DISEASE STATE EDUCATION
THYROID CANCER

Disclaimer

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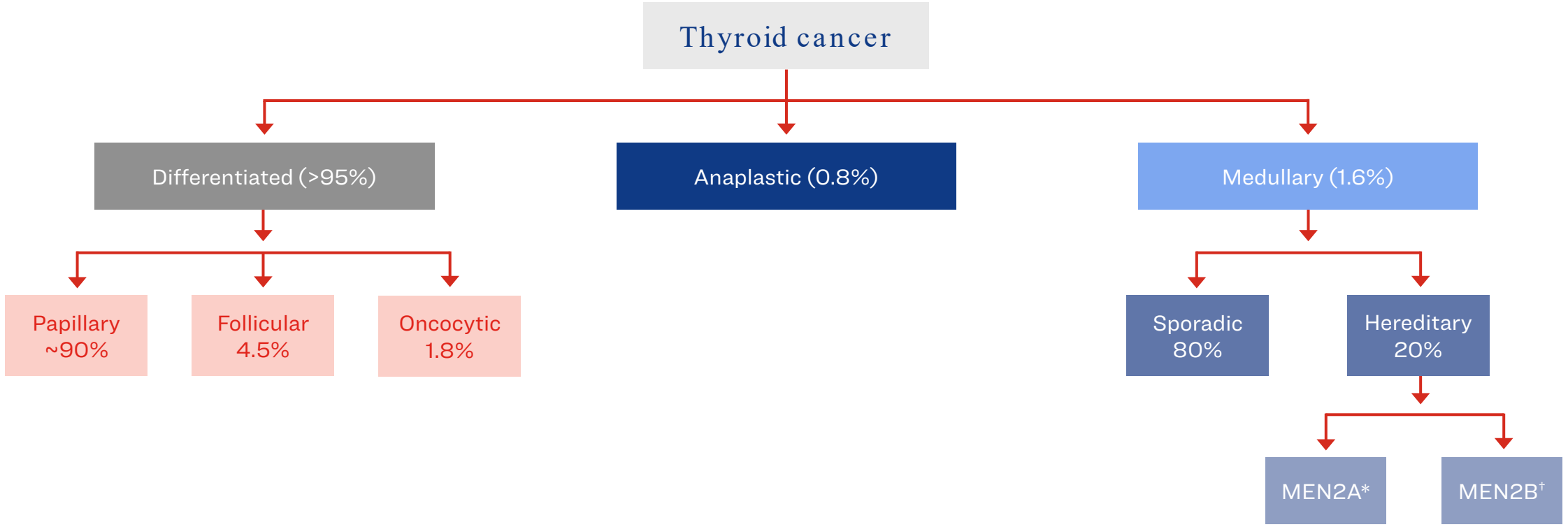
Thyroid Cancer Overview

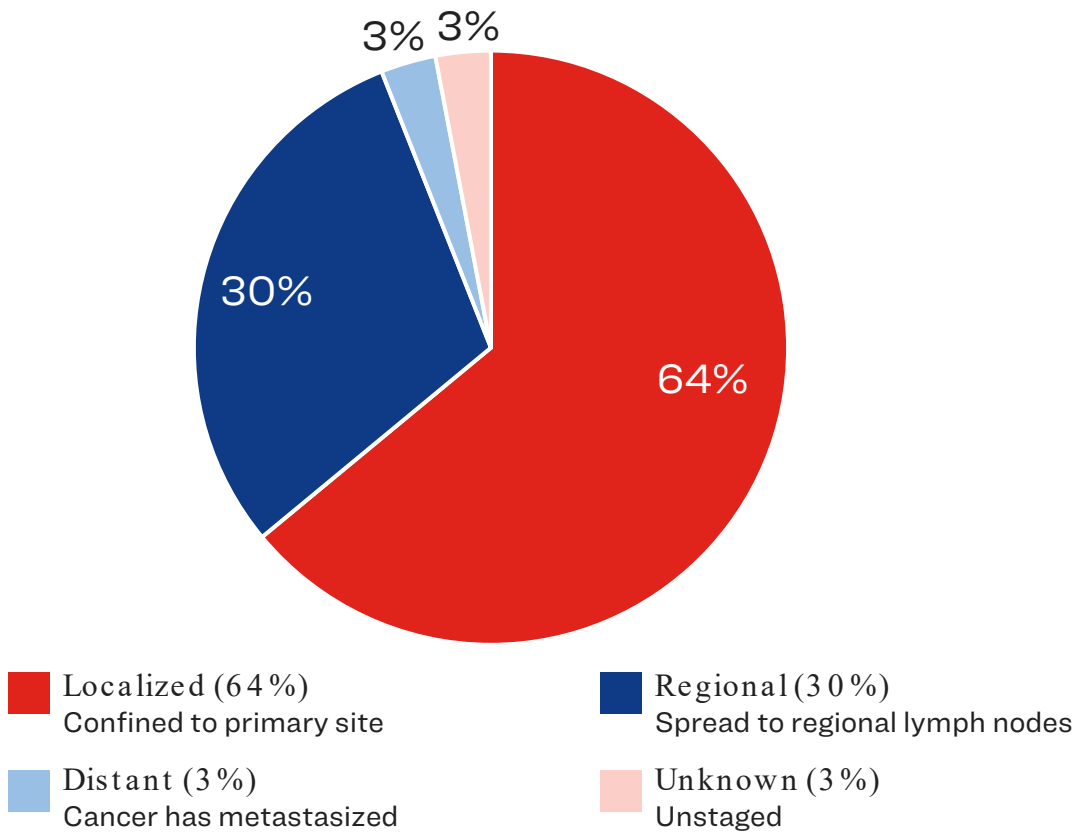
Thyroid Cancers Have Unique Histological Subtypes



