Seminars in Diagnostic Pathology 43 (2026) 151010

Contents lists available at ScienceDirect

Seminars in Diagnostic Pathology

journal homepage: www.elsevier.com/locate/semdp

Review article

Molecular findings in thyroid tumors: Practical diagnostic, prognostic, and therapeutic insights

Lauren Stark [a], Julie C. Dueber [b], Derek B. Allison [b,c,*]

[a] Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri, USA
[b] Departments of Pathology & Laboratory Medicine, University of Kentucky College of Medicine, Lexington, KY, USA
[c] Markey Cancer Center, Lexington, KY, USA

ARTICLE INFO

Keywords:
Thyroid neoplasms
Molecular alterations
BRAF
RAS
MAPK pathway

ABSTRACT

Over the last decade, there has been substantial growth in our understanding of the molecular drivers for thyroid tumors with the advent of next generation sequencing. Importantly, these drivers correlate with histopathologic features and clinical behavior. Briefly, *RAS/RAS*-like alterations result in modest activation of the MAPK pathway and produce follicular-patterned neoplasms, including follicular adenomas and follicular carcinomas, as well as non-invasive follicular thyroid neoplasm with papillary-like nuclear features and follicular subtype of papillary thyroid carcinoma (PTC). In contrast, *BRAF* V600E and related alterations result in robust activation of the MAPK pathway and display a papillary architecture with well-developed PTC nuclear features, including classic PTC and its non-follicular subtypes. Interestingly, a subset of thyroid carcinomas activates the MAPK pathway to an intermediate degree, resulting in mRNA expression patterns overlapping between the *BRAF* V600E-like and *RAS*-like categories, including tumors with fusions involving *NTRK1–3, ALK*, and *FGFR2*, which often display PTC features. In contrast, oncocytic tumors exhibit mitochondrial mutations and chromosomal copy number changes. Finally, a small subset of non-oncocytic tumors exhibits non-MAPK mechanisms of neoplasia, including transcriptional dysregulation, epigenetic alterations, or rare structural variants. In each molecular category, secondary alterations can occur; most notably *TERT* promoter and *TP53* mutations occur with increasing frequency in high-grade differentiated, poorly differentiated, and anaplastic thyroid carcinomas. This article will review the diagnostic, prognostic, and therapeutic significance of molecular alterations across the spectrum of follicular cell derived thyroid tumors and discuss strategies for investigating unusual molecular alterations encountered in clinical practice.

Introduction

Over the past decade, our understanding of the molecular landscape of thyroid tumors has expanded significantly, driven by large-scale genomic studies analyzing preoperative fine-needle aspiration (FNA) samples, thyroidectomy specimens, and metastases.[1–6] This body of genetic data has informed risk stratification, improved histologic subtyping, captured a subset of patients with germline mutations, and allowed for precision medicine in advanced thyroid carcinoma cases.[7–10]

More specifically, next-generation sequencing (NGS) studies performed on thyroid specimens have deepened our understanding of the molecular landscape of many diagnostic entities. Furthermore, other high-sensitivity platforms using DNA and RNA sequencing, as well as mRNA classifiers, now allow cell-free assays to be performed on the limited material obtained from FNAs.[5, 11, 12] These advances have improved preoperative malignancy risk assessment and inform clinical management, particularly in indeterminate Bethesda category FNA samples.

This assimilation of molecular data has resulted in the identification of recurring drivers across distinct subsets of thyroid tumors. These molecular classes include *RAS/RAS*-like alterations predominating in follicular-patterned neoplasms, *BRAF* V600E/*BRAF* V600E-like alterations defining classic papillary thyroid carcinoma (PTC) and canonical variants, and mitochondrial and copy number abnormalities characteristic of oncocytic tumors.[1–3, 13] In addition, secondary alterations in the

The authors have no conflicts of interests or financial disclosures to report.

* Corresponding author at: University of Kentucky College of Medicine, 800 Rose St, MS117, Lexington, KY 40536, USA.
E-mail address: Derek.Allison@uky.edu (D.B. Allison).

https://doi.org/10.1016/j.semdp.2026.151010

Available online 16 April 2026

TERT promoter and *TP53* genes have been recognized to promote a more aggressive phenotype. Thus, these are increasingly enriched in tumors as they progress to high-grade differentiated histologic subtypes, poorly differentiated thyroid carcinomas, and anaplastic thyroid carcinomas.[14–16] Unlike the aforementioned tumors which are all derived from thyroid follicular epithelial cells, medullary thyroid carcinoma arises from c-cells and is driven by germline or somatic *RET* mutations or, less commonly, *RAS* alterations.[17, 18]

This article will review the diagnostic, prognostic, and therapeutic significance of molecular alterations across the spectrum of follicular cell derived (or putative follicular cell derived) thyroid tumors, including follicular, papillary, and oncocytic tumors, as well as high-grade tumors and rare and emerging neoplasms. We also discuss strategies for investigating unusual molecular alterations encountered in clinical practice.

RAS-like (Follicular architecture)

Follicular cell-derived tumors with a follicular architecture share an interesting molecular profile that is enriched for *RAS* mutations or has a *RAS*-like mRNA signature.[2] The term "*RAS*-like" refers to a molecular phenotype characterized by modest activation of the MAPK pathway. This designation was first made in The Cancer Genome Atlas (TCGA) thyroid study, which used gene expression clustering to distinguish tumors with high MAPK output (*BRAF* V600E-like) from those with lower-level MAPK signaling (*RAS*-like).[1] These findings have been further validated by multiple groups.[2, 3, 19] Classically, the *RAS*-like phenotype includes mutations in the *RAS* family of genes, most notably *NRAS* and *HRAS*, and much less frequently *KRAS*.[3, 20] These alterations are detected in up to 40–50% of follicular adenomas, follicular carcinomas, and NIFTPs.[21, 22] Additional mutations that result in this molecular phenotype include *BRAF* K601E, *TSHR,* and certain inactivating alterations in negative regulators of the MAPK pathways, such as *NF1*.[23–25] These alterations share similar downstream transcriptional profiles, including modest MAPK signaling output, low-level ERK phosphorylation, and a preference for follicular growth patterns.[1–3]

Follicular adenomas, for example, are benign encapsulated neoplasms that lack invasion and do not display PTC nuclear features (Fig. 1**A**). When an invasive growth pattern emerges, the diagnosis becomes a follicular thyroid carcinoma (FTC), which is further subtyped by the extent and type of invasion. A minimally invasive FTC displays capsular invasion only, an encapsulated angioinvasive FTC displays venous invasion within the capsule or beyond (Fig. 1**C**), and a widely invasive FTC shows extensive invasion into thyroid parenchyma and often the surrounding soft tissue. Interestingly, this *RAS*-like molecular category also includes non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), which displays a follicular growth pattern, is encapsulated or well-demarcated, but has PTC-like nuclear features, noting that intranuclear pseudoinclusions are most often rare or absent (Fig. 1**B**).[1, 22] These PTC-like nuclear features are often variably present throughout the lesion and represent a spectrum of changes that are not quite "well-developed" and diffuse. Furthermore, these tumors must lack a papillary growth pattern, psammomatous calcifications, high grade features, or any other feature indicative of a histologic subtype of PTC. When a neoplasm with these features develops an invasive growth pattern, it meets criteria as an invasive encapsulated follicular variant of PTC (Fig. 1**D**). When malignant, *RAS*-like tumors are less likely to present with nodal metastases and instead have a propensity to metastasize hematogenously, including to the lungs and bone, which aligns well with the inclination for venous invasion identified in the primary lesions.[26] As a result, the *RAS*-like group of tumors represents an interesting intersection where underlying molecular alterations result in a characteristic histologic growth pattern and mode of metastasis (Table 1).

RAS-like tumors also tend to retain expression of thyroid differentiation genes such as *TG, TPO*, and *SLC5A5*, which may have implications for radioactive iodine uptake.[27] Unlike *BRAF* V600E-like tumors, these alterations do not confer the potent MAPK activation that leads to papillary architecture and the well-developed nuclear features of PTC, such as prominent pseudoinclusions. For example, *BRAF* K601E results in intermediate kinase activity, attenuated ERK signaling, and is consistently found in tumors with a follicular architecture and *RAS*-like expression signature.[25] These observations support the classification of *RAS*-like tumors as a distinct molecular subset with preserved thyroid differentiation and follicular architecture.

