.17		68%	0.164		64%
0-0.2	NR	0.489	32%	191%	0.516	29%	204%	0.496	32%	197%	0.485	30%	188%
0.2-1	R	0.155		60%	0.15		59%	0.157		63%	0.147		57%
0-0.3	NR	0.474	31%	185%	0.516	25%	203%	0.479	30%	191%	0.465	31%	180%
0.3-1	R	0.148		58%	0.13		51%	0.144		57%	0.144		56%
0-0.4	NR	0.461	31%	180%	0.482	27%	190%	0.469	30%	187%	0.443	33%	172%
0.4-1	R	0.144		56%	0.13		51%	0.139		56%	0.145		56%
0-0.5	NR	0.447	32%	174%	0.461	29%	182%	0.45	31%	179%	0.437	32%	169%
0.5-1	R	0.143		56%	0.132		52%	0.14		56%	0.138		53%
0-0.6	NR	0.454	29%	177%	0.441	29%	174%	0.439	28%	175%	0.427	31%	166%
0.6-1	R	0.133		52%	0.126		50%	0.125		50%	0.132		51%
0-0.7	NR	0.447	29%	174%	0.422	30%	166%	0.421	30%	168%	0.419	31%	162%
0.7-1	R	0.128		50%	0.127		50%	0.127		50%	0.129		50%
0-0.8	NR	0.433	29%	169%	0.398	31%	157%	0.397	33%	158%	0.401	33%	155%
0.8-1	R	0.124		48%	0.122		48%	0.13		52%	0.131		51%
0-0.9	NR	0.415	30%	162%	0.381	28%	150%	0.361	38%	144%	0.381	32%	148%
0.9-1	R	0.126		49%	0.106		42%	0.136		54%	0.122		47%
0-0.1	NR	0.484	32%	189%	0.516	29%	204%	0.534	30%	213%	0.485	30%	188%
0.2-1	R	0.155		60%	0.15		59%	0.158		63%	0.147		57%
0.1-0.2	UD	0.563		219%	0.515		203%	0.335		133%	0.483		187%
0-0.1	NR	0.486	30%	190%	0.519	25%	205%	0.532	27%	212%	0.485	30%	188%
0.3-1	R	0.148		58%	0.13		51%	0.145		58%	0.144		56%
0.1-0.3	UD	0.402		157%	0.506		200%	0.353		140%	0.375		145%
0-0.1	NR	0.487	30%	190%	0.518	25%	204%	0.532	26%	212%	0.486	30%	188%
0.4-1	R	0.144		56%	0.13		51%	0.14		56%	0.146		56%
0.1-0.4	UD	0.355		138%	0.407		161%	0.342		136%	0.3		116%
0-0.1	NR	0.487	29%	190%	0.519	25%	205%	0.532	27%	212%	0.485	28%	188%
0.5-1	R	0.143		56%	0.132		52%	0.141		56%	0.138		54%
0.1-0.5	UD	0.318		124%	0.359		142%	0.309		123%	0.307		119%
0-0.1	NR	0.487	27%	190%	0.518	24%	204%	0.533	24%	212%	0.487	27%	189%
0.6-1	R	0.133		52%	0.126		50%	0.126		50%	0.132		51%
0.1-0.6	UD	0.361		141%	0.332		131%	0.319		127%	0.301		117%
0-0.1	NR	0.488	26%	190%	0.517	25%	204%	0.534	24%	213%	0.486	27%	188%
0.7-1	R	0.128		50%	0.128		50%	0.128		51%	0.129		50%
0.1-0.7	UD	0.348		136%	0.303		120%	0.293		117%	0.291		113%
0-0.1	NR	0.487	25%	190%	0.517	24%	204%	0.535	25%	213%	0.486	27%	188%
0.8-1	R	0.124		48%	0.122		48%	0.132		52%	0.131		51%
0.1-0.8	UD	0.324		126%	0.279		110%	0.262		104%	0.263		102%
0-0.1	NR	0.488	26%	190%	0.517	21%	204%	0.535	26%	213%	0.486	25%	188%
0.9-1	R	0.126		49%	0.106		42%	0.138		55%	0.122		47%
0.1-0.9	UD	0.289		113%	0.274		108%	0.224		89%	0.25		97%
0-0.2	NR	0.489	30%	191%	0.519	25%	205%	0.495	29%	197%	0.484	30%	188%
0.3-1	R	0.148		58%	0.13		51%	0.144		57%	0.144		56%
0.2-0.3	UD	0.311		121%	0.492		194%	0.374		149%	0.226		88%
0-0.2	NR	0.49	29%	191%	0.518	25%	204%	0.495	28%	197%	0.484	30%	188%
0.4-1	R	0.144		56%	0.13		51%	0.14		56%	0.146		57%
0.2-0.4	UD	0.287		112%	0.336		132%	0.348		139%	0.163		63%
0-0.2	NR	0.49	29%	191%	0.519	25%	205%	0.495	28%	197%	0.484	29%	188%
-10.5	R	0.143		56%	0.132		52%	0.14		56%	0.139		54%
0.2-0.5	UD	0.26		102%	0.279		110%	0.292		116%	0.219		85%
0-0.2	NR	0.49	27%	191%	0.518	24%	205%	0.495	25%	197%	0.485	27%	188%
0.6-1	R	0.133		52%	0.126		50%	0.126		50%	0.132		51%
0.2-0.6	UD	0.319		124%	0.264		104%	0.311		124%	0.236		91%
0-0.2	NR	0.49	26%	191%	0.518	25%	204%	0.495	26%	197%	0.484	27%	188%
0.7-1	R	0.128		50%	0.128		50%	0.127		51%	0.129		50%
0.2-0.7	UD	0.312		122%	0.237		94%	0.278		111%	0.233		90%
0-0.2	NR	0.49	25%	191%	0.518	24%	204%	0.495	26%	197%	0.484	27%	188%
0.8-1	R	0.124		48%	0.122		48%	0.131		52%	0.131		51%
0.2-0.8	UD	0.292		114%	0.224		88%	0.239		95%	0.207		80%
0-0.2	NR	0.49	26%	191%	0.518	20%	204%	0.495	28%	197%	0.484	25%	188%
0.9-1	R	0.126		49%	0.106		42%	0.138		55%	0.122		47%
0.2-0.9	UD	0.259		101%	0.231		91%	0.199		79%	0.208		81%
0-0.3	NR	0.474	30%	185%	0.516	25%	203%	0.479	29%	191%	0.465	31%	180%
0.4-1	R	0.144		56%	0.13		51%	0.139		56%	0.146		56%
0.3-0.4	UD	0.254		99%	0.123		49%	0.293		117%	0.088		34%
0-0.3	NR	0.474	30%	185%	0.515	26%	203%	0.479	29%	191%	0.465	30%	180%