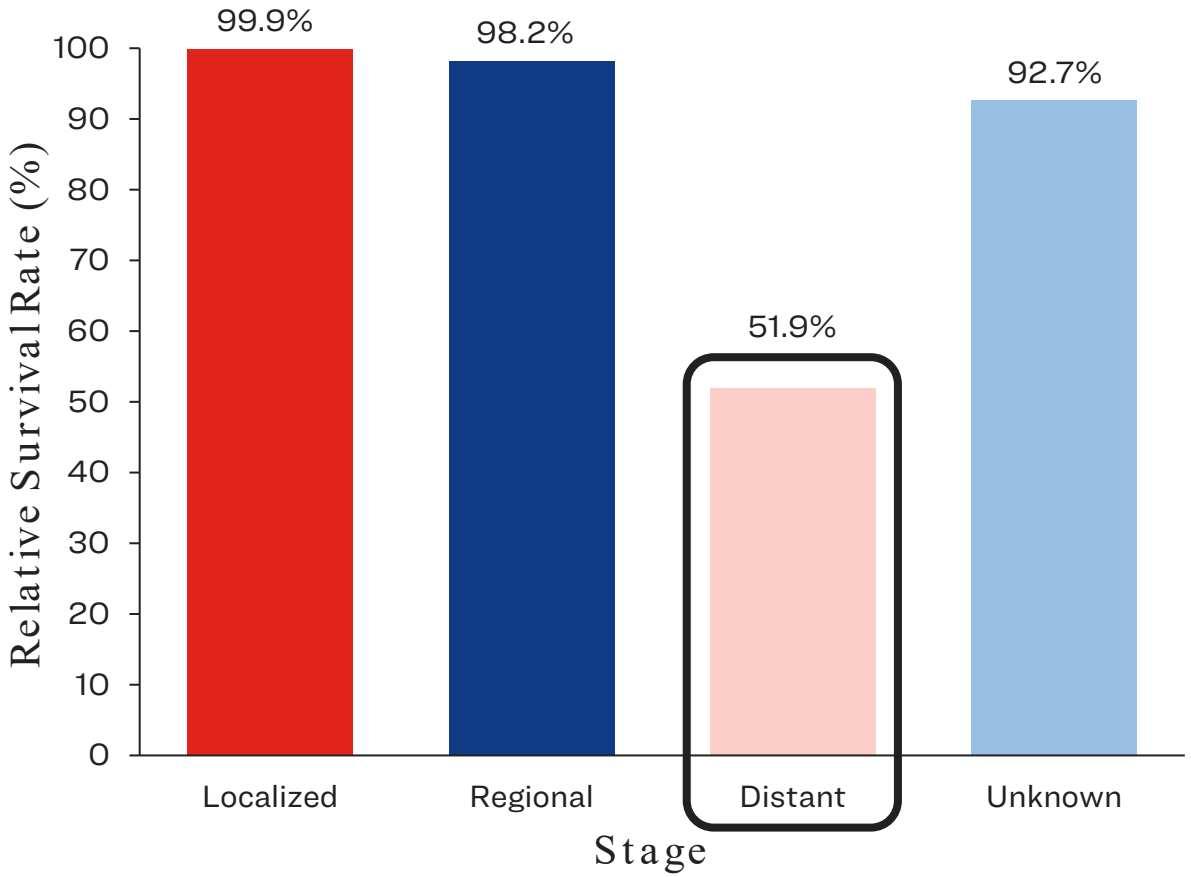
*Signs or symptoms of hyperparathyroidism or pheochromocytoma rarely present before those of MTC. †MEN2B is similar to MEN2A but is not associated with hyperparathyroidism and is more likely to have locally aggressive disease compared to MEN2A.
MEN = multiple endocrine neoplasia; MTC = medullary thyroid cancer/carcinoma.
https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf (Accessed January 3, 2024).