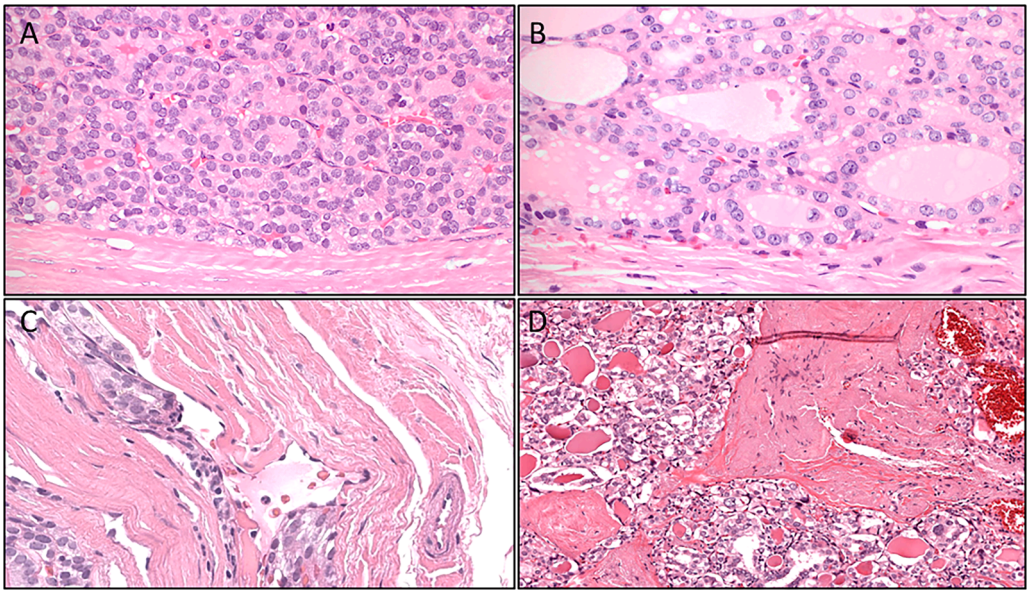

Fig. 1. *RAS*-like follicular patterned neoplasms. A) Follicular adenoma with follicular architecture, lack of PTC nuclear features, and an intact capsule (H&E stain, 40x). B) NIFTP showing a follicular architecture and variable PTC-like nuclear features, such as nuclear enlargement, nuclear grooves, and chromatin clearing. No capsular invasion is identified (H&E stain, 40x). C) Follicular carcinoma with follicular architecture and angioinvasion within the capsule and a lack of PTC nuclear features (H&E stain, 40x). D) Encapsulated follicular subtype of PTC with PTC nuclear features and capsular invasion (H&E stain, 10x).

Table 1
Selected thyroid tumor molecular summary by diagnosis*.

Tumor Entity	Key Molecular Findings	Notes / Clinical Implications
Follicular thyroid carcinoma	*RAS* mutations/*RAS*-like, including *PAX8*::*PPARG* fusions	Invasion (capsular/vascular) is diagnostic
NIFTP	*RAS* or *RAS*-like mutations; no *BRAF* p.V600E or *RET*/*NTRK* fusions	Indolent if completely excised; strict histologic criteria essential
Papillary thyroid carcinoma	*BRAF p.V600E* (40–50%)/*BRAF* V600E-like; RET/NTRK fusions (esp. in pediatric & radiation-associated cases), occasional RAS mutations (follicular subtype)	Most common thyroid carcinoma; fusion-driven cases enriched in younger patients; *BRAF* p.V600E correlates with classic morphology and higher recurrence risk
Oncocytic carcinoma	Copy number alterations (CNA), mitochondrial DNA mutations	Chromosome 7 gains predict aggressive behavior
High-grade differentiated thyroid carcinomas (HGDTC)	Same drivers as parent tumor plus secondary events, including emergence of *TERT* promoter/*TP53* mutations	Defined by mitoses ≥5/2 mm² and/or necrosis, while retaining well-differentiated morphology
Poorly differentiated thyroid carcinoma (PDTC)	Same drivers as parent tumor plus secondary events, including *TERT* promoter/*TP53* mutations	Defined by Turin criteria: insular/solid/trabecular architecture, convoluted nuclei, mitoses ≥3/2 mm², necrosis
Anaplastic thyroid carcinoma (ATC)	Same drivers as parent tumor with highest frequency of *TERT* promoter/*TP53* mutations, as well as additional secondary events (genomic instability)	Highly lethal; *BRAF* and *RET*/*NTRK* fusions guide targeted therapy
Cribriform-morular thyroid carcinoma	*APC* or *CTNNB1* (β-catenin) mutations	Now recognized as a distinct entity (no longer a PTC subtype); strong association with familial adenomatous polyposis (FAP)
Pediatric follicular cell–derived thyroid tumors	High prevalence of *RET* and *NTRK* fusions; less frequent *BRAF* p.V600E	More often present with nodal disease but generally excellent prognosis; fusion-driven biology important for risk stratification
Thyroblastoma (DICER1-associated)	*DICER1* mutations	Distinct embryonal-type tumor; typically pediatric/young adults; can be aggressive with local invasion or metastases
Other rare subsets	*DICER1* mutations in pediatric follicular cell–derived tumors (non-thyroblastoma); *ALK*, *ROS1*, *RET*, and *NTRK* fusions in unusual histologies; *EIF1AX* mutations in indeterminate nodules; *GNAS* mutation favors benign or hyperfunctioning (hot) nodule	*DICER1*-associated lesions beyond thyroblastoma range from benign nodular disease to carcinomas; fusion-positive tumors can be targetable and are enriched in radiation-associated cases
NUTM1-rearranged thyroid carcinoma	*NUTM1* fusions (e.g., *NSD3*::*NUTM1*)	Extremely rare and aggressive; positive for NUT by IHC

* See text for relevant literature citations.

BRAF V600E-like (Papillary architecture/well-developed PTC nuclear features)

PTC is the most common malignant thyroid neoplasm and is defined histologically by a combination of papillary or follicular architecture with characteristic nuclear features, including nuclear enlargement, irregular nuclear contours, nuclear grooves, chromatin clearing, and intranuclear pseudoinclusions (Fig. 2**A/2B**). Furthermore, the presence of psammomatous calcification is indicative of papillary architecture. With the exception of the follicular subtype, which lacks papillae, most PTCs are molecularly characterized by strong MAPK pathway signaling output, termed "*BRAF* V600E-like".[1–3] As this name implies, the defining alteration of this group of tumors is the *BRAF* V600E mutation, which occurs in approximately 40–50% of all PTCs and in up to 60–70% of classic PTCs.[28, 29] The criteria for subclassifying PTCs is beyond the scope of this text; however, several histologic subtypes will be reviewed in the context of recurring molecular alterations and clinical behavior.

In addition to the *BRAF* V600E mutation, the *BRAF* V600E-like group also includes *RET* fusions and *BRAF* fusions.[1–3] Some alterations, including *NTRK1–3, ALK*, and *FGFR2* fusions, show intermediate transcriptional features that overlap between *BRAF*-like and *RAS*-like profiles and are discussed in a different section below.[3] The *BRAF* V600E-like phenotype encompasses the majority of histologic variants of PTC (Table 1). Classic PTC and the tall cell subtypes are strongly associated with *BRAF* V600E mutations (Fig. 2**C**).[29, 30] The hobnail subtype is similarly enriched for *BRAF* V600E mutations and carries a worse prognosis, while the columnar cell subtype frequently harbor *BRAF* V600E mutations or MAPK-activating fusions.[31, 32] In contrast, the diffuse sclerosing variant is more commonly associated with *RET* fusions and often arises in younger patients or those with prior radiation exposure (Fig. 2**D**).[33]

Clinically, *BRAF* V600E-like tumors tend to present as infiltrative, often multifocal, PTCs with a high frequency of cervical lymph node metastases at diagnosis. These tumors generally have reduced iodine avidity compared to *RAS*-like neoplasms, which may limit the effectiveness of radioactive iodine in advanced disease.[34] In the pediatric population, fusion-driven tumors (especially those involving *RET* and *NTRK*) are more common and often respond well to targeted kinase inhibitors in the metastatic setting (Table 2).[35]

While the overall prognosis for PTC remains excellent, cases with aggressive histologic subtypes, coexisting *TERT* promoter mutations, or significant extrathyroidal extension warrant closer monitoring and more aggressive treatment strategies.

Oncocytic neoplasms

Oncocytic thyroid tumors represent a unique subtype of follicular cell-derived neoplasms that contain oncocytic cells comprising at least 75% of the tumor. These cells have abundant eosinophilic, granular cytoplasm due to the accumulation of mitochondria, a characteristic common to cells with oncocytic features in other sites (Fig. 3**A/3B**). While oncocytic tumors can be benign (oncocytic adenomas), the malignant counterpart is classified as an oncocytic carcinoma (OCA) and can be further divided into minimally invasive, encapsulated angioinvasive, and widely invasive histologic subtypes, as done with FTCs (described above). Importantly, OCAs are considered a separate entity from follicular carcinoma, despite some shared architectural features, and are distinct from both *BRAF*-like and *RAS*-like tumors based on their molecular and biological profiles (Table 1).[13, 36]

Histologically, OCAs are encapsulated tumors with capsular and/or vascular invasion, do not show the nuclear features of PTC, and lack high-grade cytologic features. Most tumors show solid or trabecular growth patterns, but a variable follicular architecture can be seen. Although the nuclei are typically round and regular, the nuclear features can be variable and occasionally display multinucleation, nuclear grooves, intranuclear pseudoinclusions, and prominent nucleoli.[37] These features can be seen in both oncocytic adenomas and OCAs; however, it is the presence or absence of invasion that distinguishes these tumors. Furthermore, the extent of vascular invasion appears to be most correlative with clinical outcomes.[38] Rare OCAs may show necrosis or increased mitotic activity and meet the criteria for high-grade differentiated oncocytic thyroid carcinoma.[39] OCAs, like FTCs, frequently metastasize hematogenously but have a higher propensity for

