

[0006a] In an aspect of the present disclosure, there is provided a use of an anti-TNF therapy in the manufacture of a medicament for treating a subject suffering from ulcerative colitis, wherein: the anti-TNF therapy is to be administered to the subject who has been determined to be responsive to the anti-TNF therapy via a classifier configured to distinguish between responsive and non-responsive subjects suffering from ulcerative colitis who have received the anti-TNF therapy (“prior subjects”),

wherein the classifier distinguishes between the responsive subjects and the non-responsive subjects on the basis of a set of variables, the set of variables comprising expression of a set of genes.

[0006b] In another aspect of the present disclosure, there is provided a method of validating response to an anti-TNF therapy in a subject suffering from ulcerative colitis, the method comprising:

receiving, by a processor of a computing device, a gene expression response signature determined to be differentially expressed between responsive and non-responsive subjects suffering from ulcerative colitis who have received the anti-TNF therapy;

analyzing, by the processor, gene expression levels of the subject relative to the gene expression response signature to determine whether the subject expresses the gene expression response signature, wherein the gene expression response signature comprises a set of genes.

[0006c] In a further aspect of the present disclosure, there is provided a system for determining or validating responsiveness to anti-TNF therapy for a subject suffering from ulcerative colitis, the system comprising:

a processor of a computing device; and

a memory having instructions stored thereon, wherein the instructions, when executed by the processor cause the processor to perform the following steps:

receiving, by the processor, a gene expression response signature determined to distinguish between responsive and non-responsive subjects suffering from ulcerative colitis who have received the anti-TNF therapy;

analyzing, by the processor, gene expression levels of the subject relative to the gene expression response signature to determine whether the subject expresses the gene expression response signature, wherein the gene expression response signature comprises a set of genes.

[0006d] In another aspect of the present disclosure, there is provided a use of an alternative to anti-TNF therapy in the manufacture of a medicament for treating a subject suffering from ulcerative colitis, wherein:

the alternative to anti-TNF therapy is to be administered to the subject who has been determined to be non-responsive to the anti-TNF therapy via a classifier configured to distinguish between responsive and non-responsive subjects suffering from ulcerative colitis who have received the anti-TNF therapy (“prior subjects”),

wherein the classifier distinguishes between the responsive subjects and the non-responsive subjects on the basis of a set of variables, the set of variables comprising expression of a set of genes.

[0007] Provided technologies, among other things, permit care providers to distinguish subjects likely to benefit from anti-TNF therapy from those who are not, reduce risks to patients, increase timing and quality of care for non-responder patient populations, increase efficiency of drug development, and avoid costs associated with administering ineffective therapy to non-responder patients or with treating side effects such patients experience upon receiving anti-TNF therapy.

[0008] Provided technologies embody and/or arise from, among other things, certain insights that include, for example, identification of the source of a problem with certain conventional approaches to defining responder vs. non-responder populations and/or that represent particularly useful strategies for defining classifiers that distinguish between such populations. For example, as described herein, the present disclosure identifies that one source of a problem with many conventional strategies for defining responder vs. non-responder populations through consideration of gene expression differences in the populations is that they typically prioritize or otherwise focus on *highest fold* changes; the present disclosure teaches that such an approach misses subtle but meaningful differences relevant to disease biology. Moreover, the present disclosure offers an insight that mapping of genes with altered expression levels onto a human interactome map (in particular onto a human interactome map that represents experimentally supported physical interactions between cellular components which, in some embodimentexamples, explicitly excludes any theoretical, calculated, or other interaction that has been proposed but not experimentally validated), can provide a useful and effective classifier for defining responders vs. non-responders to anti-TNF therapy. In some embodimentexamples, genes included in such a classifier represent a connected module on the human interactome.

[0009] In some embodimentexamples, the present disclosure provides a method of treating subjects suffering from a disease, disorder, or condition (e.g., inflammatory bowel disease, ulcerative colitis or Crohn's disease) with anti-TNF therapy, the method comprising a step of: administering the anti-TNF therapy to subjects who have been determined to display a gene expression response signature established to distinguish between responsive and non-responsive prior subjects who have received the anti-TNF therapy (e.g., where "prior subjects" refer to subjects who have previously received the anti-TNF therapy, and have been classified as responsive or non-responsive to said anti-TNF therapy).

