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SUMMARY

5 The present disclosure is based on the discovery that a biopsy samples from subjects having a variety of different cancers include a cancer cell that has at least one point mutation in a NTRK1, NTRK2, and/or NTRK3 gene that results in the expression of a TrkA, TrkB, and/or TrkC protein comprising a mutation at one or more amino acid position(s) (e.g., a substitution or a deletion). In view of this discovery, provided herein are methods of treating
10 a subject having a cancer that include administering to a subject identified as having a cancer cell that has at least one point mutation in NTRK1, NTRK2, and/or NTRK3 (e.g., any of the point mutations in NTRK1, NTRK2, and/or NTRK3 described herein) a therapeutically effective amount of a Trk inhibitor (e.g., any of the Trk inhibitors described herein or known in the art), methods of selecting a treatment including a therapeutically effective amount of a
15 Trk inhibitor (e.g., any of the Trk inhibitors described herein or known in the art) for a subject identified as having a cancer cell that has at least one point mutation in NTRK1, NTRK2, and/or NTRK (e.g., any of the point mutations in NTRK1, NTRK2, and/or NTRK3 described herein), methods of determining the likelihood that a subject having a cancer will have a positive response to a treatment based upon whether the subject has a cancer cell that has at
20 least one point mutation in NTRK1, NTRK2, and/or NTRK3 (e.g., any of the point mutations in NTRK1, NTRK2, and/or NTRK3 described herein), methods of predicting the efficacy of a Trk inhibitor (e.g., any of the Trk inhibitors described herein or known in the art) in a subject having a cancer based upon whether the subject has a cancer cell that has at least one point mutation in NTRK1, NTRK2, and/or NTRK3 (e.g., any of the point mutations in
25 NTRK1, NTRK2, and/or NTRK3 described herein), methods of determining a subject's risk for developing a cancer (e.g., any of the cancers described herein) based upon whether the subject has a cell that has at least one point mutation in NTRK1, NTRK2, and/or NTRK3 (e.g., any of the point mutations in NTRK1, NTRK2, and/or NTRK3 described herein), and methods of assisting in the diagnosis of cancer (e.g., any of the cancers described herein) in a
30 subject based upon whether the subject has a cell that has at least one point mutation in NTRK1, NTRK2, and/or NTRK3 (e.g., any of the point mutations in NTRK1, NTRK2, and/or NTRK3 described herein).

In some embodiments of the kits, the one or more probes are labeled with a detectable probe. In some embodiments of the kits, the one or more probes are covalently attached to a substrate (e.g., a film, a plate, or a bead).

Also provided herein are methods of treating a subject having a cancer that include: (a)

- 5 identifying a subject having a cancer cell that has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more amino acid position(s) selected from the group of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; at least one point mutation in a NTRK2 gene that results in the expression of a TrkB
10 protein including a mutation at one or more amino acid position(s) selected from the group of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more amino acid position(s)
15 selected from the group of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810; and (b) administering to the identified subject a therapeutically effective
20 amount of a Trk inhibitor.

In one aspect, provided herein is use of a Trk inhibitor in the manufacture of a medicament for treating a subject having a cancer, the use comprising:

identifying a subject having a cancer cell that has:

- 25 at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750;

- 30 at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or

- 35 at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810;

40 wherein the medicament is to be administered to the identified subject.

Also provided herein are methods of treating a subject identified as having a cancer cell that has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more amino acid position(s) selected from the
45 group of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more amino acid position(s) selected from the group of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788,
50 789, 804, and 805; and/or at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more amino acid position(s)

selected from the group of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, the method comprising administering to the subject a therapeutically effective amount of a Trk inhibitor.

In one aspect, provided herein is use of a Trk inhibitor in the manufacture of a medicament for treating a subject identified as having a cancer cell that has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810.

In one aspect, provided herein are methods of selecting a treatment for a subject having a cancer, the methods comprising: (a) identifying a subject having a cancer cell that has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810; and (b) selecting a treatment comprising a therapeutically effective amount of a Trk inhibitor for the identified subject.

