a) measuring a first ~~amount,~~ or activity of 51 kDa FK506 binding protein (FKBP5 protein) ~~or a first expression level of a gene encoding FKBP5 protein~~ in a first sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring FKBP5 binding activity by measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the first sample comprises primary cells; and

ii) the first sample is obtained before the GRA is administered to the subject;

b) measuring a second ~~amount or~~ activity of FKBP5 protein ~~or a second expression level of a gene encoding FKBP5 protein~~ in a second sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the second sample comprises primary cells; and

ii) the second sample is obtained after the GRA is administered to the subject; and

c) comparing the first and second ~~amounts,~~ activities, ~~or expression levels,~~ wherein a reduction in the ~~amount or~~ activity of FKBP5 protein ~~or a reduction in the expression level of the gene encoding FKBP5 protein~~ in the second sample indicates the biochemical response to the GRA.

~~**[0003b]** In another aspect of the present disclosure, there is provided an in vitro method for diagnosing Cushing's syndrome in a human subject, the method comprising:~~

~~a) measuring an amount, or activity of 51 kDa FK506 binding protein (FKBP5 protein) or an expression level of a gene encoding FKBP5 protein in a sample obtained from the subject, wherein the sample comprises primary cells; and~~

~~b) identifying the subject as likely to be suffering from Cushing's syndrome when the amount, activity or expression level is high relative to a control.~~

[0003~~c~~b] In yet another aspect of the present disclosure, there is provided an in vitro method for assessing a biochemical response in a human subject to administering to the subject a medical or surgical therapy for treatment of hypercortisolemia, the method comprising:

a) measuring a first ~~amount, or~~ activity of 51 kDa FK506 binding protein (FKBP5 protein) ~~or a first expression level of a gene encoding FKBP5 protein~~ in a first sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring FKBP5 binding activity by measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the first sample comprises primary cells; and

ii) the first sample is obtained before administering the medical or surgical therapy for treatment of hypercortisolemia to the subject;

b) measuring a second ~~amount or~~ activity of FKBP5 protein ~~or a second expression level of a gene encoding FKBP5 protein~~ in a second sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the second sample comprises primary cells; and

ii) the second sample is obtained after the medical or surgical therapy for treatment of hypercortisolemia is administered to the subject; and

c) comparing the first and second amounts, activities, or expression levels,

wherein a reduction in the ~~amount or~~ activity of FKBP5 protein ~~or a reduction in the expression level of the gene encoding FKBP5 protein~~ in the second sample indicates the biochemical response to the medical or surgical therapy for treatment of hypercortisolemia.

[0004] The present disclosure provides a method for assessing a clinical or biochemical response to a glucocorticoid receptor antagonist (GRA) in a human subject, the method comprising: a) measuring a first amount, or activity of 51 kDa FK506 binding protein

WHAT IS CLAIMED IS:

1. An in vitro method for assessing a biochemical response to a glucocorticoid receptor antagonist (GRA) in a human subject, the method comprising:

a) measuring a first ~~amount, or~~ activity of 51 kDa FK506 binding protein (FKBP5 protein) ~~or a first expression level of a gene encoding FKBP5 protein~~ in a first sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring FKBP5 binding activity by measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the first sample comprises primary cells; and

ii) the first sample is obtained before the GRA is administered to the subject;

b) measuring a second ~~amount or~~ activity of FKBP5 protein ~~or a second expression level of a gene encoding FKBP5 protein~~ in a second sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the second sample comprises primary cells; and

ii) the second sample is obtained after the GRA is administered to the subject; and

c) comparing the first and second ~~amounts,~~ activities, ~~or expression levels,~~ wherein a reduction in the ~~amount or~~ activity of FKBP5 protein ~~or a reduction in the expression level of the gene encoding FKBP5 protein~~ in the second sample indicates the biochemical response to the GRA.

2. The in vitro method of claim 1, wherein ~~one or more of i)~~ the first sample is obtained prior to administering multiple doses of GRA to the subject, and the second sample is obtained after administering the multiple doses of GRA to the subject~~; ii) the measuring of a) and/or b) comprises quantitating an amount of mRNA encoding FKBP5 protein in the sample; iii) the measuring of a) and/or b) comprises quantitating the amount of FKBP5 protein in the sample; or iv) the measuring comprises quantitating the amount of FKBP5 protein activity in the sample~~.

~~3. The in vitro method of claim 1, wherein the quantitating the amount of FKBP5 protein activity in the sample comprises measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample.~~

~~4. The in vitro method of claim 1, wherein the quantitating the amount of FKBP5 protein activity in the sample comprises measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample.~~

~~5~~3. The in vitro method of claim 1 or 2, wherein the GRA administered to the subject comprises mifepristone.

~~6~~4. The in vitro method of claim 1 or 2, wherein the GRA administered to the subject is not mifepristone.

~~7~~5. The in vitro method of claim ~~6~~4, wherein the GRA administered to the subject comprises a heteroaryl-ketone GRA.

