Research Article

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Personalized Medicine

Biomarker testing in patients diagnosed with advanced/metastatic medullary thyroid cancer in the United States

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Aim: To describe real-world testing patterns for *RET* in US patients with advanced/metastatic medullary thyroid cancer and determine consistency of real-world testing practices with national guidelines. **Materials & methods:** The authors performed a retrospective medical record analysis of patients with advanced/metastatic medullary thyroid cancer who initiated systemic therapy between 2013 and 2018. Seventy-five US-based oncologists collected the data using a customized electronic data collection form. **Results:** A total of 59.6% (121 of 203) of patients underwent testing for *RET*, and 37.2% (45 of 121) had a *RET* mutation, of which 55.6% were identified as *RET* mutation-positive before initial diagnosis. Overall, 90 (44.3%) patients were tested for biomarkers on or after initial diagnosis, with *RET* being the most tested (95.6%) biomarker. **Conclusion:** The authors' findings suggest an opportunity to improve testing rates in accordance with treatment guidelines.

Plain language summary: Mutations in the *RET* gene are common in patients with medullary thyroid cancer (MTC). As *RET* mutations are involved in the development of MTC, several treatment guidelines recommend counseling patients and testing for mutations in the *RET* gene in all patients with MTC. However, limited data are available on *RET* testing patterns in the US in this patient population. In this study, the authors determined testing patterns for *RET* in patients with advanced or metastatic MTC in the US using real-world data and found that only 60% of patients were tested for *RET* (i.e., testing for presence of *RET* mutations was observed in less than two-thirds of all patients included in the study). These results demonstrate the need for improved testing for *RET* mutations in patients with MTC in alignment with the treatment guidelines in routine clinical practice in the US.

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Keywords: advanced diagnosis • biomarker testing • genetic testing • initial diagnosis • medical record data • medullary thyroid cancer • *RET* • retrospective • sample type • time of test

Medullary thyroid cancer (MTC) is a rare cancer of the calcitonin-producing parafollicular cells (C cells) of the thyroid gland that accounts for approximately 1.6% of cases of thyroid cancer [1,2]. The American Cancer Society estimated approximately 44,280 new cases of thyroid cancer in the USA in 2021 [3]. MTC is generally diagnosed at early stages of the disease, when prognosis is favorable. Patients diagnosed with localized MTC have a 5-year survival rate of 100% [4]. However, for approximately 50% of patients diagnosed with metastatic disease at initial presentation [5], the 5-year survival rate is only 38% [4].

Approximately 25% of all patients diagnosed with MTC have a family history of the disease, primarily associated with multiple endocrine neoplasia (MEN) type 2A (MTC with pheochromocytoma, hyperparathyroidism and Cushing's syndrome) or MEN type 2B (MTC with pheochromocytoma and recognizable phenotype) [6]. Nearly all patients with MEN type 2 have germline *RET* mutations clustered in exon 10 (codons 609, 611, 618 and 620) and exon 11 (codon 634). Among patients with no family history of the disease (sporadic MTC), *RET* mutations occur in approximately 50–88% of cases [7–10]. *RET* mutations are categorized into risk levels depending

on the penetrance, aggressiveness and latency of the MTC, with M918T being the most common and highest-risk mutation [7,11,12]. With *RET* mutations observed in up to 88% of sporadic MTC cases [10] and approximately 100% of hereditary MTC cases [7] and the availability of selective *RET* inhibitor treatments (selpercatinib and pralsetinib) [13,14], it is important to test for *RET* mutations in all patients with MTC. Given the high rate of sporadic MTC, a negative germline *RET* result should be followed by testing of the tumor for actionable somatic *RET* alterations.

According to the National Comprehensive Cancer Network (NCCN) treatment guidelines for thyroid cancer [15], patients with an initial diagnosis of sporadic MTC following fine-needle aspiration and those who have undergone thyroidectomy should undergo screening for *RET* mutations. Additionally, among patients with a known family history of the disease, prospective germline genetic testing for mutations in *RET* is recommended to ensure screening for and early detection of MTC. The NCCN guidelines also recommend genetic counseling and specific mutation testing in family members [15]. Patients with MTC who are *RET* mutation-negative may also have somatic mutations in the *HRAS*, *KRAS*, *NRAS* and *BRAF* genes. The American Thyroid Association (ATA) guidelines are similar to the NCCN guidelines in terms of recommending genetic testing to detect a germline *RET* mutation in patients with sporadic *RET* mutation and testing family members. However, the ATA guidelines do not recommend testing for somatic *HRAS*, *KRAS*, *NRAS* and *BRAF* genes in patients with sporadic MTC except for academic reasons or physician preference [8,16]. *RAS* mutations are prevalent in 6–69% of patients with *RET* wild-type MTC and 2.5% of patients with *RET*-mutant sporadic MTC [17–19]. However, *RAS* mutations have shown no prognostic value for the aggressiveness of MTC [20]. Furthermore, a study in patients with sporadic MTC showed that these patients had mutations in the *MET* gene (3.0%) as well as the *TP53*, *TSHR*, *EIF1AX*, *CHK2* and *PPM1D* genes ($\leq$1.5%) [9].

Although testing for germline and somatic *RET* mutations is recommended by the NCCN and ATA treatment guidelines [8,15], there are limited data regarding testing rates in clinical practice. A previous study in the USA that involved 142 patients with MTC and intended to evaluate for consistency of testing with NCCN guidelines showed no evidence of recommended *RET* testing in 40% of cases [21]. Furthermore, the results suggested that 48% of MTC cases that were initially considered sporadic were in fact hereditary. The current study further explored the testing patterns for *RET* and other potentially actionable biomarkers in the USA using a contemporary cohort of patients diagnosed with advanced/metastatic MTC (a/mMTC), and the authors evaluated the consistency of testing patterns with national treatment guidelines.

