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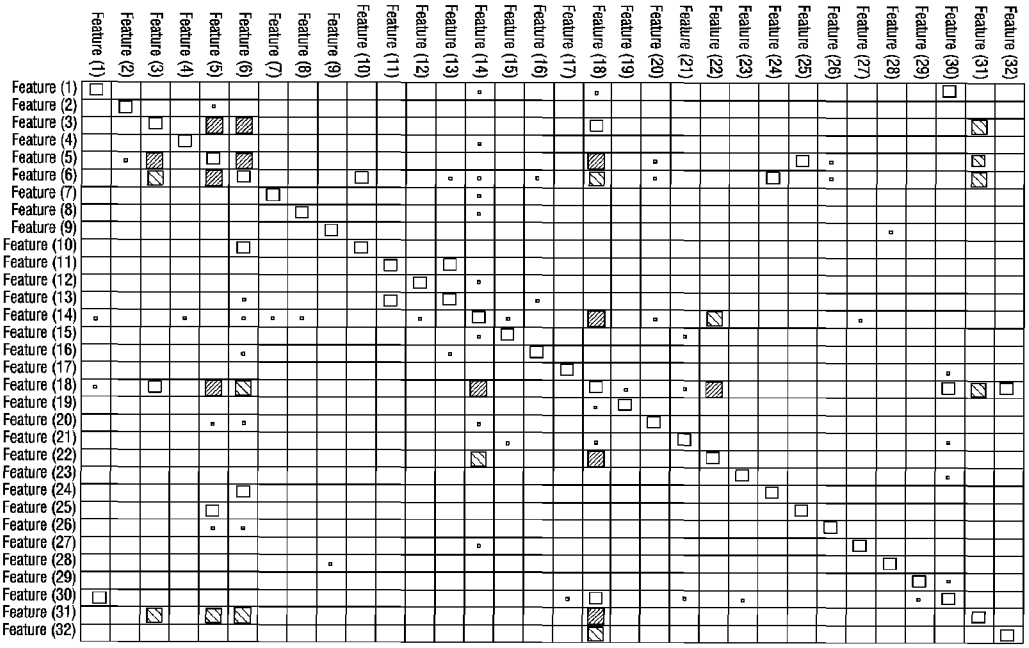

FIG. 1

(57) Abstract: A method for treating amyotrophic lateral sclerosis includes administering an effective amount of 3-methyl-l-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof to a patient who is in need thereof and meets two or more features selected from a group of identified features.

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TITLE OF THE INVENTION

METHOD FOR TREATING AMYOTROPHIC LATERAL SCLEROSIS AND METHOD FOR SUPPRESSING PROGRESS OF AMYOTROPHIC LATERAL SCLEROSIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[1] The present application is based upon and claims the benefit of priority to U.S. Provisional Application No. 62/567,873, filed October 4, 2017, the entire contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Field of the Invention

[2] The present invention relates to a method for treating amyotrophic lateral sclerosis (hereinafter also referred to as ALS) or suppressing progress of the disease, and a method for treating a symptom caused by ALS or suppressing progress of the symptom.

Description of Background Art

[3] As a medication effective for suppressing progress of ALS, there has been approved "riluzole" that suppresses glutamic acid transmission in glutamatergic nerve. However, it has also been reported that the effectiveness of riluzole cannot be confirmed. Thus, the evaluation of this drug is not consistent.

[4] ALS, which is one type of motor neuron disease, is an intractable disease. ALS starts with initial symptoms such as weakness in hands, movement disorders with fingers and fascicular contraction in upper limbs. Thereafter, ALS has amyotrophia and/or muscular weakness, bulbar paralysis and fascicular contraction in muscles, and it finally leads to respiratory failure. ALS is divided into upper limb, bulbar, lower limb and mixed types, depending on a site of onset. In all of these types, as symptoms progress, a systemic muscle group is affected.

SUMMARY OF THE INVENTION

[5] A method for treating amyotrophic lateral sclerosis at an early stage according to an embodiment of the present invention includes administering an effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof to a patient who has at least two Features of identified Feature 1 to Feature 55. The identified Feature 1 to Feature 55 are selected from the following.

1. Abnormality of gait
2. Aldolase test
3. Antinuclear antibodies (ANA) test
4. Cervical spondylosis without myelopathy
5. Creatine kinase (CK) : (CPK) test
6. Cyanocobalamin (Vitamin B-12) test
7. Degeneration of cervical intervertebral disc
8. Displacement of cervical intervertebral disc without myelopathy
9. Dysphagia
10. Folic acid; serum test
11. Serum immunofixation electrophoresis test
12. Magnetic resonance imaging test
13. Manual therapy techniques
14. Muscle weakness
15. Needle electromyography
16. Acquired deformities of ankle and foot
17. Malaise and fatigue
18. Physical therapy evaluation
19. Serum protein electrophoretic fractionation and quantitation test
20. Erythrocyte sedimentation rate test
21. Spinal stenosis in cervical region
22. Swallowing function test

23. Therapeutic procedure for neuromuscular reeducation
24. Therapeutic procedure for therapeutic exercises
25. Thyroid stimulating hormone (TSH) test
26. Unspecified hereditary and idiopathic peripheral neuropathy
27. Nervous system disorders
28. Hereditary and degenerative nervous system conditions
29. Connective tissue disease
30. Non-traumatic joint disorders
31. Multiple sclerosis
32. Paraplegia
33. Paralysis
34. Other diagnostic nervous system procedures
35. Durable Medical Equipment (DME) and supplies
36. Physical therapy
37. Laryngoscopy
38. Spinal puncture
39. Treatment of speech
40. Riluzole
41. Baclofen
42. Pyridostigmine
43. Anticonvulsants
44. Diazepam
45. Hydrocodone
46. Propoxyphene
47. Sympathomimetic Agents
48. Glycopyrrolate

49. Prednisone

50. Pregabalin

51. Clonazepam

52. Tizanidine

53. Levodopa or Carbidopa

54. Quinine

55. Tolterodine

[6] A method for suppressing progress of amyotrophic lateral sclerosis at an early stage according to another embodiment of the present invention includes administering an effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof to a patient who has at least two Features of identified feature 1 to feature 55. The identified Feature 1 to Feature 55 are selected from the following.

1. Abnormality of gait

2. Aldolase test

3. Antinuclear antibodies (ANA) test

4. Cervical spondylosis without myelopathy

5. Creatine kinase (CK) : (CPK) test

6. Cyanocobalamin (Vitamin B-12) test

7. Degeneration of cervical intervertebral disc

8. Displacement of cervical intervertebral disc without myelopathy

9. Dysphagia

10. Folic acid; serum test

11. Serum immunofixation electrophoresis test

12. Magnetic resonance imaging test

13. Manual therapy techniques

14. Muscle weakness

15. Needle electromyography
16. Acquired deformities of ankle and foot
17. Malaise and fatigue
18. Physical therapy evaluation
19. Serum protein electrophoretic fractionation and quantitation test
20. Erythrocyte sedimentation rate test
21. Spinal stenosis in cervical region
22. Swallowing function test
23. Therapeutic procedure for neuromuscular reeducation
24. Therapeutic procedure for therapeutic exercises
25. Thyroid stimulating hormone (TSH) test
26. Unspecified hereditary and idiopathic peripheral neuropathy
27. Nervous system disorders
28. Hereditary and degenerative nervous system conditions
29. Connective tissue disease
30. Non-traumatic joint disorders
31. Multiple sclerosis
32. Paraplegia
33. Paralysis
34. Other diagnostic nervous system procedures
35. Durable Medical Equipment (DME) and supplies
36. Physical therapy
37. Laryngoscopy
38. Spinal puncture
39. Treatment of speech
40. Riluzole

41. Baclofen

42. Pyridostigmine

43. Anticonvulsants

44. Diazepam

45. Hydrocodone

46. Propoxyphene

47. Sympathomimetic Agents

48. Glycopyrrolate

49. Prednisone

50. Pregabalin

51. Clonazepam

52. Tizanidine

53. Levodopa or Carbidopa

54. Quinine

55. Tolterodine

[7] A method for suppressing progress of amyotrophic lateral sclerosis at an early stage according to yet another embodiment of the present invention includes administering an effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof to a patient who has at least two Features of identified Feature 1 to Feature 11. The identified Feature 1 to Feature 11 are selected from the following.

1. Malaise and fatigue, or Muscle weakness

2. Non-traumatic joint disorder or Acquired deformities of ankle and foot

3. Connective tissue disease

4. Skin disorder

5. Nervous system disorder

6. Any change in speech

7. Office visit to: Physical therapy, Neurologist, Orthopedic surgeon, Gastroenterologist, or Otolaryngologist

8. Magnetic resonance imaging test, or Needle electromyography

9. Riluzole, Baclofen, Pyridostigmine, Anticonvulsants

10. Unusual increase in healthcare resource utilization

11. Creatine kinase (CK) : (CPK) test, Cyanocobalamin (Vitamin B-12) test, or Antinuclear antibodies (ANA) test.

BRIEF DESCRIPTION OF THE DRAWINGS

[8] A more complete appreciation of the invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings, wherein:

Figure 1 illustrates top 20 two-Feature combinations according to an embodiment of the present invention based on mutual information rank and values in periods of three to six months prior to patients are diagnosed as having ALS;

Figure 2 illustrates top 20 two-Feature combinations according to an embodiment of the present invention based on mutual information rank and values in periods of six to nine months prior to patients are diagnosed as having ALS;

Figure 3 illustrates top 20 two-Feature combinations according to an embodiment of the present invention based on mutual information rank and values in periods of nine to twelve months prior to patients are diagnosed as having ALS;

Figure 4 illustrates top 20 two-Feature combinations according to an embodiment of the present invention based on mutual information rank and values in periods of twelve to eighteen months prior to patients are diagnosed as having ALS;

Figure 5 illustrates selected 3 Feature combinations according to an embodiment of the present invention by mutual information rank;

Figure 6 illustrates selected 4 Feature combinations according to an embodiment of the present invention by mutual information rank; and

Figure 7 illustrates selected 5 Feature combinations according to an embodiment of the present invention by mutual information rank.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[9] Embodiments will now be described with reference to the accompanying drawings, wherein like reference numerals designate corresponding or identical elements throughout the various drawings.

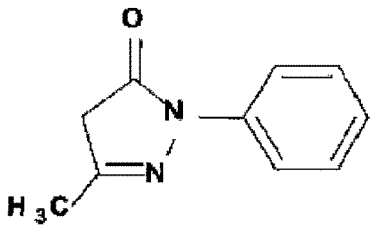
[10] Causal factors of ALS have not yet been sufficiently elucidated. The following hypotheses have been proposed as main causal factors of ALS: (1) autoimmune theory (appearance of an autoantibody against a Ca channel); (2) excessive excitatory amino acid and/or toxication theory (an increase in extracellular glutamic acid and transport disorders of glutamic acid); (3) oxidative stress disorder theory (Cu/Zn superoxide dismutase (SOD) genetic abnormality and nerve cell damage caused by free radicals); (4) cytoskeleton disorder theory (accumulation of neurofilament in motor nerve cells and appearance of inclusion bodies); and (5) deficiency of neurotrophic factors.

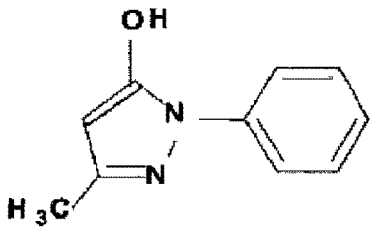
[11] Examples of symptoms caused by ALS include clinical symptoms such as decreased respiratory function, speech language impairment, swallowing disorder, movement disorder of limbs, and the like. In the present invention, a decrease in respiratory function is a preferable example. This term should be interpreted in the broadest sense as long as it conforms to the above definition and should not be construed in a way that is confined to differences in disease names. Whether or not it is a disease equivalent to ALS can be diagnosed by a doctor.

[12] Further, a preferable example of treating and/or suppressing progress of ALS or a symptom caused by ALS is suppression of a decrease in respiratory function in amyotrophic lateral sclerosis.

[13] An active ingredient of the drug of the present invention is 3-methyl-1-phenyl-2-pyrazolin-5-one. 3-methyl-1-phenyl-2-pyrazolin-5-one can be represented by the following structural formula. 3-methyl-1-phenyl-2-pyrazolin-5-one has tautomers represented by the following structural formula. However, as the active ingredient of the drug of the present invention, any of these isomers may be used.

Chemical Formula 1





[14] When any disease is found in a human body, appropriate treatment may be performed by a doctor. Drug treatment is also one of treatments. However, in drug treatment, it may be necessary to continue to administer drugs until the disease is cured. In contrast, for the drug and method of an embodiment of the present invention, during a drug treatment period, two or more 14-day drug holiday periods are provided, that is, a unit period including an administration period and a drug holiday period is repeated two or more times. Here, when an administration period and a drug holiday period are repeated two or more times, an end of this period is definitely a drug holiday period. However, it is not necessary to provide the last drug holiday period. That is, for example, when an administration period and a drug holiday period are repeated twice, this is a case of "an administration period, a drug holiday period, an administration period, and a drug holiday period. However, a case of "an administration period, a drug holiday period, and an administration period" without providing the last drug holiday period is also included in an embodiment of the present invention. Further, in an embodiment of the present invention, a drug holiday period is a period in which drug administration is not performed for 7 or more consecutive days.

[15] In an embodiment of the present invention, an administration period is a 14-day period or is a period including 10 days out of 14 days. 10 days out of 14 days mean any 10 days out of 14 consecutive days. The 10 days in which drug administration is performed may be 10 consecutive days or 10 non-consecutive days separated by 1 – 4 days in which drug administration is not performed. As an administration period, a preferred period can be selected while observing a condition of the patient.

[16] A drug holiday period in an embodiment of the present invention is preferably a 14-day period.

[17] The number of repetitions in the case where a 14-day administration period and a 14-day drug holiday period are repeated is not particularly limited as long as the number of repetitions is 2 or more. However, the number of repetitions is preferably 2 – 12, and more preferably 2 – 6.