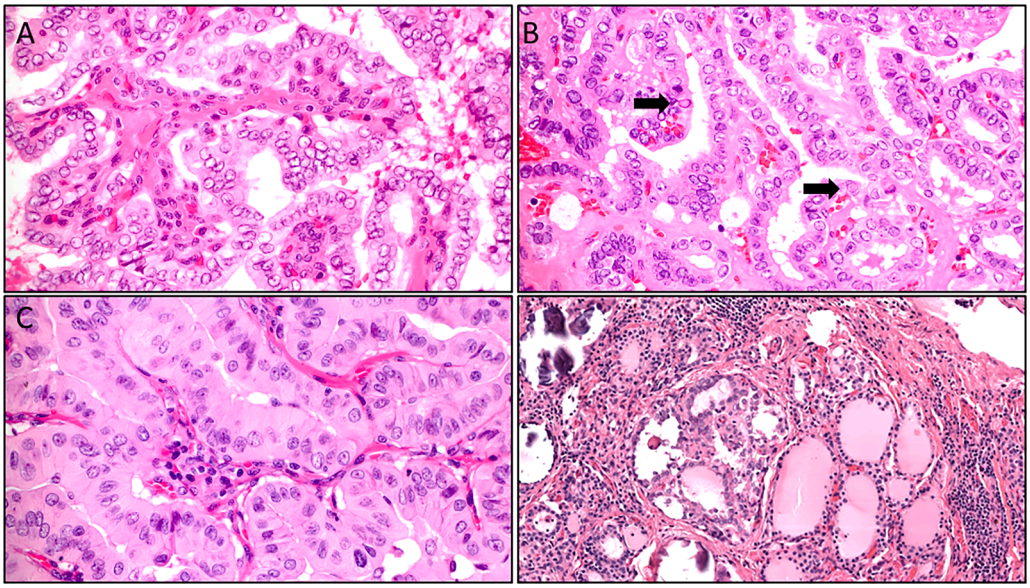

Fig. 2. *BRAF* V600-like papillary carcinomas. A) Classic PTC with papillary architecture, nuclear enlargement, irregularity, clearing, and grooves (H&E stain, 40x). B) PTC with intranuclear pseudoinclusions (black arrows) (H&E stain, 40x). C) PTC, tall cell subtype showing cells that are 2–3 times taller than they are wide. Although not shown in this focus, a trabecular growth pattern is common (H&E stain,40x). D) PTC, diffuse sclerosing subtype often shows many scattered foci of tumor, like shown, with many psammomatous calcifications and a background of stromal sclerosis and lymphocytic infiltrates. This sclerosis often creates a nodular appearance in the thyroid (H&E stain, 10x).

lymph node spread; however, some reported nodal involvement may reflect vascular tumor plugs rather than true nodal metastasis.[40] Importantly, OCAs often show reduced expression of genes related to iodine uptake and storage, which is likely the reason for their relative resistance to radioactive iodine.[41, 42]

Molecularly, oncocytic thyroid neoplasms are notable for a low frequency of canonical mutations, which can lead to false-negative molecular results on FNA specimens, though some improvements have been made in recent years.[43] Oncocytic adenomas and OCAs show frequent mitochondrial DNA mutations involving proteins related to complex I of the electron transport chain.[36, 44] These alterations result in impaired oxidative phosphorylation and a compensatory increase in the number of mitochondria in the cytoplasm, resulting in the characteristic oncocytic appearance.[44] In OCAs, chromosomal losses accumulate with many tumors revealing near-haploidy states with monosomies of chromosomes 2, 8, and 22.[36, 45, 46] Occasionally, gains in chromosomes 7, 12, and 17 are observed.[45] Increased chromosomal copy number alterations seem to correlate with histologic features, as well as worse clinical outcomes.[47] More specifically, minimally invasive OCAs are more likely to be diploid while widely invasive tumors more frequently show polysomy and amplification of chromosome 7.[13] In addition to mitochondrial complex I mutations, recent studies suggest that dysregulation of cellular metabolism through alternative mechanisms may contribute to the oncocytic phenotype. One such example involves loss of *folliculin* (*FLCN*), a tumor suppressor gene that regulates mitochondrial biogenesis, oxidative phosphorylation, and mTOR signaling and, when present in the germline, causes Birt-Hogg-Dubé syndrome. Inactivation of the FLCN protein leads to a distinct gene expression profile enriched for mitochondrial and lysosomal dysfunction, resembling that seen in classic oncocytic tumors. This observation suggests that *FLCN*-altered thyroid neoplasms may represent an emerging molecular subtype with potential oncocytic differentiation independent of traditional chromosomal or mitochondrial DNA alterations.[48–52] However, more research is needed to further elucidate various mechanisms that can result in an oncocytic phenotype in thyroid tumors.

BRAF V600E-like/RAS-like overlap carcinomas

A subset of thyroid carcinomas activate the MAPK pathway to an intermediate degree, resulting in mRNA expression patterns overlapping between the *BRAF* V600E-like and *RAS*-like categories.[1–3] This group includes tumors with fusions involving *NTRK1–3, ALK*, and *FGFR2*, which activate signaling through upstream receptor tyrosine kinases (RTKs) rather than through point mutations in downstream signaling proteins.[1] Rare fusions involving *MET* have also been identified and likely fit into this category.[1] These fusions result in constitutive dimerization and autophosphorylation of the fusion protein, leading to MAPK activation, and in many cases, concurrent PI3K/AKT pathway signaling as well. These carcinomas tend to display PTC histopathologic features and may result in nodal metastases but often maintain a relatively favorable clinical course, as a group, compared to *BRAF* V600E-like carcinomas.[1–3] These events are more common in radiation-associated or pediatric thyroid carcinomas and are most frequently seen in the context of papillary thyroid carcinoma, including the diffuse sclerosing and solid variants.[3] Because these fusions are targetable, with FDA-approved therapies such as larotrectinib (for NTRK) or alectinib (for ALK), their identification has significant clinical implications (Table 2).[53, 54]

Non-BRAF V600E-like, non-RAS-like tumors

Beyond the canonical *BRAF* V600E-like, *RAS*-like, *BRAF* V600E-like/*RAS*-like overlap, and oncocytic phenotypes, there are a number of additional alterations that can drive thyroid neoplasia that do not neatly fit into a category. These include point mutations, non-RTK fusions, and deletions that frequently involve disruption of transcriptional regulators, chromatin remodelers, or other signaling pathways. The *PAX8*::*PPARG* fusion, for instance, is associated with follicular-patterned tumors, especially FTCs, and is thought to promote tumorigenesis by dysregulating PAX8 transcriptional targets while promoting PPARG.[1, 2] On the other hand, *THADA* fusions are primarily found in benign adenomas and low-risk neoplasms (NIFTP, follicular subtype of PTC), suggesting a role in early tumorigenesis through activation of PI3K/AKT signaling.[55, 56] Similarly, *PTEN* mutations and deletions are seen in

Table 2
FDA-approved targeted therapies for advanced thyroid carcinomas.

Drug(s)	Molecular/ Protein Target (s)	Tumor Type(s)	Indication
Lenvatinib	VEGFR1–3, FGFR1–4, PDGFRα, RET, KIT	Radioactive iodine–refractory differentiated thyroid carcinoma (DTC: papillary, follicular, oncocytic, poorly differentiated)	First-line systemic therapy for progressive, unresectable, or metastatic RAI-refractory DTC[88]
Sorafenib	VEGFR1–3, RET, RAF, PDGFRβ, KIT	RAI-refractory DTC	Alternative MKI for progressive metastatic disease[89]
Cabozantinib	RET, VEGFR2, MET, AXL, KIT	RAI-refractory DTC (second-line) and progressive/ metastatic medullary thyroid carcinoma (MTC)	Approved for progressive metastatic MTC (regardless of RET status) and for RAI-refractory DTC post-VEGFR-targeted therapy[90]
Selpercatinib	RET kinase	RET fusion-positive DTC (including papillary, poorly differentiated, and anaplastic thyroid carcinoma)	Highly selective RET inhibitor; activity in advanced, progressive, or metastatic disease[91]
Pralsetinib	RET kinase	RET fusion–positive DTC	Alternative selective RET inhibitor[92, 93]
Dabrafenib + Trametinib	BRAF p.V600E (dabrafenib: BRAF inhibitor; trametinib: MEK inhibitor)	BRAF p. V600E–mutated anaplastic thyroid carcinoma (ATC)	Combination approved for unresectable or metastatic ATC harboring BRAF V600E mutation[94]
Larotrectinib	NTRK1–3 fusion	NTRK fusion–positive thyroid carcinomas (all histologic subtypes)	Tumor-agnostic approval for advanced/ metastatic NTRK fusion-positive cancers[95, 96]
Entrectinib	NTRK1–3 fusion, ROS1	NTRK fusion–positive thyroid carcinomas (all histologies)	Tumor-agnostic approval for advanced/ metastatic disease[97]
Pembrolizumab	PD-1 immune checkpoint	Tumor-agnostic: MSI-high or TMB-high (>10 mut/Mb) thyroid carcinomas; PDL1+ ATC (off-label use common)	Rarely used in DTC; most effective in ATC with PDL1 ≥1% or MSI-high tumors[98]

follicular-patterned tumors with variable behavior; these tumors often show PI3K/AKT/mTOR pathway activation rather than MAPK-driven signaling.[57] *EZH1* mutations are also associated with follicular-patterned tumors, possibly promoting epigenetic silencing and differentiation arrest.[58] Sporadic or germline *DICER1* mutations, which can be seen in multinodular disease, follicular adenomas, and follicular carcinomas, result in impaired miRNA processing and may contribute to tumor development via widespread dysregulation of gene expression.[59–61] It has been reported that DICER1 mutant thyroid tumors are often seen in younger patients and are most frequently characterized by a macrofollicular architecture with prominent atrophic changes, though focal papillary growth has also been observed.[62] Furthermore, thyroblastoma, a recently defined embryonal high-grade thyroid neoplasm, is characterized by biallelic *DICER1* mutations and exhibits a triphasic histology of primitive thyroid-like follicular cells, small round blue cells, and mesenchymal stroma, consistent with origin from early thyroid progenitors.[63, 64] Other alterations such as *SPOP, SOS1,* and *IDH1* mutations are rare but underscore the molecular heterogeneity within this category of thyroid tumors.[65]

