



# Timing of *NTRK* Gene Fusion Testing and Treatment Modifications Following TRK Fusion Status Among US Oncologists Treating TRK Fusion Cancer

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## Abstract

**Background** Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers with an estimated prevalence of less than 1% across all solid tumors. Tropomyosin receptor kinase inhibitors (TRKis) block the constitutively activated tyrosine receptor kinase (TRK) fusion protein produced in *NTRK* gene fusion positive (*NTRK*+) tumors from downstream signaling. Tropomyosin receptor kinase inhibitors are now first-line (1L) or subsequent treatment options for TRK fusion cancers.

**Objective** This study assessed timing of *NTRK* gene fusion testing and treatment modifications among patients with TRK fusion cancers.

**Patients and Methods** This was a one-time physician questionnaire with a retrospective, multisite patient chart abstraction of oncology practices in the USA. From June to September 2020, medical oncologists from the Oncology Provider Extended Network (OPEN) who treated patients with *NTRK*+ advanced/metastatic solid tumors abstracted information into electronic case report forms (eCRFs) for adult patients with advanced/metastatic solid tumors and a *NTRK*+ tumor test result with a known fusion partner. Use of *NTRK* testing in routine clinical practice among patients with advanced/metastatic solid tumors was assessed. Data included demographic, clinical, and *NTRK* gene fusion testing characteristics. Responses were summarized using descriptive statistics.

**Results** Twenty-eight community-based medical oncologists who had managed or treated 148 patients with advanced/metastatic TRK fusion cancer between 01/01/2016 and 12/31/2019 completed the survey. Lung (27%), thyroid (18%), salivary gland (14%), and colorectal (12%) were the most commonly reported tumor types. A majority (68%) tested *NTRK* status prior to 1L initiation; testing after disease progression on 1L (36%), 2L (25%), and 3L (21%) was also noted. Most oncologists (96%) reported no difficulty interpreting *NTRK* reports. Nearly all (96%) indicated using next-generation sequencing (NGS) for determining *NTRK* status. The majority (57%) indicated that age, tumor type, and performance status did not impact *NTRK* testing decisions. Less than half (46%) include TRKi therapy following *NTRK*+ determination. *NTRK* testing guidelines were commonly reviewed by physicians (89%).

**Conclusion and Relevance** Among patients with advanced/metastatic TRK fusion cancer, medical oncologists reported testing for *NTRK* fusions at diagnosis or prior to 1L. Future research should elucidate why fewer than half of oncologists surveyed (46%) would not use TRKis after *NTRK*+ status confirmation, assess clinical practices among *NTRK*+ patients, and characterize treatment patterns and clinical outcomes in real-world settings.

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### Key Points

Oncologists in this study reported that they use testing 68% of the time to identify cancers that have certain types of biomarkers, called tyrosine receptor kinase (TRK) fusions, prior to patients beginning systemic treatment such as chemotherapy.

The majority of oncologists (96%) reported no difficulties interpreting TRK fusion cancer test reports and 89% indicated that they reviewed TRK fusion cancer testing guidelines regularly.

However, less than half (46%) reported that they include tropomyosin receptor kinase inhibitors (TRKis), a targeted therapy for TRK fusion cancers, after a positive TRK fusion cancer test result.

## 1 Introduction

Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers that can present in any tumor type and may be implicated in approximately 1% of all solid tumor cancers [13]. The availability of tropomyosin receptor kinase inhibitors (TRKis) offers molecularly targeted therapy for patients with *NTRK* gene fusion positive (*NTRK*+) tumors [2, 11], but the low prevalence of such fusions and availability of testing modalities can be a potential barrier to their timely identification [9, 14].

