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REVIEW

# Consensus Statement: Recommendations on Actionable Biomarker Testing for Thyroid Cancer Management

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## Abstract

Thyroid cancer management is rapidly changing. The identification of actionable biomarkers through both germline and somatic testing are now an integral part of directing patient management. However, deficiencies and disparities within existing thyroid cancer biomarker test approaches are resulting in inconsistent application for patient care. An expert panel was convened to create consensus biomarker testing algorithms and recommendations on actionable biomarker testing for patients diagnosed with medullary thyroid cancer, non-anaplastic follicular cell-derived thyroid cancer, or anaplastic follicular cell-derived thyroid cancer who may benefit from targeted therapies. A review of international guidelines was performed to determine the current state, and a literature review was carried out to further evaluate the evidence supporting the use of actionable biomarkers in patients diagnosed with thyroid cancer. Thyroid biomarker-related gaps impacting patient care were also discussed, with an emphasis on the importance of a multidisciplinary team approach for optimal patient care. The recommendations are presented with the aim to help physicians navigate the current thyroid cancer biomarker testing landscape with its many challenges, balancing aspirational care with what is practical and feasible in terms of economic realities and jurisdictional constraints. By remaining therapy-agnostic, these algorithms and recommendations are broadly applicable.

**Keywords** Predictive · Molecular testing · Thyroid cancer · Algorithms · Cancer management · NGS · Next-generation sequencing · IHC · Immunohistochemistry · Familial thyroid carcinoma · Medullary thyroid carcinoma · Targeted therapy · *RAS* · *RET* · *NTRK* · *BRAF* · *ALK* · PD-L1 · Mismatch repair · Tumor mutational burden · Microsatellite instability · Genetic testing · Biomarkers

## Background

Thyroid cancer management is rapidly changing. Thyroid cancer classification was updated in 2022 to reflect cellular origin, histology, and molecular characteristics as well as clinical course of these tumors [1]. Follicular cell-derived thyroid cancer is a heterogenous group of neoplasms ranging broadly from follicular cell-derived differentiated thyroid carcinomas (including follicular thyroid carcinoma, invasive encapsulated follicular variant papillary thyroid carcinoma, papillary thyroid carcinoma, and oncocytic thyroid carcinoma) to high-grade non-anaplastic follicular cell-derived thyroid carcinomas (including poorly differentiated thyroid carcinoma and high-grade differentiated thyroid carcinoma) and the very aggressive and rapidly progressing anaplastic thyroid carcinomas (ATC) [1, 2]. Unlike follicular cell-derived thyroid carcinomas, medullary thyroid carcinoma (MTC) is a malignant neoplasm that originates from neuroendocrine C cells of the thyroid [1, 3]. An eventual name change from MTC to C-cell neuroendocrine neoplasm would more accurately reflect both the cell origin and recently proposed grading schemes [4–6].

Thyroid cancer incidence/prevalence is relatively low, as is the overall thyroid cancer mortality. In Canada, an estimated 6600 cases of thyroid cancer will be diagnosed in 2024, with 280 expected deaths [7], and a 97% 5-year survival [8]. Most thyroid cancers are sporadic with a small fraction of patients

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manifesting with syndromic or non-syndromic germline disease [9]. Non-anaplastic follicular cell-derived thyroid cancer makes up the majority of cases, and is the most common form of endocrine malignancy [1, 2]. These tumors have the most positive outcomes, and the initial treatment of surgery with or without radioiodine therapy is often curative [10]. MTC makes up approximately 2–4% of diagnosed cases [10, 11], and 8% of total thyroid cancer mortality [12]. ATC only comprises 1% of thyroid cancer cases diagnosed [10], but is one of the most aggressive cancers, accounting for approximately 20% of total thyroid cancer-related mortality [12], with a median survival of under 4 months [13]. However, changes in patient management, such as targeted therapies and multidisciplinary care, are associated with survival improvements [14].

Although thyroid cancer incidence rates rapidly increased in Canada between 1984 and 2013 [8], incidence rates have decreased by 4.7% annually since that time. This trend is consistent with recent international data showing that after several decades of increasing thyroid cancer incidence [15], disease burden may be starting to decline, based on the plateauing of age-standardized incidence rates and a reduction in thyroid cancer mortality and disability-adjusted life years reported from 1990 to 2019 [16]. One explanation for this perceived decline may be due to the reclassification of non-invasive follicular variant papillary thyroid carcinomas as NIFTP (non-invasive follicular thyroid neoplasm with papillary–like nuclear features) as per the 2017 WHO classification of thyroid neoplasms. NIFTP is not a benign follicular neoplasm, but a low-risk follicular cell-derived thyroid neoplasm with a negligible (very low) risk of recurrence; however, it is not being captured by cancer registries as a carcinoma.

New thyroid cancer insights are emerging with the advancing knowledge of the specific genes implicated in thyroid cancer pathogenesis and progression including *RET*, *BRAF*, *RAS*, *ALK*, *NTRK*, and *MTOR* [17–20]. Previously, the molecular landscape was used to characterize thyroid histology and morphology [21–27]. Now, the identification of actionable biomarkers—which drive or define malignancy and are targeted by drugs that are approved or on trial—is being used to direct patient management [18, 20, 27, 28].

With the knowledge of variants in a subset of heritable genes causing thyroid cancer also comes the need for germline testing. Constitutional (germline) testing for *RET* variants is necessary to identify individuals who carry genetic alterations that can be passed down to family members [6, 28–30]. MTC can indicate familial cancer syndromes such as multiple endocrine neoplasia (MEN) type 2A (MEN2A) and type 2B (MEN2B) [6, 17, 28, 31]. These familial MTC syndromes have well-characterized, pathogenic constitutional *RET* variants which have strong genotype–phenotype associations influencing the age of disease onset, tumor aggressiveness, and management [19, 28, 29]. In rare cases, variants in other genes can also cause these syndromes [6]. Additionally, approximately 3–9% of thyroid cancers of follicular cell origin are familial non-medullary thyroid carcinomas (FNMTCs), which can confer increased risks of disease to family members [30, 32].

Abundant evidence supports both *RET* and *BRAF* as actionable biomarkers in thyroid cancer. *RET* biomarker testing and the use of *RET*-targeted agents are the standard of care in patients with MTC. *RET* point mutations are common in sporadic MTCs with germline variants characterizing heritable forms of the disease [1, 6]. In contrast, *RET* rearrangements (fusions) are most common in follicular cell-derived thyroid cancer [19, 29]. *BRAF* is a key biomarker in many thyroid cancer subtypes [18, 33, 34]. *NTRK* gene fusions have been identified in ATC, in high-grade non-anaplastic follicular cell-derived thyroid cancer, and in differentiated thyroid cancers, with relevance to NTRK-targeted therapeutics [18, 35, 36]. Evidence is accumulating for *ALK* fusions in a very small fraction of thyroid cancers [18, 37–39]. In addition, evidence is emerging for the actionable biomarker measurement of PD-L1 expression levels, microsatellite instability (MSI), and DNA mismatch repair (MMR) in thyroid cancer, and tumor mutation burden (TMB), defined as the total number of somatic mutations per coding area of a tumor genome [40], particularly in ATC [40–45].

