METHODS AND SYSTEMS FOR THERAPY MONITORING AND TRIAL DESIGN

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/213,431, filed June 22, 2021, and U.S. Provisional Application No. 63/329,008, filed April 8, 2022, each of which is incorporated by reference herein in its entirety.

BACKGROUND

[0002] Therapy response for many complex diseases may continue to elude researchers and practitioners. A single stratification factor or biomarker may be insufficient to determine whether a therapy is effective in treating a particular patient. Instead, many diseases, such as autoimmune diseases, cancers, and the like, affect a multitude of biological sub-systems. (*See* e.g., Frohlich, *et al.*, *BMC Med*, 16, 150:1122-1127 (2018), which is incorporated herein by reference for all purposes). A reactive approach (e.g., a trial-and-error approach) to identifying treatment for patients may be costly and introduce risk for adverse side effects, potential disease progression, and delay of proper treatment. (*See* e.g., Mathur & Sutton, *Biomed. Rep.*, 7:3-5 (2017), which is incorporated herein by reference for all purposes).

[0003] Further, inability to determine individual response vs. therapy efficacy in clinical trials may be costly and dangerous for subjects who are only exposed to dangerous side effects without any benefit from the therapy. Once a subject is determined to be a non-responder to a particular therapy on an individual basis, they can be removed from a clinical trial, but such a delay in removal may increase the risk of serious side effects, as well as lost time and cost for the study directors. Predicting which subjects may be responsive or non-responsive early in a clinical trial may be challenging or may not always be possible if there are no predictive biomarkers available. Changes in clinical characteristics, instead, may be used determine whether a subject is or is not responding to a therapy, but such changes can take time, and be subjective in nature, especially for changes that are marked by self-assessment of individual subjects.

SUMMARY

[0003a] In one aspect, provided herein is use of a therapy in the manufacture of a medicament for determining a disease gene expression signature, wherein a test subject is to be administered a therapeutically effective amount of (i) the therapy, based at least in part on a trained machine learning classifier analyzing a disease gene expression signature to predict responsiveness of the test subject to the therapy, or (ii) a second therapy different from the therapy, based at least in part on the trained machine learning classifier analyzing the disease gene expression signature to predict non-responsiveness of the test subject to the therapy, wherein the disease gene

expression signature is determined at least in part by: receiving gene expression data from a cohort of subjects suffering from the disease, disorder, or condition; stratifying the cohort of subjects into two or more groups based at least in part on the gene expression data; calculating differences in gene expression between the two or more groups of subjects and a group of non-diseased subjects; selecting one or more genes having significant differences in gene expression between the two or more groups of subjects and the group of non-diseased subjects ("disease candidate genes"); compiling a set of disease genes comprising the disease candidate genes; and selecting at least a subset of the set of disease genes to thereby determine the disease gene expression signature.

[0003b] In another aspect, provided herein is a method of determining a disease gene expression signature for quantifying responsiveness to a therapy for subjects suffering from a disease, disorder, or condition, the method comprising: receiving gene expression data from a cohort of subjects suffering from the same disease, disorder, or condition; stratifying the cohort of subjects into two or more groups based at least in part on the gene expression data; calculating differences in gene expression between the two or more groups of subjects and a group of non-diseased subjects; selecting one or more genes having significant differences in gene expression between the two or more groups of subjects and the group of non-diseased subjects ("disease candidate genes"); compiling a set of disease genes comprising the disease candidate genes; and selecting at least a subset of the set of disease genes to thereby determine the disease gene expression signature.

[0003c] In another aspect, provided herein is a method of validating response to a therapy for a subject suffering from a disease, disorder, or condition, the method comprising: analyzing changes in a disease gene expression signature in the subject after administration of the therapy, wherein the disease gene expression signature is determined to quantify responsiveness to the therapy.

[0003d] In another aspect, provided herein is a method of monitoring therapeutic efficacy in a subject suffering from a disease, disorder, or condition, the method comprising: monitoring changes in a disease gene expression signature after administration of a therapy, wherein the disease gene expression signature has been determined at least in part by: analyzing gene expression data from a cohort of subjects suffering from the same disease, disorder, or condition as the subject; stratifying the cohort of subjects into two or more groups based on the gene expression data; determining differences in gene expression between the two or more groups of subjects and a group of non-diseased subjects; selecting one or more genes having significant differences in gene expression between the two or more groups of subjects and the group of non-diseased subjects ("disease candidate genes"); compiling a set of disease genes comprising the

disease candidate genes; and selecting at least a subset of the set of disease genes to thereby determine the disease gene expression signature.

[0003e] In another aspect, provided herein is a method of identifying and selecting subjects for a clinical trial, the method comprising: receiving gene expression data of a cohort of subjects; analyzing the gene expression data to detect the presence of a disease gene expression signature; identifying changes in the disease gene expression signature relative to gene expression of a non-diseased subject in the cohort of subjects after the cohort of subjects have been administered at least one dose of a therapy; and selecting subjects for the clinical trial who exhibit a quantifiable change in the disease gene expression signature towards gene expression of a healthy subject, wherein the disease gene expression signature is determined as described herein.

[0003f] In another aspect, provided herein is a 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 method as described herein.

[0004] To date, many approaches to determining suitability of a therapy for a particular subject may rely on a reactive approach of attempting multiple therapies, attempting to gauge patient response by assessing clinical characteristics. These approaches may delay necessary treatment and may mischaracterize the actual responsiveness of a therapy for a patient by only examining clinical characteristics of response. Therefore, there is a need for methods and systems of providing personalized treatments for patients that reliably quantify responsiveness to therapy.