Tropomyosin receptor kinase inhibitors target *NTRK*+ tumors by blocking the constitutively activated tyrosine receptor kinase (TRK) fusion protein produced by *NTRK*+ tumors from downstream signaling [14]. The US Food and Drug Administration (FDA) in 2018 approved larotrectinib and entrectinib for the treatment of TRK fusion cancer in both adult (larotrectinib and entrectinib: all ages) [4, 6, 10] and pediatric (larotrectinib: all ages, entrectinib: aged  $\geq 12$  years) populations [7]. Data that preceded the approval of larotrectinib indicated an overall response rate of 75%, including complete response among 13% and partial response among 62% of patients with *NTRK*+ tumors, irrespective of tumor type, patient age, or TRK fusion characteristics [5]. The National Comprehensive Cancer Network (NCCN) has not yet published guidelines for the use of tumor-agnostic treatments [1], however, to date, within the NCCN treatment guidelines, 25 different tumor types have incorporated treatment with a TRKi and/or testing for *NTRK* gene fusions.

A better understanding is need of how oncologists perform and assess genomic testing in the selection of systemic therapy for patients who may benefit from TRKi therapy. Such data will facilitate communication of both trial and real-world evidence (RWE) research results and could also be used to guide the dissemination of current and future TRKi therapy treatment guidelines. Finally, an understanding of the timing of *NTRK* gene fusion testing and overall physician perceptions of systemic therapy selection for TRK fusion cancers could help elucidate unmet needs among affected patients. Since TRKis are relatively new therapies and electronic medical records routinely fail to capture genomic testing accurately and uniquely, the existing evidence characterizing *NTRK* gene fusion testing patterns is therefore limited. This is particularly the case among data from patients treated outside of the clinical trial setting and outside of major cancer treatment centers.

Thus, the objective of this study was to evaluate real-world experiences of medical oncologists treating patients with TRK fusion cancers to assess timing of *NTRK* gene fusion testing and treatment modifications following an affirmation of *NTRK*+ tumor status.

## 2 Methods

Community-based medical oncologists from the Oncology Provider Extended Network (OPEN) in the USA, who had treated patients with TRK fusion cancer, were invited to participate in a retrospective patient chart review study. The OPEN community comprises more than 7000 unique providers in oncology, hematology, and urology across the USA. Over 800 of these physicians have participated in OPEN real-world research since 2016. Prior to chart data abstraction, study materials (research protocol and electronic case report forms [eCRF]) were submitted to an independent, central Institutional Review Board (Western Institutional Review Board [IRB]). The IRB determined that this study met the criteria for a waiver of authorization for use and disclosure of protected health information (PHI) and was exempt from IRB oversight. A waiver of informed consent was granted.

Medical oncologists from the OPEN community who had treated/managed adult patients with a TRK fusion cancer and had previously ordered *NTRK* gene fusion testing between January 1, 2016, and December 30, 2019, by any testing modality (e.g., next-generation sequencing [NGS], fluorescent in situ hybridization studies [FISH], immunohistochemistry [IHC]) were eligible for participation in the study. A one-time physician questionnaire collected oncologists' experience with *NTRK* gene fusion testing in routine clinical practice among patients with advanced/metastatic solid tumors. This questionnaire of physicians was not

directly related to the patient-level data, which was collected in a subsequent data abstraction of treatment patterns and outcomes for a separate publication.

Next, retrospective, de-identified patient-level data were abstracted by the participating medical oncologists. Each oncologist indicated solid tumor type for up to three patients with diagnoses of advanced/metastatic TRK fusion cancer. The limit of three eligible patients per provider, regardless of number of eligible patients with data available per provider, was imposed to minimize potential bias from a single practice. Oncologists also selected consecutively eligible patients to limit bias. Eligible patients were aged  $\geq 18$  years with a confirmed diagnosis of any advanced/metastatic solid tumor between January 1, 2016, and December 31, 2019, and had an *NTRK*+ tumor test result with a known fusion partner. Eligibility was limited to adult patients (aged  $\geq 18$  years) given the composition of the physician network. Patients were required to have at least three months of follow-up from the date of advanced/metastatic cancer diagnosis (unless deceased prior to 3 months following diagnosis). Patients were excluded with a prior primary cancer, diagnosed and treated within a year prior to 1L therapy initiation for the advanced/metastatic solid tumor of interest, as well as those participating in a clinical trial for treatment of their cancer. Data collection occurred from June through September 2020. Each completed eCRF was reviewed independently for implausible or inconsistent data. Providers were contacted with queries, and individual eCRFs that could not be validated were removed from the study dataset.

