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White Paper

American Association of Clinical Endocrinology And Associazione Medici Endocrinologi Thyroid Nodule Algorithmic Tool

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ABSTRACT

Objective: The first edition of the American Association of Clinical Endocrinology/American College of Endocrinology/Associazione Medici Endocrinologi Guidelines for the Diagnosis and Management of Thyroid Nodules was published in 2006 and updated in 2010 and 2016. The American Association of Clinical Endocrinology/American College of Endocrinology/Associazione Medici Endocrinologi multidisciplinary thyroid nodules task force was charged with developing a novel interactive electronic algorithmic tool to evaluate thyroid nodules.

Abbreviations: AACE, American Association of Clinical Endocrinology; ACR TI-RADS, American College of Radiology Thyroid Imaging Reporting and Data System; AME, Associazione Medici Endocrinologi; ATA, American Thyroid Association; CIG, computer-interpretable guideline; FNA, fine-needle aspiration; ITNUWG, International Thyroid Nodule Ultrasound Working Group; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; TNAPP, Thyroid Nodule App; US, ultrasound.

Disclaimer: This is a working document that reflects the state of the field at the time of publication. Every effort was made to achieve consensus among members of the task force. Because rapid changes in this area are expected, periodic revision is inevitable. We encourage medical professionals to use this tool in conjunction with their best clinical judgment. Any decision by practitioners to apply this tool must be made in light of local resources and individual patient circumstances and preferences.

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practice guidelines

Methods: The Thyroid Nodule App (termed TNAPP) was based on the updated 2016 clinical practice guideline recommendations while incorporating recent scientific evidence and avoiding unnecessary diagnostic procedures and surgical overtreatment. This manuscript describes the algorithmic tool development, its data requirements, and its basis for decision making. It provides links to the web-based algorithmic tool and a tutorial.
Results: TNAPP and TI-RADS were cross-checked on 95 thyroid nodules with histology-proven diagnoses.
Conclusion: TNAPP is a novel interactive web-based tool that uses clinical, imaging, cytologic, and molecular marker data to guide clinical decision making to evaluate and manage thyroid nodules. It may be used as a heuristic tool for evaluating and managing patients with thyroid nodules. It can be adapted to create registries for solo practices, large multispecialty delivery systems, regional and national databases, and research consortiums. Prospective studies are underway to validate TNAPP to determine how it compares with other ultrasound-based classification systems and whether it can improve the care of patients with clinically significant thyroid nodules while reducing the substantial burden incurred by those who do not benefit from further evaluation and treatment.
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Introduction

Thyroid nodules are common.[1] They are predominantly benign and asymptomatic and do not require evaluation, treatment, or monitoring, while the majority of thyroid malignancies are low-risk neoplasms that do not have an impact on survival.[2] Diagnosis and treatment are costly and often have a detrimental impact on a patient's physical, emotional, and financial status. In the United States, well over 500 000 fine-needle aspirations (FNAs) of thyroid nodules are performed per year, with as many as 200 000 of them being unnecessary.[3] Similarly, in European countries, such as Germany and France, with well-functioning National Health Services, the vast majority of thyroidectomies performed for nodular thyroid disease have benign histopathology,[4,5] while the minority that proves to be malignant is predominantly composed of low-risk thyroid cancers.[6,7] Guidelines from the American Association of Clinical Endocrinology (AACE), Associazione Medici Endocrinologi (AME), American Thyroid Association (ATA), and American College of Radiology[8–10] provide recommendations for reducing the collective burden of evaluating and treating thyroid nodules and low-risk thyroid cancers. However, their impact has been limited.[11,12] The variation in ultrasound (US) risk classification systems and interobserver assessments of thyroid nodule features contribute to this.[13,14]

We designed a novel electronic algorithmic tool, termed TNAPP (Thyroid Nodule App, pronounced "tee nap"). It is largely based on the 2017 European Union Thyroid Imaging Reporting and Data System lexicon for categorizing US features, along with corresponding US images and cartoons as heuristic tools.[15,16] It also incorporates nomenclature that is being developed by the International Thyroid Nodule Ultrasound Working Group (ITNUWG). One of our goals was to create an easy-to-apply tool and to ultimately compare its effectiveness with other society guidelines and published calculators.[17] This will be accomplished by demonstrating a comparable or greater reduction in the number of clinically insignificant nodules undergoing FNA, surgery, or surveillance in a variety of clinical settings and populations.

Educational Tools

Over the past 3 decades, clinical practice guidelines have emerged as an increasingly important tool to aid clinicians in managing a host of medical conditions.[8,9] Guidelines are regularly cited in publications and medical education forums, and they are used as a basis for medical decision making in both clinical and administrative settings. Yet, despite their widespread clinical use, there is substantial room for improvement.[18] This includes establishing the cost effectiveness and validity of recommendations, which are often based on expert opinion, retrospective studies, and study populations that are not generalizable.

Implementing guidelines requires:

- Creating mechanisms for vetting guideline recommendations in various clinical situations and across different populations[19] and cultures[20]
- Gauging their implementation by tracking their use and applicability
- Addressing their often formidable length and the wealth of information they contain, which makes them hard to navigate as well as absorb and retain
- Providing timely updates of narrative multiauthored, highly validated documents
- Disseminating and distributing them
- Clinicians routinely using and assessing their effectiveness in real-world settings

Novel Approach

A computer-interpretable guideline (CIG) and narrative guideline provide recommendations that may require a sequence of logical steps. When clinical decision making requires multiple steps, narrative guidelines employ a series of recommendations and may illustrate them with flowcharts. CIG decision support systems employ execution engines (programs) to electronically provide, document, and track these recommendations. CIG offers a novel approach to address some of these challenges.[21,22] CIGs have been shown to be effective in additional clinical domains, such as chronic diseases, diabetes, cancer, stroke, HIV, genetic counseling, and hypertension.[23–31] They facilitate testing and validating recommendations prospectively and retrospectively. Cross-checking histology-proven cases served as a means of testing TNAPP's logic and disambiguation by detecting contradictory or ambiguous guidance. Examples include the sequence and timing of when to implement recommendations.