[0010] In some embodimentexamples, the present disclosure provides method of treating a subject suffering from a disease, disorder, or condition (e.g., inflammatory bowel disease, ulcerative colitis

or Crohn's disease) with an anti-TNF therapy, the method comprising a step of: administering the anti-TNF therapy to subjects who have been determined not to display a gene expression response signature established to distinguish between responsive and non-responsive prior subjects who have received the anti-TNF therapy.

[0011] In some embodiment examples, the present disclosure provides method of treating a subject suffering from a disease, disorder, or condition with an anti-TNF therapy, the method comprising a step of: administering the anti-TNF therapy to subjects who have been determined to be responsive via a classifier determined to distinguish between responsive and non-responsive subjects who have received the anti-TNF therapy ("prior subjects"), wherein the classifier distinguishes between responsive and non-responsive subjects on the basis of a set of variables, the set of variables comprising expression of one or more genes selected from:

PKM	SUMO2
ADAR	NUCKS1
ANP32B	PML
ATRX	PNN
BRD7	PRKAB1
CAPN1	RBCK1
CCDC88A	RRP15
CFAP206	SNRPN
CGN	TFIP11
CIRBP	THTPA
CLTC	TMEM87A
EEA1	TNK2
ERICH1	TPR
FAM192A	TRAPPC4
FAM207A	UBA5
HHEX	UBE2D1
KLF3	VPS72
LCA5	YWHAE
MDC1	MCM5

MDM2	MED6
NFAT5	MGST2
ARCN1	MSH6
ARF6	PURA
ARNT	RABGEF1
ARPC5L	RBBP6
ASB16	RBM26
ATF7IP	RECQL
ATP6V0C	RUNX3
BRF1	SFPQ
CHFR	SGCB
EDA	SMARCA1
EFEMP2	SMC1A
ESR2	SPAG9
FAM179B	UBA2
FTH1	UBE2B
H3F3A	USPL1
HDAC4	HP1BP3
HINFP	HRAS
HNRNPK	MAX

[0012] In some ~~embodiment~~examples, the present disclosure provides a kit for evaluating a likelihood that a subject suffering from an autoimmune disorder will not respond to an anti-TNF therapy, the kit comprising a set of reagents for detecting an expression level of one or more genes selected from the group consisting of:

PKM	SUMO2
ADAR	NUCKS1
ANP32B	PML
ATRX	PNN
BRD7	PRKAB1

CLAIMS

1. Use of an anti-TNF therapy in the manufacture of a medicament for ~~A method of~~ treating a subject suffering from ulcerative colitis ~~a disease, disorder, or condition with an anti-TNF therapy, the method comprising a step of~~ wherein:

~~administering~~ the anti-TNF therapy is to be administered to ~~the subjects~~ subjects who ~~has~~ have been determined to be responsive to the anti-TNF therapy via a classifier ~~configured~~ determined to distinguish between responsive and non-responsive subjects suffering from ulcerative colitis who have received the anti-TNF therapy (“prior subjects”),

wherein the classifier distinguishes between the responsive subjects and the non-responsive subjects on the basis of a set of variables, the set of variables comprising expression of a set of one or more genes, selected from:

~~PKM~~	~~SUMO2~~
~~ADAR~~	~~NUCKS1~~
~~ANP32B~~	~~PML~~
~~ATRX~~	~~PNN~~
~~BRD7~~	~~PRKAB1~~
~~CAPN1~~	~~RBCK1~~
~~CCDC88A~~	~~RRP15~~
~~CFAP206~~	~~SNRPN~~
~~CGN~~	~~TFIP11~~
~~CIRBP~~	~~THTPA~~
~~CLTC~~	~~TMEM87A~~
~~EEA1~~	~~TNK2~~
~~ERICH1~~	~~TPR~~
~~FAM192A~~	~~TRAPPC4~~
~~FAM207A~~	~~UBA5~~
~~HHEX~~	~~UBE2D1~~
~~KLF3~~	~~VPS72~~

