[0003] There exist attempts to combine knowledge about the mode of action of treatments, specifically the targets of targeted drugs, with the results of molecular profiling of a patient in order to select an appropriate treatment. In "Personalized Medicine in a Phase I Clinical Trials Program: the MD Anderson Cancer Center Initiative" by Tsimberidou, Apostolia-Maria, Nancy G Iskander, David S Hong, Jennifer J Wheler, Gerald S Falchook, Siqing Fu, Sarina Piha-Paul, et al. (Clinical Cancer Research: an Official Journal of the American Association for Cancer Research 18, no. 22 (November 15, 2012): 6373–6383. doi:10.1158/1078-0432.CCR-12-1627), the authors test a small set of drug-target-genes for a pre-defined set of aberrations, specifically mutations. Treatments are selected that target a protein encoded by a gene with an aberration. However, their data shows that more than 7% of the patients had more than one "actionable" aberration. With more extensive profiling this percentage is expected to increase. In such cases, it is not clear, which protein / aberration should best be targeted by the treatment to be selected.

BRIEF SUMMARY OF THE DISCLOSURE

[0004] According to a first aspect of the invention, a method for generating a personalized treatment guideline for a patient comprises retrieving an identification of a disease indication of the patient. The method further comprises assigning an indication-specific score to each gene or protein of a first set of genes or proteins, the indication-specific score reflecting an evidence of the gene or protein being associated with the disease indication of the patient. The method further comprises retrieving a molecular profile of the patient, wherein the molecular profile is a set of molecular measurements indexed by a second set of genes or

proteins, the second set of genes or proteins being equal to the first set of genes or proteins or being a subset of the first set of genes or proteins. The method further comprises inferring, from the molecular profile, for each gene or protein of the first set of genes or proteins a possibly empty set of aberrations. The method further comprises assigning a profile-specific score to each gene or protein of the first set of genes or proteins, the profile-specific score reflecting a degree of how much the function of the genes or proteins is altered by the aberrations. The method further comprises assigning a patient-specific score to each gene or protein of the first set of genes or proteins, the patient-specific score of each gene or protein being based on both its indication-specific score and its profile-specific score. The method further comprises retrieving a set of targeted treatments, together with associated target proteins and/or the corresponding genes, from a treatment database. The method further comprises assigning a score to each targeted treatment from the set of targeted treatments by aggregating the patient-specific scores at least over its associated target proteins and/or corresponding genes that are in the first set of genes or proteins. The method further comprises generating the personalized treatment guideline as an ordered list of the targeted treatments, wherein the order of the targeted treatments is determined by their score.

[0005] In comparison to existing methods for treatment selection and/or assignment of patients to trials, the approach outlined above has qualitative advantages. The invention also allows to prioritize the most important mutations in the mechanistically most important proteins, thus providing a new level of actionability beyond established biomarkers. In a patient where no previously

described biomarker is found, this approach may be used to define the most likely actionable novel biomarker in the patient.

[0006] One advantage over the approach described by Tsimberidou et al. is that it provides a principled, bio-medically founded solution to the case of molecular aberrations being found in more than one gene or protein. This case is expected to be the standard case, once the profiling is performed to cover a large number of genes and/or proteins, which is desirable with respect to a comprehensive assessment and understanding of the patient and his/her disease. The method further comprises assigning a profile-specific score to each gene or protein of the first set of genes or proteins, the profile-specific score reflecting a degree of how much the function of the genes or proteins is altered as compared to a fixed reference state. Specifically, this score allows for going beyond a simple binary attribution of genes and/or proteins as either being mutated or not. In some embodiments, this invention further allows to match treatments to aberrations based on indirect, so-called downstream effects, hence providing treatment selection guidance even in cases in which no treatment directly targets a gene or protein with an aberration.

[0007] The invention thus resolves cases in which patients have more than one "actionable" aberration by combining the patient-specific molecular information and the treatment-specific molecular information further with a clinico-molecular disease model, specifically a scoring of genes and/or proteins that represents several aspects of their involvement into the disease. In this way, treatments can be prioritized that are most likely to impact the disease mechanism.

[0008] While much of this invention is described in the context of oncology, which is a preferred area of its application, it should be understood that the invention is of a general nature that extends to all kinds of diseases and conditions that have a molecular foundation (as opposed to, for instance, bone fractures, which are physical or mechanical in nature).

[0009] In embodiments of this invention that are directed towards treatment ranking or prioritization, an important choice is the selection of a set of treatments to be ranked. An obvious choice is to consider all treatments that are approved for the indication of the present patient. An alternative choice is to consider all treatments that are either approved or under development for that indication. In some application areas, for instance some rare cancers, there may not exist any approved treatments, or the set of existing approved treatments may already be exhausted for a given patient, meaning that these treatments have been tried unsucessfully or that they are not applicable due to some counter-indication like an idiosyncracy or a toxic interaction with another vital medication. Then it can be useful to consider treatments that are approved for a broader disease indication area, which is here defined as a set of related indications. Relatedness of indications may be judged according to a disease ontology, for instance MeSH or MedDRA. The necessary and sufficient degree of relatedness of indications may depend on the numbers of treatments available for related indications.

[0010] According to a first embodiment, the treatments are manually entered. According to another embodiment, the treatments are selected based on the disease indication of the patient or on a disease indication area of the patient.

[0011] The method may further comprise a step of outputting the personalized treatment guideline to a user as a list comprising one or more of the highest ordered targeted treatments, in particular by displaying them on a screen or display or by printing them onto paper.