Materials & methods

The study design used by the authors has been published elsewhere [22]. Briefly, in this retrospective study, the authors analyzed medical records of patients diagnosed with a/mMTC in the US who started systemic therapy between 1 January 2013, and 31 December 2018. Patients may initially have been diagnosed with a/mMTC or earlier-stage MTC that later progressed to a/mMTC. Patient data were recorded through death or last date of medical record entry (Figure 1). Data were collected using a customized electronic data collection form completed by US-based practicing oncologists. Eligible patients were chosen using a quasi-random selection of medical records [22].

The study protocol was reviewed by the institutional review board of RTI International. The study was not considered to be human subject research in accordance with Code of Federal Regulations Title 45 section 46 and was therefore deemed exempt from review.

Patients $\geq$12 years of age with histologically and/or cytologically confirmed MTC who initiated systemic treatment (single agent or combination) during the period noted earlier and had complete medical records for data abstraction were eligible for inclusion. Patients were excluded if they had other malignancies (except MEN type 2-associated pheochromocytoma that was either removed or stable, nonmelanoma skin cancer or *in situ* cervical cancer) or had been free of any other cancers $\geq$5 years before initiation of systemic treatment on the index date or had participated in a clinical trial involving an interventional drug as a first-line systemic treatment for a/mMTC [22].

The proportion of patients who underwent biomarker testing for *RET* and other biomarkers (*HRAS*, *BRAF*, *KRAS* and *NRAS*) was recorded. Details were recorded for each test, including timing of testing, tissue used and method of analysis (e.g., next-generation sequencing, real-time PCR, reverse transcription PCR, Sanger sequencing, fluorescence *in situ* hybridization and immunohistochemistry screening). No data were recorded specific to *RET* somatic versus *RET* germline assessment [22]. Therefore, in this study, *RET* mutation refers to *RET* germline and/or somatic mutations.

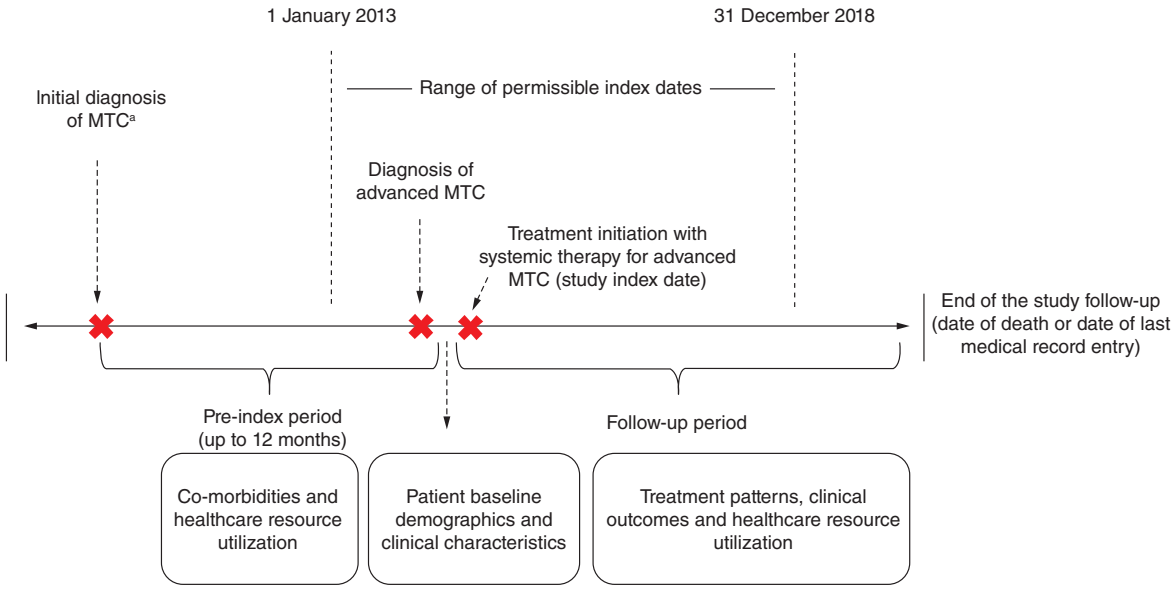

Figure 1. Study design.
[a]Only relevant for patients who were initially diagnosed with an earlier stage of the disease and subsequently experienced disease progression or recurrence with advanced disease between 1 January 2013 and 31 December 2018. Patient may be diagnosed with earlier stage MTC and/or advanced MTC before or during the pre-index period (up to 12 months).
MTC: Medullary thyroid cancer.

All analyses were descriptive in nature and were performed using SAS 9.4 (SAS Institute Inc., NC, USA) [22]. Data were summarized using descriptive statistics, including mean ± standard deviation, median (interquartile range) and number with percentage, as applicable. Results were qualitatively compared with NCCN Clinical Practice Guidelines for Thyroid Cancer (version 1.2021) [15].

Results

Physician & patient characteristics

Seventy-five physicians who treated patients with MTC provided data for 203 eligible patients [23]. Mean patient age (standard deviation) at a/mMTC diagnosis was 52.2 years (10.4), and 58.6% were female. Most (168 of 203; 82.8%) patients had stage IV MTC at initial diagnosis. Demographic and clinical characteristics of the study cohort are presented in Table 1. Findings related to treatment patterns and clinical outcomes have been presented previously [22].