LCA5	YWHAE
MDC1	MCM5
MDM2	MED6
NFAT5	MGST2
ARCN1	MSH6
ARF6	PURA
ARNT	RABGEF1
ARPC5L	RBBP6
ASB16	RBM26
ATF7IP	RECQL
ATP6V0C	RUNX3
BRF1	SFPQ
CHFR	SGCB
EDA	SMARCA1
EFEMP2	SMC1A
ESR2	SPAG9
FAM179B	UBA2
FTH1	UBE2B
H3F3A	USPL1
HDAC4	HP1BP3
HINFP	HRAS
HNRNPK	MAX

2. ~~The method of claim 1, wherein the one or more genes is selected from:~~

SUMO2	PKM
ADAR	NUCKS1
ANP32B	PML
ATRX	PNN
BRD7	PRKAB1
CAPN1	RBCK1

CCDC88A	RRP15
CFAP206	SNRPN
CGN	TFIP11
CIRBP	THTPA
CLTC	TMEM87A
EEA1	TNK2
ERICH1	TPR
FAM192A	TRAPPC4
FAM207A	UBA5
HHEX	UBE2D1
KLF3	VPS72
LCA5	YWHAE
MDC1	-
MDM2	
NFAT5	

3. — The method of claim 1, wherein the one or more genes is selected from:

SUMO2	PKM
ARGN1	MCM5
ARF6	MED6
ARNT	MGST2
ARPC5L	MSH6
ASB16	PURA
ATF7IP	RABGEF1
ATP6V0C	RBBP6
BRF1	RBM26
CHFR	RECQL
EDA	RUNX3
EFEMP2	SFPQ
ESR2	SGCB

~~FAM179B~~	~~SMARCA1~~
~~FTH1~~	~~SMC1A~~
~~H3F3A~~	~~SPAG9~~
~~HDAC4~~	~~UBA2~~
~~HINFP~~	~~UBE2B~~
~~HNRNPK~~	~~USPL1~~
~~HP1BP3~~	~~-~~
~~HRAS~~	
~~MAX~~	

4. ~~The method of claim 1, wherein the one or more genes comprises SUMO2 and PKM:~~

5. ~~The method of claim 1, wherein the set of variables comprises an expression level of two or more genes selected from:~~

~~PKM~~	~~SUMO2~~
~~ADAR~~	~~NUCKS1~~
~~ANP32B~~	~~PML~~
~~ATRX~~	~~PNN~~
~~BRD7~~	~~PRKAB1~~
~~CAPN1~~	~~RBCK1~~
~~CCDC88A~~	~~RRP15~~
~~CFAP206~~	~~SNRPN~~
~~CGN~~	~~TFIP11~~
~~CIRBP~~	~~THTPA~~
~~CLTC~~	~~TMEM87A~~
~~EEA1~~	~~TNK2~~
~~ERICH1~~	~~TPR~~
~~FAM192A~~	~~TRAPPC4~~
~~FAM207A~~	~~UBA5~~
~~HHEX~~	~~UBE2D1~~

KLF3	VPS72
LCA5	YWHAE
MDC1	MCM5
MDM2	MED6
NFAT5	MGST2
ARCN1	MSH6
ARF6	PURA
ARNT	RABGEF1
ARPC5L	RBBP6
ASB16	RBM26
ATF7IP	RECQL
ATP6V0C	RUNX3
BRF1	SFPQ
CHFR	SGCB
EDA	SMARCA1
EFEMP2	SMC1A
ESR2	SPAG9
FAM179B	UBA2
FTH1	UBE2B
H3F3A	USPL1
HDAC4	HP1BP3
HINFP	HRAS
HNRNPK	MAX