[18] In a case where an administration period of 10 days out of 14 days and a 14-day drug holiday period are repeated after an initial 14-day administration period followed by an initial 14-day drug holiday period, the number of repetitions of the administration period of 10 days out of 14 days and the 14-day drug holiday period is not particularly limited as long as the number of repetitions is 1 or more. However, the number of repetitions is preferably 1 – 11, and more preferably 1 – 5.

[19] In another embodiment, drug administration can be repeated daily or nearly daily without providing a drug holiday period.

[20] In administering the active ingredient, the administration route is not particularly limited, and the active ingredient may be administered orally or parenterally. Further, bolus administration and sustained administration may be possible. In the case of sustained administration, intravenous administration by infusion, transdermal administration, oral administration using a sublingual tablet, oral and intrarectal administration using a sustained-release drug product, and the like may be used. However, intravenous administration by infusion is preferable. In the case of performing bolus administration by injection or intravenous administration by infusion, for example, injectable drugs described in Japanese Patent Laid-Open Publication No. SHO 63-132833 and Japanese Patent Laid-Open Publication No. 2011-62529 may be used. The entire contents of these publications are incorporated herein by reference.

[21] A daily dose of the active ingredient may be appropriately selected according to conditions such as age and condition of the patient. In the case of intravenous administration by infusion with providing an administration period and a drug holiday period, for an adult, an amount of 3-methyl-1-phenyl-2-pyrazolin-5-one (when the active ingredient is 3-methyl-1-phenyl-2-pyrazolin-5-one, an amount of 3-methyl-1-phenyl-2-pyrazolin-5-one; when the active ingredient is a physiologically acceptable salt of 3-methyl-1-phenyl-2-pyrazolin-5-one, an equivalent amount of 3-methyl-1-phenyl-2-pyrazolin-5-one) is preferably about 15 – 240 mg, more preferably about 30 – 180 mg, even more preferably about 60 – 120 mg, and particularly preferably about 60 mg. In the case where 3-methyl-1-phenyl-2-pyrazolin-5-one is administered orally, the dose is preferably pharmacokinetically substantially equivalent to the intravenous administration. A specific example is a dose for which it is recognized that a change over time of a concentration of unchanged 3-methyl-1-phenyl-2-pyrazolin-5-one of the administered 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof in a plasma is substantially equivalent. Examples of oral administration dosage forms include oral administration using a suspension formulation, a buccal film, a sublingual tablet,

and a sustained-release drug product, and the like. For an adult, a daily amount of 3-methyl-1-phenyl-2-pyrazolin-5-one is preferably about 240 – 3,600 mg such as about 240 mg, about 800 mg, about 1,600 mg, about 2,400 mg, about 3,600 mg, and more preferably about 800 – 2,400 mg.

[22] In the case where intravenous administration by infusion is repeated daily or nearly daily without providing a drug holiday period, for an adult, a daily amount of 3-methyl-1-phenyl-2-pyrazolin-5-one is preferably about 60 mg, about 120 mg, or about 180 mg, and particularly preferably about 60 mg, or about 120 mg.

[23] In the case where 3-methyl-1-phenyl-2-pyrazolin-5-one is administered orally, for an adult, a daily amount of 3-methyl-1-phenyl-2-pyrazolin-5-one is preferably about 240 – 3,600 mg such as about 240 mg, about 800 mg, about 1,600 mg, about 2,400 mg, about 3,600 mg, and more preferably about 800 – 2,400 mg.

[24] The number of doses per day during a drug administration period is not limited and a preferred number of doses per day can be selected while observing a condition of the patient. However, considering the burden of the patient, the number of doses per day is preferably 3, 2 and 1, and more preferably 1.

[25] In the case of intravenous administration by infusion, an administration rate is desirably about 0.5 – 5 mg/minute, about 0.5 – 1 mg/minute, or about 1 – 5 mg/minute in the amount of 3-methyl-1-phenyl-2-pyrazolin-5-one, and, in terms of time, about 15 – 480 minutes, and preferably about 30 – 120 minutes, more preferably about 30 – 60 minutes, and even more preferably about 60 minutes

[26] Regarding a drug, a treatment method or a disease progress suppression method according to an embodiment of the present invention, a patient receiving medication has at least two Features among the following identified Feature 1 to Feature 55:

1. Abnormality of gait
2. Aldolase test
3. Antinuclear antibodies (ANA) test
4. Cervical spondylosis without myelopathy
5. Creatine kinase (CK) : (CPK) test
6. Cyanocobalamin (Vitamin B-12) test

7. Degeneration of cervical intervertebral disc
8. Displacement of cervical intervertebral disc without myelopathy
9. Dysphagia
10. Folic acid; serum test
11. Serum immunofixation electrophoresis test
12. Magnetic resonance imaging test
13. Manual therapy techniques
14. Muscle weakness
15. Needle electromyography
16. Acquired deformities of ankle and foot
17. Malaise and fatigue
18. Physical therapy evaluation
19. Serum protein electrophoretic fractionation and quantitation test
20. Erythrocyte sedimentation rate test
21. Spinal stenosis in cervical region
22. Swallowing function test
23. Therapeutic procedure for neuromuscular reeducation
24. Therapeutic procedure for therapeutic exercises
25. Thyroid stimulating hormone (TSH) test
26. Unspecified hereditary and idiopathic peripheral neuropathy
27. Nervous system disorders
28. Hereditary and degenerative nervous system conditions
29. Connective tissue disease
30. Non-traumatic joint disorders
31. Multiple sclerosis
32. Paraplegia

33. Paralysis
34. Other diagnostic nervous system procedures
35. Durable Medical Equipment (DME) and supplies
36. Physical therapy
37. Laryngoscopy
38. Spinal puncture
39. Treatment of speech
40. Riluzole
41. Baclofen
42. Pyridostigmine
43. Anticonvulsants
44. Diazepam
45. Hydrocodone
46. Propoxyphene
47. Sympathomimetic Agents
48. Glycopyrrolate
49. Prednisone
50. Pregabalin
51. Clonazepam
52. Tizanidine
53. Levodopa or Carbidopa
54. Quinine
55. Tolterodine

[27] "Abnormality of gait" means that a patient has been diagnosed with a disease of "abnormality of gait" indicated by ICD-9 code 781.2 or has a symptom corresponding to the disease of "abnormality of gait."

[28] "Aldolase test" means that a patient has received a procedure of "aldorase" indicated by CPT code 82085 or an equivalent procedure.

[29] "Antimuclear antibodies (ANA) test" means that a patient has received a procedure of "antimuclear antibodies (ANA)" indicated by CPT code 86038 or an equivalent procedure.

[30] "Cervical spondylosis" means that a patient has been diagnosed with a disease of "cervical spondylosis without myelopathy" indicated by ICD-9 code 721.0 or has a symptom corresponding to the disease of "cervical spondylosis without myelopathy."

[31] "Cyanocobalamin (Vitamin B-12) test" means that a patient has received a procedure of "cyanocobalamin (Vitamin B-12)" indicated by CPT code 82607 or an equivalent procedure.

[32] "Degeneration of cervical intervertebral disc" means that a patient has been diagnosed with a disease of "degeneration of cervical intervertebral disc" indicated by ICD-9 code 722.4 or has a symptom corresponding to the disease of "degeneration of cervical intervertebral disc."

[33] "Displacement of cervical intervertebral disc without myelopathy" means that a patient has been diagnosed with a disease of "displacement of cervical intervertebral disc without myelopathy" indicated by ICD-9 code 722.0 or has a symptom corresponding to the disease of "displacement of cervical intervertebral disc without myelopathy."

[34] "Dysphagia" means that a patient has been diagnosed with a disease of "dysphagia; unspecified" indicated by ICD-9 code 787.20 or has a symptom corresponding to the disease of "dysphagia; unspecified."

[35] "Folic acid; serum test" means that a patient has received a procedure of "folic acid; serum" indicated by CPT code 82746 or an equivalent procedure.

[36] "Serum immunofixation electrophoresis test" means that a patient has received a procedure of "immunofixation electrophoresis; serum" indicated by CPT code 86334 or an equivalent procedure.

[37] "Magnetic resonance imaging test" means that a patient has received a procedure of "injection; gadolinium-based magnetic resonance contrast agent; not otherwise specified (nos); per ml" indicated by CPT code A9579, a procedure of "magnetic resonance (eg; proton) imaging; brain (including brain stem); without contrast material" indicated by CPT code 70551, a procedure of "magnetic resonance (eg; proton) imaging; brain (including brain stem); without contrast material; followed by contrast material(s) and further sequences" indicated by CPT code 70553, a procedure of "magnetic resonance (eg; proton) imaging; spinal canal and contents; cervical; without contrast material" indicated by CPT code 72141,

a procedure of "magnetic resonance (eg; proton) imaging; spinal canal and contents; lumbar; without contrast material" indicated by CPT code 72148, or a procedure of "magnetic resonance (eg; proton) imaging; spinal canal and contents; without contrast material; followed by contrast material(s) and further sequences; cervical" indicated by CPT code 72156, or a procedure equivalent to these procedures.

[38] "Manual therapy techniques" means that a patient has received a procedure of "manual therapy techniques (eg; mobilization/manipulation; manual lymphatic drainage; manual traction); 1 or more regions; each 15 minutes" indicated by CPT code 97140 or an equivalent procedure.

[39] "Muscle weakness" means that a patient has been diagnosed with a disease of "muscle weakness (generalized)" indicated by ICD-9 code 728.87 or has a symptom corresponding to the disease of "muscle weakness (generalized)."

[40] "Needle electromyography" means that a patient has received a procedure of "needle electromy ography; 1 extremity with or without related paraspinal areas" indicated by CPT code 95860 or a procedure of "needle electromyography; 2 extremities with or without related paraspinal areas" indicated by CPT code 95861, or a procedure equivalent to these procedures.

[41] "Acquired deformities of ankle and foot" means that a patient has been diagnosed with a disease of "other acquired deformities of ankle and foot" indicated by ICD-9 code 736.79 or has a symptom corresponding to the disease of "other acquired deformities of ankle and foot."

[42] "Malaise and fatigue" means that a patient has been diagnosed with a disease of "other malaise and fatigue" indicated by ICD-9 code 780.79 or has a symptom corresponding to the disease of "other malaise and fatigue."

[43] "Physical therapy evaluation" means that a patient has received a procedure of "physical therapy evaluation" indicated by CPT code 97001 or an equivalent procedure.

[44] "Serum protein electrophoretic fractionation and quantitation test" means that a patient has received a procedure of "protein; electrophoretic fractionation and quantitation; serum" indicated by CPT code 84165 or an equivalent procedure.

[45] "Erythrocyte sedimentation rate test" means that a patient has received a procedure of "sedimentation rate; erythrocyte; automated" indicated by CPT code 85652 or a procedure of "sedimentation rate; erythrocyte; non-automated" indicated by CPT code 85651, or a procedure equivalent to these procedures.

[46] "Spinal stenosis in cervical region" means that a patient has been diagnosed with a disease of "spinal stenosis in cervical region" indicated by ICD-9 code 723.0 or has a symptom corresponding to the disease of "spinal stenosis in cervical region."

[47] "Swallowing function; with cineradiography/videoradiography" means that a patient has received a procedure of "swallowing function; with cineradiography/videoradiography" indicated by CPT code 74230 or an equivalent procedure.

[48] "Therapeutic procedure for neuromuscular reeducation of movement; balance; coordination; kinesthetic sense; posture; and/or proprioception for sitting and/or standing activities" means that a patient has received a procedure of "therapeutic procedure; 1 or more areas; each 15 minutes; neuromuscular reeducation of movement; balance; coordination; kinesthetic sense; posture; and/or proprioception for sitting and/or standing activities" indicated by CPT code 97112 or an equivalent procedure.

[49] "Therapeutic procedure for therapeutic exercises to develop strength and endurance; range of motion and flexibility" means that a patient has received a procedure of "therapeutic procedure; 1 or more areas; each 15 minutes; therapeutic exercises to develop strength and endurance; range of motion and flexibility" indicated by CPT code 97110, or an equivalent procedure.

[50] "Thyroid stimulating hormone (TSH) test" means that a patient has received a procedure of "thyroid stimulating hormone (TSH)" indicated by CPT code 84443 or an equivalent procedure.

[51] "Unspecified hereditary and idiopathic peripheral neuropathy" means that a patient has been diagnosed with a disease of "unspecified hereditary and idiopathic peripheral neuropathy" indicated by ICD-9 code 356.9 or has a symptom corresponding to the disease of "unspecified hereditary and idiopathic peripheral neuropathy."

[52] "Nervous system disorders" means that a patient has been diagnosed with a disease of "other nervous system disorders" or has a symptom corresponding to the disease of "other nervous system disorders."

[53] "Hereditary and degenerative nervous system conditions" means that a patient has been diagnosed with a disease of "other hereditary and degenerative nervous system conditions" or has a symptom corresponding to the disease of "other hereditary and degenerative nervous system conditions."

[54] "Connective tissue disease" means that a patient has been diagnosed with a disease of "connective tissue disease" or has a symptom corresponding to the disease of "connective tissue disease."

[55] "Non-traumatic joint disorders" means that a patient has been diagnosed with a disease of "other non-traumatic joint disorders" or has a symptom corresponding to the disease of "other non-traumatic joint disorders."

[56] "Multiple sclerosis" means that a patient has been diagnosed with a disease of "multiple sclerosis" or has a symptom corresponding to the disease of "multiple sclerosis."

[57] "Paraplegia" means that a patient has been diagnosed with a disease of "paraplegia" or has a symptom corresponding to the disease of "paraplegia."

[58] "Paralysis" means that a patient has been diagnosed with a disease of "paralysis" or has a symptom corresponding to the disease of "paralysis."

[59] "Other diagnostic nervous system procedures" means that a patient has received a procedure of "other diagnostic nervous system procedures" or an equivalent procedure.

[60] "Durable Medical Equipment (DME) and supplies" means that a patient has received a procedure of "Durable Medical Equipment (DME) and supplies" or an equivalent procedure.

[61] "Physical therapy" means that a patient has received a procedure of "physical therapy" or an equivalent procedure.

[62] "Laryngoscopy" means that a patient has received a procedure of "laryngoscopy" or an equivalent procedure.

[63] "Spinal puncture" means that a patient has received a procedure of "spinal puncture" or an equivalent procedure.

