

benefit. *See, e.g.,* M.T. Abreu, “Anti-TNF Failures in Crohn’s Disease,” *Gastroenterol Hepatol (N.Y.)*, 7(1):37-39 (Jan. 2011); *see also* Ding *et al.*, “Systematic review: predicting and optimising response to anti-TNF therapy in Crohn’s disease – algorithm for practical management,” *Aliment Pharmacol. Ther.*, 43(1):30-51 (Jan. 2016) (reporting that “[p]rimary nonresponse to anti-TNF treatment affects 13–40% of patients.”).

[0008] Provided technologies, among other things, permit care providers to distinguish between or among categories of subjects – e.g., subjects likely to benefit from a particular therapy (e.g., anti-TNF therapy) from those who are not, those who are more likely to achieve or suffer a particular outcome or side effect, etc. In some examples, such provided technologies thus reduce risks to patients, increase timing and quality of care for non-responder patient populations, increase efficiency of drug development, and/or avoid costs associated with administering ineffective therapy to non-responder patients or with treating side effects such patients experience upon receiving the relevant therapy (e.g., anti-TNF therapy).

[0008a] In one aspect, the present disclosure refers to a use of an anti-TNF therapy in the manufacture of a medicament for treating subjects suffering from an autoimmune disorder, the use comprising that the anti-TNF therapy is to be administered to subjects who have been determined to be responsive via a classifier established to distinguish between responsive and non-responsive prior subjects in a cohort who have received the anti-TNF therapy; wherein the classifier is developed by assessing: one or more genes whose expression levels significantly correlate to clinical responsiveness or non-responsiveness; at least one of: presence of one or more single nucleotide polymorphisms (SNPs) in an expressed sequence of the one or more genes; or at least one clinical characteristic of the responsive and non-responsive prior subjects; and wherein the classifier is validated by an independent cohort than the cohort who have received the anti-TNF therapy.

[0008b] In another aspect, the present disclosure refers to a use of a therapy in the manufacture of a medicament for treating a subject suffering from an autoimmune disease, the use comprising that the therapy is to be administered to subjects who have been classified as responsive or non-responsive via a classifier established to distinguish between responsive and non-responsive prior subjects in a cohort who have received an anti-TNF therapy; wherein, if the subject is classified as responsive by the classifier, that an anti-TNF therapy is to be administered; and if the subject is classified as non-responsive by the classifier, that an alternative to anti-TNF therapy is to be administered; and the classifier is developed by assessing: one or more genes whose expression levels significantly

correlate to clinical responsiveness or non-responsiveness; at least one of: presence of one or more single nucleotide polymorphisms (SNPs) in an expressed sequence of the one or more genes; or at least one clinical characteristic of the responsive and non-responsive prior subjects; and the classifier is validated by an independent cohort than the cohort who have received the anti-TNF therapy.

[0008c] In another aspect, the present disclosure refers to a use of an anti-TNF therapy in the manufacture of a medicament for treating subjects suffering from an autoimmune disorder, the use comprising that the anti-TNF therapy is to be administered to subjects who have been determined to be responsive via a classifier established to distinguish between responsive and non-responsive prior subjects who have received the anti-TNF therapy; wherein the classifier that is developed by assessing: one or more genes whose expression levels significantly correlate to clinical responsiveness or non-responsiveness; and at least one of: presence of one or more single nucleotide polymorphisms (SNPs) in an expressed sequence of the one or more genes; or at least one clinical characteristic of the responsive and non-responsive prior subjects.

[0009] In some examples, the present disclosure provides a method of treating subjects with particular therapy (e.g., anti-TNF therapy), the method comprising a step of: administering the therapy to subjects who have been determined to be responsive via a classifier established to distinguish between subjects expected to be responsive vs non-responsive to the therapy.

[0010] Among other things, examples of a classifier useful for determining whether a subject is responsive or non-responsive to certain therapies, and/or to achieve or suffer from a particular outcome or side effect, is described further herein, as well as methods of preparing such a classifier.

[0011] 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.

[0012] For example, as described herein, the present disclosure utilizes an insight provided by WO 2019/178546 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* (i.e., significant) changes; as described in WO 2019/178546, such an approach misses subtle but meaningful

differences relevant to disease biology. Moreover, the present disclosure also utilizes the insight, also described in WO 2019/178546, 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 examples, 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 certain therapies, and in particular to anti-TNF therapy. In some examples, genes included in such a classifier represent a connected module on the human interactome.