Despite these promising advances, deficiencies and disparities within the current thyroid cancer molecular testing landscape continue to result in inconsistent application to patient care. Recent publications have highlighted challenges in the treatment of thyroid cancer in Europe [15] and have called attention to the need for improved guidance, particularly for molecular testing [15, 46]. Challenges include the lack of concordance between national and international (European Society for Medical Oncology [ESMO]) guidelines, inconsistent and inadequate reimbursement for testing in different jurisdictions, testing methodologies of varying sensitivities, and inconsistent infrastructure [15, 46]. A recent study reviewed European recommendations, especially with respect to predictive molecular testing for advanced/metastatic thyroid cancer management, highlighted the disparities between theory and practice, focusing on challenges related to variable access to infrastructure, therapies, and expertise [46]. This review highlighted the need to develop standardized, accessible molecular genotyping approaches but concluded that "a clear algorithm for molecular testing in thyroid cancer cannot be adopted," citing the current shortage of evidence, practical barriers, and lack of clear testing guidelines [46]. The authors noted that some existing European guidelines focus on therapeutics rather than on molecular testing, which is challenging as different agents are approved in different jurisdictions [46].

Notable similarities exist between Europe and Canada related to thyroid cancer biomarker testing challenges. In both jurisdictions, the use of biomarker testing for

the management of diagnosed thyroid cancer patients is highly variable, with region-specific issues including access to testing and treatment reimbursement. Molecular testing access and availability is constrained by both knowledge and resources. In addition, many gaps and inconsistencies exist in the Canadian context with respect to molecular testing in thyroid cancer, as approaches are provincial in nature and not consistent with each other.

The patient most likely to be impacted by these shortcomings is the high-risk thyroid cancer patient. The high-risk patient is defined as one who is radioactive iodine-resistant and has reached an actionable phase in their treatment trajectory where systematic therapy is being considered [47]. To address these issues and fill the biomarker testing gaps in a rapidly changing thyroid cancer landscape, an expert panel created consensus biomarker testing algorithms on actionable biomarker selection to guide clinical management of the patient diagnosed with thyroid cancer. These include recommendations to guide germline (constitutional) and tumor (somatic) testing of patients diagnosed with MTC, germline and tumor testing in patients diagnosed with non-anaplastic follicular cell-derived thyroid cancer, and tumor testing in patients diagnosed with anaplastic follicular cell-derived thyroid cancer (ATC). Recommended methods for the detection of actionable biomarkers are also discussed.

## Methods

### Steering Committee and Expert Panel Composition

A phased approach was taken to developing consensus molecular testing algorithms and recommendations on actionable biomarker testing to guide clinical management of the diagnosed thyroid cancer patient. Selection of both the Steering Committee and Expert Panel was based on recognized expertise of the participants, inclusion of key specialties involved in patient care, and geographic representation to provide pan-Canadian perspectives. The Steering Committee included endocrinologists, an endocrine pathologist, a medical geneticist, and endocrine and medical oncologists. The Expert Panel was comprised of endocrinologists ($n = 2$), an endocrine pathologist, an endocrine oncologist, medical oncologists ($n = 5$), a medical geneticist, radiation oncologists ($n = 2$), a nuclear medicine specialist, and a hematologist-oncologist.

### Literature Search Methodology

To identify evidence to support the development of consensus testing algorithms and recommendations, current international, published guidelines published in English in Europe and North America in the last 10 years were identified as a starting point.

To extend the evidence base beyond current published guidelines, beginning with the understanding that *RET* and *BRAF* testing are well established in thyroid cancer and therefore do not require a comprehensive literature search to support their inclusion in testing algorithms, a targeted literature search was performed to obtain additional evidence for actionable biomarkers that are not as well established. The following keyword search strategy was used: "thyroid cancer" or "thyroid carcinoma" and "MMR," "mismatch repair" or "PD-L1" or "TMB" or "tumor mutational burden" or "tumour mutational burden" or "MSI" or "microsatellite instability" or "NTRK" or "ALK". Because the algorithms aimed to cover actionable biomarker testing for patients diagnosed with thyroid cancer rather than molecular testing to confirm diagnosis or to assess indeterminate fine needle aspirate samples, the Boolean operator "not" was used to exclude the keywords "indeterminate fine needle aspirate" or indeterminate FNA" or "indeterminate thyroid nodule" from the search results. The search results were filtered to include only those from the past 10 years.

A total of 461 publications were imported for screening. Title, abstract, and full-text screening were performed by a single reviewer using the following inclusion criteria: randomized controlled trials, systematic reviews, cohort studies, case–control studies, or cross-sectional studies, and longitudinal studies in human subjects published in English. Pilot studies, case studies, case series, published guidelines, reviews, editorials, letters, and other non-research sources were supplemented. After screening titles and abstracts, then full-texts, 18 articles were selected for data extraction (Supplement 1). Citation searching was also performed to ensure that all relevant articles were captured.

### Algorithm Development and Consensus Process

The Steering Committee met twice virtually to identify unmet needs of the thyroid cancer medical and patient communities, to define the project objectives and approach, and to identify experts from other medical specialties to form the Expert Panel. Molecular testing algorithms and recommendations were developed based on the review of existing published guidelines, published evidence, and on the clinical experiences of the Steering Committee members, which were then refined through discussion and synthesis by expert consensus.

Two virtual meetings were convened with the Expert Panel to review and refine biomarker testing algorithms and accompanying recommendations. The Expert Panel distinguished between three levels of actionability with respect to the algorithms. In areas where a high level of evidence supporting biomarker testing existed, and where biomarker testing is standard of care

internationally, biomarker testing was designated as a "must" be done to meet the minimum current standard of care in Canada. Where consistent evidence existed of a net benefit in patient outcomes, and where most patients would choose to have the testing if given the option, biomarker testing was designated as "recommended" in the algorithms and recommendations. Where evidence supporting biomarker testing was of a lower quality or was inconsistent with respect to supporting a net benefit to patient outcomes, biomarker testing was designated as to be "considered" in the algorithms and recommendations.

After revising the algorithms and recommendations according to the expert panel's feedback, the full panel then voted via an electronic survey to indicate whether they agreed or disagreed with key aspects of the algorithms and recommendations. Elements of the algorithms and recommendations were accepted if 80% of the expert panel voted in favor. Points of disagreement along with the rationale for disagreement were noted, and additional discussions took place via email and online meetings to reach a consensus. All expert panel members who participated in evaluating current published guidelines and algorithm development are included as authors of this manuscript.

Algorithms and recommendations do not address molecular testing to aid in the initial diagnosis of thyroid cancer, nor do they address patients with indeterminate results from FNA of thyroid nodules, as these topics are covered very comprehensively in existing published guidelines [28, 48].

The algorithms were developed, and the manuscript was written without the use of large language models (LLMs).

## Results

The Expert Panel had a high level of consensus throughout the process and in the final algorithms. Areas of discussion highlight the aspects of thyroid cancer molecular testing and care which need to be addressed and improved.

### Actionable Biomarker Testing to Aid in the Management of Patients Diagnosed with Medullary Thyroid Cancer (MTC)

A stepwise approach to germline and tumor/somatic testing specifically for *RET* variants needs to be conducted for those diagnosed with MTC (Fig. 1).

