Review Article

Role of Genetic Testing in the Management of Indeterminate Thyroid Nodules in the Indian Setting

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Abstract

The increased detection of thyroid nodules in the human population has led to an increase in the number of thyroid surgeries without an improvement in survival outcomes. Though the choice for surgery is straightforward in malignant thyroid nodules, the decision is far more complex in those nodules that get categorized into indeterminate thyroid nodules (ITN) by fine needle aspiration. Therefore, there is a pressing need to develop a tool that will aid in decision-making among the ITN. In this context, the development of various molecular testing (MT) panels has helped to confirm or rule out malignancy, reducing unnecessary surgeries and potentially guiding the extent of surgery as well. Currently, such tests are widely used among the Western population but these MT panels are not used by the South Asian population because of non-availability of validated panels and the high cost involved. There is a need to develop a suitable panel which is population-specific and validate the same. In this review, we would focus on current trends in the management of ITN among the South Asian population and how to develop a novel MT panel which is cost-effective, with high diagnostic accuracy obviating the need for expensive panels that already exist.

Keywords: Asia, cytodiagnosis, India, molecular diagnostic technique, molecular testing, thyroid nodule

Introduction

Thyroid cancer has been ranked as the ninth most common type of cancer in terms of incidence globally, according to Global Cancer Observatory(GLOBOCAN) 2020.[1] The majority of thyroid cancers (more than 90%) are differentiated thyroid cancers (DTC).[2,3] There are global variations in the incidence of DTC which is likely due to a number of factors, including differences in population demographics, genetics and environmental exposure.

The wide availability of high-resolution ultrasonography (USG) and its inappropriate usage has led to an increase in the detection of incidental thyroid nodules and an increasing prevalence of thyroid nodule to 68%. However, only 7–15% of these nodules carry an underlying risk of malignancy (ROM).[3,4] Technological advancements have led to at least 50% increase in the incidence of thyroid malignancy in women around the world, and an increased incidence may also be linked to iodine fortification.[5,6] This has led to an exponential increase in the number of thyroid nodule detection and surgeries; however, the survival rates still remain the same. Hence, the benefit of surgically treating such patients should be relooked[1,7-9].

Thyroid nodules are commonly evaluated using fine needle aspiration cytology (FNAC), which is considered the gold standard. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which was updated in 2023, is a standard system for reporting findings from FNAC of thyroid nodules. It categorizes FNAC findings into six categories among which category 2 is benign wherein the ROM is 5% or less, while categories 5 and 6 fall more in favour of malignancy (70–98%) necessitating surgery. About 20–25% of the nodules are categorized as categories 3 and 4 and are called indeterminate

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thyroid nodules (ITN), and the ROM in this group ranges from 15% to 40%.[10,11] This category includes atypia of undetermined significance (AUS)/follicular lesion of undetermined significance and follicular neoplasm (FN)/suspicious for a follicular neoplasm.[11,12] Nodules that fall under the ITN present a challenge in management as further evaluation is required to determine whether follow-up or surgery is necessary.

The Thyroid Imaging Reporting and Data System (TIRADS) is a standardized, reproducible and evidence-based system for the interpretation of USG images of the thyroid gland. It has improved the risk stratification of thyroid nodules that need further evaluation. Different organizations and bodies [e.g., the American College of Radiologists (ACR-TIRADS), the European Thyroid Association (EU-TIRADS) and the Korean Society of Thyroid Radiology (K-TIRADS)] have proposed different criteria for TIRADS classification, but the general principle remains the same.[13-16] As per ACR-TIRADS, performing FNAC is recommended only if USG characterizes the nodule as TR5 and larger than 1 cm, TR4 and larger than 1.5 cm, or TR3 and larger than 2.5 cm. This approach helps to prevent unnecessary FNAC and avoid pursuing further evaluation for indolent nodules.[15]