RET mutation testing overall

Most (169 of 203; 83.3%) patients in this study did not have evidence of hereditary clinical syndromes. A total of 59.6% (121 of 203) of patients were tested for *RET* mutations, and the remaining 40.4% (82 of 203) were either not tested or their testing status was unknown. Of the patients tested for *RET* mutations, 37.2% (45 of 121) had a mutation, with M918T being the most common mutation identified (18 of 45; 40.0%) [22].

RET mutation testing before initial diagnosis of MTC

A total of 25.6% (52 of 203) of patients underwent biomarker testing for *RET* mutation prior to diagnosis of MTC, of whom 48.1% (25 of 52) were identified with a mutation. In these patients, M918T was the most common *RET* mutation (11 of 25; 44.0%), and 16.0% (four of 25) of patients had documented clinical syndromes (Table 2).

RET mutation & other biomarker testing on or after initial diagnosis of MTC

Of the 203 patients, 90 (44.3%) underwent biomarker testing on or after initial diagnosis of MTC, with *RET* testing performed in 86 (95.6%). Among patients who underwent testing for *RET* mutations on or after initial

Table 1. Baseline patient characteristics.

Characteristic	Overall (N = 203)	Stage I–III MTC (n = 30)	Stage IVA–C MTC (n = 168)	*RET*+ mutation (n = 45)
Age at advanced diagnosis, years				
Mean (SD)	52.2 (10.4)	48.4 (11.0)	53.0 (10.1)	46.6 (9.7)
Median (IQR)	53.0 (44.0–59.0)	49.5 (42.0–58.0)	54.0 (46.0–59.0)	46.0 (39.0–54.0)
Distribution by age group, years, n (%)				
<18	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
18–34	9 (4.4)	6 (20.0)	3 (1.8)	5 (11.1)
35–44	42 (20.7)	6 (20.0)	34 (20.2)	17 (37.8)
45–54	64 (31.5)	9 (30.0)	54 (32.1)	13 (28.9)
55–64	66 (32.5)	6 (20.0)	58 (34.5)	9 (20.0)
65–74	18 (8.9)	3 (10.0)	15 (8.9)	1 (2.2)
75–84	4 (2.0)	0 (0.0)	4 (2.4)	0 (0.0)
85+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sex, n (%)				
Female	119 (58.6)	19 (63.3)	96 (57.1)	26 (57.8)
Male	84 (41.4)	11 (36.7)	72 (42.9)	19 (42.2)
Race, n (%)				
White	134 (66.0)	23 (76.7)	109 (64.9)	24 (53.3)
Black/African–American	45 (22.2)	5 (16.7)	39 (23.2)	10 (22.2)
Asian, Native Hawaiian or other Pacific Islander	18 (8.9)	2 (6.7)	15 (8.9)	6 (13.3)
Other	1 (0.5)	0 (0.0)	0 (0.0)	1 (2.2)
Do not know	6 (3.0)	0 (0.0)	6 (3.6)	4 (8.9)
Ethnicity, n (%)				
Hispanic or Latina/Latino	25 (12.3)	4 (13.3)	21 (12.5)	5 (11.1)
Not Hispanic or Latina/Latino	163 (80.3)	25 (83.3)	135 (80.4)	33 (73.3)
Unknown or not reported	15 (7.4)	1 (3.3)	12 (7.1)	7 (15.6)
Primary insurance, n (%)				
Commercial insurance, through employer	112 (55.2)	19 (63.3)	89 (53.0)	28 (62.2)
Commercial insurance, through state expanded Medicaid program	19 (9.4)	1 (3.3)	18 (10.7)	5 (11.1)
Commercial insurance, other or additional details unavailable	7 (3.4)	2 (6.7)	5 (3.0)	0 (0.0)
Medicare	30 (14.8)	4 (13.3)	26 (15.5)	3 (6.7)
Medicaid	25 (12.3)	3 (10.0)	21 (12.5)	4 (8.9)
Enrolled in both Medicare and Medicaid	4 (2.0)	1 (3.3)	3 (1.8)	1 (2.2)
Do not know	6 (3.0)	0 (0.0)	6 (3.6)	4 (8.9)
Total follow-up duration, months				
Mean (SD)	24.5 (16.0)	24.4 (19.7)	24.6 (15.6)	28.8 (18.0)
Median (IQR)	21.1 (15.0–28.5)	19.0 (11.5–27.3)	21.3 (15.6–29.2)	25.5 (17.9–34.5)
Site(s) of local extension or metastasis at time of a/mMTC diagnosis, n (%)				
Distant lymph nodes	111 (54.7)	–	–	20 (44.4)
Bone	69 (34.0)	–	–	18 (40.0)
Brain	14 (6.9)	–	–	6 (13.3)
Liver	56 (27.6)	–	–	19 (42.2)
Local structures	58 (28.6)	–	–	12 (26.7)
Lung/pleura	81 (39.9)	–	–	15 (33.3)

[†]Karnofsky scores were converted to the ECOG scale.
CEA: Carcinoembryonic antigen; ECOG PS: Eastern Cooperative Oncology Group performance status; IQR: Interquartile range; MTC: Medullary thyroid cancer; SD: Standard deviation.

Table 1. Baseline patient characteristics (cont.).