Responses regarding provider characteristics and *NTRK* gene fusion testing patterns from the physician questionnaire, as well as demographic, clinical characteristics, and treatment abstracted from patient medical records into eCRFs, were presented using descriptive statistics. All analyses were conducted in SAS v9.4.

## 3 Results

### 3.1 Provider Characteristics

In total, 28 medical oncologists provided data. Oncologists were geographically distributed across the USA: 25% Northeast, 14% Midwest, 39% South, 21% West. The majority (71%) reported their primary practice setting as private community practice, while 25% reported practicing at academic centers or affiliated teaching hospitals and 4% as solo practitioners. Urban, suburban, and rural practice settings were reported among 42.9%, 35.7%, and 21.4% of the medical oncologists, respectively. Oncologists' median number of years in practice was 17 (range 13–23 years) and the oncologists had managed or treated 148 adult patients diagnosed

with *NTRK*+ advanced/metastatic solid tumors between January 1, 2016, and December 31, 2019 (Table 1).

### 3.2 Neurotrophic Tyrosine Receptor Kinase Gene Fusion Testing and Treatment Decision Making

The majority of medical oncologists (57%) indicated that age, tumor type, and Eastern Cooperative Oncology Group (ECOG) performance status did not impact *NTRK* gene fusion testing decisions (Fig. 1). When asked what training and/or resources were reviewed for *NTRK* gene fusion testing recommendations, medical oncologists reported that clinical guidelines (e.g., NCCN guidelines, ESMO Scale for Clinical Actionability of molecular Targets [ESCAT]) were most commonly reviewed (89%), followed by peer-reviewed literature (75%) and continuing medical education (57%) (Fig. 2). Over two-thirds (68%) of medical oncologists reported that they perform *NTRK* gene fusion testing at diagnosis (i.e., prior to 1L therapy initiation), over one-third perform testing following disease progression on 1L therapy (36%), one-quarter following 2L therapy (25%), and one-fifth following third-line (3L) therapy (21%) (Fig. 3). Nearly all (96%) indicated that they use NGS for determining *NTRK* gene fusion status, with FISH as the second most frequently used test (29%). Most medical oncologists (96%) self-reported little-to-no difficulty interpreting *NTRK* gene fusion testing reports. Of the medical oncologists self-reporting little-to-no difficulty interpreting reports, 39% indicated that they always have *NTRK* gene fusion testing reports interpreted by a third party, whereas 57% stated that they interpret the reports themselves. Treatment with a TRKi therapy following identification of a TRK fusion cancer was associated with fewer than half (46%) of responding medical oncologists. Of the 28 oncologists, 11% began testing for *NTRK* gene fusions in 2016 or 2017, 61% in 2018, and the remaining 28% in 2019.

### 3.3 Patient Demographics and Clinical Characteristics

The 28 participating medical oncologists entered patient-level data on 73 patients (of the 148 patients reported in total) with an *NTRK*+ solid tumor. Patient demographic and clinical characteristics are presented in Table 2. Patients' median age at diagnosis of advanced/metastatic cancer was 61 years (range 55–68 years) and the overall sample showed a relatively even distribution between sex assigned at birth (52.1% male, 47.9% female). Lung (27.4%), thyroid (17.8%), salivary gland (13.7%) and colorectal (12.3%) were the most frequently reported tumor types, each present in  $> 10\%$  of the cohort.