#### Recommendation 1: Constitutional (germline) Testing for *RET* Variants Is Required for All Patients at the Initial Diagnosis of MTC

Constitutional (germline) testing for *RET* variants is necessary to identify patients with MTC who have a familial cancer syndrome [6, 28, 29]. Although most patients with *RET* germline variants have a pre-existing familial cancer history, a small number (up to 10%) of patients presenting with sporadic MTC have de novo germline variants, which can subsequently be passed down to family members [17,

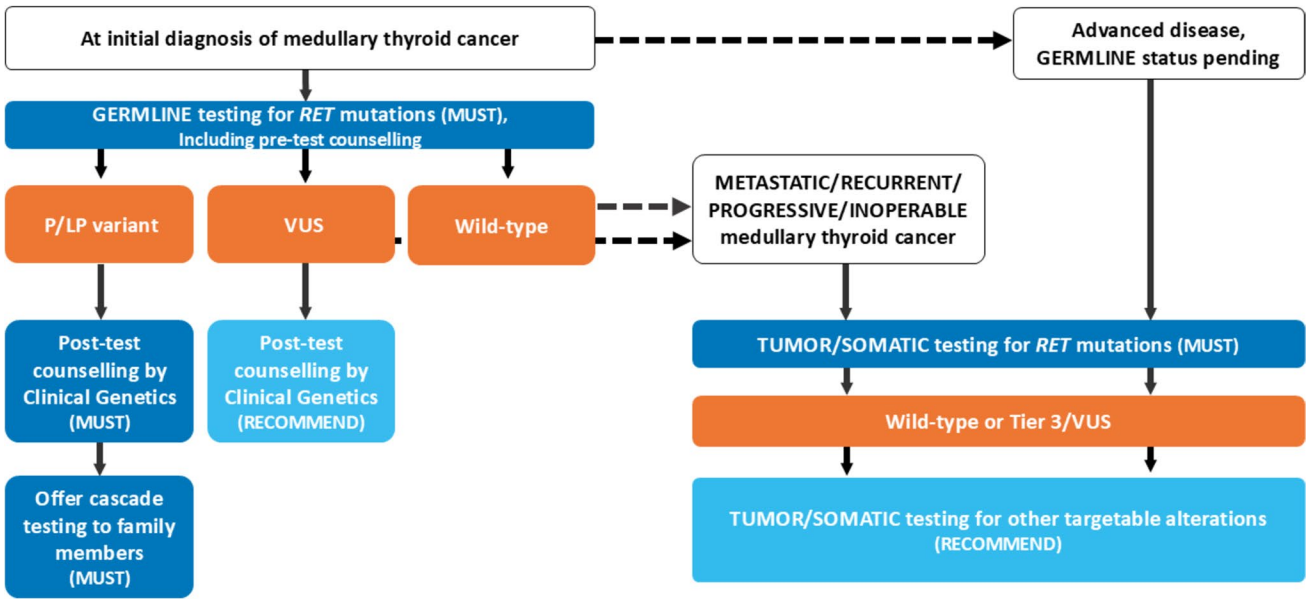


**Fig. 1** Actionable biomarker testing to aid in the management of patients diagnosed with medullary thyroid cancer (MTC). White/clear shading represents the patient's clinical diagnosis/stage; orange shading represents molecular test results. Dark blue shading conveys a necessary action for molecular testing or clinical provision, while light blue shading conveys a recommended action. Solid black arrows indicate a necessary pathway; dashed black shading represents "if/when" pathways. Abbreviations: P/LP, pathogenic/Likely pathogenic; VUS, variant of unknown significance

28, 29]. Recommended testing methods for *RET* variants are next-generation sequencing (NGS) or polymerase chain reaction (PCR) (Table 1). Pre-test genetic counselling is required for patients receiving germline testing, to obtain appropriate informed consent. This can be facilitated by the treating physician, who can also request germline testing on a blood sample. This process is known as mainstreaming, which refers to the incorporation of genetic testing into the standard practices of clinical care [49]. Alternatively, the patient can be referred to a clinical genetics service for pre-test counselling and ordering of testing: in some jurisdictions, there can be a long wait to access these services, and treatment should not be delayed while waiting for test results [28].

**Recommendation 2: Post-test Counselling by Clinical Genetics Is Necessary for All Patients with A Germline Pathogenic/Likely Pathogenic (P/LP) *RET* Variant and Recommended for All Those with a Germline Variant of Unknown Significance (VUS).**

For those with a germline *RET* P/LP variant, post-test counselling by clinical genetics is necessary to explore the presence of MEN syndromes and to initiate cascade testing of family members, consistent with guidelines [17, 28, 29, 31]. Post-test counselling is also recommended for patients with a germline *RET* variant of unknown significance (VUS) as these patients may require additional follow-up. A more detailed explanation of variant classifications of P/LP/VUS

**Table 1** Methods for detection of actionable biomarkers in thyroid cancer

| Biomarker | IHC | FISH | PCR | DNA-based NGS | RNA-based NGS |
|---|---|---|---|---|---|
| ***RET* mutations** [29, 50] | — | — | ● | ●● | — |
| ***RET* fusions** [29] | — | ●● | ●* | ●† | ●●† |
| ***BRAF* p.V600E mutation** [51, 52] | ●● | — | ●●§ | ●● | — |
| ***ALK* fusions** [37, 53] | ● | ●● | ●* | ●† | ●●† |
| ***NTRK* fusions** [36, 54, 55] | ●[a] | ●● | ●* | ●† | ●●† |
| **PD-L1 expression** [42, 43, 56, 57] | ●●¶ | — | — | — | — |
| **MMR deficiency/MSI#** [41, 54, 58, 59] | ●● | — | ●● | ●●[b] | — |
| **TMB** [40, 58] | — | — | — | ●●[c] | — |

Method recommendations: -, not useful or not performed. ●, lower clinical utility. ●●, higher clinical utility. Abbreviations: *IHC* immunohistochemistry, *FISH* fluorescence in-situ hybridization, *RT-PCR* reverse-transcription polymerase chain reaction, *NGS* next-generation sequencing, *TMB* tumor mutation burden, *MMR* mismatch repair, *MSI* microsatellite instability

*RT-PCR has a risk of lower sensitivity when there are many possible fusion partners

†RNA-based NGS has high sensitivity and specificity for fusions and confirms the presence of the fusion transcript. Appropriately designed DNA-based NGS has moderate sensitivity and moderate to high specificity for fusions

‡IHC testing of the four MMR proteins: MLH1, MSH2, MSH6 and PMS2 can be used to assess MSI

§For patients with ATC, a rapid turnaround time for *BRAF* results is necessary. Depending on the laboratory's methods for PCR testing, IHC testing may provide faster results

¶IHC testing for PD-L1 expression can vary in sensitivity and specificity depending on the test used and the interpretation scheme applied. The test used should be either: (1) a clinically validated commercial PD-L1 companion diagnostic assay or (2) a laboratory-developed test that is validated in accordance with fit-for-purpose principles against a clinically validated reference standard. This is an area where new data are rapidly emerging

#Microsatellite instability is caused by deficiency in the mismatch repair system. MMR deficiency can be assessed with IHC, which is available in most laboratories. Some laboratories may have PCR tests for MSI, which is a reasonable alternative to MMR IHC

[a]Pan-TRK IHC has higher non-specific results, so should be followed by RT-PCR and/or RNA-based NGS [36]

[b]Evidence supports the use of NGS to detect MMR/MSI [54]; however, access is limited for thyroid cancer, with IHC more readily available

[c]Tumor mutation burden (TMB) is defined as the total number of somatic mutations per coding area of a tumor genome. TMB-high levels are slightly lower in thyroid cancer (TC) than in some other cancers, while TMB-high is generally defined in tumors showing 17–20 mutations per 1.2–1.5 MB [58], in TC ≥ 10 mutations per MB [40], or even > 5 per MB is considered high [57]. This test is not yet in common use for any tumor type

(for germline variants) and Tier1/2/3 (for somatic variants) is included in Supplement 2.