Characteristic	Overall (N = 203)	Stage I–III MTC (n = 30)	Stage IVA–C MTC (n = 168)	*RET*+ mutation (n = 45)
Time from initial to advanced diagnosis in months among patients initially diagnosed with stage I–III disease				
Mean (SD)	26.3 (33.0)	–	–	37.5 (64.0)
Median (IQR)	14.1 (8.2–28.8)	–	–	12.6 (10.1–17.0)
Stage at advanced MTC diagnosis among patients initially diagnosed with stage I–III disease or stage unknown, n (%)				
Unresectable locally advanced MTC	11 (5.4)	–	–	1 (2.2)
Metastatic MTC	24 (11.8)	–	–	6 (13.3)
ECOG PS at advanced MTC diagnosis, n (%)[†]				
0	49 (28.3)	–	–	14 (33.3)
1	93 (53.8)	–	–	22 (52.4)
2	28 (16.3)	–	–	5 (11.9)
3	2 (1.2)	–	–	1 (2.4)
4	1 (0.6)	–	–	0 (0.0)
CEA test performed at baseline, n (%)	108 (53.2)	–	–	26 (57.8)

[†]Karnofsky scores were converted to the ECOG scale.
CEA: Carcinoembryonic antigen; ECOG PS: Eastern Cooperative Oncology Group performance status; IQR: Interquartile range; MTC: Medullary thyroid cancer; SD: Standard deviation.

Table 2. *RET* testing prior to initial diagnosis of medullary thyroid cancer.

Characteristic (N = 203)	Patients, n (%)
Tested before initial diagnosis, n (%)	
Yes	52 (25.6)
No	143 (70.4)
Unknown	8 (3.9)
Clinical syndromes in patients tested before initial diagnosis, n (%)	52 (25.6)
MEN2A	2 (3.8)
MEN2B	1 (1.9)
Familial MTC	3 (5.8)
No hereditary clinical syndrome	43 (82.7)
Unknown	3 (5.8)
***RET* mutation identification site in patients tested before initial diagnosis, n (%)**	25 (48.1)
M918T	11 (44.0)
C634R	6 (24.0)
C634G	0 (0.0)
Other	0 (0.0)
Unknown	8 (32.0)
No mutation	27 (51.9)
Clinical syndromes in *RET*-positive patients tested before initial diagnosis, n (%)	25 (48.1)
MEN2A	2 (8.0)
MEN2B	1 (4.0)
Familial MTC	1 (4.0)
No hereditary clinical syndrome	18 (72.0)
Unknown	3 (12.0)
Clinical syndromes in patients not tested before initial diagnosis, n (%)	143 (70.4)
MEN2A	6 (4.2)
MEN2B	4 (2.8)
Familial MTC	12 (8.4)
No hereditary clinical syndrome	120 (83.9)
Unknown	1 (0.7)

MEN2A: Multiple endocrine neoplasia type 2A; MEN2B: Multiple endocrine neoplasia type 2B; MTC: Medullary thyroid cancer.

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Table 3. Testing on or after initial diagnosis of medullary thyroid cancer.

Parameter	*RET*	*HRAS*	*BRAF*	*KRAS*	*NRAS*
Evaluated on or after initial diagnosis of MTC, n (%)	86 (95.6)	25 (27.8)	54 (60.0)	35 (38.9)	29 (32.2)
Evaluated before diagnosis of advanced MTC but after initial diagnosis, n (%)	5 (5.8)	4 (16.0)	4 (7.4)	2 (5.7)	3 (10.3)
Evaluated on or after diagnosis of advanced MTC, n (%)	54 (62.8)	9 (36.0)	35 (64.8)	18 (51.4)	12 (41.4)
Exact order/result date not reported, n (%)	27 (31.4)	12 (48.0)	15 (27.8)	15 (42.9)	14 (48.3)
Evaluation for gene requested, n (%)					
Request for specific gene	55 (64.0)	10 (40.0)	33 (61.1)	13 (37.1)	13 (44.8)
Not specifically requested	16 (18.6)	10 (40.0)	14 (25.9)	13 (37.1)	10 (34.5)
Do not know	15 (17.4)	5 (20.0)	7 (13.0)	9 (25.7)	6 (20.7)
Mutation status, n (%)					
Mutation identified	29 (33.7)	2 (8.0)	6 (11.1)	4 (11.4)	2 (6.9)
No mutation	45 (52.3)	22 (88.0)	45 (83.3)	25 (71.4)	24 (82.8)
Result inconclusive	2 (2.3)	0 (0.0)	0 (0.0)	1 (2.9)	1 (3.4)
Result unavailable	10 (11.6)	1 (4.0)	3 (5.6)	5 (14.3)	2 (6.9)
Time from initial diagnosis of MTC to order/result date of evaluation, months	n = 86	n = 25	n = 54	n = 35	n = 29
Mean (SD)	0.5 (0.6)	7.1 (13.1)	6.6 (12.3)	0.7 (0.9)	0.5 (0.8)
Median (IQR)	0.6 (0.1–0.7)	0.7 (0.0–14.1)	0.7 (0.0–13.2)	0.7 (0.1–1.4)	0.1 (0.0–1.4)
Time from diagnosis of advanced MTC to order/result date of evaluation, months					
Mean (SD)	1.9 (7.7)	0.6 (0.7)	2.1 (9.3)	0.5 (0.7)	0.5 (0.6)
Median (IQR)	0.5 (0.4–0.6)	0.4 (0.2–0.5)	0.5 (0.3–0.5)	0.3 (0.2–0.5)	0.3 (0.2–0.5)

IQR: Interquartile range; MTC: Medullary thyroid cancer; SD: Standard deviation.

diagnosis, 29 (33.7%) were identified with mutations, with M918T being the most frequently occurring (12 of 29; 41.4%).