Early Detection of Thyroid Cancer Is Associated With Improved Patient Outcomes

Cases by Stage

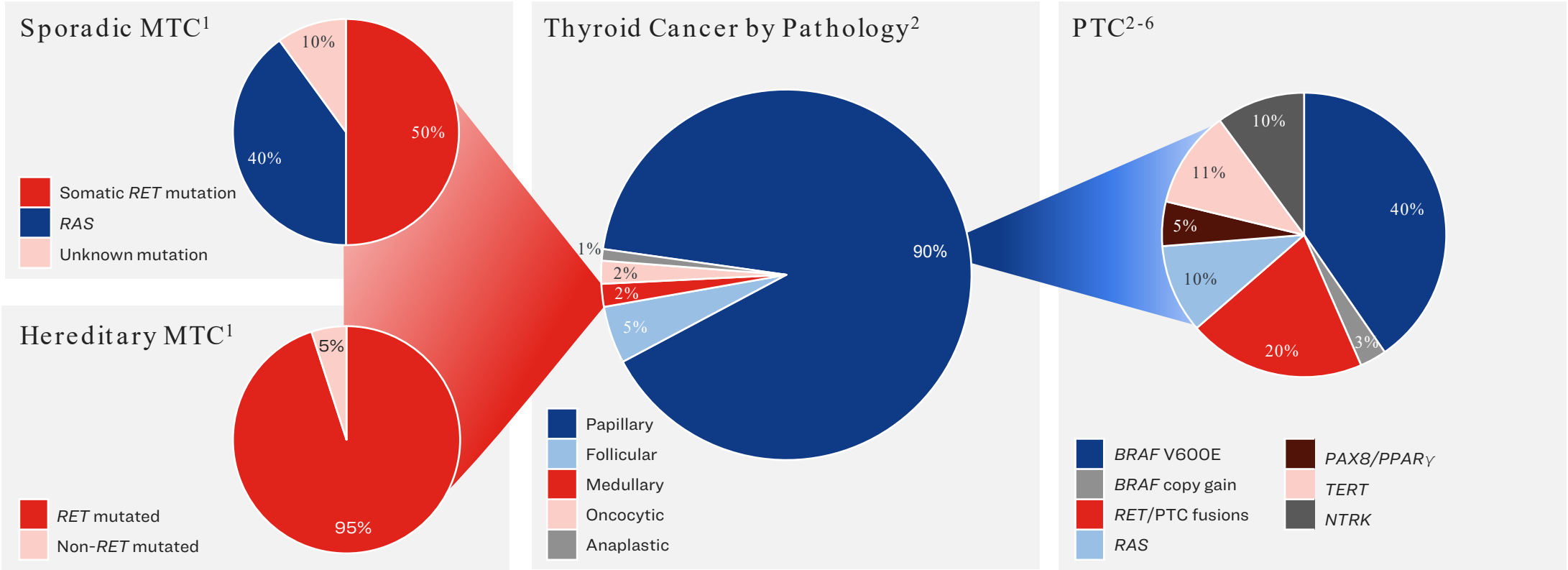


5-Year Relative Survival



https://seer.cancer.gov/statfacts/html/thyro.html (Accessed May 17, 2024).

Genomic Alterations in Advanced Thyroid Cancer

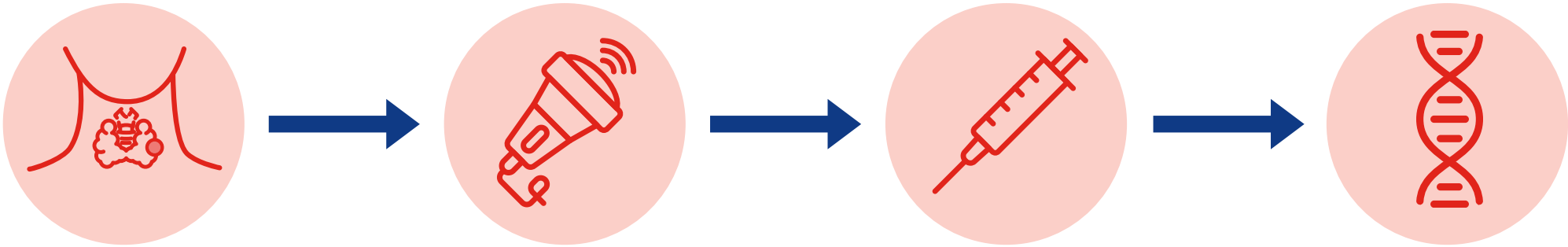


Percentages may not add up to 100% due to rounding and variance in reporting.
BRAF = v-raf murine sarcoma viral oncogene homolog B; NTRK = neurotrophic tyrosine receptor kinase; PAX8 = paired box 8; PPARγ = peroxisome proliferator-activated receptor gamma; PTC = papillary thyroid cancer/carcinoma; RAS = rat sarcoma; RET = rearranged during transfection; TERT = telomerase reverse transcriptase.

1. Hlozek J, et al. *Biomedicines*. 2022;10:1515. 2. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf (Accessed January 3, 2024). 3. Higgins MJ, Forastiere A, Marur S. *Oncology*. 2009;23(9):768-775. 4. Acquaviva G, et al. *Histopathology*. 2018;72:6-31. 5. Ciampi R, et al. *Endocr Pathol*. 2005;16(2):99-105. 6. Rangel-Pozzo A, et al. *Cancers*. 2020;12:3146.

Diagnosing Thyroid Cancer

Patient Journey to Receiving a Thyroid Cancer Diagnosis



Patient presents with suspected thyroid nodule, and sonography is performed.

Nodule is deemed suspicious on high-resolution ultrasound.