TABLE 37d-continued

Models GM2068, GM2090, GM2094 and GM2277 (pages 121-126).

		Model:											
		GM2068			GM2090			GM2094			GM2277		
threshold	response prediction	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all
0.5-1	R	0.143		56%	0.132		52%	0.14		56%	0.138		54%
0.3-0.5	UD	0.224		87%	0.108		43%	0.203		81%	0.215		83%
0-0.3	NR	0.475	28%	185%	0.516	25%	203%	0.479	26%	191%	0.465	28%	180%
0.6-1	R	0.133		52%	0.127		50%	0.126		50%	0.132		51%
0.3-0.6	UD	0.323		126%	0.154		61%	0.279		111%	0.238		92%
0-0.3	NR	0.475	27%	185%	0.516	25%	203%	0.479	27%	191%	0.465	28%	180%
0.7-1	R	0.128		50%	0.128		51%	0.127		51%	0.129		50%
0.3-0.7	UD	0.312		121%	0.139		55%	0.239		95%	0.234		91%
0-0.3	NR	0.475	26%	185%	0.516	24%	204%	0.479	27%	191%	0.465	28%	180%
0.8-1	R	0.124		48%	0.123		48%	0.131		52%	0.131		51%
0.3-0.8	UD	0.286		112%	0.154		61%	0.198		79%	0.202		78%
0-0.3	NR	0.475	27%	185%	0.516	21%	204%	0.479	29%	191%	0.465	26%	180%
0.9-1	R	0.126		49%	0.106		42%	0.137		55%	0.122		47%
0.3-0.9	UD	0.246		96%	0.182		72%	0.161		64%	0.205		79%
0-0.3	NR	0.461	31%	180%	0.482	27%	190%	0.469	30%	187%	0.443	31%	172%
0.5-1	R	0.143		56%	0.132		52%	0.14		56%	0.138		53%
0.4-0.5	UD	0.191		74%	0.086		34%	0.106		42%	0.332		129%
0-0.4	NR	0.461	29%	180%	0.483	26%	190%	0.469	27%	187%	0.444	30%	172%
0.6-1	R	0.133		52%	0.126		50%	0.126		50%	0.131		51%
0.4-0.6	UD	0.373		146%	0.17		67%	0.275		109%	0.301		117%
0-0.4	NR	0.462	28%	180%	0.482	27%	190%	0.469	27%	187%	0.444	29%	172%
0.7-1	R	0.128		50%	0.128		51%	0.127		51%	0.129		50%
0.4-0.7	UD	0.337		131%	0.145		57%	0.227		90%	0.279		108%
0-0.4	NR	0.462	27%	180%	0.483	25%	190%	0.469	28%	187%	0.443	30%	172%
0.8-1	R	0.124		48%	0.123		48%	0.131		52%	0.131		51%
0.4-0.8	UD	0.296		115%	0.161		64%	0.182		72%	0.228		88%
0-0.4	NR	0.462	27%	180%	0.483	22%	190%	0.469	29%	187%	0.443	28%	172%
0.9-1	R	0.126		49%	0.106		42%	0.137		55%	0.122		47%
0.4-0.9	UD	0.244		95%	0.191		75%	0.146		58%	0.221		86%
0-0.5	NR	0.447	30%	174%	0.461	28%	182%	0.45	28%	179%	0.437	30%	169%
0.6-1	R	0.133		52%	0.127		50%	0.125		50%	0.131		51%
0.5-0.6	UD	0.71		277%	0.224		88%	0.343		137%	0.275		106%
0-0.5	NR	0.448	29%	175%	0.461	28%	182%	0.45	28%	179%	0.437	30%	169%
0.7-1	R	0.128		50%	0.128		51%	0.127		50%	0.129		50%
0.5-0.7	UD	0.431		168%	0.168		66%	0.259		103%	0.252		98%
0-0.5	NR	0.448	28%	175%	0.462	27%	182%	0.45	29%	179%	0.437	30%	169%
0.8-1	R	0.124		48%	0.123		48%	0.13		52%	0.131		51%
0.5-0.8	UD	0.332		129%	0.177		70%	0.195		78%	0.194		75%
0-0.5	NR	0.448	28%	175%	0.462	23%	182%	0.45	30%	179%	0.436	28%	169%
0.9-1	R	0.126		49%	0.106		42%	0.137		55%	0.122		47%
0.5-0.9	UD	0.257		100%	0.204		81%	0.15		60%	0.2		78%
0-0.6	NR	0.455	28%	177%	0.441	29%	174%	0.439	29%	175%	0.427	30%	166%
0.7-1	R	0.128		50%	0.128		50%	0.127		51%	0.129		50%
0.6-0.7	UD	0.28		109%	0.085		33%	0.088		35%	0.216		84%
0-0.6	NR	0.455	27%	177%	0.441	28%	174%	0.439	30%	175%	0.427	31%	166%
0.8-1	R	0.124		48%	0.122		48%	0.131		52%	0.131		51%
0.6-0.8	UD	0.244		95%	0.154		61%	0.072		29%	0.139		54%
0-0.6	NR	0.455	28%	177%	0.441	24%	174%	0.439	31%	175%	0.427	29%	166%
0.9-1	R	0.126		49%	0.106		42%	0.137		55%	0.122		47%
0.6-0.9	UD	0.188		73%	0.199		78%	0.071		28%	0.179		69%
0-0.7	NR	0.447	28%	174%	0.422	29%	166%	0.421	31%	168%	0.419	31%	162%
0.8-1	R	0.124		48%	0.122		48%	0.13		52%	0.131		51%
0.7-0.8	UD	0.217		84%	0.184		72%	0.061		24%	0.082		32%
0-0.7	NR	0.447	28%	174%	0.422	25%	167%	0.422	32%	168%	0.419	29%	162%
0.9-1	R	0.126		49%	0.105		42%	0.137		55%	0.122		47%
0.7-0.9	UD	0.151		59%	0.221		87%	0.067		26%	0.171		66%
0-0.8	NR	0.433	29%	169%	0.398	27%	157%	0.397	35%	158%	0.401	30%	155%
0.9-1	R	0.126		49%	0.106		42%	0.137		55%	0.122		47%
0.8-0.9	UD	0.079		31%	0.253		100%	0.069		28%	0.208		81%

