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Management Approach to Thyroid Nodules

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Abstract

Thyroid nodules are a major health problem worldwide. The prevalence of palpable thyroid nodules in the general population is approximately 5% in women and 1% in men living in parts of the world with sufficient iodine. High resolution neck and thyroid ultrasound can detect thyroid nodules in a significant proportion of randomly selected individuals, with higher frequencies in women and the elderly population. The importance of thyroid nodules lies in the need to rule out cancer. The majority of thyroid nodules are benign, clinically irrelevant, and can be safely managed with a good surveillance program. The detection and diagnosis of differentiated thyroid cancer have evolved over the years with increased use of high resolution cervical and thyroid ultrasound, fine needle aspiration biopsy (FNAB), molecular testing, and thyroglobulin as a serum tumor marker. An algorithm that utilizes high resolution ultrasound and, when indicated, FNAB, and molecular testing for the diagnosis of thyroid nodules, facilitates a personalized, risk-based protocol that promotes high-quality care and minimizes cost and unnecessary testing. Our paper reviews the current, evidence-based management of newly diagnosed thyroid nodules.

Keywords

Thyroid Nodules, Thyroid Cancer, Thyroid FNA, Thyroid Nodule Workup

1. Introduction

Thyroid nodules are a major health problem worldwide. The prevalence of palpable thyroid nodules in the general population is approximately 5% in women and 1% in men living in parts of the world with sufficient iodine [1]. In contrast, high resolution neck and thyroid ultrasound can detect thyroid nodules

in approximately 19% to 68% of randomly selected people, with higher frequencies in women and the elderly [2] [3]. The clinical importance of thyroid nodules lies in the need to rule out thyroid cancer, which occurs anywhere between 7% and 15% of cases, varying according to gender, age, history of exposure to radiation, family history, among other factors [4] [5].

The detection and diagnosis of differentiated thyroid cancer have evolved over the years with increased use of high resolution cervical and thyroid ultrasound, fine needle aspiration biopsy (FNAB), molecular testing, and thyroglobulin as a serum tumor marker. In this chapter, we will address the current evidence-based management of thyroid nodules.

2. Definition of Thryoid Nodules

A thyroid nodule is defined as a discrete lesion within the thyroid gland that is radiologically different from the surrounding thyroid parenchyma. Certain palpable lesions may not resemble a distinct radiologic abnormality [6]. Such abnormalities do not meet the stringent definition for a thyroid nodule. Nonpalpable nodules detected on ultrasound or by other imaging studies are termed incidentally discovered nodules or "incidentalomas" [7]. Nonpalpable nodules have the same risk of malignancy as do ultrasonographically confirmed palpable nodules of the same size [8]. Usually, only nodules greater than 1 cm in size should be evaluated since they have a greater potential to be clinically significant cancers [9]. Sporadically, there may be thyroid nodules less than 1 cm that require further evaluation because of clinical symptoms or associated lymphadenopathy [4] [9]. In very rare instances, some nodules less than 1 cm lack these ultrasonographic and clinical warning signs yet may nonetheless cause future morbidity and mortality.

3. Initial Assessment of Thyroid Nodules

Upon discovery of a thyroid nodule, a complete clinical history and a physical examination centered on the thyroid gland and adjacent regional lymph nodes should be performed. Relevant historical factors that predict malignancy in a thyroid nodule include a history of childhood radiation therapy to the head and neck region, total body radiation for bone marrow transplant, exposure to ionizing radiation in childhood or adolescence, familial thyroid carcinoma, or hereditary thyroid cancer syndrome (Cowden syndrome, familial polypoid adenomatosis, Carney complex, Werner syndrome, multiple endocrine neoplasia 2A, or multiple endocrine neoplasia 2B), a rapidly growing thyroid nodule and/or hoarseness [10] [11].