Other Uses

The use of a computer-based tool can be tracked, used as a stand-alone tool for medical education, and integrated into an electronic health record. It can be used as a decision tool for single-use anonymized patient data entry that is not retained (akin to a

mortgage calculator). It also may serve as a platform for different types of registries that store data for analysis and be used to study the impact of algorithms and recommendations on clinical outcomes. Registries could be created for solo practices, large multispecialty delivery systems, regional and national databases, and research consortiums. Hence, a computer-based tool has the potential to be a powerful instrument in a wide range of settings for studying health outcomes as well as their costs.

Methods

The AACE/AME Thyroid Nodule Task Force was formed in 2017 to update the 2016 clinical practice guideline for the diagnosis and management of thyroid nodules.[8] The charge of the task force was to provide an updated approach to managing thyroid nodules. Rather than beginning with a narrative guideline as it had done in 2006, 2010, and 2016,[8,32,33] the task force was asked to create an algorithmic tool based on prior recommendations, an updated literature review, and an expert opinion. Unlike what had been done in 2014,[21] it did not create different pathways and recommendations for Europe and the United States, areas of iodine sufficiency and insufficiency, and whether or not calcitonin determinations were routinely done during the initial evaluation of a thyroid nodule.

Areas of expertise were expanded. Previously, the task force was entirely composed of European and American endocrinologists. The task force now included endocrine surgeons, general surgeons and otolaryngologists, pathologists, an informatician, and a health economist.

The task force met regularly over 3 years during international meetings, including the AME annual congress, AACE annual meeting, ATA annual meeting, and the World Thyroid Congress, or by teleconference. Comprehensive minutes were taken by task force members and subsequently reviewed by all task force members. Revisions to the algorithmic tool were continually posted on the web for further review. This manuscript, written by the task force, describes the development and contents of the algorithmic tool. It was reviewed by the Chairs of the AACE Thyroid Disease State Network and the AACE Executive Committee.

TNAPP is web-based (https://aace-thyroid.deontics.com) and features a tutorial on how to use it (https://deontics-external-publication.s3-eu-west-1.amazonaws.com/aace/Thyroid+nodule+App+videos.pptx).

Factors Serving as the Basis for TNAPP's Decision Algorithmic Tool

Exclusion Factors

The impetus of the algorithmic tool was to provide guidance in the *initial* evaluation of ambulatory patients with thyroid nodules that were not extremely likely to be malignant. Thus, nodules in those who presented with elevated calcitonin levels, multiple endocrine neoplasia type 2 syndromes, previously documented thyroid cancer, and suspicious lymphadenopathy were excluded (Table 1).

Clinical Factors

Clinical factors were composed of features ***in favor of*** performing FNA, termed Clinical 2, and those with features ***against*** performing FNA, termed Clinical 1 (Table 2). These factors were not given relative weights. When factors for and against doing an FNA are present, clinical judgment becomes the default decision-making factor (ie, other medical conditions that take precedence at the time).

Table 1
Exclusion Criteria

Clinical criteria
- Family history of thyroid cancer: familial DTC or MTC or other syndromes
- PET-positive or sestamibi-positive nodule
- Elevated calcitonin
- Clinical or imaging finding of regional adenopathy suspicious of malignancy
- Known diagnosis of thyroid cancer
- Either a hard consistency or a fixed nodule

Ultrasound criteria
- Obvious extrathyroidal extension or invasion

Abbreviations: DTC = differentiated thyroid cancer; MTC = medullary thyroid cancer; PET = positron emission tomography.

US Characteristics

A numeric scoring system based on the risk of malignancy associated with each US feature was created to categorize each nodule as US 1, 2, or 3 (low, intermediate, or high risk, respectively) (Table 3) In Lieu of our prior descriptive (A, B, and C) classification.[8] In the algorithmic tool, American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) scores are simultaneously displayed if a sufficient number of criteria to generate a score are entered (Fig. 1). ACR TI-RADS was chosen because its scoring system is based on the same discrete US criteria as TNAPP. The ATA classification system, for example, was not used because it employs pattern recognition.

US Images and Cartoons

While the TNAPP was being created, the multisociety ITNUWG was working to create a universal terminology for US descriptors. Three members of the task force, representing 2 societies (AACE and ATA) and who were also members of the ITNUWG, periodically updated the task force on its progress. The lexicon (Table 4) incorporates some of the ITNUWG terminology in effect at the time of publication. A subgroup of the TNAPP task force was charged with submitting US images that featured all the lexicon's terms at the time that this manuscript was written. Corresponding cartoons with explanatory captions were then created to illustrate key US

Table 2
Clinical Criteria for (Clinical 2) and against (Clinical 1) FNA of Thyroid Nodules

Clinical 1: One or more of the following clinical factors are against performing FNA:
- Low thyrotropin[a] and not on thyroid hormone
- Autonomous nodule on imaging
- Prior benign FNA of the same nodule
- Other medical conditions that take precedence at the time
- History of prior lobectomy with vocal cord paralysis
- Significant comorbidity making thyroid surgery high risk at the time
- Limited life expectancy (<1 year)

Clinical 2: One or more of the following clinical factors favors FNA:
- Head and neck radiation in the past
- Compressive symptoms: dysphonia, dysphagia, or dyspnea without another cause
- Nodule position either posterior or adjacent to thyroid capsule or trachea
- History of documented growth
- History of progressive growth ie, ≥50% increase in volume in ≤1 year, especially of the solid component, or 20% increase in 1 dimension
- History of sudden enlargement
- Planned thyroid or parathyroid surgery
- Cosmetic concerns
- Patient preference or anxiety
- Protocol requiring documentation of cancer

Abbreviation: FNA = fine-needle aspiration.
[a] Below normal range for assay being used or default to <0.5 mU/L; up to 1.0 mU/L for multinodular goiter.[8,9]