In the current era, molecular testing (MT) is widely recognized as one of the most critical components of the management of ITN, to categorize the nodule as benign or malignant, and has been incorporated into various guidelines.[11,17] MT has reduced the unnecessary surgeries by 49% to 66%.[18,19] There are many countries where MT is unavailable and patients are either offered surgery or advised follow-up based on the risk assessed by the treating physician. However, more than 70% of patients with ITN end up in surgery.[8,10] In India, the currently available diagnostic MT cost (at least 3000 USD) is manifold when compared to the cost of thyroidectomy.[20,21] Furthermore, performing thyroidectomy can be associated with complications associated with vocal cord palsy and hypocalcaemia.[22] Moreover, these tests are not readily available and have not been validated, thus making surgery a standard of care in most cases. In this review, we aim to explore the role of genetic testing in managing ITN in the Indian setting. Also, we will discuss various measures that can be taken to optimize the utility of MT for thyroid cancer in India.

ITN and ROM

A meta-analysis by Vong HG *et al*. has shown that the prevalence of ITN is greater in Western populations when compared to the Asian population (15.6% vs 11.9%). This can be related to a high prevalence of follicular variant papillary thyroid carcinoma (FvPTC) when compared to classical papillary thyroid carcinoma (PTC) among the Western population. The ROM in patients in the AUS group is 41.9% in the Asian population and 25.4% in the Western population (P = 0.002). However, it is also worthwhile noting that the resection rate was higher in the Western population when compared to the Asian population (51.3% vs 37.6%; P = 0.048). Asian pathologists classify FNAC of equivocal PTC nuclear features as category 3, whereas it would be category 5 in the Western world.[9] A meta-analysis by Ngo *et al*. comparing Asian and Western populations noted a higher ROM among patients with ITN in the Asian population, when MT was used (78.3% vs 36.5%) compared to when it was not used (41.9% vs 25.4%).[23] There is a high prevalence (more than 50%) of malignancy in the Indian population based on individual studies of ITN patients who have undergone surgery.[24-27]

Effect of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) on ITN

According to the fourth edition of the World Health Organization (WHO) Classification of Tumors of Endocrine Organ, NIFTP has an extremely low likelihood of developing into a malignant tumour. In fact, it has been compared to carcinoma *in situ* in breast cancer, leading to a reclassification of NIFTP as a neoplasm rather than a cancer[14] but a few cases of nodal and distant metastasis have been noted; so, Nikiforov *et al*. introduced more rigorous criteria in 2018 for classifying NIFTP. These updated criteria include the use of mutation analysis as an aid in the classification process.[28]

A meta-analysis by Haaga *et al*. demonstrated that the prevalence of NIFTP is 4.4% in the Western and 1.8% in the Asian population. The low prevalence of NIFTP among the Asian population is partly attributable to a conservative approach of managing thyroid nodules with follow-up. The majority of NIFTP belonged to ITN (29.8% in Bethesda 3 and 28% in Bethesda 4). Considering NIFTP as benign entity, the ROM reduced to 7.4% (from 36.6% to 29.2%) in Bethesda 3 nodules and 9% (from 35.1% to 26.1%) in Bethesda 4 nodules. However, in the Asian population, risk reduction was 4.7% in Bethesda 3 nodules and 6.0% in Bethesda 4 nodules.[29] A meta-analysis by Rana *et al*. showed the prevalence of NIFTP is 14.4% in India.[30] A study by George *et al*. in the Indian population noted RAS mutation in 10% of NIFTP patients.[31] Other mutations common in NIFTP include THADA fusions, PPARc-PAX8 fusions and BRAFK601E.[32] With the introduction of NIFTP, there were major issues on MT as it influenced both the positive predictive value (PPV) (e.g. ThyroSeq v2 PPV reduced from 42% to 33%) and the negative predictive value (NPV) (e.g., with Afirma Gene Expression Classifier (GEC), the NPV reduced from 96% to 81%).[20]

Utility of MT using statistical terminologies and data

One should understand that NPV and PPV depend on the prevalence of malignancy, characteristic of MT, patient characteristics and cytopathology results. MT can be grossly categorized as 'rule-in' or 'rule-out' tests, depending on their intended purpose and diagnostic criteria [Figure 1].