In one aspect, provided herein are methods of selecting a treatment for a subject having a cancer, the methods comprising selecting a treatment comprising a therapeutically effective amount of a Trk inhibitor for a subject identified as having a cancer cell that has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; at least one point mutation in a NTRK2

gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805;

5 and/or at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625,
10 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810.

In one aspect, provided herein are methods of determining the likelihood that a subject having a cancer will have a positive response to treatment with a Trk inhibitor, the
15 methods comprising: (a) determining whether a cancer cell in a sample obtained from the subject has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; at least one
20 point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or at least one point mutation in a NTRK3 gene that results in the
25 expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677,
30 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810; and (b) determining that a subject having a cancer cell that has the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene,

and/or the at least one point mutation in a NTRK3 gene, has an increased likelihood of having a positive response to treatment with a Trk inhibitor.

In one aspect, provided herein are methods of determining the likelihood that a subject having cancer will have a positive response to treatment with a Trk inhibitor, the methods comprising: determining that a subject having a cancer cell that has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group of: 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, has an increased likelihood of having a positive response to treatment with a Trk inhibitor.

In one aspect, provided herein are methods of predicting the efficacy of a Trk inhibitor in a subject having cancer, the methods comprising: (a) determining whether a cancer cell in a sample obtained from the subject has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino

acid position(s) selected from the group of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810; and (b) determining that a Trk inhibitor is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene.

In one aspect, provided are methods of predicting the efficacy of a Trk inhibitor in a subject having cancer, the methods comprising: determining that a Trk inhibitor is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810.

In some embodiments of any of the use or methods described herein, the cancer is selected from the group of: adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma, bladder urothelial carcinoma, bile duct adenocarcinoma, bladder carcinoma, bladder urothelial carcinoma, bone chordoma, bone marrow leukemia lymphocytic chronic, bone marrow leukemia non-

tissue Ewing sarcoma, soft tissue hemangioendothelioma, soft tissue inflammatory myofibroblastic tumor, soft tissue leiomyosarcoma, soft tissue liposarcoma, soft tissue neuroblastoma, soft tissue paraganglioma, soft tissue perivascular epithelioid cell tumor, soft tissue sarcoma, soft tissue synovial sarcoma, stomach adenocarcinoma, stomach adenocarcinoma diffuse-type, stomach adenocarcinoma intestinal type, stomach adenocarcinoma intestinal type, stomach leiomyosarcoma, thymus carcinoma, thymus thymoma lymphocytic, thyroid papillary carcinoma, unknown primary adenocarcinoma, unknown primary carcinoma, unknown primary malignant neoplasm, lymphoid neoplasm, unknown primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell carcinoma, unknown undifferentiated neuroendocrine carcinoma, unknown primary undifferentiated small cell carcinoma, uterus carcinosarcoma, uterus endometrial adenocarcinoma, uterus endometrial adenocarcinoma endometrioid, uterus endometrial adenocarcinoma papillary serous, and uterus leiomyosarcoma.

In some embodiments of any of the use or methods described herein, the subject is previously identified or diagnosed as having the cancer. In some embodiments of any of the use or methods described herein, the step of identifying a subject having a cancer cell that has the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene includes performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene, in a cancer cell in a sample from the subject. In some embodiments of any of the use or methods described herein, the assay is selected from the group of: denaturing gradient gel electrophoresis (DGGE), temperature gradient gel electrophoresis (TGGE), temperature gradient capillary electrophoresis, a single strand conformational polymorphism assay, a molecular beacon assay, a dynamic hybridization assay, a PCR-based assay, and denaturing high performance liquid chromatography. In some embodiments of any of the use or methods described herein, the assay includes sequencing a segment of the NTRK1 gene comprising the at least one point mutation, a segment of the NTRK2 gene comprising the at least one point mutation, and/or a segment of the NTRK3 gene comprising the at least one point mutation.