**Table 1** Characteristics of participating oncologists

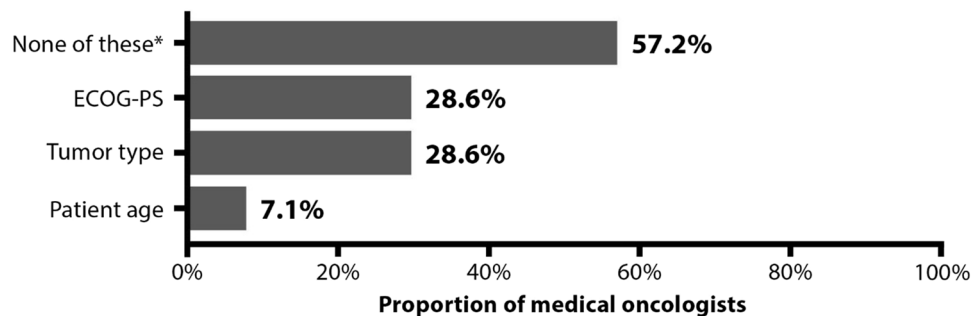
	Number of physicians ( <i>N</i> = 28)	
Practice type ( <i>n</i> , %)		
Solo practitioner	1	3.6%
Small private community practice (2–5 physicians)	9	32.1%
Medium-sized private community practice (6–10 physicians)	6	21.4%
Large private community practice (> 10 physicians)	5	17.9%
Community-based hospital owned by an academic center	1	3.6%
Academic medical center	3	10.7%
Affiliated teaching hospital	3	10.7%
VA/military hospital/DoD	0	0.0%
Practice location ( <i>n</i> , %) <sup>a</sup>		
Northeast	7	25.0%
Midwest	4	14.3%
South	11	39.3%
West	6	21.4%
Practice setting ( <i>n</i> , %)		
Urban	12	42.9%
Suburban	10	35.7%
Rural	6	21.4%
Oncologist years in practice (median, [SD] IQR)	17.0	[6.7] 13–23
Oncologist specialty ( <i>n</i> , %) <sup>b</sup>		
Medical oncology	10	35.7%
Hematology/oncology	20	71.4%
Number of adult patients with an <i>NTRK</i> + (with known fusion partner) solid tumor oncologists treated between 01/01/2016–12/31/2019 with at least 3 months of follow-up		
Total across all physicians (median [IQR] per physician) <sup>c</sup>	148	4 (2–8)

DoD Department of Defense, IQR interquartile range, *NTRK*+ neurotrophic tropomyosin-related kinase gene fusion-positive, SD standard deviation, VA Veterans Affairs

<sup>a</sup>Northeast (CT, DE, MA, ME, MD, NH, NJ, NY, PA, RI, VT), Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI), South (AL, AR, DC, FL, GA, KY, LA, MS, NC, OK, SC, TN, TX, VA, WV), West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)

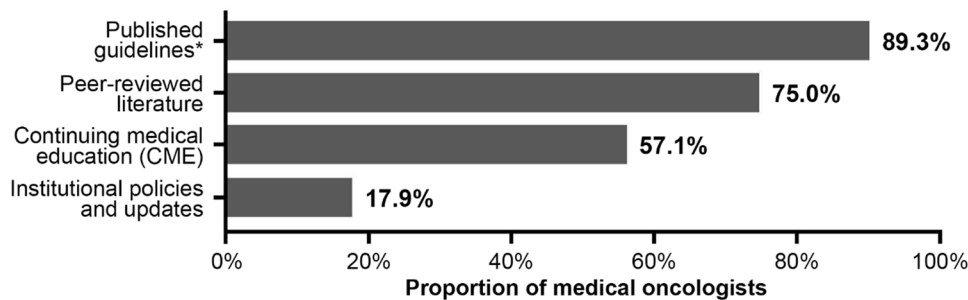
<sup>b</sup>Categories not mutually exclusive

<sup>c</sup>One (1) physician reported 30 patients and was excluded from calculation



