

SUMMARY

[0006] The methods described herein were developed to provide a means for predicting outcome in the treatment of psoriasis with an anti-TNF agent. By applying statistical modeling using RNA-seq along with in vitro genomic data on cytokine responses for a cohort of etanercept treated psoriatic patients, the disclosure provides effective risk assessment for drug response. By demonstrating that transcriptome data correlates with treatment outcome, the disclosure demonstrates that gene expression changes in healthy appearing uninvolved skin is most predictive of therapeutic responses. Prior to this disclosure, studies focused on inflamed skin for identifying biomarkers. By using integrative approaches, methods for assessing future drug response have been developed.

[0007] In some examples-aspects, the disclosure provides a method for treating psoriasis in a subject, the method comprising measuring a level of at least one biomarker in a biological sample of uninvolved skin isolated from the subject, wherein the level of the biomarker is increased or decreased relative to a mean baseline level of the biomarker in uninvolved skin in a population of psoriatic patients indicating that the subject will be responsive to treatment with an anti-TNF agent; and administering to the subject indicated to be responsive to treatment an effective amount of an anti-TNF agent.

[0008] The disclosure provides a method for treating psoriasis in a subject, the method comprising measuring a level of at least one biomarker in a biological sample of uninvolved skin isolated from the subject prior to treatment with an anti-tumor necrosis factor (anti-TNF) agent, wherein the at least one biomarker is

- (a) ubiquitin specific protease 18 (USP18) and the level of USP18 is increased relative to a control level;
- (b) keratin, type II cytoskeletal 2 epidermal (KRT2) and the level of KRT2 is decreased relative to a control level;
- (c) interleukin 4 receptor (IL4R) and the level of IL4R is increased relative to a control level;
- (d) sex-determining region Y-box transcription factor 5 (SOX5), and the level of SOX5 is decreased relative to a control level;

(e) interferon induced with helicase C domain 1 (IFIH1), and the level of IFIH1 is increased relative to a control level; or

(f) a combination of biomarkers of any two or more of (a)-(e),

wherein the increased or decreased level of the biomarker in the subject relative to the control level predicts that the subject will be responsive to treatment with the anti-TNF agent, and

wherein the control level is the mean level of the biomarker in uninvolved skin in a population of subjects suffering from psoriasis prior to treatment with the anti-TNF agent; and

administering an effective amount of an anti-TNF agent to the subject predicted to be responsive to treatment.

In some aspects, the disclosure provides a use of an anti-TNF agent in the manufacture of a medicament for treating psoriasis in a subject, wherein the use comprises:

measuring a level of at least one biomarker in a biological sample of uninvolved skin isolated from the subject prior to treatment with the anti-tumor necrosis factor (anti-TNF) agent, wherein the at least one biomarker is

(a)ubiquitin specific protease 18 (USP18) and the level of USP18 is increased relative to a control level;

(b)keratin, type II cytoskeletal 2 epidermal (KRT2) and the level of KRT2 is decreased relative to a control level;

(c)interleukin 4 receptor (IL4R) and the level of IL4R is increased relative to a control level;

(d) sex-determining region Y-box transcription factor 5 (SOX5), and the level of SOX5 is decreased relative to a control level;

(e) interferon induced with helicase C domain 1 (IFIH1), and the level of IFIH1 is increased relative to a control level; or

(f) a combination of biomarkers of any two or more of (a)-(e),

wherein the increased or decreased level of the biomarker in the subject relative to the control level predicts that the subject will be responsive to treatment with the anti-TNF agent, and

wherein the control level is the mean level of the biomarker in uninvolved skin in a population of subjects suffering from psoriasis prior to treatment with the anti-TNF agent; and

an effective amount of the anti-TNF agent is to be administered to the subject predicted to be responsive to treatment.

[0009] In some [aspectsexamples](#), the at least one biomarker is USP18. In some [aspectsexamples](#), the at least one biomarker is KRT2. In some [aspectsexamples](#), the at least one biomarker is IL4R. In some [aspectsexamples](#), the at least one biomarker is SOX5. In some [aspectsexamples](#), the at least one biomarker is IFIH1. In some [aspectsexamples](#), the at least one biomarker is a combination of any two or more of USP18, KRT2, IL4R, SOX5, and IFIH1. In some [aspectsexamples](#), the at least one biomarker is a combination of any two or more of USP18, KRT2, IL4R, SOX5, or IFIH1 as set out in any of the combinations in Table 1.