Cribriform morular thyroid carcinoma (CMTC) is a rare but distinctive tumor that is not part of the *BRAF* V600E-like or *RAS*-like molecular groups. These tumors are strongly associated with germline *APC* mutations in the context of familial adenomatous polyposis (FAP), but they can also occur sporadically through somatic *CTNNB1* mutations.[66] Both alterations lead to constitutive activation of the Wnt/β-catenin signaling pathway, which is central to CMTC tumorigenesis, and results in nuclear and cytoplasmic β-catenin immunoreactivity.[66] Morphologically, these tumors display a characteristic mixture of cribriform, trabecular, and solid architecture with squamoid morules (Figs. 4**A/4B**). Although generally indolent, recognition of CMTC is important due to its genetic implications for FAP and its unique molecular profile.

Hyalinizing trabecular tumor (HTT) is another rare but distinct follicular cell–derived neoplasm in this category with recurrent *PAX8*::*GLIS1* and *PAX8*::*GLIS3* fusions.[67, 68] HTTs are a low-risk neoplasm and tend to be well-circumscribed and composed of elongated tumor cells in a trabecular growth pattern, admixed with hyaline material. Interestingly, nuclear grooves and frequent intranuclear pseudoinclusions are present, which may mimic PTC at first glance.[69]

A rare but emerging entity in this category is *NUTM1*-rearranged thyroid carcinoma, defined by gene fusions involving the *NUTM1* gene, most often with *NSD3* or other bromodomain family members as the fusion partner.[70, 71] These tumors are highly aggressive, poorly differentiated, and typically arise in younger patients without prior thyroid disease. Histologically, they often exhibit solid or nested growth with regions showing abrupt squamoid differentiation and pockets of intratumoral neutrophils (Figs. 4**C/4D**). Molecularly, these tumors show epigenetic dysregulation through the fusion of *NUTM1* to chromatin modifiers, leading to global transcriptional reprogramming and growth arrest blockade.[72, 73] While *NUTM1*-rearranged carcinomas have been more commonly described in the mediastinum and head and neck, a small number of confirmed thyroid primaries have now been reported.[70, 71] These tumors are rapidly progressive and generally unresponsive to standard therapies.

High-Grade follicular cell-derived tumors and anaplastic thyroid carcinoma

High-grade follicular cell-derived carcinomas are tumors with aggressive behavior and a prognosis that falls between well-differentiated thyroid carcinomas and anaplastic thyroid carcinoma (ATC). This category includes high-grade differentiated thyroid carcinomas (HGDTC) and poorly differentiated thyroid carcinoma (PDTC). These tumors retain some architectural or cytologic features of follicular origin but are unified by high-grade features such as tumor necrosis and/or increased mitotic activity (Figs. 5**A-5D**).

HGDTCs are defined as tumors that maintain either papillary, follicular, or oncocytic morphology but with at least one of the following: ≥5 mitoses per 2 mm^2 or coagulative tumor necrosis. Despite the differentiated morphology, HGDTCs show higher rates of extrathyroidal extension, metastasis, and disease-specific mortality than their well-differentiated counterparts. They retain their signatures, which are typically *BRAF* V600E-like in PTCs, *RAS*-like in FTCs, or mitochondrial/copy number abnormalities in OCAs.[14, 74, 75] Furthermore, secondary alterations in the *TERT* promoter and *TP53* mutations begin to emerge.[76, 77] Additional changes, such as chromosome 1q gain, support a stepwise progression.[78]

In contrast, PDTC is defined by the Turin criteria: a solid/trabecular/insular growth pattern, absence of papillary carcinoma nuclear features, and at least one high-grade feature (≥3 mitoses per 2 mm^2, necrosis, or convoluted nuclei).[79] PDTCs are often widely invasive with frequent angioinvasion and extrathyroidal extension, due to the fact that *RAS*-like

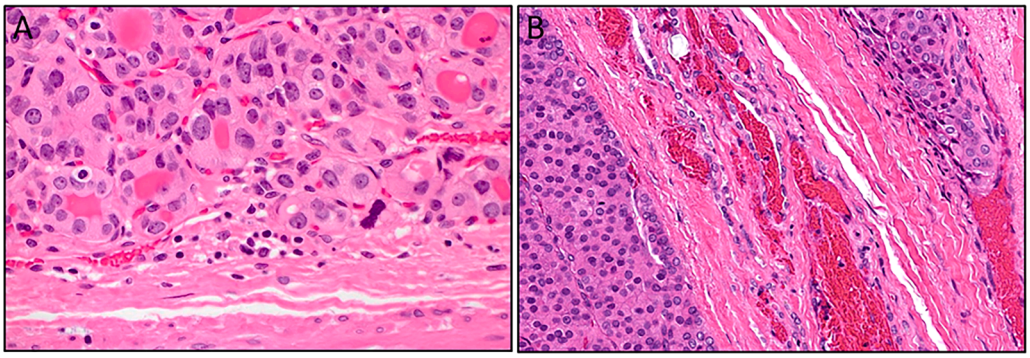

Fig. 3. Oncocytic neoplasms. A) Oncocytic adenoma with the characteristic dense granular eosinophilic cytoplasm, follicular arrangement, and intact capsule (H&E stain, 40x). B) Oncocytic carcinoma with the characteristic oncocytic cytoplasm, solid architecture, and vascular invasion (H&E stain, 20x).

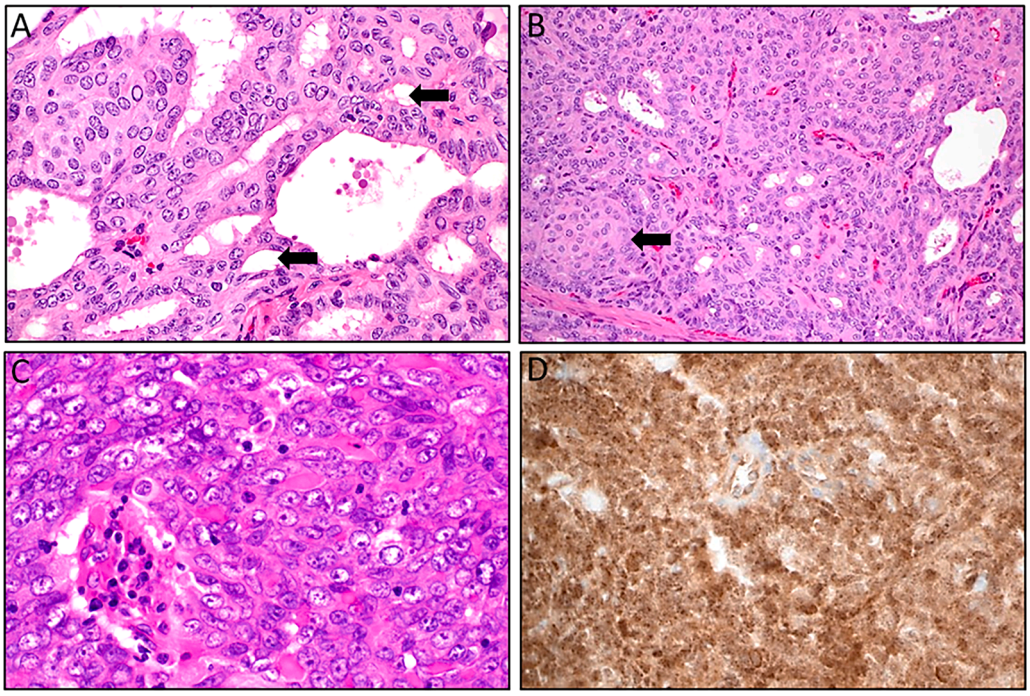

Fig. 4. Rare thyroid carcinomas. A) Cribriform morular thyroid carcinoma showing a cribriform growth pattern (black arrows). B) Same case showing squamoid morules (black arrow) lacking keratinization. This patient was from a family with a history of familial adenomatous polyposis (H&E stain, 20x). C) NUT carcinoma displaying sheets of malignant cells with focal colloid production and enlarged nuclei with open chromatin, prominent nucleoli. A focus of a neutrophilic abscess is present (H&E stain, 40x). D) NUT immunohistochemical stain showing strong, diffuse, speckled nuclear positivity (NUT stain, 40x).

signatures are more common in these tumors than *BRAF* V600E-like signatures.[75] However, PDTCs can arise from PTC which do show *BRAF* V600E-like features. Compared to their well-differentiated counterparts, these tumors are enriched for *TERT* promoter and *TP53* mutations, though not as frequently as ATC.