Rule-in test

When there is a high suspicion of malignancy among ITN, then a rule-in test (high PPV and high specificity) would be better.[8,23,27] The minimal PPV of a test was aimed to be close

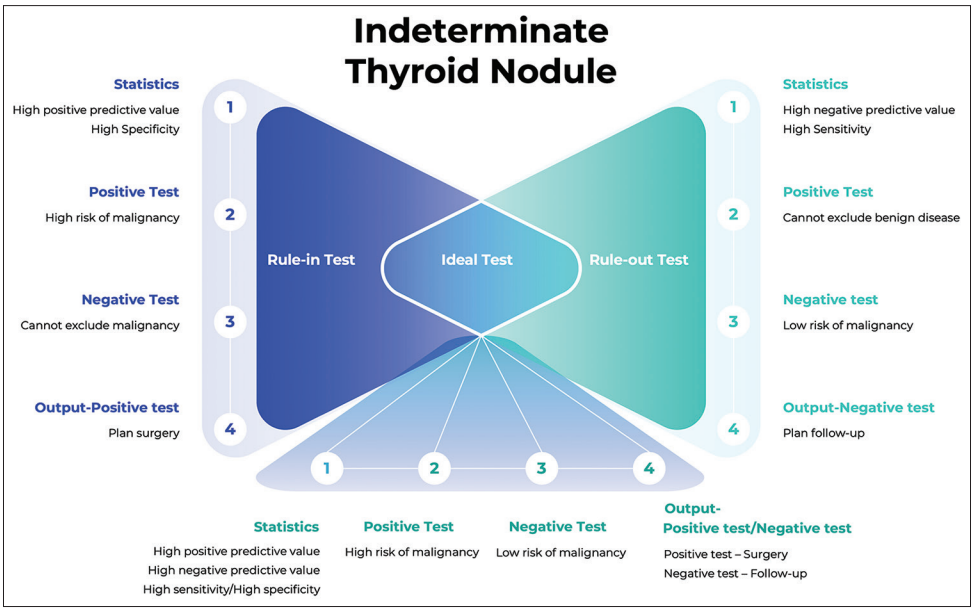

Figure 1: Utility of different molecular testing using rule-in, rule-out and ideal test

to the ROM associated with Bethesda 5 nodule, that is 50–75%. Thus, many studies targeted a PPV of over 60% which can be derived if the specificity of the test is above 80% when the prevalence of disease is over 25%.[21] An ideal rule-in test should have a PPV of 95%; so, a radical surgery (i.e., total thyroidectomy) could be planned.[10]

Rule-out test

A rule-out test would have a high NPV of more than 95%, which is similar to FNAC diagnosis of a benign thyroid nodule.[8] The performance of MT mainly depends on the prevalence of malignancy in ITN.[33,34] So, when we approach a population where the prevalence of malignancy among ITN is low (e.g., Western population), a rule-out test (high NPV and high sensitivity) would help, as PPV will be lower.[35] A study by Vargas-Salas *et al*. noted that, to get a NPV of more than 95%, the sensitivity should be more than 90% and the prevalence of malignancy should be less than 35%. A highly specific rule-out test would identify the true benign tumours among those classified as benign based on FNAC and imaging and thus has a direct impact on cost-effectiveness.[21] A negative MT, in this category, would mean that the chance of malignancy in the nodule is equivalent to benign thyroid nodule (i.e. <5%), and so, the patient can be safely followed up.[17]

Benign call rate (BCR)

The BCR is the proportion of ITN that may receive a benign or negative molecular test result. This rate reflects the number of surgeries that are avoided due to MT, as ITNs with negative results can be managed similarly to benign thyroid nodules. The BCR is a crucial metric for assessing the effectiveness of MT. The BCR for Afirma GEC was 48% and 66% for Genomic Sequencing Classifier (GSC). The BCR for ThyroSeq v2 was 65% and it improved to 74% in ThyroSeq v3.[19,34,35] At present, ThyroSeq v3 and Afirma GSC are the two main MT panels in clinical use and they avoid surgery more than the predecessors.[35] Further, it should be remembered that the mutations among ITN depend on the population under study and cannot be blindly extrapolated to all.[34]

