

[0008] In one example, the present disclosure provides for a computer-implemented method, comprising: (a) obtaining information about a plurality of subjects with cancer at a first time point, wherein the information comprises for each subject of the plurality of subjects at least a genetic profile of a tumor obtained by genotyping nucleic acids from a cell-free bodily fluid and any treatment provided to the subject before the first time point, and determining a first state of each of the plurality of subjects based on the information at the first time point to produce a set of first states; (b) obtaining the information about the plurality of subjects at one or more second time points subsequent to the first time point, and determining a second state of each of the plurality of subjects at each of the one or more second time points based on the information at a given one of the one or more second time points, to produce a set of subsequent states; and (c) using the set of first states from (a) and the set of subsequent states from (b) to generate a predictive algorithm that is configured to determine a probability that a given first state will result in a second state among a set of states at a later time point subsequent to the given first state. In some examples, the method further comprises (d) for the given first state among a set of states at an earlier time point, determining the probability that the given first state will result in the second state among the set of states at the later time point; and (e) generating an electronic output indicative of the probability determined in (d).

[0009] In one example, the present disclosure provides for a computer-implemented method, comprising: (a) obtaining information about a plurality of subjects with cancer at a first time point, wherein the information comprises, for each subject of the plurality of subjects, at least a genetic profile of a tumor obtained by genotyping at least 50 genes and any treatment provided to the subject before the first time point, and determining a first state of each of the plurality of subjects based on the information at the first time point, to produce a set of first states; (b) obtaining the information about the plurality of subjects at one or more second time points subsequent to the first time point, and determining a second state of each of the plurality of subjects at each of the one or more second time points based on the information at a given one of the one or more second time points, to produce a set of subsequent states; and (c) using the set of first states from (a) and the set of subsequent states from (b) to generate a predictive algorithm that is configured to determine a probability that a given first state will result in a second state among a set of states at a later time point subsequent to the given first state. In some examples, the method further comprises (d) for the given first state among a set of states at an earlier time point, determining the probability that the given first state will result in the second state among the set of states at the later time point; and (e) generating an electronic output indicative of the probability determined in (d).

[0010] In some examples, obtaining the information comprises sequencing cell-free deoxyribonucleic acid (cfDNA) from the plurality of subjects and, optionally, performing a medical interview of each of the plurality of subjects. In some examples, treatment was provided to the subject before the first time point. In some examples, the methods comprise generating one or more decision trees, each decision tree comprising a root node, one or more decision branches, one or more decision nodes, and one or more terminal nodes, wherein a state at the root node represents the first time point, the one or more decision branches represent alternative treatments, and the one or more decision nodes and the one or more terminal nodes represent subsequent states. In some examples, the one or more decision branches comprise a plurality of decision branches. In some examples, the subsequent states comprise a viability state(s) of the subjects indicative of the subjects being alive or deceased. In some examples, the subsequent states comprise a subject survival rate. In some examples, each of the first states comprises a common set of one or more somatic mutations. In some examples, the information further comprises a subject profile.

[0011] In some examples, the probability is at least in part a function of treatment choice from among a plurality of treatment choices. In some examples, the one or more second time points comprises a plurality of subsequent time points. In some examples, the methods further comprise determining the probability at a plurality of subsequent time points. In some examples, the time points comprise at least three time points or at least four time points. In some examples, the first time point is prior to the subject receiving the treatment and the subsequent time point is after the subject receiving the treatment. In some examples, a second treatment is administered after the subsequent time point based on the subsequent state at the subsequent time point.