ATC is the most aggressive form of follicular cell-derived thyroid carcinomas with a median overall survival of 6 months, even with the advent of targeted therapies and immune checkpoint inhibitors.[80,81] Tumor cells are undifferentiated and are negative for thyroglobulin, though, half retain expression of PAX8, which can help confirm a primary thyroid origin in the absence of a differentiated component.[82] Histologically, as shown in Figs. 5**E**-5**H**, tumors may be pleomorphic, spindled/sarcomatoid, or show squamous features and typically show significant extrathyroidal extension, which can cause life-threatening airway compression. Necrosis, high mitotic activity, and atypical mitoses are frequent. ATC typically evolves from well-differentiated or PDTC precursors and accumulate additional mutations, including *TERT* promoter, *TP53*, PIK3CA, PTEN, CDKN2A/B loss, and SWI/SNF mutations (e.g., ARID1A, SMARCB1).[83] These tumors have high chromosomal instability and high tumor mutational burdens, with variable PD-L1 expression.[84, 85]

ATC is unresponsive to radioactive iodine and TSH suppression. Management includes surgery (if feasible), radiation, and systemic therapy. Molecular profiling has transformed treatment, with targeted therapies showing benefit in subsets: BRAF/MEK inhibitors for *BRAF*-mutant tumors, RET/NTRK inhibitors for fusion-positive cases, and checkpoint inhibitors for those with PD-L1 expression or mismatch repair deficiency (see Table 2 for additional details). However, the overall prognosis remains poor for most patients, emphasizing the need for early diagnosis and aggressive management.

Integrating molecular findings into clinical practice

The application of molecular testing in thyroid diagnostics is most impactful in the preoperative evaluation of indeterminate FNA samples (Bethesda III and IV), where cytology alone cannot reliably distinguish

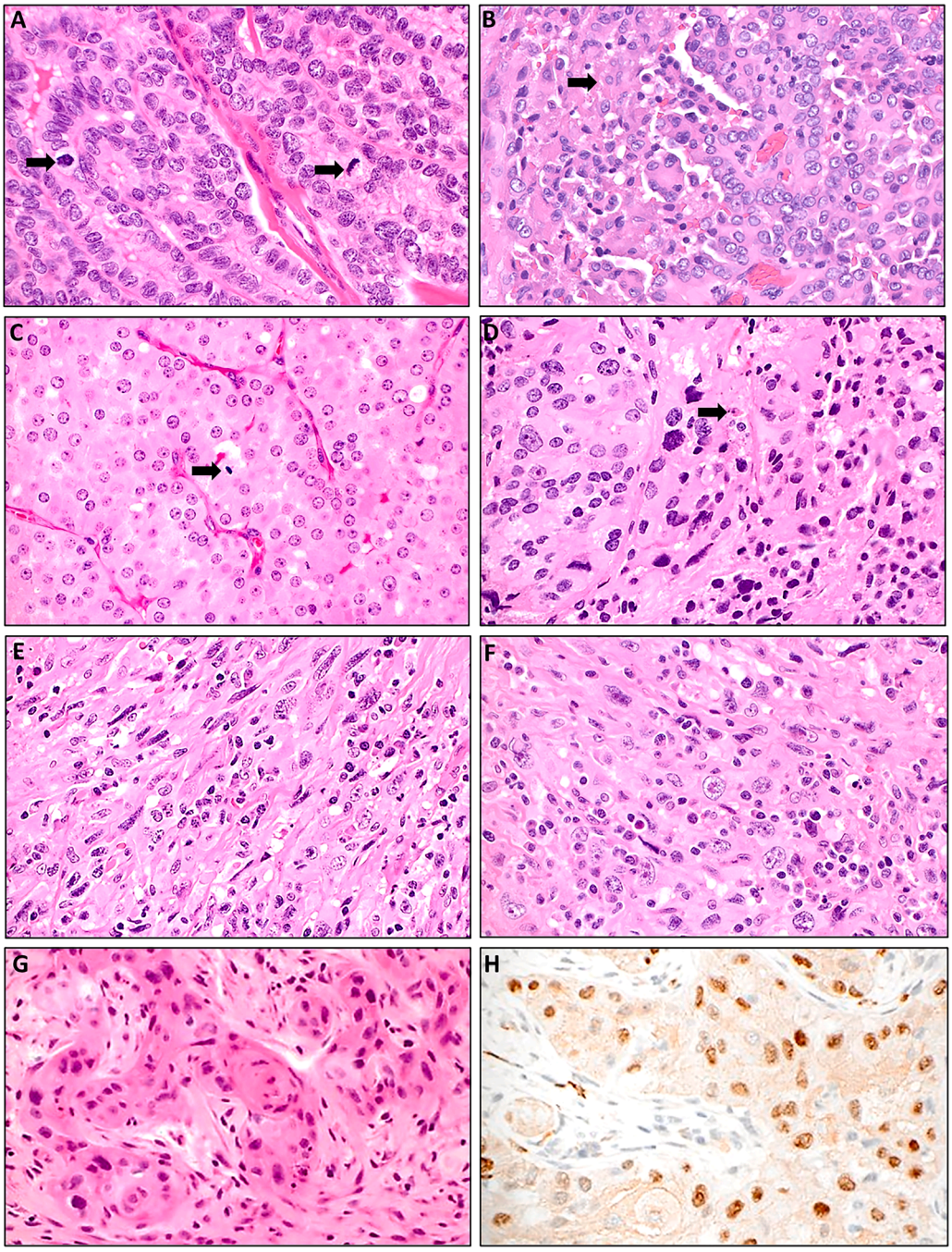

Fig. 5. Aggressive thyroid carcinomas. A) High-grade differentiated papillary thryoid carcinoma with follicular architecture, PTC-like nuclear features, and mitotic activity (black arrows) (H&E stain, 40x). B) High-grade differentiated PTC showing a papillary growth pattern, conventional nuclear features, and necrosis (black arrow) (H&E stain, 40x). C) High-grade differentiated oncocytic carcinoma displaying oncocytic cytoplasm and mitotic activity (black arrow) (H&E stain, 40x). D) Poorly differentiated thyroid carcinoma with solid growth, lack of PTC nuclear features, convoluted nuclear contours, and apoptotic bodies (black arrow) and necrosis (H&E stain, 40x). E, F) Anaplastic thyroid carcinoma with sarcomatoid features (H&E stain, 40x). G) Anaplastic thyroid carcinoma with squamous features (H&E stain, 40x). H) Anaplastic thyroid carcinoma with squamous features from the previous panel showing retained nuclear PAX8 immunohistochemical staining (PAX8 stain, 40x).

benign from malignant follicular and oncocytic lesions. Commercially available molecular panels (e.g., ThyroSeq, Afirma, ThyGeNEXT/ThyraMIR) now combine DNA and RNA mutational testing with microRNA classifiers to refine malignancy risk.[86] Detection of *BRAF* V600E or *BRAF* V600E-like signature or *RET* or *NTRK* fusions virtually establishes a diagnosis of malignancy. Conversely, the detection of a *RAS* mutation or *RAS*-like signature supports more conservative management with a lobectomy. Absence of these alterations is consistent with a low malignancy risk and, when it correlates with clinical and radiologic parameters, often resulting in clinical follow-up.

Beyond the indeterminate nodule, molecular data also inform surgical extent and postoperative risk stratification. For example, identifying high-risk mutations (e.g., *TERT* promoter or *TP53* mutations) in a differentiated carcinoma can justify a more extensive initial resection and closer postoperative surveillance. In advanced or metastatic disease, molecular profiling is essential for identifying actionable alterations that define eligibility for FDA-approved targeted therapies (e.g., selective RET inhibitors for *RET*-altered tumors, BRAF and MEK inhibitors for

BRAF p.V600E–mutated anaplastic thyroid carcinoma) (Table 2). Furthermore, molecular testing on pediatric tumors may be helpful to rule out or raise the possibility of a germline predisposition syndrome.

When confronted with a rare or unfamiliar molecular alteration, clinicians should confirm the finding and use curated genomic resources such as cBioPortal, ClinVar, or OncoKB, as well as multidisciplinary molecular tumor boards, to determine its significance.[87] This structured approach ensures that molecular findings are not interpreted in isolation but integrated into the broader clinical, radiologic, and pathologic context, ultimately improving diagnostic accuracy, therapeutic decision-making, and patient outcomes.