[0012] According to a variant, a method for selecting a treatment for a patient comprises the steps: generating a personalized treatment guideline for the patient by executing the method steps as specified herein, and selecting the first targeted treatment from the ordered list of the targeted treatments of the personalized treatment guideline. The method may also comprise administering a selected treatment to the patient.

[0013] According to a second aspect of the invention, a method for selecting patients for a clinical trial of a treatment comprises retrieving identifications of disease indications of a set of patients. The method further comprises assigning, for every patient, an indication-specific score to each gene or protein of a first set of genes or proteins, the indication-specific score reflecting an evidence of the gene or protein being associated with the disease indication of the patient. The method further comprises retrieving, for every patient, a molecular profile of the patient, wherein the molecular profile is a set of molecular measurements indexed by a second set of genes or proteins, the second set of genes or proteins being equal to the first set of genes or proteins or being a subset of the first set of genes or proteins. The method further comprises inferring, from the molecular profile, for each gene or protein of the first set of genes or proteins a possibly empty set of aberrations. The method further comprises assigning, for every patient, a profile-specific score to each gene or protein of the first set of genes or proteins, the profile-specific score reflecting a degree of how much the function of the genes or

1. Oktober 2013

Molecular Health AG M68829PC FLZ/BJN

CLAIMS

1. Method for generating a personalized treatment guideline for a patient, comprising the steps:

retrieving an identification of a disease indication of the patient,

assigning an indication-specific score to each gene or protein of a first set of genes or proteins,

the indication-specific score reflecting an evidence of the gene or protein being associated with the disease indication of the patient,

retrieving a molecular profile of the patient,

wherein the molecular profile is a set of molecular measurements indexed by a second set of genes or proteins, the second set of genes or proteins being equal to the first set of genes or proteins or being a subset of the first set of genes or proteins,

inferring, from the molecular profile, for each gene or protein of the first set of genes or proteins a possibly empty set of aberrations,

assigning a profile-specific score to each gene or protein of the first set of genes or proteins,

the profile-specific score reflecting a degree of how much the function of the genes or proteins is altered by the aberrations,

assigning a patient-specific score to each gene or protein of the first set of genes or proteins,

the patient-specific score of each gene or protein being based on both its indication-specific score and its profile-specific score,

retrieving a set of targeted treatments, together with associated target proteins and/or the corresponding genes, from a treatment database,

assigning a score to each targeted treatment from the set of targeted treatments by aggregating the patient-specific scores at least over its associated target proteins and/or the corresponding genes, and

generating the personalized treatment guideline as an ordered list of the targeted treatments, wherein the order of the targeted treatments is determined by their score.

2. The method of claim 1,

wherein the treatments are selected based on the disease indication of the patient or a disease indication area of the patient.

3. Method for selecting a treatment for a patient, comprising the steps:

generating a personalized treatment guideline for the patient by executing the method steps according to claim 1 or claim 2, and

selecting the first targeted treatment from the ordered list of the targeted treatments of the personalized treatment guideline.

4. Method for selecting patients for a clinical trial of a treatment, comprising the steps:

retrieving identifications of disease indications of a set of patients,

assigning, for every patient, an indication-specific score to each gene or protein of a first set of genes or proteins,

the indication-specific score reflecting an evidence of the gene or protein being associated with the disease indication of the patient,

retrieving, for every patient, a molecular profile of the patient,

wherein the molecular profile is a set of molecular measurements indexed by a second set of genes or proteins, the second set of genes or proteins being equal to the first set of genes or proteins or being a subset of the first set of genes or proteins,

inferring, from the molecular profile, for each gene or protein of the first set of genes or proteins a possibly empty set of aberrations,

assigning, for every patient, a profile-specific score to each gene or protein of the first set of genes or proteins,

the profile-specific score reflecting a degree of how much the function of the genes or proteins is altered by the aberrations,

assigning, for every patient, a patient-specific score to each gene or protein of the first set of genes or proteins,

the patient-specific score of each gene or protein being based on both its indication-specific score and its profile-specific score,

retrieving, for the treatment, associated target proteins and/or the corresponding genes from a treatment database,

which are also in the first set of genes and proteins,

assigning a score to every patient from the set of patients by aggregating the patient-specific scores at least over its associated target proteins and/or the corresponding genes, and

generating an ordered list of the patients, wherein the order of the patients is determined by their score.

5. The method of any of the preceding claims, wherein the patient-specific score is a product of its indication-specific score and its profile-specific score.

6. The method of any of the preceding claims, wherein the profile-specific score is set to zero if the gene or protein has no aberrations.

7. The method of any of the preceding claims, wherein assigning a profile-specific score to each gene or protein of the first set of genes or proteins comprises the following steps:

computing an aberration-specific functional impact score for each aberration,

computing a protein- or gene-specific direct functional impact score for each protein or gene by

aggregating the aberration-specific functional impact scores over the aberrations associated with the gene or protein.

8. The method of any of the preceding claims 1 to 6, wherein assigning a profile-specific score to each gene or protein of the first set of genes or proteins comprises the following steps:

computing an aberration-specific functional impact score for each aberration,

computing a protein- or gene-specific indirect functional impact score for each protein or gene by

aggregating the aberration-specific functional impact scores over the aberrations associated with a set of second genes or proteins, the set including the first gene or protein and a set of genes or proteins that are upstream of the first gene or protein according to a molecular interaction network.

9. The method of claim 7 or claim 8, wherein the aggregation of aberration-specific functional impact scores takes into account an indication of the direction of the impact of an aberration on the function of a gene or protein, wherein positive and negative signs of the aberration-specific functional impact score correspond to an activating and inactivating impact, respectively.