[0010] In some [aspectsexamples](#), the level of USP18 is increased by at least about 86% or more relative to the control level. In some [aspectsexamples](#), the level of KRT2 is decreased by at least about 99% or more relative to the control level. In some [aspectsexamples](#), the level of IL4R is increased by at least about 36% or more relative to the control level. In some [aspectsexamples](#), the level of SOX5 is decreased by at least about 89% or more relative to the control level. In some [aspectsexamples](#), the level of IFIH1 is increased by at least about 49% or more relative to the control level.

[0011] In some [aspectsexamples](#), the level is a measure of the level of a nucleic acid or protein present in the biological sample. In some [aspectsexamples](#), the nucleic acid is deoxyribonucleic acid. In some [aspectsexamples](#), the nucleic acid is ribonucleic acid.

[0012] In some [aspectsexamples](#), the anti-TNF agent is etanercept, infliximab, adalimumab, certolizumab pegot, or golimumab or a biosimilar thereof. In some [aspectsexamples](#), the anti-TNF agent is thalidomide, lenalidomide, pomalidomide, a xanthine derivative, or bupropion.

[0013] In some aspectsexamples, the psoriasis is plaque psoriasis, guttate psoriasis, inverse psoriasis, intertriginous psoriasis, pustular psoriasis, erythrodermic psoriasis, or psoriatic arthritis.

[0014] In some aspectsexamples, the method further comprises administering to the subject at least one additional treatment or medication for psoriasis.

[0015] In some aspectsexamples, the subject is a human subject.

[0016] In some aspectsexamples, the level of the biomarker is measured with an immunoassay, Northern blot analysis, reverse transcription quantitative polymerase chain reaction, RNA sequencing, or high-throughput sequencing.

[0017] In some aspectsexamples, the subject treated with the anti-TNF agent shows PASI improvement by about 12 weeks of treatment. In some aspectsexamples, PASI improvement is observed earlier than 12 weeks after treatment. In some aspectsexamples, the PASI improvement is at least about 10% of PASI improvement.

[0018] The disclosure provides a method for prognosing responsiveness to an anti-TNF agent in treatment of psoriasis in a subject, the method comprising measuring a level of at least one biomarker in a biological sample of uninvolved skin isolated from the subject prior to treatment with an anti-tumor necrosis factor (anti-TNF) agent, wherein the at least one biomarker is

- (a) ubiquitin specific protease 18 (USP18);
- (b) keratin, type II cytoskeletal 2 epidermal (KRT2);
- (c) interleukin 4 receptor (IL4R);
- (d) sex-determining region Y-box transcription factor 5 (SOX5);
- (e) interferon induced with helicase C domain 1 (IFIH1); or
- (f) a combination of biomarkers of any two or more of (a)-(e), and

comparing the level with a control level, wherein the control level is the mean level of the biomarker in uninvolved skin in a population of subjects suffering from psoriasis prior to treatment with the anti-TNF agent,

wherein when the level of USP18, ILR4, and/or IFIH1 in the subject is increased relative to the control level of the biomarker, the subject is predicted to be responsive to treatment with the anti-TNF agent;

wherein when the level of KRT2 and/or SOX5 in the subject is decreased relative to the control level of the biomarker, the subject is predicted to be responsive to treatment with the anti-TNF agent;

wherein when the level of USP18, ILR4, and/or IFIH1 in the subject is not increased relative to the control level of the biomarker, the subject is predicted to be non-responsive to treatment with the anti-TNF agent; and/or

wherein when the level of KRT2 and/or SOX5 in the subject is not decreased relative to the control level of the biomarker, the subject is predicted to be non-responsive to treatment with the anti-TNF agent.

In some aspects, the disclosure provides an *in vitro* method for prognosing responsiveness to an anti-TNF agent in treatment of psoriasis in a subject, wherein the method comprises

measuring a level of the at least one biomarker in a biological sample of uninvolved skin isolated from the subject prior to treatment with an anti-tumor necrosis factor (anti-TNF) agent, wherein the at least one biomarker is

(a) ubiquitin specific protease 18 (USP18);

(b) keratin, type II cytoskeletal 2 epidermal (KRT2);

(c) interleukin 4 receptor (IL4R);

(d) sex-determining region Y-box transcription factor 5 (SOX5);