~~8~~6. The in vitro method of any of claims 1 to ~~7~~5, wherein the first or second samples comprise whole blood, or a fraction thereof, or wherein the first or second samples comprise nasal epithelial scraping samples, or wherein the first and second samples comprise whole blood, or a fraction thereof.

~~9~~7. The in vitro method of any of claims 1 to ~~8~~6, wherein the patient a) is in need of administration of the glucocorticoid receptor antagonist (GRA); b) has elevated levels of cortisol; or c) has cancer and the first and second samples comprise tumor cells.

~~10~~8. The in vitro method of claim 1, wherein the first and second samples comprise whole blood, or a fraction thereof.

~~11~~9. The in vitro method of any of claims 1 to ~~10~~8, wherein the method comprises administering an increased amount of GRA to the subject in the absence of a detected reduction in the

~~amount or~~ activity of FKBP5 protein ~~or a detected reduction in the expression level of the gene encoding FKBP5 protein~~ in the second sample.

~~12. An in vitro method for diagnosing Cushing's syndrome in a human subject, the method comprising:~~

~~a) measuring an amount, or activity of 51 kDa FK506 binding protein (FKBP5 protein) or an expression level of a gene encoding FKBP5 protein in a sample obtained from the subject, wherein the sample comprises primary cells; and~~

~~b) identifying the subject as likely to be suffering from Cushing's syndrome when the amount, activity or expression level is high relative to a control.~~

~~13. The in vitro method of claim 12, wherein the measuring comprises quantitating an amount of mRNA encoding FKBP5 protein in the primary cells of the sample.~~

~~14. The in vitro method of claim 12, wherein the measuring comprises a) quantitating the amount of FKBP5 protein in the primary cells of the sample, or b) quantitating the FKBP5 protein activity in the primary cells of the sample.~~

~~15. The in vitro method of claim 12, 13, or 14, wherein the quantitating the FKBP5 protein activity in the primary cells of the sample comprises quantitating FKBP5 protein peptidyl-prolyl cis-trans isomerase activity in the primary cells of the sample.~~

~~16. The in vitro method of claim 12, 13, or 14, wherein the quantitating the FKBP5 protein activity in the primary cells of the sample comprises quantitating the amount of FKBP5 protein bound to GR in the primary cells of the sample.~~

~~17. The in vitro method of any of claims 12, 13, or 14, wherein the sample obtained from the subject comprises whole blood, or a fraction thereof, and optionally wherein the subject has undergone transsphenoidal surgery before the sample is obtained from the subject.~~

~~18. The in vitro method of any of claims 12 to 17, wherein the method comprises administering a treatment for Cushing's syndrome when the amount or activity of FKBP5 protein or the expression level of the gene encoding FKBP5 protein is high relative to a control and optionally,~~

~~wherein the administering the treatment for Cushing's syndrome comprises administering to the subject a glucocorticoid receptor antagonist (GRA).~~

~~19~~10. An in vitro method for assessing a biochemical response in a human subject to administering to the subject a medical or surgical therapy for treatment of hypercortisolemia, the method comprising:

a) measuring a first ~~amount, or~~ activity of 51 kDa FK506 binding protein (FKBP5 protein) ~~or a first expression level of a gene encoding FKBP5 protein~~ in a first sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring FKBP5 binding activity by measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the first sample comprises primary cells; and

ii) the first sample is obtained before administering the medical or surgical therapy for treatment of hypercortisolemia to the subject;

b) measuring a second ~~amount or~~ activity of FKBP5 protein ~~or a second expression level of a gene encoding FKBP5 protein~~ in a second sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the second sample comprises primary cells; and

ii) the second sample is obtained after the medical or surgical therapy for treatment of hypercortisolemia is administered to the subject; and

c) comparing the first and second amounts, activities, or expression levels,

wherein a reduction in the ~~amount or~~ activity of FKBP5 protein ~~or a reduction in the expression level of the gene encoding FKBP5 protein~~ in the second sample indicates the biochemical response to the medical or surgical therapy for treatment of hypercortisolemia.

~~20~~11. The in vitro method of claim ~~19~~10, wherein the medical or surgical therapy for treatment of hypercortisolemia is selected from the group consisting of: inhibition of steroidogenesis, administration of an ACTH modulator, GRA administration, transsphenoidal surgery, repeat transsphenoidal surgery, unilateral adrenalectomy, bilateral adrenalectomy, radiotherapy, resection of a non-pituitary ACTH-secreting tumor, treatment

with a peptide receptor radionuclide therapy, and combinations thereof, ~~and optionally, a) wherein the inhibition of steroidogenesis comprises administration of ketoconazole, levoketoconazole, metyrapone, LCI699, mitotane, aminoglutethimide, etomidate, or a combination thereof; b) wherein the administration of an ACTH modulator comprises administration of a dopamine agonist, somatostatin, a somatostatin analog, retinoic acid, R-roscovitine, or a combination thereof; c) wherein the dopamine agonist is selected from the group consisting of bromocriptine and cabergoline; and d)~~ wherein the method comprises administering an additional medical or surgical therapy for treatment of hypercortisolemia in an absence of a detected reduction in the amount or activity of FKBP5 protein or reduction in the expression level of the gene encoding FKBP5 protein in the second sample.