Conclusion

In summary, the molecular characterization of follicular cell-derived thyroid neoplasms has revealed several molecular phenotypes that correlate with distinct histologic patterns, biological behavior, and therapeutic vulnerabilities. Most thyroid neoplasms fall within the two main categories: *RAS*-like or *BRAF* V600E-like depending on the degree in which they activate the MAPK pathway. *RAS*-like tumors have low level MAPK activation and typically display a follicular growth pattern and, when malignant, spread hematogenously. Conversely, *BRAF* V600E-like tumors show strong MAPK activation, are typically PTCs, and tend to spread to lymph nodes. Between these lie RTK fusion-driven tumors (e.g., *NTRK, ALK, RET, FGFR2*), which exhibit intermediate MAPK pathway activation and are enriched in pediatric and radiation-associated papillary thyroid carcinomas. Oncocytic tumors form a separate category driven by mitochondrial mutations and chromosomal copy number alterations rather than MAPK signaling activation. Finally, a smaller group of non-BRAF/non-RAS/non-oncocytic tumors show diverse mechanisms of neoplasia and do not neatly fit into one of the aforementioned phenotypes. Alterations include transcriptional dysregulation (PAX8 fusions), Wnt/β-catenin signaling (*APC/ CTNNB1*, cribriform morular carcinoma), epigenetic alteration (EZH1, SPOP), impaired miRNA processing (*DICER1*-mutant follicular lesions and thyroblastoma), and rare structural variants (*NUTM1*-rearranged thyroid carcinoma). Finally, high-grade differentiated and poorly differentiated thyroid carcinomas retain molecular features of their differentiated precursor but acquire mutations in *TERT* promoter, *TP53*, and chromatin remodeling genes that can drive dedifferentiation, while ATC represents the culmination of these events with widespread genomic instability and loss of lineage fidelity. This expanding molecular taxonomy has not only refined diagnostic classification but has also enabled risk stratification, informed prognostication, and opened the door to targeted therapies in both early and advanced thyroid cancer management.

CRediT authorship contribution statement

Lauren Stark: Writing – review & editing, Writing – original draft, Visualization. **Julie C. Dueber:** Writing – review & editing, Visualization, Supervision, Conceptualization. **Derek B. Allison:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors of this manuscript have no conflicts of interest or financial disclosures to report.

References

1. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014;159(3):676–690. https://doi.org/10.1016/j.cell.2014.09.050.
2. Yoo SK, Lee S, Kim SJ, et al. Comprehensive analysis of the transcriptional and mutational landscape of follicular and papillary thyroid cancers. *PLoS Genet*. 2016;12(8), e1006239. https://doi.org/10.1371/journal.pgen.1006239.
3. Tang AL, Kloos RT, Aunins B, et al. Pathologic features associated with molecular subtypes of well-differentiated thyroid cancer. *Endocr Pract*. 2021;27(3):206–211. https://doi.org/10.1016/j.eprac.2020.09.003.
4. Morand GB, Tessler I, Thurnheer SE, et al. Molecular alteration patterns predict tumor behavior in papillary thyroid carcinoma independent of tumor size: insights from an international multicenter retrospective study. *Thyroid Res*. 2025;18(1):14. https://doi.org/10.1186/s13044-025-00231-0.
5. Chiosea S, Hodak SP, Yip L, et al. Molecular profiling of 50 734 Bethesda III-VI thyroid nodules by ThyroSeq v3: implications for personalized management. *J Clin Endocrinol Metab*. 2023;108(11):2999–3008. https://doi.org/10.1210/clinem/dgad220.
6. Steward DL, Carty SE, Sippel RS, et al. Performance of a multigene genomic classifier in thyroid nodules with indeterminate cytology: a prospective blinded multicenter study. *JAMA Oncol*. 2019;5(2):204–212. https://doi.org/10.1001/jamaoncol.2018.4616.
7. Landa I, Cabanillas ME. Genomic alterations in thyroid cancer: biological and clinical insights. *Nat Rev Endocrinol*. 2024;20(2):93–110. https://doi.org/10.1038/s41574-023-00920-6.
8. Mete O, Boucher A, Schrader KA, et al. Consensus Statement: recommendations on actionable biomarker testing for thyroid cancer management. *Endocr Pathol*. 2024;35(4):293–308. https://doi.org/10.1007/s12022-024-09836-x.
9. Mosele MF, Westphalen CB, Stenzinger A, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO precision medicine working group. *Ann Oncol*. 2024;35(7):588–606. https://doi.org/10.1016/j.annonc.2024.04.005.
10. Ma LX, Espin-Garcia O, Bedard PL, et al. Clinical application of next-generation sequencing in advanced thyroid cancers. *Thyroid*. 2022;32(6):657–666. https://doi.org/10.1089/thy.2021.0542.
11. Yang Z, Zhang T, Layfield L, Esebua M. Performance of Afirma gene sequencing classifier versus gene expression classifier in thyroid nodules with indeterminate cytology. *J Am Soc Cytopathol*. 2022;11(2):74–78. https://doi.org/10.1016/j.jasc.2021.07.002.
12. Tumati A, Egan CE, Lee-Saxton YJ, et al. Clinical utility of a microRNA classifier in cytologically indeterminate thyroid nodules with RAS mutations: a multi-institutional study. *Surgery*. 2024;175(1):234–240. https://doi.org/10.1016/j.surg.2023.07.042.
13. Ganly I, Makarov V, Deraje S, et al. Integrated genomic analysis of hürthle cell cancer reveals oncogenic drivers, recurrent mitochondrial mutations, and unique chromosomal landscapes. *Cancer Cell*. 2018;34(2), e5. https://doi.org/10.1016/j.ccell.2018.07.002.
14. Xu B, David J, Dogan S, et al. Primary high-grade non-anaplastic thyroid carcinoma: a retrospective study of 364 cases. *Histopathology*. 2022;80(2):322–337. https://doi.org/10.1111/his.14550.
15. Xu B, Ghossein R. Genomic landscape of poorly differentiated and anaplastic thyroid carcinoma. *Endocr Pathol*. 2016;27(3):205–212. https://doi.org/10.1007/s12022-016-9445-4.
16. Pozdeyev N, Gay LM, Sokol ES, et al. Genetic analysis of 779 advanced differentiated and anaplastic thyroid cancers. *Clinical Cancer Res*. 2018;24(13):3059–3068. https://doi.org/10.1158/1078-0432.Ccr-18-0373.
17. Romei C, Ciampi R, Elisei R. A comprehensive overview of the role of the RET proto-oncogene in thyroid carcinoma. *Nat Rev Endocrinol*. 2016;12(4):192–202. https://doi.org/10.1038/nrendo.2016.11.
18. Ciampi R, Romei C, Ramone T, et al. Genetic landscape of somatic mutations in a large cohort of sporadic medullary thyroid carcinomas studied by next-generation targeted sequencing. *IScience*. 2019;20:324–336. https://doi.org/10.1016/j.isci.2019.09.030.
19. Alzumaili B, Sadow PM. Update on molecular diagnostics in thyroid pathology: a review. *Genes (Basel)*. 2023;14(7). https://doi.org/10.3390/genes14071314.
20. Odate T, Oishi N, Vuong HG, Mochizuki K, Kondo T. Genetic differences in follicular thyroid carcinoma between Asian and western countries: a systematic review. *Gland Surg*. 2020;9(5):1813–1826. https://doi.org/10.21037/gs-20-356.
21. Jeong SH, Hong HS, Kwak JJ, Lee EH. Analysis of RAS mutation and PAX8/pparγ rearrangements in follicular-derived thyroid neoplasms in a Korean population: frequency and ultrasound findings. *J Endocrinol Invest*. 2015;38(8):849–857. https://doi.org/10.1007/s40618-015-0311-x.
22. Xu B, Ghossein RA. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): an update. *Head Neck Pathol*. 2020;14(2):303–310. https://doi.org/10.1007/s12105-019-01124-z.
23. Nicolson NG, Murtha TD, Dong W, et al. Comprehensive genetic analysis of follicular thyroid carcinoma predicts prognosis independent of histology. *J Clin Endocrinol Metab*. 2018;103(7):2640–2650. https://doi.org/10.1210/jc.2018-00277.
24. Hou P, Liu D, Shan Y, et al. Genetic alterations and their relationship in the phosphatidylinositol 3-kinase/akt pathway in thyroid cancer. *Clin Cancer Res*. 2007;13(4):1161–1170. https://doi.org/10.1158/1078-0432.Ccr-06-1125.
25. Webster A, Elshazli RM, Pinion D, et al. The prevalence and prognostic implications of BRAF K601E mutations in thyroid neoplasms: a systematic review and meta-analysis. *Head Neck*. 2024;46(12):3133–3145. https://doi.org/10.1002/hed.27950.
26. Pereira M, Williams VL, Hallanger Johnson J, Valderrabano P. Thyroid cancer incidence trends in the United States: association with changes in professional guideline recommendations. *Thyroid*. 2020;30(8):1132–1140. https://doi.org/10.1089/thy.2019.0415.
27. Riccio I, Laforteza A, Landau MB, et al. Decoding RAS mutations in thyroid cancer: a meta-analysis unveils specific links to distant metastasis and increased mortality. *Am J Otolaryngol*. 2025;46(1), 104570. https://doi.org/10.1016/j.amjoto.2024.104570.

