

WHAT IS CLAIMED IS:

1 1. A method of differentially diagnosing Cushing's Disease from Ectopic
 2 Cushing's Syndrome in a patient with an established diagnosis of ACTH-dependent Cushing's
 3 Syndrome, the method comprising:
 4 (i) determining a baseline cortisol level and a baseline adrenocorticotrophic
 5 hormone (ACTH) level from one or more pretreatment samples taken from the patient;
 6 (ii) administering a glucocorticoid receptor antagonist (GRA) to the patient for a
 7 period of not less than 5 weeks and in an amount effective to raise ACTH levels in a healthy
 8 individual by at least two-fold;
 9 (iii) determining a second ACTH level and a second cortisol level from one or
 10 more second samples taken from the patient in step (ii) after 5 weeks of treatment with GRA;
 11 (iv) calculating a baseline ratio of cortisol to ACTH using the baseline levels of
 12 cortisol and ACTH, and calculating a GRA-exposed ratio of cortisol to ACTH using the second
 13 cortisol and ACTH levels; and,
 14 (v) diagnosing the patient as having Ectopic Cushing's Syndrome if the GRA-
 15 exposed ratio of cortisol to ACTH has decreased by greater than 50% compared to the baseline
 16 ratio, or diagnosing the patient as a having Cushing's Disease if the GRA-exposed ratio of
 17 cortisol to ACTH has increased by greater than 50% compared to the baseline ratio.

1 2. The method of claim 1 wherein the GRA is a non-steroidal GRA.

1 3. The method of claim 1 wherein the GRA is mifepristone, the one or more
 2 second samples are taken from the patient after mifepristone has been administered for a
 3 minimum of 6 weeks and on a daily basis equal to between 5-20 mg/kg of the patient.

1 4. The method of claim 1 wherein the GRA is selected from the group
 2 consisting of (R)-4a-(ethoxymethyl)-1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl)sulfonyl)-
 3 4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline; 6-((1r,4r)-4-phenylcyclohexyl)-5-(3-
 4 (trifluoromethyl)benzyl)pyrimidine-2,4(1H,3H)-dione; (R)-(1-(4-fluorophenyl)-6-((4-
 5 (trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-
 6 yl)(thiazol-2-yl)methanone; (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-
 7 4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-

8 yl)methanone; and ((4aR,8aS)-1-(4-fluorophenyl)-6-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-
9 4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-
10 yl)methanone.

1 5. The method of claim 1 where in the determining of the second ACTH and
2 cortisol levels is after administration of a GRA for a period of between 6 and 10 weeks.

1 6. The method of claim 1 where the pretreatment samples and second
2 samples are from saliva.

1 7. The method of claim 1 where the pretreatment samples and second
2 samples are from plasma and measured in $\mu\text{g/dl}$.

1 8. The method of claim 1 where the pretreatment samples and second
2 samples are from 24-hour urine collections.

1 9. A system for differentially diagnosing Cushing's Disease from Ectopic
2 Cushing's Syndrome in a patient with an established diagnosis of ACTH-dependent Cushing's
3 Syndrome, the system comprising:
4 a processor;
5 a memory coupled with the processor via an interconnect;
6 a communications interface coupled with the interconnect and adapted to receive
7 a first set of values and a second set of values corresponding to analytical results from samples
8 obtained from the patient;
9 a comparison engine communicatively coupled with the processor, wherein the
10 comparison engine is configured to:
11 receive the first set of values, which represent a set of pre-treatment values
12 corresponding to a baseline cortisol level and baseline adrenocorticotrophic hormone
13 (ACTH) or a baseline ratio of the baseline cortisol level to the baseline ACTH level;
14 receive the second set values, which represent a set of post-treatment
15 values corresponding to a cortisol level and an ACTH level or a ratio of the cortisol to the
16 ACTH level of the patient after a minimum of 5 weeks of treatment with a glucocorticoid

17 receptor antagonist (GRA) in an amount effective to raise cortisol levels in a healthy
18 individual by at least two-fold; and
19 compare the first set of values and the second set of values to determine a
20 differential relationship between the pre-treatment values and the post-treatment values;
21 and
22 an output module communicatively coupled with the processor and configured to
23 output an indication, wherein the indication represents a positive diagnosis for Ectopic Cushing's
24 Syndrome if the differential relationship represents a pre-determined decrease of the exposed-
25 GRA levels as compared to the baseline levels and the indication represents a positive diagnosis
26 for Cushing's Disease if the differential relationship represents a pre-determined increase of the
27 exposed-GRA levels as compared to the baseline levels.