**Fig. 1** Factors affecting medical oncologists' decision-making process regarding *NTRK* gene fusion testing among patients with potentially *NTRK*+ tumors (listed are performance status, tumor type,

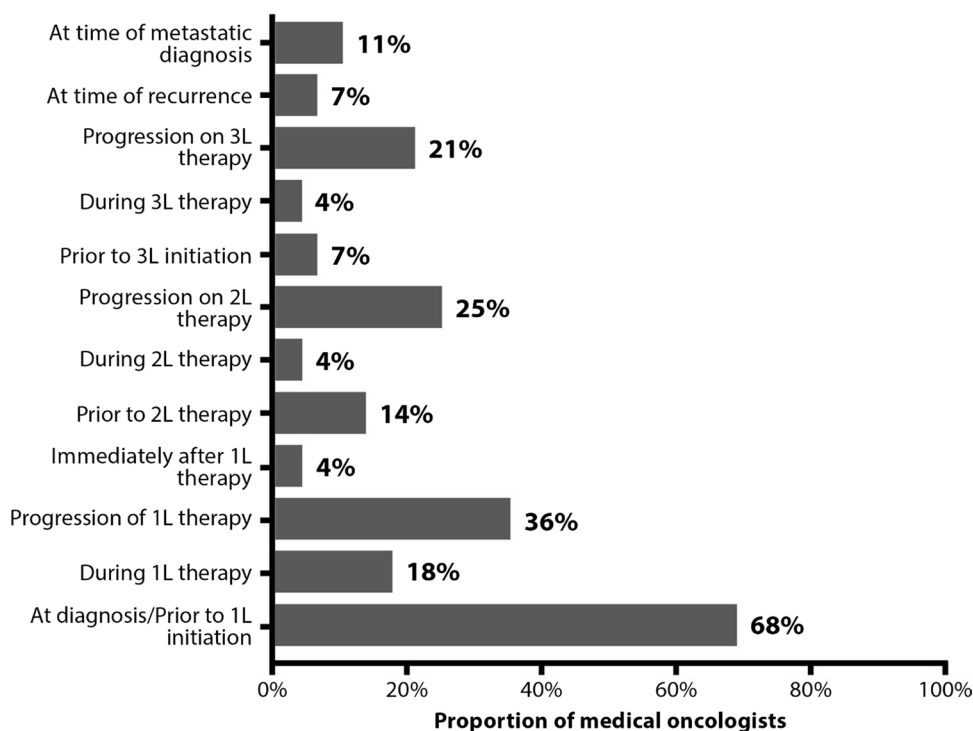
patient age, or none of these). \*Patient age, tumor type, ECOG-PS. ECOG-PS Eastern Cooperative Oncology Group Performance Status, *NTRK*+ neurotrophic tropomyosin-related kinase gene fusion-positive



**Fig. 2** Training and/or resources reviewed by medical oncologists for NTRK gene fusion testing recommendations (listed are published guidelines, peer-reviewed literature, continuing medical education, and institutional policies and updates). \*e.g., ESMO, ESMO Scale for

Clinical Actionability of Molecular Targets, National Comprehensive Cancer Network. ESMO European Society for Medical Oncology, NTRK+ neurotrophic tropomyosin-related kinase gene fusion

**Fig. 3** Timing of NTRK gene fusion testing (ranging from diagnosis to during later lines of therapy). Total percentage exceeds 100% as participating oncologists indicated timing of NTRK gene fusion testing across all NTRK+ patients. 1L first-line, 2L second-line, 3L third-line, NTRK+ neurotrophic tropomyosin-related kinase gene fusion-positive



### 3.4 Testing Patterns

Among these 73 patients, NGS was used to identify NTRK gene fusions in 83.6% (including NGS large or full panel, NGS short or limited panel, and IHC followed by confirmatory NGS), followed by FISH in 15.1%. Testing for NTRK gene fusions occurred most frequently prior to 1L therapy initiation (43% of patients) and prior to second-line (2L) therapy initiation in 20.5% of patients. Larotrectinib (56%) and entrectinib (25%) were reported as the most commonly used treatments following identification of a TRK fusion cancer (Table 2).