To derive a good molecular panel, tumour histopathology should be the gold standard, without which the true prevalence of malignancy will not be known, and the applicability of MT may be in question. The impact of this factor was noted in the meta-analysis of studies on Afirma GEC, where most patients who tested negative did not undergo surgery and the true prevalence of disease was not known.[34]

Currently available MT

MT that are currently widely available are listed below:

- Mutation/fusion (M/F)-based test
- RNA-based
- miRNA-based
- Multiplatform-based approach
- Others: liquid biopsy

Currently available important MT along with their performance when the panel was introduced are tabulated in Table 1. Table 2 shows the performance of the MT in the post-marketing period.

Mutation/fusion-based test

The detection of $BRAF^{V600E}$ in thyroid malignancy bykimura et al. in 2003 led to a stepping stone for further molecular diagnosis in thyroid malignancy. $BRAF^{V600E}$ constitutes the most common BRAF mutation (98–99%), which is noted in 29% to 83% of PTC,[36] the presence of which is hypothesized due to high dietary iodine content intake. The presence of the TERT promoter mutation (C228T), which was first described in 2013, has been demonstrated only in the malignant thyroid nodule. The RAS mutation has been noted in follicular thyroid carcinoma (FTC). The prevalence of N-RAS, H-RAS and

Table 1: Demonstrates currently available important MT along with its performance

Molecular testing	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Afirma GEC[46]	92	52	47	93
7-gene panel[40]	AUS/FN: 63/57	AUS/FN: 99/97	AUS/FN: 88/87	AUS/FN: 94/86
ThyraGenX®/ThyraMIR®[50]	89	85	74	94
ThyraMIR®/ThyGeNEXT®[51]	93	90	74	95
RosettaGX Reveal[49]	100	80	41	100
ThyroSeq v2[42]	90	93	83	96
ThyroSeq v2.1[70]	91	92	77	97
Afirma GSC[47]	91	68	47	96
ThyroSeq v3[12]	94	82	66	97

Table 2: Demonstrates the performance and utility of different MT based on meta-analysis

Molecular testing	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Afirma GEC[32,34,43]	95-98	12-25	39-45	88-91
ThyroSeq v2[32,43]	84-86	75-78	51-58	93-95
Afirma GSC[32,62]	95-96	51-53	60-63	91-96
ThyroSeq v3[32,62]	95-99	50-64	70-78	92-96

K-RAS mutation in FTC is 8.5%, 3.5% and 1%, respectively. RET/PTC rearrangements were noted in 87% of patients post-Chernobyl radiation exposure and 6.8% of sporadic cases. TP53 mutations were noted in 80% of anaplastic thyroid carcinoma (ATC) and 26% of poorly differentiated thyroid cancer (PDTC), and it has not been seen in benign variants.[2,37] A study by Rashid *et al*. on ATC showed P53 mutation (20.5%) is common next to BRAF mutations (29.4%) among the Indian population.[38] A study comparing ATC and PDTC showed that ATC has high TP53 mutation (73% vs 8%), mutation in genes encoding for PI3K/AKT/mTOR pathway (39% vs 11%) and TERT promotor mutation (73% vs 40%). PDTC that met Turin proposal criteria was associated with a RAS-like mutation, and others had BRAF mutation. The EIF1AX was noted in 1% of PTC and 10% of PDTC and ATC.[39] Understanding and knowing the mutation profile in the population helps to plan a suitable next-generation sequencing (NGS) panel, for the population with ITN.