10. The method of any of the preceding claims, wherein assigning a score to a treatment further takes into account a directionality of the impact of the treatment on its targets in aggregating over them by adding profile-specific scores of targets that are inhibited or antagonized by the treatment and subtracting profile-specific scores of targets that are activated or stimulated or agonized by the treatment.

11. The method of any of the preceding claims, wherein assigning a score to each treatment is extended such that patient-specific scores are further aggregated over

genes and/or proteins downstream of its targets according to a molecular interaction network.

12. System (1) for generating a personalized treatment guideline for a patient and/or for selecting patients for a clinical trial of a treatment, comprising a processing unit (2) with:

an interface (4) for providing a first set of genes or proteins to the system (1),

an interface (3) for providing identifications of disease indications of patients to the system (1),

a module (12) for assigning, for an identification of a disease indication of a patient, an indication-specific score to each gene or protein of the first set of genes or proteins,

the indication-specific score reflecting an evidence of the gene or protein being associated with the disease indication of the patient,

an interface (5) for providing molecular profiles of patients to the system (1),

wherein a molecular profile is a set of molecular measurements indexed by a second set of genes or proteins, the second set of genes or proteins being equal to the first set of genes or proteins or being a subset of the first set of genes or proteins,

a module (13) for assigning, for a molecular profile of a patient, a profile-specific score to each gene or protein of the first set of genes or proteins, wherein the module (13) for assigning the profile-specific score is adapted to inferring, from the molecular profile, for each gene or protein of the first set of genes or proteins a possibly empty set of aberrations,

a module (14) for assigning a patient-specific score to each gene or protein of the first set of genes or proteins,

the patient-specific score of each gene or protein being based on both its indication-specific score and its profile-specific score,

an interface (6) for providing targeted treatments, together with associated target proteins and/or the corresponding genes, from a treatment database to the system (1), and

a module (15) for assigning a score to patients and to treatments by aggregating the patient-specific scores at least over the associated target proteins and/or the corresponding genes, wherein the module (15) for assigning the score to patients and to treatments is adapted to generating ordered lists of patients or treatments, wherein the order of the patients or treatments is determined by their score.

13. The system of claim 12,

wherein the module (13) for assigning the profile-specific score is adapted to assigning an aberration-specific functional impact score for each aberration and to aggregating the functional impact score over the aberrations if there are two or more aberrations in the gene or protein and assigning zero to the gene or protein if the gene or protein has no aberrations.

[0003] There exist attempts to combine knowledge about the mode of action of treatments, specifically the targets of targeted drugs, with the results of molecular profiling of a patient in order to select an appropriate treatment. In "Personalized Medicine in a Phase I Clinical Trials Program: the MD Anderson Cancer Center Initiative" by Tsimberidou, Apostolia-Maria, Nancy G Iskander, David S Hong, Jennifer J Wheler, Gerald S Falchook, Siqing Fu, Sarina Piha-Paul, et al. (Clinical Cancer Research: an Official Journal of the American Association for Cancer Research 18, no. 22 (November 15, 2012): 6373–6383. doi:10.1158/1078-0432.CCR-12-1627), the authors test a small set of drug-target-genes for a pre-defined set of aberrations, specifically mutations. Treatments are selected that target a protein encoded by a gene with an aberration. However, their data shows that more than 7% of the patients had more than one "actionable" aberration. With more extensive profiling this percentage is expected to increase. In such cases, it is not clear, which protein / aberration should best be targeted by the treatment to be selected.

BRIEF SUMMARY OF THE DISCLOSURE

[0004] According to a first aspect of the invention, a method for generating a personalized treatment guideline for a patient, comprising the steps:

retrieving an identification of a disease indication of the patient as a user's input, from an electronic health record or electronic medical record or from a patient database comprising medical records of a candidate set of patients,

assigning an indication-specific score to each gene or protein of a first set of genes or proteins, the first set of genes or proteins being part of the

human microbiome, the indication-specific score reflecting an evidence of the gene or protein being associated with the disease indication of the patient,

wherein the indication-specific score of each gene or protein is computed by first assigning numerical values to attributes indicating degrees of potential relationship to the indication and then by forming a weighted sum of the numerical values or of any monotonic transformation of the numerical values over the attributes, the attributes comprising at least one of the following list:

a) The gene or protein is a drug target,

b) The gene or protein is a biomarker or part of a biomarker,

c) The gene or protein is disease-associated,

d) The gene or protein is an oncogene or a product of an oncogene, respectively,

e) The gene or protein is a tumor suppressor,

f) The gene or protein has a cancer pathway association,

g) The gene or protein is gene ontology annotated for cancer relevant processes,

h) The gene or protein is part of a cancer-associated gene fusion,

i) The gene or protein has a tractable domain,

j) The gene or protein is embryonic lethal, and

k) The gene or protein is highly mutated in the specific indication;

retrieving a molecular profile of the patient, wherein the molecular profile is a set of molecular measurements of DNA or RNA extracted from the patient, indexed by a second set of genes or proteins, the second set of genes or proteins being equal to the first set of genes or proteins or being a subset of the first set of genes or proteins,

inferring, from the molecular profile, for each gene or protein of the first set of genes or proteins a possibly empty set of aberrations as the differences of the molecular profile to a reference profile from a control sample of the patient or from other individuals,

assigning a profile-specific score to each gene or protein of the first set of genes or proteins, the profile-specific score reflecting a degree of how much the function of the genes or proteins is altered by the aberrations,