### 4 Discussion

The present analysis represents the first real-world study of NTRK gene fusion testing patterns among oncologists. Study results demonstrated that medical oncologists most frequently reported testing for NTRK gene fusions at diagnosis, prior to the initiation of 1L therapy initiation. The majority (89%) reported having begun NTRK gene fusion testing in the post-approval era for larotrectinib [8] and entrectinib [7]. Oncologists also reported high confidence in their ability to interpret NTRK testing reports. As broad molecular profiling continues to evolve, correct interpretation and appropriate

**Table 2** Patient-level characteristics

	Number of patients ( <i>N</i> = 73)*	
Age at diagnosis of advanced/metastatic solid cancer, years (median, IQR)	61	55–68
Sex assigned at birth (male <i>n</i> , %)	38	52.1%
Solid tumor type ( <i>n</i> , %)		
Lung	20	27.4%
Thyroid	13	17.8%
Salivary gland	10	13.7%
Colorectal	9	12.3%
Other soft tissue sarcomas	7	9.6%
Cholangiocarcinoma	6	8.2%
Breast	5	6.8%
Pancreatic	3	4.1%
Tests or panel types for determining patient's <i>NTRK</i> gene fusion status ( <i>n</i> , %)		
Next generation sequencing (NGS)	61	83.6%
Fluorescent in situ hybridization studies (FISH)	11	15.1%
Full panel or select panel	1	1.4%
Timing of <i>NTRK</i> tests/panels for determining patients' <i>NTRK</i> gene fusion status ( <i>n</i> , %) <sup>1</sup>		
Baseline (around diagnosis)/prior to 1L initiation	31	42.5%
During 1L therapy	6	8.2%
Immediately after 1L therapy	9	12.3%
Prior to initiation 2L+ therapy	15	20.5%
At time of recurrence	6	8.2%
At time of metastatic diagnosis	8	11.0%
After 2L therapy	2	2.7%
Treatment/therapy immediately following <i>NTRK</i> + gene fusion test ( <i>n</i> , %)		
Larotrectinib	41	56.2%
Entrectinib	18	24.7%
Pemetrexed	2	2.7%
Chemo-immunotherapy	2	2.7%
FOLFOX plus bevacizumab	2	2.8%
Alectinib	1	1.4%
Carboplatin/pemetrexed/pembrolizumab	1	1.4%
Cisplatin/gemcitabine	1	1.4%
FOLFOX	1	1.4%
Pembrolizumab	1	1.4%
Pembrolizumab plus chemotherapy	1	1.4%
Trabectedin	1	1.4%
Chemotherapy (not specified)	1	1.4%
Patient status at time of chart abstraction ( <i>n</i> , %)		
Alive, on current treatment	49	67.1%
Alive, but needs new treatment	2	2.7%
Alive, receiving palliative care only	1	1.4%
Deceased	21	28.8%

1L first-line, 2L second-line, IQR interquartile range, NGS next-generation sequencing; *NTRK*+ neurotrophic tropomyosin-related kinase gene fusion-positive, SD standard deviation

\*Physicians (*N* = 28) submitted patient-level data for up to 3 *NTRK*+ patients meeting study inclusion criteria

<sup>a</sup>Not mutually exclusive

utilization of results will be critical to facilitate timely choice of cancer therapy. While *NTRK* gene fusions do exist across multiple tumor types and some are actionable for therapy selection, perception of actionable targets for tumor types may not be associated with genomic testing. A recent retrospective study found co-occurrence of *NTRK* gene fusions and other actionable biomarkers to be uncommon [3]

Despite self-reported physician confidence in interpreting *NTRK* testing reports, less than half (46%) reported including TRKi therapy following *NTRK*+ determination. The approval of larotrectinib<sup>3</sup> was the second tumor-agnostic FDA approval, following pembrolizumab, and the first approved TRKi for solid tumors that have an *NTRK* gene fusion. Currently, mismatch repair (MMR) and microsatellite instability (MSI) are the only other tumor agonistic biomarkers used to predict treatment response. Tyrosine receptor kinase fusion cancers are rare but additional research should elucidate why, despite NCCN recommendations across multiple tumor types, less than half (46%) of oncologists surveyed did not use TRKi therapy after *NTRK*+ confirmation.