2. The use of claim 1, wherein the classifier is a trained machine learning classifier.

3. The use of claim 2, wherein the trained machine learning classifier is obtained at least in part by:

- (i) determining, for each of the set of genes, a significance of correlation with response outcome to the anti-TNF therapy among the responsive subjects as compared to the non-responsive subjects,
 - (ii) selecting a reduced subset of the set of genes with highest significance of correlation with response outcome to the anti-TNF therapy, and
 - (iii) training a classifier to classify whether expression of the reduced subset of the set of genes is indicative of response or non-response, wherein the training comprises using (1) gene expression levels of the reduced subset of the set of genes in biological samples from the responsive subjects and the non-responsive subjects and (2) a responsive outcome of the responsive subjects or a non-responsive outcome of the non-responsive subjects.
- 4. The use of claim 3, wherein the trained machine learning classifier is obtained at least in part by further:
 - (iv) validating the classifier on a second independent cohort of subjects who have received the anti-TNF therapy and have been determined as either responding to the anti-TNF therapy or not responding to the anti-TNF therapy.
- 5. The use of claim 4, wherein the trained machine learning classifier is obtained at least in part by further:
 - (v) selecting a cutoff score for the validated classifier, such that the validated classifier achieves a true negative (TNR) of at least about 0.5 and a negative predictive value of at least about 0.6.
- 6. The use of claim 3, wherein the reduced subset of the set of genes has highest significance of correlation with non-response to the anti-TNF therapy.
- 67. The ~~method~~use of any one of claims 1-~~56~~, wherein the anti-TNF therapy is or comprises ~~administration of~~ infliximab, adalimumab, etanercept, cirtolizumab pegol, golilumab, or biosimilars thereof.

- ~~78.~~ The methoduse of any one of claims 1-~~67~~, wherein the anti-TNF therapy is or comprises ~~administration of~~ infliximab or adalimumab.
89. The methoduse of any one of claims 1-~~78~~, wherein the anti-TNF therapy is or comprises infliximab.
- ~~9.~~ ~~The method of any one of claims 1-8, wherein the disease, disorder, or condition is an autoimmune disorder.~~
- ~~10.~~ ~~The method of claim 9, wherein the autoimmune disorder is selected from rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (adult or pediatric), ulcerative colitis, inflammatory bowel disease, chronic psoriasis, plaque psoriasis, hidradenitis suppurativa, asthma, uveitis, juvenile idiopathic arthritis, vitiligo, Graves' ophthalmopathy (also known as thyroid eye disease, or Graves' orbitopathy), and multiple sclerosis.~~
- ~~11.~~ ~~The method of claim 10, wherein the disease, disorder, or condition is ulcerative colitis.~~
- ~~1210.~~ The methoduse of any one of claims 1-~~911~~, wherein the ~~classification of the~~ subject has been determined to be responsive to the anti-TNF therapy at least in part by analysis of a biological sample from the subject.
- ~~1311.~~ The methoduse of claim ~~1012~~, wherein the biological sample is analyzed by microarray, RNA sequencing, real-time quantitative reverse transcription PCR (qRT-PCR), bead array, or ELISA.
- ~~1412.~~ The methoduse of any one of claims 1-~~1113~~, wherein the classifier has previously been validated by analyzing gene expression levels in biological samples from the responsive subjects and the non-responsive subjects~~a first cohort of subjects who have previously received the anti-TNF therapy ("prior subjects") and have been determined to respond ("responders") or not to respond ("non-responders") to the anti-TNF therapy~~ to identify

genes that show statistically significant differences in expression level between the responsive subjects~~responders~~ and the non-responsive subjects~~responders~~ (“signature genes”).

- 1513. The method~~use~~ of claim 1214, wherein the signature genes are mapped onto a biological network.
- 1614. The method~~use~~ of claim 1315, wherein a subset of signature genes are selected on the basis of their connectivity in the biological network to provide a candidate gene list.
- 1715. The method~~use~~ of claim 1416, further comprising training a classifier on expression levels of the genes of the candidate gene list from the first cohort of subjects to identify a subset of the prior subjects having a pattern of expression of the candidate gene list indicative that the subset of prior subjects are unlikely to respond to the anti-TNF therapy, to thereby obtain a trained classifier.
- 1816. The method~~use~~ of claim 1517, further comprising validating the trained classifier via analysis of a second cohort comprising an independent and blinded group of responders and non-responders, and selecting a cutoff score such that the classifier distinguishes about 50% of prior subjects that are non-responsive to the anti-TNF therapy to thereby provide a validated classifier.
- 1917. The method~~use~~ of claim 1618, wherein the validated classifier distinguishes about 65% of prior subjects that are non-responsive to the anti-TNF therapy.
- 2018. The method~~use~~ of claim 1719, wherein the validated classifier distinguishes about 70% of prior subjects that are non-responsive to the anti-TNF therapy.
- 2119. The method~~use~~ of claim 1820, wherein the validated classifier distinguishes about 80% of prior subjects that are non-responsive to the anti-TNF therapy.