[64] "Treatment of speech" means that a patient has received a procedure of "treatment of speech" or an equivalent procedure.

[65] "Riluzole" means that a patient has been prescribed a medication containing "Riluzole" as an active ingredient.

[66] "Baclofen" means that a patient has been prescribed "Baclofen."

[67] "Pyridostigmine" means that a patient has been prescribed a medication containing "Pyridostigmine" as an active ingredient.

[68] "Anticonvulsants" means that a patient has been prescribed one or more medications containing active ingredients classified as "Anticonvulsants."

[69] "Diazepam" means that a patient has been prescribed a medication containing "Diazepam" as an active ingredient.

[70] "Hydrocodone" means that a patient has been prescribed a medication containing "Hydrocodone" as an active ingredient.

[71] "Propoxyphene" means that a patient has been prescribed a medication containing "Propoxyphene" as an active ingredient.

[72] "Propoxyphene" means that a patient has been prescribed a medication containing "Sympathomimetic Agents" as active ingredients.

[73] "Glycopyrrolate" means that a patient has been prescribed a medication containing "Glycopyrrolate" as an active ingredient.

[74] "Prednisone" means that a patient has been prescribed a medication containing "Prednisone" as an active ingredient.

[75] "Pregabalin" means that a patient has been prescribed a medication containing "Pregabalin" as an active ingredient.

[76] "Clonazepam" means that a patient has been prescribed a medication containing "Clonazepam" as an active ingredient.

[77] "Tizanidine" means that a patient has been prescribed a medication containing "Tizanidine" as an active ingredient.

[78] "Levodopa or Carbidopa" means that a patient has been prescribed a medication containing "Levodopa" as an active ingredient or a medication containing "Carbidopa" as an active ingredient.

[79] "Quinine" means that a patient has been prescribed a medication containing "Quinine" as an active ingredient.

[80] "Tolterodine" means that a patient has been prescribed a medication containing "Tolterodine" as an active ingredient.

[81] A patient having a feature identified by the present invention is highly likely to be an ALS patient as compared to other patients, and it is expected that it is particularly effective to administer a medication containing 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof to the patient.

[82] Further, regarding a drug, a treatment method or a disease progress suppression method according to an embodiment of the present invention, a patient receiving medication may meet one or more of the following Features:

- Skin disorders

- Any changes in speech

- Office visit to: physical therapy, neurologist, orthopedic surgeon, gastroenterologist, or otolaryngologist

- Unusual increase in healthcare resource utilization (i.e. increase doctor visit, procedures (MRI, EMG) new diagnosis, prescriptions)

- Unusually higher healthcare utilization

[83] A change in speech notable, noted, recognizable and/or recognized by a medical profession such as a medical doctor, a nurse, a therapist, and a health care provider.

[84] An unusual increase in healthcare resource utilization notable, noted, recognizable or recognized by a medical profession such as a medical doctor, a nurse, a therapist, and a health care provider.

[85] An unusually higher healthcare utilization notable, noted, recognizable or recognized by a medical profession such as a medical doctor, a nurse, a therapist, and a health care provider.

[86] Regarding a drug, a treatment method or a disease progress suppression method according to an embodiment of the present invention, during a certain time period before receiving initial administration of 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof, a patient receiving medication preferably has at least two Features among the Feature 1 to Feature 55. The time period may be a certain time period within 120 months before receiving the initial administration. More preferably, the time period is a certain time period within 96 months, 72 months, 60 months, 48 months, 36 months, 24 months, or 12 months before receiving the initial administration.

[87] The start and end of the time period are not particularly limited as long as the time period is within 120 months before receiving the initial administration. The time period may include one time period or two or more time periods, and lengths of the time periods may be the same or different. The number of the time periods is not particularly limited, but is preferably 1 – 20, more preferably 1 – 15, and even more preferably any one of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. Lengths of the time periods are not particularly limited, but can be 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, 15 months, 18 months, 24 months, 30 months, 36 months, 48 months, 60 months, 72 months, 96 months, and 120 months. In some embodiments, before receiving initial administration, in at least one of periods of 0 to 3 months, 3 to 6 months, 6 to 9 months, 9 to 12 months, 12 to 18 months, 18 to 24 months, 24 to 36 months, and 36 to 48 months, a patient receiving medication has at least two Features among the Feature 1 to Feature 55.

[88] In another embodiment of the present invention, regarding a drug, a treatment method or a disease progress suppression method, a patient receiving medication has at least one pair of Features identified in the following pair 1 to pair 46:

1. Feature (1) and Feature (14)
2. Feature (1) and Feature (18)
3. Feature (1) and Feature (30)
4. Feature (2) and Feature (5)
5. Feature (3) and Feature (5)
6. Feature (3) and Feature (6)
7. Feature (3) and Feature (18)
8. Feature (3) and Feature (31)
9. Feature (4) and Feature (14)
10. Feature (5) and Feature (6)
11. Feature (5) and Feature (18)
12. Feature (5) and Feature (20)
13. Feature (5) and Feature (25)
14. Feature (5) and Feature (26)
15. Feature (5) and Feature (31)
16. Feature (6) and Feature (10)
17. Feature (6) and Feature (13)
18. Feature (6) and Feature (14)
19. Feature (6) and Feature (16)
20. Feature (6) and Feature (18)
21. Feature (6) and Feature (20)
22. Feature (6) and Feature (24)
23. Feature (6) and Feature (26)
24. Feature (6) and Feature (31)

25. Feature (7) and Feature (14)

26. Feature (8) and Feature (14)

27. Feature (9) and Feature (28)

28. Feature (11) and Feature (13)

29. Feature (12) and Feature (14)

30. Feature (13) and Feature (16)

31. Feature (14) and Feature (15)

32. Feature (14) and Feature (18)

33. Feature (14) and Feature (20)

34. Feature (14) and Feature (22)

35. Feature (14) and Feature (27)

36. Feature (15) and Feature (21)

37. Feature (17) and Feature (30)

38. Feature (18) and Feature (19)

39. Feature (18) and Feature (21)

40. Feature (18) and Feature (22)

41. Feature (18) and Feature (30)

42. Feature (18) and Feature (31)

43. Feature (18) and Feature (32)

44. Feature (21) and Feature (30)

45. Feature (23) and Feature (30)

46. Feature (29) and Feature (30)

Feature (1) is "Abnormality of gait";

Feature (2) is "Aldolase";

Feature (3) is "Antinuclear antibodies (ANA)";

Feature (4) is "Cervical spondylosis without myelopathy";

Feature (5) is "Creatine kinase (CK); (CPK); total";

Feature (6) is "Cyanocobalamin (Vitamin B-12)";

Feature (7) is "Degeneration of cervical intervertebral disc";

Feature (8) is "Displacement of cervical intervertebral disc without myelopathy";

Feature (9) is "Dysphagia; unspecified";

Feature (10) is "Folic acid; serum";

Feature (11) is "Injection; gadolinium-based magnetic resonance contrast agent; not otherwise specified (nos); per ml";

Feature (12) is "Magnetic resonance (eg; proton) imaging; brain (including brain stem); without contrast material";

Feature (13) is "Magnetic resonance (eg; proton) imaging; brain (including brain stem); without contrast material; followed by contrast material (s) and further sequences";

Feature (14) is "Magnetic resonance (eg; proton) imaging; spinal canal and contents; cervical; without contrast material";

Feature (15) is "Magnetic resonance (eg; proton) imaging; spinal canal and contents; lumbar; without contrast material";

Feature (16) is "Magnetic resonance (eg; proton) imaging; spinal canal and contents; without contrast material; followed by contrast material (s) and further sequences; cervical";

Feature (17) is "Manual therapy techniques (eg; mobilization/ manipulation; manual lymphatic drainage; manual traction); 1 or more regions; each 15 minutes";

Feature (18) is "Muscle weakness (generalized)";

Feature (19) is "Needle electromyography; 1 extremity with or without related paraspinal areas";

Feature (20) is "Needle electromyography; 2 extremities with or without related paraspinal areas";

Feature (21) is "Other acquired deformities of ankle and foot";

Feature (22) is "Other malaise and fatigue";

Feature (23) is "Physical therapy evaluation";

Feature (24) is "Protein; electrophoretic fractionation and quantitation; serum";

Feature (25) is "Sedimentation rate; erythrocyte; automated";

Feature (26) is "Sedimentation rate; erythrocyte; non-automated";

Feature (27) is "Spinal stenosis in cervical region";

Feature (28) is "Swallowing function; with cineradiography/videoradiography";

Feature (29) is "Therapeutic procedure; 1 or more areas; each 15 minutes; neuromuscular reeducation of movement; balance; coordination; kinesthetic sense; posture; and/or proprioception for sitting and/or standing activities";

Feature (30) is "Therapeutic procedure; 1 or more areas; each 15 minutes; therapeutic exercises to develop strength and endurance; range of motion and flexibility";

Feature (31) is "Thyroid stimulating hormone (TSH)";

Feature (32) is "Unspecified hereditary and idiopathic peripheral neuropathy".

[89] Further, regarding a drug, a treatment method or a disease progress suppression method according to yet another embodiment, a patient receiving medication has at least 3 Features, preferably at least 4 Features, and more preferably at least 5 Features among the following identified Features:

1. Malaise and fatigue, or Muscle weakness
2. Non-traumatic joint disorder or Acquired deformities of ankle and foot
3. Connective tissue disease
4. Skin disorder
5. Nervous system disorder
6. Any change in speech
7. Office visit to: Physical therapy, Neurologist, Orthopedic surgeon, Gastroenterologist, or Otolaryngologist
8. Magnetic resonance imaging test, or Needle electromyography
9. Riluzole, Baclofen, Pyridostigmine, Anticonvulsants

10. Unusual increase in healthcare resource utilization

11. Creatine kinase (CK) : (CPK) test, Cyanocobalamin (Vitamin B-12) test, or Antinuclear antibodies (ANA) test

[90] Regarding a drug, a treatment method or a disease progress suppression method of another embodiment, before receiving initial administration of 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof, in at least one of periods of 0 to 3 months, 3 to 6 months, 6 to 9 months, 9 to 12 months, 12 to 18 months, 18 to 24 months, 24 to 36 months, and 36 to 48 months, a patient receiving medication has at least 3 Features, preferably at least 4 Features, and more preferably at least 5 Features among the following identified Features:

1. Malaise and fatigue, or Muscle weakness

2. Non-traumatic joint disorder or Acquired deformities of ankle and foot

3. Connective tissue disease

4. Skin disorder

5. Nervous system disorder

6. Any change in speech

7. Office visit to: Physical therapy, Neurologist, Orthopedic surgeon, Gastroenterologist, or Otolaryngologist

8. Magnetic resonance imaging test, or Needle electromyography

9. Riluzole, Baclofen, Pyridostigmine, Anticonvulsants

10. Unusual increase in healthcare resource utilization

11. Creatine kinase (CK) : (CPK) test, Cyanocobalamin (Vitamin B-12) test, or Antinuclear antibodies (ANA) test

[91] In this embodiment, it is also possible that a numerical value between 0 and 1 is appropriately selected for each of the identified Features and weighting is performed for each of the Features. In this case, for a patient receiving medication, before receiving initial administration of 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof, in at least one of periods of 0 to 3 months, 3 to 6 months, 6 to 9 months, 9 to 12

months, 12 to 18 months, 18 to 24 months, 24 to 36 months, and 36 to 48 months, a sum of the numerical values of the above-identified Features is 3 or more, preferably 4 or more, and more preferably 5 or more.

[92] Further, regarding a drug, a treatment method or a disease progress suppression method according to another embodiment, before receiving initial administration of 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof, in periods of 0 to 3 months, 3 to 6 months, 6 to 9 months, 9 to 12 months, 12 to 18 months, 18 to 24 months, 24 to 36 months, and 36 to 48 months, a sum of numbers of Features that a patient receiving medication has among the following identified Features is at least 15, preferably at least 20, and more preferably at least 25.

1. Malaise and fatigue, or Muscle weakness
2. Non-traumatic joint disorder or Acquired deformities of ankle and foot
3. Connective tissue disease
4. Skin disorder
5. Nervous system disorder
6. Any change in speech
7. Office visit to: Physical therapy, Neurologist, Orthopedic surgeon, Gastroenterologist, or Otolaryngologist
8. Magnetic resonance imaging test, or Needle electromyography
9. Riluzole, Baclofen, Pyridostigmine, Anticonvulsants
10. Unusual increase in healthcare resource utilization
11. Creatine kinase (CK) : (CPK) test, Cyanocobalamin (Vitamin B-12) test, or Antinuclear antibodies (ANA) test

[93] Regarding the drug, the treatment method or the disease progress suppression method of this embodiment, it is also possible that a numerical value between 0 and 1 is appropriately selected for each of the identified Features and weighting is performed for each of the Features. In this case, for a patient receiving medication, before receiving initial administration of 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof, in periods of 0 to 3 months, 3 to 6 months, 6 to 9 months, 9 to 12 months, 12 to 18

months, 18 to 24 months, 24 to 36 months, and 36 to 48 months, a sum of the numerical values of the above-identified Features is 15 or more, preferably 20 or more, and more preferably 25 or more.

[94] Regarding a drug, a treatment method or a disease progress suppression method according to another embodiment, a step may be provided in which a patient having an identified Feature is selected before receiving initial administration of 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof.

[95] Figure 1 illustrates top 20 two-Feature combinations based on mutual information rank and values in periods of three to six months prior to patients are diagnosed as having ALS. Top 20 two-Feature combinations in three to six month periods prior to diagnosis plotted in Feature-to-Feature heat maps. Each axis lists all single Features included in combinations. Block representations of mutual information values of the Feature combinations are plotted at the Feature intersections on grid, with larger and darker blocks representing higher mutual information values.

[96] Figure 2 illustrates top 20 two-Feature combinations based on mutual information rank and values in periods of six to nine months prior to patients are diagnosed as having ALS. Top 20 two-Feature combinations in six to nine month periods prior to diagnosis plotted in Feature-to-Feature heat maps. Each axis lists all single Features included in combinations. Block representations of mutual information values of the Feature combinations are plotted at the Feature intersections on grid, with larger and darker blocks representing higher mutual information values.