A study on multiple genes using NGS panel by Nikiforov *et al*. was a game changer. The seven-gene panel comprising $BRAF^{v600E}$, *NRAS* codon 61, *HRAS* codon 61 and *KRAS* codons 12-/13-point mutations and *RET/PTC1*, *RET/PTC3* and *PAX8/PPAR* rearrangements detected mutations which were prevalent in 70% of thyroid cancers and thus aided in its diagnosis. It was a good rule-in test.[8,40,41]

ThyroSeq v2 by CBLPath used a detection of >1000 hotspot mutation in 14 genes and 42 gene fusions. The test could be used both as a rule-in and rule-out test.[42,43]

ThyroSeq v3 by CBLPath included NGS-based analysis of 112 cancer-related genes for point mutations, gene fusions, copy number alterations or abnormal gene expression. Each genetic alternation was given value from 0 to 2 based on the strength of association with malignancy, literature review and previous report available from the institution. The final genomic classifier score of 2 and above is considered a positive test and <2 as a negative test.[12,44,45] It can be used as rule-in/rule-out test [Table 1].

mRNA-based analysis

Veracyte Inc., introduced Afirma GEC (South San Francisco, CA, USA) which used microarray technology to check 167 different genes, and this included 142 common mutations and 25 uncommon mutations associated with thyroid cancers. It would categorize a nodule as benign and suspicious and is a good rule-out test.[10,46]

Afirma GSC included 12 classifiers which has 10,196 genes which will categorize the nodule into benign or suspicious. It is a good rule-in/rule-out test.[47] The performance of GSC suffered heavily when the test was introduced in different institutions/settings (e.g., PPV of 14% vs 57%).[45,48]

A prospective single-centre study compared the two MT panels that randomized Bethesda 3/4 nodules to Afirma GEC versus ThyroSeq v2 MT the BCR differed (ThyroSeq 77% vs GEC 43%).[17] A randomized controlled trial has shown no significant difference between ThyroSeq v3 and Afirma GSC and both could avoid a diagnostic surgery in 49% of the patients.[44] Unlike preliminary test results, meta-analysis showed a wide variation suggesting that no ideal test is yet available [Table 2].

MiRNA-Based Platforms

RosettaGX Reveal is a miRNA-based platform. miRNA is very stable and thus does not require a fresh FNA sample, and the test can be conducted from routinely prepared FNA smear. The assay involves 24 selected miRNAs. The analysis involves combining several linear discriminant analysis steps along with a K-nearest neighbour-based classifier.[49]

Multiplatform-based approach

ThyraMIR®/ThyGenX® are tests developed by Interpace Diagnostics. They used FNA samples to check a seven-gene mutation fusion panel which includes BRAF, RAS, RET and PAX8 along with 10 miRNA gene alternations. The test result will be reported as positive, if either of the tests is reported positive or negative[50]

ThyraMIR®/ThyGeNEXT® (MPTX) was also developed by Interpace Diagnostics. They used cells from the cytology slides which were used to classify nodules as ITN. A validated panel of 10 specific microRNAs was used in ThyraMIR. Test results were reported as negative, moderate or positive.[51]

Others

A study by Dutta *et al*. on cell-free DNA (cfDNA) noted that a cut-off of 67.9 ng/ml could predict malignancy in the ITN with a sensitivity of 100% and specificity of 92.3%.[52] A study by the same group on driver mutation in plasma on ITN noted a sensitivity of 84.38%, specificity of 79.31%, PPV of 81.82% and NPV of 82.14%.[25]

A meta-analysis has shown that they are mostly rule-out tests, despite being thought of as an ideal testing platform [Tables 1 and 2]. While the Afirma panel has not disclosed its mRNA panel, global research on more than a dozen of M/F genes has led to the development of a diagnostic panel suitable for the population under study, and the addition of miRNA can add more utility to the MT.

MT status in India [Table 3]

Studies are limited to M/F panels, and only a few genes have been studied. Most of the Indian studies on malignant thyroid nodules have looked at BRAF mutation,[36] RAS,[25,53,54] TERT,[25] RET/PTC[25,53-56] and PAX8-PPARG[25] alterations. These MT have been widely used in the evaluation of malignant nodules. MT are performed mostly on tissue samples and few in FNAC and plasma. MT on ITN are few[25,52,54] despite a high prevalence of thyroid nodule, and there is a clear lacuna.