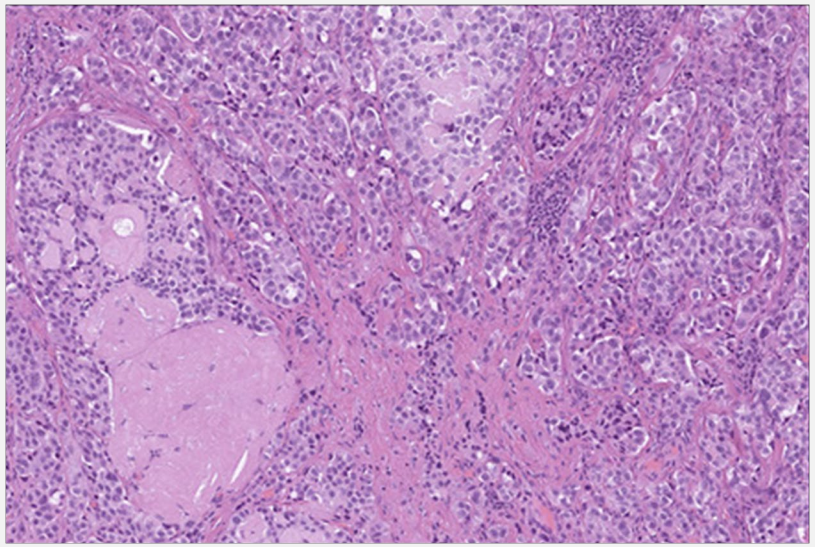
FNA cytology and scoring is performed using the Bethesda system.

Thyroidectomy is performed for confirmed malignancies. Highly suspicious nodules with inconclusive FNA cytology are recommended for molecular testing or repeat FNA.

FNA = fine-needle aspiration.

Haugen BR, et al. *Thyroid*. 2016;26(10):10.1089/thy.2015.0020.

Classification of Medullary Thyroid Cancers



Histological Features of MTC[1]

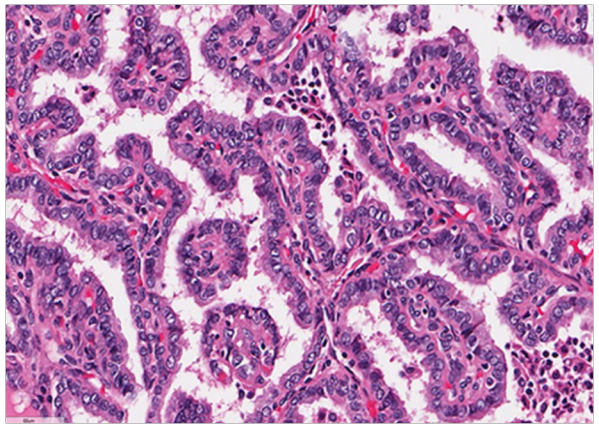
Dyscohesive cells that may be spindle-shaped, plasmacytoid, or epithelioid; eccentric nuclei exhibit “salt & pepper” chromatin granularity[2]

When determining if a thyroid nodule is consistent with MTC classification, the following should be evaluated:

- Age of patient at presentation
- Genomic testing for germline *RET* mutations
- Serum levels of calcitonin and CEA*
- Pathological features of FNA biopsy through IHC[2]:
  - Presence of markers, such as calcitonin, chromogranin, and CEA
  - Absence of Tg
  - High Ki-67 proliferation index[1]

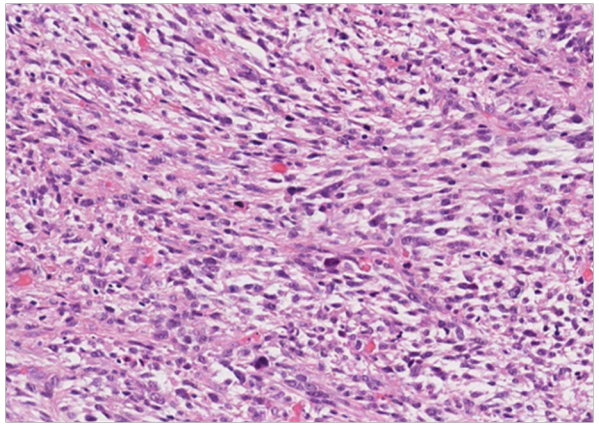
*CEA is not considered a diagnostic marker of MTC; however, it is useful for evaluating disease progression, and it is recommended to be measured concurrently with calcitonin.
CEA = carcinoembryonic antigen; IHC = immunohistochemistry; Tg = thyroglobulin.
Image reproduced from Juhlin CC, Mete O, Baloch ZW. *Endocr Relat Cancer*. 2022;30(2):e220293.
1. Juhlin CC, Mete O, Baloch ZW. *Endocr Relat Cancer*. 2022;30(2):e220293. 2. Wells SA, et al. *Thyroid*. 2015;25(6):567-610.

Classification of Nonmedullary Thyroid Cancers



Differentiated Thyroid Cancers[1]

- DTCs can vary greatly in histological features depending on the variant of tumor[1-3]
  - Reported characteristics should include tumor size, presence of extrathyroidal extension, and lymph node metastasis
- Measurement of serum Tg or anti-Tg antibodies is not recommended for patients with suspected DTCs[3]
- Molecular testing for status of the following markers for FNA biopsies with suspicious cytology may aid in diagnosis and surgical decision-making[3]:
  - *BRAF*
  - *RAS*
  - *RET/PTC*
  - *PAX8/PPAR*γ



Anaplastic Thyroid Cancers[1,4]

- ATCs are highly dedifferentiated cancers with few characteristics of noncancerous thyroid cells with a rapid growth rate and highly variable histopathology
  - Spindle cell morphologies and giant cell morphologies are common presentations for these tumors
  - Known to be highly invasive
- IHC evaluation of the following markers is essential for ATC diagnosis:
  - Absence of Tg and TTF-1
  - Presence of PAX8 (in the proper morphological context)
  - High Ki-67 proliferation index
  - *BRAF*^{V600E}
- Genomic profiling is not sufficient for diagnosis of ATC, but it may be useful in differential diagnosis