Table 3
US Classification Levels 1, 2, and 3

US risk category	Corresponding US feature(s)	Numerical score
US 1 (low): 0-2	**Benign or low-risk US features**	
One or more of the corresponding low-risk features are present, and none of the intermediate or high-risk features are present	Nodule composition on US is spongiform (uniformly microcystic throughout)	0
	Nodule margin on US is either smooth, ill-defined, or cannot be determined	0
	Nodule shape on US is oval or round	0
	Nodule is cystic **and** anechoic	0
	Either solid or mixed **and** marked hyperechoic nodule (described as white knight) is often seen in a gland with clear features of Hashimoto thyroiditis	0
	Comet-tail echogenic foci and its variants are present on US	0
	Either solid or mixed **and** hyperechoic nodule	1
	Either solid or mixed **and** isoechoic nodule **and** size <20 mm **and** none of the US 2/3 features, such as microcalcifications, intranodular macrocalcifications, peripheral rim calcifications, echogenic foci difficult to characterize, spiculated or irregular margin, or extrathyroidal extension	2
	Mixed solid cystic nodule that has reverberating artifacts, which is a low-risk feature compared with an eccentric mural component (excluded from scoring)	No score
	Peripheral vascularity (excluded from scoring)	No score
	Mixed solid cystic nodule has a solid concentric/spongiform-like component (excluded from scoring)	No score
US 2 (intermediate): 3-4	**Intermediate-risk US features**	
One or more of the corresponding intermediate-risk features are present, and none of the high-risk features are present	Nodule margin on US is irregular with protrusion into adjacent thyroid tissue	1
	Echogenic foci, including either intranodular macrocalcifications or foci that are difficult to characterize, or peripheral rim calcifications. including either interrupted rim calcification or uninterrupted rim calcifications	1
	Nodule composition on US is either solid or mixed **and** the echogenicity of the solid part is either slightly hypoechoic or hypoechoic	3
	Either solid or mixed nodule **and** isoechoic **and** either size ≥20 mm or at least one more US 2 feature, such as an irregular margin or intranodular macrocalcifications or foci that are difficult to characterize or peripheral rim calcifications **and** none of the US 3 characteristics, such as microcalcifications, extrathyroidal extension, or spiculated margins	3
	Mixed solid cystic nodule has a solid eccentric mural component (excluded from scoring)	No score
	Solid or mixed nodule with solid part showing intranodular vascularity (excluded from scoring)	No score
	Mixed solid cystic nodule has indeterminate hyperechoic spots, which increase the risk of malignancy (excluded from scoring)	No score
US 3 (high): ≥5	**High-risk US features**	
One or more of the corresponding high-risk features are present	Nodule margin on US is spiculated or has sharp angles	5
	Nodule echogenicity on US is profoundly hypoechoic	5
	Microcalcifications are present within the nodule	5
	Nodule shape on US is taller-than-wide	5
	Solid **and** hypoechoic **and** either intranodular macrocalcifications or nonspecific echogenic foci or peripheral rim calcifications present (excluded from scoring)	No score
	Extrathyroidal extension is noted on the US (excluded from scoring)	No score

Abbreviation: US = ultrasound.
The sum of points does not denote absolute risk. The categorization of characteristics and all of the *possible* combinations of these characteristics under US 1, 2, and 3, unambiguously establish whether a nodule falls within the low, intermediate or high risk for being malignant.

features. The US images and corresponding cartoons comprise an imaging library (Fig. 2).

Cytology

Bethesda cytology categories I-VI were used to classify findings.[34] Categories as well as descriptions of the findings in each class or subcategory are listed in Table 5.

Summary of Inputs (Entered by the User) and Outputs (Guidance Produced by TNAPP) (Fig. 3)

Inputs

1. Clinical features (Table 2): There are 26 clinical features in total. Although clinical factors are key determinants of the risk of malignancy, none are required for running the TNAPP.
2. US features (Tables 3 and 4): There are 36 US features in total. Size, composition, and echogenicity are the only data that have to be provided for TNAPP to categorize the US as US 1 (low risk), US 2 (intermediate risk), or US 3 (high risk).
3. Cytology features (Table 5): There are a combined total of 45 options from which to select. These are comprised of main categories (6), subcategories (33), or a combination of a main category and subcategory (6). All are optional inputs.

Outputs

1. Checks **eligibility for using the TNAPP (Table 1)**: Yes/no
2. Calculates AACE **US category** of the nodule as low, intermediate, or high risk **(Table 3)**: US 1/US 2/US 3
3. Calculates **AACE clinical category** for factors arguing against and for performing an FNA **(Table 2)**: Clinical 1/Clinical 2
4. Provides guidance about **whether to perform an FNA** and advice about follow-up
5. Uses **results of FNA** when available to serve as the basis for recommending surgery, considering the use of molecular markers, repeating FNA, and duration of follow-up, if any
6. Simultaneously **calculates ACR TI-RADS risk category**: TR1/TR2/TR3/TR4/TR5 when a sufficient number of US features are provided
7. **Simultaneously displays TI-RADS biopsy advice** regarding FNA/follow-up whenever TI-RADS can be calculated
8. **Calculates malignancy probability ranges** based on published risk for malignancy—some prior to the introduction of noninvasive follicular thyroid neoplasm with papillary-