Patients who have *RET* P/LP germline testing results do not require further tumor/somatic testing for *RET* variants. These patients can be considered for selective *RET*-targeted therapy based on germline testing results, since the germline variant will also be present in the tumor tissue.

#### Recommendation 3: Cascade Testing Must Be Offered to Family Members of Those Who Have a Constitutional (Germline) *RET* P/LP Variant

Cascade testing helps to identify those who have familial MTC syndromes, prior to the emergence of clinical symptoms of thyroid and other endocrine cancers. This aids in clinical management of these patients and also identifies those who may be candidates for targeted therapy, consistent with published guidelines [28, 31].

#### Recommendation 4: Somatic Tumor Tissue Testing for *RET* Variants Is Required for Those with Advanced Disease, with Unknown or Negative Germline *RET* Variant Status

Approximately 75–80% of all cases of MTC occur sporadically [6, 28], and of these, approximately 50% have somatic *RET* variants [6, 31], but this number may be even higher in patients with distant metastases [6]. Somatic tumor tissue testing for *RET* variants is required when patients who have germline *RET* VUS, or with no variants identified, progress to metastatic/recurrent/progressive/inoperable MTC, especially when targeted therapy is being considered. This is consistent with published guidelines [6, 17, 50]. Tumor/somatic testing is also required for patients with advanced disease whose germline status is pending, as the turnaround time for germline testing can be lengthy in some geographic regions, and the results of the testing are needed to inform treatment decisions. As *RET* variants are identifiable on testing of DNA (single nucleotide variants or small insertions/deletions) or RNA (fusions), the recommended testing method for *RET* variants in MTC is NGS or appropriately designed PCR assays (see Table 1 for details) [29]. Clinicians are advised to become familiar with the different testing modalities that are available in their local laboratories.

#### Recommendation 5: Tumor/Somatic Testing for Other Targetable Alterations Is Recommended

Gene variants other than *RAS* or *RET* make up only a very small proportion of those identified in sporadic MTC. Further tumor/somatic testing for other targetable alterations is recommended for all thyroid cancer patients with advanced disease who have no variants identified or Tier III results from tumor testing, including *BRAF* and *ALK* [6].

Table 1 compares testing methods for these biomarkers. IHC (when validated using rigorous protocols) and PCR are both recommended for *BRAF* p.V600E testing, with IHC providing the most rapid results. NGS is a preferred approach for simultaneous multigene testing such as for *BRAF* p.V600E, *ALK* and *NTRK* fusions. While DNA-based NGS is needed to detect variants such as *BRAF* p.V600E, RNA-based NGS has high sensitivity and specificity for fusions while also confirming presence of predicted fusion transcripts. DNA-based NGS has moderate sensitivity and moderate to high specificity for fusions due to difficulty of coverage of all intronic regions at the DNA level, and lack of fusion transcript confirmation [29]. Unfortunately, NGS is often not available or reimbursed in some jurisdictions and takes up to 2–3 weeks in Canadian centers. FISH or RNA-based NGS are also recommended for stand-alone *ALK* testing, with IHC and RT-PCR as alternatives for detecting these fusions. *NTRK* fusions are rare, consisting of only about 2% of gene variants in thyroid cancer [35], and a common approach to stand-alone *NTRK f*usion testing is an initial screen using pan-TRK IHC which is then followed by RT-PCR or RNA-based NGS [35, 36]. Where multi-gene NGS testing is already being done, consideration could be given to including *NTRK* gene fusion testing in the panel, which avoids the need for an initial screen by IHC.

### Constitutional (Germline) Testing in Patients Diagnosed with Non-Anaplastic Follicular Cell-Derived Thyroid Cancer

Constitutional testing is necessary for patients diagnosed with non-anaplastic follicular cell-derived thyroid cancer who have a clinical history or specific pathological or biomarker features consistent with a potential germline pathogenesis. Pathological indicators may include the following: (1) multiple cellular follicular cell-derived thyroid nodules (benign and/or malignant) with microfollicular growth, in association with immunohistochemical global phosphatase and tensin homolog (PTEN) loss in all nodules, in PTEN-hamartoma syndrome; (2) PTEN-hamartoma syndrome-like histological features with global loss of succinate dehydrogenase complex subunit B (SDHB) immunohistochemistry in one or more than one nodule, in PTEN-like syndrome and SDH-deficiency syndrome; (3) follicular nodular disease including those with involuted areas or multiple follicular adenomas with papillary architecture and synchronous follicular patterned differentiated thyroid carcinomas and/or non-invasive follicular thyroid neoplasm with papillary-like nuclear features, and background thyroid parenchyma involutional changes in the setting of normal thyroid-stimulating hormone (TSH) levels, in DICER1 syndrome; and (4) multiple follicular adenomas with papillary architecture in association with differentiated thyroid carcinomas and suppressed TSH levels in Carney complex (due to germline *PRKAR1A* variant) and McCune-Albright syndrome (due to somatic *GNAS*

mosaicism) [9, 60]. A pathologically distinct entity known as "cribriform-morular thyroid carcinoma" can be a harbinger of familial adenomatous polyposis (FAP) syndrome. Cribriform-morular thyroid carcinomas (formerly known as a subtype of papillary thyroid carcinoma) are no longer considered to be of follicular cell origin; thus, they are classified as primary thyroid carcinomas of uncertain cytogenesis [1, 2, 26, 60]. However, any patient with cribriform-morular thyroid carcinoma requires germline *APC* testing [1, 60]. Constitutional testing is also necessary for those with syndromic manifestations suspicious for other hereditary cancer syndromes not included above or in Table 2 [9, 32, 60, 61] (Fig. 2). The same holds true for those who have two or more first-degree relatives with papillary thyroid carcinoma or three or more first-degree relatives with follicular cell-derived thyroid cancer [28, 30, 60] (Fig. 2, Table 2).

Patients who meet the criteria for both germline testing and tumor testing (Fig. 3) should receive tumor testing first, with follow-up germline testing for those with P/LP results to determine whether the variant is present in the germline.

### Recommendation 6: Selection and Eligibility for Constitutional Germline Testing in Patients Diagnosed with Non-Anaplastic Follicular Cell-Derived Thyroid Cancer Will Most Likely be Determined by Multidisciplinary Team Members Including the Pathologist, the Treating Clinician, and Genetics Provider

While the majority of non-anaplastic follicular cell-derived thyroid cancers arise from sporadic mutations, about 3–9% result from familial non-medullary thyroid cancers (FNMTC) [9, 28, 61]. FNMTC can be more aggressive than the sporadic form [28]. Only 5% of FNMTC have well-characterized driver mutations, and the histological and molecular characteristics are still not as well defined as in hereditary C-cell neoplasia [9, 60]. Identification of patients with FNMTC is necessary to facilitate genetic testing of family members and to initiate surveillance for associated malignancies as appropriate [61].