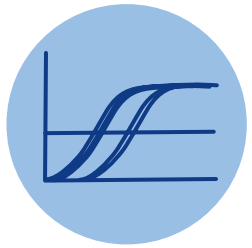
ATC = anaplastic thyroid cancer/carcinoma; DTC = differentiated thyroid cancer/carcinoma; TTF-1 = thyroid transcription factor 1.
Images reproduced from Baloch ZW, et al. *Endocr Pathol*. 2022;33:27-63.
1. Baloch ZW, et al. *Endocr Pathol*. 2022;33:27-63. 2. Schmidbauer B, et al. *Int J Mol Sci*. 2017;18(6):1292. 3. Haugen BR, et al. *Thyroid*. 2016;26(10):10.1089/thy.2015.0020. 4. Bible KC, et al. *Thyroid*. 2021;31(3):doi:10.1089/thy.2020.0944.

Single Analyte Diagnostic Methods Used in Precision Oncology

Protein or **Nucleic Acid** Detection Techniques

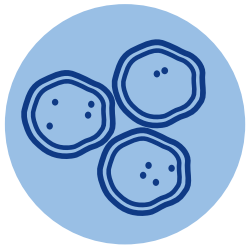
Immunohistochemistry[1-3]

- Detects protein expression
- Microscopy-based technique
- Unable to determine gene sequence or identify specific fusion partners



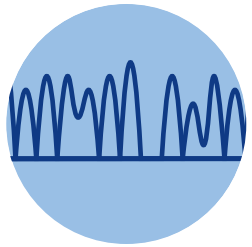
Polymerase chain reaction[4-7]

- Detects regions of interest within DNA or RNA
- Only detects known alterations



Fluorescence *in situ* hybridization[8,9]

- Visualizes specific genes/regions within a tissue sample
- Fluorescent microscopy-based technique
- Unable to determine gene sequence and limited to detection of known variations



Sanger sequencing[7,9-11]

- Detects SNVs, indels (insertions and deletions), and some fusion events in DNA
- Low-plex and low sensitivity traditional molecular method

SELECTED ASSAYS

- Variety of protein-specific antibodies available for use[1-3]

- ARMS-PCR[4,12]
- ddPCR[7,13]
- RT-PCR[5,6]
- qPCR[4]

- Variety of gene and region-specific probes available for use[8]

- PCR enrichment may be used to amplify specific DNA regions of interest for sequencing[4]

For source information, please see speaker notes.
ARMS = amplification refractory mutation system; ddPCR = droplet digital polymerase chain reaction; PCR = polymerase chain reaction; qPCR = quantitative polymerase chain reaction; RT-PCR = reverse transcription polymerase chain reaction; SNV = single-nucleotide variant.

Lilly

Comprehensive Diagnostic Methods Used in Precision Oncology

Nucleic Acid Detection Techniques

Next-generation sequencing[1,2]

- High-throughput testing of most actionable thyroid cancer biomarkers
- Detects all classes of genomic alterations
- Can test multiple genes of interests on limited material from biopsies or cytological samples
- Commonly used panels in thyroid cancers[a] include Afirma® GSC, ThyroSeq® v3, and ThyGeNEXT® + ThyraMIR®

NGS DNA tumor sequencing[3]	NGS RNA tumor sequencing[3]	NGS plasma sequencing[4]
• Allows for whole-genome or whole-exome sequencing	• Can analyze at the transcriptome level, including all types of RNA transcripts (mRNA, rRNA, tRNA, micro-RNA, and non-coding RNA) • mRNA sequencing can detect gene fusions	• Enrichment is performed on ctDNA collected by liquid biopsy • TAT is typically much shorter than that needed for tissue NGS

For source information, please see speaker notes.

[a]This list is not all-inclusive and does not represent all laboratories and tests. This list is intended for informational purposes and your considerations only, and it is based on publicly available information for these organizations.

ctDNA = circulating tumor DNA; GSC = genomic sequencing classifier; mRNA = messenger RNA; NGS = next-generation sequencing; rRNA = ribosomal RNA; TAT = turnaround time; tRNA = transfer RNA.