[0013] The present disclosure further provides an insight that particularly useful therapeutic classifiers are developed through use of cross-platform data. For example, the present disclosure teaches that combination of differential gene expression analysis with sequence analysis, e.g., single nucleotide polymorphism (SNP) analysis, of expressed sequences is particularly useful in development of therapeutic classifiers (i.e., of classifiers that predict likelihood that subject(s) will respond to and/or will achieve or suffer one or more particular outcome or side effect(s), etc. when/if administered a relevant therapy.

[0014] A significant known problem with various therapies (e.g., anti-TNF) therapies is that response rates are inconsistent. Indeed, recent international conferences designed to bring together leading scientists and clinicians in the fields of immunology and rheumatology to identify unmet needs in these fields almost universally identify uncertainty in response rates as an ongoing challenge. For example, the 19th annual International Targeted Therapies meeting, which held break-out sessions relating to challenges in treatment of a variety of diseases, including rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, systemic lupus erythematosus, and connective tissue diseases (e.g. Sjogren's syndrome, systemic sclerosis, vasculitis including Bechet's and IgG4 related disease), identified certain issues common to all of these diseases, specifically, "the need for better understanding the heterogeneity within each disease . . . so that predictive tools for therapeutic responses can be developed. See Winthrop, *et al.*, "The unmet need in rheumatology: Reports from the targeted therapies meeting 2017," *Clin. Immunol.* pii: S1521-6616(17)30543-0, Aug. 12, 2017. Similarly, extensive literature relating to treatment of Crohn's Disease with anti-TNF therapy consistently bemoans erratic response rates and inability to predict which patients

will benefit. *See, e.g.,* M.T. Abreu, “Anti-TNF Failures in Crohn’s Disease,” *Gastroenterol Hepatol* (N.Y.), 7(1):37-39 (Jan. 2011); *see also* Ding *et al.*, “Systematic review: predicting and optimising response to anti-TNF therapy in Crohn’s disease – algorithm for practical management,” *Aliment Pharmacol. Ther.*, 43(1):30-51 (Jan. 2016) (reporting that “[p]rimary nonresponse to anti-TNF treatment affects 13–40% of patients.”).

[0015] Thus, a significant number of patients to whom anti-TNF therapy is currently being administered do not benefit from the treatment, and could even be harmed. Known risks of serious infection and malignancy associated with anti-TNF therapy are so significant that product approvals typically require so-called “black box warnings” be included on the label. Other potential side effects of such therapy include, for example, congestive heart failure, demyelinating disease, and other systemic side effects. Furthermore, given that several weeks to months of treatment are required before a patient is identified as not responding to anti-TNF therapy (i.e., is a non-responder to anti-TNF therapy), proper treatment of such patients can be significantly delayed as a result of the current inability to identify responder vs non-responder subjects. *See, e.g.,* Roda *et al.*, “Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management,” *Clin. Tranl. Gastroenterol.*, 7(1):e135 (Jan. 2016) (citing Hanauer *et al.*, “ACCENT I Study group. Maintenance Infliximab for Crohn’s disease: the ACCENT I randomized trial,” *Lancet* 59:1541-1549 (2002); Sands *et al.*, “Infliximab maintenance therapy for fistulizing Crohn’s disease,” *N. Engl. J. Med.* 350:876-885 (2004)).

[0016] Accordingly, in some examples, the present disclosure provides a method of treating subjects with 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 established to distinguish between responsive and non-responsive prior subjects who have received the anti-TNF therapy wherein the classifier that is developed by assessing: one or more genes whose expression levels significantly correlate (e.g., in a linear and/or non-linear manner) to clinical responsiveness or non-responsiveness; and at least one of: presence of one or more single nucleotide polymorphisms (SNPs) in an expressed sequence of the one or more genes; or at least one clinical characteristic of the responsive and non-responsive prior subjects.

[0017] In some examples, the present disclosure provides a method of treating an inflammatory disease, disorder, or condition comprising a step of administering an anti-TNF

therapy to subjects classified as responsive by application of a classifier determined to predict responsiveness of subjects with at least 90% accuracy across a population of at least 170 subjects.

[0018] In some examples, the present disclosure provides a method of developing a classifier for stratifying subjects with respect to one or more therapeutic attributes comprising steps of: analyzing sequence data of RNA expressed in subjects representing at least two different categories with respect to at least one of the therapeutic attributes; assessing the presence of one or more single nucleotide polymorphisms (SNPs) from the sequence data; determining the presence of the one or more SNPs correlates with the at least one therapeutic attribute; and including the one or more SNPs in the classifier.