(e) interferon induced with helicase C domain 1 (IFIH1); or

(f) a combination of biomarkers of any two or more of (a)-(e), and

comparing the level with a control level, wherein the control level is the mean level of the biomarker in uninvolved skin in a population of subjects suffering from psoriasis prior to treatment with the anti-TNF agent,

wherein when the level of USP18, ILR4, and/or IFIH1 in the subject is increased relative to the control level of the biomarker, the subject is predicted to be responsive to treatment with the anti-TNF agent;

wherein when the level of KRT2 and/or SOX5 in the subject is decreased relative to the control level of the biomarker, the subject is predicted to be responsive to treatment with the anti-TNF agent;

wherein when the level of USP18, ILR4, and/or IFIH1 in the subject is not increased relative to the control level of the biomarker, the subject is predicted to be non-responsive to treatment with the anti-TNF agent; and/or

wherein when the level of KRT2 and/or SOX5 in the subject is not decreased relative to the control level of the biomarker, the subject is predicted to be non-responsive to treatment with the anti-TNF agent.

[0019] In some [aspectsexamples](#), the method for prognosing responsiveness further comprises administering an effective amount of the anti-TNF agent to treat the subject predicted to be responsive to treatment with the anti-TNF agent.

[0020] In some [aspectsexamples](#), the at least one biomarker is USP18. In some [aspectsexamples](#), the at least one biomarker is KRT2. In some [aspectsexamples](#), the at least one biomarker is IL4R. In some [aspectsexamples](#), the at least one biomarker is SOX5. In some [aspectsexamples](#), the at least one biomarker is IFIH1. In some [aspectsexamples](#), the at least one biomarker is a combination of any two or more of USP18, KRT2, IL4R, SOX5, or IFIH1. In some [aspectsexamples](#), the at least one biomarker is a combination of any two or more of USP18, KRT2, IL4R, SOX5, or IFIH1 as set out in any of the combinations in Table 1.

[0021] In some [aspectsexamples](#), the level of USP18 is increased by at least about 86% or more relative to the control level. In some [aspectsexamples](#), the level of KRT2 is decreased by at least about 99% or more relative to the control level. In some [aspectsexamples](#), the level of IL4R is increased by at least about 36% or more relative to the control level. In some [aspectsexamples](#), the level of SOX5 is decreased by at least about 89% or more relative to the control level. In some [aspectsexamples](#), the level of IFIH1 is increased by at least about 49% or more relative to the control level.

[0022] In some [aspectsexamples](#), the level is a measure of the level of a nucleic acid or protein present in the biological sample. In some [aspectsexamples](#), the nucleic acid is deoxyribonucleic acid. In some [aspectsexamples](#), the nucleic acid is ribonucleic acid.

[0023] In some aspectsexamples, the anti-TNF agent is etanercept, infliximab, adalimumab, certolizumab pegot, or golimumab or a biosimilar thereof. In some aspectsexamples, the anti-TNF agent is thalidomide, lenalidomide, pomalidomide, a xanthine derivative, or bupropion.

[0024] In some aspectsexamples, the psoriasis is plaque psoriasis, guttate psoriasis, inverse psoriasis, intertriginous psoriasis, pustular psoriasis, erythrodermic psoriasis, or psoriatic arthritis.

[0025] In some aspectsexamples, the method further comprises administering to the subject at least one additional treatment or medication for psoriasis.

[0026] In some aspectsexamples, the subject is a human subject.

[0027] In some aspectsexamples, the level of the biomarker is measured with an immunoassay, Northern blot analysis, reverse transcription quantitative polymerase chain reaction, RNA sequencing, or high-throughput sequencing.

[0028] In some aspectsexamples, the subject treated with the anti-TNF agent shows PASI improvement by about 12 weeks of treatment. In some aspectsexamples, PASI improvement is observed earlier than 12 weeks after treatment. In some aspectsexamples, the PASI improvement is at least about 10% of PASI improvement.

[0029] ~~The~~ In some aspects, the disclosure provides a kit comprising reagents for measuring a level of at least one biomarker in a biological sample of uninvolved skin isolated from a subject suffering from psoriasis prior to treatment with an anti-tumor necrosis factor (anti-TNF) agent, wherein the at least one biomarker is

- (a) ubiquitin specific protease 18 (USP18);
- (b) keratin, type II cytoskeletal 2 epidermal (KRT2);
- (c) interleukin 4 receptor (IL4R);
- (d) sex-determining region Y-box transcription factor 5 (SOX5);
- (e) interferon induced with helicase C domain 1 (IFIH1); or
- (f) a combination of biomarkers of any two or more of (a)-(e), and

wherein the level is the level of nucleic acid or protein of the biomarker in the biological sample.