TABLE 37e

Models GM2338, GM3102, GM3150 and GM3332 (pages 126-131).

Model:		GM2338			GM3102			GM3150			GM3332		
threshold	response prediction	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all
NA	All	0.251		100%	0.263		100%	0.26		100%	0.262		100%
0-0.1	NR	0.662		264%	0.605		230%	0.584		225%	0.612		234%
0.1-1	R	0.163	25%	65%	0.167	28%	63%	0.163	28%	63%	0.183	30%	70%
0-0.2	NR	0.616		246%	0.588		224%	0.512		197%	0.523		200%
0.2-1	R	0.155	25%	62%	0.146	25%	55%	0.162	32%	62%	0.168	32%	64%
0-0.3	NR	0.537		214%	0.564		215%	0.503		194%	0.535		204%
0.3-1	R	0.156	29%	62%	0.136	24%	52%	0.152	30%	59%	0.14	26%	54%
0-0.4	NR	0.488		195%	0.531		202%	0.474		182%	0.51		195%
0.4-1	R	0.154	32%	61%	0.136	26%	52%	0.149	31%	57%	0.141	28%	54%
0-0.5	NR	0.467		186%	0.506		193%	0.45		173%	0.502		192%
0.5-1	R	0.152	33%	61%	0.131	26%	50%	0.146	32%	56%	0.13	26%	50%
0-0.6	NR	0.436		174%	0.483		184%	0.426		164%	0.486		186%
0.6-1	R	0.15	34%	60%	0.135	28%	51%	0.143	34%	55%	0.123	25%	47%
0-0.7	NR	0.439		175%	0.457		174%	0.432		166%	0.461		176%
0.7-1	R	0.136	31%	54%	0.128	28%	49%	0.122	28%	47%	0.122	26%	47%
0-0.8	NR	0.417		166%	0.432		164%	0.4		154%	0.446		170%
0.8-1	R	0.134	32%	53%	0.124	29%	47%	0.119	30%	46%	0.117	26%	45%
0-0.9	NR	0.402		160%	0.384		146%	0.362		139%	0.41		156%
0.9-1	R	0.117	29%	47%	0.13	34%	49%	0.127	35%	49%	0.115	28%	44%
0-0.1	NR	0.661		264%	0.611		233%	0.584		225%	0.587		224%
0.2-1	R	0.156	24%	62%	0.145	24%	55%	0.162	28%	63%	0.169	29%	64%
0.1-0.2	UD	0.355		142%	0.479		182%	0.166		64%	0.281		107%
0-0.1	NR	0.662		264%	0.609		232%	0.583		225%	0.583		223%
0.3-1	R	0.157	24%	63%	0.136	22%	52%	0.153	26%	59%	0.141	24%	54%
0.1-0.3	UD	0.229		91%	0.436		166%	0.252		97%	0.431		165%
0-0.1	NR	0.663		264%	0.609		232%	0.584		225%	0.581		222%
0.4-1	R	0.154	23%	62%	0.136	22%	52%	0.15	26%	58%	0.141	24%	54%
0.1-0.4	UD	0.219		87%	0.362		138%	0.239		92%	0.383		146%
0-0.1	NR	0.663		265%	0.609		231%	0.584		225%	0.578		221%
0.5-1	R	0.152	23%	61%	0.132	22%	50%	0.148	25%	57%	0.131	23%	50%
0.1-0.5	UD	0.217		87%	0.338		129%	0.23		89%	0.39		149%
0-0.1	NR	0.664		265%	0.607		231%	0.584		225%	0.577		220%
0.6-1	R	0.15	23%	60%	0.135	22%	51%	0.144	25%	55%	0.124	21%	47%
0.1-0.6	UD	0.21		84%	0.299		114%	0.223		86%	0.373		142%
0-0.1	NR	0.665		265%	0.609		232%	0.584		225%	0.578		221%
0.7-1	R	0.136	20%	54%	0.128	21%	49%	0.123	21%	47%	0.123	21%	47%
0.1-0.7	UD	0.245		98%	0.283		108%	0.267		103%	0.337		129%
0-0.1	NR	0.664		265%	0.607		231%	0.583		225%	0.579		221%
0.8-1	R	0.134	20%	54%	0.125	21%	48%	0.12	21%	46%	0.119	21%	45%
0.1-0.8	UD	0.234		93%	0.264		101%	0.242		93%	0.323		123%
0-0.1	NR	0.665		265%	0.606		231%	0.583		225%	0.581		222%
0.9-1	R	0.117	18%	47%	0.131	22%	50%	0.129	22%	50%	0.117	20%	45%
0.1-0.9	UD	0.246		98%	0.222		85%	0.208		80%	0.284		108%
0-0.2	NR	0.616		246%	0.587		223%	0.51		196%	0.516		197%
0.3-1	R	0.156	25%	62%	0.137	23%	52%	0.152	30%	59%	0.14	27%	54%
0.2-0.3	UD	0.134		54%	0.363		138%	0.43		166%	0.65		248%
0-0.2	NR	0.616		246%	0.588		224%	0.512		197%	0.515		197%
0.4-1	R	0.154	25%	61%	0.136	23%	52%	0.149	29%	58%.	0.141	27%	54%
0.2-0.4	UD	0.169		68%	0.258		98%	0.296		114%	0.487		186%
0-0.2	NR	0.616		246%	0.586		223%	0.511		197%	0.512		196%
-10.5	R	0.152	25%	60%	0.132	23%	50%	0.147	29%	57%	0.13	25%	50%
0.2-0.5	UD	0.178		71%	0.253		96%	0.263		101%	0.471		180%
0-0.2	NR	0.617		246%	0.587		224%	0.512		197%	0.512		196%
0.6-1	R	0.15	24%	60%	0.136	23%	52%	0.144	28%	55%	0.123	24%	47%
0.2-0.6	UD	0.179		71%	0.208		79%	0.243		94%	0.424		162%
0-0.2	NR	0.618		247%	0.588		224%	0.512		197%	0.514		196%
0.7-1	R	0.136	22%	54%	0.129	22%	49%	0.122	24%	47%	0.123	24%	47%
0.2-0.7	UD	0.224		89%	0.215		82%	0.295		114%	0.362		138%
0-0.2	NR	0.618		246%	0.588		224%	0.511		197%	0.516		197%
0.8-1	R	0.134	22%	53%	0.126	21%	48%	0.12	23%	46%	0.118	23%	45%
0.2-0.8	UD	0.215		86%	0.205		78%	0.258		99%	0.338		129%
0-0.2	NR	0.619		247%	0.588		224%	0.511		197%	0.518		198%
0.9-1	R	0.117	19%	47%	0.132	22%	50%	0.128	25%	49%	0.117	23%	45%
0.2-0.9	UD	0.232		92%	0.171		65%	0.214		83%	0.285		109%
0-0.3	N	0.537		214%	0.564		215%	0.504		194%	0.535		204%
0.4-1	R	0.153	28%	61%	0.136	24%	52%	0.149	30%	57%	0.141	26%	54%
0.3-0.4	UD	0.199		80%	0.148		56%	0.212		82%	0.114		44%
0-0.3	NR	0.538		215%	0.564		215%	0.503		194%	0.532		203%
0.5-1	R	0.151	28%	60%	0.132	23%	50%	0.147	29%	56%	0.131	25%	50%
0.3-0.5	UD	0.201		80%	0.194		74%	0.205		79%	0.293		112%