[0019] In some examples, the present disclosure provides, in a method of developing a classifier for stratifying subjects with respect to one or more therapeutic attributes by analyzing sequence data of RNA expressed in subjects representing at least two different categories with respect to at least one of the therapeutic attributes, the improvement that comprises: assessing presence of one or more single nucleotide polymorphisms (SNPs) from the sequence data; determining the presence of the one or more SNPs correlates with the at least one therapeutic attribute; and including the one or more SNPs in the classifier.

[0020] In some examples, the present disclosure provides a method of treating subjects suffering from an autoimmune disorder, the method comprising a step of: administering an anti-TNF therapy to subjects who have been determined to be responsive via a classifier established to distinguish between responsive and non-responsive prior subjects in a cohort who have received the anti-TNF therapy; wherein the classifier is developed by assessing: one or more genes whose expression levels significantly correlate (e.g., in a linear and/or non-linear manner) to clinical responsiveness or non-responsiveness; at least one of: presence of one or more single nucleotide polymorphisms (SNPs) in an expressed sequence of the one or more genes; or at least one clinical characteristic of the responsive and non-responsive prior subjects; and wherein the classifier is validated by an independent cohort than the cohort who have received the anti-TNF therapy.

[0021] In some examples, the classifier predicts responsiveness of subjects with at least 90% accuracy across a population of at least 170 subjects. In some examples, the one or more genes are characterized by their topological properties when mapped on a human interactome map. In

some examples, the SNPs are identified in reference to a human genome. In some examples, the classifier is developed by assessing each of: the one or more genes whose expression levels significantly correlate (e.g., in a linear and/or non-linear manner) to clinical responsiveness or non-responsiveness; presence of the one or more SNPs; and the at least one clinical characteristic.

[0022] In some examples, the one or more genes are selected from:

ARPC1A	LOC100506083
ATAT1	MORN2
ATRAID	NGF
CD27	RHOBTB1
CHMP7	RNGTT
COMMD5	SETD9
CORO2B	SNX8
CYSLTR2	SPINT2
DNAJC7	SPON2
GOLGA1	SSNA1
HPCA	STOML2
IMPDH2	SUOX
KAT8	TMEM258
KLHDC3	UBL7-AS1

[0023] In some examples, the at least one clinical characteristic is selected from: body-mass index (BMI), gender, age, race, previous therapy treatment, disease duration, C-reactive protein level, presence of anti-cyclic citrullinated peptide, presence of rheumatoid factor, patient global assessment, treatment response rate (e.g., ACR20, ACR50, ACR70), and combinations thereof. In

some examples, the classifier identifies at least 40% of subjects within a population that are non-responsive with at least 90% accuracy, wherein the population comprises at least 170 subjects.

[0024] In some examples, the anti-TNF therapy comprises administration of infliximab, adalimumab, etanercept, certolizumab pegol, golimumab, or biosimilars thereof. In some examples, the disease, disorder, or condition is selected from rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, chronic psoriasis, hidradenitis suppurativa, multiple sclerosis, and juvenile idiopathic arthritis. In some examples, the classifier is established using microarray analysis derived from the responsive and non-responsive prior subjects. In some examples, the classifier is validated using RNAseq data derived from the independent cohort. In some examples, the SNPs are selected from Table 5.

[0025] In some examples, the present disclosure provides a method of administering a therapy to a subject suffering from an autoimmune disease, the method comprising administering the therapy to subjects who have been classified as responsive or non-responsive via a classifier established to distinguish between responsive and non-responsive prior subjects in a cohort who have received the anti-TNF therapy; wherein, if the subject is classified as responsive by the classifier, administering an anti-TNF therapy; and if the subject is classified as non-responsive by the classifier, administering an alternative to anti-TNF therapy; and the classifier is developed by assessing: one or more genes whose expression levels significantly correlate (e.g., in a linear and/or non-linear manner) to clinical responsiveness or non-responsiveness; at least one of: presence of one or more single nucleotide polymorphisms (SNPs) in an expressed sequence of the one or more genes; or at least one clinical characteristic of the responsive and non-responsive prior subjects; and the classifier is validated by an independent cohort than the cohort who have received the anti-TNF therapy.

[0026] In some examples, the classifier predicts responsiveness of subjects with at least 90% accuracy across a population of at least 170 subjects. In some examples, the classifier is developed by assessing each of: the one or more genes whose expression levels significantly correlate (e.g., in a linear and/or non-linear manner) to clinical responsiveness or non-responsiveness; presence of the one or more SNPs; and the at least one clinical characteristic.