28. Rashid FA, Munkhdelger J, Fukuoka J, Bychkov A. Prevalence of BRAF(V600E) mutation in Asian series of papillary thyroid carcinoma-a contemporary systematic review. *Gland Surg*. 2020;9(5):1878–1900. https://doi.org/10.21037/gs-20-430.
29. Soares P, Póvoa AA, Melo M, et al. Molecular pathology of non-familial follicular epithelial-derived thyroid cancer in adults: from RAS/BRAF-like tumor designations to Molecular risk stratification. *Endocr Pathol*. 2021;32(1):44–62. https://doi.org/10.1007/s12022-021-09666-1.
30. Wang X, Cheng W, Liu C, Li J. Tall cell variant of papillary thyroid carcinoma: current evidence on clinicopathologic features and molecular biology. *Oncotarget*. 2016;7(26):40792–40799. https://doi.org/10.18632/oncotarget.8215.
31. Lubitz CC, Economopoulos KP, Pawlak AC, et al. Hobnail variant of papillary thyroid carcinoma: an institutional case series and molecular profile. *Thyroid*. 2014;24(6):958–965. https://doi.org/10.1089/thy.2013.0573.
32. Janovitz T, Williamson DFK, Wong KS, Dong F, Barletta JA. Genomic profile of columnar cell variant of papillary thyroid carcinoma. *Histopathology*. 2021;79(4):491–498. https://doi.org/10.1111/his.14374.
33. Chou A, Qiu MR, Crayton H, et al. A detailed histologic and molecular assessment of the diffuse sclerosing variant of papillary thyroid carcinoma. *Mod Pathol*. 2023;36(12), 100329. https://doi.org/10.1016/j.modpat.2023.100329.
34. Chen P, Yao Y, Tan H, Li J. Systemic treatments for radioiodine-refractory thyroid cancers. *Front Endocrinol (Lausanne)*. 2024;15, 1346476. https://doi.org/10.3389/fendo.2024.1346476.
35. Boucai L, Zafereo M, Cabanillas ME. Thyroid Cancer: a review. *Jama*. 2024;331(5):425–435. https://doi.org/10.1001/jama.2023.26348.
36. Gopal RK, Kübler K, Calvo SE, et al. Widespread chromosomal losses and mitochondrial DNA alterations as genetic drivers in hürthle cell carcinoma. *Cancer Cell*. 2018;34(2), e5. https://doi.org/10.1016/j.ccell.2018.06.013.
37. Wu HH, Clouse J, Ren R. Fine-needle aspiration cytology of hürthle cell carcinoma of the thyroid. *Diagn Cytopathol*. 2008;36(3):149–154. https://doi.org/10.1002/dc.20750.
38. Luo Y, Jiang H, Xu W, et al. Clinical, pathological, and molecular characteristics correlating to the occurrence of radioiodine refractory differentiated thyroid carcinoma: a systematic review and meta-analysis. *Front Oncol*. 2020;10, 549882. https://doi.org/10.3389/fonc.2020.549882.
39. Bai S, Baloch ZW, Samulski TD, Montone KT, LiVolsi VA. Poorly differentiated oncocytic (hürthle cell) follicular carcinoma: an institutional experience. *Endocr Pathol*. 2015;26(2):164–169. https://doi.org/10.1007/s12022-015-9367-6.
40. Bishop JA, Wu G, Tufano RP, Westra WH. Histological patterns of locoregional recurrence in hürthle cell carcinoma of the thyroid gland. *Thyroid*. 2012;22(7):690–694. https://doi.org/10.1089/thy.2011.0407.
41. Ibrahimpasic T, Ghossein R, Carlson DL, et al. Outcomes in patients with poorly differentiated thyroid carcinoma. *J Clin Endocrinol Metab*. 2014;99(4):1245–1252. https://doi.org/10.1210/jc.2013-3842.
42. Metovic J, Vignale C, Annaratone L, et al. The oncocytic variant of poorly differentiated thyroid carcinoma shows a specific immune-related gene expression profile. *J Clin Endocrinol Metab*. 2020;105(12). https://doi.org/10.1210/clinem/dgaa655.
43. Wong KS, Angell TE, Barletta JA, Krane JF. Hürthle cell lesions of the thyroid: progress made and challenges remaining. *Cancer Cytopathol*. 2021;129(5):347–362. https://doi.org/10.1002/cncy.22375.
44. Gasparre G, Porcelli AM, Bonora E, et al. Disruptive mitochondrial DNA mutations in complex I subunits are markers of oncocytic phenotype in thyroid tumors. *Proc Natl Acad Sci U S A*. 2007;104(21):9001–9006. https://doi.org/10.1073/pnas.0703056104.
45. Mazzucchelli L, Burckhardt E, Hirsiger H, Kappeler A, Laissue JA. Interphase cytogenetics in oncocytic adenomas and carcinomas of the thyroid gland. *Hum Pathol*. 2000;31(7):854–859. https://doi.org/10.1053/hupa.2000.8444.
46. Corver WE, Ruano D, Weijers K, et al. Genome haploidisation with chromosome 7 retention in oncocytic follicular thyroid carcinoma. *PLoS One*. 2012;7(6), e38287. https://doi.org/10.1371/journal.pone.0038287.
47. Erickson LA, Jalal SM, Goellner JR, et al. Analysis of hurthle cell neoplasms of the thyroid by interphase fluorescence in situ hybridization. *Am J Surg Pathol*. 2001;25(7):911–917. https://doi.org/10.1097/00000478-200107000-00009.
48. Hassan FA, Slone C, McDonald RJ, et al. Folliculin (FLCN) in thyroid tumors: incidence, significance, and role as a driver gene and secondary alteration. *Curr Oncol*. 2025;32(4). https://doi.org/10.3390/curroncol32040224.
49. Benusiglio PR, Gad S, Massard C, et al. Case Report: expanding the tumour spectrum associated with the Birt-Hogg-Dubé cancer susceptibility syndrome. *F1000Res*. 2014;3:159. https://doi.org/10.12688/f1000research.4205.1.
50. Bongetti EK, Raj R, Cooke DR, Mathew MC. Metastatic follicular thyroid cancer in a patient with Birt-Hogg-Dubé syndrome. *Clin Case Rep*. 2021;9(1):102–104. https://doi.org/10.1002/ccr3.3454.
51. Dong L, Gao M, Hao WJ, et al. Case report of Birt-Hogg-Dubé Syndrome: germline mutations of FLCN detected in patients with renal cancer and thyroid cancer. *Medicine*. 2016;95(22), e3695. https://doi.org/10.1097/md.0000000000003695.
52. Ashraf AM, Hassan F, Dawkins AA, Dueber JC, Allison DB, Bocklage TJ. Oncocytic thyroid tumours with pathogenic FLCN mutations mimic oncocytic papillary thyroid carcinoma on fine-needle aspiration. *Cytopathology*. 2025. https://doi.org/10.1111/cyt.70019.
53. Waguespack SG, Drilon A, Lin JJ, et al. Efficacy and safety of larotrectinib in patients with TRK fusion-positive thyroid carcinoma. *Eur J Endocrinol*. 29 2022;186(6):631–643. https://doi.org/10.1530/eje-21-1259.
54. Buriolla S, Zapelloni G, Cipri C, Pelizzari G, Follador A, Cortiula F. Alectinib for the treatment of papillary thyroid carcinoma harbouring STRN – ALKfusion. *Eur J Cancer*. 2025;216. https://doi.org/10.1016/j.ejca.2024.115193.
55. Morariu EM, McCoy KL, Chiosea SI, et al. Clinicopathologic characteristics of thyroid nodules positive for the THADA-IGF2BP3 fusion on preoperative molecular analysis. *Thyroid*. 2021;31(8):1212–1218. https://doi.org/10.1089/thy.2020.0589.
56. Panebianco F, Kelly LM, Liu P, et al. THADA fusion is a mechanism of IGF2BP3 activation and IGF1R signaling in thyroid cancer. *Proc Natl Acad Sci U S A*. 2017;114(9):2307–2312. https://doi.org/10.1073/pnas.1614265114.
57. Bandargal S, Rajab M, Forest VI, et al. Characteristics of PTEN mutation in thyroid tumours: a retrospective chart review. *Cancers (Basel)*. 2023;15(5). https://doi.org/10.3390/cancers15051575.
58. Jung CK, Kim Y, Jeon S, Jo K, Lee S, Bae JS. Clinical utility of EZH1 mutations in the diagnosis of follicular-patterned thyroid tumors. *Hum Pathol*. 2018;81:9–17. https://doi.org/10.1016/j.humpath.2018.04.018.
59. Jitpasutham T, Andrianus S, Gubbiotti M, et al. Thyroid nodules with DICER1 mutation or PTEN alteration: a comparative cytologic, clinical, and molecular study of 117 FNA cases. *Cancer Cytopathol*. 2024;132(6):370–385. https://doi.org/10.1002/cncy.22811.
60. Chong A-S, Nikiforov YE, Condello V, et al. Prevalence and spectrum of DICER1 mutations in adult-onset thyroid nodules with indeterminate cytology. *J Clinic Endocrinol Metabol*. 2021;106(4), e968–e977. https://doi.org/10.1210/clinem/dgab025.
61. Wang Y, Li G, Kong W, et al. DICER1 mutations in Bethesda category II, III, and IV thyroid nodules: a mutually exclusive relationship with BRAFV600E mutation. *Cancer Cytopathol*. 2025;133(8), e70029. https://doi.org/10.1002/cncy.70029.
62. Condello V, Roberts JW, Stenman A, Larsson C, Viswanathan K, Juhlin CC. Atrophic changes in thyroid tumors are strong indicators of underlying DICER1 mutations: a bi-institutional genotype-phenotype correlation study. *Virchows Arch*. 2024;485(1):105–114. https://doi.org/10.1007/s00428-024-03802-y.
63. Rooper LM. From malignant thyroid teratoma to thyroblastoma: evolution of a newly-recognized DICER1 -associated malignancy. *Adv Anat Pathol*. 2023;30(2):136–145. https://doi.org/10.1097/pap.0000000000000364.
64. Rooper LM, Bynum JP, Miller KP, et al. Recurrent DICER1 hotspot mutations in malignant thyroid gland teratomas: molecular characterization and proposal for a separate classification. *Am J Surg Pathol*. 2020;44(6):826–833. https://doi.org/10.1097/pas.0000000000001430.
65. Bim LV, Carneiro TNR, Buzatto VC, et al. Molecular signature expands the landscape of driver negative thyroid cancers. *Cancers (Basel)*. 2021;13(20). https://doi.org/10.3390/cancers13205184.
66. Cameselle-Teijeiro JM, Peteiro-González D, Caneiro-Gómez J, et al. Cribriform-morular variant of thyroid carcinoma: a neoplasm with distinctive phenotype associated with the activation of the WNT/β-catenin pathway. *Mod Pathol*. 2018;31(8):1168–1179. https://doi.org/10.1038/s41379-018-0070-2.
67. Nikiforova MN, Nikitski AV, Panebianco F, et al. GLIS rearrangement is a genomic hallmark of hyalinizing trabecular tumor of the thyroid gland. *Thyroid*. 2019;29(2):161–173. https://doi.org/10.1089/thy.2018.0791.
68. Marchiò C, Da Cruz Paula A, Gularte-Merida R, et al. PAX8-GLIS3 gene fusion is a pathognomonic genetic alteration of hyalinizing trabecular tumors of the thyroid. *Mod Pathol*. 2019;32(12):1734–1743. https://doi.org/10.1038/s41379-019-0313-x.
69. Nielsen L, Gallardo AMC, Alonso PP, et al. Diagnostic clues for hyalinizing trabecular tumor on fine needle aspiration cytology. *Cytojournal*. 2023;20:19. https://doi.org/10.25259/Cytojournal_34_2023.
70. Allison DB, Rueckert J, Cornea V, Lee CY, Dueber J, Bocklage T. Thyroid carcinoma with NSD3::NUTM1 fusion: a case with thyrocyte differentiation and colloid production. *Endocr Pathol*. 2022;33(2):315–326. https://doi.org/10.1007/s12022-021-09700-2.
71. Barletta JA, Gilday SD, Afkhami M, et al. NUTM1 -rearranged carcinoma of the thyroid: a distinct subset of NUT carcinoma characterized by frequent NSD3 -NUTM1 fusions. *Am J Surg Pathol*. 2022;46(12):1706–1715. https://doi.org/10.1097/pas.0000000000001967.
72. Alekseyenko AA, Walsh EM, Zee BM, et al. Ectopic protein interactions within BRD4-chromatin complexes drive oncogenic megadomain formation in NUT midline carcinoma. *Proc Natl Acad Sci U S A*. 2017;114(21), E4184–e4192. https://doi.org/10.1073/pnas.1702086114.
73. Alekseyenko AA, Walsh EM, Wang X, et al. The oncogenic BRD4-NUT chromatin regulator drives aberrant transcription within large topological domains. *Genes Dev*. 2015;29(14):1507–1523. https://doi.org/10.1101/gad.267583.115.
74. Landa I, Ganly I, Chan TA, et al. Frequent somatic TERT promoter mutations in thyroid cancer: higher prevalence in advanced forms of the disease. *J Clin Endocrinol Metab*. 2013;98(9), E1562–6. https://doi.org/10.1210/jc.2013-2383.
75. Landa I, Ibrahimpasic T, Boucai L, et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *J Clin Invest*. 2016;126(3):1052–1066. https://doi.org/10.1172/jci85271.
76. Liu X, Qu S, Liu R, et al. TERT promoter mutations and their association with BRAF V600E mutation and aggressive clinicopathological characteristics of thyroid cancer. *J Clin Endocrinol Metab*. 2014;99(6), E1130–6. https://doi.org/10.1210/jc.2013-4048.
77. Xu B, Ghossein R. Genomic landscape of poorly differentiated and anaplastic thyroid carcinoma. *Endocr Pathol*. 2016;27(3):205–212. https://doi.org/10.1007/s12022-016-9445-4.
78. Wong KS, Dong F, Telatar M, et al. Papillary thyroid carcinoma with high-grade features versus poorly differentiated thyroid carcinoma: an analysis of clinicopathologic and molecular features and outcome. *Thyroid*. 2021;31(6):933–940. https://doi.org/10.1089/thy.2020.0668.
79. Volante M, Collini P, Nikiforov YE, et al. Poorly differentiated thyroid carcinoma: the Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach. *Am J Surg Pathol*. 2007;31(8):1256–1264. https://doi.org/10.1097/PAS.0b013e3180309e6a.