In some embodiments of any of the use or methods described herein, the Trk inhibitor is a crystalline form of the compound of Formula I:

NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene as having an increased likelihood of developing a cancer.

In one aspect, provided herein are methods of determining a subject's risk for developing a cancer, the methods comprising identifying a subject having a cell that has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group of: 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, as having an increased likelihood of developing a cancer.

In one aspect, provided herein are methods of assisting in the diagnosis of a cancer in a subject, the methods comprising: (a) determining whether a cell in a sample obtained from the subject has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282,

283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810; and (b) determining that a subject having a cell that has the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene, has an increased likelihood of having a cancer.

In one aspect, provided are methods of assisting in the diagnosis of a cancer in a subject, the methods comprising determining that a subject having a cell that has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, has an increased likelihood of having a cancer.

In some embodiments of any of the methods described herein, the subject is identified as having been exposed to a significant level of carcinogen(s). In some embodiments of any of the methods described herein, the subject is suspected of having a cancer. In some embodiments of any of the methods described herein, the subject has one or more symptoms of cancer. In some embodiments of any of the methods described herein, the cancer is selected from the group of: adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma,

In some embodiments of any of the use or methods described herein, the TrkA protein includes a mutation at one or more amino acid positions selected from the group of S241F, S241H, S241Y, R314G, R314H, R314L, R314P, N318S, G319S, S320F, V321M, I510T, V511M, L512F, L512R, S552R, A553T, R554P, R554Q, R554W, A636E, A636T, A636V, G637E, G637W, M638V, R649L, R649W, R654C, R654H, N655Y, D679N, D679Y, Y680H, T687I, M688I, L689M, P690H, R692C, R692H, P695S, P696L, E697K, E747K, R748L, R748Q, R748W, P749Q, R750C, R750H, and R750L; the TrkB protein includes a mutation at one or more amino acid position(s) selected from the group of M240I, N241D, E242K, R251G, R251K, I252V, S256L, S257F, D258N, I264M, A314E, A314G, A314V, L315F, G401A, G401E, G401R, T426I, G427S, R428Q, A440S, A440T, A440V, R598C, R598S, K599M, D600H, H602N, R603S, L664M, T665M, T665S, Q666L, Q666R, A677T, A678T, A678V, G679D, M680I, V689M, R691C, D692N, F746I, T747M, T748M, E749K, Q784H, G785V, R786Q, V787F, L788M, Q789E, G804E, C805R, and C805Y; and/or the TrkC protein includes a mutation at one or more amino acid position(s) selected from the group of V221I, R222Q, E223D, D242N, W243C, I244T, T269A, T269M, T270M, T270Q, T270V, V271L, V271M, E276D, D277E, D277G, D277N, T281I, T281P, T282M, T283A, T283K, T283M, S296I, S296R, V297I, V325M, R326C, R326G, R326H, R326L, R326P, N328S, P329N, P329S, P330Q, E344G, E344V, S345F, K346N, H349Y, V350E, E351D, Y353F, Q354K, D537E, D537Y, I538N, V539M, L540M, G545C, G545D, G550R, K551E, L560V, P562L, P562Q, P562R, P562T, K575E, D576N, P577S, P582Q, P582W, K583%, D584E, D584N, V601A, V601I, K602R, F603L, Y604F, Y604H, Y604N, C607F, G608C, G608E, G608S, D609G, D609H, D609N, D609V, G610R, P612A, P612L, P612S, P612T, D624Y, L625M, N626K, K627N, K627R, F628L, L629F, L629I, P634L, P634T, D635H, A636E, A636V, M637I, M637K, M637V, E650V, L651P, G652R, G652V, L653F, L653P, H677Y, R678Q, D679G, D679N, V687A, V687I, G688R, A689E, A689V, Y705N, S706I, T707M, D708N, P715L, P715S, S716Y, G717R, T730N, M731I, M731L, L732I, P738H, P738S, Y744F, R745P, R745W, K746R, K746T, G786C, G786S, R787C, R787H, R787S, P796L, P796S, D801N, Q808H, R809W, and E810K.