In general, patients eligible for germline testing include those whose tumors have pathological and/or biomarker features indicating a need for germline testing or who have syndromic manifestations [1, 9, 60, 61] and/or two or more first-degree relatives with thyroid cancer [1, 9, 28, 30, 32, 60, 61]. For those with syndromic manifestations (where non-thyroid neoplasms dominate the clinical manifestations), clinical and pathological features often guide gene testing. As the histopathological findings of those without syndromic manifestations are usually non-specific [9, 60], important indicators for genetic screening and counselling include the 2022 WHO selection criteria which require exclusion of a non-syndromic non-medullary thyroid carcinoma (unassociated with ionizing radiation or hereditary cancer syndrome) when one of two rigid criteria are met: (a) at least three first-degree relatives with follicular cell-derived thyroid carcinoma or (b) the presence of papillary thyroid carcinoma in two or more first-degree relatives [1, 60]. In addition, the documentation of follicular nodular disease/multinodular goiter in at least three first- or second-degree kindreds of an index patient with a differentiated thyroid carcinoma (often PTC) is also considered among experts [9]. Table 2 summarizes

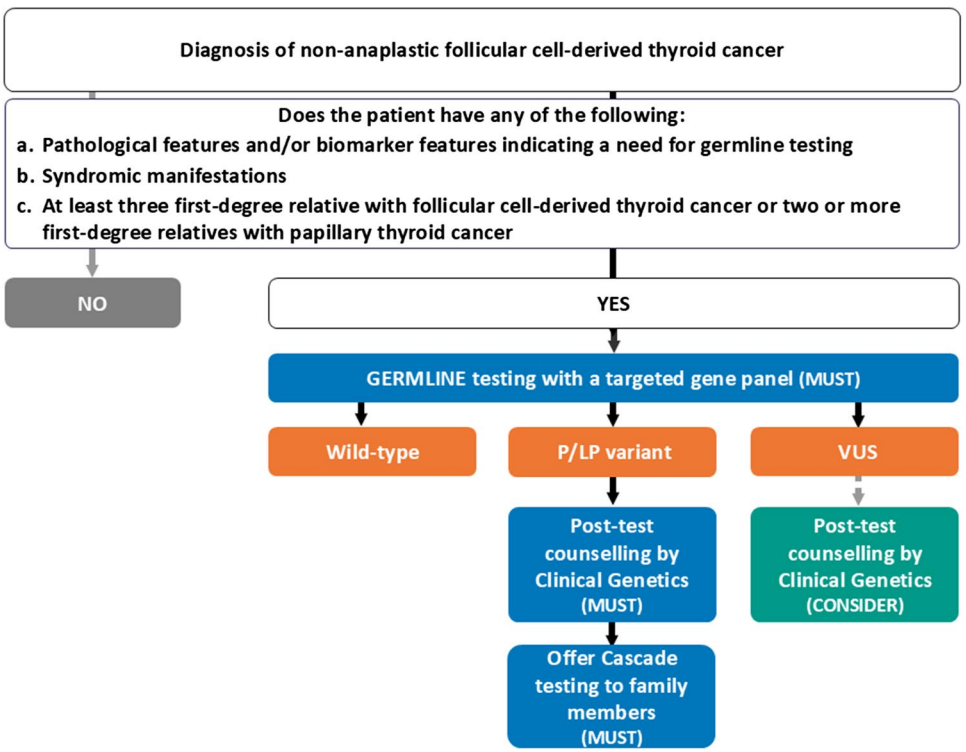


**Fig. 2** Constitutional (germline) testing in patients diagnosed with non-anaplastic follicular cell-derived thyroid cancer. White/clear shading represents the patient's clinical diagnosis/stage; orange shading represents molecular test results. Dark blue shading conveys a necessary action for molecular testing or clinical provision, green shading represents an action to be considered for clinical provision, and grey shading represents no further action needs to be taken. Solid black arrows indicate a necessary pathway, a solid grey arrow indicates no further action, and a dashed grey arrow indicates a pathway to be considered. Abbreviations: P/LP, pathogenic/likely pathogenic; VUS, variant of unknown significance

**Table 2** Syndromic and non-syndromic non-medullary thyroid carcinomas [9, 60, 62–68]

| | |
|---|---|
| **Syndromic Non-Medullary Thyroid Carcinoma (Non-thyroid neoplasms predominate in the clinical manifestation)** | |
| **Germline** | |
| PTEN hamartoma tumor syndrome (*PTEN*)* | |
| Familial Adenomatous Polyposis syndrome (*APC*) | |
| DICER1 syndrome (*DICER1*) | |
| Carney Complex (*PRKAR1A*) | |
| Werner syndrome (*WRN*) | |
| **Somatic Mosaicism** | |
| McCune-Albright syndrome (*GNAS*) | |
| **Non-Syndromic Non-Medullary Thyroid Carcinoma (Inherited/familial non-medullary thyroid neoplasm not associated with well-defined tumor syndromes)** | |
| **Susceptibility genes** | |
| 1p13.2 (*WDR77*) | 14q13.3 (*NKX2-1/TTF1*) |
| 1p36.31 (*PLEKHG5*) | 15q21.1 (*DUOX2*) |
| 1q41 (*BROX*) | 15q23 (*MAP2K5*) |
| 4q21.21 (*ANXA3*) | 16p13.3 (*SRRM2*) |
| 6p21.33 (*SAPCD1*) | 17p13.2 (*P2RX5*) |
| 7q31.33 (*POT1*) | 17q21.2 (*FKBP10*) |
| 9q22.23 (*FOXE1/TTF2*) | 19p13.11 (*NDUFA13*) |
| 10q25.3 (*HABP2*) | 19p12.1 (*TIMM44*) |
| 12q14.2 (*SRGAP1*) | 19q13.33 (*NOP53*) |
| 12q22 (*NTN4*) | 20p12.3 (*PLCB1*) |
| 14q11.2 (*C14orf93/RTFC*) | 22q12.1 (*CHEK2*) |
| 14q32.13 (*SERPINA1*) | 22q (*DGCR8*) |
| **Chromosomal loci with proposed full name for the unknown gene and symbol** | |
| 1q21 designated as Familial PTC with papillary renal neoplasia (*fPTC/PRN*) | |
| 2q21 designated as *Non-medullary thyroid carcinoma 3 (NMTC3)* | |
| 8p23.1-p22 designated as Familial thyroid epithelial neoplasia (*FTEN*) | |
| 8q24.22 designated as PTC susceptibility candidate 1 (*PTCSC1*) | |
| 14q designated as Multinodular goiter 1 (*MNG1*) | |
| 14q.13.3 designated as PTC susceptibility candidate 3 (*PTCSC3*) | |
| 19p13.2 designated as Thyroid tumor with cell oxyphilia (*TCO*) | |

This table summarizes key well-defined syndromic conditions (as recognized in the 2022 WHO classification) typically conferred by rare variants as well as susceptibility genes and loci that may be more common than in nature [9, 60, 62–68]. Apart from *CHEK2* and *POT1*, most of the candidate genes and loci are not yet available or actionable for routine clinical use. Knowledge of these associations will be important with the increasing breadth of genetic testing modalities such as genome-wide sequencing approaches that may help to explain some portion of familial disease either independently or through use in polygenic risk scores. Although traditionally not being recognized as components of syndromic non-medullary thyroid carcinoma, recent evidence has raised the link between non-medullary follicular cell-derived thyroid carcinoma and other cancer predisposition syndromes such as Li-Fraumeni and Lynch syndromes

*PTEN hamartoma tumor syndrome includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, PTEN-related Proteus syndrome and PTEN-related Proteus-like syndrome. A subset of patients with PTEN-like manifestations may also occur in the context of other alterations including but not limited to *SDH*x and *RASAL1* mutations and *KLLN* hypermethylation

key well-defined syndromic conditions (as recognized in the 2022 WHO classification) typically conferred by rare variants as well as susceptibility genes and loci that may be more common than in nature [9, 60, 62–68]. Apart from *CHEK2* and *POT1*, most of the candidate genes and loci are not yet available or actionable for routine clinical use. Knowledge of these associations will be important with the increasing breadth of genetic testing modalities such as genome-wide sequencing approaches that may help to explain some portion of familial disease either independently or through use in polygenic risk scores. Although traditionally not being recognized as components of syndromic non-medullary thyroid carcinoma, recent evidence has raised the link between non-medullary follicular cell-derived thyroid carcinoma and other cancer syndromes (e.g., Li-Fraumeni syndrome, Lynch syndrome) [62–68]. Patients with germline variants may still develop neoplasms unrelated to their genetic predisposition or additional actionable molecular alterations; therefore, considerations for somatic testing algorithms are applicable regardless of germline status (see recommendation 9).