[0027] In some examples, the at least one clinical characteristic is selected from: body-mass index (BMI), gender, age, race, previous therapy treatment, disease duration, C-reactive protein level, presence of anti-cyclic citrullinated peptide, presence of rheumatoid factor, patient global assessment, treatment response rate (e.g., ACR20, ACR50, ACR70), and combinations thereof. In some examples, the anti-TNF therapy comprises administration of infliximab, adalimumab, etanercept, certolizumab pegol, golimumab, or biosimilars thereof.

[0028] In some examples, the alternative to anti-TNF therapy is selected from rituximab, sarilumab, tofacitinib citrate, lefunomide, vedolizumab, tocilizumab, anakinra, and abatacept.

[0029] In some examples, the disease, disorder, or condition is selected from rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, chronic psoriasis, hidradenitis suppurativa, multiple sclerosis, and juvenile idiopathic arthritis.

[0030] In some examples, the present disclosure provides a method of developing a classifier for stratifying subjects with respect to one or more therapeutic attributes comprising steps of: analyzing sequence data of RNA expressed in subjects representing at least two different categories with respect to at least one of the therapeutic attributes; assessing the presence of one or more single nucleotide polymorphisms (SNPs) from the sequence data; determining the presence of the one or more SNPs correlates with the at least one therapeutic attribute; and including the one or more SNPs in the classifier.

[0031] In some examples, the present disclosure provides, in a method of developing a classifier for stratifying subjects with respect to one or more therapeutic attributes by analyzing sequence data of RNA expressed in subjects representing at least two different categories with respect to at least one of the therapeutic attributes, the improvement that comprises: assessing presence of one or more single nucleotide polymorphisms (SNPs) from the sequence data; and determining the presence of the one or more SNPs correlates with the at least one therapeutic attribute; and including the one or more SNPs in the classifier.

[0032] In some examples, the one or more therapeutic attributes is selected from the group consisting of: risk of developing a particular disease, disorder or condition, likelihood of a particular outcome for a particular disease, disorder, or condition, likelihood of response to a

particular therapy. In some examples, the one or more therapeutic attributes are the likelihood of response to a particular therapy. In some examples, the particular therapy is anti-TNF therapy. In some examples, assessing the presence of the one or more SNPs comprises comparing the sequence data of RNA to a reference human genome.

[0033] In some examples, the present disclosure provides a method of treating a subject suffering from an autoimmune disease, the method comprising steps of: (a) receiving, by a processor of a computing device, data corresponding to expression levels of each of one or more genes of the subject, where the genes are selected from Table 1; (b) automatically determining, by the processor, a classification of the subject as responsive or non-responsive to an anti-TNF therapy using the data received in step (a); and, optionally, (c) administering an alternative to anti-TNF therapy to the subject for treatment of the autoimmune disease if the subject is classified as non-responsive to the anti-TNF therapy; or administering the anti-TNF therapy if the subject is classified as responsive to the anti-TNF therapy.

[0034] In some examples, the processor in step (a) further receives data corresponding to at least one of: one or more clinical characteristics; or one or more single nucleotide polymorphisms (SNPs).

[0035] In some examples, the one or more clinical characteristics are selected from: body-mass index (BMI), gender, age, race, previous therapy treatment, disease duration, C-reactive protein (CRP) level, presence of anti-cyclic citrullinated peptide, presence of rheumatoid factor, patient global assessment, treatment response rate (e.g., ACR20, ACR50, ACR70), and combinations thereof. In some examples, the autoimmune disease is selected from rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, chronic psoriasis, hidradenitis suppurativa, and juvenile idiopathic arthritis. In some examples, the autoimmune disease is rheumatoid arthritis or ulcerative colitis.

[0036] In some examples, the alternative to anti-TNF therapy is selected from rituximab, sarilumab, tofacitinib citrate, lefunomide, vedolizumab, tocilizumab, anakinra, and abatacept. In some examples, the anti-TNF therapy is selected from infliximab, adalimumab, etanercept, certolizumab pegol, golimumab, or biosimilars thereof.

[0037] In some examples, step (b) comprises automatically determining said classification using a machine learning model. In some examples, the machine learning model is a random forest model.