Relevant physical findings suggesting possible malignancy include vocal cord paralysis, cervical lymphadenopathy, and fixation of the thyroid nodule to surrounding tissues [12]. With the discovery of a thyroid nodule greater than 1 cm in any diameter, a serum thyroid stimulating hormone level (TSH) should be obtained (recommendation # 2 of the American Thyroid Association [ATA])

[9]. If the TSH is low, a thyroid scan should be performed (this is the only indication nowadays to perform this study) to document whether the thyroid nodule is hyperfunctioning ("hot", tracer uptake is greater than the adjacent normal thyroid), iso-functioning ("warm", tracer uptake is equal to the surrounding normal thyroid), or non-functioning ("cold", tracer uptake is less than the adjacent normal thyroid tissue) [13]. Since hyperfunctioning thyroid nodules rarely contain malignancy, if one is found that corresponds to the nodule in question, a cytological evaluation is not necessary [9]. If there is obvious or subclinical hyperthyroidism, an additional evaluation with a thyroid scan is required [13]. High serum levels of TSH, even within high normal range, are associated with an increased risk of malignancy in the thyroid nodule, as well as a more advanced stage of the thyroid cancer [14].

Thyroglobulin (Tg) has a very high specificity for thyroid tissue and has led to its evaluation as a disease marker for more than 30 years. Serum Tg concentrations were found to be increased in a range of thyroid disorders, most prominently in advanced thyroid carcinoma [15] [16]. Nevertheless, considerable overlap was found between levels observed in benign thyroid disorders and those observed in tumor patients. Furthermore, many patients with relatively small thyroid carcinomas had serum Tg concentrations that fell within the range of values found in healthy individuals [16]. Based on this evidence during the initial evaluation of thyroid nodules, it is not recommended to routinely obtain serum Tg (recommendation 3 of the ATA) [9]. As mentioned previously serum levels of Tg may be elevated in the vast majority of thyroid diseases (benign and malignant) and it is an insensitive and nonspecific test for the diagnosis of thyroid cancer [17] [18]. Even when the diagnosis of thyroid cancer is established standard preoperative measurement of serum Tg or anti-Tg antibodies is not recommended by the ATA (recommendation # 34) [9]. Evidence from a systematic review and meta-analysis indicated that elevated preoperative levels of serum Tg may foresee a higher sensitivity for postoperative surveillance with serum Tg [19]. Anti-Tg antibodies obtained in the preoperative period do not appear to be an independent preoperative prognosticator of stage in patients with differentiated thyroid cancer (DTC), but the evidence is limited [19]. Evidence from the National Thyroid Cancer Treatment Cooperative Study (a large thyroid cancer registry that enrolled patients between 1987 and 2011), serum anti-Tg antibody status was not significantly associated with stage of disease on multivariate analysis, or with disease-free or overall survival on univariate or multivariate analyses [20]. Data that preoperative measurement of serum Tg impacts patient management or outcomes is not yet available.

The usefulness of serum calcitonin in the initial assessment of thyroid nodules has been evaluated in non-randomized prospective studies [21] [22] [23] [24], with mixed results, therefore, the ATA cannot recommend either for or against the routine measurement of serum calcitonin in patients with thyroid nodules (recommendation 4 of the ATA) [9].

A high-resolution ultrasound of the neck and thyroid should be performed in all patients with suspected thyroid nodules, nodular goiter, or any radiographic abnormality that suggests a thyroid nodule detected incidentally in another imaging study (computed tomography or magnetic resonance imaging, or 18 FDG-PET) (recommendation 6 of the ATA) [9]. The neck and thyroid ultrasound should evaluate the following characteristics [4] [9] [13]:

- The thyroid parenchyma:
  - Homogeneous or heterogeneous
- The size of the thyroid gland
- The size, location, and ultrasonographic features of any thyroid nodule
- The presence or absence of suspicious cervical lymph nodes in the central or lateral compartments of the neck

The characteristics that should be evaluated on ultrasound are [25] [26]:

- Node size (in three dimensions)
- The location (example—right upper lobe/if it is anterior or posterior)
- Description of the ultrasonographic characteristics of the thyroid nodule:
  - Composition of the nodule:
    - Solid, cystic or spongiform
  - Echogenicity:
    - Isoechoic, hyperechoic, hypoechoic
  - Margins:
    - Regular
    - Irregular: (defined as infiltrative, microlobulated or speculated)
  - Presence and type of calcifications:
    - Macro or microcalcifications
  - Shape:
    - If the nodule is taller than wider
  - Vascularity:
    - Central or peripheral

The ultrasonographic pattern associated with a thyroid nodule confers a risk of malignancy, and combined with the size of the nodule, guides decision-making (**Table 1**). The ultrasonographic pattern of high suspicion of malignancy includes hypoechoic nodules, solid nodules, or nodules with mixed components (a solid and partially cystic hypoechoic nodule) with one or more of the following characteristics: irregular margins (infiltrative, microlobulated), microcalcifications, shape than wider, peripheral calcifications on the cyst wall, evidence of extra thyroid extension [27] [28] [29].