1 10. The method of claim 15, wherein the output module is configured such
2 that the pre-determined decrease corresponding to a positive diagnosis for Ectopic Cushing's
3 Syndrome is a decrease of the exposed-GRA ratio of greater than 50% as compared to the
4 baseline ratio.

1 11. The method of claim 15, wherein the output module is configured such
2 that the pre-determined increase corresponding to a positive diagnosis for Cushing's Disease is
3 an increase of the exposed-GRA ratio of greater than 50% as compared to the baseline ratio.

1 12. The method of claim 15, wherein the comparison engine is further
2 configured such that comparing the first and second set of values comprises determining which
3 of the set of post-treatment values have changed from the set of pre-treatment values, and
4 wherein the output module is further configured output another indication to the
5 user representing which of the set of post-treatment values have changed from the set of pre-
6 treatment values, wherein the values are labeled in terms of post and pre-treatment values and
7 wherein an increase in the ratio of cortisol to ACTH predicts a positive diagnosis for Cushing's
8 Disease and wherein a decrease in the ratio of cortisol to ACTH predicts a positive diagnosis for
9 Ectopic Cushing's Syndrome.

1 13. The system of claim 9, wherein the output module communicates said
2 indication to the user in terms of a positive diagnosis of either Cushing's Disease or Ectopic
3 Cushing's Syndrome.

1 14. The system of claim 9 further comprising:
2 an analytic device for measuring cortisol and ACTH levels in patient samples
3 where the device is coupled to the processor in a manner permitting the output of the levels to the
4 processor as one or more values.

1 15. A method of differentially diagnosing Cushing's Disease from Ectopic
2 Cushing's Syndrome in a patient with an established diagnosis of ACTH-dependent Cushing's
3 Syndrome, the method comprising:
4 obtaining, with a computing system associated with a treating physician, a first set
5 of values representing a baseline cortisol level and a baseline ACTH level or a baseline ratio
6 between the baseline cortisol and ACTH levels corresponding to one or more pre-treatment
7 samples from the patient;
8 obtaining, with the computing system, a second set of values representing an
9 exposed-GRA cortisol level and an exposed-GRA ACTH level or a ratio between the exposed-
10 GRA cortisol and ACTH levels corresponding to one or more post-treatment samples from the
11 patient obtained after undergoing a GRA treatment according to a predetermined protocol;
12 determining, with the computing system, a differential relationship between the
13 first and second set of values; and
14 outputting to a user, with the computing system, an indication representing a
15 positive diagnosis for Ectopic Cushing's Syndrome, if the differential relationship represents a
16 pre-determined decrease of the exposed-GRA levels as compared to the baseline levels; and
17 outputting to a user, with the computing system, an indication representing a
18 positive diagnosis for Cushing's Disease, if the differential relationship represents a pre-
19 determined increase of the exposed-GRA levels as compared to the baseline levels.

1 16. The method of claim 15, wherein the pre-determined treatment protocol
2 includes administration of GRA to the patient for a minimum of five weeks in an amount
3 effective to raise ACTH and cortisol levels in a healthy individual by at least two-fold.

1 17. The method of claim 15, wherein an indication representing a positive
2 diagnosis for Ectopic Cushing's Syndrome is output if the pre-determined decrease corresponds
3 to a decrease of the exposed-GRA ratio of greater than 50% as compared to the baseline ratio.

1 18. The method of claim 15, wherein an indication representing a positive
2 diagnosis for Cushing's Disease is output, if the pre-determined increase corresponds to an
3 increase of the exposed-GRA ratio of greater than 50% as compared to the baseline ratio.