TABLE 37e-continued

Models GM2338, GM3102, GM3150 and GM3332 (pages 126-131).

Model:		GM2338			GM3102			GM3150			GM3332		
threshold	response prediction	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all	ARR	Risk Ratio	ARR Vs. all
0-0.3	NR	0.538		215%	0.564		215%	0.504		194%	0.531		203%
0.6-1	R	0.15	28%	60%	0.135	24%	52%	0.143	28%	55%	0.124	23%	47%
0.3-0.6	UD	0.194		77%	0.145		55%	0.202		78%	0.291		111%
0-0.3	NR	0.539		215%	0.565		215%	0.504		194%	0.532		203%
0.7-1	R	0.135	25%	54%	0.128	23%	49%	0.122	24%	47%	0.123	23%	47%
0.3-0.7	UD	0.25		100%	0.178		68%	0.272		105%	0.244		93%
0-0.3	NR	0.539		215%	0.564		215%	0.503		194%	0.532		203%
0.8-1	R	0.134	25%	53%	0.125	22%	48%	0.12	24%	46%	0.119	22%	45%
0.3-0.8	UD	0.233		93%	0.175		67%	0.237		91%	0.239		91%
0-0.3	NR	0.54		215%	0.564		215%	0.503		194%	0.533		204%
0.9-1	R	0.117	22%	46%	0.131	23%	50%	0.128	25%	49%	0.117	22%	45%
0.3-0.9	UD	0.248		99%	0.147		56%	0.194		75%	0.206		79%
0-0.3	NR	0.489		195%	0.529		202%	0.474		182%	0.508		194%
0.5-1	R	0.152	31%	61%	0.131	25%	50%	0.147	31%	57%	0.13	26%	50%
0.4-0.5	UD	0.204		81%	0.243		93%	0.198		76%	0.426		163%
0-0.4	NR	0.489		195%	0.531		202%	0.474		182%	0.507		194%
0.6-1	R	0.15	31%	60%	0.135	25%	51%	0.143	30%	55%	0.123	24%	47%
0.4-0.6	UD	0.191		76%	0.142		54%	0.197		76%	0.351		134%
0-0.4	NR	0.49		196%	0.531		202%	0.473		182%	0.508		194%
0.7-1	R	0.136	28%	54%	0.128	24%	49%	0.122	26%	47%	0.123	24%	47%
0.4-0.7	UD	0.274		109%	0.186		71%	0.295		113%	0.272		104%
0-0.4	NR	0.49		195%	0.53		202%	0.473		182%	0.509		194%
0.8-1	R	0.134	27%	53%	0.125	24%	48%	0.12	25%	46%	0.118	23%	45%
0.4-0.8	UD	0.245		98%	0.18		69%	0.243		94%	0.258		99%
0-0.4	NR	0.49		196%	0.53		202%	0.473		182%	0.509		194%
0.9-1	R	0.117	24%	47%	0.131	25%	50%	0.128	27%	49%	0.116	23%	44%
0.4-0.9	UD	0.26		104%	0.146		56%	0.192		74%	0.215		82%
0-0.5	NR	0.467		186%	0.504		192%	0.45		173%	0.501		192%
0.6-1	R	0.15	32%	60%	0.134	27%	51%	0.143	32%	55%	0.123	25%	47%
0.5-0.6	UD	0.184		73%	0		0%	0.195		75%	0.287		110%
0-0.5	NR	0.468		187%	0.506		193%	0.45		173%	0.502		192%
0.7-1	R	0.136	29%	54%	0.127	25%	49%	0.122	27%	47%	0.122	24%	47%
0.5-0.7	UD	0.302		120%	0.161		61%	0.336		129%	0.209		80%
0-0.5	NR	0.467		186%	0.506		193%	0.45		173%	0.502		192%
0.8-1	R	0.134	29%	54%	0.125	25%	47%	0.119	26%	46%	0.118	24%	45%
0.5-0.8	UD	0.256		102%	0.164		62%	0.254		98%	0.212		81%
0-0.5	NR	0.468		187%	0.506		193%	0.45		173%	0.502		192%
0.9-1	R	0.117	25%	47%	0.131	26%	50%	0.128	28%	49%	0.116	23%	44%
0.5-0.9	UD	0.27		108%	0.131		50%	0.19		73%	0.18		69%
0-0.6	NR	0.436		174%	0.484		184%	0.426		164%	0.485		185%
0.7-1	R	0.136	31%	54%	0.128	26%	49%	0.122	29%	47%	0.122	25%	47%
0.6-0.7	UD	0.474		189%	0.227		86%	0.519		200%	0.135		52%
0-0.6	NR	0.436		174%	0.483		184%	0.425		164%	0.485		185%
0.8-1	R	0.134	31%	54%	0.125	26%	48%	0.119	28%	46%	0.117	24%	45%
0.6-0.8	UD	0.303		121%	0.2		76%	0.282		108%	0.174		67%
0-0.6	NR	0.437		174%	0.483		184%	0.426		164%	0.505		193%
0.9-1	R	0.117	27%	47%	0.131	27%	50%	0.127	30%	49%	0.119	24%	45%
0.6-0.9	UD	0.299		119%	0.146		56%	0.189		73%	0.172		66%
0-0.7	NR	0.439		175%	0.457		174%	0.432		166%	0.461		176%
0.8-1	R	0.134	31%	54%	0.125	27%	48%	0.119	28%	46%	0.117	25%	45%
0.7-0.8	UD	0.164		65%	0.168		64%	0.147		57%	0.215		82%
0-0.7	NR	0.44		175%	0.457		174%	0.432		166%	0.461		176%
0.9-1	R	0.117	27%	47%	0.131	29%	50%	0.127	29%	49%	0.115	25%	44%
0.7-0.9	UD	0.246		98%	0.114		43%	0.102		39%	0.16		61%
0-0.8	NR	0.417		166%	0.431		164%	0.401		154%	0.446		170%
0.9-1	R	0.117	28%	47%	0.13	30%	50%	0.127	32%	49%	0.115	26%	44%
0.8-0.9	UD	0.294		117%	0.085		33%	0.063		24%	0.134		51%