wherein assigning the profile-specific score to each gene or protein of the first set of genes or proteins comprises the following steps:

computing an aberration-specific functional impact score for each aberration taking into account the direction of the impact of an aberration on the function of a gene or protein, wherein positive and negative signs of the aberration-specific functional impact score correspond to an activating and inactivating impact, respectively, and

computing a protein- or gene-specific direct functional impact score for each protein or gene by computing a weighted sum, a quantile, a median, a

maximum or a geometric mean of the aberration-specific functional impact scores over the aberrations associated with the gene or protein, or

computing a protein- or gene-specific indirect functional impact score for each protein or gene by computing a weighted sum, a quantile, a median, a maximum or a geometric mean of the aberration-specific functional impact scores over the aberrations associated with another set of genes or proteins, the another set including the gene or protein and a set of genes or proteins that are upstream of the gene or protein according to a molecular interaction network, the molecular interaction network being a directed graph, consisting of nodes each of which represents a gene or a protein, and of edges each of which connects two nodes,

and wherein the profile-specific score is set equal to the direct functional impact score, equal to the indirect functional impact score or equal to a weighted sum of these,

assigning a patient-specific score to each gene or protein of the first set of genes or proteins, the patient-specific score of each gene or protein being a sum, a weighted sum or a product of its indication-specific score and its profile-specific score,

retrieving a set of targeted treatments, together with associated target genes or proteins, as a user's input or by selecting treatments that are approved or under investigation for the indication of the patient or for related indications from a treatment database, the treatment database storing treatments, in particular drugs and drug combinations, together with information on the genes or proteins that are the targets of the drugs,

assigning a score to each targeted treatment from the set of targeted treatments by calculating a sum or a weighted sum over the patient-specific scores of the associated target genes or proteins, and

generating the personalized treatment guideline as an ordered list of the targeted treatments, wherein the order of the targeted treatments is determined by their score

[0005] Also disclosed herein is a method for generating a personalized treatment guideline for a patient comprises retrieving an identification of a disease indication of the patient. The method further comprises assigning an indication-specific score to each gene or protein of a first set of genes or proteins, the indication-specific score reflecting an evidence of the gene or protein being associated with the disease indication of the patient. The method further comprises retrieving a molecular profile of the patient, wherein the molecular profile is a set of molecular measurements indexed by a second set of genes or proteins, the second set of genes or proteins being equal to the first set of genes or proteins or being a subset of the first set of genes or proteins. The method further comprises inferring, from the molecular profile, for each gene or protein of the first set of genes or proteins a possibly empty set of aberrations. The method further comprises assigning a profile-specific score to each gene or protein of the first set of genes or proteins, the profile-specific score reflecting a degree of how much the function of the genes or proteins is altered by the aberrations. The method further comprises assigning a patient-specific score to each gene or protein of the first set of genes or proteins, the patient-specific score of each gene or protein being based on both its indication-specific score and its profile-specific score. The method further comprises retrieving a set of targeted treatments,

together with associated target proteins and/or the corresponding genes, from a treatment database. The method further comprises assigning a score to each targeted treatment from the set of targeted treatments by aggregating the patient-specific scores at least over its associated target proteins and/or corresponding genes that are in the first set of genes or proteins. The method further comprises generating the personalized treatment guideline as an ordered list of the targeted treatments, wherein the order of the targeted treatments is determined by their score.

[0006] In comparison to existing methods for treatment selection and/or assignment of patients to trials, the approach outlined above has qualitative advantages. The invention also allows to prioritize the most important mutations in the mechanistically most important proteins, thus providing a new level of actionability beyond established biomarkers. In a patient where no previously described biomarker is found, this approach may be used to define the most likely actionable novel biomarker in the patient.

[0007] One advantage over the approach described by Tsimberidou et al. is that it provides a principled, bio-medically founded solution to the case of molecular aberrations being found in more than one gene or protein. This case is expected to be the standard case, once the profiling is performed to cover a large number of genes and/or proteins, which is desirable with respect to a comprehensive assessment and understanding of the patient and his/her disease. The method further comprises assigning a profile-specific score to each gene or protein of the first set of genes or proteins, the profile-specific score reflecting a degree of how much the function of the genes or proteins is altered as compared to a fixed reference state. Specifically, this score allows for going beyond a simple

binary attribution of genes and/or proteins as either being mutated or not. In some embodiments, this invention further allows to match treatments to aberrations based on indirect, so-called downstream effects, hence providing treatment selection guidance even in cases in which no treatment directly targets a gene or protein with an aberration.

[0008] The invention thus resolves cases in which patients have more than one "actionable" aberration by combining the patient-specific molecular information and the treatment-specific molecular information further with a clinico-molecular disease model, specifically a scoring of genes and/or proteins that represents several aspects of their involvement into the disease. In this way, treatments can be prioritized that are most likely to impact the disease mechanism.

[0009] While much of this invention is described in the context of oncology, which is a preferred area of its application, it should be understood that the invention is of a general nature that extends to all kinds of diseases and conditions that have a molecular foundation (as opposed to, for instance, bone fractures, which are physical or mechanical in nature).

[0010] In embodiments of this invention that are directed towards treatment ranking or prioritization, an important choice is the selection of a set of treatments to be ranked. An obvious choice is to consider all treatments that are approved for the indication of the present patient. An alternative choice is to consider all treatments that are either approved or under development for that indication. In some application areas, for instance some rare cancers, there may not exist any approved treatments, or the set of existing approved treatments may already be

exhausted for a given patient, meaning that these treatments have been tried unsucessfully or that they are not applicable due to some counter-indication like an idiosyncracy or a toxic interaction with another vital medication. Then it can be useful to consider treatments that are approved for a broader disease indication area, which is here defined as a set of related indications. Relatedness of indications may be judged according to a disease ontology, for instance MeSH or MedDRA. The necessary and sufficient degree of relatedness of indications may depend on the numbers of treatments available for related indications.