In one aspect, provided are kits comprising one or more probes that each specifically hybridize to: a segment of a NTRK1 gene that encodes a mutation at one of amino acid positions 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750 in a TrkA protein; a segment of a NTRK2 gene that encodes a mutation at one of amino acid positions

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

Figure 1 is a diagram showing the position of the different point mutations detected in the NTRK3 gene (Summary) and the point mutations in NTRK3 gene that are associated with specific histologies (bottom nine rows).

Figure 2 is a diagram showing the position of all the different point mutations detected in the NTRK3 gene with confirmed expression above background (Summary) and the point mutations in the NTRK3 gene with confirmed expression above background that are associated with specific histologies (bottom nine rows).

Figure 3 is a graphic showing the position of a valine at amino acid position 689 or a methionine at amino acid position 689 relative to the asparagine at amino acid position 529 in TrkB protein.

DETAILED DESCRIPTION

A variety of different NTRK1, NTRK2, and NTRK3 point mutations were discovered in biopsy samples from subjects having a variety of different cancers. In view of this discovery, provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein) that include administering to a subject identified as having a cancer cell that has at least one point mutation in NTRK1, NTRK2, and/or NTRK3 (e.g., any of the point mutations in NTRK1, NTRK2, and/or NTRK3 described herein) a therapeutically effective amount of a Trk inhibitor (e.g., any of the Trk inhibitors described herein), methods of selecting a treatment including a therapeutically effective amount of a Trk inhibitor (e.g., any of the Trk inhibitors described herein) for a subject identified as having a cancer cell that

WHAT IS CLAIMED IS:

1. Use of a Trk inhibitor in the manufacture of a medicament for treating a subject having a cancer, the use comprising:

identifying a subject having a cancer cell that has:

at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750;

at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or

at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810;

wherein the medicament is to be administered to the identified subject.

2. Use of a Trk inhibitor in the manufacture of a medicament for treating a subject identified as having a cancer cell that has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or at least one point mutation in a

NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810.

3. A method of selecting a treatment for a subject having a cancer, the method comprising:

(a) identifying a subject having a cancer cell that has:

at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750;

at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or

at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810; and

(b) selecting a treatment comprising a therapeutically effective amount of a Trk inhibitor for the identified subject.

determining that a Trk inhibitor is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has:

at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750;

at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or

at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810.

9. The use of claim 1 or 2, or the method of any one of claims 3-8, wherein the cancer is selected from the group consisting of: adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma, bladder urothelial carcinoma, bile duct adenocarcinoma, bladder carcinoma, bladder urothelial carcinoma, bone chordoma, bone marrow leukemia lymphocytic chronic, bone marrow leukemia non-lymphocytic acute myelocytic, bone marrow lymph proliferative disease, bone marrow multiple myeloma, bone sarcoma, brain astrocytoma, brain glioblastoma, brain medulloblastoma, brain meningioma, brain oligodendroglioma, breast adenoid cystic carcinoma, breast carcinoma, breast ductal carcinoma in situ, breast invasive ductal carcinoma, breast invasive lobular carcinoma, breast metaplastic carcinoma, cervix neuroendocrine carcinoma, cervix squamous cell carcinoma, colon adenocarcinoma, colon carcinoid tumor, duodenum adenocarcinoma, endometrioid tumor, esophagus adenocarcinoma, esophagus and stomach carcinoma, eye intraocular melanoma, eye

unknown primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell carcinoma, unknown undifferentiated neuroendocrine carcinoma, unknown primary undifferentiated small cell carcinoma, uterus carcinosarcoma, uterus endometrial adenocarcinoma, uterus endometrial adenocarcinoma endometrioid, uterus endometrial adenocarcinoma papillary serous, and uterus leiomyosarcoma.

10. The use or method of any one of claims 1-9, wherein the subject is previously identified or diagnosed as having the cancer.