DISCUSSION

[0357] Using GWAS, we have found SNPs having a predictive ability of GA response, which are presented in tables 1-3 or table 16. We have also created predictive models which predict with high accuracy the response to GA based on a certain set of SNPs from tables 1-3 or table 16. Other models can be created which use one or more SNPs from tables 1-3 or table 16 or combinations of one or more SNPs indicated in tables 1-3 or table 16 with clinical variables described in the application or others which can be contemplated by the person skilled in the art, in order to predict the response to GA. In addition, kits based on SNPs or models of the invention may be used in order to predict whether a patient is a responder or a non-responder to GA. Predicting whether a subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis is a responder to GA based on the determination of the patient's genotype at one or more SNP from table 1-3 or table 16 or a combination of SNPs indicated in tables 1-3 with clinical variables should assist in planning an effective treatment for patients afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis.

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1. A method for treating a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis with a pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier, comprising the steps of:

- i. determining a genotype of the subject at one or more single nucleotide polymorphisms (SNPs) selected from the group consisting of: rs1007328, rs10083547, rs10136012, rs10214633, rs10277267, rs1040194, rs1041897, rs10853605, rs10931091, rs10935015, rs10935016, rs10935019, rs10950359, rs10950371, rs10988087, rs11009827, rs11009835, rs11081859, rs11599624, rs11617134, rs11618546, rs11694344, rs11709339, rs11719825, rs11761457, rs11907046, rs12055694, rs12256889, rs1229542, rs1229553, rs1229555, rs1229558, rs1229562, rs1229563, rs1229564, rs1229568, rs12340584, rs1234567, rs1234947, rs1237625, rs12488259, rs12494606, rs12496278, rs12524041, rs12529764, rs12532459, rs12540494, rs12593600, rs12633010, rs12637073, rs12639443, rs1264423, rs1282540, rs1282546, rs12968586, rs1299325, rs13021482, rs13042992, rs1320648, rs13238613, rs13245980, rs1415557, rs1538123, rs1573706, rs1591661, rs1611185, rs1683691, rs16999008, rs17007730, rs17087180, rs17104665, rs17104742, rs17134651, rs17575455, rs17588454, rs17666347, rs17771939, rs17807327, rs17807445, rs1886308, rs1892974, rs1941973, rs2033471, rs2088713, rs214526, rs2155262, rs2177073, rs2187495, rs2277431, rs2305623, rs2374730, rs2461319, rs2487889, rs2487896, rs2508806, rs2511064, rs2521643, rs2521644, rs2530121, rs2530123, rs2685484, rs2722396, rs2722398, rs28861531, rs2895215, rs2937395, rs3135391, rs35831078, rs3742228, rs401618, rs4148871, rs4255033, rs4281882, rs4289164, rs4306478, rs4343256, rs4344916, rs4369324, rs4435429, rs4445746, rs4466940, rs4468448, rs4483642, rs4565951, rs4578835, rs4634524, rs4799760, rs4809955, rs4811492, rs496486, rs552994, rs6015147, rs6025923, rs6025927, rs6091820, rs6097782, rs6097790, rs6097793, rs6097797, rs6097801, rs6123749, rs6543934, rs6558102, rs656975, rs657302, rs6584894, rs660075, rs6713772, rs6909321, rs6971202, rs702355, rs7080507, rs7086707, rs7093143, rs7178587, rs7180867, rs7232734, rs7238006, rs7244801, rs7317000, rs751370, rs752979, rs7619350, rs7633210, rs7714122, rs7789703, rs7803164, rs7806265, rs7916897, rs7955917, rs7963693, rs8099595, rs8118441, rs844602, rs844608, rs844610, rs844612, rs844626, rs860722, rs873216, rs884266, rs894857, rs913882, rs9315048, rs9332420, rs933863, rs933864, rs9378319, rs9378684, rs9392358, rs9405541, rs9405546, rs947603, rs948029, rs948032, rs949298, rs9508834, rs9944913, rs9952995, and rs998051,
- ii. identifying the subject as a predicted responder to glatiramer acetate if the genotype is