Fine needle aspiration biopsy (FNAB) is the most accurate and cost-effective way de evaluate suspicious thyroid nodules (recommendation # 7 of the ATA) [9]. Thyroid nodules with a higher probability of obtaining a non-diagnostic cytology (cystic component greater than 25% to 50%) or a sampling error (nodules difficult to palpate or located in the posterior portion of the thyroid lobe), it is preferred to perform a FNAB ultrasound guided [31] [32].

Figure 1, **Figure 2** and **Table 2** provide an algorithm for the initial assessment

Table 1. Ultrasonographic patterns of thyroid nodules, estimated risk of malignancy, and management guidelines of thyroid nodules after FNAB [9] [30].

Ultrasonographic Pattern	Ultrasonographic Characteristics	Estimated Risk of Malignancy	FNA Size Cutoff (largest dimension)
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of extra thyroid extension (ETE)	Greater than 70% - 90%	FNA at equal or greater than 1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins without microcalcifications, ETE, or taller than wide shape	10% al 20%	FNA at equal or greater than 1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or ETE, or taller than wide shape	5% al 10%	FNA at equal or greater than 1.5 cm
Very low suspicion	Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate, or high suspicion patterns	Less than 3%	Consider FNA at equal or greater 2 cm Observation without FNA is also an option
Benign	Purely cystic nodules (no solid component)	Less than 1%	No biopsy

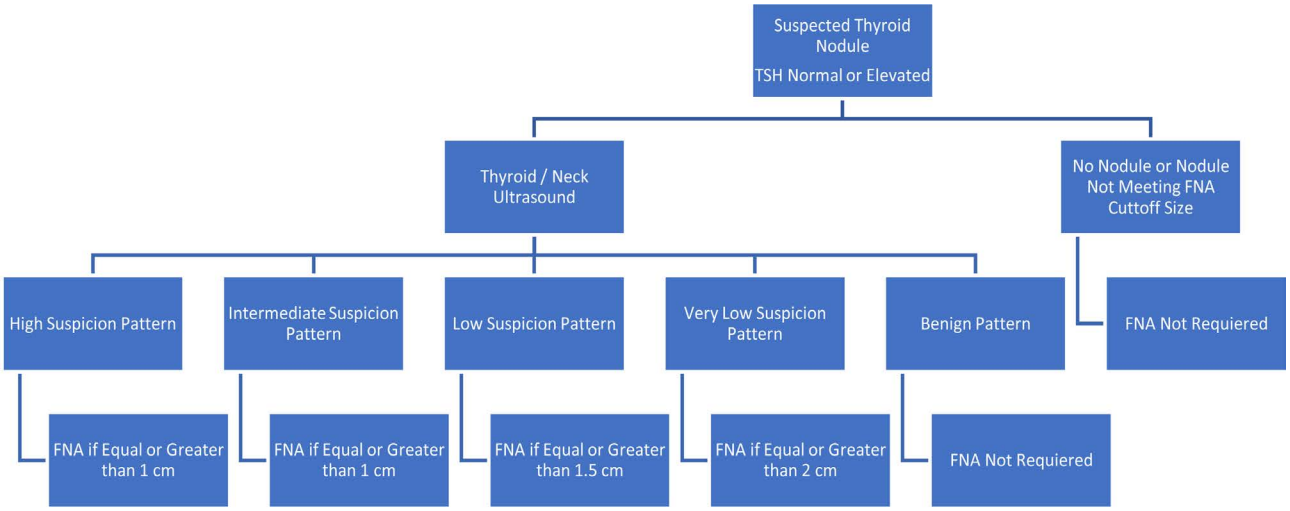

Figure 1. Algorithm for the initial evaluation and treatment of patients with thyroid nodules according to the ultrasound pattern.