2220. The ~~method~~use of claim 1921, wherein the validated classifier distinguishes about 90% of prior subjects that are non-responsive to the anti-TNF therapy.
2321. The ~~method~~use of claim 2022, wherein the validated classifier distinguishes about 100% of prior subjects that are non-responsive to the anti-TNF therapy.
2422. The ~~method~~use of claim 1618, wherein the validated classifier distinguishes at least 50% of prior subjects that are non-responsive to the anti-TNF therapy with at least 60% NPV.
2523. The ~~method~~use of claim 2422, wherein the validated classifier distinguishes at least 50% of prior subjects that are non-responsive to the anti-TNF therapy with at least 80% NPV.
2624. The ~~method~~use of claim 2523, wherein the validated classifier distinguishes at least 50% of prior subjects that are non-responsive to the anti-TNF therapy with at least 90% NPV.
2725. The ~~method~~use of claim 2624, wherein the validated classifier distinguishes at least 50% of prior subjects that are non-responsive to the anti-TNF therapy with at least 95% NPV.
2826. The ~~method~~use of claim 2725, wherein the validated classifier distinguishes at least 50% of prior subjects that are non-responsive to the anti-TNF therapy with about 100% NPV.
27. The use of any one of claims 1-26, wherein the classifier comprises a neural network.
2928. A method of validating response to an anti-TNF therapy in a subject suffering from ulcerative colitis, the method comprising:
- receiving, by a processor of a computing device, a gene expression response signature determined to be differentially expressed~~distinguish~~ between responsive and non-responsive subjects suffering from ulcerative colitis who have received~~to~~ the anti-TNF therapy;

analyzing, by the processor, gene expression levels of the subject relative to the gene expression response signature to determine whether the subject expresses the gene expression response signature, wherein the gene expression response signature comprises a set of one or more genes, ~~selected from:~~

PKM	SUMO2
ADAR	NUCKS1
ANP32B	PML
ATRX	PNN
BRD7	PRKAB1
CAPN1	RBCK1
CCDC88A	RRP15
CFAP206	SNRPN
CGN	TFIP11
CIRBP	THTPA
CLTC	TMEM87A
EEA1	TNK2
ERICH1	TPR
FAM192A	TRAPPC4
FAM207A	UBA5
HHEX	UBE2D1
KLF3	VPS72
LCA5	YWHAE
MDC1	MCM5
MDM2	MED6
NFAT5	MGST2
ARGN1	MSH6
ARF6	PURA
ARNT	RABGEF1
ARPC5L	RBBP6
ASB16	RBM26

ATF7IP	RECQL
ATP6V0C	RUNX3
BRF1	SFPQ
CHFR	SGCB
EDA	SMARCA1
EFEMP2	SMC1A
ESR2	SPAG9
FAM179B	UBA2
FTH1	UBE2B
H3F3A	USPL1
HDAC4	HP1BP3
HINFP	HRAS
HNRNPK	MAX

3029. A system for determining or validating responsiveness to anti-TNF therapy for a subject suffering from ulcerative colitisa-disease, the system comprising:

a processor of a computing device; and

a memory having instructions stored thereon, wherein the instructions, when executed by the processor cause the processor to perform the following steps:

receiving, by the processor, a gene expression response signature determined to distinguish between responsive and non-responsive subjects suffering from ulcerative colitis who have receivedto the anti-TNF therapy;

analyzing, by the processor, gene expression levels of the subject relative to the gene expression response signature to determine whether the subject expresses the gene expression response signature, wherein the gene expression response signature comprises a set of one or more genes, selected from:

