

to the patient; (b) comparing the expression level of the at least three genes to a reference expression level of the at least three genes, wherein a change in the level of expression of the at least three genes in the patient sample relative to the reference level identifies a patient who is likely to respond to treatment with a VEGF antagonist, wherein the change in the level of expression of the at least three genes in the patient sample is an increase relative to the reference level, and (c) selecting a VEGF antagonist as the therapy if the patient is identified as likely to respond to treatment with a VEGF antagonist; or (d) selecting a therapy that is not a VEGF antagonist if the patient is not identified as likely to respond to treatment with a VEGF antagonist, wherein the VEGF antagonist is an anti-VEGF antibody.

In some embodiments, the reference level is the median level of expression of the at least one gene in the population of patients. In some embodiments, the change in level of expression of the at least one gene in the patient sample is an increase relative to the reference level. In some embodiments, the change in level of expression of the at least one gene in the patient sample is a decrease relative to the reference level. In some embodiments, the methods further comprise detecting expression of at least a second, third, fourth, or more gene set forth in Table 1 or 2 in the biological sample from the patient. In some embodiments, the therapy of (d) is an agent selected from the group consisting of: an anti-neoplastic agent, a chemotherapeutic agent, a growth inhibitory agent, a cytotoxic agent, and combinations thereof. In some embodiments, the methods further comprise (e) administering an effective amount of a VEGF antagonist to the patient if the patient is identified as likely to respond to treatment with a VEGF antagonist. In some embodiments, the VEGF antagonist is an anti-VEGF antibody, such as bevacizumab. In some embodiments, the methods further comprising administering an effective amount of at least a second agent. In some embodiments, the second agent is selected from the group consisting of: an anti-neoplastic agent, a chemotherapeutic agent, a growth inhibitory agent, a cytotoxic agent, and combinations thereof.

In a further aspect, there is provided a method of identifying a biomarker for determining responsiveness to a VEGF antagonist, the method comprising: (a) detecting the expression of a candidate biomarker in a biological sample obtained from a patient prior to administration of a VEGF antagonist to the patient; and (b) comparing the expression of the candidate biomarker to a reference expression level of the candidate biomarker, wherein a change in the level of expression of the candidate biomarker in the patient sample relative to the reference level identifies the candidate biomarker as a biomarker of a patient who will likely respond to treatment with a VEGF antagonist, wherein the VEGF antagonist is an anti-VEGF antibody and the change in the level of expression of the candidate biomarker in the patient sample is an increase relative to the reference level.

wherein the change in the level of expression of the biomarker in the patient sample relative to the reference level is determined by calculating a VDV signature score (VDV_i) for the patient sample according to the algorithm:

$$VDV_i = \frac{1}{\sqrt{n}} \sum_{g=1}^n Z_{g,i}$$

wherein $Z_{g=1,i}, Z_{g=2,i}, \dots, Z_{g=n,i}$ are standardized z-scores of expression values for each biomarker g , from $g=1$ to $g=n$, of the sample i , and

wherein a VDV_i below a first defined threshold indicates a decrease relative to the reference level, and a VDV_i above a second defined threshold indicates an increase relative to the reference level.

In some embodiments, the reference level is the median level of expression of the at least one gene in a population of patients

being tested for the likelihood they will respond to a VEGF antagonist. In some embodiments, the reference level is the expression level of the at least one gene in a sample previously obtained from the patient. In some embodiments, the patient was previously treated with a VEGF antagonist and is currently experiencing metastasis. In some
 5 embodiments, the VEGF antagonist is an anti-VEGF antibody, such as bevacizumab. Further, the methods can further include (c) selecting a candidate biomarker having a change in level of expression relative to the reference for use as a biomarker for determining responsiveness to VEGF antagonist treatment.

In another aspect, there is provided a method for diagnosing an angiogenic disorder in
 10 a patient, the method comprising the steps of: (a) detecting the expression level of at least three genes set forth in Table 1 or 2 or a biomarker identified according to methods such as those described above in a sample obtained from the patient prior to any administration of a VEGF antagonist to the patient; (b) comparing the expression level of the at least three genes or biomarker to a reference level of the at least three genes or biomarker, wherein a change in
 15 the level of expression of the at least three genes or biomarker in the patient sample relative to the reference level identifies a patient having an angiogenic disorder; and (c) selecting an VEGF antagonist for treatment of said patient when a change in the level of expression of the at least three genes or biomarker in the patient sample relative to the reference level is detected, wherein the VEGF antagonist is an anti-VEGF antibody,

20 wherein the change in the level of expression of the at least three genes or biomarker in the patient sample relative to the reference level is determined by calculating a VDV signature score (VDV_i) for the patient sample according to the algorithm:

$$VDV_i = \frac{1}{\sqrt{n}} \sum_{g=1}^n Z_{g,i}$$

wherein $Z_{g=1,i}, Z_{g=2,i}, \dots, Z_{g=n,i}$ are standardized z-scores of expression values for each gene or biomarker g , from $g=1$ to $g=n$, of the sample i , and

25 wherein a VDV_i below a first defined threshold indicates a decrease relative to the reference level, and a VDV_i above a second defined threshold indicates an increase relative to the reference level.