[0012] In some examples, the information about the plurality of subjects comprises one or more characteristics from patient profiles of the subjects, which characteristics are selected from the group consisting of: age, sex, gender, genetic profile, enzyme levels, organ function, quality of life, frequency of medical interventions, remission status, and patient outcome. In some examples, the genetic profile comprises a genotype of a subject at one or more loci that increases cancer risk, impacts pharmacokinetics, or impacts drug sensitivity. In some examples, the information about the plurality of subjects comprises one or more characteristics from tumor profiles of the subjects, which characteristics are selected from the group consisting of: one or more genetic variants, tissue of origin, tumor burden, tumor drug sensitivity, and tumor stage. In some examples, the one or more characteristics are determined by assaying cell-free nucleic acid molecules from the subjects. In some examples, the one or more genetic variants are quantified to determine a proportion of cell-

free nucleic acid molecules comprising the one or more somatic mutations. In some examples, the methods further comprise determining if the proportion of the one or more somatic mutations is increasing or decreasing between the first time point and the one or more subsequent time points. In some examples, the methods, further comprise determining if the proportion of the one or more somatic mutations is increasing or decreasing amongst a plurality of the one or more subsequent time points. In some examples, the proportion of the one or more somatic mutations is increasing. In some examples, the one or more somatic mutations is increasing, and further wherein the somatic mutations are associated with resistance to the treatment. In some examples, the assaying comprises high-throughput sequencing.

[0013] In another example, the present disclosure provides a method, comprising: (a) obtaining information about a subject with a cancer at a first time point, wherein the information comprises at least one characteristic of the subject from a patient profile, a tumor profile, or a treatment; (b) determining an initial state of the subject based on the information at the first time point; (c) determining a probability for each of a plurality of subsequent states at each of one or more subsequent time points based on the initial state of the subject, thereby providing a set of probabilities with regards to state outcomes; (d) generating a recommendation of a treatment for the cancer based at least in part on the set of probabilities with regards to state outcomes that optimizes for a probability that subject obtains a particular outcome; and (e) generating an electronic output indicative of the recommendation generated in (d). In some examples, the probability is at least in part a function of a treatment choice from among a plurality of treatment choices. In some examples, the one or more subsequent time points comprises a plurality of subsequent time points. In some examples, the method further comprises determining the probability at a plurality of subsequent time points. In some examples, the time points comprise at least three time points. In some examples, the time points comprise at least four time points. In some examples, the first time point is prior to the subject receiving the treatment and the subsequent time point is after the subject receiving the treatment. In some examples, a second treatment is administered after the subsequent time point based on the subsequent state at the subsequent time point. In some examples, the at least one characteristic of the subject is from the patient profile and is selected from the group consisting of: age, gender, genetic profile, enzyme levels, organ function, quality of life, frequency of medical interventions, remission status, and patient outcome.

[0014] In some examples, the genetic profile comprises a genotype of a subject at one or more loci that is a heritable oncogene. In some examples, the genetic profile comprises a genotype of a subject at one or more loci that impacts pharmacokinetics. In some examples, the genetic profile comprises a genotype of a subject at one or more loci that impacts drug

sensitivity. In some examples, the at least one characteristic of the subject is from the tumor profile and is selected from the group consisting of: one or more somatic mutations, tissue of origin, tumor burden, tumor drug sensitivity, and tumor stage. In some examples, the at least one characteristic is determined by assaying cell-free nucleic acid molecules from the subject.

[0015] In some examples, the somatic mutations are quantified to determine a proportion of cell-free nucleic acid molecules derived from the tumor comprising the one or more somatic mutations.

[0016] In some examples, the method further comprises determining if the proportion of the one or more somatic mutations is increasing or decreasing between the first time point and the one or more subsequent time points. In some examples, the method further comprises determining if the proportion of the one or more somatic mutations is increasing or decreasing amongst a plurality of the one or more subsequent time points. In some examples, the assaying comprises high-throughput sequencing. In some examples, the tumor profile is not derived from a tumor tissue biopsy.

[0017] In one example, the present disclosure provides a method, comprising: (a) obtaining information about a subject comprising at least a genetic profile of a tumor and a treatment previously or currently provided to the subject, if any, and determining an initial state of the subject based on the information; (b) providing a decision tree, wherein a root node represents an initial subject state, decision branches represent alternative treatments available to the subject, chance nodes represent points of uncertainty, and decision nodes or terminal nodes represent subsequent states; (c) providing a course of treatment for the subject that maximizes a probability of the subject achieving a living state at a terminal node; and (d) generating an electronic output indicative of the course of treatment determined in (c).