### Recommendation 7: Post-test Counselling by Clinical Genetics Is Required for All Patients with a Pathogenic/Likely Pathogenic (P/LP) Constitutional (Germline) Variant and Can Be Considered for All Those with a Variant of Unknown Significance (VUS)

The standard practice for patients with P/LP variant results from germline testing is for them to receive post-test genetic counselling [17, 28, 29, 31]. Post-test genetic counselling can be considered for those with VUS gene alterations, particularly if the VUS is in a gene with known relevance to thyroid cancer management. For VUS occurring in genes without known relevance to targeted therapy, a consultation with clinical genetics may be less urgent, less necessary, or even less useful. A more detailed explanation of P/LP/VUS is included in Supplement 1.

### Recommendation 8: Cascade Testing Must Be Offered to Family Members of Those Who Have a Germline P/LP Variant

Cascade testing is also recommended for family members of those who have germline P/LP variants, in accordance with standard practices [28, 31]. This is not only to identify other family members who may have this gene variant, but also to initiate surveillance for potentially associated malignancies [61].

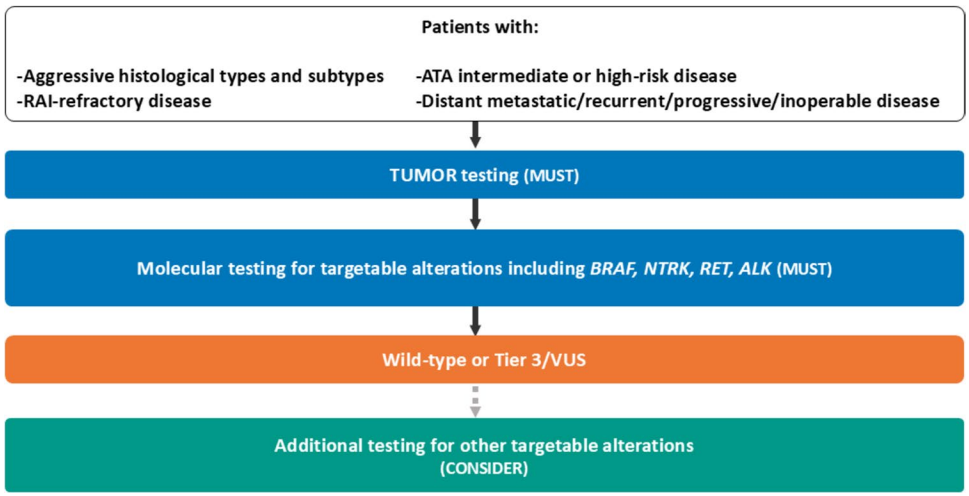


**Fig. 3** Tumor testing of actionable biomarkers in patients diagnosed with non-anaplastic follicular cell-derived thyroid cancer. White/clear shading represents the patient's clinical diagnosis/stage; orange shading represents molecular test results. Dark blue shading conveys a necessary action for molecular testing or clinical provision; green shading represents an action to be considered for clinical provision. Solid black arrows indicate a necessary pathway, and a dashed grey arrow indicates a pathway to be considered. Abbreviations: VUS, variant of unknown significance

## Tumor Testing of Actionable Biomarkers in Patients Diagnosed with Non-Anaplastic Follicular Cell-Derived Thyroid Cancer

### Recommendation 9: Tumor Testing Is Recommended for Patients with Non-anaplastic Follicular Cell-Derived Thyroid Cancer with Aggressive Histology and Subtypes, ATA Intermediate or High-Risk Disease, RAI-Refractory Disease, and Distant Metastatic/Recurrent/Progressive/Inoperable Disease.

All patients with advanced or high-risk disease should be considered for prospective/reflex testing (Fig. 3), to ensure that tumor testing results are available to guide therapy selection. Progressive disease is specifically included in the indications for tumor testing, as it covers the full spectrum of clinical adverse disease manifestations that may not be included in the other criteria. This includes those patients with wild-type results from germline testing, and those who had P/LP variants in germline genes not relevant to selection of targeted therapies.

NCCN guidelines recommend somatic testing to identify actionable variants in those patients with structurally persistent/recurrent locoregional or distant metastatic disease, including advanced, progressive, or threatening disease [28]. In addition, our expert consensus adopted the inclusion of aggressive histological types and subtypes, and the ATA intermediate or high-risk disease for somatic (tumor) testing (Fig. 3). However, the ultimate consensus position of the group was that it is important for optimal patient care to test early in patients for whom these results may eventually be needed.

### Recommendation 10: Molecular Testing for Targetable Alterations Including *BRAF*, *NTRK*, *RET*, and *ALK* Must Be Prioritized

Somatic/tumor testing is represented in a stepwise fashion, with effective testing strategies for actionable gene alterations in *BRAF* [51, 52, 69], *NTRK* [50, 54], *RET* [29, 50], and *ALK* [28, 37, 53] to identify patients who could potentially benefit from targeted treatments [18, 27]. This is consistent with the published guidelines and consensus recommendations reviewed [18, 20, 50]. Additionally, NCCN guidelines recommend that patients be enrolled in a clinical trial if available [28]. Evidence for *ALK*-targeted therapy in thyroid cancer is not as well supported by evidence as for *BRAF* and *RET*-targeted agents. Experts noted this may change as practice evolves, and as access to funded therapy is expanded. Biomarker testing methods are compared in Table 1 and discussed under recommendation 5.

### Recommendation 11: Consider Additional Testing for Other Targetable Alterations in All Patients with *BRAF*/*NTRK*/*RET*/*ALK* Wild-Type or Tier3/VUS Results

Other rare, actionable molecular alterations may occur in a small percentage of patients with non-anaplastic follicular cell-derived thyroid cancer. Whole exome sequencing or a comprehensive solid tumor NGS panel can be considered to identify actionable rare variants for which targeted therapies or clinical trials are available.

In addition, for solid tumors, high microsatellite instability (MSI) [41, 54], DNA mismatch repair deficiency (dMMR) [41, 54], and high tumor mutational burden TMB [28, 40, 70], as well as PD-L1 expression status

[28, 56, 70], can be predictive markers for response to immune checkpoint inhibitors [58]. The relationships between MSI/dMMR, TMB, and PD1/PD-L1 status are complex and can differ between tumor types [40, 57, 58, 71]. We look forward to more evidence in this area to guide additional testing in thyroid cancer.

## Tumor Testing of Actionable Biomarkers in Patients Diagnosed with Anaplastic Follicular Cell-Derived Thyroid Carcinoma (ATC)

### Recommendation 12: Rapid Testing and Treatment of ATC Patients is Priority. Flag the Multidisciplinary Team to Develop an Urgent Treatment Plan

All published guidelines emphasize the rapid evaluation of ATC patients and integrated decision making of multidisciplinary specialists who are highly experienced in treating this cancer [28, 72]. A balance is needed regarding whether to refer a patient to a high-volume center with expertise in treating ATC [28], versus starting *BRAF*-targeted therapy more quickly at a regional treatment center.