Advantages of using M/F panel approach

- M/F panels are extensively researched for their diagnostic utility.
- Preventing unnecessary surgery: M/F panel helps to diagnose malignancy in ITN, and this potentially could avoid surgery in three-fourths of the nodules currently operated. Thus, this would improve the quality of life of patients.[18,57]
- Reproducibility: A major advantage of using M/F panels is with respect to easy reproducibility and validation.
- Preoperative prediction of histology: The presence of BRAF is noted in about 40% of papillary thyroid carcinoma. TP53 and CTNNB1 have been noted in ATP and RET in medullary thyroid carcinoma.
- Preoperative planning and the extent of surgery: Based on a retrospective analysis, it was estimated that a 11% to 44% surgical plan (e.g., lobectomy or total thyroidectomy) could have changed if MT was available preoperatively.[10] For example, the presence of BRAF, RET/PTC1 rearrangement and TERT mutation may

Table 3: Various MT conducted in India

Mutation	Author/year of publication/specimen/number	Tumour category analysed	Prevalence
BRAF	Chakraborthy *et al*. 2012. Tissue, *n*=140 (36)	PTC, FTC, MCT, FA, FH, HCA	33% (overall) 53.4% (in PTC)
	Khan *et al*. 2014 Tissue, *n*=60[63]	PTC, FTC, PDTC	25%
	Nair *et al*. 2017. Tissue, *n*=59[64]	cPTC, FvPTC	51%
	Krishnamurthy *et al*. 2017. Tissue, *n*=79[65]	cPTC, FvPTC, FTC	31.6%
	Hemalatha *et al*. 2018. FNAC, *n*=277[26]	All categories	27.2% (overall) 46% (in malignancy)
	Ahmad *et al*. 2018. Tissue, *n*=95[66]	PTC, FTC, MTC, FA, HCA	38%
	George *et al*. 2018. Tissue, *n*=109[53]	cPTC, FvPTC, TvPTC, OvPTC	51.38%
	Chirayath *et al*. 2019. FNAC, *n*=54[27]	Indeterminate nodule	4%
	Vishwanath *et al*. 2019 FNAC, *n*=20[54]	All categories	35%
	Anand *et al*. 2021. FNAC/Histopathology specimen, *n*=45[67]	TBSRTC category IV/V	28.9%
	Kumari *et al*. 2021. FNAC, *n*=45[68]	PTC	73%
	Ashwini *et al*. 2022. Tissue, *n*=15[69]	PTC	13%
	Dutta *et al*. 2023. Plasma, *n*=223[25]	All categories	18.8%
RAS	George *et al*. 2018. Tissue, *n*=109[53]	cPTC, FVPTC, TvPTC, OvPTC	7.3%
	Vishwanath *et al*. 2019. FNAC, *n*=20[54]	All categories	40%
	Dutta *et al*. 2023. Plasma, *n*=223[25]	All categories	9.9%
TERT	Dutta *et al*. 2023. Plasma, *n*=223[25]	All categories	0.4%
RET/PTC	Rao *et al*. 2014. Tissue, *n*=30[56]	cPTC, FvPTC, SvPTC, OvPTC	87.5%
	George *et al*. 2018. Tissue, *n*=109[53]	cPTC, FvPTC, TvPTC, OvPTC	0%
	Khan *et al*. 2018. Tissue, *n*=48[55]	PTC, FTC, other cancer	20.8%
	Vishwanath *et al*. 2019. FNAC, *n*=20[54]	All categories	0%
	Dutta *et al*. 2023. Plasma, *n*=223[25]	All categories	0.4%
PAX8-PPARG	Dutta *et al*. 2023. Plasma, *n*=223[25]	All categories	0%

PTC=papillary thyroid carcinoma; cPTV=classic PTC; FvPTC=follicular variant of PTC; TvPTC=tall cell variant of PTC; SvPTC=solid variant of PTC; OvPTC=oncocytic variant of PTC; FTC=follicular thyroid carcinoma; MTC=medullary thyroid carcinoma; HTC=Hurthle cell thyroid cancer; PDTC=poorly differentiated thyroid cancer; FA=follicular adenoma; FH=follicular hyperplasia

warrant a total thyroidectomy, and lobectomy may suffice in the presence of RAS mutations as the disease can be follicular in origin or benign.[10,58] Also, BRAF mutations have been associated with a central compartment nodal metastasis (56%) and suggest the need for central compartment clearance at the time of surgery, and the need for a sentinel lymph node biopsy in the case of RET/PTC is a question that needs to be answered.[41] The need for completion thyroidectomy for a patient can be explained better based on a mutation profile, than just a histopathological diagnosis.[32]