[0011] According to a first embodiment, the treatments are manually entered. According to another embodiment, the treatments are selected based on the disease indication of the patient or on a disease indication area of the patient.

[0012] The method may further comprise a step of outputting the personalized treatment guideline to a user as a list comprising one or more of the highest ordered targeted treatments, in particular by displaying them on a screen or display or by printing them onto paper.

[0013] According to a variant, a method for selecting a treatment for a patient comprises the steps: generating a personalized treatment guideline for the patient by executing the method steps as specified herein, and selecting the first targeted treatment from the ordered list of the targeted treatments of the personalized treatment guideline. The method may also comprise administering a selected treatment to the patient.

[0013A] According to a second aspect of the invention, a method for selecting a treatment for a patient, comprising the steps:

generating a personalized treatment guideline for the patient by executing the method steps described in the first aspect, and

selecting the first targeted treatment from the ordered list of the targeted treatments of the personalized treatment guideline

[0013B] According to a third aspect there is provided a method for selecting patients for a clinical trial of a treatment, comprising the steps:

retrieving identifications of disease indications of a set of patients as a user's input, from an electronic health record EHR or electronic medical record EMR or from a patient database comprising medical records of a candidate set of patients,

assigning, for every patient, an indication-specific score to each gene or protein of a first set of genes or proteins, the first set of genes or proteins being part of the human microbiome, the indication-specific score reflecting an evidence of the gene or protein being associated with the disease indication of the patient,

wherein the indication-specific score of each gene or protein is computed by first assigning numerical values to attributes indicating degrees of potential relationship to the indication and then by forming a weighted sum of the numerical values or of any monotonic transformation of the numerical values over the attributes, the attributes comprising at least one of the following list:

a) The gene or protein is a drug target,

b) The gene or protein is a biomarker or part of a biomarker,

c) The gene or protein is disease-associated,

d) The gene or protein is an oncogene or a product of an oncogene, respectively,

e) The gene or protein is a tumor suppressor,

f) The gene or protein has a cancer pathway association,

g) The gene or protein is gene ontology annotated for cancer relevant processes,

h) The gene or protein is part of a cancer-associated gene fusion,

i) The gene or protein has a tractable domain,

j) The gene or protein is embryonic lethal, and

k) The gene or protein is highly mutated in the specific indication;

retrieving, for every patient, a molecular profile of the patient, wherein the molecular profile is a set of molecular measurements of DNA or RNA extracted from the patient, indexed by a second set of genes or proteins, the second set of genes or proteins being equal to the first set of genes or proteins or being a subset of the first set of genes or proteins,

inferring, from the molecular profile, for each gene or protein of the first set of genes or proteins a possibly empty set of aberrations as the differences of the molecular profile to a reference profile from a control sample of the patient or from other individuals,

assigning, for every patient, a profile-specific score to each gene or protein of the first set of genes or proteins, the profile-specific score reflecting a degree of how much the function of the genes or proteins is altered by the aberrations,

wherein assigning the profile-specific score to each gene or protein of the first set of genes or proteins comprises the following steps:

computing an aberration-specific functional impact score for each aberration taking into account the direction of the impact of an aberration on the function of a gene or protein, wherein positive and negative signs of the aberration-specific functional impact score correspond to an activating and inactivating impact, respectively, and

computing a protein- or gene-specific direct functional impact score for each protein or gene by computing a weighted sum, a quantile, a median, a maximum or a geometric mean of the aberration-specific functional impact scores over the aberrations associated with the gene or protein, or

computing a protein- or gene-specific indirect functional impact score for each protein or gene by computing a weighted sum, a quantile, a median, a maximum or a geometric mean of the aberration-specific functional impact scores over the aberrations associated with another set of genes or proteins, the another set including the gene or protein and a set of genes or proteins that are upstream of the gene or protein according to a molecular interaction network, the molecular interaction network being a directed graph, consisting of nodes each of which represents a gene or a protein, and of edges each of which connects two nodes,

and wherein the profile-specific score is set equal to the direct functional impact score, equal to the indirect functional impact score or equal to a weighted sum of these,

assigning, for every patient, a patient-specific score to each gene or protein of the first set of genes or proteins, the patient-specific score of each gene or protein being a sum, a weighted sum or a product of its indication-specific score and its profile-specific score,

retrieving, for the treatment, associated target genes or proteins from a treatment database, the treatment database storing treatments, in particular drugs and drug combinations, together with information on the genes or proteins that are the targets of the drugs, which are also in the first set of genes or proteins,

assigning a score to every patient from the set of patients by calculating a sum or a weighted sum over the patient-specific scores of the associated target genes or proteins, and

generating an ordered list of the patients, wherein the order of the patients is determined by their score.