PKM	SUMO2
ADAR	NUCKS1
ANP32B	PML
ATRX	PNN

BRD7	PRKAB1
CAPN1	RBCK1
CCDC88A	RRP15
CFAP206	SNRPN
CGN	TFIP11
CIRBP	THTPA
CLTC	TMEM87A
EEA1	TNK2
ERICH1	TPR
FAM192A	TRAPPC4
FAM207A	UBA5
HHEX	UBE2D1
KLF3	VPS72
LCA5	YWHAE
MDC1	MCM5
MDM2	MED6
NFAT5	MGST2
ARCN1	MSH6
ARF6	PURA
ARNT	RABGEF1
ARPC5L	RBBP6
ASB16	RBM26
ATF7IP	RECQL
ATP6V0C	RUNX3
BRF1	SFPQ
CHFR	SGCB
EDA	SMARCA1
EFEMP2	SMC1A
ESR2	SPAG9
FAM179B	UBA2

~~FTH1~~	~~UBE2B~~
~~H3F3A~~	~~USPL1~~
~~HDAC4~~	~~HP1BP3~~
~~HINFP~~	~~HRAS~~
~~HNRNPK~~	~~MAX~~

31. ~~The system of claim 30, wherein the gene expression response signature comprises an expression level of one or more genes selected from~~

~~ADAR~~	~~NUCKS1~~
~~ANP32B~~	~~PML~~
~~ATRX~~	~~PNN~~
~~BRD7~~	~~PRKAB1~~
~~CAPN1~~	~~RBCK1~~
~~CCDC88A~~	~~RRP15~~
~~CFAP206~~	~~SNRPN~~
~~CGN~~	~~TFIP11~~
~~CIRBP~~	~~THTPA~~
~~CLTC~~	~~TMEM87A~~
~~EEA1~~	~~TNK2~~
~~ERICH1~~	~~TPR~~
~~FAM192A~~	~~TRAPPC4~~
~~FAM207A~~	~~UBA5~~
~~HHEX~~	~~UBE2D1~~
~~KLF3~~	~~VPS72~~
~~LCA5~~	~~YWHAE~~
~~MDC1~~	~~-~~
~~MDM2~~	
~~NFAT5~~	

32. ~~The system of claim 30, wherein the gene expression response signature comprises an expression level of one or more genes selected from~~

ARCN1	MCM5
ARF6	MED6
ARNT	MGST2
ARPC5L	MSH6
ASB16	PURA
ATF7IP	RABGEF1
ATP6V0C	RBBP6
BRF1	RBM26
CHFR	RECQL
EDA	RUNX3
EFEMP2	SFPQ
ESR2	SGCB
FAM179B	SMARCA1
FTH1	SMC1A
H3F3A	SPAG9
HDAC4	UBA2
HINFP	UBE2B
HNRNPK	USPL1
HP1BP3	-
HRAS	
MAX	

33. ~~The system of claim 30, wherein the gene expression response signature comprises an expression level of SUMO2 and/or PKM.~~

34. ~~The system of any one of claims 30-33, wherein the disease is an autoimmune disease.~~

- ~~35. The system of claim 34, wherein the autoimmune disease is selected from rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (adult or pediatric), ulcerative colitis, inflammatory bowel disease, chronic psoriasis, plaque psoriasis, hidradenitis suppurativa, asthma, uveitis, juvenile idiopathic arthritis, vitiligo, Graves' ophthalmopathy (also known as thyroid eye disease, or Graves' orbitopathy), and multiple sclerosis.~~
- ~~36. The system of claim 35, wherein the disease, disorder, or condition is ulcerative colitis.~~
- ~~3730.~~ The system of ~~any one of claims 2930-36~~, wherein the anti-TNF therapy is or comprises ~~administration of~~ infliximab, adalimumab, etanercept, cirtolizumab pegol, golimumab, or biosimilars thereof.
- ~~3831.~~ The system of any one of claims ~~29-30-37~~, wherein the anti-TNF therapy is or comprises ~~administration of~~ infliximab or adalimumab.
- ~~3932.~~ The system of any one of claims ~~29-3130-38~~, wherein the anti-TNF therapy is or comprises ~~administration of~~ infliximab.
- ~~4033.~~ The system of any one of claims ~~29-3230-39~~, wherein the levels of gene expression of the subject are measured by at least one of a microarray, RNA sequencing, real-time quantitative reverse transcription PCR (qRT-PCR), bead array, and ELISA.
- ~~4134.~~ The system of any one of claims ~~29-3330-40~~, wherein the levels of gene expression of the subject are measured by RNA sequencing.
- ~~4235.~~ Use of an alternative to anti-TNF therapy in the manufacture of a medicament for ~~A method of treating a subject~~~~subjects~~ suffering from ~~ulcerative colitis~~~~a disease, disorder, or condition with an alternative to anti-TNF therapy, the method comprising a step of~~~~wherein:~~
~~administering~~ the alternative to anti-TNF therapy is to be administered to the subject who ~~has~~~~have~~ been determined to be non-responsive to the anti-TNF therapy via a