[97] Figure 3 illustrates top 20 two-Feature combinations based on mutual information rank and values in periods of nine to twelve months prior to patients are diagnosed as having ALS. Top 20 two-Feature combinations in nine to twelve month periods prior to diagnosis plotted in Feature-to-Feature heat maps. Each axis lists all single Features included in combinations. Block representations of mutual information values of the Feature combinations are plotted at the Feature intersections on grid, with larger and darker blocks representing higher mutual information values.

[98] Figure 4 illustrates top 20 two-Feature combinations based on mutual information rank and values in periods of twelve to eighteen months prior to patients are diagnosed as having ALS. Top 20 two-Feature combinations in twelve to eighteen month periods prior to diagnosis plotted in Feature-to-Feature heat maps. Each axis lists all single Features included in combinations. Block representations of mutual information values of the Feature

combinations are plotted at the Feature intersections on grid, with larger and darker blocks representing higher mutual information values.

[99] Figure 5 illustrates selected 3 Feature combinations by mutual information rank in periods of thirty-six to forty-eight months, twenty-four to thirty-six months, eighteen to twenty-four months, twelve to eighteen months, nine to twelve months, six to nine months, and three to six months prior to patients are diagnosed as having ALS.

[100] Figure 6 illustrates selected 4 Feature combinations by mutual information rank in periods of eighteen to twenty-four months, twelve to eighteen months, nine to twelve months, six to nine months, and three to six months prior to patients are diagnosed as having ALS.

[101] Figure 7 illustrates selected 5 Feature combinations by mutual information rank in periods of eighteen to twenty-four months, twelve to eighteen months, nine to twelve months, six to nine months, and three to six months prior to patients are diagnosed as having ALS.

[102] In Figure 7, Feature (1) to Feature (32) are the same as above.

[103] Feature (33) is "Immunofixation electrophoresis; serum"

[104] International Publication No. WO 2002/034264 describes that 3-methyl-1-phenyl-2-pyrazolin-5-one is useful for treating ALS. However, the dosage form, the dose, the number of doses and the like of this compound to an ALS patient are not specifically disclosed. International Publication No. WO 2005/075434 describes a drug for treating and/or suppressing progress of amyotrophic lateral sclerosis or a symptom caused by amyotrophic lateral sclerosis, which includes 3-methyl-1-phenyl-2-pyrazolin-5-one as an active ingredient, where a drug holiday period of one or more days is established one or more times in a period of treating and/or suppressing progress of the disease. Further, a method has been reported in which 30 mg of 3-methyl-1-phenyl-2-pyrazolin-5-one is administered to an ALS patient by infusion for 14 days followed by administering it for 10 days per month (Neurotherapy, 2003, Vol.20, No. 5, pages 557-564). A method for treating ALS has been reported in which 3-methyl-1-phenyl-2-pyrazolin-5-one is administered to patients with a particularly high therapeutic effect among ALS patients in need of treatment.

[105] Diagnostic criteria for ALS include EL Escorial diagnostic criteria, EL Escorial revised Airlie House diagnostic criteria, Awaji diagnostic criteria, and the like.

[106] It has been reported that an average time period from appearance of an initial symptom of ALS to receiving a diagnosis of ALS is one year. There are multiple factors for the delay in diagnosis of ALS. The first is that a period from the appearance of the initial symptom to a first visit to a doctor is long. The second is that an early symptom of ALS is similar to that of other diseases. On average, three doctors are visited by an ALS patient

from the first doctor visit to when a final diagnosis is received (Paganoni S, et al. Amyotroph Lateral Scler Frontotemporal Degener. 2014; 15 (5 – 6), 453). Therefore, new treatment method and suppression method are necessary for shortening a period from appearance of an initial symptom of ALS to when a final diagnosis is received and for treating an ALS patient at an early stage or suppressing progress of ALS of an ALS patient at an early stage.

[107] ALSFRS-R is a severity index for an ALS patient and includes a total of 12 evaluation items regarding motor dysfunction of limbs, bulbar dysfunction, and respiratory dysfunction. For example, in clinical trials, by comparing an ALSFRS-R score before start of administration of an active ingredient to a patient, an ALSFRS-R score of a certain period after the start of the administration, and/or an ALSFRS-R score after the administration, an effect of the active ingredient may be confirmed.

[108] An example of a method for synthesizing 3-methyl-1-phenyl-2-pyrazolin-5-one, which is the active ingredient of the present invention, is a manufacturing method described in European Patent Publication No. 208874 (or Japanese Patent Publication No. HEI 5-31523). The entire contents of these publications are incorporated herein by reference.

[109] Examples of the active ingredient of the drug in the present invention include 3-methyl-1-phenyl-2-pyrazolin-5-one, a physiologically acceptable salt thereof, a hydrate thereof, and a solvate thereof. Examples of physiologically acceptable salts include salts with mineral acids such as hydrochloric acid, hydrobromide, and phosphoric acid; salts with organic acids such as methanesulfonic acid, p-toluenesulfonic acid, acetic acid, oxalic acid, citric acid, malic acid, and maric acid; salts with alkali metals such as sodium, and potassium; salts with alkaline earth metals such as magnesium; and salts with amines such as ammonia, ethanolamine, and 2-amino-2-methyl-1-propanol. In addition, the type of salt is not particularly limited as long as the salt is physiologically acceptable.

[110] 3-methyl-1-phenyl-2-pyrazolin-5-one or a salt thereof, which is the active ingredient of the drug of the present invention, may be directly administered to a patient. However, it is preferable to provide a drug product obtained by adding the active ingredient and pharmacologically and pharmaceutically acceptable additives.

[111] As the pharmacologically and pharmaceutically acceptable additives, for example, an excipient, a disintegrating agent or a disintegration aid, a binding agent, a lubricant, a coating agent, a pigment, a diluent, a base, a solubilizer or a solubilizing agent, an isotonizing agent, a pH regulator, a stabilizer, a propellant, an adhesive, and the like may be used. Examples of drug products suitable for oral administration include tablets, capsules, powders, fine granules, granules, liquid drugs, syrups, and the like. Examples of drug products suitable for

parenteral administration include injectable drugs, drops, adhesive skin patches, suppositories, and the like.

[112] As additives for drug products suitable for oral administration, for example, the following additives may be used: excipients such as glucose, lactose, D-mannitol, starch, or crystalline cellulose; disintegrating agents or disintegration aids such as carboxymethylcellulose, starch, or carboxymethylcellulose calcium; binding agents such as hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, or gelatin; lubricants such as magnesium stearate or talc; coating agents such as hydroxypropylmethylcellulose, white sugar, polyethylene glycol or titanium oxide; and bases such as vaseline, liquid paraffin, polyethylene glycol, gelatin, kaolin, glycerin, purified water, or hard fat.

[113] For drug products suitable for injection or infusion, the following additives for drug products may be used: solubilizers or solubilizing agents, which are capable of forming aqueous injectable drugs or injectable drugs dissolvable when used, such as distilled water for injection, physiological saline, propylene glycol and the like; isotonizing agents such as glucose, sodium chloride, D-mannitol, glycerin and the like; pH regulators such as inorganic acids, organic acids, inorganic bases or organic bases; and the like.

[114] A cerebral protective agent (injectable drug) containing 3-methyl-1-phenyl-2-pyrazolin-5-one as an active ingredient has already been used clinically (generic name: "Edaravone"; trade name: "Radicut (registered trademark)," "Radicava (registered trademark)": manufactured by and commercially available from Mitsubishi Tanabe Pharma Co., Ltd.). Therefore, as the 3-methyl-1-phenyl-2-pyrazolin-5-one used in the drug and method of the present invention, the above drug products may be directly used.

EXAMPLES

[115] In the following, the embodiments of the present invention are further described based on Examples. However, the scope of the present invention is not limited to the following Examples.

Method

[116] The TruvenMarketScan® database, containing patient-level claims for 170+ million patients, was used without any code pre-selection for this analysis.

[117] Patients with ALS were identified using ICD-9 code 335.20 and ICD-10 code G12.21. Patient demographics were reported for a nationwide set of patients with an ALS ICD-9 or ICD-10 code between January 2010 and June 2016. Patients from the full nationwide adjudicated claims database covering 2006 through 2014 with an ALS ICD-9 code and a minimum of 1 year of adjudicated claims history prior to ALS diagnosis were included in the frequency analyses. Patients from the full nationwide adjudicated claims database covering 2006 through 2014 with an ALS ICD-9 code and a minimum of 5 years of adjudicated claims history prior to ALS diagnosis were included in the disease progression analysis.

[118] This analysis utilized 2 data ranking methods: a frequency method and a mutual information (MI) method; the MI measure was used to quantify the statistical relevance of every feature in MarketScan® to a future ALS diagnosis in the US; the relative frequency of pertinent events was computed to rank the differentiating features

[119] In these analyses, patients from the full national data set were included (n=13,882).

[120] Features considered included diagnosis codes, procedure codes, medications, standard provider types, and standard care facility types.

[121] An ensembled suite of classifiers developed through machine learning techniques were applied to the MarketScan® claims database to optimize the selection and ranking of ALS diagnosis predictors.

[122] Diagnosis predictors were derived from the differentiating features selected by mutual information and ranked using machine learning techniques.

[123] Features were analyzed in combination in addition to individual features. Combinations of up to five of drugs, procedures and diagnosis. Combinations of same feature types (drug 1 + drug 2, procedure 1 + procedure 2) as well as multiple feature types (procedure + diagnosis)

[124] Diagnosis predictors were specifically looked for within the following time brackets: 3, 6, 9, 12, 18, 24, 36, 48, and 60 months before the initial ALS diagnosis.

[125] Regarding mutual information (MI) values of Feature 1-Feature 2 combinations in periods of 3 – 6 months, 6 – 9 months, 9 – 12 months and 12 – 18 months before the initial ALS diagnosis, top 20 MI values in each of these periods are shown in the following table.

[126]

Feature 1	Feature 2	Mutual Information (MI) Value of Feature 1–Feature 2 Combination				Number of Top 20 Appearances
		3–6 Months	6–9 Months	9–12 Months	12–18 Months	
Feature (1)	Feature (14)			0.00096	0.00137	2
Feature (1)	Feature (18)		0.00128			1
Feature (1)	Feature (30)	0.00321	0.00178	0.00105		3
Feature (2)	Feature (5)			0.00086		1
Feature (3)	Feature (5)	0.00462	0.00135	0.00088	0.00122	4
Feature (3)	Feature (6)	0.00437	0.00152	0.00109	0.00161	4
Feature (3)	Feature (18)	0.00326			0.00144	2
Feature (3)	Feature (31)	0.00383				1
Feature (4)	Feature (14)		0.00129			1
Feature (5)	Feature (2)			0.00086		1
Feature (5)	Feature (3)	0.00462	0.00135	0.00088	0.00122	4
Feature (5)	Feature (6)	0.00424	0.00172	0.00082	0.00129	4
Feature (5)	Feature (18)	0.00423	0.00160	0.00082		3
Feature (5)	Feature (20)				0.00124	1
Feature (5)	Feature (25)	0.00318		0.00087		2
Feature (5)	Feature (26)				0.00112	1
Feature (5)	Feature (31)	0.00356				1
Feature (6)	Feature (3)	0.00437	0.00152	0.00109	0.00161	4
Feature (6)	Feature (5)	0.00424	0.00172	0.00082	0.00129	4
Feature (6)	Feature (10)	0.00302				1
Feature (6)	Feature (13)			0.00078		1
Feature (6)	Feature (14)				0.00115	1
Feature (6)	Feature (16)				0.00113	1
Feature (6)	Feature (18)	0.00392	0.00148	0.00092	0.00127	4
Feature (6)	Feature (20)			0.00080		1
Feature (6)	Feature (24)	0.00340				1
Feature (6)	Feature (26)				0.00112	1
Feature (6)	Feature (31)	0.00383				1
Feature (7)	Feature (14)				0.00120	1
Feature (8)	Feature (14)		0.00133			1
Feature (9)	Feature (28)		0.00151	0.00092		2
Feature (10)	Feature (6)	0.00302				1
Feature (11)	Feature (13)	0.00304	0.00122			2
Feature (12)	Feature (14)				0.00145	1
Feature (13)	Feature (6)			0.00078		1
Feature (13)	Feature (11)	0.00304	0.00122			2
Feature (13)	Feature (16)		0.00133		0.00126	2
Feature (14)	Feature (1)			0.00096	0.00137	2
Feature (14)	Feature (4)		0.00129			1
Feature (14)	Feature (6)				0.00115	1

Feature (14)	Feature (7)				0.00120	1
Feature (14)	Feature (8)		0.00133			1
Feature (14)	Feature (12)				0.00145	1
Feature (14)	Feature (15)				0.00117	1
Feature (14)	Feature (18)	0.00402	0.00147		0.00167	3
Feature (14)	Feature (20)		0.00124			1
Feature (14)	Feature (22)	0.00365			0.00114	2
Feature (14)	Feature (27)		0.00130		0.00132	2
Feature (15)	Feature (14)				0.00117	1
Feature (15)	Feature (21)				0.00117	1
Feature (16)	Feature (6)				0.00113	1
Feature (16)	Feature (13)		0.00133		0.00126	2
Feature (17)	Feature (30)		0.00150	0.00094		2
Feature (18)	Feature (1)		0.00128			1
Feature (18)	Feature (3)	0.00326			0.00144	2
Feature (18)	Feature (5)	0.00423	0.00160	0.00082		3
Feature (18)	Feature (6)	0.00392	0.00148	0.00092	0.00127	4
Feature (18)	Feature (14)	0.00402	0.00147		0.00167	3
Feature (18)	Feature (19)				0.00113	1
Feature (18)	Feature (21)			0.00085		1
Feature (18)	Feature (22)	0.00466	0.00135	0.00091		3
Feature (18)	Feature (30)	0.00309	0.00121	0.00084		3
Feature (18)	Feature (31)	0.00392				1
Feature (18)	Feature (32)	0.00338		0.00088		2
Feature (19)	Feature (18)				0.00113	1
Feature (20)	Feature (5)				0.00124	1
Feature (20)	Feature (6)			0.00080		1
Feature (20)	Feature (14)		0.00124			1
Feature (21)	Feature (15)				0.00117	1
Feature (21)	Feature (18)			0.00085		1
Feature (21)	Feature (30)		0.00127	0.00082		2
Feature (22)	Feature (14)	0.00365			0.00114	2
Feature (22)	Feature (18)	0.00466	0.00135	0.00091		3
Feature (23)	Feature (30)		0.00188	0.00124		2
Feature (24)	Feature (6)	0.00340				1
Feature (25)	Feature (5)	0.00318		0.00087		2
Feature (26)	Feature (5)				0.00112	1
Feature (26)	Feature (6)				0.00112	1
Feature (27)	Feature (14)		0.00130		0.00132	2
Feature (28)	Feature (9)		0.00151	0.00092		2
Feature (29)	Feature (30)			0.00095		1
Feature (30)	Feature (1)	0.00321	0.00178	0.00105		3
Feature (30)	Feature (17)		0.00150	0.00094		2
Feature (30)	Feature (18)	0.00309	0.00121	0.00084		3
Feature (30)	Feature (21)		0.00127	0.00082		2
Feature (30)	Feature (23)		0.00188	0.00124		2
Feature (30)	Feature (29)			0.00095		1

Feature (31)	Feature (3)	0.00383				1
Feature (31)	Feature (5)	0.00356				1
Feature (31)	Feature (6)	0.00383				1
Feature (31)	Feature (18)	0.00392				1
Feature (32)	Feature (18)	0.00338		0.00088		2

[127] A numerical value in each cell indicates a mutual information (MI) value of a Feature 1 – Feature 2 combination. A hatched cell indicates a combination for which the MI value is not among the top 20.