  - AA at rs10214633, rs10277267, rs10935015, rs10935019, rs10988087, rs11081859, rs11694344, rs12256889, rs12340584, rs12494606, rs1415557, rs17007730, rs17087180, rs17104665, rs17104742, rs17588454, rs17807327, rs1892974, rs2088713, rs214526, rs2374730, rs4255033, rs4306478, rs4343256, rs4344916, rs4435429, rs4578835, rs4809955, rs496486, rs6015147, rs6097790, rs6584894, rs6713772, rs6909321, rs702355, rs7086707, rs7180867, rs7317000, rs844608, rs844610, rs933863, rs9392358, rs948029, or rs9508834,
  - AT at rs12524041 or rs7806265,
  - AG at rs10277267, rs10950359, rs11599624, rs13245980, rs1415557, rs2521643, rs4255033, rs6584894, rs6909321, rs702355, or rs844626,
  - AC at rs12256889, rs1229542, rs214526, rs6097793, rs7086707, rs7180867, rs844608, or rs844610,
  - TT at rs1007328, rs10931091, rs11617134, rs11709339, rs11719825, rs11761457, rs1229553, rs1234567, rs1234947, rs12532459, rs12593600, rs1264423, rs13042992, rs1320648, rs1538123, rs1591661, rs17134651, rs17666347, rs17771939, rs2461319, rs2508806, rs2722396, rs2722398, rs2895215, rs401618, rs4369324, rs4483642, rs4565951, rs4811492, rs552994, rs6025923, rs6025927, rs6097797, rs657302, rs7232734, rs751370, rs7633210, rs7714122, rs7803164, rs7806265, rs7916897, rs8118441, rs844612, rs9378319, or rs9952995,
  - GT at rs12532459, rs2722398, rs4369324, or rs7093143,
  - CT at rs10950371, rs11761457, rs1229562, rs12529764, rs13021482, rs13238613, rs1538123, rs1591661, rs1611185, rs17807445, rs1941973, rs2461319, rs2685484, rs2895215, rs4634524,

rs4799760, rs6097797, rs7080507, rs7238006, rs7789703, 7803164, rs844612, or rs947603,

GG at rs10083547, rs10136012, rs10950359, rs11599624, rs12055694, rs1229558, rs1237625, rs12496278, rs12540494, rs12633010, rs12637073, rs1282540, rs1282546, rs12968586, rs1299325, rs13245980, rs16999008, rs17104665, rs17104742, rs2033471, rs2155262, rs2487889, rs2487896, rs2511064, rs2521643, rs2530121, rs2530123, rs28661531, rs3135391, rs4148871, rs4289164, rs4445746, rs6097801, rs6543934, rs6558102, rs656975, rs6971202, rs7093143, rs7244801, rs752979, rs7619350, rs7955917, rs844626, rs873216, rs894857, rs9315048, rs9332420, rs933864, rs948032, rs949298, or rs998051,

CG at rs11618546 or rs860722, or

CC at rs1041897, rs10853605, rs10935016, rs10950371, rs11009827, rs11009835, rs11618546, rs11907046, rs1229542, rs1229555, rs1229562, rs1229563, rs1229564, rs1229568, rs12488259, rs12639443, rs13021482, rs13238613, rs1573706, rs1683691, rs17575455, rs17807445, rs2177073, rs2187495, rs2277431, rs2521644, rs2685484, rs2937395, rs4281882, rs4466940, rs4468448, rs4634524, rs4799760, rs6091820, rs6097782, rs6097793, rs6123749, rs660075, rs7080507, rs7789703, rs7963693, rs8099595, rs844602, rs860722, rs884266, rs913882, rs9378684, rs9405541, rs9405546, rs947603, or rs9944913; and

iii. administering the pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier to the subject only if the subject it identified as a predicted responder to glatiramer acetate.

2. The method of claim **1**, wherein administering the pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier comprises administering to the human subject three subcutaneous injections of the pharmaceutical composition over a period of seven days with at least one day between every subcutaneous injection.

3. The method of claim **2**, wherein the pharmaceutical composition is a unit dose of a 1 ml aqueous solution comprising 40 mg of glatiramer acetate.

4. The method of claim **1**, wherein the pharmaceutical composition is a unit dose of a 1 ml aqueous solution comprising 20 mg of glatiramer acetate.

5. The method of claim **1**, wherein the pharmaceutical composition is a unit dose of a 0.5 ml aqueous solution comprising 20 mg of glatiramer acetate.

6. (canceled)

7. The method of claim **1**, wherein the pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier is administered as monotherapy.

8. The method of claim **1**, wherein the pharmaceutical composition comprising glatiramer acetate and a pharmaceutically acceptable carrier is administered in combination with at least one other multiple sclerosis drug.