classifier ~~configured~~determined to distinguish between responsive and non-responsive subjects suffering from ulcerative colitis who have received the anti-TNF therapy (“prior subjects”),

~~wherein~~and the classifier distinguishes between the responsive subjects and the non-responsive subjects on the basis of a set of variables, the set of variables comprising expression of a set of one or more genes, ~~selected from:~~

PKM	SUMO2
ADAR	NUCKS1
ANP32B	PML
ATRX	PNN
BRD7	PRKAB1
CAPN1	RBCK1
CCDC88A	RRP15
CFAP206	SNRPN
CGN	TFIP11
CIRBP	THTPA
CLTC	TMEM87A
EEA1	TNK2
ERICH1	TPR
FAM192A	TRAPPC4
FAM207A	UBA5
HHEX	UBE2D1
KLF3	VPS72
LCA5	YWHAE
MDC1	MCM5
MDM2	MED6
NFAT5	MGST2
ARCN1	MSH6
ARF6	PURA

ARNT	RABGEF1
ARPC5L	RBBP6
ASB16	RBM26
ATF7IP	RECQL
ATP6V0C	RUNX3
BRF1	SFPQ
CHFR	SGCB
EDA	SMARCA1
EFEMP2	SMC1A
ESR2	SPAG9
FAM179B	UBA2
FTH1	UBE2B
H3F3A	USPL1
HDAC4	HP1BP3
HINFP	HRAS
HNRNPK	MAX

36. The use of claim 35, wherein the classifier is a trained machine learning classifier.

37. The use of claim 36, wherein the trained machine learning classifier is obtained at least in part by:

(i) determining, for each of the set of genes, a significance of correlation with response outcome to the anti-TNF therapy among the responsive subjects as compared to the non-responsive subjects,

(ii) selecting a reduced subset of the set of genes with highest significance of correlation with response outcome to the anti-TNF therapy, and

(iii) training a classifier to classify whether expression of the reduced subset of the set of genes is indicative of response or non-response, wherein the training comprises using (1) gene expression levels of the reduced subset of the set of genes in biological samples from the responsive subjects and the non-responsive subjects and (2) a responsive outcome of the responsive subjects or a non-responsive outcome of the non-responsive subjects.

38. The use of claim 37, wherein the trained machine learning classifier is obtained at least in part by further:

(iv) validating the classifier on a second independent cohort of subjects who have received the anti-TNF therapy and have been determined as either responding to the anti-TNF therapy or not responding to the anti-TNF therapy.

39. The use of claim 38, wherein the trained machine learning classifier is obtained at least in part by further:

(v) selecting a cutoff score for the validated classifier, such that the validated classifier achieves a true negative (TNR) of at least about 0.5 and a negative predictive value of at least about 0.6.

40. The use of claim 39, wherein the reduced subset of the set of genes has highest significance of correlation with non-response to the anti-TNF therapy.

41. The method use of claim any one of claims 35-40 42, wherein the alternative to anti-TNF therapy is or comprises rituximab, sarilumab, tofacitinib citrate, lefunomide, vedolizumab, tocilizumab, anakinra, ~~or~~ abatacept.

42. The use of any one of claims 35-41, wherein the subject has been determined to be non-responsive to the anti-TNF therapy at least in part by analysis of a biological sample from the subject.

43. The use of claim 42, wherein the biological sample is analyzed by microarray, RNA sequencing, real-time quantitative reverse transcription PCR (qRT-PCR), bead array, or ELISA.

44. The use of any one of claims 35-43, wherein the classifier has previously been validated by analyzing gene expression levels in biological samples from the responsive subjects and the non-responsive subjects to identify genes that show statistically significant

differences in expression level between the responsive subjects and the non-responsive subjects (“signature genes”).