BRAF was evaluated in 54 (60.0%), *KRAS* in 35 (38.9%), *NRAS* in 29 (32.2%) and *HRAS* in 25 (27.8%) patients undergoing biomarker testing. Table 3 presents the mutation status and other testing details for biomarker testing on or after initial diagnosis of MTC. Figure 2 shows that testing for *RET* only on or after initial diagnosis of MTC occurred in 35.6% (32 of 90) of patients and that it was also tested in various combination with other biomarkers among other patients.

Type of sample tested after initial diagnosis

Solid tissue samples were more commonly tested than blood samples for all biomarker tests recorded after initial diagnosis. New MTC tumor tissue was the most commonly used sample for biomarker testing for *RET* (46 of 82; 56.1%), *HRAS* (16 of 25; 64.0%), *BRAF* (23 of 54; 42.6%), *KRAS* (23 of 35; 65.7%) and *NRAS* (19 of 29; 65.5%). Archival tumor tissue use was the highest for *BRAF* (23 of 54; 42.6%) followed by *RET* (23 of 82; 28.0%). Liquid biopsy sample was used for testing for *RET* in 14.6% patients while its use ranged from 13.0 to 24.1% for other biomarkers (Figure 3).

Tests (or testing laboratories) & test types used for biomarker testing after initial diagnosis

The most frequently used test for biomarker testing was FoundationOne CDx, which was utilized for tests conducted in >60% of patients who underwent biomarker testing after initial diagnosis (Figure 4). Consistent with the tests used, next-generation sequencing was the most frequently used method (or type of test) for biomarker testing in this patient cohort (Figure 5). Types of test performed alone or in combination among patients who underwent biomarker testing after initial diagnosis of MTC are presented in Supplementary Figure 1. A total of 44.3% (90 of 203) of patients received testing for at least one biomarker, and a total of 229 tests were conducted to detect potential mutations after initial diagnosis of MTC. With regard to the 229 tests, the most commonly used method was next-generation sequencing (115 of 229; 50.2%) followed by PCR (32 of 229; 14.0%), reverse transcription PCR (five of 229; 2.2%), Sanger sequencing (three of 229; 1.3%), FISH (two of 229; 0.9%) and immunohistochemistry screening (one of 229; 0.4%). The test method was unknown for 31.0% (71 of 229) of tests conducted.

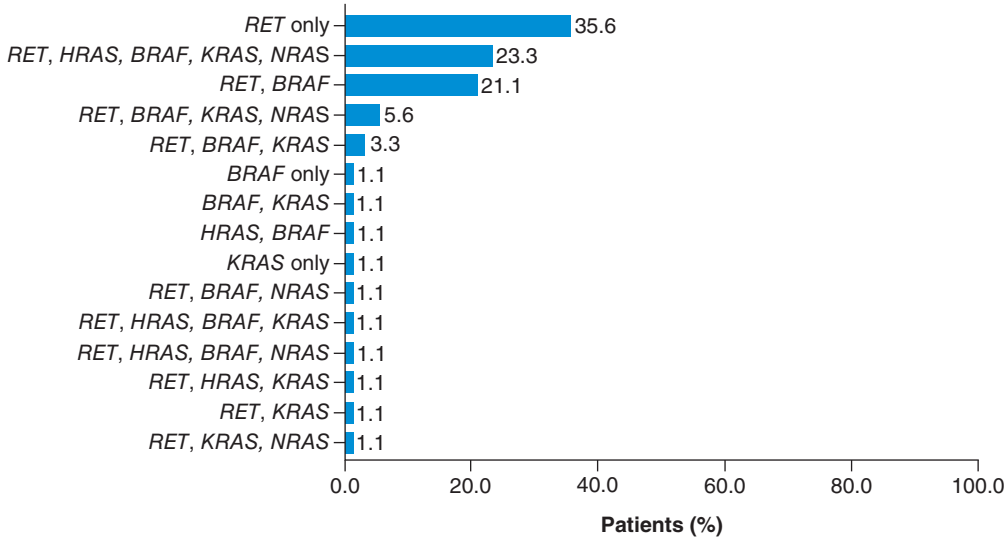

Figure 2. Unique combinations of biomarker mutations tested on or after initial diagnosis of medullary thyroid cancer (n = 90).
All data are presented as %.
BRAF: v-raf murine sarcoma viral oncogene homolog B1; HRAS: Harvey rat sarcoma; KRAS: Kirsten rat sarcoma; MTC: Medullary thyroid cancer; n: Patients in the group; NRAS: Neuroblastoma rat sarcoma; RET: REarranged during transfection.