[128] In the table above, a patient who has Feature 1 – Feature 2 combination is highly likely to be an ALS patient, and it is particularly effective to administer a medication containing 3-methyl-1-phenyl-2-pyrazolin-5-one to an ALS patient in an early stage of onset of the disease.

[129] Correspondence between Features (1) to (33) and Feature, code and code type in ICD-9 code, CPT code, or HCPCS code is shown below.

[130]

Feature		Code		Code Type
Feature (1)	Abnormality of gait	ICD-9	781.2	Diagnosis
Feature (2)	Aldolase	CPT	82085	Procedure
Feature (3)	Antinuclear antibodies (ANA);	CPT	86038	Procedure
Feature (4)	Cervical spondylosis without myelopathy	ICD-9	721.0	Diagnosis
Feature (5)	Creatine kinase (CK); (CPK); total	CPT	82550	Procedure
Feature (6)	Cyanocobalamin (Vitamin B-12);	CPT	82607	Procedure
Feature (7)	Degeneration of cervical intervertebral disc	ICD-9	722.4	Diagnosis
Feature (8)	Displacement of cervical intervertebral disc without myelopathy	ICD-9	722.0	Diagnosis
Feature (9)	Dysphagia; unspecified	ICD-9	787.20	Diagnosis
Feature (10)	Folic acid; serum	CPT	82746	Procedure
Feature (11)	Injection; gadolinium-based magnetic resonance contrast agent; not otherwise specified (nos); per ml	HCPCS	A9579	Procedure
Feature (12)	Magnetic resonance (eg; proton) imaging; brain (including brain stem); without contrast material	CPT	70551	Procedure
Feature (13)	Magnetic resonance (eg; proton) imaging; brain (including brain stem); without contrast material; followed by contrast material(s) and further sequences	CPT	70553	Procedure
Feature (14)	Magnetic resonance (eg; proton) imaging; spinal canal and contents; cervical; without contrast material	CPT	72141	Procedure
Feature (15)	Magnetic resonance (eg; proton) imaging; spinal canal and contents; lumbar; without contrast material	CPT	72148	Procedure

Feature (16)	Magnetic resonance (eg; proton) imaging; spinal canal and contents; without contrast material; followed by contrast material(s) and further sequences; cervical	CPT	72156	Procedure
Feature (17)	Manual therapy techniques (eg; mobilization/ manipulation; manual lymphatic drainage; manual traction); 1 or more regions; each 15 minutes	CPT	97140	Procedure
Feature (18)	Muscle weakness (generalized)	ICD-9	728.87	Diagnosis
Feature (19)	Needle electromyography; 1 extremity with or without related paraspinal areas	CPT	95860	Procedure
Feature (20)	Needle electromyography; 2 extremities with or without related paraspinal areas	CPT	95861	Procedure
Feature (21)	Other acquired deformities of ankle and foot	ICD-9	736.79	Diagnosis
Feature (22)	Other malaise and fatigue	ICD-9	780.79	Diagnosis
Feature (23)	Physical therapy evaluation	CPT	97001	Procedure
Feature (24)	Protein; electrophoretic fractionation and quantitation; serum	CPT	84165	Procedure
Feature (25)	Sedimentation rate; erythrocyte; automated	CPT	85652	Procedure
Feature (26)	Sedimentation rate; erythrocyte; non-automated	CPT	85651	Procedure
Feature (27)	Spinal stenosis in cervical region	ICD-9	723.0	Diagnosis
Feature (28)	Swallowing function; with cineradiography/videoradiography	CPT	74230	Procedure
Feature (29)	Therapeutic procedure; 1 or more areas; each 15 minutes; neuromuscular reeducation of movement; balance; coordination; kinesthetic sense; posture; and/or proprioception for sitting and/or standing activities	CPT	97112	Procedure
Feature (30)	Therapeutic procedure; 1 or more areas; each 15 minutes; therapeutic exercises to develop strength and endurance; range of motion and flexibility	CPT	97110	Procedure
Feature (31)	Thyroid stimulating hormone (TSH)	CPT	84443	Procedure
Feature (32)	Unspecified hereditary and idiopathic peripheral neuropathy	ICD-9	356.9	Diagnosis
Feature (33)	Immunofixation electrophoresis; serum	CPT	86334	Procedure

[131] -Top 20 two-Feature combinations in 3-6, 6-9, 9-12, and 12-18 month periods prior to diagnosis plotted in Feature-to-Feature heat maps (Figure 1 to 4). Block representations of mutual information (MI) values of the Feature combinations are plotted at the Feature intersections on grid, with larger and darker blocks representing higher MI values.

[132] Diagnostic labs, including antinuclear antibodies, creatine kinase, thyroid stimulating hormone, and cyanocobalamin (vitamin B-12), tend to cluster together

[133] Muscle weakness is prominent throughout, and seems to pair with different lab tests and imaging over time.

[134] Muscle weakness and malaise/fatigue are a strong pair of Features throughout the 18 months prior to diagnosis.

[135] Physical therapy is an important part of two-Feature combination

[136] TOOL #1: Patient or Physician Checklist

SYMPTOM OR EVENT	HAVE YOU EXPERIENCED THIS WITHIN THE PAST 3 YEARS (CHECK ALL THAT APPLY)
Fatigue or Muscle Weakness	
Non-traumatic Joint disorder, deformities of foot or ankles	
Connective Tissue Disorders	
Skin Disorders	
Nervous System Disorder	
Any change in speech	
Office visit to: Physical Therapy, Neurologist, orthopedic surgeon, gastroenterologist,or otolaryngologist visits	
Had an imaging procedure such as EMG or MRI	
Prescribed any of these medications: Riluzole, Baclofen Pyridostigmine, Anticonvulsants	

[137] How to use TOOL #1: When symptoms or events listed in the "SYMPTOM OR EVENT" column are experienced within the last 3 years, cells on the right side corresponding to all applicable items are checked.

[138] Interpretation: When a patient has experienced 4 or more of the 9 symptoms/events, the patient is highly likely to be an ALS patient, and it is particularly effective to administer a medication containing 3-methyl-1-phenyl-2-pyrazolin-5-one to the patient.

[139] TOOL #2: To be completed by patient or physician

			OPTIONAL INFORMATION TO COMPLETE	
	I HAVE EXPERIENCED	CHECK ALL THAT APPLY	How many months ago did you FIRST experience this symptom or event	Is this symptom or event persistent (YES or NO)
CATEGORY A	Fatigue or Muscle Weakness			
	Connective Tissue Disorder			
	Unusual increase in healthcare resource utilization (i.e., increase doctor visits, procedures (MRI, EMG) new diagnosis, prescriptions)			
	Nervous System Disorders			
	Skin Disorders			
CATEGORY B	Prescribed medications: Riluzole, Baclofen, Pyridostigine, Anticonvulsants			
	Labs: CK, Vit B 12, or ANA checked or monitored			
	Foot or Ankle deformity			
	Change in Speech			
	Skin Disorder			

[140] How to use TOOL #2: When a patient has experienced symptoms or events listed in the "I HAVE EXPERIENCED" column, cells in the "CHECK ALL THAT APPLY" column corresponding to all applicable items are checked. Optionally, additional information is written in the "How many months ago did you FIRST experience this symptom or event" column and the "Is this symptom or event persistent (YES or NO)" column.

[141] Interpretation: A patient who meets the following conditions is highly likely to be an ALS patient and it is particularly effective to administer a medication containing 3-methyl-1-phenyl-2-pyrazolin-5-one to the patient when:

- The patient have experience 3 or more of the 5 symptoms/events listed in Category A,

OR

- The patient have experienced 2 or more symptoms or events in Category A, PLUS 3 symptoms/events in Category B

[142] TOOL #3: To be completed by patient as part of medical history

	Check ALL of the timeframes that you experienced this 'event' in each of the timeframes below, during past								TOTAL
	0-3 months	3-6 months	6-9 months	9-12 months	12-18 months	18-24 months	24-36 months	36-48 months	ADD the total number of events across all timeframes
Fatigue or Muscle Weakness									
Ankle or Foot deformity									
Connective Tissue Disorder									
Nervous System Disorder									
Labs checked or monitored for CK, Vit B12, or ANA									
Imaging: MRI or EMG									
Unusually Higher Healthcare Utilization									
TOTAL NUMBER OF EVENTS									

[143] TOOL #3: Example

	Check ALL of the timeframes that you experienced this 'event' in each of the timeframes below, during past								TOTAL
	0-3 months	3-6 months	6-9 months	9-12 months	12-18 months	18-24 months	24-36 months	36-48 months	ADD the total number of events across all timeframes
Fatigue or Muscle Weakness	X	X	X	X		x	x	x	
Ankle or Foot deformity	X	X	X	X	x	X	x		
Connective Tissue Disorder	X	X	X	X	X				
Nervous System Disorder	X	X	X	x	X				
Labs checked or monitored for CK, Vit B12, or ANA	X	X	x					x	
Imaging: MRI or EMG	X								
Unusually Higher Healthcare Utilization	X	X							
TOTAL NUMBER OF EVENTS	7	6	5	4	3	2	2	2	

[144] How to use TOOL #3: When a patient has experienced events listed in the leftmost column in time periods of 0 – 3 months, 3 – 6 months, 6 – 9 months, 9 – 12 months, 12 – 18 months, 18 – 24 months, 24 – 36 months, and 36 – 48 months prior to using the TOOL #3, all cells of the applicable time periods are checked.

Interpretation:

[145] When the patient scored a 5 in any timeframe, or the patient's total is greater than 25, the patient is highly likely to be an ALS patient, and it is particularly effective to administer a medication containing 3-methyl-1-phenyl-2-pyrazolin-5-one to the patient.

[146] TOOL #4: Algorithm that can be uploaded into an Electronic Health Record database, derivation from TOOL#3

[147] Calculate risk potential for ALS diagnosis in the future. When the risk potential is > X, the patient is highly likely to be an ALS patient and it is particularly effective to administer a medication containing 3-methyl-1-phenyl-2-pyrazolin-5-one to the patient.

[148] Risk Potential = (Event: Fatigue or Muscle Weakness * number of timeframes event occurred) + (Event: Ankle or Foot deformity * number of timeframes event occurred) + (Event: Connective Tissue Disorder * number of timeframes event occurred) + (Event: Nervous System Disorder * number of timeframes event occurred) + (Event: Labs checked or monitored for CK, Vit B12, or ANA * number of timeframes event occurred) + (Event: Imaging: MRI or EMG * number of timeframes event occurred) + (Event: Unusually Higher Healthcare Utilization * number of timeframes event occurred)

- Assign a value of '1' if the event/symptom occurred. Assign a value of '0' if the event/symptom did not occur.
- Add value to equation to take into account combinatorial considerations
- Potential to weight the values pending the timeframe it occurred

[149]

	Check ALL of the timeframes that you experienced this 'event' in each of the timeframes below, during past							
	0-3 months	3-6 months	6-9 months	9-12 months	12-18 months	18-24 months	24-36 months	36-48 months
Fatigue or Muscle Weakness								
Ankle or Foot deformity								
Connective Tissue Disorder								
Nervous System Disorder								
Labs checked or monitored for CK, Vit B12, or ANA								
Imaging: MRI or EMG								
Unusually Higher Healthcare Utilization								
TOTAL NUMBER OF EVENTS								

[150] Interpretation: When the risk potential is > X, the patient is highly likely to be an ALS patient and it is particularly effective to administer a medication containing 3-methyl-1-phenyl-2-pyrazolin-5-one to the patient.

[151] A patient having a specific Feature is highly likely to be an ALS patient and it is particularly effective to administer a medication containing 3-methyl-1-phenyl-2-pyrazolin-5-one to the patient at an early stage

[152] According to an embodiment of the present invention, treating amyotrophic lateral sclerosis at an early stage or suppressing progress of amyotrophic lateral sclerosis at an early stage includes administering an effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or

a physiologically acceptable salt thereof to a patient who has at least two Features of identified Feature 1 to Feature 55. The identified Feature 1 to Feature 55 are selected from the following.