11. The use of claim 1 or the method of any one of claims 3, 5, and 7, wherein the step of identifying a subject having a cancer cell that has the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene comprises performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene, in a cancer cell in a sample from the subject.

12. The use or method of claim 11, wherein the assay is selected from the group consisting of: denaturing gradient gel electrophoresis (DGGE), temperature gradient gel electrophoresis (TGGE), temperature gradient capillary electrophoresis, a single strand conformational polymorphism assay, a molecular beacon assay, a dynamic hybridization assay, a PCR-based assay, and denaturing high performance liquid chromatography.

13. The use or method of claim 11, wherein the assay comprises sequencing a segment of the NTRK1 gene comprising the at least one point mutation, a segment of the NTRK2 gene comprising the at least one point mutation, and/or a segment of the NTRK3 gene comprising the at least one point mutation.

14. The use or method of any one of claims 1-13, wherein the Trk inhibitor is a crystalline form of the compound of Formula I:

31. The use or method of any one of claims 1-30, wherein:

the TrkA protein comprises a mutation at one or more amino acid positions selected from the group consisting of S241F, S241H, S241Y, R314G, R314H, R314L, R314P, N318S, G319S, S320F, V321M, I510T, V511M, L512F, L512R, S552R, A553T, R554P, R554Q, R554W, A636E, A636T, A636V, G637E, G637W, M638V, R649L, R649W, R654C, R654H, N655Y, D679N, D679Y, Y680H, T687I, M688I, L689M, P690H, R692C, R692H, P695S, P696L, E697K, E747K, R748L, R748Q, R748W, P749Q, R750C, R750H, and R750L;

the TrkB protein comprises a mutation at one or more amino acid position(s) selected from the group consisting of M240I, N241D, E242K, R251G, R251K, I252V, S256L, S257F, D258N, I264M, A314E, A314G, A314V, L315F, G401A, G401E, G401R, T426I, G427S, R428Q, A440S, A440T, A440V, R598C, R598S, K599M, D600H, H602N, R603S, L664M, T665M, T665S, Q666L, Q666R, A677T, A678T, A678V, G679D, M680I, V689M, R691C, D692N, F746I, T747M, T748M, E749K, Q784H, G785V, R786Q, V787F, L788M, Q789E, G804E, C805R, and C805Y; and/or

the TrkC protein comprises a mutation at one or more amino acid position(s) selected from the group consisting of V221I, R222Q, E223D, D242N, W243C, I244T, T269A, T269M, T270M, T270Q, T270V, V271L, V271M, E276D, D277E, D277G, D277N, T281I, T281P, T282M, T283A, T283K, T283M, S296I, S296R, V297I, V325M, R326C, R326G, R326H, R326L, R326P, N328S, P329N, P329S, P330Q, E344G, E344V, S345F, K346N, H349Y, V350E, E351D, Y353F, Q354K, D537E, D537Y, I538N, V539M, L540M, G545C, G545D, G550R, K551E, L560V, P562L, P562Q, P562R, P562T, K575E, D576N, P577S, P582Q, P582W, K583%, D584E, D584N, V601A, V601I, K602R, F603L, Y604F, Y604H, Y604N, C607F, G608C, G608E, G608S, D609G, D609H, D609N, D609V, G610R, P612A, P612L, P612S, P612T, D624Y, L625M, N626K, K627N, K627R, F628L, L629F, L629I, P634L, P634T, D635H, A636E, A636V, M637I, M637K, M637V, E650V, L651P, G652R, G652V, L653F, L653P, H677Y, R678Q, D679G, D679N, V687A, V687I, G688R, A689E, A689V, Y705N, S706I, T707M, D708N, P715L, P715S, S716Y, G717R, T730N, M731I, M731L, L732I, P738H, P738S, Y744F, R745P, R745W, K746R, K746T, G786C, G786S, R787C, R787H, R787S, P796L, P796S, D801N, Q808H, R809W, and E810K.