[0013C] According to a fourth aspect there is provided a system for generating a personalized treatment guideline for a patient and/or for selecting patients for a clinical trial of a treatment, comprising a processing unit with:

an interface for providing a first set of genes or proteins to the system (1), the first set of genes or proteins being part of the human microbiome,

an interface for providing identifications of disease indications of patients to the system,

a module for assigning, for an identification of a disease indication of a patient, an indication-specific score to each gene or protein of the first set of genes or proteins, the indication-specific score reflecting an evidence of the gene or protein being associated with the disease indication of the patient,

wherein the indication-specific score of each gene or protein is computed by first assigning numerical values to attributes indicating degrees of potential relationship to the indication and then by forming a weighted sum of the numerical values or of any monotonic transformation of the numerical values over the attributes, the attributes comprising at least one of the following list:

a) The gene or protein is a drug target,

b) The gene or protein is a biomarker or part of a biomarker,

c) The gene or protein is disease-associated,

d) The gene or protein is an oncogene or a product of an oncogene, respectively,

e) The gene or protein is a tumor suppressor,

f) The gene or protein has a cancer pathway association,

g) The gene or protein is gene ontology annotated for cancer relevant processes,

h) The gene or protein is part of a cancer-associated gene fusion,

i) The gene or protein has a tractable domain,

j) The gene or protein is embryonic lethal, and

k) The gene or protein is highly mutated in the specific indication;

an interface for providing molecular profiles of patients to the system, wherein a molecular profile is a set of molecular measurements of DNA or RNA extracted from a patient, indexed by a second set of genes or proteins, the second set of genes or proteins being equal to the first set of genes or proteins or being a subset of the first set of genes or proteins,

a module for assigning, for a molecular profile of a patient, a profile-specific score to each gene or protein of the first set of genes or proteins, wherein the module for assigning the profile-specific score is adapted to inferring, from the molecular profile, for each gene or protein of the first set of genes or proteins a possibly empty set of aberrations as the differences of the molecular profile to a reference profile from a control sample of the patient or from other individuals,

wherein assigning the profile-specific score to each gene or protein of the first set of genes or proteins comprises the following steps:

computing an aberration-specific functional impact score for each aberration taking into account the direction of the impact of an aberration on the function of a gene or protein, wherein positive and negative signs of the

aberration-specific functional impact score correspond to an activating and inactivating impact, respectively, and

computing a protein- or gene-specific direct functional impact score for each protein or gene by computing a weighted sum, a quantile, a median, a maximum or a geometric mean of the aberration-specific functional impact scores over the aberrations associated with the gene or protein, or

computing a protein- or gene-specific indirect functional impact score for each protein or gene by computing a weighted sum, a quantile, a median, a maximum or a geometric mean of the aberration-specific functional impact scores over the aberrations associated with another set of genes or proteins, the another set including the gene or protein and a set of genes or proteins that are upstream of the gene or protein according to a molecular interaction network, the molecular interaction network being a directed graph, consisting of nodes each of which represents a gene or a protein, and of edges each of which connects two nodes,

and wherein the profile-specific score is set equal to the direct functional impact score, equal to the indirect functional impact score or equal to a weighted sum of these,

a module for assigning a patient-specific score to each gene or protein of the first set of genes or proteins, the patient-specific score of each gene or protein being a sum, a weighted sum or a product of its indication-specific score and its profile-specific score,

an interface for providing targeted treatments, together with associated target genes or proteins, as a user’s input or by selecting treatments

that are approved or under investigation for the indication of the patient or for related indications from a treatment database, the treatment database storing treatments, in particular drugs and drug combinations, together with information on the genes or proteins that are the targets of the drugs, to the system, and

a module for assigning a score to patients and to treatments by calculating a sum or a weighted sum over the patient-specific scores of the associated target genes or proteins, wherein the module for assigning the score to patients and to treatments is adapted to generating ordered lists of patients or treatments, wherein the order of the patients or treatments is determined by their score.

[0013D] Also disclosed herein is a method for selecting patients for a clinical trial of a treatment comprises retrieving identifications of disease indications of a set of patients. The method further comprises assigning, for every patient, an indication-specific score to each gene or protein of a first set of genes or proteins, the indication-specific score reflecting an evidence of the gene or protein being associated with the disease indication of the patient. The method further comprises retrieving, for every patient, a molecular profile of the patient, wherein the molecular profile is a set of molecular measurements indexed by a second set of genes or proteins, the second set of genes or proteins being equal to the first set of genes or proteins or being a subset of the first set of genes or proteins. The method further comprises inferring, from the molecular profile, for each gene or protein of the first set of genes or proteins a possibly empty set of aberrations. The method further comprises assigning, for every patient, a profile-specific score to each gene or protein of the first set of genes or proteins, the profile-specific score reflecting a degree of how much the function of the genes or

CLAIMS

1. Method for generating a personalized treatment guideline for a patient, comprising the steps:

   retrieving an identification of a disease indication of the patient as a user's input, from an electronic health record or electronic medical record or from a patient database comprising medical records of a candidate set of patients,

   assigning an indication-specific score to each gene or protein of a first set of genes or proteins, the first set of genes or proteins being part of the human microbiome, the indication-specific score reflecting an evidence of the gene or protein being associated with the disease indication of the patient,

   wherein the indication-specific score of each gene or protein is computed by first assigning numerical values to attributes indicating degrees of potential relationship to the indication and then by forming a weighted sum of the numerical values or of any monotonic transformation of the numerical values over the attributes, the attributes comprising at least one of the following list:

   a) The gene or protein is a drug target,

   b) The gene or protein is a biomarker or part of a biomarker,

   c) The gene or protein is disease-associated,

   d) The gene or protein is an oncogene or a product of an oncogene, respectively,

   e) The gene or protein is a tumor suppressor,

   f) The gene or protein has a cancer pathway association,

   g) The gene or protein is gene ontology annotated for cancer relevant processes,

h) The gene or protein is part of a cancer-associated gene fusion,

i) The gene or protein has a tractable domain,

j) The gene or protein is embryonic lethal, and

k) The gene or protein is highly mutated in the specific indication;