[0030] In some aspectsexamples, the kit further comprises a means for comparing the level of the nucleic acid or protein of the biomarker in the biological sample with a control level, wherein the control level is the mean level of the biomarker in uninvolved skin in a population of subjects suffering from psoriasis prior to treatment with the anti-TNF agent. In some aspectsexamples, the biological sample is obtained from a biopsy of uninvolved skin from a subject suffering from psoriasis. In some aspectsexamples, the biological sample is obtained from a biopsy of uninvolved skin from a subject suffering from psoriasis prior to treatment with an anti-TNF agent.

[0031] The disclosure provides use of measurement of an increased or decreased level of at least one biomarker in a biological sample of uninvolved skin from a subject suffering from psoriasis in comparison to measurement of a control level, wherein the control level is the mean level of the biomarker in uninvolved skin in a population of subjects suffering from psoriasis prior to treatment with the anti-TNF agent, for prognosing responsiveness of the subject to treatment with an anti-tumor necrosis factor (anti-TNF) agent, wherein the at least one biomarker is

- (a) ubiquitin specific protease 18 (USP18);
- (b) keratin, type II cytoskeletal 2 epidermal (KRT2);
- (c) interleukin 4 receptor (IL4R);
- (d) sex-determining region Y-box transcription factor 5 (SOX5);
- (e) interferon induced with helicase C domain 1 (IFIH1); or
- (f) a combination of biomarkers of any two or more of (a)-(e), and

wherein when the level of USP18, ILR4, and/or IFIH1 in the subject is increased relative to the control level of the biomarker, the subject is predicted to be responsive to treatment with the anti-TNF agent;

wherein when the level of KRT2 and/or SOX5 in the subject is decreased relative to the control level of the biomarker, the subject is predicted to be responsive to treatment with the anti-TNF agent;

wherein when the level of USP18, ILR4, and/or IFIH1 in the subject is not increased relative to the control level of the biomarker, the subject is predicted to be non-responsive to treatment with the anti-TNF agent; and/or

wherein when the level of KRT2 and/or SOX5 in the subject is not decreased relative to the control level of the biomarker, the subject is predicted to be non-responsive to treatment with the anti-TNF agent.

[0032] In some [aspectsexamples](#), the at least one biomarker is USP18. In some [aspectsexamples](#), the at least one biomarker is KRT2. In some [aspectsexamples](#), the at least one biomarker is IL4R. In some [aspectsexamples](#), the at least one biomarker is SOX5. In some [aspectsexamples](#), the at least one biomarker is IFIH1. In some [aspectsexamples](#), the at least one biomarker is a combination of any two or more of USP18, KRT2, IL4R, SOX5, or IFIH1. In some [aspectsexamples](#), the at least one biomarker is a combination of any two or more of USP18, KRT2, IL4R, SOX5, or IFIH1 as set out in any of the combinations in Table 1.

[0033] In some [aspectsexamples](#), the level of USP18 is increased by at least about 86% or more relative to the control level. In some [aspectsexamples](#), the level of KRT2 is decreased by at least about 99% or more relative to the control level. In some [aspectsexamples](#), the level of IL4R is increased by at least about 36% or more relative to the control level. In some [aspectsexamples](#), the level of SOX5 is decreased by at least about 89% or more relative to the control level. In some [aspectsexamples](#), the level of IFIH1 is increased by at least about 49% or more relative to the control level.

[0034] In some [aspectsexamples](#), the level is a measure of the level of a nucleic acid or protein present in the biological sample. In some [aspectsexamples](#), the nucleic acid is deoxyribonucleic acid. In some [aspectsexamples](#), the nucleic acid is ribonucleic acid.

[0035] In some [aspectsexamples](#), the anti-TNF agent is etanercept, infliximab, adalimumab, certolizumab pegot, or golimumab or a biosimilar thereof. In some [aspectsexamples](#), the anti-TNF agent is thalidomide, lenalidomide, pomalidomide, a xanthine derivative, or bupropion.

[0036] In some [aspectsexamples](#), the psoriasis is plaque psoriasis, guttate psoriasis, inverse psoriasis, intertriginous psoriasis, pustular psoriasis, erythrodermic psoriasis, or psoriatic arthritis.

[0037] In some [aspectsexamples](#), the method further comprises administering to the subject at least one additional treatment or medication for psoriasis.