1. Abnormality of gait
2. Aldolase test
3. Antinuclear antibodies (ANA) test
4. Cervical spondylosis without myelopathy
5. Creatine kinase (CK) : (CPK) test
6. Cyanocobalamin (Vitamin B-12) test
7. Degeneration of cervical intervertebral disc
8. Displacement of cervical intervertebral disc without myelopathy
9. Dysphagia
10. Folic acid; serum test
11. Serum immunofixation electrophoresis test
12. Magnetic resonance imaging test
13. Manual therapy techniques
14. Muscle weakness
15. Needle electromyography
16. Acquired deformities of ankle and foot
17. Malaise and fatigue
18. Physical therapy evaluation
19. Serum protein electrophoretic fractionation and quantitation test
20. Erythrocyte sedimentation rate test
21. Spinal stenosis in cervical region
22. Swallowing function test
23. Therapeutic procedure for neuromuscular reeducation
24. Therapeutic procedure for therapeutic exercises

25. Thyroid stimulating hormone (TSH) test
26. Unspecified hereditary and idiopathic peripheral neuropathy
27. Nervous system disorders
28. Hereditary and degenerative nervous system conditions
29. Connective tissue disease
30. Non-traumatic joint disorders
31. Multiple sclerosis
32. Paraplegia
33. Paralysis
34. Other diagnostic nervous system procedures
35. Durable Medical Equipment (DME) and supplies
36. Physical therapy
37. Laryngoscopy
38. Spinal puncture
39. Treatment of speech
40. Riluzole
41. Baclofen
42. Pyridostigmine
43. Anticonvulsants
44. Diazepam
45. Hydrocodone
46. Propoxyphene
47. Sympathomimetic Agents
48. Glycopyrrolate
49. Prednisone
50. Pregabalin

51. Clonazepam

52. Tizanidine

53. Levodopa or Carbidopa

54. Quinine

55. Tolterodine

[153] In some embodiments, it is possible that a 14-day administration period and a 14-day drug holiday period are repeated, or an administration period of 10 days out of 14 days and a 14-day drug holiday period are repeated after an initial 14-day administration period followed by an initial 14-day drug holiday period. Preferably, administration periods and drug holiday periods are such that an administration period of 10 days out of 14 days and a 14-day drug holiday period are repeated after an initial 14-day administration period followed by an initial 14-day drug holiday period.

[154] In another embodiment, drug administration can be repeated daily without providing a drug holiday period.

[155] Preferably, symptoms caused by amyotrophic lateral sclerosis are decreased respiratory function, speech language impairment, swallowing disorder, or movement disorder of limbs.

[156] Preferably, in a time period from 60 months before initial administration of 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof to the patient to the initial administration, the patient meets at least two Features among the above Feature 1 to Feature 55. A more preferred time period is from 18 months before the initial administration to the initial administration.

[157] Further, an embodiment of the present invention includes a drug containing 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof as an active ingredient for treating or suppressing progress of amyotrophic lateral sclerosis. A patient receiving medication has at least two Features among identified Feature 1 to Feature 55.

[158] The identified Feature 1 to Feature 55 are selected from the following.

1. Abnormality of gait

2. Aldolase test

3. Antinuclear antibodies (ANA) test

4. Cervical spondylosis without myelopathy
5. Creatine kinase (CK) : (CPK) test
6. Cyanocobalamin (Vitamin B-12) test
7. Degeneration of cervical intervertebral disc
8. Displacement of cervical intervertebral disc without myelopathy
9. Dysphagia
10. Folic acid; serum test
11. Serum immunofixation electrophoresis test
12. Magnetic resonance imaging test
13. Manual therapy techniques
14. Muscle weakness
15. Needle electromyography
16. Acquired deformities of ankle and foot
17. Malaise and fatigue
18. Physical therapy evaluation
19. Serum protein electrophoretic fractionation and quantitation test
20. Erythrocyte sedimentation rate test
21. Spinal stenosis in cervical region
22. Swallowing function test
23. Therapeutic procedure for neuromuscular reeducation
24. Therapeutic procedure for therapeutic exercises
25. Thyroid stimulating hormone (TSH) test
26. Unspecified hereditary and idiopathic peripheral neuropathy
27. Nervous system disorders
28. Hereditary and degenerative nervous system conditions
29. Connective tissue disease

30. Non-traumatic joint disorders
31. Multiple sclerosis
32. Paraplegia
33. Paralysis
34. Other diagnostic nervous system procedures
35. Durable Medical Equipment (DME) and supplies
36. Physical therapy
37. Laryngoscopy
38. Spinal puncture
39. Treatment of speech
40. Riluzole
41. Baclofen
42. Pyridostigmine
43. Anticonvulsants
44. Diazepam
45. Hydrocodone
46. Propoxyphene
47. Sympathomimetic Agents
48. Glycopyrrolate
49. Prednisone
50. Pregabalin
51. Clonazepam
52. Tizanidine
53. Levodopa or Carbidopa
54. Quinine
55. Tolterodine

[159] Further, an embodiment of the present invention includes 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof for treating or suppressing progress of amyotrophic lateral sclerosis. A patient receiving medication has at least two Features among identified Feature 1 to Feature 55.

[160] The identified Feature 1 to Feature 55 are selected from the following.

1. Abnormality of gait
2. Aldolase test
3. Antinuclear antibodies (ANA) test
4. Cervical spondylosis without myelopathy
5. Creatine kinase (CK) : (CPK) test
6. Cyanocobalamin (Vitamin B-12) test
7. Degeneration of cervical intervertebral disc
8. Displacement of cervical intervertebral disc without myelopathy
9. Dysphagia
10. Folic acid; serum test
11. Serum immunofixation electrophoresis test
12. Magnetic resonance imaging test
13. Manual therapy techniques
14. Muscle weakness
15. Needle electromyography
16. Acquired deformities of ankle and foot
17. Malaise and fatigue
18. Physical therapy evaluation
19. Serum protein electrophoretic fractionation and quantitation test
20. Erythrocyte sedimentation rate test
21. Spinal stenosis in cervical region

22. Swallowing function test
23. Therapeutic procedure for neuromuscular reeducation
24. Therapeutic procedure for therapeutic exercises
25. Thyroid stimulating hormone (TSH) test
26. Unspecified hereditary and idiopathic peripheral neuropathy
27. Nervous system disorders
28. Hereditary and degenerative nervous system conditions
29. Connective tissue disease
30. Non-traumatic joint disorders
31. Multiple sclerosis
32. Paraplegia
33. Paralysis
34. Other diagnostic nervous system procedures
35. Durable Medical Equipment (DME) and supplies
36. Physical therapy
37. Laryngoscopy
38. Spinal puncture
39. Treatment of speech
40. Riluzole
41. Baclofen
42. Pyridostigmine
43. Anticonvulsants
44. Diazepam
45. Hydrocodone
46. Propoxyphene
47. Sympathomimetic Agents

48. Glycopyrrolate
49. Prednisone
50. Pregabalin
51. Clonazepam
52. Tizanidine
53. Levodopa or Carbidopa
54. Quinine
55. Tolterodine

[161] The embodiments of the present invention include a drug administration method and a drug useful for treating or suppressing progress of ALS or a symptom caused by ALS. Further, the drug administration method and the drug according to the embodiments of the present invention allow the drug to be administered to ALS patients at an early stage upon onset of ALS. Further, the drug administration method and the drug according to the embodiments of the present invention allow an ALS patient to be selected at an early stage upon onset of ALS and allow the drug to be administered to the patient, and allow a high therapeutic effect or a high disease progress suppression effect to be obtained.

[162] Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

CLAIMS

1. A method for treating amyotrophic lateral sclerosis, comprising:

administering an effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof to a patient who is in need thereof and meets at least two Features selected from Feature 1 to Feature 55,

wherein the Feature 1 to Feature 55 are

1. Abnormality of gait
2. Aldolase test
3. Antinuclear antibodies (ANA) test
4. Cervical spondylosis without myelopathy
5. Creatine kinase (CK) : (CPK) test
6. Cyanocobalamin (Vitamin B-12) test
7. Degeneration of cervical intervertebral disc
8. Displacement of cervical intervertebral disc without myelopathy
9. Dysphagia
10. Folic acid; serum test
11. Serum immunofixation electrophoresis test
12. Magnetic resonance imaging test
13. Manual therapy techniques
14. Muscle weakness
15. Needle electromyography
16. Acquired deformities of ankle and foot
17. Malaise and fatigue
18. Physical therapy evaluation
19. Serum protein electrophoretic fractionation and quantitation test
20. Erythrocyte sedimentation rate test

21. Spinal stenosis in cervical region
22. Swallowing function test
23. Therapeutic procedure for neuromuscular reeducation
24. Therapeutic procedure for therapeutic exercises
25. Thyroid stimulating hormone (TSH) test
26. Unspecified hereditary and idiopathic peripheral neuropathy
27. Nervous system disorders
28. Hereditary and degenerative nervous system conditions
29. Connective tissue disease
30. Non-traumatic joint disorders
31. Multiple sclerosis
32. Paraplegia
33. Paralysis
34. Other diagnostic nervous system procedures
35. Durable Medical Equipment (DME) and supplies
36. Physical therapy
37. Laryngoscopy
38. Spinal puncture
39. Treatment of speech
40. Riluzole
41. Baclofen
42. Pyridostigmine
43. Anticonvulsants
44. Diazepam
45. Hydrocodone
46. Propoxyphene

47. Sympathomimetic Agents

48. Glycopyrrolate

49. Prednisone

50. Pregabalin

51. Clonazepam

52. Tizanidine

53. Levodopa or Carbidopa

54. Quinine

55. Tolterodine

2. The method according to claim 1, wherein the patient further meets at least one additional Feature selected from a skin disorder, a change in speech, an office visit to a physical therapist, a neurologist, an orthopedic surgeon, a gastroenterologist, or an otolaryngologist, an unusual increase in healthcare resource utilization including increase in doctor visit, a procedure including MRI and EMG, a new diagnosis, and a prescription, and unusually higher healthcare utilization.

3. The method according to claim 1, wherein the patient meets at least one Pair of the Features selected from Pair 1 to Pair 46, and the Pair 1 to Pair 46 are

1. Feature (1) and Feature (14)
2. Feature (1) and Feature (18)
3. Feature (1) and Feature (30)
4. Feature (2) and Feature (5)
5. Feature (3) and Feature (5)
6. Feature (3) and Feature (6)
7. Feature (3) and Feature (18)
8. Feature (3) and Feature (31)

9. Feature (4) and Feature (14)
10. Feature (5) and Feature (6)
11. Feature (5) and Feature (18)
12. Feature (5) and Feature (20)
13. Feature (5) and Feature (25)
14. Feature (5) and Feature (26)
15. Feature (5) and Feature (31)
16. Feature (6) and Feature (10)
17. Feature (6) and Feature (13)
18. Feature (6) and Feature (14)
19. Feature (6) and Feature (16)
20. Feature (6) and Feature (18)
21. Feature (6) and Feature (20)
22. Feature (6) and Feature (24)
23. Feature (6) and Feature (26)
24. Feature (6) and Feature (31)
25. Feature (7) and Feature (14)
26. Feature (8) and Feature (14)
27. Feature (9) and Feature (28)
28. Feature (11) and Feature (13)
29. Feature (12) and Feature (14)
30. Feature (13) and Feature (16)
31. Feature (14) and Feature (15)
32. Feature (14) and Feature (18)
33. Feature (14) and Feature (20)
34. Feature (14) and Feature (22)

35. Feature (14) and Feature (27)

36. Feature (15) and Feature (21)

37. Feature (17) and Feature (30)

38. Feature (18) and Feature (19)

39. Feature (18) and Feature (21)

40. Feature (18) and Feature (22)

41. Feature (18) and Feature (30)

42. Feature (18) and Feature (31)

43. Feature (18) and Feature (32)

44. Feature (21) and Feature (30)

45. Feature (23) and Feature (30)

46. Feature (29) and Feature (30)

4. The method according to claim 1, wherein the patient meets at least two Features selected from the Feature 1 to the Feature 55 during a period between a first administration of the effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or the physiologically acceptable salt thereof to the patient and 120 months prior to the first administration.

5. The method according to claim 1, wherein the administering comprises repeating a 14-day administration period and a 14-day drug holiday period, or establishing an initial 14-day administration period and an initial 14-day drug holiday period and then repeating an administration period for 10 out of 14 days and a 14-day drug holiday period.

6. The method according to claim 1, wherein the administering comprises administering the effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or the physiologically acceptable salt thereof to the patient every day or near every day.

7. The method according to claim 1, further comprising:

selecting the patient who meets at least two Features selected from the Feature 1 to the Feature 55 prior to a first administration of the effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or the physiologically acceptable salt thereof to the patient.

8. A method for suppressing progress of amyotrophic lateral sclerosis, comprising:

administering an effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof to a patient who is in need thereof and meets at least two Features selected from Feature 1 to Feature 55,

wherein the Feature 1 to Feature 55 are

1. Abnormality of gait
2. Aldolase test
3. Antinuclear antibodies (ANA) test
4. Cervical spondylosis without myelopathy
5. Creatine kinase (CK) : (CPK) test
6. Cyanocobalamin (Vitamin B-12) test
7. Degeneration of cervical intervertebral disc
8. Displacement of cervical intervertebral disc without myelopathy
9. Dysphagia
10. Folic acid; serum test
11. Serum immunofixation electrophoresis test
12. Magnetic resonance imaging test
13. Manual therapy techniques
14. Muscle weakness
15. Needle electromyography
16. Acquired deformities of ankle and foot
17. Malaise and fatigue
18. Physical therapy evaluation

19. Serum protein electrophoretic fractionation and quantitation test
20. Erythrocyte sedimentation rate test
21. Spinal stenosis in cervical region
22. Swallowing function test
23. Therapeutic procedure for neuromuscular reeducation
24. Therapeutic procedure for therapeutic exercises
25. Thyroid stimulating hormone (TSH) test
26. Unspecified hereditary and idiopathic peripheral neuropathy
27. Nervous system disorders
28. Hereditary and degenerative nervous system conditions
29. Connective tissue disease
30. Non-traumatic joint disorders
31. Multiple sclerosis
32. Paraplegia
33. Paralysis
34. Other diagnostic nervous system procedures
35. Durable Medical Equipment (DME) and supplies
36. Physical therapy
37. Laryngoscopy
38. Spinal puncture
39. Treatment of speech
40. Riluzole
41. Baclofen
42. Pyridostigmine
43. Anticonvulsants
44. Diazepam

45. Hydrocodone

46. Propoxyphene

47. Sympathomimetic Agents

48. Glycopyrrolate

49. Prednisone

50. Pregabalin

51. Clonazepam

52. Tizanidine

53. Levodopa or Carbidopa

54. Quinine

55. Tolterodine

9. The method according to claim 8, wherein the patient further meets at least one additional Feature selected from a skin disorder, a change in speech, an office visit to a physical therapist, a neurologist, an orthopedic surgeon, a gastroenterologist, or an otolaryngologist, an unusual increase in healthcare resource utilization including increase in doctor visit, a procedure including MRI and EMG, a new diagnosis, and a prescription, and unusually higher healthcare utilization.