An inherent challenge in ATC is obtaining an accurate diagnosis particularly in correctly distinguishing ATC from other high-grade malignancies including primary thyroid lymphoma, sarcomas, and metastatic cancers (especially from lung) [1, 26, 28, 72]. Diagnosis is challenging as the ATC histopathological spectrum is variable, reflecting genetic and genomic complexity [1, 26, 72]. Ultimately, a tissue-based pathological assessment is required to ensure that the diagnosis is accurate and exclude other high-grade malignancies that can simulate ATC [26, 72]. ATC is extremely aggressive and so care for these patients must be prioritized and any treatments must start as soon as possible [72].

### Recommendation 13: All Patients Diagnosed with ATC Must Immediately Undergo Rapid Tumor Testing Using Rigorously Validated *BRAF* p.V600E Mutation-Specific Immunohistochemistry (e.g., VE1 Antibody)

Experts agreed that *BRAF* p.V600E reflexive testing (rapid PCR or IHC) and NGS can ideally be initiated at the same time (Fig. 4). This is a priority recommendation, and the specifics of testing are provided in the algorithm. Although IHC is generally quicker and available in more centers than rapid PCR, rapid PCR can be done if that is what is available and funded at the center of practice, as *BRAF* p.V600E testing must be initiated as soon as possible. A meta-analysis of the diagnostic performance of *BRAF* p.V600E IHC demonstrated that it is highly sensitive but may have limitations in specificity. Rigorous laboratory validation is required to reduce variability in results [52].

While both NCCN [28] and ATA [72] guidelines and a meta-analysis [52] are in agreement with this recommendation, ESMO recommends NGS analysis of cancer-associated genes as the preferred approach, if available [17, 50]. The expert panel's rationale for the recommendation is that the turnaround time for immunohistochemistry (IHC) or rapid PCR results is typically much faster than the turnaround time for NGS. All experts agree that this is an area where urgency is required, because of actionability and the rapid progression of disease.

### Recommendation 14: Additional Testing for Other Targetable Alterations Including *BRAF, ALK, NTRK*, and *RET* Is Necessary in ATC

Concurrent molecular testing using NGS is the preferred approach to confirm the *BRAF* p.V600E IHC results and to identify other targetable alterations including *ALK*, *NTRK*, and *RET* [17, 28, 54, 72]. Biomarker testing methods are compared in Table 1 and discussed under recommendation 5.

### Recommendation 15: Additional Testing for Other Targetable Alterations Is Recommended for Patients with ATC

Many published guidelines recommend molecular profiling of ATC to find any possibilities for targeted therapies, including immune checkpoint inhibitors and/or clinical trials [17, 28]. Whole exome sequencing or a comprehensive solid tumor NGS panel can be considered as discussed in recommendation 11 to identify actionable rare variants. There is also evidence to support testing for high MSI [41, 54], MMR [41, 54], high TMB [28, 40, 72], and PD-L1 expression [28, 56, 72], depending on what is funded or available. Patients with ATC may be potential candidates for immune checkpoint inhibitors [73].

## Retesting of Actionable Biomarkers

Additional alterations may be acquired during disease progression that might warrant a consideration of further tumor testing. Experts are reluctant to re-biopsy the tumor unless another targeted therapy may be an option; however, there is little evidence to support re-testing in thyroid cancer nor does evidence exist for when to conduct this testing. Liquid biopsy (cell-free DNA (cfDNA)) from tumors may be a consideration, with the caveat that this is still investigational and sometimes challenging [29]. In the thyroid cancer context, this approach cannot be recommended yet as there is not sufficient evidence for its use and validated

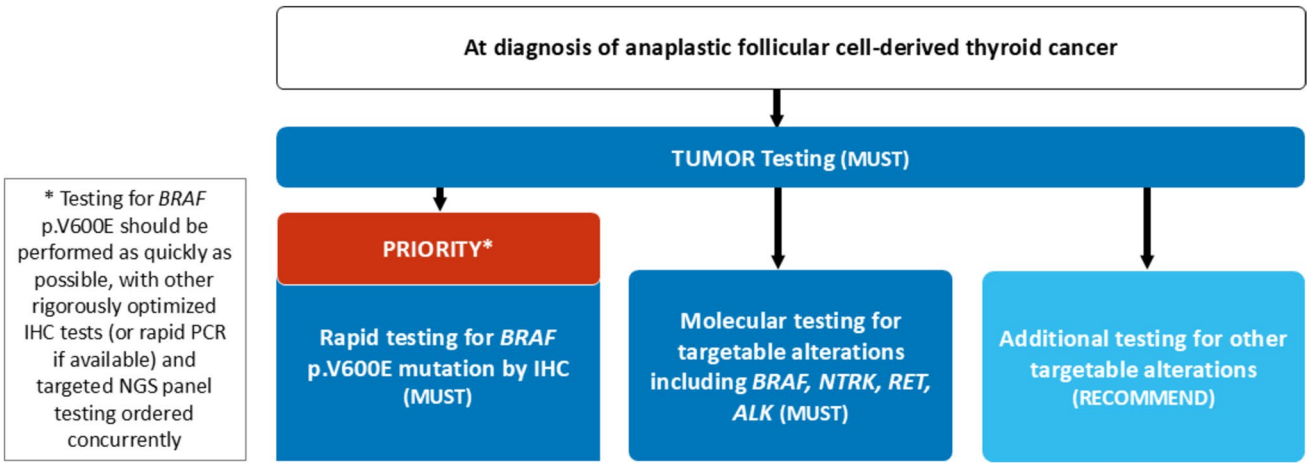


**Fig. 4** Tumor testing of actionable biomarkers in patients diagnosed with anaplastic follicular cell-derived thyroid carcinoma. White/clear shading represents the patient's clinical diagnosis/stage, dark blue shading conveys a necessary action for molecular testing or clinical provision, red shading indicates a priority action, and light blue shading represents a recommended action. Solid black arrows indicate a necessary pathway

clinical-grade assays are lacking for this indication [29, 72].

### Recommended Methods for Detection of Actionable Biomarkers in Thyroid Cancer

Table 1 recommends methods for detection of actionable biomarkers in thyroid cancer. Evidence for molecular testing methods is accumulating. Some of the methods described in this table were developed and validated in other malignancies [29, 54, 58, 59], so they may not be ideal or optimized for the detection of actionable biomarkers in thyroid cancer.

Several papers recommend a sequential screening approach (for example, first testing for *BRAF* p.V600E before *NTRK* fusions) to first exclude more common biomarkers, and only test less common biomarkers in patients negative for the common biomarkers [18, 36]. In addition, some publications recommend using one testing method for initial screening, followed by confirmatory testing using a different method, for example, initially screening with IHC, followed by FISH (for *ALK*) [37], PCR (MSI) [58], or FISH, RT-PCR, or NGS (for *NTRK*) [54]. Evidence for the optimal methods for detection of various biomarkers in thyroid cancer is still emerging and may vary based on availability and/or local access to testing methodologies. Published guidelines differ in their recommendations for testing methods. Laboratories may choose different tests that align with their workflow, as long as they have been validated for use in thyroid cancer specimens according to fit-for-purpose principles [74].