9. The method of claim **1**, wherein the genotype is determined at one or more single nucleotide polymorphisms (SNPs) selected from the group consisting of:

a) rs947603, rs1007328, rs1573706, rs2177073, rs2487896, rs2511064, rs2521644, rs3135391, rs4148871, rs4343256, rs4344916, rs4369324, rs4445746, rs6097801, rs9508834, rs9944913, rs10853605, rs10931091, rs10950359, rs10988087, rs11599624, rs11617134, rs12256889, rs12639443, rs13042992, rs13238613, rs17087180, rs17575455, rs17771939 and rs17807327;

b) rs9508834, rs17807327, rs4344916, rs12639443, rs17087180 and rs17771939;

c) rs4344916, rs12639443, rs17087180 and rs17771939;

d) rs4344916, rs12639443, rs17087180 and rs17771939;

e) rs4344916, rs12639443, rs17087180, rs17771939 and rs9508834;

f) rs4344916, rs12639443, rs17087180, rs17771939 and rs17807327; or

g) rs4344916, rs12639443, rs17087180, rs17771939, rs9508834 and rs17807327.

10.-**16**. (canceled)

17. The method of claim **1**, wherein the genotype is determined at SNPs:

a) rs2521644, rs12256889, rs214526, rs17771939, rs496486, and rs949298, and preferably a score is assigned to each genotype of each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the scores are approximately as shown in tables 7a-f;

b) rs2521644, rs12256889, rs214526, rs17771939, rs496486, and rs2511064, and preferably a score is assigned to each genotype of each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the scores are approximately as shown in tables 9a-f, or preferably a relative weight is assigned to each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the relative weight is approximately as shown in table 10;

c) rs12256889, rs17771939, rs2511064, and rs2521644, and preferably a score is assigned to each genotype of each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the scores are approximately as shown in tables 9a-f, or preferably a relative weight is assigned to each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the relative weight is approximately as shown in table 11;

d) rs11599624, rs12639443, rs13042992, rs13238613, rs17087180, rs17771939, rs17807327, rs2487896, rs3135391, rs4148871, rs4343256, rs4344916, and rs9508834;

e) rs12256889, rs12639443, rs13238613, rs1573706, rs17087180, rs17771939, rs17807327, rs2487896, rs4343256, rs4344916, rs4369324, rs4445746, and rs9944913;

f) rs10988087, rs12639443, rs13042992, rs13238613, rs1573706, rs17087180, rs17771939, rs17807327, rs4148871, rs4344916, rs6097801, and rs9508834;

g) rs10988087, rs12256889, rs12639443, rs17087180, rs17771939, rs2177073, rs2521644, rs4344916, rs4369324, rs6097801, rs9508834, and rs9944913;

h) rs10966087, rs11617134, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2487896, rs4148871, rs4344916, rs4445746, rs6097801, and rs9508834;

i) rs10988087, rs11617134, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2487896, rs2521644, rs4148871, rs4344916, rs4445746, and rs6097801;

j) rs10988087, rs12256889, rs12639443, rs17087180, rs17771939, rs17807327, rs2487896, rs4148871, rs4344916, rs6097801, and rs9508834;

k) rs1007328, rs11617134, rs12639443, rs13238613, rs1573706, rs17087180, rs17771939, rs17807327, rs4343256, rs4344916, rs9508834, and rs9944913;

l) rs12639443, rs17087180, rs17771939, rs17807327, rs2487896, rs4146871, rs4343256, rs4344916, rs4369324, rs4445746, rs6097801, rs9508834, and rs9944913;

m) rs1617134, rs12639443, rs17087180, rs17771939, rs17807327, rs2487896, rs3135391, rs4148871, rs4344916, rs4369324, rs6097801, rs9508834, and rs9944913;

n) rs10988087, rs12639443, rs13238613, rs17087180, rs17771939, rs2487896, rs4148871, rs4343256, rs4344916, and rs9508834;

o) rs11617134, rs12256889, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2177073, rs2487896, rs4343256, rs4344916, rs6097801, and rs9508834;

p) rs10950359, rs11617134, rs12639443, rs17087180, rs17771939, rs2487896, rs2511064, rs3135391, rs4148871, rs4343256, rs4344916, rs9508834, and rs9944913;

q) rs12256889, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2487896, rs2521644, rs4344916, and rs6097801;

r) rs10950359, rs10988087, rs11599624, rs12256889, rs12639443, rs13042992, rs17087180, rs17771939, rs17807327, rs2521644, rs3135391, rs4344916, and rs9508834;

s) rs1007328, rs10950359, rs12256889, rs12639443, rs13042992, rs1573706, rs17087180, rs17771939, rs17807327, rs4343256, rs4344916, rs947603, and rs9508834; or

t) rs11599624, rs12256889, rs12639443, rs1573706, rs17087180, rs17771939, rs17807327, rs2177073, rs2487896, rs4344916, rs6097801, rs9508834, and rs9944913.

18.-**41**. (canceled)

42. The method of claim **17**, wherein a score is assigned to each genotype of each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the scores are approximately as shown in tables 18a-s and 19a-h.

43. The method of claim **17**, wherein a relative weight is assigned to each SNP, for the purpose of determining if the human subject is a predicted responder to glatiramer acetate, wherein the relative weight is approximately as shown in one of tables 20-36, wherein the table selected corresponds to the SNPs at which a genotype was determined.

44.-**50**. (canceled)

51. The method of claim **1**, wherein the human subject is a naive patient.

52. The method of claim **1**, wherein the human subject has been previously administered glatiramer acetate.

53. The method of claim **1**, wherein the human subject has been previously administered a multiple sclerosis drug other than glatiramer acetate.

54. The method of claim **1**, wherein the genotype of the subject at said one or more SNPs is obtained indirectly by determining the genotype of the subject at a SNP that is in linkage diseguilibrium with said one or more SNPs.