retrieving a molecular profile of the patient, wherein the molecular profile is a set of molecular measurements of DNA or RNA extracted from the patient, indexed by a second set of genes or proteins, the second set of genes or proteins being equal to the first set of genes or proteins or being a subset of the first set of genes or proteins,

inferring, from the molecular profile, for each gene or protein of the first set of genes or proteins a possibly empty set of aberrations as the differences of the molecular profile to a reference profile from a control sample of the patient or from other individuals,

assigning a profile-specific score to each gene or protein of the first set of genes or proteins, the profile-specific score reflecting a degree of how much the function of the genes or proteins is altered by the aberrations,

wherein assigning the profile-specific score to each gene or protein of the first set of genes or proteins comprises the following steps:

computing an aberration-specific functional impact score for each aberration taking into account the direction of the impact of an aberration on the function of a gene or protein, wherein positive and negative signs of the aberration-specific functional impact score correspond to an activating and inactivating impact, respectively, and

computing a protein- or gene-specific direct functional impact score for each protein or gene by computing a weighted sum, a quantile, a median, a maximum or a geometric mean of the aberration-specific functional impact scores over the aberrations associated with the gene or protein, or

computing a protein- or gene-specific indirect functional impact score for each protein or gene by computing a weighted sum, a quantile, a

median, a maximum or a geometric mean of the aberration-specific functional impact scores over the aberrations associated with another set of genes or proteins, the another set including the gene or protein and a set of genes or proteins that are upstream of the gene or protein according to a molecular interaction network, the molecular interaction network being a directed graph, consisting of nodes each of which represents a gene or a protein, and of edges each of which connects two nodes,

and wherein the profile-specific score is set equal to the direct functional impact score, equal to the indirect functional impact score or equal to a weighted sum of these,

assigning a patient-specific score to each gene or protein of the first set of genes or proteins, the patient-specific score of each gene or protein being a sum, a weighted sum or a product of its indication-specific score and its profile-specific score,

retrieving a set of targeted treatments, together with associated target genes or proteins, as a user's input or by selecting treatments that are approved or under investigation for the indication of the patient or for related indications from a treatment database, the treatment database storing treatments, in particular drugs and drug combinations, together with information on the genes or proteins that are the targets of the drugs,

assigning a score to each targeted treatment from the set of targeted treatments by calculating a sum or a weighted sum over the patient-specific scores of the associated target genes or proteins, and

generating the personalized treatment guideline as an ordered list of the targeted treatments, wherein the order of the targeted treatments is determined by their score.

2. Method for selecting a treatment for a patient, comprising the steps:

generating a personalized treatment guideline for the patient by executing the method steps according to claim 1, and

selecting the first targeted treatment from the ordered list of the targeted treatments of the personalized treatment guideline.

3. Method for selecting patients for a clinical trial of a treatment, comprising the steps:

retrieving identifications of disease indications of a set of patients as a user's input, from an electronic health record EHR or electronic medical record EMR or from a patient database comprising medical records of a candidate set of patients,

assigning, for every patient, an indication-specific score to each gene or protein of a first set of genes or proteins, the first set of genes or proteins being part of the human microbiome, the indication-specific score reflecting an evidence of the gene or protein being associated with the disease indication of the patient,

wherein the indication-specific score of each gene or protein is computed by first assigning numerical values to attributes indicating degrees of potential relationship to the indication and then by forming a weighted sum of the numerical values or of any monotonic transformation of the numerical values over the attributes, the attributes comprising at least one of the following list:

a) The gene or protein is a drug target,

b) The gene or protein is a biomarker or part of a biomarker,

c) The gene or protein is disease-associated,

d) The gene or protein is an oncogene or a product of an oncogene, respectively,

e) The gene or protein is a tumor suppressor,

f) The gene or protein has a cancer pathway association,

g) The gene or protein is gene ontology annotated for cancer relevant processes,

h) The gene or protein is part of a cancer-associated gene fusion,

i) The gene or protein has a tractable domain,

j) The gene or protein is embryonic lethal, and

k) The gene or protein is highly mutated in the specific indication;

retrieving, for every patient, a molecular profile of the patient, wherein the molecular profile is a set of molecular measurements of DNA or RNA extracted from the patient, indexed by a second set of genes or proteins, the second set of genes or proteins being equal to the first set of genes or proteins or being a subset of the first set of genes or proteins,

inferring, from the molecular profile, for each gene or protein of the first set of genes or proteins a possibly empty set of aberrations as the differences of the molecular profile to a reference profile from a control sample of the patient or from other individuals,

assigning, for every patient, a profile-specific score to each gene or protein of the first set of genes or proteins, the profile-specific score reflecting a degree of how much the function of the genes or proteins is altered by the aberrations,

wherein assigning the profile-specific score to each gene or protein of the first set of genes or proteins comprises the following steps:

computing an aberration-specific functional impact score for each aberration taking into account the direction of the impact of an aberration on the function of a gene or protein, wherein positive and negative signs of the aberration-specific functional impact score correspond to an activating and inactivating impact, respectively, and

computing a protein- or gene-specific direct functional impact score for each protein or gene by computing a weighted sum, a quantile, a median, a maximum or a geometric mean of the aberration-specific functional impact scores over the aberrations associated with the gene or protein, or

computing a protein- or gene-specific indirect functional impact score for each protein or gene by computing a weighted sum, a quantile, a median, a maximum or a geometric mean of the aberration-specific functional impact scores over the aberrations associated with another