[0018] In one example, the present disclosure provides a method, comprising: (a) establishing one or more communications links over a communication network with one or more medical service providers; (b) receiving over the communications network from the one or more medical service providers medical information about one or more subjects; (c) receiving from the medical service provider one or more samples comprising cell-free deoxyribonucleic acid (cfDNA) from each of the one or more subjects; (d) sequencing the cfDNA and identifying one or more genetic variants present in the cfDNA; (e) creating or supplementing a database with information for each of the one or more subjects, the information comprising both identified genetic variants and received medical information; and (f) using the database and a computer implemented algorithm, generating at least one predictive model that predicts, based on an initial state of a subject, the probability of a subsequent state for each of a plurality of different therapeutic interventions.

[0019] In one example, the present disclosure provides a non-transitory computer-readable medium comprising machine executable code that, upon execution by one or more computer processors, implements a method comprising: (a) obtaining information about a plurality of subjects with cancer at a first time point, wherein the information comprises, for each subject of the plurality of subjects, at least a genetic profile of a tumor obtained by genotyping nucleic acids from a cell-free bodily fluid and any treatment provided to the subject before the first time point, and determining a first state of each of the plurality of subjects based on the information at the first time point, to produce a set of first states; (b) obtaining the information about the plurality of subjects at one or more second time points subsequent to the first time point, and determining a second state of each of the plurality of subjects at each of the one or more second time points based on the information at a given one of the one or more second time points, to produce a set of subsequent states; and (c) using the set of first states from (a) and the set of subsequent states from (b) to generate a predictive algorithm that is configured to determine a probability that a given first state will result in a second state among a set of states at a later time point subsequent to the given first state.

[0020] In one example, the present disclosure provides a non-transitory computer-readable medium comprising machine executable code that, upon execution by one or more computer processors, implements a method comprising: (a) obtaining information about a plurality of subjects with cancer at a first time point, wherein the information comprises, for each subject of the plurality of subjects, at least a genetic profile of a tumor obtained by genotyping at least 50 genes and any treatment provided to the subject before the first time point, and determining a first state of each of the plurality of subjects based on the information at the first time point, to produce a set of first states; (b) obtaining the information about the plurality of subjects at one or more second time points subsequent to the first time point, and determining a second state of each of the plurality of subjects at each of the one or more second time points based on the information at a given one of the one or more second time points, to produce a set of subsequent states; and (c) using the set of first states from (a) and the set of subsequent states from (b) to generate a predictive algorithm that is configured to determine a probability that a given first state will result in a second state among a set of states at a later time point subsequent to the given first state.

[0021] In one example, the present disclosure provides a method, comprising: (a) obtaining information about a subject comprising at least a genetic profile of a tumor and a treatment previously or currently provided to the subject, if any, and determining an initial state of the subject based on the information; (b) providing a decision tree, wherein a root node represents an initial subject state, decision branches represent alternative treatments available to the subject,

chance nodes represent points of uncertainty, and decision nodes or terminal nodes represent subsequent states; (c) providing a course of treatment for the subject that maximizes a probability of the subject achieving a living state at a terminal node; and (d) administering the course of treatment to the subject. In some examples, the method further comprises: (e) at a second time point subsequent to the initial state, obtaining information about a subject comprising at least a genetic profile of a tumor and a treatment previously or currently provided to the subject, if any, and determining an second state of the subject among a plurality of subsequent states based on the information; (f) based on the second state, providing a subsequent course of treatment for the subject that maximizes probability of the subject achieving a living state at a terminal node; and (g) administering the subsequent course of treatment to the subject. In some examples, the method further comprises: (e) at a second time point subsequent to the initial state, obtaining information about a subject comprising at least a genetic profile of a tumor and a treatment previously or currently provided to the subject, if any, and determining an second state of the subject among a plurality of subsequent states based on the information; (f) based on the second state, providing a subsequent course of treatment for the subject that maximizes probability of the subject achieving a living state at a terminal node; and (g) administering the subsequent course of treatment to the subject.