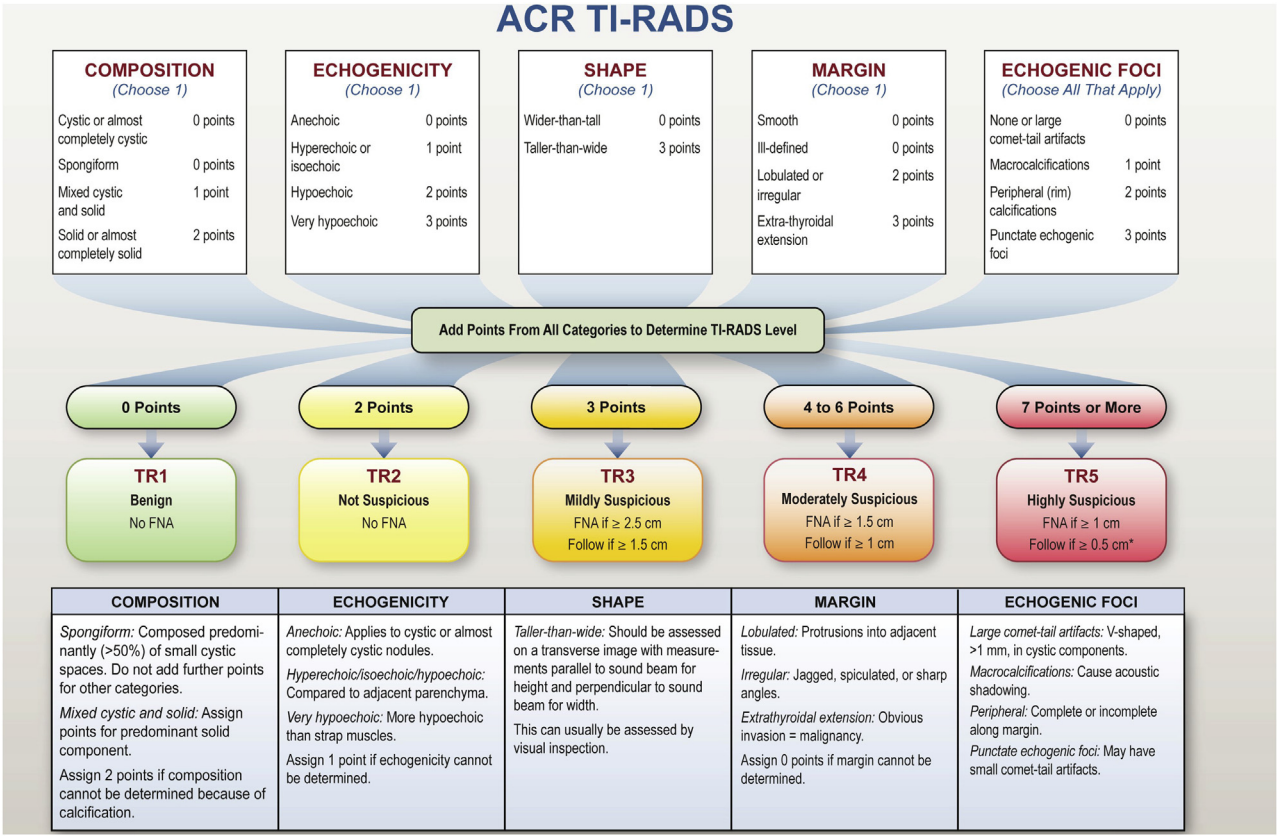

Fig. 1. American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS). Reprinted with permission from Tessler FN, et al. J Am Coll Radiol. 2017; 14:589. American College of Radiology.

Table 4
Ultrasound Lexicon

Reporting category	Reporting lexicon
Composition	Cystic or almost completely cystic
	Spongiform: uniformly microcystic throughout nodule
	Mixed: cystic and solid
	Solid
	Indeterminate composition
Echogenicity	Marked hyperechoic: ie, white knight nodule in thyroiditis
	Hyperechoic
	Isoechoic
	Anechoic
	Hypoechoic or slightly hypoechoic
	Profoundly hypoechoic
	Indeterminate echogenicity
Shape	Oval or round
	Taller-than-wide
Margins	Smooth or regular (including halos)
	Irregular with protrusion into adjacent thyroid tissue
	Spiculated or sharp angles
	Obvious extrathyroidal extension or invasion
	Ill-defined
	Indeterminate margins
Peripheral rim calcifications	Uninterrupted rim calcification
	Interrupted rim calcification
	None
Echogenic foci	Absent
	Comet-tail and its variants
	Echogenic foci that cannot be characterized
	Intranodular macrocalcifications
	Microcalcifications
	Unknown
Vascularity	Peripheral or low vascularity
	Intranodular vascularity
Features in a solid component within a mixed nodule	Eccentric mural component
	Concentric spongiform-like component
	Reverberating artifacts
	Indeterminate hyperechoic spots

(*continued on next column*)

Table 4 (*continued*)

like nuclear features (NIFTP)—for each Bethesda category (Table 5). Because NIFTP is a surgical diagnosis of an indolent or premalignant lesion, it was considered malignant

9. Provides **alerts** whenever inconsistent data are entered (eg, spongiform and high-risk features, such as microcalcifications, etc)

Grids

Grids or tables, based on US classification (US 1, 2, or 3), clinical categorization (Clinical 1 or Clinical 2), size (<5, 5-10, >10-20, >20-40, or >40 mm), and Bethesda classification (I-VI), were created (Table 6, prior to FNA, and Table 7, after FNA). Each cell in each grid, totaling 30 for Table 6 and 180 for Table 7, was internally reviewed multiple times and ultimately populated with a consensus recommendation based on the 2016 Clinical Practice Guideline,[8] updated literature review, and expert opinion.