## Discussion

This consensus statement presents four algorithms describing actionable biomarker testing for patients diagnosed with MTC, non-anaplastic follicular cell-derived thyroid cancer, and anaplastic follicular cell-derived thyroid cancer who may benefit from targeted therapies. These algorithms are aimed to help physicians navigate the current thyroid cancer biomarker testing landscape with its many challenges. The algorithms balance aspirational care (what thyroid cancer experts wish to provide for their patients, based on available evidence) with what is practical/pragmatic and feasible in terms of economic realities and jurisdictional constraints. The algorithms do not include recommendations for specific treatments; new therapies are continually being introduced but vary with regard to regulatory approval and funding. By remaining therapy-agnostic, these algorithms and recommendations are broadly applicable.

This work does not aim to duplicate the NCCN [28], ATA [31, 48, 72], ESMO [17, 50], and ETA [20] guidelines or other expert recommendations [18, 46], but to discuss and address some of the biomarker-related gaps impacting patient care. Some published guidelines do not include details of biomarker testing [20, 31] and others describe molecular testing solely for diagnosis and prognostication [48]. This manuscript aims to specifically provide practical recommendations for actionable biomarker testing for patients diagnosed with thyroid cancer, including testing methodologies and time points, which are not usually addressed in most current published guidelines [46].

A recent review by Capdevila et al. described the different clinical laboratory methods that could be used to identify

molecular alterations in thyroid cancer, citing the advantages and disadvantages of each method [18]. Their approach differed from ours as they presented treatment algorithms based on whether IHC was available versus other methods, which is a practical approach to adapt to different technologies, infrastructure, and resources that may be available at a particular center [18]. As a result, some of their recommendations differed from those in this manuscript. This is an evolving area, where each center's access to new and different methodologies varies, so clinicians must advocate for thyroid cancer testing to be included under local testing mandates.

The lack of consistently high-level evidence was the biggest challenge when creating the algorithms for actionable biomarker testing in thyroid cancer. As articulated by Horgan et al., evidence for actionable biomarker testing in thyroid cancer is uneven and relatively low quality, and much is based on relatively small retrospective studies [15]. Although one meta-analysis was specifically conducted on the sensitivity and specificity of IHC to detect *BRAF* p.V600E mutations in primary or metastatic thyroid tumor specimens [52], some of the other biomarker testing evidence is from studies with small proportions of thyroid cancer patients [40, 41, 70], or from other tumor types [29, 54, 58, 59, 71]. In the absence of evidence, these algorithms and recommendations were based on the expert consensus of knowledge derived from the clinical practice of Canadian thyroid cancer experts, who regularly treat patients with aggressive thyroid cancer.

Few thyroid cancer guidelines currently recommend germline testing for patients diagnosed with non-anaplastic follicular cell-derived thyroid cancer unless patients have a personal or family history of cancer [28, 30]. The current consensus further expanded on the criteria of genetic testing in patients with non-medullary thyroid carcinoma (Fig. 2).

This manuscript identified aspects of thyroid cancer biomarker testing and care which need to be addressed and improved. More evidence is needed for all aspects of actionable biomarker testing in thyroid cancer including more accurate thyroid-specific biomarker thresholds. PD-L1 expression is variable in different thyroid cancer cell types [56, 75]. Even though ATCs generally express PD-L1 at higher expression levels than other thyroid cancers [56, 75], this may be lower than other solid tumors leaving some uncertainty about their relationship to potential benefits of PD-1/PD-L1 inhibition therapies [42, 43]. TMB-high levels are frequently lower in thyroid cancer than in many other solid tumors [73]. TMB-high is generally defined in tumors showing 17–20 mutations per 1.2–1.5 MB [58]; however, in thyroid cancer, $\geq 10$ mutations per MB [40] or even $> 5$ per MB is considered relatively high [57]. ATCs have a significantly higher TMB than non-anaplastic follicular cell-derived thyroid neoplasms, and most ATCs do not meet the high TMB threshold of $> 10$ mutations/MB, despite this tumor type having complex genomic landscapes [72, 76].

Evidence for the use of immune checkpoint inhibitors specifically in thyroid cancer, as well as how to select patients who could benefit from such therapy, is needed. Several therapeutic agents have received tumor-agnostic approval to treat cancers with specific molecular alterations, biomarkers, or other cellular characteristics such as MSI-high. MSI is a molecular phenotype for dMMR, and MSI-high/dMMR tumors are characterized by a large number of DNA mutations including single base mismatches, insertions, and deletions [58, 59]. Generally, MSI-high is a result of deficiency in mismatch repair and so these biomarkers are assumed to be concordant [58, 59], but they can be uncoupled in some tumor types such as colorectal cancer [59]. Solid tumors with high MSI/dMMR generally respond to immune checkpoint inhibitors [54, 59], and there is some evidence for response in thyroid cancers [41].

More future work is also needed to guide research into the use of liquid biopsies and cfDNA assays to mitigate the need for updated tumor tissue re-biopsies, expand knowledge on acquired resistance, and identify additional treatment targets. The use of liquid biopsy is advancing throughout all oncology and experts look forward to having an ongoing liquid biopsy for all patients who are being treated with immune therapy and targeted therapies.

By far, the biggest barrier for actionable biomarker testing for thyroid cancer is a lack of dedicated testing infrastructure and resources; not all tests are available or funded in all centers or jurisdictions. Clear algorithms and strong recommendations will not compensate for the lack of biomarker testing infrastructure and resources and may even stress limited resources further. During the algorithm creation process, the expert panel discussed how increased biomarker testing may impact Canadian pathology and laboratory resources when the patient is not in immediate need of targeted or immune checkpoint inhibitor therapy. The intention of publishing this consensus statement was to emphasize the importance of testing patients for actionable biomarkers as quickly and as accurately as possible to ensure optimal patient outcomes. Resources and infrastructure allocations will ideally be guided by emerging evidence.

These algorithms provide valuable guidance and direction for molecular testing for thyroid cancer and address some of the gaps and inconsistencies in other published guidelines with respect to molecular testing. Actionable biomarker analysis is only one necessary step to improve the care of thyroid cancer patients. Test results need to be correctly interpreted, and clinical treatment and follow-up need to be appropriately administered by a multidisciplinary care team. The importance of a multidisciplinary team approach was emphasized in the algorithms and in the published guidelines reviewed. Medical oncologists, endocrinologists, pathologists, surgeons, and

genetics providers have differing points of view regarding the algorithm/seeing the patient, which can be influenced by local/regional health care resources, access, and test development. For endocrinologists and most oncologists, the target patient is one with current need for testing and therapy based on imaging or symptoms and the results of molecular testing. Pathologists and surgeons have a different perspective based on a histological view, which supports predictive testing for patients at high risk, facilitated at larger centers through weekly rounds or tumor boards. Clinicians at smaller centers must have ways to access the specialists at larger centers or to advance their patients for discussion at tumor boards so that their patients can benefit. Genetics providers need to support timely access to germline testing via mainstreaming approaches, and provide counselling and cascade genetic testing to patients and their families, respectively. In addition, patients need access to the newest agents which have already attained approval in some jurisdictions.

Molecular testing in thyroid carcinoma is perpetually evolving. As such, we will likely see wider adoption of other molecular targets in the MAPK and PI3K/AKT/PTEN pathways given their relevance to sporadic and germline forms of thyroid cancers. We are hopeful that these algorithms will encourage international dialogue about updating testing and management of those patients diagnosed with thyroid cancer. The field is moving fast, evidence will continue to emerge, and testing algorithms and recommendations will necessarily evolve as a result.

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