~~The method can further include (e) selecting a VEGF antagonist for treatment of the patient when a change in the level of expression of the at least one gene in the patient sample relative~~
 30 ~~to the reference level is detected. In addition, the method can further include (d) administering a VEGF antagonist to the patient. In addition, the methods described herein can include a step of obtaining a sample from a patient, as described herein. Further, the methods described herein can be carried out on patients diagnosed with cancer, as described herein, to determine an optimal treatment regimen.~~

In any of the aspects and embodiments set forth above, the change in the level of expression of the at least one gene or biomarker in the patient sample relative to the reference level can be determined by calculating a VDV signature score (VDV_i) for the patient sample according to the algorithm:

$$VDV_i = \frac{1}{\sqrt{n}} \sum_{g=1}^n Z_{g,i}$$

- 5 in which $Z_{g=1,i}, Z_{g=2,i}, \dots, Z_{g=n,i}$ are standardized z-scores of expression values for each gene or biomarker g , from $g=1$ to $g=n$, of the sample i , and in which a VDV_i below a first defined threshold indicates a decrease relative to the reference level, and a VDV_i above a second

(a) detecting the expression of a candidate biomarker in a biological sample obtained from a patient prior to administration of a VEGF antagonist to the patient; and

(b) comparing the expression of the candidate biomarker to a reference expression level of the candidate biomarker, wherein a change in the level of expression of the candidate biomarker in the patient sample relative to the reference level identifies the candidate biomarker as a biomarker of a patient who will likely respond to treatment with a VEGF antagonist, wherein the VEGF antagonist is an anti-VEGF antibody and the change in the level of expression of the candidate biomarker in the patient sample is an increase relative to the reference level.

wherein the change in the level of expression of the biomarker in the patient sample relative to the reference level is determined by calculating a VDV signature score (VDV_i) for the patient sample according to the algorithm:

$$VDV_i = \frac{1}{\sqrt{n}} \sum_{g=1}^n Z_{g,i}$$

wherein $Z_{g=1,i}, Z_{g=2,i}, \dots, Z_{g=n,i}$ are standardized z-scores of expression values for each biomarker g, from g=1 to g=n, of the sample i, and

wherein a VDV_i below a first defined threshold indicates a decrease relative to the reference level, and a VDV_i above a second defined threshold indicates an increase relative to the reference level.

21. The method of claim 20, wherein the reference level is the median level of expression of the candidate biomarker in a population of patients being tested for the likelihood they will respond to a VEGF antagonist.

22. The method of claim 20, wherein the reference level is the expression level of the candidate biomarker in a sample previously obtained from the patient.

23. The method of claim 22, wherein the patient was previously treated with a VEGF antagonist and is currently experiencing metastasis.

24. The method of claim 20, wherein the anti-VEGF antibody is bevacizumab.

25. The method of claim 20, further comprising (c) selecting a candidate biomarker having a change in level of expression relative to the reference for use as a biomarker for determining responsiveness to VEGF antagonist treatment.

26. A method for diagnosing an angiogenic disorder in a patient, the method comprising the steps of:

(a) detecting the expression level of at least three genes set forth in Table 1 or 2 or a biomarker identified according to the method of claim 20 in a sample obtained from the patient prior to any administration of a VEGF antagonist to the patient;

(b) comparing the expression level of the at least three genes or biomarker to a reference level of the at least three genes or biomarker, wherein a change in the level of expression of the

at least three genes or biomarker in the patient sample relative to the reference level identifies a patient having an angiogenic disorder; and

(c) selecting an VEGF antagonist for treatment of said patient when a change in the level of expression of the at least three genes or biomarker in the patient sample relative to the reference level is detected, wherein the VEGF antagonist is an anti-VEGF antibody,

wherein the change in the level of expression of the at least three genes or biomarker in the patient sample relative to the reference level is determined by calculating a VDV signature score (VDV_i) for the patient sample according to the algorithm:

$$VDV_i = \frac{1}{\sqrt{n}} \sum_{g=1}^n Z_{g,i}$$

wherein $Z_{g=1,i}, Z_{g=2,i}, \dots, Z_{g=n,i}$ are standardized z-scores of expression values for each gene or biomarker g , from $g=1$ to $g=n$, of the sample i , and

wherein a VDV_i below a first defined threshold indicates a decrease relative to the reference level, and a VDV_i above a second defined threshold indicates an increase relative to the reference level.

27. The method of any one of claims 1, 2, ~~or 14, 20, or 26~~, wherein the change in the level of expression of the at least three genes or biomarker in the patient sample relative to the reference level is determined by calculating a VDV signature score (VDV_i) for the patient sample according to the algorithm:

$$VDV_i = \frac{1}{\sqrt{n}} \sum_{g=1}^n Z_{g,i}$$

wherein $Z_{g=1,i}, Z_{g=2,i}, \dots, Z_{g=n,i}$ are standardized z-scores of expression values for each gene or biomarker g , from $g=1$ to $g=n$, of the sample i , and

wherein a VDV_i below a first defined threshold indicates a decrease relative to the reference level, and a VDV_i above a second defined threshold indicates an increase relative to the reference level.

28. The method of claim 27, wherein the expression values for each gene or biomarker g , from $g=1$ to $g=n$, are qRT-PCR values for each gene g , from $g=1$ to $g=n$.

29. The method of claim 27, wherein the first defined threshold is from -4 to -0.5 and the second defined threshold is from 0.5 to 4.

30. The method of claim 29, wherein the first defined threshold is from -4 to -1 and the second defined threshold is from 1 to 4.

31. The method of claim 30, wherein the first defined threshold is from -4 to -1.5 and the second defined threshold is from 1.5 to 4.

32. The method of claim 31, wherein the first defined threshold is from -4 to -2 and the second defined threshold is from 2 to 4.