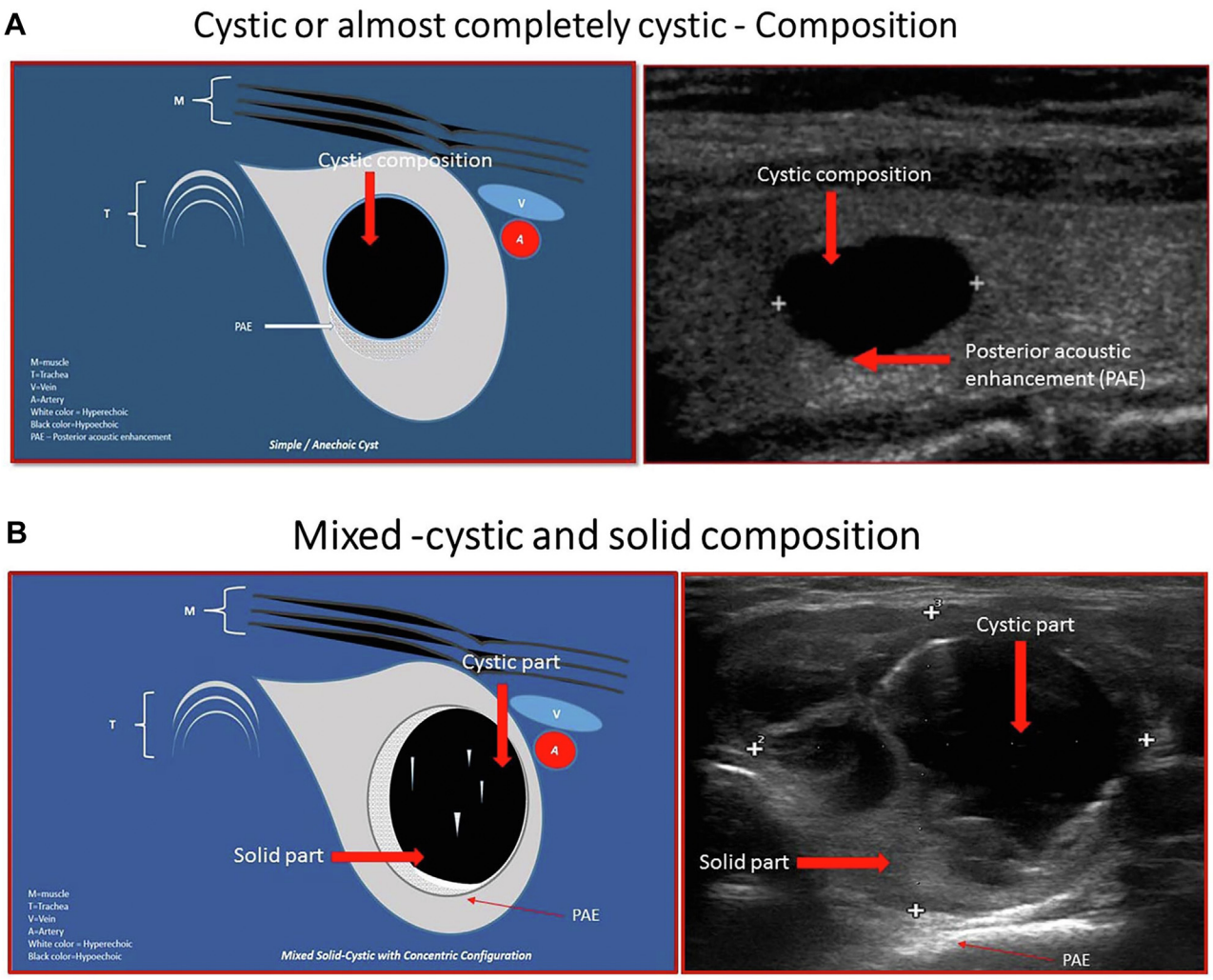

Fig. 2. Representative thyroid ultrasound images and corresponding cartoons. *A*, Cystic or almost completely cystic composition. The cyst is anechoic with posterior enhancement (brightness behind the cyst). *B*, Mixed (cystic and solid) composition. The cystic component causes posterior acoustic enhancement. *C*, Spongiform composition. Minute cystic spaces comprise >75% of the nodule. These cystic spaces have posterior acoustic enhancement, which accounts for the small bright linear areas (lamellations). *D*, Solid composition. The solid nodule is slightly hypoechoic compared with the thyroid parenchyma.

Collectively, the recommendations found in each cell, which are not displayed to the user, serve as the basis for the recommendation provided by TNAPP.

Cross-checking TNAPP

Cases were submitted (Fig. 4) to test the user interface and detect any flaws in the logic used to make recommendations as well as the guidance itself. The authors were asked to submit 10 or more cases with surgical outcomes whose personal or familial history of thyroid cancer, serum thyrotropin level, diagnostic US, indication for FNA, and cytologic report were known. Six task force members from 3 U.S. and 2 European thyroid referral centers provided 10 or more cases, giving a total of 108 cases. Thirteen cases had the following exclusion criteria (Table 1): 5 elevated calcitonin levels, 4 familial thyroid cancer syndromes, 2 diagnoses of thyroid cancer, 1 suspicious cervical adenopathy, and 1 nodule that was positron emission tomography-positive. All 95 remaining cases (100%) had sufficient data to employ the TNAPP, but only 78 (82%) had sufficient US data to make a TI-RADS determination and guidance based on it. There was 79% concordance between TI-RADS and the TNAPP recommendation for whether to perform an FNA. Of the 95 cases that met inclusion criteria, there was insufficient information in 17 cases (18%) to use TI-RADS to provide a recommendation.

Future Studies

We are presently embarking on a prospective multicenter TNAPP validation trial. It will include establishing the impact of NIFTP on the classification of thyroid nodules and surgical recommendations for all noninvasive follicular variants of papillary thyroid cancer.[35,36]

Limitations

There are several limitations to TNAPP:

- The subjective nature of weighting factors for and against a clinical intervention
- US interpretation, such as hypoechogenicity and calcification, for nodules with predominantly follicular architecture
- Bethesda cytology categorization, particularly Bethesda category III