set of genes or proteins, the another set including the gene or protein and a set of genes or proteins that are upstream of the gene or protein according to a molecular interaction network, the molecular interaction network being a directed graph, consisting of nodes each of which represents a gene or a protein, and of edges each of which connects two nodes,

and wherein the profile-specific score is set equal to the direct functional impact score, equal to the indirect functional impact score or equal to a weighted sum of these,

assigning, for every patient, a patient-specific score to each gene or protein of the first set of genes or proteins, the patient-specific score of each gene or protein being a sum, a weighted sum or a product of its indication-specific score and its profile-specific score,

retrieving, for the treatment, associated target genes or proteins from a treatment database, the treatment database storing treatments, in particular drugs and drug combinations, together with information on the genes or proteins that are the targets of the drugs, which are also in the first set of genes or proteins,

assigning a score to every patient from the set of patients by calculating a sum or a weighted sum over the patient-specific scores of the associated target genes or proteins, and

generating an ordered list of the patients, wherein the order of the patients is determined by their score.

4. The method of any of the preceding claims, wherein the profile-specific score is set to zero if the gene or protein has no aberrations.

5. The method of any of the preceding claims, wherein assigning the score to a treatment or patient further takes into account a directionality of the impact of the treatment on its associated target genes or proteins by adding the profile-specific scores of target genes or proteins that are inhibited or antagonized by the treatment and by subtracting the profile-specific scores of target genes or proteins that are activated or stimulated or agonized by the treatment.

6. The method of any of the preceding claims, wherein assigning the score to a treatment or patient involves the step that patient-specific scores are further aggregated over genes or proteins downstream of their associated target genes or proteins according to the molecular interaction network.

7. System for generating a personalized treatment guideline for a patient and/or for selecting patients for a clinical trial of a treatment, comprising a processing unit with:

an interface for providing a first set of genes or proteins to the system (1), the first set of genes or proteins being part of the human microbiome,

an interface for providing identifications of disease indications of patients to the system,

a module for assigning, for an identification of a disease indication of a patient, an indication-specific score to each gene or protein of the first set of genes or proteins, the indication-specific score reflecting an evidence of the gene or protein being associated with the disease indication of the patient,

wherein the indication-specific score of each gene or protein is computed by first assigning numerical values to attributes indicating degrees of potential relationship to the indication and then by forming a weighted sum of the numerical values or of any monotonic transformation of the numerical values over the attributes, the attributes comprising at least one of the following list:

a) The gene or protein is a drug target,

b) The gene or protein is a biomarker or part of a biomarker,

c) The gene or protein is disease-associated,

d) The gene or protein is an oncogene or a product of an oncogene, respectively,

e) The gene or protein is a tumor suppressor,

f) The gene or protein has a cancer pathway association,

g) The gene or protein is gene ontology annotated for cancer relevant processes,

h) The gene or protein is part of a cancer-associated gene fusion,

i) The gene or protein has a tractable domain,

j) The gene or protein is embryonic lethal, and

k) The gene or protein is highly mutated in the specific indication;

an interface for providing molecular profiles of patients to the system, wherein a molecular profile is a set of molecular measurements of DNA or RNA extracted from a patient, indexed by a second set of genes or proteins, the second set of genes or proteins being equal to the first set of genes or proteins or being a subset of the first set of genes or proteins,

a module for assigning, for a molecular profile of a patient, a profile-specific score to each gene or protein of the first set of genes or proteins, wherein the module for assigning the profile-specific score is adapted to inferring, from the molecular profile, for each gene or protein of the first set of genes or proteins a possibly empty set of aberrations as the differences of the molecular profile to a reference profile from a control sample of the patient or from other individuals,

wherein assigning the profile-specific score to each gene or protein of the first set of genes or proteins comprises the following steps:

computing an aberration-specific functional impact score for each aberration taking into account the direction of the impact of an aberration on the function of a gene or protein, wherein positive and negative signs of the aberration-specific functional impact score correspond to an activating and inactivating impact, respectively, and

computing a protein- or gene-specific direct functional impact score for each protein or gene by computing a weighted sum, a quantile, a median, a maximum or a geometric mean of the aberration-specific functional impact scores over the aberrations associated with the gene or protein, or

computing a protein- or gene-specific indirect functional impact score for each protein or gene by computing a weighted sum, a quantile, a

median, a maximum or a geometric mean of the aberration-specific functional impact scores over the aberrations associated with another set of genes or proteins, the another set including the gene or protein and a set of genes or proteins that are upstream of the gene or protein according to a molecular interaction network, the molecular interaction network being a directed graph, consisting of nodes each of which represents a gene or a protein, and of edges each of which connects two nodes,

and wherein the profile-specific score is set equal to the direct functional impact score, equal to the indirect functional impact score or equal to a weighted sum of these,

a module for assigning a patient-specific score to each gene or protein of the first set of genes or proteins, the patient-specific score of each gene or protein being a sum, a weighted sum or a product of its indication-specific score and its profile-specific score,

an interface for providing targeted treatments, together with associated target genes or proteins, as a user's input or by selecting treatments that are approved or under investigation for the indication of the patient or for related indications from a treatment database, the treatment database storing treatments, in particular drugs and drug combinations, together with information on the genes or proteins that are the targets of the drugs, to the system, and

a module for assigning a score to patients and to treatments by calculating a sum or a weighted sum over the patient-specific scores of the associated target genes or proteins, wherein the module for assigning the score to patients and to treatments is adapted to generating ordered lists of patients or treatments, wherein the order of the patients or treatments is determined by their score.