10. The method according to claim 8, wherein the patient meets at least one Pair of the Features selected from Pair 1 to Pair 46, and the Pair 1 to Pair 46 are

1. Feature (1) and Feature (14)

2. Feature (1) and Feature (18)

3. Feature (1) and Feature (30)

4. Feature (2) and Feature (5)

5. Feature (3) and Feature (5)

6. Feature (3) and Feature (6)

7. Feature (3) and Feature (18)
8. Feature (3) and Feature (31)
9. Feature (4) and Feature (14)
10. Feature (5) and Feature (6)
11. Feature (5) and Feature (18)
12. Feature (5) and Feature (20)
13. Feature (5) and Feature (25)
14. Feature (5) and Feature (26)
15. Feature (5) and Feature (31)
16. Feature (6) and Feature (10)
17. Feature (6) and Feature (13)
18. Feature (6) and Feature (14)
19. Feature (6) and Feature (16)
20. Feature (6) and Feature (18)
21. Feature (6) and Feature (20)
22. Feature (6) and Feature (24)
23. Feature (6) and Feature (26)
24. Feature (6) and Feature (31)
25. Feature (7) and Feature (14)
26. Feature (8) and Feature (14)
27. Feature (9) and Feature (28)
28. Feature (11) and Feature (13)
29. Feature (12) and Feature (14)
30. Feature (13) and Feature (16)
31. Feature (14) and Feature (15)
32. Feature (14) and Feature (18)

33. Feature (14) and Feature (20)

34. Feature (14) and Feature (22)

35. Feature (14) and Feature (27)

36. Feature (15) and Feature (21)

37. Feature (17) and Feature (30)

38. Feature (18) and Feature (19)

39. Feature (18) and Feature (21)

40. Feature (18) and Feature (22)

41. Feature (18) and Feature (30)

42. Feature (18) and Feature (31)

43. Feature (18) and Feature (32)

44. Feature (21) and Feature (30)

45. Feature (23) and Feature (30)

46. Feature (29) and Feature (30)

11. The method according to claim 8, wherein the patient meets at least two Features selected from the Feature 1 to the Feature 55 during a period between a first administration of the effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or the physiologically acceptable salt thereof to the patient and 120 months prior to the first administration.

12. The method according to claim 8, wherein the administering comprises repeating a 14-day administration period and a 14-day drug holiday period, or establishing an initial 14-day administration period and an initial 14-day drug holiday period and then repeating an administration period for 10 out of 14 days and a 14-day drug holiday period.

13. The method according to claim 8, wherein the administering comprises administering the effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or the physiologically acceptable salt thereof to the patient every day or near every day.

14. The method according to claim 8, further comprising:

selecting the patient who meets at least two Features selected from the Feature 1 to the Feature 55 prior to a first administration of the effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or the physiologically acceptable salt thereof to the patient.

15. A method for suppressing progress of amyotrophic lateral sclerosis, comprising:

administering an effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or a physiologically acceptable salt thereof to a patient who is in need thereof and meets at least two Features selected from Feature 1 to Feature 11,

wherein the Feature 1 to Feature 11 are

1. Malaise and fatigue, or Muscle weakness
2. Non-traumatic joint disorder or Acquired deformities of ankle and foot
3. Connective tissue disease
4. Skin disorder
5. Nervous system disorder
6. Any change in speech
7. Office visit to: Physical therapy, Neurologist, Orthopedic surgeon, Gastroenterologist, or Otolaryngologist
8. Magnetic resonance imaging test, or Needle electromyography
9. Riluzole, Baclofen, Pyridostigmine, Anticonvulsants
10. Unusual increase in healthcare resource utilization
11. Creatine kinase (CK) : (CPK) test, Cyanocobalamin (Vitamin B-12) test, or Antinuclear antibodies (ANA) test.

16. The method according to claim 15, further comprising:

selecting the patient who meets at least two Features selected from the Feature 1 to the Feature 11 prior to a first administration of the effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or the physiologically acceptable salt thereof to the patient.

17. The method according to claim15, wherein the patient meets at least two Features selected from the Feature 1 to the Feature 11 during a period between a first administration of the effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or the physiologically acceptable salt thereof to the patient and 120 months prior to the first administration.

18. The method according to claim 15, wherein the administering comprises repeating a 14-day administration period and a 14-day drug holiday period, or establishing an initial 14-day administration period and an initial 14-day drug holiday period and then repeating an administration period for 10 out of 14 days and a 14-day drug holiday period.

19. The method according to claim 15, wherein the administering comprises administering the effective amount of 3-methyl-1-phenyl-2-pyrazolin-5-one or the physiologically acceptable salt thereof to the patient every day or near every day.

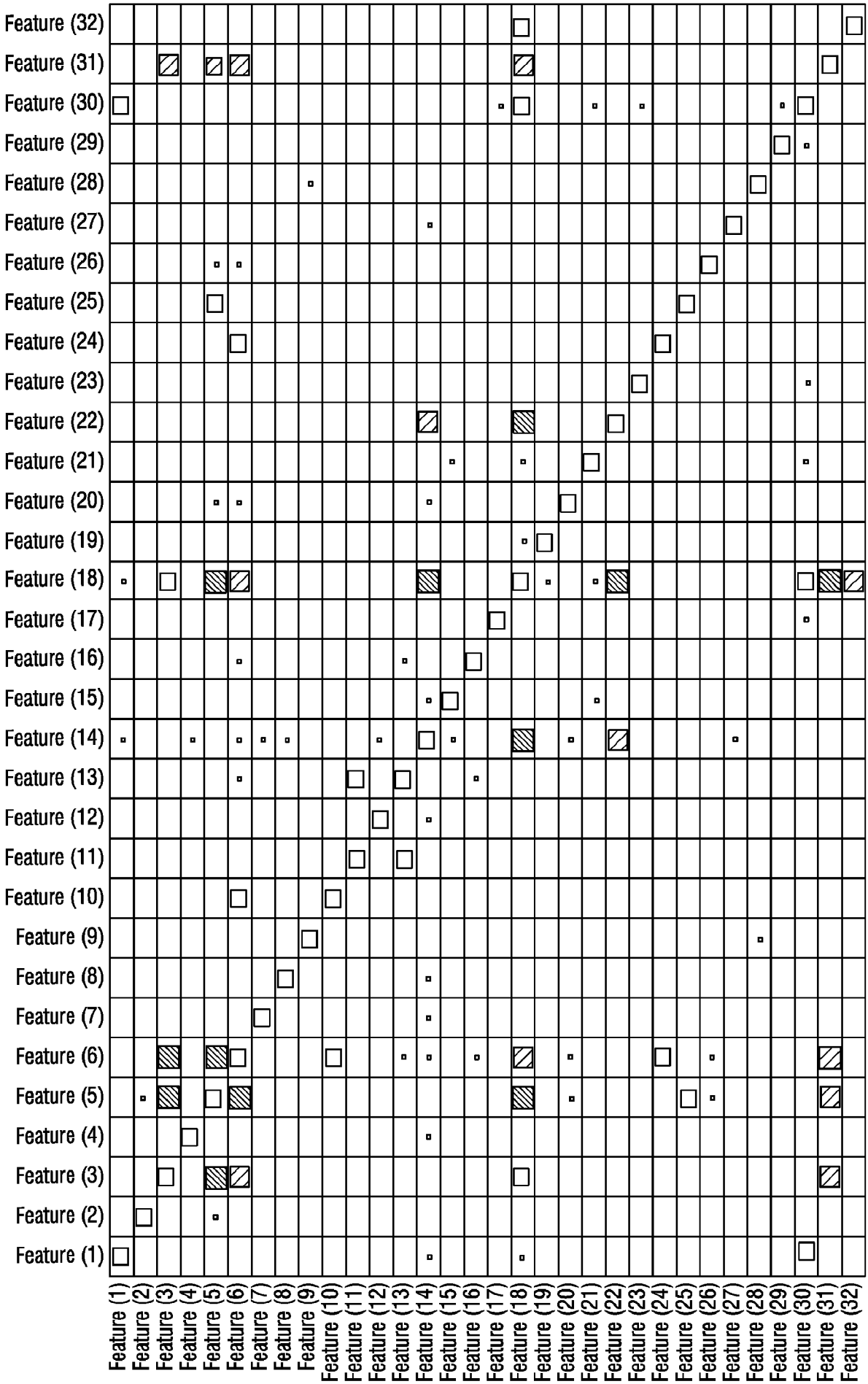

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FIG. 1

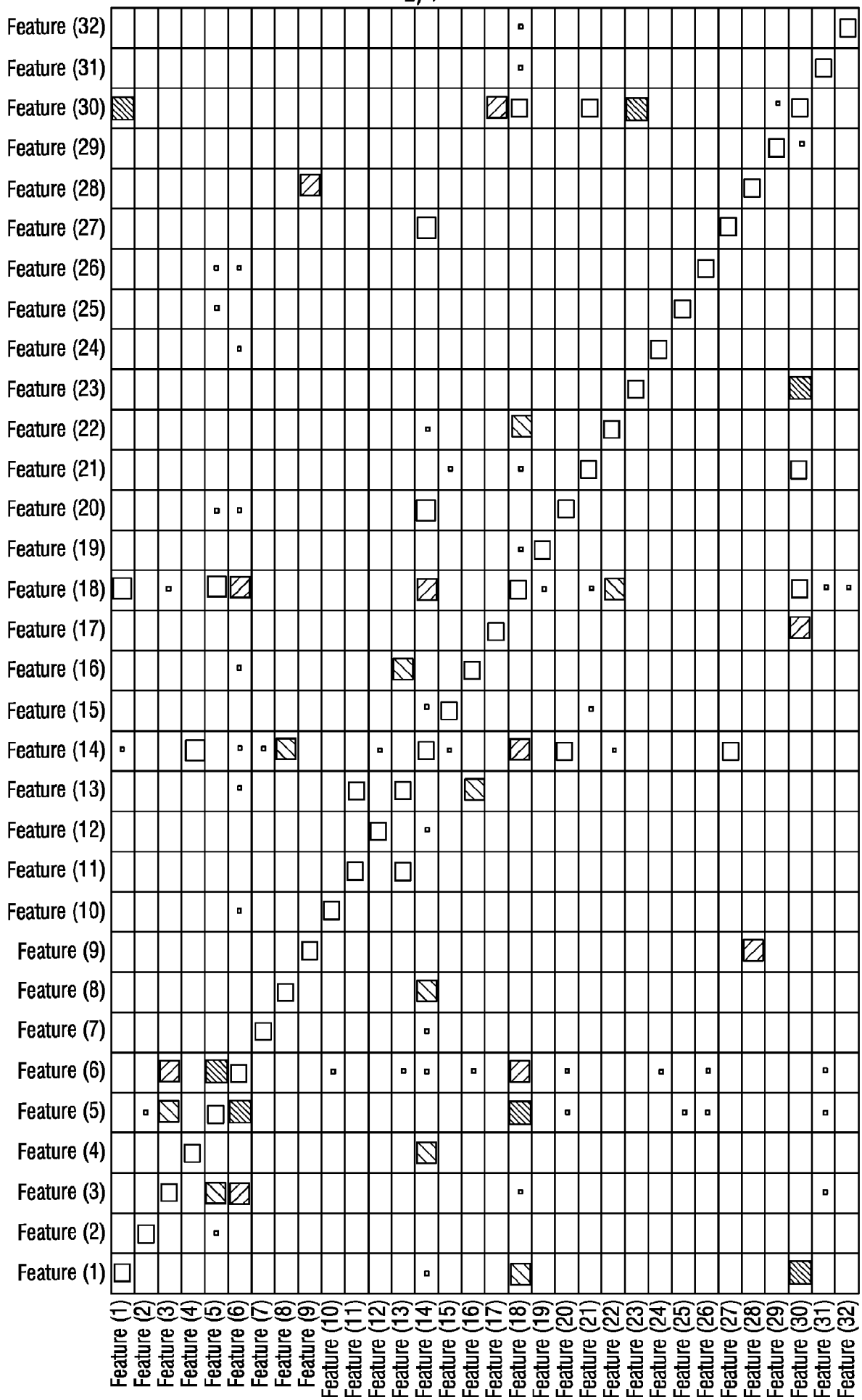
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FIG. 2