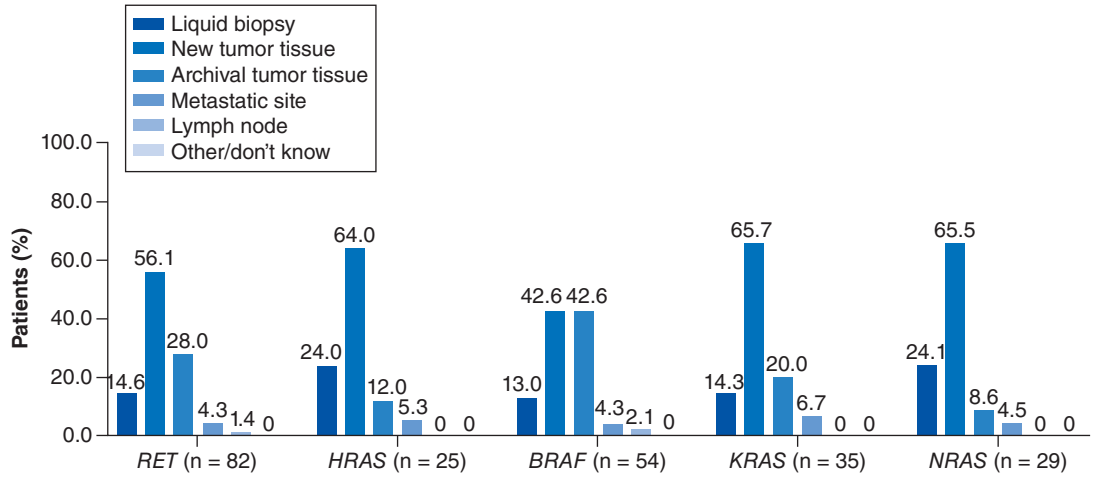

Figure 3. Types of samples tested for *RET* and other mutations after initial diagnosis of medullary thyroid cancer.
All data are presented as %.
BRAF: v-raf murine sarcoma viral oncogene homolog B1; HRAS: Harvey rat sarcoma; KRAS: Kirsten rat sarcoma; MTC: Medullary thyroid cancer; n: Patients in the group; NRAS: Neuroblastoma rat sarcoma; RET: REarranged during transfection.

Discussion

The clinical utility of *RET* mutation testing has been established in patients with MTC given the association with hereditary syndromes, and US FDA approval of targeted *RET* inhibitors (selpercatinib and pralsetinib) has added to the clinical rationale for testing for *RET* mutations in patients with MTC [13,14,24,25]. The current study evaluated the characteristics and patterns of biomarker testing among patients with a/mMTC in a real-world setting. Of the patients included in this study, 59.6% (121 of 203) were tested for a *RET* mutation, and 37.2% (45 of 121) of those tested had *RET* mutation-positive disease. Most patients were tested after initial diagnosis. Of the 28 patients with clinical syndromes of MEN type 2A, MEN type 2B or familial MTC, 12 (42.86%) tested positive for a *RET* mutation at any point in time (i.e., either before or after initial diagnosis). These patients were likely to have a

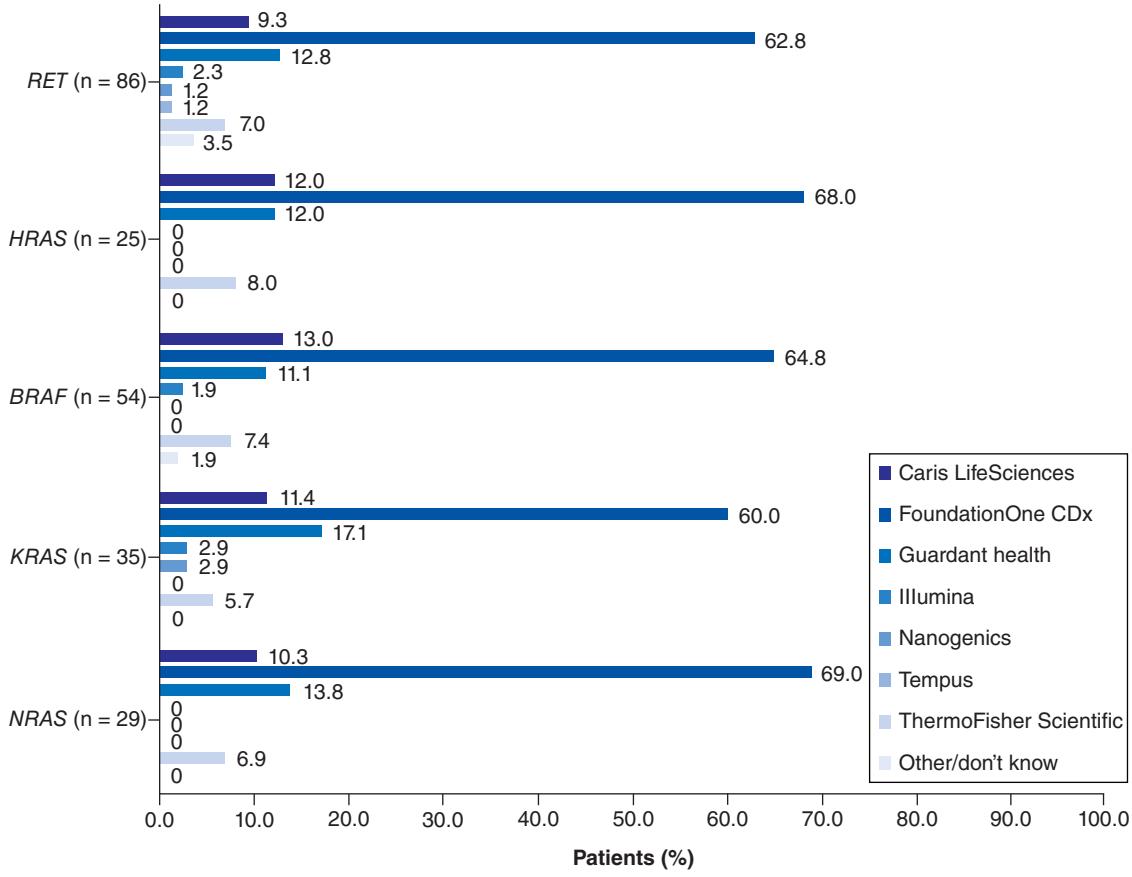

Figure 4. Tests used after initial diagnosis of medullary thyroid cancer.
All data are presented as %.
BRAF: v-raf murine sarcoma viral oncogene homolog B1; HRAS: Harvey rat sarcoma; KRAS: Kirsten rat sarcoma; MTC: Medullary thyroid cancer; n: Patients in the group; NRAS: Neuroblastoma rat sarcoma; RET: REarranged during transfection.