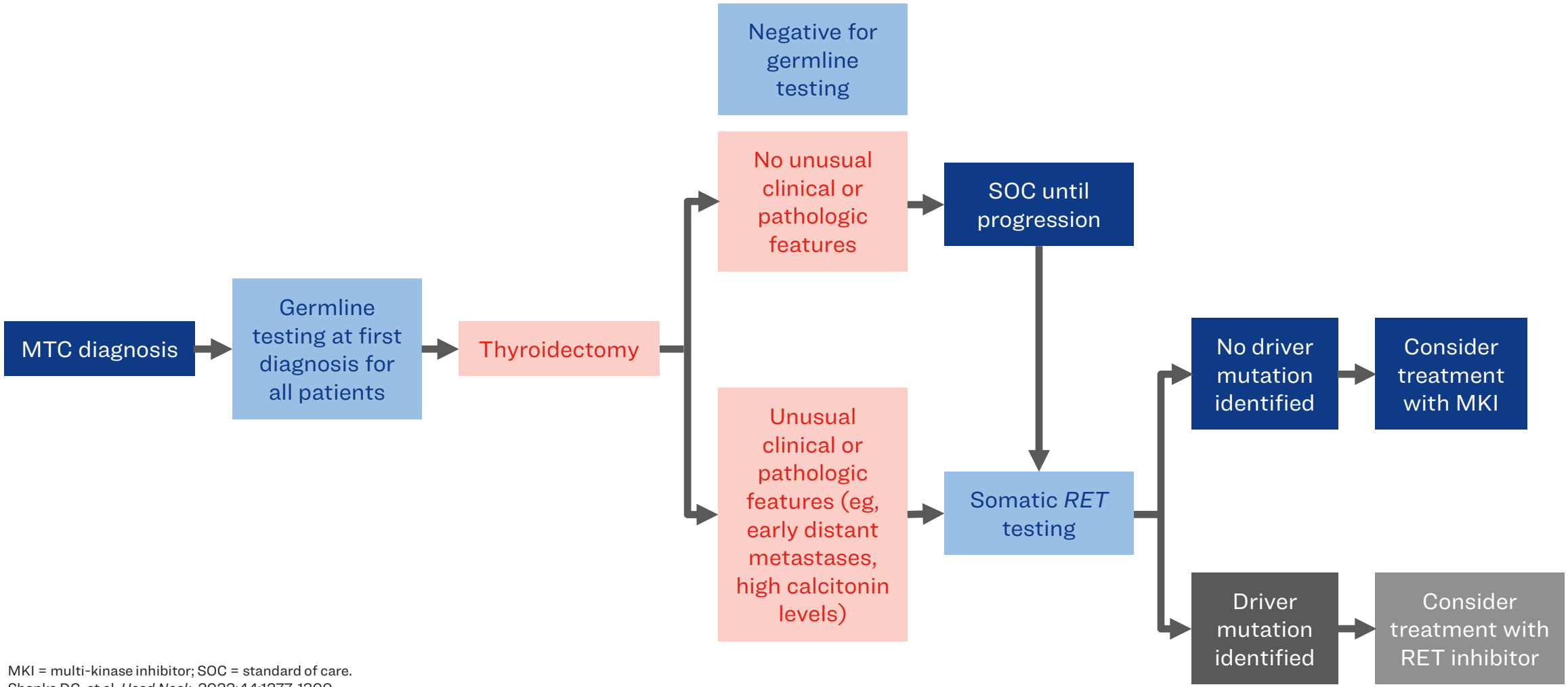
Molecular Testing Options to Identify Targetable Alterations in Thyroid Cancers

	Single Analyte Testing			Comprehensive Testing		
Target	PCR-Based Methods	FISH Testing	IHC Staining	NGS DNA Tumor Sequencing	NGS Plasma Sequencing	NGS RNA Tumor Sequencing
Medullary thyroid cancers[1]						
RET rearrangements[2,3]	✓	✓		✓	✓	✓
Nonmedullary thyroid cancers[4,5]						
BRAF V600E[2,6]	✓		✓	✓	✓	✓
NTRK fusions[2,7]		✓	✓	✓	✓	✓
RET rearrangements[2,3,8]	✓	✓		✓	✓	✓

Targeted NGS testing covers the vast majority of genes of interest for thyroid cancer, requires less DNA/RNA, and usually offers results in 1-2 weeks.[4]

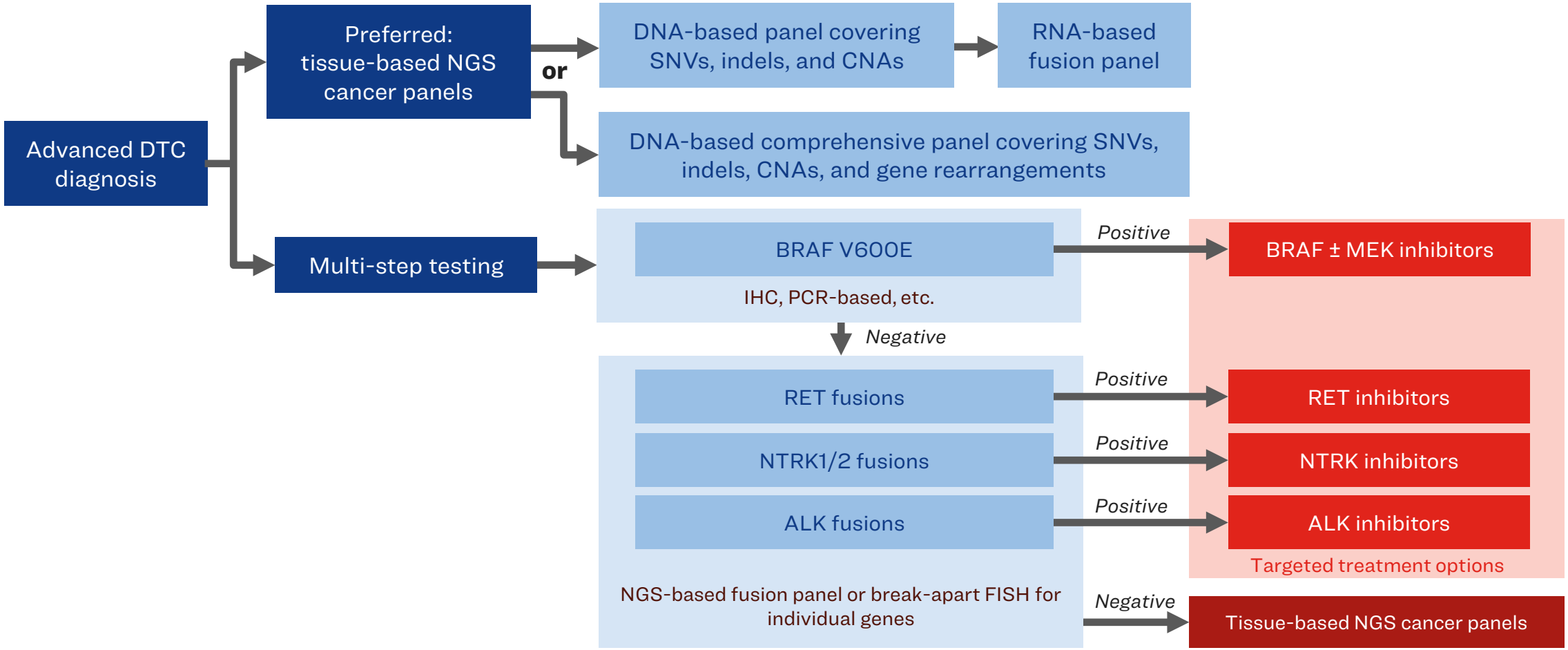
For source information, please see speaker notes.
FISH = fluorescence *in situ* hybridization; PCR = polymerase chain reaction.