[0022] In one example, the present disclosure provides a method, comprising providing a course of treatment among a plurality of alternative treatments for a subject with cancer, wherein the subject has been characterized by a decision tree comprising a plurality of decision branches, each decision branch representing an alternative treatment among the plurality of alternative treatments, which course of treatment maximizes a probability of the subject achieving a living state at a terminal node.

[0022a] In one aspect, the present disclosure provides a computer-implemented method, comprising: (a) obtaining information about a plurality of subjects with cancer at a first time point, wherein the information comprises, for each subject of the plurality of subjects, at least a genetic profile of a tumor indicating genetic variants, and one or more treatment provided to the subject prior to the first time point, and determining a first state of each of the plurality of subjects based on the information at the first time point, to produce a set of first states, wherein obtaining the information comprises sequencing cell-free deoxyribonucleic acid (cfDNA) from the plurality of subjects; (b) obtaining the information about the plurality of subjects at one or more second time points subsequent to the first time point, and determining a second state of each of the plurality of subjects at each of the one or more second time points based on the information at a given one of the one or more second time points, to produce a set of subsequent

states; and (c) using the set of first states from (a) and the set of subsequent states from (b) to generate a predictive algorithm that is configured to determine a probability that a given first state will result in a respective second state among a set of states at a later time point subsequent to the given first state, wherein the probability is at least in part a function of treatment choice from among a plurality of treatment choices and the predictive algorithm corresponds to a decision tree that includes:

a root node corresponding to the first state and indicating a genetic variant included in one or more genetic profiles of one or more tumors,

one or more branches emanating from the root node and leading to one or more intermediate nodes, wherein a first portion of the intermediate nodes correspond to a treatment of the one or more treatments and a second portion of the intermediate nodes correspond to an additional genetic variant indicating resistance to the treatment, and

a terminal node indicating an outcome of the treatment with respect to a subject, wherein the terminal node and one or more intermediate nodes correspond to one or more subsequent states of the set of subsequent states.

[0022b] In one aspect, the present disclosure provides a non-transitory computer-readable medium comprising machine executable code that, upon execution by one or more computer processors, implements the method as described herein.

[0023] Additional examples and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative example of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different examples, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0024] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

CLAIMS

1. A computer-implemented method, comprising:

(a) obtaining information about a plurality of subjects with cancer at a first time point, wherein the information comprises, for each subject of the plurality of subjects, at least a genetic profile of a tumor indicating genetic variants, and one or more treatment provided to the subject prior to the first time point, and determining a first state of each of the plurality of subjects based on the information at the first time point, to produce a set of first states, wherein obtaining the information comprises sequencing cell- free deoxyribonucleic acid (cfDNA) from the plurality of subjects;

(b) obtaining the information about the plurality of subjects at one or more second time points subsequent to the first time point, and determining a second state of each of the plurality of subjects at each of the one or more second time points based on the information at a given one of the one or more second time points, to produce a set of subsequent states; and

(c) using the set of first states from (a) and the set of subsequent states from (b) to generate a predictive algorithm that is configured to determine a probability that a given first state will result in a respective second state among a set of states at a later time point subsequent to the given first state, wherein the probability is at least in part a function of treatment choice from among a plurality of treatment choices and the predictive algorithm corresponds to a decision tree that includes:

a root node corresponding to the first state and indicating a genetic variant included in one or more genetic profiles of one or more tumors,

one or more branches emanating from the root node and leading to one or more intermediate nodes, wherein a first portion of the intermediate nodes correspond to a treatment of the one or more treatments and a second portion of the intermediate nodes correspond to an additional genetic variant indicating resistance to the treatment, and

a terminal node indicating an outcome of the treatment with respect to a subject, wherein the terminal node and one or more intermediate nodes correspond to one or more subsequent states of the set of subsequent states.