55. A kit for identifying a human subject afflicted with multiple sclerosis or a single clinical attack consistent with multiple sclerosis as a predicted responder or as a predicted non-responder to glatiramer acetate, the kit comprising at least one probe specific for a SNP selected from the group consisting of rs1007328, rs10083547, rs10136012, rs10214633, rs10277267, rs1040194, rs1041897, rs10853605, rs10931091, rs10935015, rs10935016, rs10935019, rs10950359, rs10950371, rs10988087, rs11009827, rs11009835, rs11081859, rs11599624, rs11617134, rs11618546, rs11694344, rs11709339, rs11719825, rs11761457, rs11907046, rs12055694, rs12256889, rs1229542, rs1229553, rs1229555, rs1229558, rs1229562, rs1229563, rs1229564, rs1229568, rs12340584, rs1234567, rs1234947, rs1237625, rs12488259, rs12494606, rs12496278, rs12524041, rs12529764, rs12532459, rs12540494, rs12593600, rs12633010, rs12637073, rs12639443, rs1264423, rs1282540, rs1282546, rs12968586, rs1299325, rs13021482, rs13042992, rs1320648, rs13238613, rs13245980, rs1415557, rs1538123, rs1573706, rs1591661, rs1611185, rs1683691, rs16999008, rs17007730, rs17087180, rs17104665, rs17104742, rs17134651, rs17575455, rs17588454, rs17666347, rs17771939, rs17807327, rs17807445, rs1886308, rs1892974, rs1941973, rs2033471, rs2088713, rs211526, rs2155262, rs2177073, rs2187495, rs2277431, rs2305623, rs2374730, rs2461319, rs2487889, rs2487896, rs2508806, rs2511064, rs2521643, rs2521644, rs2530121, rs2530123, rs2685484, rs2722396, rs2722398, rs28861531, rs2895215, rs2937395, rs3135391, rs35831078, rs3742228, rs401618, rs4148871, rs4255033, rs4281882, rs4289164, rs4306478, rs4343256, rs4344916, rs4369324, rs4435429, rs4445746, rs4466940, rs4468448, rs4483642, rs4565951, rs4578835, rs4634524, rs4799760, rs4809955, rs4811492, rs496486, rs552994, rs6015147, rs6025923, rs6025927, rs6091820, rs6097782, rs6097790, rs6097793, rs6097797, rs6097801, rs6123749, rs6543934, rs6558102, rs656975, rs657302, rs6584894, rs660075, rs6713772, rs6909321, rs6971202, rs702355, rs7080507, rs7086707, rs7093143, rs7178587, rs7180867, rs7232734, rs7238006, rs7244801, rs7317000, rs751370, rs752979, rs7619350, rs7633210, rs7714122, rs7789703, rs7803164, rs7806265, rs7916897, rs7955917, rs7963693, rs8099595, rs8118441, rs844602, rs844608, rs844610, rs844612, rs844626, rs860722, rs873216, rs884266, rs894857, rs913882, rs9315048, rs9332420, rs933863, rs933864, rs9378319, rs9378684, rs9392358, rs9405541, rs9405546, rs947603, rs948029, rs948032, rs949298, rs9508834, rs9944913, rs9952995, and rs998051.

56.-**85**. (canceled)

86. A probe for identifying the genotype of a SNP selected from the group consisting of rs1007328, rs10083547, rs10136012, rs10214633, rs10277267, rs1040194, rs1041897, rs10853605, rs10931091, rs10935015, rs10935016, rs10935019, rs10950359, rs10950371, rs10988087, rs11009827, rs11009835, rs11081859, rs11599624, rs11617134, rs11618546, rs11694344, rs11709339, rs11719825, rs11761457, rs11907046, rs12055694, rs12256889, rs1229542, rs1229553, rs1229555, rs1229558, rs1229562, rs1229563, rs1229564, rs1229568, rs12340584, rs1234567, rs1234947, rs1237625, rs12488259, rs12494606, rs12496278, rs12524041, rs12529764, rs12532459, rs12540494, rs12593600, rs12633010, rs12637073, rs12639443, rs1264423, rs1282540, rs1282546, rs12968586, rs1299325, rs13021482, rs13042992, rs1320648, rs13238613, rs13245980, rs1415557, rs1538123, rs1573706, rs1591661, rs1611185, rs1683691, rs16999008, rs17007730, rs17087180, rs17104665, rs17104742, rs17134651, rs17575455, rs17588454, rs17666347, rs17771939, rs17807327, rs17807445, rs1886308, rs1892974, rs1941973, rs2033471, rs2088713, rs214526, rs2155262, rs2177073, rs2187495, rs2277431, rs2305623, rs2374730, rs2461319, rs2487889, rs2487896, rs2508806, rs2511064, rs2521643, rs2521644, rs2530121, rs2530123, rs2685484, rs2722396, rs2722398, rs28861531, rs2895215, rs2937395, rs3135391, rs35831078, rs3742228, rs401618, rs4148871, rs4255033, rs4281882, rs4289164, rs4306478, rs4343256, rs4344916, rs4369324, rs4435429, rs4445746, rs4466940, rs4468448, rs4483642, rs4565951, rs4578835, rs4634524, rs4799760, rs4809955, rs4811492, rs496486, rs552994, rs6015147, rs6025923, rs6025927, rs6091820, rs6097782, rs6097790, rs6097793, rs6097797, rs6097801, rs6123749, rs6543934, rs6558102, rs656975, rs657302, rs6584894, rs660075, rs6713772, rs6909321, rs6971202, rs702355, rs7080507, rs7086707, rs7093143, rs7178587, rs7180867, rs7232734, rs7238006, rs7244801, rs7317000, rs751370, rs752979, rs7619350, rs7633210, rs7714122, rs7789703, rs7803164, rs7806265, rs7916897, rs7955917, rs7963693, rs8099595, rs8118441, rs844602, rs844608, rs844610, rs844612, rs844626, rs860722, rs873216, rs884266, rs894857, rs913882, rs9315048, rs9332420, rs933863, rs933864, rs9378319, rs9378684, rs9392358, rs9405541, rs9405546, rs947603, rs948029, rs948032, rs949298, rs9508834, rs9944913, rs9952995, and rs998051.

87-98. (canceled)

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