Consensus Testing Algorithm for MTC



MKI = multi-kinase inhibitor; SOC = standard of care.
Shonka DC, et al. *Head Neck*. 2022;44:1277-1300.

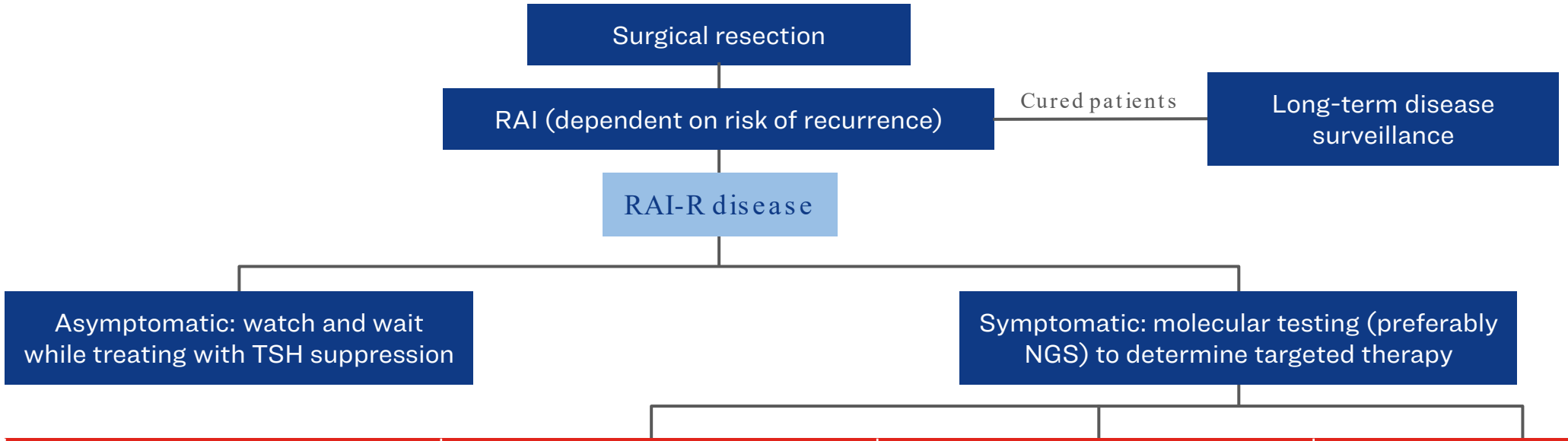
Consensus Testing Algorithm for Advanced DTC



ALK = anaplastic lymphoma kinase; CNA = copy number aberration; MEK = mitogen-activated protein kinase.
Shonka DC, et al. *Head Neck*. 2022;44:1277-1300.

Treatment of Thyroid Cancer

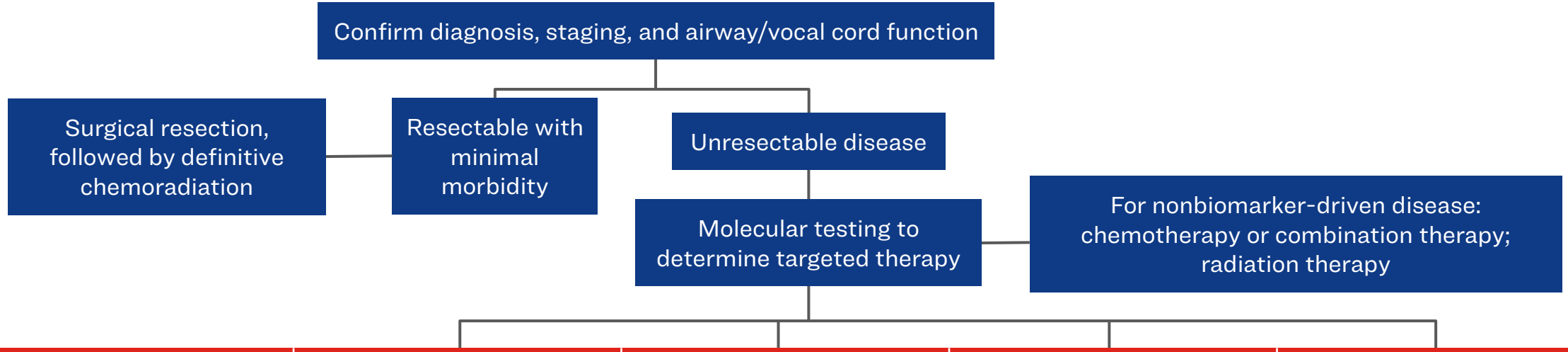
Treatment Algorithm for DTCs[1-3]