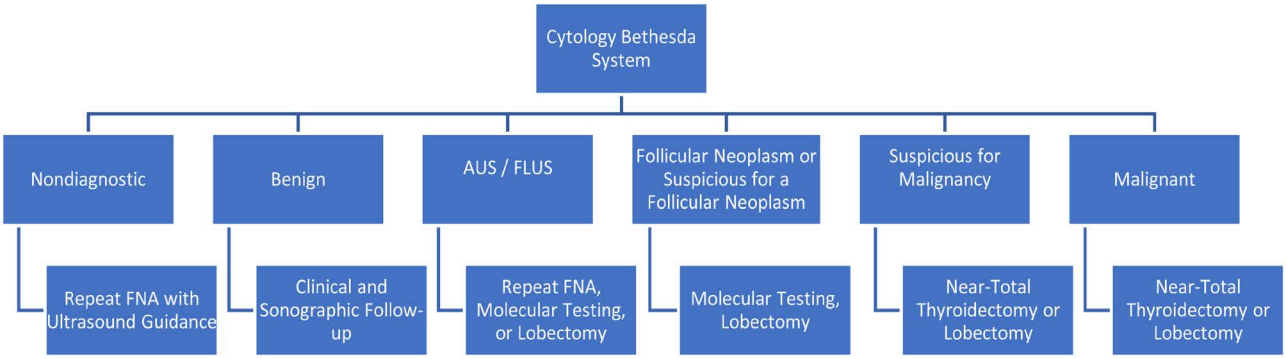

Figure 2. Algorithm for the treatment of patients with thyroid nodules according to the pattern the result of FNAB [30] [33].

Table 2. The 2017 Bethesda system for reporting thyroid Cytopathology [30].

Diagnostic Category	Risk of Malignancy if NIFTP Not Cancer	Risk of Malignancy if NIFTP Equals Cancer	Usual Management
Non-diagnostic or unsatisfactory	5% to 10%	5% to 10%	Repeat FNA with ultrasound guidance
Benign	0% to 3%	0% to 3%	Clinical and sonographic follow-up
Atypia of undetermined significance or follicular lesion of undetermined significance	6% to 18%	10% to 30%	Repeat FNA, molecular testing, or lobectomy
Follicular neoplasm or suspicious for a follicular neoplasm	10% to 40%	25% to 40%	Molecular testing, or lobectomy
Suspicious for malignancy	45% to 60%	50% to 75%	Near-total thyroidectomy or lobectomy
Malignant	94% to 96%	97% to 99%	Near-total thyroidectomy or lobectomy

and management of patients with thyroid nodules based on their ultrasonographic pattern and the results of FNAB [9].

4. The Bethesda System

In the year 2007 the National Cancer Institute Thyroid FNA State of the Science Conference presented consensus recommendations known as the Bethesda System for Reporting Thyroid Cytopathology [34] [35]. The Bethesda system includes six diagnostic categories and offers an approximation of cancer risk within each category based upon literature review and expert opinion (**Table 2**) [30].

Current studies that utilized the criteria and terminology of the Bethesda system to a large series of patients have shown a good concordance in reporting FNA cytology, with 89% to 95% of samples being satisfactory for interpretation, 55% to 74% reported as definitively benign, and 2% to 5% as definitively malignant [36] [37] [38] [39]. The left-over samples are cytologically indeterminate, including atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS) in 2% to 18% of the thyroid nodules, follicular neoplasm or suspicious for follicular neoplasm (FN/SFN) in 2% to 25% of the thyroid nodules, and suspicious for malignancy in 1% to 6% of the thyroid nodules. The Bethesda system has proven highly beneficial, allowing physicinas to speak with the same terminology and better convey malignant risk.