1 19. The method of claim 15, wherein obtaining the baseline ratio comprises
2 receiving, with the computing system, each of a baseline cortisol level and a baseline ACTH
3 level and determining the baseline ratio therefrom.

1 20. The method of claim 15, wherein obtaining the first set of values
2 comprises storing, in a memory of the computing system, the first set of values designated as
3 corresponding to baseline levels of the patient and
4 obtaining the second set of values comprises storing the second set of values, in
5 the memory, designated as corresponding to exposed-GRA levels of the patient.

1 21. The method of claim 15, wherein obtaining the baseline ratio comprises
2 receiving, with the computing system, each of a baseline cortisol level and a baseline ACTH
3 level and determining the baseline ratio therefrom.

1 22. The method of claim 15, wherein obtaining the first and second set of
2 values comprises accessing the first and second set of values remotely through a server of a
3 medical facility or laboratory associated with the patient.

1 23. The method of claim 15, wherein the percentage is 50% of the baseline
2 ratio for each of the pre-determined increase and pre-determined decrease.

1 24. The method of claim 16, wherein the GRA is mifepristone.

1

1 25. A method of concurrently treating Cushing's Syndrome and differentially
 2 diagnosing Cushing's Disease from Ectopic Cushing's Syndrome in a patient with an established
 3 diagnosis of ACTH-dependent Cushing's Syndrome, the method comprising:
 4 (i) determining a baseline cortisol level and a baseline adrenocorticotrophic
 5 hormone (ACTH) level from one or more pretreatment samples taken from the patient;
 6 (ii) administering a glucocorticoid receptor antagonist (GRA) effective to treat
 7 Cushing's Syndrome in the patient, thereby treating Cushing's Syndrome;
 8 (iii) continuing said treatment of Cushing's Syndrome by administering said GRA
 9 to the patient for a period of not less than 5 weeks and in an amount effective to raise ACTH and
 10 cortisol levels in a healthy individual by at least two fold;
 11 (iv) determining a second ACTH level and a second cortisol level from one or
 12 more second samples taken from the patient in step (iii);
 13 (v) calculating a baseline ratio of cortisol to ACTH ("baseline C:A ratio") using
 14 the baseline levels of cortisol and ACTH, and calculating a GRA-exposed ratio of cortisol to
 15 ACTH ("GRA-exposed C:A ratio") using the second cortisol and ACTH levels; and,
 16 (vi) diagnosing the patient as having Ectopic Cushing's Syndrome if the GRA-
 17 exposed ratio of cortisol to ACTH has decreased by greater than 50% compared to the baseline
 18 ratio, or diagnosing the patient as having Cushing's Disease if the GRA-exposed ratio of
 19 cortisol to ACTH has increased by greater than 50% compared to the baseline ratio.

1 26. The method of claim 25 wherein the GRA is a non-steroidal GRA.

1 27. The method of claim 25 wherein the GRA is mifepristone, the one or more
 2 second samples are taken from the patient after mifepristone has been administered for a
 3 minimum of 6 weeks and on a daily basis equal to between 5-20 mg/kg of the patient.

1 28. The method of claim 25 wherein the GRA is selected from the group
 2 consisting of (R)-4a-(ethoxymethyl)-1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl)sulfonyl)-
 3 4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline; 6-((1r,4r)-4-phenylcyclohexyl)-5-(3-
 4 (trifluoromethyl)benzyl)pyrimidine-2,4(1H,3H)-dione; (R)-(1-(4-fluorophenyl)-6-((4-
 5 (trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-
 6 yl)(thiazol-2-yl)methanone; (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-

7 4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-
8 yl)methanone; and ((4aR,8aS)-1-(4-fluorophenyl)-6-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-
9 4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-
10 yl)methanone..

1 29. The method of claim 25 where in the determining of the second ACTH
2 and cortisol levels is after administration of a GRA for a period of between 6 and 10 weeks.