[0038] In some aspectsexamples, the subject is a human subject.

[0039] In some aspectsexamples, the level of the biomarker is measured with an immunoassay, Northern blot analysis, reverse transcription quantitative polymerase chain reaction, RNA sequencing, or high-throughput sequencing.

[0040] In some aspectsexamples, the subject treated with the anti-TNF agent shows PASI improvement by about 12 weeks of treatment. In some aspectsexamples, PASI improvement is observed earlier than 12 weeks after treatment. In some aspectsexamples, the PASI improvement is at least about 10% of PASI improvement.

[0041] In various aspectsexamples, the disclosure includes methods, kits, and uses of any one biomarker or combination of biomarkers disclosed herein for the prognosis and treatment of psoriasis based upon the expression of the biomarker or a combination of biomarkers.

[0042] This disclosure also provides a method for determining if a biomarker will be predictive of whether a subject suffering from psoriasis will respond to treatment with an anti-TNF agent, the method comprising (1) measuring the level of expression of one or more TNF-induced and/or or interferon (IFN)-induced genes in a biopsy of uninvolved skin and PASI score in a population of subjects suffering from psoriasis prior to treatment with the anti-TNF agent; (2) treating the population of subjects with an anti-TNF agent for at least about 12 weeks; (3) track changes of the transcriptomes over the treatment course; and (4) identify differentially expressed transcripts associated with improved PASI score after controlling for body mass index (BMI), gender, and age of the patients.

[0043] The foregoing summary is not intended to define every aspect of the disclosure, and additional aspects are described in other sections, such as the following detailed description. The entire document is intended to be related as a unified disclosure, and it should be understood that all combinations of features described herein are contemplated, even if the combination of features are not found together in the same sentence, or paragraph, or section of this document. Other features and advantages of the invention will become apparent from the following detailed description. It should be understood, however, that the detailed description

and the specific examples, while indicating specific embodiments of the disclosure, are given by way of illustration only, because various changes and modifications

CLAIMS

What is Claimed is:

1. ~~Use of an anti-TNF agent in the manufacture of a medicament for~~A method
~~for~~ treating psoriasis in a subject, wherein the ~~method-use comprising~~comprises:

measuring a level of at least one biomarker in a biological sample of uninvolved skin isolated from the subject prior to treatment with ~~an-the~~ anti-tumor necrosis factor (anti-TNF) agent, wherein the at least one biomarker is

(a) ubiquitin specific protease 18 (USP18) and the level of USP18 is increased relative to a control level;

(b) keratin, type II cytoskeletal 2 epidermal (KRT2) and the level of KRT2 is decreased relative to a control level;

(c) interleukin 4 receptor (IL4R) and the level of IL4R is increased relative to a control level;

(d) sex-determining region Y-box transcription factor 5 (SOX5), and the level of SOX5 is decreased relative to a control level;

(e) interferon induced with helicase C domain 1 (IFIH1), and the level of IFIH1 is increased relative to a control level; or

(f) a combination of biomarkers of any two or more of (a)-(e),

wherein the increased or decreased level of the biomarker in the subject relative to the control level predicts that the subject will be responsive to treatment with the anti-TNF agent, and

wherein the control level is the mean level of the biomarker in uninvolved skin in a population of subjects suffering from psoriasis prior to treatment with the anti-TNF agent; and

~~administering~~ an effective amount of ~~an-the~~ anti-TNF agent is to be administered to the subject predicted to be responsive to treatment.