germline *RET* mutation, as they were diagnosed with hereditary clinical syndromes, as reported previously [26,27]. Although this study did not differentiate between germline and somatic testing for *RET*, hereditary factors are important considerations for the early diagnosis and clinical care of patients with MTC [24]. In clinical practice, germline testing is useful for classifying patients with MTC into sporadic or hereditary cases, establishing familial risk of MTC and initiating early screening protocols for those at risk [28,29], whereas somatic *RET* testing allows for prognosis and decision-making with regard to treatment in patients with MTC [29,30].

There have been limited real-world studies in the US evaluating biomarker testing in patients diagnosed with MTC. Parkhurst *et al.* conducted a study at Kaiser Permanente Southern California using an integrated medical record system to determine whether patients with MTC were offered *RET* testing in accordance with NCCN guidelines for thyroid cancer [21]. The researchers observed that 40.0% of patients had not received germline or somatic *RET* testing, and the majority of patients who were considered to have sporadic MTC actually had hereditary MTC. In the current study, a similar proportion (40.4%) of patients were not tested. Thus, both studies demonstrate the underutilization of biomarker testing for *RET* mutations in patients with a/mMTC in the USA.

There are also few studies outside the US that have evaluated the testing rates for *RET* mutations in patients with MTC. Mathiesen *et al.* showed that 13.0% of patients were not receiving biomarker germline or somatic testing [31] in accordance with European Society for Medical Oncology guidelines [32]. An Adelphi Disease Specific Program™ for thyroid cancer also showed that *RET* testing was not performed in 25.0% of patients with MTC in Europe [33].

The approval of selpercatinib and pralsetinib, based on results of the LIBRETTO-001 and ARROW trials [13,14,34], showed that *RET* testing is important before initiating treatment in patients with *RET*-mutant

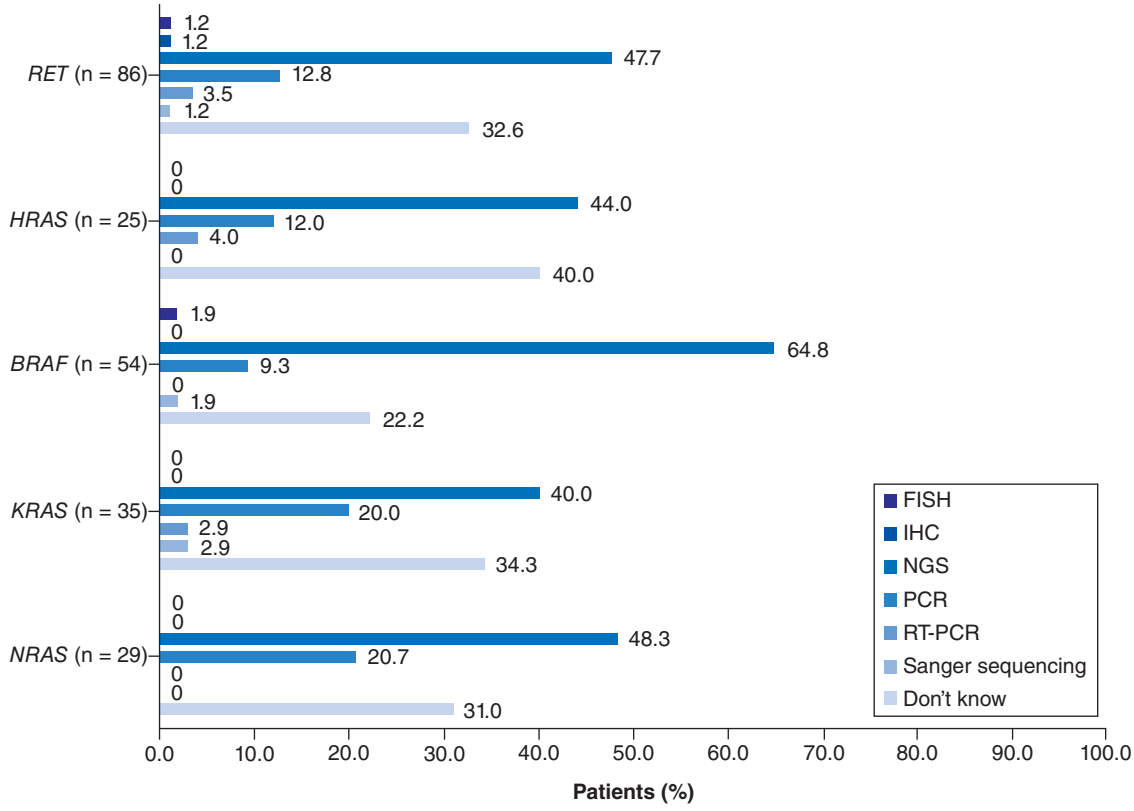

Figure 5. Type of test conducted after initial diagnosis of medullary thyroid cancer.
All data are presented as %.
BRAF: v-raf murine sarcoma viral oncogene homolog B1; HRAS: Harvey rat sarcoma; KRAS: Kirsten rat sarcoma; MTC: Medullary thyroid cancer; n: Patients in the group; NRAS: Neuroblastoma rat sarcoma; RET: REarranged during transfection.