1 30. The method of claim 25 where the pretreatment samples and second
2 samples are from saliva.

1 31. The method of claim 25 where the pretreatment samples and second
2 samples are from plasma and measured in µg/dl.

1 32. The method of claim 25 where the pretreatment samples and second
2 samples are from 24-hour urine collections.

1 33. A method of concurrently treating Cushing's Syndrome and differentially
2 diagnosing Cushing's Disease from Ectopic Cushing's Syndrome in a patient with an established
3 diagnosis of ACTH-dependent Cushing's Syndrome, the method comprising:
4 obtaining, with a computing system associated with a treating physician, a first set
5 of values representing a baseline cortisol level and a baseline ACTH level or a baseline ratio
6 between the baseline cortisol and ACTH levels corresponding to one or more pre-treatment
7 samples from the patient; then
8 administering a glucocorticoid receptor antagonist (GRA) effective to treat
9 Cushing's Syndrome in the patient, thereby treating Cushing's Syndrome; then
10 obtaining, with the computing system, a second set of values representing an
11 exposed-GRA cortisol level and an exposed-GRA ACTH level or a ratio between the exposed-
12 GRA cortisol and ACTH levels corresponding to one or more post-treatment samples from the
13 patient obtained after undergoing a GRA treatment according to a predetermined protocol;
14 determining, with the computing system, a differential relationship between the
15 first and second set of values; and

16 outputting to a user, with the computing system, an indication representing a
17 positive diagnosis for Ectopic Cushing's Syndrome, if the differential relationship represents a
18 pre-determined decrease of the exposed-GRA levels as compared to the baseline levels; and
19 outputting to a user, with the computing system, an indication representing a
20 positive diagnosis for Cushing's Disease, if the differential relationship represents a pre-
21 determined increase of the exposed-GRA levels as compared to the baseline levels.

1 34. The method of claim 33, wherein the pre-determined treatment protocol
2 includes administration of GRA to the patient for a minimum of five weeks in an amount
3 effective to raise ACTH and cortisol levels in a healthy individual by at least two-fold.

1 35. The method of claim 33, wherein an indication representing a positive
2 diagnosis for Ectopic Cushing's Syndrome is output if the pre-determined decrease corresponds
3 to a decrease of the exposed-GRA ratio of greater than 50% as compared to the baseline ratio,
4 wherein said exposed-GRA ratio comprises a ratio between the exposed-GRA cortisol and
5 ACTH levels corresponding to one or more post-treatment samples from the patient obtained
6 after undergoing a GRA treatment according to a predetermined protocol.

1 36. The method of claim 33, wherein an indication representing a positive
2 diagnosis for Cushing's Disease is output, if the pre-determined increase corresponds to an
3 increase of the exposed-GRA ratio of greater than 50% as compared to the baseline ratio,
4 wherein said exposed-GRA ratio comprises a ratio between the exposed-GRA cortisol and
5 ACTH levels corresponding to one or more post-treatment samples from the patient obtained
6 after undergoing a GRA treatment according to a predetermined protocol.

1 37. The method of claim 33, wherein obtaining the baseline ratio comprises
2 receiving, with the computing system, each of a baseline cortisol level and a baseline ACTH
3 level and determining the baseline ratio therefrom.

1 38. The method of claim 33, wherein obtaining the first set of values
2 comprises storing, in a memory of the computing system, the first set of values designated as
3 corresponding to baseline levels of the patient and

4 obtaining the second set of values comprises storing the second set of values, in
5 the memory, designated as corresponding to exposed-GRA levels of the patient.

1 39. The method of claim 33, wherein obtaining the baseline ratio comprises
2 receiving, with the computing system, each of a baseline cortisol level and a baseline ACTH
3 level and determining the baseline ratio therefrom.

1 40. The method of claim 33, wherein obtaining the first and second set of
2 values comprises accessing the first and second set of values remotely through a server of a
3 medical facility or laboratory associated with the patient.

1 41. The method of claim 33, wherein the percentage is 50% of the baseline
2 ratio for each of the pre-determined increase and pre-determined decrease.

1