2. The ~~method-use~~ of claim 1, wherein the at least one biomarker is USP18.

3. The ~~use method~~ of claim 1, wherein the at least one biomarker is KRT2.

4. The ~~use method~~ of claim 1, wherein the at least one biomarker is IL4R.

5. The ~~use method~~ of claim 1, wherein the at least one biomarker is SOX5.

6. The ~~use method~~ of claim 1, wherein the at least one biomarker is IFIH1.

7. The ~~use method~~ of claim 1, wherein the at least one biomarker is a combination of any two or more of USP18, KRT2, IL4R, SOX5, or IFIH1.
8. The ~~method use~~ of claim 1, wherein the at least one biomarker is a combination of any two or more of USP18, KRT2, IL4R, SOX5, or IFIH1 as set out in any of the combinations in Table 1.
9. The ~~method use~~ of claim 1 or 2, wherein the level of USP18 is increased by at least about 86% or more relative to the control level.
10. The ~~method use~~ of claim 1 or 3, wherein the level of KRT2 is decreased by at least about 99% or more relative to the control level.
11. The ~~method use~~ of claim 1 or 4, wherein the level of IL4R is increased by at least about 36% or more relative to the control level.
12. The ~~method use~~ of claim 1 or 5, wherein the level of SOX5 is decreased by at least about 89% or more relative to the control level.
13. The ~~method use~~ of claim 1 or 6, wherein the level of IFIH1 is increased by at least about 49% or more relative to the control level.
14. The ~~method use~~ of any one of claims 1-13, wherein the level is a measure of the level of a nucleic acid or protein present in the biological sample.
15. The ~~method use~~ of claim 14, wherein the nucleic acid is deoxyribonucleic acid.
16. The ~~method use~~ of claim 14, wherein the nucleic acid is ribonucleic acid.
17. The ~~method use~~ of any one of claims 1-16, wherein the anti-TNF agent is etanercept, infliximab, adalimumab, certolizumab pegot, or golimumab.
18. The ~~method use~~ of any one of claims 1-16, wherein the anti-TNF agent is thalidomide, lenalidomide, pomalidomide, a xanthine derivative, or bupropion.
19. The ~~method use~~ of any one of claims 1-18, wherein the psoriasis is plaque psoriasis, guttate psoriasis, inverse psoriasis, intertriginous psoriasis, pustular psoriasis, erythrodermic psoriasis, or psoriatic arthritis.
20. The ~~method use~~ of any one of claims 1-19, ~~wherein further comprising administering to~~ the subject is to be further administered with at least one additional treatment or medication for psoriasis.
21. The ~~method use~~ of any one of claims 1-20, wherein the subject is a human subject.

22. The ~~method~~use of any one of claims 1-21, wherein the level of the biomarker is measured with an immunoassay, Northern blot analysis, reverse transcription quantitative polymerase chain reaction, RNA sequencing, or high-throughput sequencing.

23. The ~~method~~use of any one of claims 1-22, wherein the subject treated with the anti-TNF agent shows PASI improvement by about 12 weeks of treatment.

24. The ~~method~~use of claim 23, wherein the PASI improvement is at least about 10% of PASI improvement.

25. An *in vitro* method for prognosing responsiveness to an anti-TNF agent in treatment of psoriasis in a subject, wherein the method ~~comprising~~comprises:

measuring a level of the at least one biomarker in a biological sample of uninvolved skin isolated from the subject prior to treatment with an anti-tumor necrosis factor (anti-TNF) agent, wherein the at least one biomarker is

- (a) ubiquitin specific protease 18 (USP18);
- (b) keratin, type II cytoskeletal 2 epidermal (KRT2);
- (c) interleukin 4 receptor (IL4R);
- (d) sex-determining region Y-box transcription factor 5 (SOX5);
- (e) interferon induced with helicase C domain 1 (IFIH1); or
- (f) a combination of biomarkers of any two or more of (a)-(e), and

comparing the level with a control level, wherein the control level is the mean level of the biomarker in uninvolved skin in a population of subjects suffering from psoriasis prior to treatment with the anti-TNF agent,

wherein when the level of USP18, ILR4, and/or IFIH1 in the subject is increased relative to the control level of the biomarker, the subject is predicted to be responsive to treatment with the anti-TNF agent;

wherein when the level of KRT2 and/or SOX5 in the subject is decreased relative to the control level of the biomarker, the subject is predicted to be responsive to treatment with the anti-TNF agent;

wherein when the level of USP18, ILR4, and/or IFIH1 in the subject is not increased relative to the control level of the biomarker, the subject is predicted to be non-responsive to treatment with the anti-TNF agent; and/or

wherein when the level of KRT2 and/or SOX5 in the subject is not decreased relative to the control level of the biomarker, the subject is predicted to be non-responsive to treatment with the anti-TNF agent.

~~26. The method of claim 25 further comprising administering an effective amount of the anti-TNF agent to treat the subject predicted to be responsive to treatment with the anti-TNF agent.~~

~~27~~26. The method of claim 25-~~or 26~~, wherein the at least one biomarker is USP18.

~~28~~27. The method of claim 25-~~or 26~~, wherein the at least one biomarker is KRT2.

~~29~~28. The method of claim 25-~~or 26~~, wherein the at least one biomarker is IL4R.

~~30~~29. The method of claim 25-~~or 26~~, wherein the at least one biomarker is SOX5.