[0038] In some examples, step (b) comprises automatically determining said classification without use of a clinical covariate classifier (CC). In some examples, step (b) comprises automatically determining said classification without use of a combined genomic-clinical classifier (GCC). In some examples, step (b) comprises automatically determining said classification without use of a clinical covariate classifier (CC) and without use of a combined genomic-clinical classifier (GCC).

[0039] In some examples, the present disclosure provides a method comprising the steps of: (a) receiving, by a processor of a computing device, data corresponding to expression levels of each of one or more genes of a subject suffering from an autoimmune disease (e.g., rheumatoid arthritis), said one or more genes comprising at least one member (e.g., one, two, three, four, five, six, seven, eight, nine, ten, or all eleven member(s)) selected from the group consisting of CORO2B, STOML2, CHMP7, SPINT2, CYSLTR2, SSNA1, IMPDH2, GOLGA1, SUOX, ARPC1A, and KLHDC3; (b) automatically determining, by the processor, a classification of the subject as non-responsive to an anti-TNF therapy using the data received in step (a); and, optionally, (c) prescribing and/or administering a second therapy (e.g., an alternative to the first therapy, e.g., an alternative to anti-TNF therapy) to the subject for treatment of the disease, thereby avoiding prescription of and/or administration of the first therapy to the subject.

[0040] In some examples the present disclosure provides a method comprising the steps of: (a) receiving, by a processor of a computing device, data corresponding to expression levels of each of one or more genes of a subject suffering from a disease (e.g., an autoimmune disease, e.g., rheumatoid arthritis), said one or more genes comprising at least one member (e.g., one, two, three, four, five, six, seven, eight, nine, ten, or all eleven member(s)) selected from the group consisting of CORO2B, STOML2, CHMP7, SPINT2, CYSLTR2, SSNA1, IMPDH2, GOLGA1, SUOX, ARPC1A, and KLHDC3; (b) automatically determining, by the processor, a classification of the subject as responsive to a first therapy (e.g., anti-TNF therapy) using the data received in step (a); and, optionally, (c) prescribing and/or administering the first therapy to the subject for treatment of the disease.

[0041] In some examples, step (b) comprises automatically determining said classification using a machine learning model (e.g., a random forest model). In some examples, step (b) comprises automatically determining said classification *without* use of a clinical covariate classifier (CC) and *without* use of a combined genomic-clinical classifier (GCC).

[0042] In some examples, the present disclosure provides a pipeline (e.g., a computer architecture pipeline) for analysis of genomic data (e.g., next gen RNA-seq data) of a subject (e.g., and for determination of a classification of said subject based on said genomic data), said pipeline comprising a plurality of modules, each module capable of being independently validated following an update of said module.

[0043] In some examples, said plurality of modules comprises one or more machine learning models.

[0044] In some examples, said plurality of modules comprises one or more known bioinformatics modules (e.g., RSEM and/or STAR) and one or more proprietary classification module(s).

[0045] In some examples, the present disclosure provides a method of classifying a subject suffering from an autoimmune disease as likely responsive or likely non-responsive to an anti-TNF therapy prior to any administration of said anti-TNF therapy to said subject, the method comprising steps of: (a) receiving, by a processor of a computing device, data corresponding to an expression level for the subject of each of one or more genes selected from the group consisting of the following:

ARPC1A	LOC100506083
ATAT1	MORN2
ATRAID	NGF
CD27	RHOBTB1
CHMP7	RNGTT
COMMD5	SETD9
CORO2B	SNX8
CYSLTR2	SPINT2
DNAJC7	SPON2
GOLGA1	SSNA1
HPCA	STOML2
IMPDH2	SUOX
KAT8	TMEM258

KLHDC3	UBL7-AS1
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and (b) automatically determining, by the processor, a classification of the subject as responsive or non-responsive to the anti-TNF therapy using the data received in step (a).

[0046] In some examples, a method of classifying a subject suffering from an autoimmune disease as likely responsive or likely non-responsive to an anti-TNF therapy prior to any administration of said anti-TNF therapy to said subject, further comprises: (c) prescribing and/or administering an alternative to anti-TNF therapy to the subject for treatment of the autoimmune disease if the subject is classified in step (b) as non-responsive to the anti-TNF therapy; or administering the anti-TNF therapy to the subject if the subject is classified in step (b) as responsive to the anti-TNF therapy.

[0047] In some examples, the processor in step (a) further receives data corresponding to at least one of (i) and (ii) as follows: (i) one or more clinical characteristics of the subject; (ii) one or more single nucleotide polymorphisms (SNPs) for the subject.