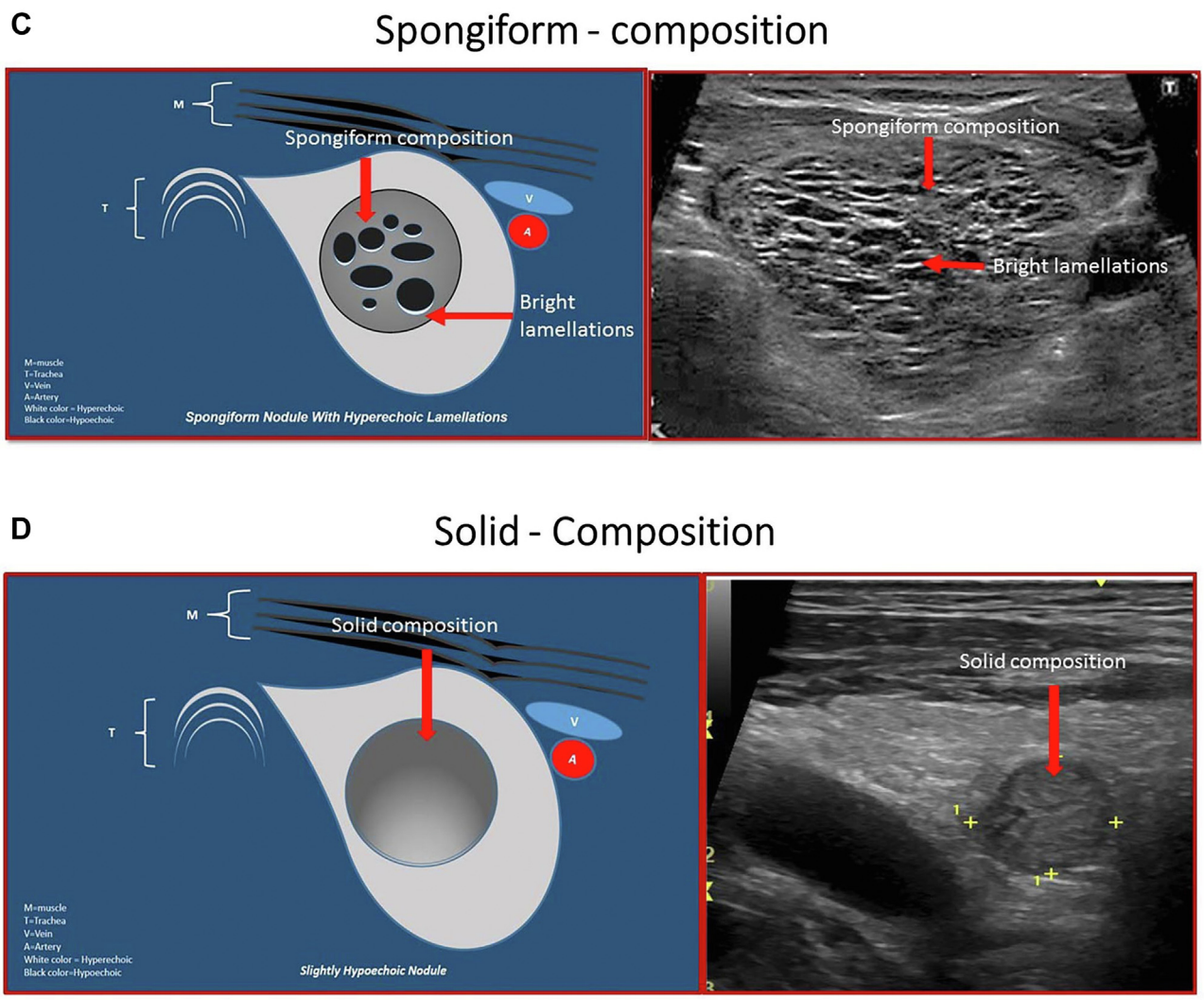

Fig. 2. (continued).

- Using a small sample size of cancer-enriched, nonrandomly selected cases to crosscheck TNAPP
- Paucity of randomized controlled trials to support recommendations regarding thyroid nodule management
- The cost effectiveness of determining molecular markers is yet to be established

Conclusion

The AACE/AME TNAPP is an innovative approach to providing updated recommendations for managing thyroid nodules. It is an electronic tool that is an easily revised "living document." As opposed to a single-document narrative clinical practice guideline, TNAPP is composed of modular knowledge components that can be readily expanded compared with other guidelines and speedily modified by continuously evaluating its usage and efficacy.

Once it is prospectively validated, we foresee employing this tool in a variety of settings. We trust that it will facilitate the care of patients with clinically significant thyroid nodules while reducing the substantial burden incurred by those who would not benefit from further evaluation and treatment.

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Disclosure

Cochairs:
J.R.G. and E.P. have no multiplicity of interest to declare.
Task Force Members:
C.C.L. is the primary author for the 2020 American Association of Endocrine Surgeons Thyroidectomy Guidelines. A.F. is the

Table 5
Bethesda System for Reporting Thyroid Cytopathology

Bethesda category	Bethesda subcategory
I. Nondiagnostic or unsatisfactory	Virtually acellular specimen Cyst fluid only Other (obscuring blood, clotting artifact, drying artifact, etc)
II. Benign	Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc) Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context Consistent with granulomatous (subacute) thyroiditis Other
III. Atypia of undetermined significance or follicular lesion of undermined significance	Focal cytologic (nuclear) atypia Extensive but mild cytologic (nuclear) atypia Atypical cyst-lining cells A scantly cellular specimen with architectural atypia Cytologic (nuclear) and architectural atypia (NIFTP may be present) Hürthle cell aspirates with low-risk pattern Atypia, not otherwise specified, not papillary type Psammomatous calcifications in the absence of cellular atypia Atypical lymphoid cells; rule out lymphoma
IV. Follicular neoplasm or suspicious of a Follicular neoplasm	Cellular aspirate composed of follicular cells with altered architectural pattern and microfollicle formation Cellular aspirate composed of follicular cells with almost exclusively Hürthle cell features Follicular-patterned aspirates with mild nuclear changes (NIFTP may be present)
V. Suspicious for malignancy	Suspicious for papillary thyroid carcinoma Suspicious for medullary thyroid carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma Other
VI. Malignant	Papillary thyroid carcinoma Poorly-differentiated carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features (specify) Metastatic malignancy Non-Hodgkin lymphoma Other