~~31~~30. The method of claim 25-~~or 26~~, wherein the at least one biomarker is IFIH1.

~~32~~31. The method of claim 25-~~or 26~~, wherein the at least one biomarker is a combination of any two or more of USP18, KRT2, IL4R, SOX5, and IFIH1.

~~33~~32. The method of claim 25-~~or 26~~, wherein the at least one biomarker is a combination of any two or more of USP18, KRT2, IL4R, SOX5, and IFIH1 as set out in any of the combinations in Table 1.

~~34~~33. The method of claim 25, ~~or 26, or 27~~, wherein the level of USP18 is increased by at least about 86% or more relative to the control level.

~~35~~34. The method of claim 25, ~~26, or 28~~27, wherein the level of KRT2 is decreased by at least about 99% or more relative to the control level.

~~36~~35. The method of claim 25, ~~26, or 29~~28, wherein the level of IL4R is increased by at least about 36% or more relative to the control level.

~~37~~36. The method of claim 25, ~~26, or 30~~29, wherein the level of SOX5 is decreased by at least about 89% or more relative to the control level.

~~38~~37. The method of claim 25, ~~26, or 30~~29, wherein the level of IFIH1 is increased by at least about 49% or more relative to the control level.

~~39~~38. The method of any one of claims 25-~~28~~27, wherein the level is a measure of the level of a nucleic acid or protein present in the biological sample.

~~40~~39. The method of claim ~~39~~38, wherein the nucleic acid is deoxyribonucleic acid.

~~41~~40. The method of claim ~~39~~38, wherein the nucleic acid is ribonucleic acid.

~~4241.~~ The method of any one of claims 25-~~4140~~, wherein the anti-TNF agent is etanercept, infliximab, adalimumab, certolizumab pegot, or golimumab.

~~4342.~~ The method of any one of claims 25-~~4140~~, wherein the anti-TNF agent is thalidomide, lenalidomide, pomalidomide, a xanthine derivative, or bupropion.

~~4443.~~ The method of any one of claims 25-~~4342~~, wherein the psoriasis is plaque psoriasis, guttate psoriasis, inverse psoriasis, intertriginous psoriasis, pustular psoriasis, erythrodermic psoriasis, or psoriatic arthritis.

~~45.—The method of any one of claims 25-44, further comprising administering to the subject at least one additional treatment or medication for psoriasis.~~

~~4644.~~ The method of any one of claims 25-~~4543~~, wherein the subject is a human subject.

~~4745.~~ The method of any one of claims 25-~~4644~~, wherein the level of the biomarker is measured with an immunoassay, Northern blot analysis, reverse transcription quantitative polymerase chain reaction, RNA sequencing, or high-throughput sequencing.

~~4846.~~ The method of any one of claims 25-~~4745~~, wherein the subject predicted to be responsive to treatment with the anti-TNF agent is expected to show PASI improvement by about 12 weeks of treatment.

~~4947.~~ The method of claim ~~4846~~, wherein the PASI improvement is expected to be at least about 10% of PASI improvement.

~~5048.~~ A kit comprising reagents for measuring a level of at least one biomarker in a biological sample of uninvolved skin isolated from a subject suffering from psoriasis prior to treatment with an anti-tumor necrosis factor (anti-TNF) agent, wherein the at least one biomarker is

- (a) ubiquitin specific protease 18 (USP18);
- (b) keratin, type II cytoskeletal 2 epidermal (KRT2);
- (c) interleukin 4 receptor (IL4R);
- (d) sex-determining region Y-box transcription factor 5 (SOX5);
- (e) interferon induced with helicase C domain 1 (IFIH1); or
- (f) a combination of biomarkers of any two or more of (a)-(e), and

wherein the level is the level of nucleic acid or protein of the biomarker in the biological sample.

5149. The kit of claim 5048, further comprising a means for comparing the level of the nucleic acid or protein of the biomarker in the biological sample with a control level, wherein the control level is the mean level of the biomarker in uninvolved skin in a population of subjects suffering from psoriasis prior to treatment with the anti-TNF agent.

5250. The kit of claim 5048 or 5149, wherein the biological sample is obtained from a biopsy of uninvolved skin from a subject suffering from psoriasis.