2. The method of claim 1, further comprising:
 - (d) for the given first state among a set of states at an earlier time point, determining the probability that the given first state will result in the second state among the set of states at the later time point; and
 - (e) generating an electronic output indicative of the probability determined in (d).
3. The method of claim 1, wherein obtaining the information comprises performing a medical interview of each of the plurality of subjects.
4. The method of claim 1, wherein treatment was provided to the subject before the first time point.
5. The method of claim 1, wherein:
 - a state at the root node represents the first time point,
 - the first portion of the one or more intermediate nodes include one or more chance nodes, individual chance nodes of the one or more chance nodes indicating a probability of at least one subsequent state; and
 - the second portion of the one or more intermediate nodes include one or more decision nodes that represent subsequent states.
6. The method of claim 5, wherein the one or more decision branches comprise a plurality of decision branches.
7. The method of claim 1, wherein the subsequent states comprise a viability state(s) of the subjects indicative of the subjects being alive or deceased.
8. The method of claim 7, wherein the subsequent states comprise subject survival rate.
9. The method of claim 1, wherein each of the first states comprises a common set of one or more somatic mutations.
10. The method of claim 1, wherein the information further comprises a subject profile.

11. The method of claim 1, wherein the one or more second time points comprises a plurality of subsequent time points.
12. The method of claim 11, further comprising determining the probability at a plurality of subsequent time points.
13. The method of claim 12, wherein the time points comprise at least three time points or at least four time points.
14. The method of claim 1, wherein the first time point is prior to the subject receiving a first treatment included in the one or more treatments and the subsequent time point is after the subject received the first treatment.
15. The method of claim 1, wherein a second treatment of the one or more treatments is to be administered after the subsequent time point based on the subsequent state at the subsequent time point.
16. The method of claim 1, wherein the information about the plurality of subjects comprises one or more characteristics from patient profiles of the subjects, which characteristics are selected from the group consisting of: age, sex, gender, genetic profile, enzyme levels, organ function, quality of life, frequency of medical interventions, remission status, and patient outcome.
17. The method of claim 16, wherein the genetic profile comprises a genotype of a subject at one or more loci that increases cancer risk, impacts pharmacokinetics, or impacts drug sensitivity.
18. The method of claim 1, wherein the information about the plurality of subjects comprises one or more characteristics from tumor profiles of the subjects, which characteristics are selected from the group consisting of: one or more genetic variants, tissue of origin, tumor burden, tumor drug sensitivity, and tumor stage.
19. The method of claim 18, wherein the one or more characteristics are

determined by assaying cell-free nucleic acid molecules from the subjects.

20. The method of claim 19, wherein the one or more genetic variants are quantified to determine a proportion of cell-free nucleic acid molecules comprising the one or more somatic mutations.

21. The method of claim 20, further comprising determining if the proportion of the one or more somatic mutations is increasing or decreasing between the first time point and the one or more subsequent time points.

22. The method of claim 20, further comprising determining if the proportion of the one or more somatic mutations is increasing or decreasing amongst a plurality of the one or more subsequent time points.

23. The method of claim 21 or 22, wherein the proportion of the one or more somatic mutations is increasing.

24. The method of claim 23, wherein the one or more somatic mutations is increasing, and further wherein the somatic mutations are associated with resistance to the treatment.

25. The method of claim 19, wherein the assaying comprises high-throughput sequencing.

26. The method of claim 1, wherein the genes are at least one of oncogenes or proto-oncogenes.

27. The method of claim 26, wherein the oncogenes and proto-oncogenes comprise genes listed in Figure 5.

28. A non-transitory computer-readable medium comprising machine executable code that, upon execution by one or more computer processors, implements the method of claim 1.