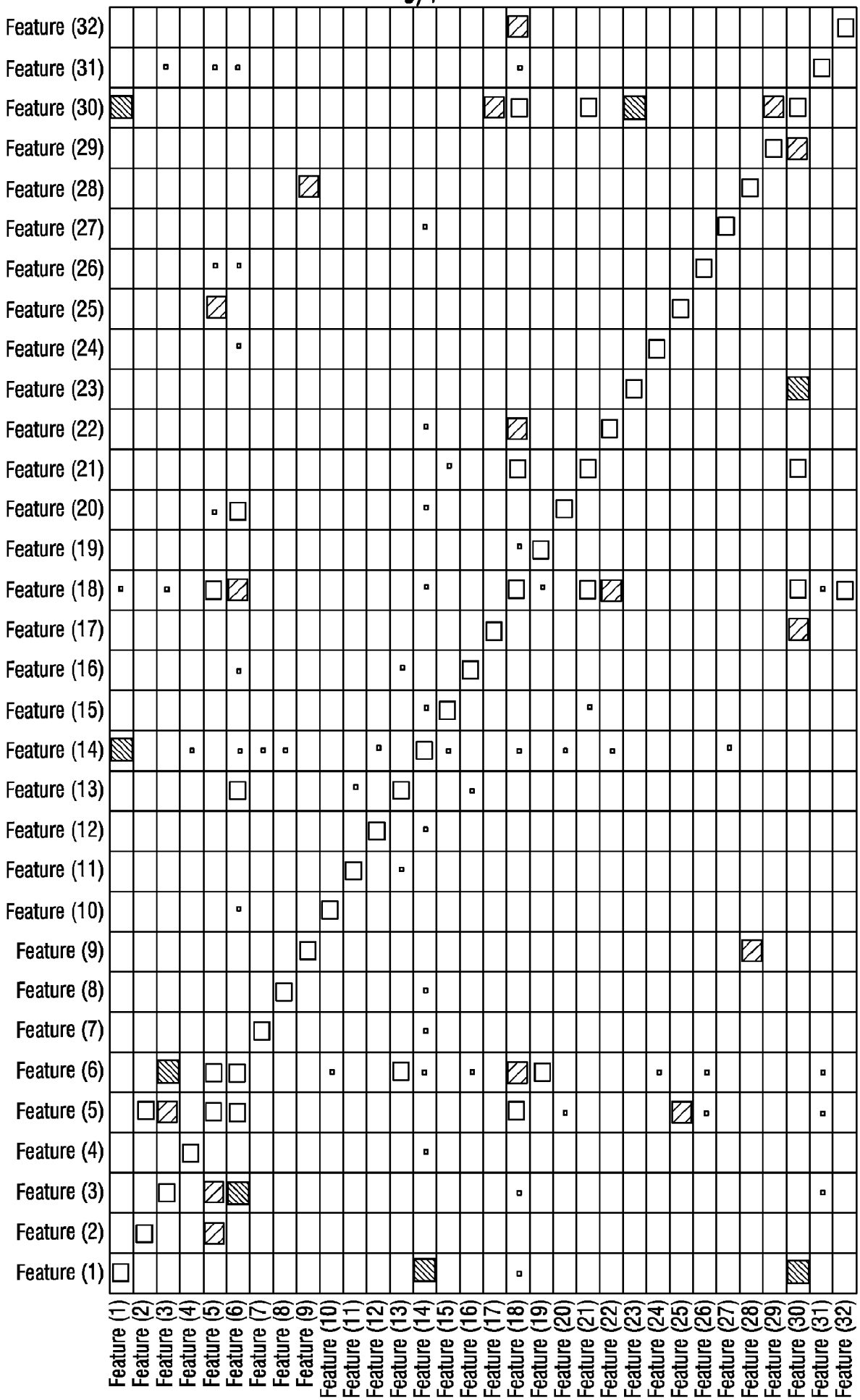
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FIG. 3

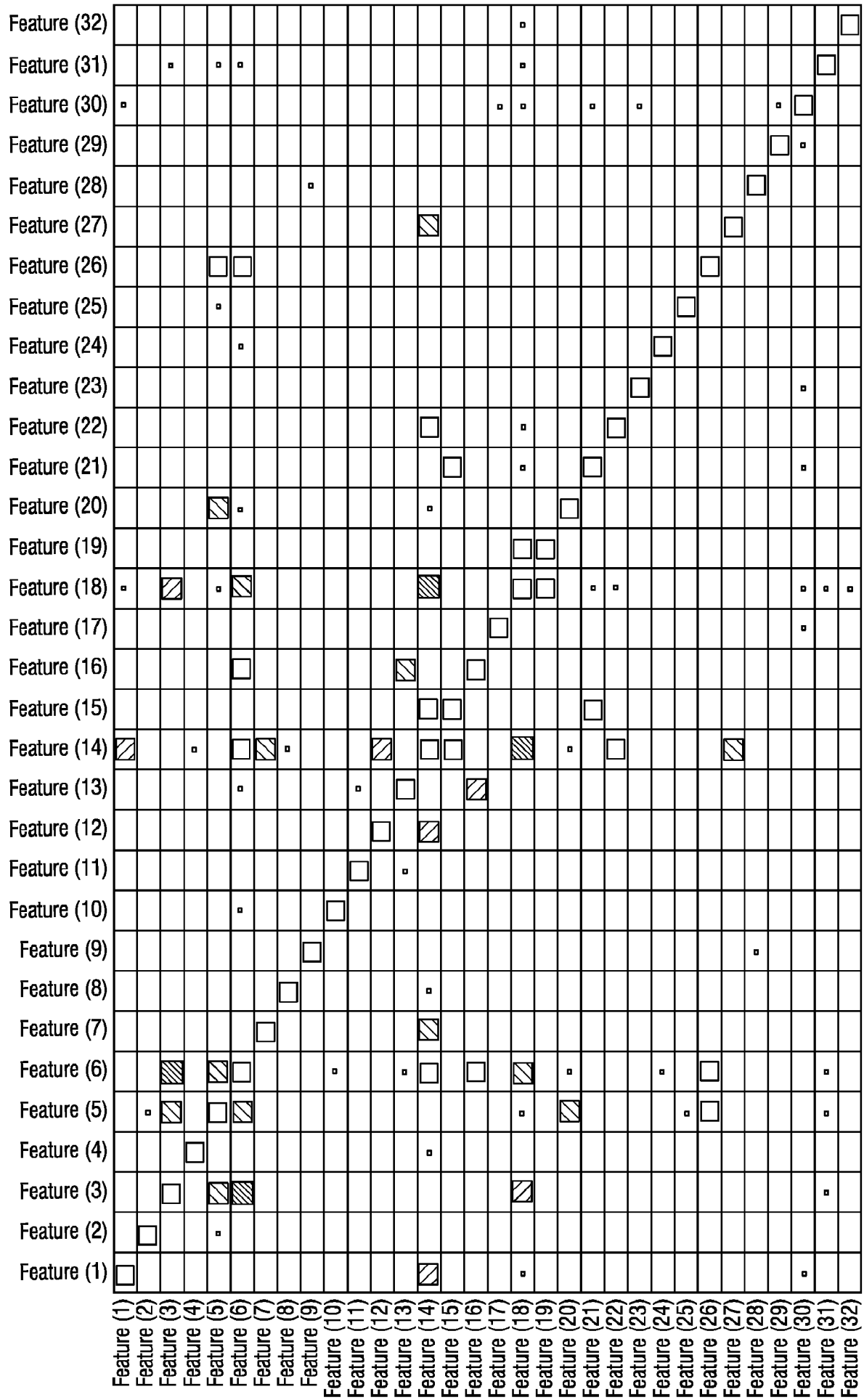
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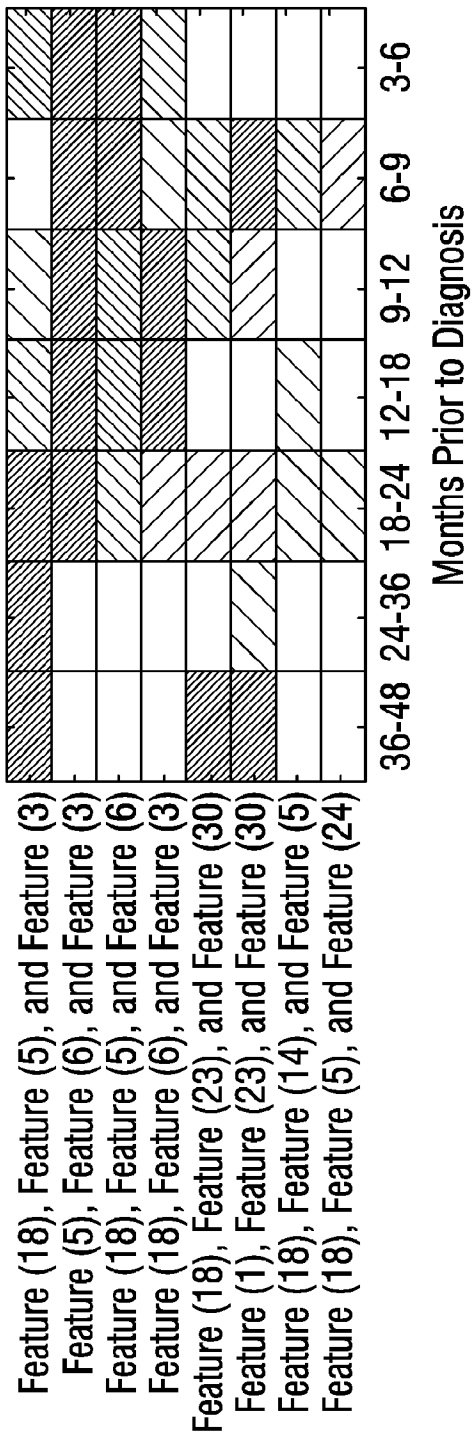
FIG. 4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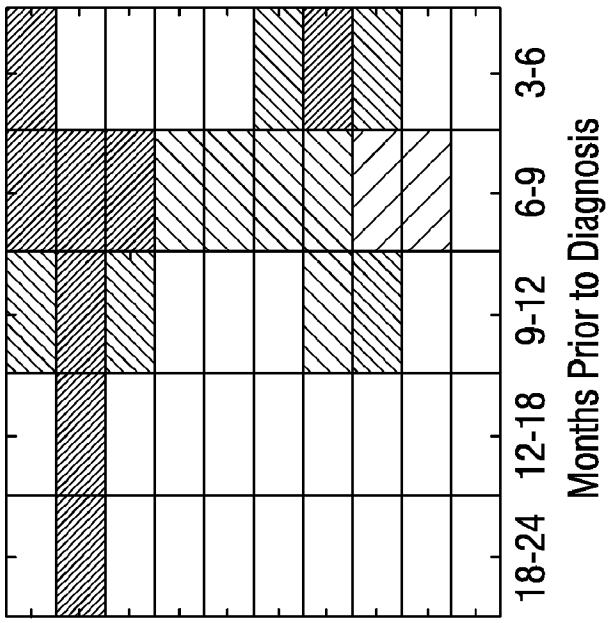
36-48 24-36 18-24 12-18 9-12 6-9 3-6
Months Prior to Diagnosis

FIG. 5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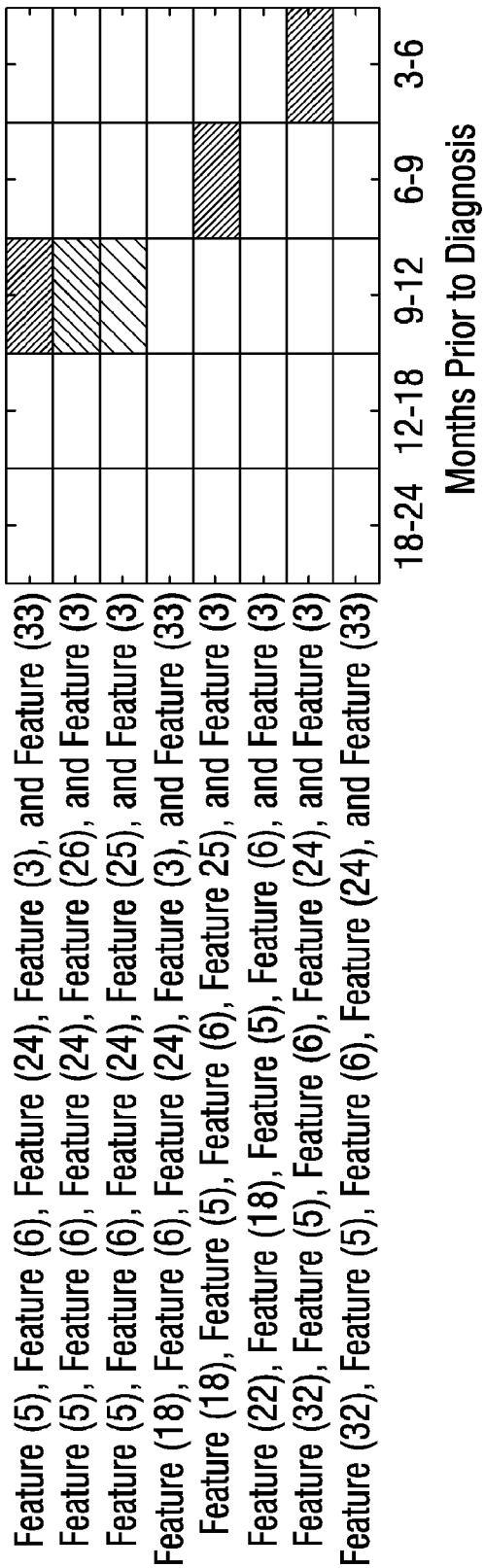
9-12
6-9
3-6
Months Prior to Diagnosis

FIG. 6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18-24 12-18 9-12 6-9 3-6
Months Prior to Diagnosis

FIG. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/020184

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4152 A61P25/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anonymous: "HIGHLIGHTS OF PRESCRIBING INFORMATION for Radicava", , 1 May 2017 (2017-05-01), XP055474759, Retrieved from the Internet: URL:https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209176lbl.pdf [retrieved on 2018-05-14] page 8	1-19

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[X] Further documents are listed in the continuation of Box C.

[ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 May 2018	17/07/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Büttner, Ulf

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial", LANCET NEUROLOGY, LANCET PUBLISHING GROUP, LONDON, GB, vol. 16, no. 7, 15 May 2017 (2017-05-15), pages 505-512, XP085075187, ISSN: 1474-4422, DOI: 10.1016/S1474-4422(17)30115-1 page 506, last paragraph	1-19
X	AKIMOTO MAKOTO: "Open-label 24-week extension study of edaravone (MCI-186) in amyotrophic lateral sclerosis", AMYOTROPHIC LATERAL SCLEROSIS AND FRONTOTEMPORAL DEGENERATION, vol. 18, no. sup1, 5 September 2017 (2017-09-05), pages 55-63, XP055474850, ISSN: 2167-8421, DOI: 10.1080/21678421.2017.1364269 page 56	1-19
A	BAKKER LEONHARD A ET AL: "Assessment of the factorial validity and reliability of the ALSFRS-R: a revision of its measurement model", JOURNAL OF NEUROLOGY - ZEITSCHRIFT FUER NEUROLOGIE, SPRINGER VERLAG, BERLIN, DE, vol. 264, no. 7, 12 June 2017 (2017-06-12) , pages 1413-1420, XP036272887, ISSN: 0340-5354, DOI: 10.1007/S00415-017-8538-4 [retrieved on 2017-06-12] table 2	1-19
A	BROOKS B R ET AL: "El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis", AMYOTHROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON DISORDERS, MARTIN DUNITZ, LONDON, GB, vol. 1, no. 5, 30 November 2000 (2000-11-30), pages 293-299, XP009505362, ISSN: 1466-0822, DOI: 10.1080/146608200300079536 table 1	1-19

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