[0048] In some examples, the processor in step (a) receives data corresponding to one or more clinical characteristics of the subject selected from the group consisting of body-mass index (BMI), gender, age, race, previous therapy treatment, disease duration, C-reactive protein (CRP) level, presence of anti-cyclic citrullinated peptide, presence of rheumatoid factor, patient global assessment, and treatment response rate (e.g., ACR20, ACR50, ACR70).

[0049] In some examples, the processor in step (a) receives data corresponding to one or more SNPs listed in Table 5.

[0050] In some examples, the autoimmune disease is a member selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, chronic psoriasis, hidradenitis suppurativa, and juvenile idiopathic arthritis. In some examples, the autoimmune disease is rheumatoid arthritis or ulcerative colitis.

[0051] In some examples, the alternative to anti-TNF therapy comprises at least one member selected from the group consisting of rituximab, sarilumab, tofacitinib citrate, lefunomide, vedolizumab, tocilizumab, anakinra, and abatacept.

[0052] In some examples, the anti-TNF therapy comprises at least one member selected from the group consisting of infliximab, adalimumab, etanercept, cirtolizumab pegol, goliluma, and a biosimilar of any of the foregoing.

[0053] In some examples, the alternative to anti-TNF therapy does **not** comprise any member of the group consisting of infliximab, adalimumab, etanercept, cirtolizumab pegol, goliluma, and any biosimilar of any of the foregoing.

[0054] In some examples, step (b) comprises automatically determining said classification using a machine learning model. In some examples, the machine learning model is a random forest model.

[0055] In some examples, step (b) comprises automatically determining said classification without use of a clinical covariate classifier (CC). In some examples, step (b) comprises automatically determining said classification without use of a combined genomic-clinical classifier (GCC). In some examples, step (b) comprises automatically determining said classification without use of a clinical covariate classifier (CC) and without use of a combined genomic-clinical classifier (GCC).

[0056] In some examples, the present disclosure provides a method of classifying a subject suffering from an autoimmune disease as likely responsive or likely non-responsive to an anti-TNF therapy prior to any administration of said anti-TNF therapy to said subject, the method comprising the steps of: (a) receiving, by a processor of a computing device, data corresponding to an expression level of each of one or more genes of a subject suffering from the autoimmune disease said one or more genes comprising at least one member selected from the group consisting of CORO2B, STOML2, CHMP7, SPINT2, CYSLTR2, SSNA1, IMPDH2, GOLGA1, SUOX, ARPC1A, and KLHDC3; (b) automatically determining, by the processor, a classification of the subject as likely responsive or likely non-responsive to the anti-TNF therapy using the data received in step (a).

[0057] In some examples, a method of classifying a subject suffering from an autoimmune disease as likely responsive or likely non-responsive to an anti-TNF therapy prior to any administration of said anti-TNF therapy to said subject, further comprises: (c) prescribing and/or administering an alternative to anti-TNF therapy to the subject for treatment of the autoimmune

disease if the subject is classified in step (b) as non-responsive to the anti-TNF therapy; or administering the anti-TNF therapy to the subject if the subject is classified in step (b) as responsive to the anti-TNF therapy.

[0058] In some examples, the autoimmune disease is rheumatoid arthritis.

[0059] In some examples, step (a) comprises receiving data corresponding to an expression level of each of at least two genes selected from the group consisting of CORO2B, STOML2, CHMP7, SPINT2, CYSLTR2, SSNA1, IMPDH2, GOLGA1, SUOX, ARPC1A, and KLHDC3.

[0060] In some examples, step (a) comprises receiving data corresponding to an expression level of each of at least three genes selected from the group consisting of CORO2B, STOML2, CHMP7, SPINT2, CYSLTR2, SSNA1, IMPDH2, GOLGA1, SUOX, ARPC1A, and KLHDC3.

[0061] In some examples, step (a) comprises receiving data corresponding to an expression level of each of at least five genes selected from the group consisting of CORO2B, STOML2, CHMP7, SPINT2, CYSLTR2, SSNA1, IMPDH2, GOLGA1, SUOX, ARPC1A, and KLHDC3.

[0062] In some examples, the processor in step (a) further receives data corresponding to at least one of (i) and (ii) as follows: (i) one or more clinical characteristics of the subject; (ii) one or more single nucleotide polymorphisms (SNPs) for the subject.