45. The use of claim 44, wherein the signature genes are mapped onto a biological network.
46. The use of claim 45, wherein a subset of signature genes are selected on the basis of their connectivity in the biological network to provide a candidate gene list.
47. The use of claim 46, further comprising training a classifier on expression levels of the genes of the candidate gene list from the first cohort of subjects to identify a subset of the prior subjects having a pattern of expression of the candidate gene list indicative that the subset of prior subjects are unlikely to respond to the anti-TNF therapy, to thereby obtain a trained classifier.
48. The use of claim 47, further comprising validating the trained classifier via analysis of a second cohort comprising an independent and blinded group of responders and non-responders, and selecting a cutoff score such that the classifier distinguishes about 50% of prior subjects that are non-responsive to the anti-TNF therapy to thereby provide a validated classifier.
49. The use of claim 48, wherein the validated classifier distinguishes about 65% of prior subjects that are non-responsive to the anti-TNF therapy.
50. The use of claim 49, wherein the validated classifier distinguishes about 70% of prior subjects that are non-responsive to the anti-TNF therapy.
51. The use of claim 50, wherein the validated classifier distinguishes about 80% of prior subjects that are non-responsive to the anti-TNF therapy.
52. The use of claim 51, wherein the validated classifier distinguishes about 90% of prior subjects that are non-responsive to the anti-TNF therapy.

53. The use of claim 52, wherein the validated classifier distinguishes about 100% of prior subjects that are non-responsive to the anti-TNF therapy.
54. The use of claim 48, wherein the validated classifier distinguishes at least 50% of prior subjects that are non-responsive to the anti-TNF therapy with at least 60% NPV.
55. The use of claim 54, wherein the validated classifier distinguishes at least 50% of prior subjects that are non-responsive to the anti-TNF therapy with at least 80% NPV.
56. The use of claim 55, wherein the validated classifier distinguishes at least 50% of prior subjects that are non-responsive to the anti-TNF therapy with at least 90% NPV.
57. The use of claim 56, wherein the validated classifier distinguishes at least 50% of prior subjects that are non-responsive to the anti-TNF therapy with at least 95% NPV.
58. The use of claim 57, wherein the validated classifier distinguishes at least 50% of prior subjects that are non-responsive to the anti-TNF therapy with about 100% NPV.
59. The use of any one of claims 35-58, wherein the classifier comprises a neural network.
- ~~44. A kit for evaluating a likelihood that a subject having an autoimmune disorder will not respond to an anti-TNF therapy, the kit comprising a set of reagents for detecting an expression level of one or more genes selected from the group consisting of~~

PKM	SUMO2
ADAR	NUCKS1
ANP32B	PML
ATRX	PNN
BRD7	PRKAB1
CAPN1	RBCK1
CCDC88A	RRP15

CFAP206	SNRPN
CGN	TFIP11
GIRBP	THTPA
GLTG	TMEM87A
EEA1	TNK2
ERICH1	TPR
FAM192A	TRAPPC4
FAM207A	UBA5
HHEX	UBE2D1
KLF3	VPS72
LCA5	YWHAE
MDC1	MCM5
MDM2	MED6
NEAT5	MGST2
ARCN1	MSH6
ARF6	PURA
ARNT	RABGEF1
ARPC5L	RBBP6
ASB16	RBM26
ATF7IP	RECQL
ATP6V0C	RUNX3
BRF1	SFPQ
CHFR	SGCB
EDA	SMARCA1
EFEMP2	SMC1A
ESR2	SPAG9
FAM179B	UBA2
FTH1	UBE2B
H3F3A	USPL1
HDAC4	HP1BP3

HINFP	HRAS
HNRNPK	MAX

- ~~45. The kit of claim 44, wherein the set of reagents is suitable for detecting at least SUMO2 and PKM.~~
- ~~46. The kit of claim 44 or 45, wherein the autoimmune disorder is ulcerative colitis~~
- ~~47. Use of a kit according to any of claims 44-46 for the selection of a subject having an autoimmune disorder to receive an anti-TNF therapy.~~