- NIFTP: ITN carries a high risk of NIFTP, whose diagnosis and categorization could be probably guided with M/F panel.[11,59] NIFTP is considered a benign entity, and so, such tumours can be conservatively managed with limited surgery.[29,60]
- Predicting aggressive tumours: The presence of BRAF is associated with Extrathyroidal extension (ETE) and central compartment nodal metastasis and advanced-stage disease.[36] RET/PTC is associated with aggressive disease with 35% presenting with lateral neck nodal metastasis and 8% with distant metastasis. RAS/PAX8/PPARG/BRAFK601E-positive tumours show an encapsulated picture and a lesser association with risk of nodal metastasis and ETE.[2,17,41]
- Risk of distant metastasis: A study by Yip *et al*. with matched cohort without distant metastasis showed that the presence of TERT mutations, late hit mutations, such as TP53, AKT1 and PIK3CA, was associated high risk of distant metastasis.[17,61]
- Risk stratification of disease: The American Thyroid Association (ATA) has currently included the BRAF mutation in the indeterminate risk category. Recurrence has been associated with mutations.
- Targeted therapy: For recurrent tumours and those with radioactive iodine (RAI) resistance, targeted therapy based on the mutation profile will help in further management.
- Re-expression of sodium-iodide symporter (NIS): Mitogen-activated protein kinase (MEK) inhibitor, selumetinib, whose oncogenic driver pathways, mediated by BRAFV600E, has role in re-expression of NIS, and this would help in RAI therapy.[19]

How does one establish a MT panel?

The currently available and widely validated MT have different performance on meta-analysis. This challenges the use and interpretation of MT[62] [Table 2]. MT in FNAC specimens of thyroid would be ideal as it would allow the clinician to compare the reports with the existing global population. The sample size needs to be calculated based on the prevalence of ITN and the prevalence of malignancy in ITN. Feasibility, logistics and support at all levels starting from the sample collection, transport, storage, DNA/RNA extraction and testing need to be considered. The centre should have a low non-diagnostic result and the appropriate number of ITN in FNAC samples. There must be a high degree of concordance between cytology, surgery and ROM. The diagnostic MT should be restricted to ITN or else it would result in overtreatment or undertreatment of patients.[44] It would be ideal to consider MT in patients with ITN who undergo surgery; so, histopathology will be considered the gold standard.

In the Indian scenario, where the prevalence of malignancy is more than 50% in ITN, it would be better to develop a rule-in test with a multigene NGS panel which would target specific well-documented hotspots and then to arrive at an ideal test by adding more mutations, fusion, copy number alterations, abnormal gene expression or miRNA.[33,44] The validation of such tests in a specific population needs to be conducted. An indigenous molecular diagnostic kit suitable for the population might play a major role in the development of a diagnostic MT.

The diagnostic MT should be used judiciously and only when required.[20] There are some situations where MT although applicable in ITN may not be useful. This may include patient factors (wanting surgery for cosmesis, fear of cancer, compressive symptoms, malignancy-related symptoms), tumour-related factors (large tumour, clinical and radiological features suspicious of malignancy) and surgery as per patient preference.[21] All in all, there is a need to develop a cost-effective, validated diagnostic tool which can be made widely available.

Conclusion

The prevalence of mutations in a malignant nodule in the Asian setting appears to be similar to the Western population, but the malignancy rate among the ITN is high in India. Given the numerous advantages of M/F panels, a cost-effective panel that aids in disease management, including the extent of surgery, is needed in a developing country, such as India. An in-house NGS panel needs to be introduced, standardized and validated. This would help in the improvement of the quality in the management of ITN.

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Conflicts of interest

There are no conflicts of interest.

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