[0063] In some examples, the processor in step (a) receives data corresponding to one or more clinical characteristics of the subject selected from the group consisting of body-mass index (BMI), gender, age, race, previous therapy treatment, disease duration, C-reactive protein (CRP) level, presence of anti-cyclic citrullinated peptide, presence of rheumatoid factor, patient global assessment, and treatment response rate (e.g., ACR20, ACR50, ACR70).

[0064] In some examples, the processor in step (a) receives data corresponding to one or more SNPs listed in Table 5.

[0065] In some examples, the present disclosure provides a system for classifying a subject suffering from an autoimmune disease as likely responsive or likely non-responsive to an anti-TNF therapy prior to any administration of said anti-TNF therapy to said subject, the system comprising: a processor; and a memory having instructions thereon, the instructions, when executed by the processor, causing the processor to: (a) receive a set of data, said set of data

comprising an expression level for the subject of each of one or more genes selected from the group consisting of the following:

ARPC1A	LOC100506083
ATAT1	MORN2
ATRAID	NGF
CD27	RHOBTB1
CHMP7	RNGTT
COMMD5	SETD9
CORO2B	SNX8
CYSLTR2	SPINT2
DNAJC7	SPON2
GOLGA1	SSNA1
HPCA	STOML2
IMPDH2	SUOX
KAT8	TMEM258
KLHDC3	UBL7-AS1

and (b) automatically determine a classification of the subject as responsive or non-responsive to the anti-TNF therapy using the set of data.

[0066] In some examples, the set of data further comprises data corresponding to at least one of (i) and (ii) as follows: (i) one or more clinical characteristics of the subject; (ii) one or more single nucleotide polymorphisms (SNPs) for the subject.

[0067] In some examples, the set of data comprises data corresponding to one or more clinical characteristics of the subject selected from the group consisting of body-mass index (BMI), gender, age, race, previous therapy treatment, disease duration, C-reactive protein (CRP) level, presence of anti-cyclic citrullinated peptide, presence of rheumatoid factor, patient global assessment, and treatment response rate (e.g., ACR20, ACR50, ACR70).

[0068] In some examples, the set of data comprises one or more SNPs listed in Table 5.

[0069] In some examples, the autoimmune disease is a member selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, chronic psoriasis, hidradenitis suppurativa, and juvenile idiopathic arthritis. In some examples, the autoimmune disease is rheumatoid arthritis or ulcerative colitis. In some examples, the autoimmune disease is rheumatoid arthritis.

CLAIMS

1. Use of an anti-TNF therapy in the manufacture of a medicament for treating subjects suffering from an autoimmune disorder, the use comprising that

the anti-TNF therapy is to be administered to subjects who have been determined to be responsive via a classifier established to distinguish between responsive and non-responsive prior subjects in a cohort who have received the anti-TNF therapy;

wherein the classifier is developed by assessing:

one or more genes whose expression levels significantly correlate to clinical responsiveness or non-responsiveness;

at least one of:

presence of one or more single nucleotide polymorphisms (SNPs) in an expressed sequence of the one or more genes; or

at least one clinical characteristic of the responsive and non-responsive prior subjects; and

wherein the classifier is validated by an independent cohort than the cohort who have received the anti-TNF therapy.
2. The use of claim 1, wherein the classifier predicts responsiveness of subjects with at least 90% accuracy across a population of at least 170 subjects.
3. The use of claims 1 or 2, wherein the one or more genes are characterized by their topological properties when mapped on a human interactome map.
4. The use of any one of claims 1-3, wherein the SNPs are identified in reference to a human genome.
5. The use of any one of claims 1-4, wherein the classifier is developed by assessing each of:

- the one or more genes whose expression levels significantly correlate to clinical responsiveness or non-responsiveness;
- presence of the one or more SNPs; and
- the at least one clinical characteristic.
6. The use of any one of claims 1-5, wherein the one or more genes are selected from: ARPC1A, ATAT1, ATRAID, CD27, CHMP7, COMMD5, CORO2B, CYSLTR2, DNAJC7, GOLGA1, HPCA, IMPDH2, KAT8, KLHDC3, LOC100506083, MORN2, NGF, RHOBTB1, RNGTT, SETD9, SNX8, SPINT2, SPON2, SSNA1, STOML2, SUOX, TMEM258, and UBL7 AS1.
 7. The use of any one of claims 1-6, wherein the at least one clinical characteristic is selected from: body-mass index (BMI), gender, age, race, previous therapy treatment, disease duration, C-reactive protein level, presence of anti-cyclic citrullinated peptide, presence of rheumatoid factor, patient global assessment, treatment response rate (e.g., ACR20, ACR50, ACR70), and combinations thereof.
 8. The use of any one of claims 1-6, wherein the classifier identifies at least 40% of subjects within a population that are non-responsive with at least 90% accuracy, wherein the population comprises at least 170 subjects.
 9. The use of any one of claims 1-8, wherein the anti-TNF therapy comprises administration of infliximab, adalimumab, etanercept, certolizumab pegol, golimumab, or biosimilars thereof.
 10. The use of any one of claims 1-9, wherein the autoimmune disorder is selected from rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, chronic psoriasis, hidradenitis suppurativa, multiple sclerosis, and juvenile idiopathic arthritis.