80. Marchand-Crety C, Pascard M, Debreuve-Theresette A, et al. Prognostic factors and survival score for patients with anaplastic thyroid carcinoma: a retrospective study from a regional registry. *Anticancer Res*. 2021;41(3):1555–1561. https://doi.org/10.21873/anticanres.14915.
81. g.
82. Lai WA, Hang JF, Liu CY, et al. PAX8 expression in anaplastic thyroid carcinoma is less than those reported in early studies: a multi-institutional study of 182 cases using the monoclonal antibody MRQ-50. *Virchows Arch*. 2020;476(3):431–437. https://doi.org/10.1007/s00428-019-02708-4.
83. Volante M, Lam AK, Papotti M, Tallini G. Molecular pathology of poorly differentiated and anaplastic thyroid cancer: what do pathologists need to know? *Endocr Pathol*. 2021;32(1):63–76. https://doi.org/10.1007/s12022-021-09665-2.
84. Zeng PYF, Prokopec SD, Lai SY, et al. The genomic and evolutionary landscapes of anaplastic thyroid carcinoma. *Cell Rep*. 2024;43(3), 113826. https://doi.org/10.1016/j.celrep.2024.113826.
85. Chintakuntlawar AV, Rumilla KM, Smith CY, et al. Expression of PD-1 and PD-L1 in anaplastic thyroid cancer patients treated with multimodal therapy: results from a retrospective study. *J Clinic Endocrinol Metabol*. 2017;102(6):1943–1950. https://doi.org/10.1210/jc.2016-3756.
86. Piecoro DW, DB Allison. Precision medicine in cytopathology. *Surg Pathol Clin*. 2024;17(3):329–345. https://doi.org/10.1016/j.path.2024.04.002.
87. Miller RW, Hutchcraft ML, Weiss HL, et al. Molecular Tumor Board-assisted care in an advanced cancer population: results of a phase II clinical trial. *JCO Precis Oncol*. 2022;6, e2100524. https://doi.org/10.1200/po.21.00524.
88. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med*. 2015;372(7):621–630. https://doi.org/10.1056/NEJMoa1406470.
89. Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet*. 2014;384(9940):319–328. https://doi.org/10.1016/s0140-6736(14)60421-9.
90. Brose MS, Robinson B, Sherman SI, et al. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2021;22(8):1126–1138. https://doi.org/10.1016/S1470-2045(21)00332-6.
91. Wirth LJ, Brose MS, Subbiah V, et al. Durability of response with Selpercatinib in patients with RET-activated thyroid cancer: long-term safety and efficacy from LIBRETTO-001. *J Clin Oncol*. 2024;42(27):3187–3195. https://doi.org/10.1200/jco.23.02503.
92. Subbiah V, Hu MI, Wirth LJ, et al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. *Lancet Diab Endocrinol*. 2021;9(8):491–501. https://doi.org/10.1016/s2213-8587(21)00120-0.
93. Subbiah V, Hu MI, Mansfield AS, et al. Pralsetinib in patients with advanced/metastatic rearranged during transfection (RET)-altered thyroid cancer: updated efficacy and safety data from the ARROW study. *Thyroid*. 2024;34(1):26–40. https://doi.org/10.1089/thy.2023.0363.
94. Busaidy NL, Konda B, Wei L, et al. Dabrafenib versus Dabrafenib + Trametinib in BRAF-mutated radioactive iodine refractory differentiated thyroid cancer: results of a randomized, phase 2, open-label multicenter trial. *Thyroid*. 2022;32(10):1184–1192. https://doi.org/10.1089/thy.2022.0115.
95. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med*. 2018;378(8):731–739. https://doi.org/10.1056/NEJMoa1714448.
96. Marcus L, Donoghue M, Aungst S, et al. FDA approval summary: entrectinib for the treatment of NTRK gene fusion Solid tumors. *Clin Cancer Res*. 2021;27(4):928–932. https://doi.org/10.1158/1078-0432.Ccr-20-2771.
97. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21(2):271–282. https://doi.org/10.1016/s1470-2045(19)30691-6.
98. Xu L, Dong X, Deng T, Lu F, Chen W, Wu G. The efficacy and safety of Pembrolizumab in anaplastic thyroid carcinoma: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. 2025;103(3):281–289. https://doi.org/10.1111/cen.15291.