~~53. Use of measurement of an increased or decreased level of at least one biomarker in a biological sample of uninvolved skin from a subject suffering from psoriasis in comparison to measurement of a control level, wherein the control level is the mean level of the biomarker in uninvolved skin in a population of subjects suffering from psoriasis prior to treatment with the anti-TNF agent, for prognosing responsiveness of the subject to treatment with an anti-tumor necrosis factor (anti-TNF) agent, wherein the at least one biomarker is~~

- ~~(a) ubiquitin specific protease 18 (USP18);~~
- ~~(b) keratin, type II cytoskeletal 2 epidermal (KRT2);~~
- ~~(c) interleukin 4 receptor (IL4R);~~
- ~~(d) sex-determining region Y-box transcription factor 5 (SOX5);~~
- ~~(e) interferon induced with helicase C domain 1 (IFIH1); or~~
- ~~(f) a combination of biomarkers of any two or more of (a)-(e), and~~

~~wherein when the level of USP18, ILR4, and/or IFIH1 in the subject is increased relative to the control level of the biomarker, the subject is predicted to be responsive to treatment with the anti-TNF agent;~~

~~wherein when the level of KRT2 and/or SOX5 in the subject is decreased relative to the control level of the biomarker, the subject is predicted to be responsive to treatment with the anti-TNF agent;~~

~~wherein when the level of USP18, ILR4, and/or IFIH1 in the subject is not increased relative to the control level of the biomarker, the subject is predicted to be non-responsive to treatment with the anti-TNF agent; and/or~~

~~wherein when the level of KRT2 and/or SOX5 in the subject is not decreased relative to the control level of the biomarker, the subject is predicted to be non-responsive to treatment with the anti-TNF agent.~~

~~54. The use of claim 53, wherein the at least one biomarker is USP18.~~

~~55. The use of claim 53, wherein the at least one biomarker is KRT2.~~

- ~~56.—The use of claim 53, wherein the at least one biomarker is IL4R.~~
- ~~57.—The use of claim 53, wherein the at least one biomarker is SOX5.~~
- ~~58.—The use of claim 53, wherein the at least one biomarker is IFIH1.~~
- ~~59.—The use of claim 53, wherein the at least one biomarker is a combination of any two or more of USP18, KRT2, IL4R, SOX5, or IFIH1.~~
- ~~60.—The use of claim 53, wherein the at least one biomarker is a combination of any two or more of USP18, KRT2, IL4R, SOX5, or IFIH1 as set out in any of the combinations in Table 1.~~
- ~~61.—The use of claim 53 or 54, wherein the level of USP18 is increased by at least about 86% or more relative to the control level.~~
- ~~62.—The use of claim 53 or 55, wherein the level of KRT2 is decreased by at least about 99% or more relative to the control level.~~
- ~~63.—The use of claim 53 or 56, wherein the level of IL4R is increased by at least about 36% or more relative to the control level.~~
- ~~64.—The use of claim 53 or 57, wherein the level of SOX5 is decreased by at least about 89% or more relative to the control level.~~
- ~~65.—The use of claim 53 or 58, wherein the level of IFIH1 is increased by at least about 49% or more relative to the control level.~~
- ~~66.—The use of any one of claims 53-65, wherein the level is a measure of the level of a nucleic acid or protein present in the biological sample.~~
- ~~67.—The use of claim 66, wherein the nucleic acid is deoxyribonucleic acid.~~
- ~~68.—The use of claim 66, wherein the nucleic acid is ribonucleic acid.~~
- ~~69.—The use of any one of claims 53-68, wherein the anti-TNF agent is etanercept, infliximab, adalimumab, certolizumab pegol, or golimumab.~~
- ~~70.—The use of any one of claims 53-68, wherein the anti-TNF agent is thalidomide, lenalidomide, pomalidomide, a xanthine derivative, or bupropion.~~
- ~~71.—The use of any one of claims 53-70, wherein the psoriasis is plaque psoriasis, guttate psoriasis, inverse psoriasis, intertriginous psoriasis, pustular psoriasis, erythrodermic psoriasis, or psoriatic arthritis.~~
- ~~72.—The use of any one of claims 53-71, wherein the subject is a human subject.~~

~~73. The use of any one of claims 53-72, wherein the level of the biomarker is measured with an immunoassay, Northern blot analysis, reverse transcription quantitative polymerase chain reaction, RNA sequencing, or high-throughput sequencing.~~

~~74. The use of any one of claims 53-73, wherein the subject predicted to be responsive to treatment with the anti-TNF agent is expected to show PASI improvement by about 12 weeks of treatment.~~

~~75. The use of claim 74, wherein the PASI improvement is expected to be at least about 10% of PASI improvement.~~