Abbreviation: NIFTP = noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

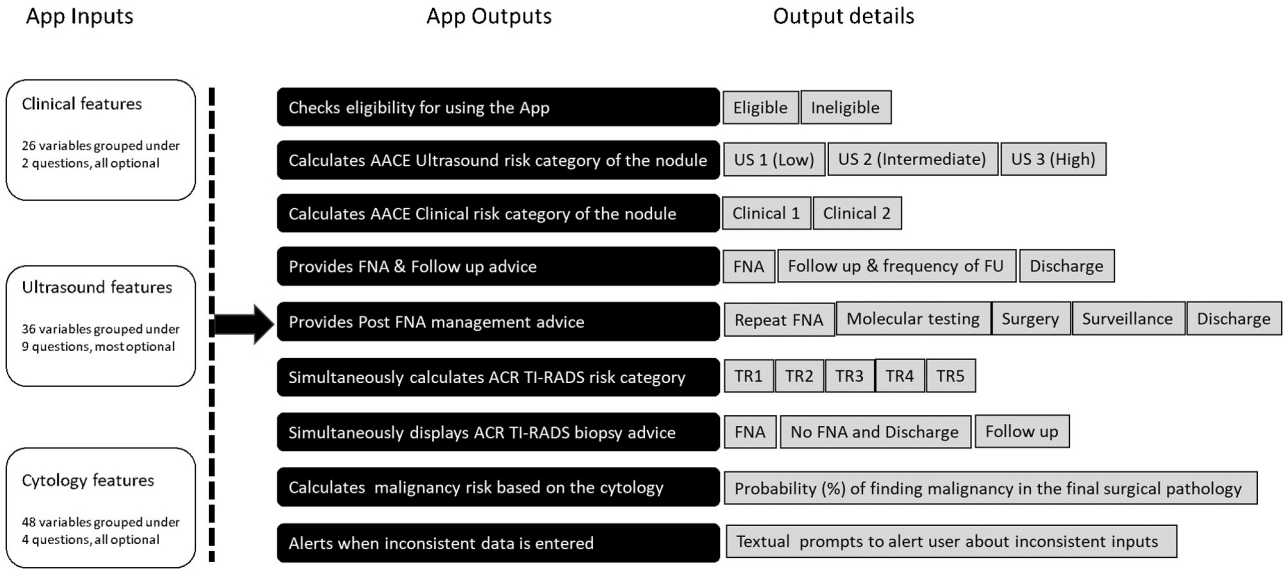

Fig. 3. Summary of Thyroid Nodule App inputs (entered by the user) and outputs (guidance produced by the Thyroid Nodule App). *AACE* = American Association of Clinical Endocrinology; *ACR TI-RADS* = American College of Radiology Thyroid Imaging Reporting and Data System; *FNA* = fine-needle aspiration; *FU* = follow up; *US* = ultrasound.

Table 6
Grid Based on Ultrasound Classification Prior to FNA

Nodule size	Clinical 1	Clinical 2
<5 mm		
Ultrasound 1	No follow-up	No follow-up
Ultrasound 2	No follow-up	No follow-up
Ultrasound 3	Monitor at 18-24 mo then stop	Monitor at 18-24 mo then stop
5-10 mm		
Ultrasound 1	No follow-up	No follow-up
Ultrasound 2	Monitor at 18-24 mo	Either • Consider FNA • If no FNA, then monitor at 12-24 mo
Ultrasound 3	Either • Consider FNA • If no FNA, then monitor at 18-24 mo	Either • Consider FNA • If no FNA, then monitor at 12-24 mo
>10-20 mm		
Ultrasound 1	Monitor at 12-24 mo	Monitor at 12 mo
Ultrasound 2	Either • Consider FNA • If no FNA, then monitor at 12 mo	Recommend FNA
Ultrasound 3	Recommend FNA	Recommend FNA
>20-40 mm		
Ultrasound 1	Either • Consider FNA • If no FNA, then monitor at 12 mo	Either • Consider FNA • If no FNA, then monitor at 12 mo
Ultrasound 2	Recommend FNA	Recommend FNA
Ultrasound 3	Recommend FNA	Recommend FNA
>40 mm		
Ultrasound 1	Recommend FNA	Recommend FNA
Ultrasound 2	Recommend FNA	Recommend FNA
Ultrasound 3	Recommend FNA	Recommend FNA

Abbreviation: FNA = fine-needle aspiration.

Table 7
Grid Based on Ultrasound Classification Post FNA

US Classification	Bethesda I	Bethesda II	Bethesda III	Bethesda IV	Bethesda V	Bethesda VI
<5 mm[a]	**No recommendation**	**No recommendation**	**No recommendation**	**No recommendation**	**No recommendation**	**No recommendation**
5-10 mm						
US 1 Clinical 1[a]	**No recommendation**	**No recommendation**	**No recommendation**	**No recommendation**	**No recommendation**	**No recommendation**
US 1 Clinical 2[a]	**No recommendation**	**No recommendation**	**No recommendation**	**No recommendation**	**No recommendation**	**No recommendation**
US 2 Clinical 1[a]	**No recommendation**	**No recommendation**	**No recommendation**	**No recommendation**	**No recommendation**	**No recommendation**
US 2 Clinical 2[a]	**Repeat FNA**	- **Discharge** - Consider repeat US within 24 mo	- **Consider molecular testing**[b] - **Consider surgery** - **Consider active surveillance**	- **Consider molecular testing**[b] - **Consider surgery** - Consider active surveillance in select cases	- **Offer surgery** - Consider active surveillance in select cases	- **Offer surgery** - Consider active surveillance in select cases
US 3 Clinical 1	**Repeat FNA**	- **Repeat US within 12 mo** - Consider repeat FNA	- **Consider molecular testing**[b] - **Consider surgery** - **Consider active surveillance**	- **Offer surgery** - Consider molecular testing[b]	- **Offer surgery** - Consider active surveillance in select cases	- **Offer surgery** - Consider active surveillance in select cases
US 3 Clinical 2	**Repeat FNA**	**Repeat FNA**	- **Consider molecular testing**[b] - **Consider surgery** - Consider active surveillance in select cases	- **Offer surgery** - Consider molecular testing[b]	**Offer surgery**	**Offer surgery**
>10-20 mm						
US 1 Clinical 1[a]	**No recommendation**					
US 1 Clinical 2	**Repeat FNA**	- **Discharge** - Consider repeat US within 24 mo	- **Consider molecular testing**[b] - **Consider surgery** - **Consider active surveillance**	- **Offer surgery** - Consider molecular testing[b] - Consider active surveillance in select cases	**Offer surgery**	**Offer surgery**
US 2 Clinical 1	**Repeat FNA**	**Repeat US at 12-18 mo; if stable, discharge**	- **Consider molecular testing**[b] - **Consider surgery** - **Consider active surveillance**	- **Offer surgery** - Consider molecular testing[b]	**Offer surgery**	**Offer surgery**

(*continued on next page*)

Table 7 (*continued*)