5. Non-Diagnostic or Unsatisfactory FNA Results

Non-diagnostic or unsatisfactory FNAB are those that do not meet the established quantitative or qualitative requirements to say that the cytological assessment is adequate (the presence of at least six well-visualized groups of follicular cells, each group containing at least 10 well-preserved epithelial cells, preferably in a single slide) [30] [34] [40]. When FNA is performed in a thyroid nodule and the initial cytology result is non-diagnostic, FNAB should be repeated with the support of ultrasound guidance, and if available, cytological assessment should be performed at the time of FNAB (recommendation # 10 of the ATA) [9] [41]

[42] [43]. It has been suggested that FNAB should be repeated no earlier than three months after initial FNAB to avoid a falsely positive interpretation due to reactive changes induced by the biopsy [44]. Two recent studies have questioned the need for a three-month waiting period after the first FNAB because they found no correlation between the diagnostic/accuracy performance of the second FNAB and the waiting time between procedures [45] [46]. Thyroid nodules that have undergone multiple FNABs that turned out to be non-diagnostic without having an ultrasonographic pattern of high suspicion can undergo a period of observation vs. surgical excision to have a definitive histopathological diagnosis (recommendation 10 of the ATA) [9]. Surgical excision should be considered for histopathologic diagnosis if the cytologically non-diagnostic nodule has a high suspicion sonographic pattern, growth of the nodule (greater than 20% in two dimensions), is detected during US surveillance, or clinical risk factors for malignancy are present [9].

In several published series of patients classified according to the Bethesda system, non-diagnostic samples constituted 2% to 16% of all FNAB samples, of which 7% to 26% were resected [36] [37] [47]. The frequency of malignancy among all the FNAB initially classified as non-diagnostic was 2% to 4% and among the non-diagnostic samples that were finally resected the frequency of malignancy 9% to 32% [36] [37] [47].

6. Benign Cytology

If the thyroid nodule turns out to be benign in cytology after FNAB, no additional diagnostic or treatment studies are needed immediately (recommendation 11 of the ATA) [9]. Although prospective studies are lacking, the rates of malignancy in the retrospective series range from 1% to 2% [30] [33] [48] [49] [50].

7. Atypia of Undetermined Significance (AUS) or Follicular Lesion of Undetermined Significance (FLUS) on Cytology

Based on the Bethesda system, this diagnostic category is reserved for specimens that contain cells with architectural and/or nuclear atypia that are more prominent than expected for benign changes, but not sufficient to be placed in one of the highest-risk diagnostic categories [30] [33] [34] [51]. In the studies that used the criteria established by the Bethesda system, the risk of cancer for patients with AUS/FLUS who underwent surgery was 6% to 18% if NIFT (non-invasive follicular thyroid neoplasia with papillary nuclear characteristics) it is not considered cancer, and 10% to 30% if NIFT is considered a cancer [24].

For thyroid nodules with AUS/FLUS cytology after a FNAB, with clinical and ultrasonographic features of concern, the assessment can be continued by repeating the FNAB or if the technology is available, molecular tests can be used to complement the risk assessment of malignancy instead of preceding directly with a strategy of either surveillance or diagnostic surgery (lobectomy). Patient preference should be considered in decision-making (recommendation 15 of the

ATA) [9]. If FNAB is not repeated, and molecular tests are not performed, or both studies were inconclusive, a diagnostic surgical excision may be performed for the thyroid nodules with Bethesda AUS/FLUS classification, according to the clinical risk factors, the ultrasonographic pattern, and patient preference (recommendation 15 of the ATA) [9].

8. Folicular Neoplasm/Suspicious Folicular Neoplasm Cytology (FN/SFN)

This diagnostic category of the Bethesda system is used for cellular aspirates:

- Composed by follicular cells arranged in an altered architectural pattern characterized by cell crowding and/or microfollicular formation, lacking nuclear characteristics of papillary carcinoma

  or

- Composed almost exclusively oncocytic cells (Hurthle) [30] [33] [34] [52] [53].

This is a category has an intermediate risk of malignancy in the Bethesda system, with an estimated risk of malignancy between 10% amd 40% if NIFT is not considered cancer and between 25% to 40% if NIFT is considered cancer [9] [30]. This category represents 1% to 25% (average, 10%) of all FNA samples [9].

Diagnostic surgical excision (lobectomy) is the long-established standard for the treatment of thyroid nodules with a FN/SFN cytology. However, if you have the technology, after taking into account the clinical assessment and the ultrasonographic characteristics, molecular tests can be used to complement the assessment of the risk of malignancy instead of proceeding directly with surgery (recommendation 16) of the ATA) [9]. Patient preference should be considered in clinical decision making. If the molecular tests cannot be performed or are indeterminate, surgical excision can be considered for the definitive diagnosis of thyroid nodules classified as FN/SFN (recommendation 16 of the ATA) [9].