a/mMTC. The phase I/II LIBRETTO-001 trial for selpercatinib showed an overall response rate of 69.0% in patients with *RET*-mutant MTC previously treated with cabozantinib or vandetanib, with the response lasting ≥6 months in 76.0% of patients [13,34]. The phase I/II ARROW trial for pralsetinib also showed an overall response rate of 60.0% in patients with *RET*-mutant-positive MTC who had been previously treated with vandetanib or cabozantinib, with 79.0% of patients showing a response ≥6 months [14]. Data from these trials showed an overall response rate of 73.0 and 66.0% for selpercatinib and pralsetinib, respectively, in patients with a/mMTC carrying a *RET* mutation who were naive to systemic treatment [13,14,34]. Despite differences in the clinical implications of germline versus somatic *RET* mutations in patients with MTC, the FDA-approved indication for the use of selpercatinib and pralsetinib (both currently available selective *RET* kinase inhibitors) in patients with a/mMTC does not distinguish between germline and somatic mutations (referring only to '*RET*-mutant MTC'). As *RET* is the sole recognized genomic biomarker for MTC [25], testing of *RET* mutations in hereditary and sporadic MTC is needed to determine the appropriate use of these targeted therapies [24].

The findings of the current study highlight the need to improve the utilization of *RET* mutation testing in current real-world practice in the USA. Not all patients in this study received biomarker testing and the study is limited by the lack of data about reasons for not conducting biomarker testing. Exploring these factors in the USA in future studies could help develop solutions to better implement the recommendations for testing by the ATA [8] and NCCN guidelines (version 1.2021) [15]. The Adelphi study in Europe evaluated reasons for not testing for *RET* mutations in patients with MTC [33]. The primary reason for not testing was the delay in getting results (26%). In Germany, cost (25.0%) was the other major factor for not testing for genomic biomarkers, whereas in the UK, guideline restrictions (27.0%) were the other major factor.

In addition to the rate of *RET* testing in the overall sample, the current study also presented the rate of *RET* testing at different times with respect to diagnosis of MTC; namely, before initial diagnosis (52 of 203; 25.6%) and

on or after initial diagnosis (86 of 203; 42.4%). It is important to note that the results may not be generalizable to a broader population of patients with MTC in the USA as a result of the small and nonrandom selection of providers and patients for this study. Although the generalizability is limited given the convenience sample of physicians who participated in the study and provided patient data, the authors' physician sample represented multiple medical specialties (i.e., physicians with a varied case load and physicians with a broad range of experience treating patients as well as various practice settings and geographic regions). Each physician provided data for a median of only two patients, thereby increasing the representativeness of the sample. Furthermore, the retrospective nature of data collection could not avoid missing or unknown data, and the results of this study, although consistent with prior research, do not provide definitive evidence of underutilization of genomic biomarker testing in patients with MTC across the USA. Data specific to germline versus somatic testing were not collected, which limits the interpretation of study findings. For the before diagnosis time period, data were also not collected on the sample used for *RET* testing, limiting the ability to infer whether the test was intended to evaluate a germline mutation. Therefore, although the intention of *RET* identification for clinical care is unknown in the current study, the implications for *RET* inhibitor treatment in patients with a/mMTC are the same for those with a somatic or germline mutation [13,14]. Future research should further investigate the use of biomarker testing following approval of *RET* inhibitors. The rates of biomarker testing may have been impacted following the availability of these targeted agents for patients with MTC.

Conclusion

The overall testing rate of 59.6% for *RET* mutations in patients with a/mMTC observed in this study was lower than that recommended in the guidelines. Although the current study provides contemporary evidence regarding the rates of biomarker testing in patients with a/mMTC, future studies with a larger sample size are needed to better understand the compliance of biomarker testing with guidelines. In addition, physicians' reasons for not recommending biomarker testing and patients' reasons for not undergoing biomarker testing may be explored in future studies.

Summary points

- Mutations in the *RET* gene are common in patients with medullary thyroid cancer (MTC).
- National guidelines for thyroid cancer treatment recommend patient counseling and testing for the *RET* gene in all patients with MTC.
- Overall, 60% of patients included in this real-world study were tested for *RET*.
- The rate of testing for *RET* before initial diagnosis of MTC was 25.6% (52 of 203).
- Among patients who underwent biomarker testing on or after initial diagnosis of MTC, *RET* was the most tested biomarker (86 of 90; 95.6%).
- Study findings suggest an opportunity to improve testing rates in accordance with treatment guidelines.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/pme-2022-0050

Author contributions

All authors (a) made a significant contribution to the work reported including conception, study design, execution, acquisition of data, analysis, and interpretation; (b) took part in drafting, revising, or critically reviewing the article; (c) gave final approval of the version to be published; and (d) agree to be accountable for the content of the article.

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Ethical conduct of research

The study protocol was reviewed by the institutional review board of RTI International. The study was not considered to be human subject research in accordance with Code of Federal Regulations Title 45 section 46 and was therefore deemed exempt from review.

Data sharing statement

The datasets generated and/or analyzed during the current study are not publicly available because of individual data privacy but may be available from the corresponding author on request.

Previous presentation

Minor portions of data were previously presented at the American Head and Neck Society 10th International Conference on Head and Neck Cancer. Available at https://eventpilotadmin.com/web/page.php?page=IntHtml&project=AHNS21&id=113010.

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