US Classification	Bethesda I	Bethesda II	Bethesda III	Bethesda IV	Bethesda V	Bethesda VI
US 2 Clinical 2	**Repeat FNA**	**Repeat US at 12-18 mo and repeat FNA**	- **Consider molecular testing**[b] - **Consider surgery** - Consider active surveillance in select cases	- **Offer surgery** - Consider molecular testing[b]	**Offer surgery**	**Offer surgery**
US 3 Clinical 1	**Repeat FNA**	**Repeat FNA within 12 mo**	- **Consider molecular testing**[b] - **Consider surgery**	- **Offer surgery** - Consider molecular testing[b]	**Offer surgery**	**Offer surgery**
US 3 Clinical 2	**Repeat FNA**	**Repeat FNA within 6-12 mo**	- **Offer surgery** - Consider molecular testing[b]	- **Offer surgery** - Consider molecular testing[b]	**Offer surgery**	**Offer surgery**
>20-40 mm						
US 1 Clinical 1	**Repeat FNA**	- **US follow-up at 12-24 mo** - Consider surgery or US-guided minimally invasive procedures based on size or symptoms after confirmatory FNA	- **Consider molecular testing**[b] - **Consider surgery** - Consider active surveillance in select cases	- **Offer surgery** - Consider molecular testing[b]	**Offer surgery**	**Offer surgery**
US 1 Clinical 2	**Repeat FNA**	- **US follow-up at 12 mo** - Consider surgery - Consider US-guided minimally invasive procedures based on size or symptoms after confirmatory FNA in select cases	- **Consider molecular testing**[b] - **Consider surgery**	- **Offer surgery** - Consider molecular testing[b]	**Offer surgery**	**Offer surgery**
US 2 Clinical 1	**Repeat FNA**	- **US follow-up at 12 mo** - Consider surgery - Consider US-guided minimally invasive procedures based on size or symptoms after confirmatory FNA in select cases	- **Consider molecular testing**[b] - **Consider surgery**	- **Offer surgery** - Consider molecular testing[b]	**Offer surgery**	**Offer surgery**
US 2 Clinical 2	**Repeat FNA**	- **US follow-up at 6 mo and repeat FNA** - Consider surgery - Consider US-guided minimally invasive procedures based on size or symptoms after confirmatory FNA in select cases	- **Consider molecular testing**[b] - **Consider surgery**	- **Offer surgery** - Consider molecular testing[b]	**Offer surgery**	**Offer surgery**
US 3 Clinical 1	**Repeat FNA**	- **Repeat FNA** - Consider surgery	- **Offer surgery** - Consider molecular testing[b]	- **Offer surgery** - Consider molecular testing[b] in select cases	**Offer surgery**	**Offer surgery**
US 3 Clinical 2	**Repeat FNA**	- **Offer surgery** - Consider repeat FNA	- **Offer surgery** - Consider molecular testing[b] in select cases	**Offer surgery**	**Offer surgery**	**Offer surgery**
>40 mm						
US 1 Clinical 1	**Repeat FNA**	- **Offer US-guided minimally invasive procedures based on size or symptoms after confirmatory FNA** - Consider surgery - Consider confirmatory FNA and US follow-up at 12 mo	- **Offer surgery** - Consider molecular testing[b]	- **Offer surgery** - Consider molecular testing[b] in select cases	**Offer surgery**	**Offer surgery**
US 1 Clinical 2	**Repeat FNA**	- **Offer surgery** - Consider US-guided minimally invasive procedures based on size or symptoms after confirmatory FNA in select cases	**Offer surgery**	**Offer surgery**	**Offer surgery**	**Offer surgery**

Table 7 (*continued*)

US Classification	Bethesda I	Bethesda II	Bethesda III	Bethesda IV	Bethesda V	Bethesda VI
		- Consider confirmatory FNA and US follow-up at 6-12 mo				
US 2 Clinical 1	**Repeat FNA**	- **Offer surgery** - Consider US-guided minimally invasive procedures based on size or symptoms after confirmatory FNA in select cases - Consider confirmatory FNA and US follow-up at 6-12 mo	**Offer surgery**	**Offer surgery**	**Offer surgery**	**Offer surgery**
US 2 Clinical 2	**Repeat FNA**	**Offer surgery**	**Offer surgery**	**Offer surgery**	**Offer surgery**	**Offer surgery**
US 3 Clinical 1	**Repeat FNA**	**Offer surgery**	**Offer surgery**	**Offer surgery**	**Offer surgery**	**Offer surgery**
US 3 Clinical 2	**Repeat FNA**	**Offer surgery**	**Offer surgery**	**Offer surgery**	**Offer surgery**	**Offer surgery**

Abbreviations: FNA = fine-needle aspiration; US = ultrasound.
Minimally invasive procedures include cyst drainage, ethanol injection, and thermal ablation.
Bold text indicates the recommended option or preferred option(s) when more than 1 option is recommended.
[a] When biopsy or FNA is not recommended by TNAPP, recommendations are not given.
[b] Molecular testing is recommended when results would influence management.

Total cases	108	
Cases excluded from analysis as one of 7 exclusion criteria met	13 (108)	12%
Cases used for analysis	95 (108)	88%
Number of cases with TNAPP was able to provide recommendations	95 (95)	100%
Number of cases where TIRADS was able to provide recommendations	78 (95)	82%
Concordance between TIRADS and TNAPPS	62 (78)	79%
Number of cases in which final histology was cancer	53 (95)	55%
Number of cases in which final histology was cancer of size > 10 mm	42 (95)	44%
Number of cases with histology proven cancer of size > 10 mm, where FNA was not recommended by TNAPP	0 (42)	0%
Number of cases with histology proven cancer of size > 10 mm, where FNA was not recommended by TIRADS	5 (29)	17%

Fig. 4. Summary of the 108 cases used to test the user interface of TNAPP and detect any flaws in the logic used to make recommendations as well as the guidance itself. *FNA* = fine-needle aspiration; *TI-RADS* = Thyroid Imaging Reporting and Data System; *TNAPP* = Thyroid Nodule App.

European Thyroid Association writing committee member for guidelines on interventional techniques for begin thyroid nodules. M.L. is a consultant for Horizon, speaker for Eisai, and has received research grant support from Interpace, Quidel, Roche, and Takeda. V.P. is the founder and Chief Marketing Officer of Deontics Ltd. All other task force members have no multiplicity of interest to declare.

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