Indication	MKI*	*RET* Fusions	*NTRK* Alterations
First line	MKI[4,5]	RET inhibitor[6]	NTRK inhibitors[7-9]
Second/third line	MKI[10]	Chemotherapy[†1,2]	

For source information, please see speaker notes.
*MKIs are considered standard first-line therapy for RAI-R DTC.[1,2] †Cytotoxic chemotherapy has historically proven to be ineffective in RAI-R DTC; however, it may have selective benefit in patients who are unresponsive to kinase inhibitors.[1]
RAI = radioactive iodine; RAI-R = radioactive iodine-refractory; TSH = thyroid-stimulating hormone.

Treatment Algorithm for ATCs[1-3]



Indication	*BRAF* V600E*	*RET* Fusions	*NTRK* Alterations	PD-L1 Expression
First line	BRAF inhibitor[4]	RET inhibitor[5]	NTRK inhibitor[6,7,8]	Immuno-oncology therapies[1,9]
Second/third line	*Therapeutic decision-making in the setting of PD after initial therapy, regardless of somatic mutational status or therapy, is very complex and not easily defined. Best supportive care (hospice) should also be discussed as an option, and it is recommended that care decisions be guided by an expert in ATC therapeutics.[1]*			

For source information, please see speaker notes.
*IHC evaluation for *BRAF* V600E should be incorporated into initial assessment of advanced thyroid cancers while awaiting NGS results.
FDA = US Food and Drug Administration; PD = progressive disease.

Treatment Algorithm for MTCs[1-3]

Thyroid nodule with confirmed FNA diagnosis of MTC

- Ultrasound of neck
- Measure serum levels of calcitonin and CEA

Resectable disease

Total thyroidectomy and central neck dissection with dissection of lymph nodes in lateral compartments

Postoperative assessment

- Serum calcitonin and CEA
- Neck ultrasound

If disease progresses following surgical resection, consider systemic therapy.

Nonresectable disease

Molecular testing to identify therapeutic options

Indication	MKIs	*RET* Mutations
First line	MKI[4,5]	RET inhibitor[6]
Second/third line	MKI[7,8]	MKI[4,5]

1. Wells SA, et al. *Thyroid.* 2015;25(6):567-610. 2. Salgado SA, et al. *Am Soc Clin Oncol Educ Book.* 2023;43:e389708. 3. Filetti S, et al. *Annals Oncol.* 2019;30:1856-1883. 4. https://clinicaltrials.gov/study/NCT00704730 (Accessed May 17, 2024). 5. https://clinicaltrials.gov/study/NCT00410761 (Accessed May 17, 2024). 6. https://clinicaltrials.gov/study/NCT03157128 (Accessed May 17, 2024). 7. https://clinicaltrials.gov/study/NCT00784303 (Accessed May 17, 2024). 8. https://clinicaltrials.gov/study/NCT00390325 (Accessed May 17, 2024).

Current Therapeutic Options for Thyroid Carcinoma

Therapy Type	Cancer Type				
	DTC (PTC, FTC, and Hürthle Cell Carcinoma)	ATC		MTC	
		Locoregional	Systemic or Progressive Disease	Locoregional	Systemic or Progressive Disease
Chemotherapy	• Doxorubicin*[1,2]	• Paclitaxel[3] • Carboplatin[3]	• Docetaxel[3] • Doxorubicin[2,3] • Paclitaxel[3]		
Targeted Therapies					
Immuno-oncology therapies	• Pembrolizumab†[3]	• Pembrolizumab†[3]	• Pembrolizumab†[4] • Spartalizumab‡[3]	• Pembrolizumab†[3]	• Pembrolizumab†[4]
MKIs	• Lenvatinib[1] • Sorafenib[1]			• Vandetanib[5] • Cabozantinib[5]	• Vandetanib[5,6] • Cabozantinib[5,6]
BRAF^{V600E} inhibitors		• Dabrafenib/Trametinib[3]			
NTRK inhibitors	• Larotrectinib[2] • Entrectinib[3]	• Larotrectinib[2,3] • Entrectinib[3]			
RET inhibitors	• Selpercatinib[3]	• Selpercatinib[3]		• Selpercatinib[3]	• Selpercatinib[3]

For source information, please see speaker notes.
*Indicated for DTC in patients contraindicated or unresponsive to MKIs. †Therapy not indicated for use in thyroid cancers and conditionally available for investigative use in patients with high PD-L1 expression and no other targetable alterations. ‡Investigational therapy.
FTC = follicular thyroid cancer/carcinoma.