Limitations of this study include the potential for patient and provider selection bias. For example, providers may come from cancer treatment centers with access to molecular pathologists to assist with *NTRK* testing report interpretations. Moreover, it is possible that patient characteristics and clinical/treatment patterns may not be reflective of all patients within the TRK fusion cancer population. This study focused on adult patients, given the composition of the physician network (OPEN) used, despite the higher incidence of TRK fusion cancers occurring in children and adolescents. Treatment with TRKi therapy may differ in younger populations, where entrectinib is approved for those aged  $\geq 12$  years and larotrectinib is approved for all ages. Moreover, the finding that most oncologists reported little-to-no difficulty in interpreting *NTRK* gene fusion testing reports may be associated with studying oncologists treating biomarker-driven tumors and may not apply to all providers. However, we have endeavored to attenuate such limitations to external validity by collecting data from oncologists in representative community practice settings. Second, certain data elements recorded by physicians in patient records may be recorded differently than those reported in clinical trials, as timepoints and criteria for assessment in clinical practice may be less stringent. Last, the primary purpose of data recorded in patient medical records are intended to aid clinical management and not research.

A strength of this study is its significant size since *NTRK*+ solid tumors comprise only 1% of solid tumors. Additionally, the required follow-up period for patients with abstracted chart data was at least three months. Finally, the selection of the cohort from community practices supports

greater generalizability of the patient-level data on *NTRK* gene fusion testing and TRKi use in the real-world setting.

## 5 Conclusion

Among TRK fusion cancers, medical oncologists most frequently reported testing for *NTRK* gene fusions at diagnosis or prior to 1L therapy. Since less than one-third of oncologists report that ECOG performance status, tumor type, or patient age constitute factors that determine whether to test for *NTRK* gene fusions, further research is needed to identify physicians' rationale for *NTRK* gene fusion testing. Despite nearly 90% of oncologists reporting that they review clinical guidelines to inform *NTRK* gene fusion testing, future research should also elucidate why less than half (46%) of oncologists surveyed would not use TRKi therapy after obtaining *NTRK*+ tumor confirmation. An opportunity to highlight treatment recommendations among patients with TRK fusion cancer in the commonly reviewed clinical guidelines (e.g., NCCN, European Society for Medical Oncology [ESMO], ESMO Scale for Clinical Actionability of molecular Targets [ESCAT]) exists to ensure that patients receive the most appropriate and timely treatment.

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## Declarations

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**Conflicts of interest/competing interests:** A.J.K. and A.G.: employees and owns stock in Cardinal Health. T.K.: employee and owns stock in Bayer USA. A.K., R.A., T.A.G.: employees of Bayer USA at the time of study conduct.

**Ethics approval and consent to participate** This research study was conducted retrospectively from data obtained for clinical purposes. As described in Methods, prior to chart data abstraction, study materials (research protocol and eCRF) were submitted to an independent, central Institutional Review Board (Western Institutional Review Board [IRB]). The IRB determined that this study met the criteria for a waiver of authorization for use and disclosure of PHI and was exempt from IRB oversight. A waiver of informed consent was granted.

**Consent for publication** Not applicable.

**Availability of data and material** The datasets generated during and/or analyzed during the current study are not publicly available due to presence of protected health information (PHI).

**Code availability** Not applicable.

**Authors' contributions** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by all authors. The first draft of the manuscript was writ-

ten by A.J.K. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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