11. The use of any one of claims 1-10, wherein the classifier is established using microarray analysis derived from the responsive and non-responsive prior subjects.
12. The use of any one of claims 1-11, wherein the classifier is validated using RNAseq data derived from the independent cohort.
13. The use of any one of claims 1-12, wherein the SNPs are selected from: chr1.161644258, chr1.2523811, chr11.107967350, chr17.38031857, chr7.128580042, rs10774624, rs10985070, rs11889341, rs1571878, rs1633360, rs17668708, rs1877030, rs1893592, rs1980422, rs2228145, rs2233424, rs2236668, rs2301888, rs2476601, rs3087243, rs3218251, rs331463, rs34536443, rs34695944, rs4239702, rs4272, rs45475795, rs508970, rs5987194, rs657075, rs6715284, rs706778, rs72634030, rs73013527, rs73194058, rs773125, rs7752903, rs8083786, and rs9653442.
14. Use of a therapy in the manufacture of a medicament for treating a subject suffering from an autoimmune disease, the use comprising that

the therapy is to be administered to subjects who have been classified as responsive or non-responsive via a classifier established to distinguish between responsive and non-responsive prior subjects in a cohort who have received an anti-TNF therapy;

wherein, if the subject is classified as responsive by the classifier, that an anti-TNF therapy is to be administered; and if the subject is classified as non-responsive by the classifier, that an alternative to anti-TNF therapy is to be administered; and

the classifier is developed by assessing:

one or more genes whose expression levels significantly correlate to clinical responsiveness or non-responsiveness;

at least one of:

presence of one or more single nucleotide polymorphisms (SNPs) in an expressed sequence of the one or more genes; or

at least one clinical characteristic of the responsive and non-responsive prior subjects; and

the classifier is validated by an independent cohort than the cohort who have received the anti-TNF therapy.

15. The use of claim 14, wherein the classifier predicts responsiveness of subjects with at least 90% accuracy across a population of at least 170 subjects.
16. The use of claim 15, wherein the classifier is developed by assessing each of:
 - the one or more genes whose expression levels significantly correlate to clinical responsiveness or non-responsiveness;
 - presence of the one or more SNPs; and
 - the at least one clinical characteristic.
17. The use of any one of claims 14-16, wherein the at least one clinical characteristic is selected from: body-mass index (BMI), gender, age, race, previous therapy treatment, disease duration, C-reactive protein level, presence of anti-cyclic citrullinated peptide, presence of rheumatoid factor, patient global assessment, treatment response rate (e.g., ACR20, ACR50, ACR70), and combinations thereof.
18. The use of any one of claims 14-17, wherein the anti-TNF therapy comprises administration of infliximab, adalimumab, etanercept, certolizumab pegol, golimumab, or biosimilars thereof.
19. The use of any one of claims 14-18, wherein the alternative to anti-TNF therapy is selected from is selected from rituximab, sarilumab, tofacitinib citrate, lefunomide, vedolizumab, tocilizumab, anakinra, and abatacept.
20. The use of claim 19, wherein the autoimmune disorder is selected from rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, chronic psoriasis, hidradenitis suppurativa, multiple sclerosis, and juvenile idiopathic arthritis.

21. Use of an anti-TNF therapy in the manufacture of a medicament for treating subjects suffering from an autoimmune disorder, the use comprising that

the anti-TNF therapy is to be administered to subjects who have been determined to be responsive via a classifier established to distinguish between responsive and non-responsive prior subjects who have received the anti-TNF therapy;

wherein the classifier that is developed by assessing:

one or more genes whose expression levels significantly correlate to clinical responsiveness or non-responsiveness; and

at least one of:

presence of one or more single nucleotide polymorphisms (SNPs) in an expressed sequence of the one or more genes; or

at least one clinical characteristic of the responsive and non-responsive prior subjects.