9. Suspicious Cytology for Malignancy

This diagnostic category of the Bethesda system represents 1% to 6% of all FNABs and is reserved for aspirates with cytological features that generate a high suspicion of malignancy (mainly for papillary thyroid carcinoma) but that are not sufficient for a conclusive diagnosis [30] [33] [34] [54]. This is the highest risk category for indeterminate cytology in the Bethesda System, with an estimated cancer risk of 45% to 60% if NIFT is not considered cancer and 50% to 75% if NIFT is considered cancer [30]. Due to the high risk of cancer, the diagnosis of suspicious papillary carcinoma is an indication for surgery [9].

If FNAB results in a suspicious cytology for papillary thyroid carcinoma, the surgical treatment should be very similar to the management of a frankly malignant reported for the FNA. Factors that we must take into account in offering the definitive treatment with a suspicious cytology for papillary thyroid carcinoma, are the clinical risk factors, the ultrasonographic characteristics, the pa-

tient's preference, and possibly the results of the molecular tests (BRAF, RAS, RET/PTC, PAX8/PPAR) (recommendation 17 of the ATA) [9].

10. Malignant Cytology

If the cytological result is diagnostic of primary thyroid malignancy, surgery is usually recommended (recommendation 12 of the ATA) [9].

A cytology diagnosis of primary thyroid malignancy will almost always lead to thyroid surgery. However, in some parts of the world under research protocol active surveillance can be offered as an alternative to immediate surgery in certain patients who meet some very specific criteria [45] [46]:

- Patients with very low risk tumors (papillary microcarcinomas without clinically evident metastases or local invasion, and without convincing cytological evidence of aggressive disease)
- Patients with high surgical risk due to multiple comorbidities
- Patients with a relatively short lifespan (severe cardiopulmonary disease, other malignancies, very old age)
- Patients with concurrent medical or surgical problems that must be addressed before thyroid surgery

11. Molecular Studies in the Assessment of Thyroid Nodules

The principal proposed of molecular markers in indeterminate thyroid FNA specimens is diagnostic (ruling out or ruling in malignancy), with the connotation of a companion use to inform decision-making on primary surgical treatment (*i.e.*, the decision to perform surgery and if so, the extent of surgery) [9].

Several studies on the use of molecular tests in patients with indeterminate FNA cytology respectively evaluated a panel of seven genes for genetic mutations and chromosomal rearrangement (BRAF, RAS, RET/PTC, PAX8/PPAR) [55], an expression gene classifier (GEC 167; expression of the messenger RNA of 167 genes) [56], and immunohistochemistry of galectin-3 (in cell blocks) [57]. An ideal "rule-in" test would have a positive predictive value (PPV) for histopathologically proven malignancy similar to a malignant cytologic diagnosis (98.6%), and an ideal "rule-out" test would have a negative predictive value (NPV) similar to a benign cytologic diagnosis (96.3%) (predictive value estimates are based on a meta-analysis of performance of the Bethesda system) [38], and these would hold true with a reasonable degree of precision and reproducibility. Currently, there is no single optimal molecular test that can definitively confirm or rule out a malignancy in all cases of indeterminate cytology, and more studies are needed in the long term to demonstrate clinical utility before it becomes the standard but the future of the evaluation of thyroid nodules and the management is going in this direction.

12. Conclusion

Thyroid nodules are very common, being detected in up to 65% of the general

population with a lifetime risk for developing a palpable thyroid nodule been anywhere between 5% and 10%, however, high resolution ultrasound has revealed thyroid nodules in 19% to 68% of randomly selected individuals. The vast majority of thyroid nodules is benign, clinically irrelevant, and can be safely managed with a good surveillance program. The main objective of the initial evaluation and long-term management of thyroid nodules is the identification of the thyroid nodules that harbor a clinically significant cancer, cause symptoms, or may progress leading eventually to a surgical solution. A process that utilizes high resolution neck and thyroid ultrasound, when indicated FNA, and molecular testing, allows a personalized, risk-based approach that encourages high-quality care and minimizes cost and needless testing.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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