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PROGNOSTIC GENETIC MARKER-GUIDED RISK STRATIFICATION AND MANAGEMENT OF THYROID CANCER

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INTRODUCTION

Thyroid cancer is a common endocrine malignancy, which histologically includes follicular epithelial cell-derived thyroid cancer and para-follicular C cell-derived medullary thyroid cancer (MTC).¹ The former consists of papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and anaplastic thyroid cancer (ATC). PTC and FTC are the most common thyroid cancer, accounting for 80–90% and 5–10% of all thyroid malignancies, respectively. ATC and MTC are uncommon, each accounting for 2–3% of thyroid malignancies. PTC is further classified into several variants, including most commonly conventional PTC (CPTC), followed by follicular-variant PTC (FVPTC), tall-cell PTC (TCPTC) and a few other rare variants.^{1–3}

PTC and FTC are differentiated thyroid cancer (DTC), which are generally indolent clinically with a low overall mortality but significant recurrence rate with the current treatments. Disease recurrence of thyroid cancer is associated with increased risk of patient morbidity and mortality. ATC can develop from preexisting DTC or *de novo*. Although ATC is uncommon, it is the most aggressive type of thyroid cancer, with a rapid lethality. There is also poorly differentiated thyroid cancer (PDTC), which can develop from DTC and has an intermediate clinical aggressiveness between DTC and ATC. PTC of tumor ≥ 1.0 cm is uniquely defined as papillary thyroid microcarcinoma (PTMC),⁴ which has an excellent clinical outcome in general but can be associated with poor prognosis and even mortality in

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some patients. The main goal in the clinical management of thyroid cancer is to prevent disease recurrence, patient morbidity and mortality while minimizing treatment-associated adverse consequences. Achievement of the optimal balance between therapeutic benefits and treatment complications rely on accurate risk stratification of thyroid cancer. This is currently pursued primarily based on the assessment of clinicopathological backgrounds, which has achieved considerably improved accuracy with comprehensive clinical approaches in recent years.⁵ Yet, controversies on how to optimally manage patients with thyroid cancer are still commonly encountered in clinical practice and in academic forums. The main challenge is that classical clinicopathological risk assessment is often inaccurate in thyroid cancer. An example is that clinically apparent low-risk thyroid cancer may turn out to be aggressive with poor outcomes, making clinical judgement and hence treatment decision making challenging. As a result, over-treatment of inherently low-risk thyroid cancer and under-treatment of potentially aggressive thyroid cancer are both common. Given the rapid increase in thyroid cancer incidence in recent decades and the currently large number of living patients with thyroid cancer,^{2,6} better risk stratification for more accurate management of thyroid cancer has become an even more important task than ever.

Molecular-based risk stratification of thyroid cancer has become an attractive strategy in guiding precision management of thyroid cancer in recent years.⁷ This is practically particularly important and promising for DTC given its high incidence^{2,6} and well-known prognostic molecular markers,^{1,7-14} which will be the main focus of the present discussion.

MAJOR ONCOGENIC GENETIC ALTERATIONS IN THYROID CANCER

Among the many genetic alterations in thyroid cancer, the prognostically most promising are oncogenic mutations, most prominently *BRAF*V600E and *TERT* promoter mutations and a few others.^{1,7-14} The occurrence of these mutations has an excellent concordance between the primary DTC and the matched metastatic tumor, consistent with their role in the progression of thyroid cancer.¹⁵

1) BRAF V600E Mutation in Thyroid Cancer

The *BRAF*V600E mutation was initially found to exist in thyroid cancer in 2003,¹⁶⁻²¹ which occurred with a prevalence of about 45–50% in PTC, 25–30% in ATC, and none in FTC and benign thyroid neoplasm.¹³ This is the most common activating point mutation in the *BRAF* gene, resulting in a valine-to-glutamic acid change in the BRAF protein, causing constitutive activation of the BRAF protein kinase and hence oncogenic activation of the MAP kinase pathway.²² Over the last 15 years, numerous studies have devoted to the characterization of the prognostic value of this mutation.^{1,7,9,10,12-14,23} In 2005, a Johns Hopkins study for the first time demonstrated the association of *BRAF*V600E with poor clinical outcomes of PTC, including increased disease recurrence and radioactive iodine (RAI) refractoriness of recurrent tumors, in addition to aggressive pathological behaviors, such as extrathyroidal invasion and lymph node metastasis.²⁴ Subsequent studies widely confirmed these findings although inconsistent studies were sometimes also reported.^{14,25} A multicenter study on 2,099 cases of PTC demonstrated that *BRAF*V600E had an independent prognostic value for the recurrence of PTC.²⁶ A separate multicenter study on

1,849 patients with PTC showed a strong association between *BRAFV600E* and PTC-specific mortality.²⁷ Overall, these and other studies demonstrate an important oncogenic role of *BRAFV600E* in the progression and aggressiveness of PTC.

2) TERT Promoter Mutations in Thyroid Cancer

The telomerase reverse transcriptase (*TERT*) was initially identified and characterized with a fundamental function to maintain the integrity of chromosomes by adding telomeres to their ends in early 1980's.^{28,29} *TERT* is now widely known to also promote various cancer-hallmark cellular and molecular activities.³⁰ These functions of *TERT* drive cell immortality and oncogenesis. Two somatic mutations, chr5:1,295,228C>T and chr5:1,295,250C>T (termed here as C228T and C250T, respectively), in the promoter of the *TERT* gene were found in melanoma^{31,32} and other cancers, including thyroid cancer.³³ Both *TERT* promoter mutations are predicted to generate a consensus binding site for E-twenty-six (ETS) transcription factors and confer the *TERT* promoter increased transcriptional activities.^{31,32} GABPA, an ETS transcriptional factor, was demonstrated to selectively bind the mutant promoter of the *TERT* gene and promote the expression of *TERT*.³⁴ Indeed, *TERT* promoter mutations were found to be associated with increased expression of mRNA and protein of *TERT* and telomere length.³⁵ *TERT*C228T is far more common than *TERT*C250T in thyroid cancer and the two collectively occur in 10–15% DTC, 40–45% PDTC and ATC, and virtually none in benign thyroid neoplasm.^{8,11} *TERT* promoter mutations have been widely found to be associated with aggressive tumor behaviors and poor clinical outcomes of thyroid cancer; it occurs particularly common in aggressive DTC, PDTC, and ATC and is associated with increased recurrence and mortality of DTC.^{15,33,36–45} These studies suggest a strong oncogenic role of *TERT* promoter mutations in the development of aggressiveness of thyroid cancer.

3) Genetic Duet of BRAF V600E and TERT Promoter Mutations in Thyroid Cancer

The initial 2013 study reporting *TERT* promoter mutations in thyroid cancer also reported an interesting association between *BRAFV600E* and *TERT* promoter mutations in PTC.³³ This phenomenon has been widely confirmed in many other studies in both primary PTC and metastatic PTC.^{8,11,15} The prevalence of the genetic duet of *BRAFV600E* and *TERT* promoter mutations in primary PTC was 7.7 % (145/1892) on average.¹¹ Several studies also reported an association between *TERT* promoter mutations and the *BRAFV600E* mutation in melanoma,^{31,46} suggesting that this is a general phenomenon in human cancer. Given the known oncogenic role of *BRAFV600E* and *TERT* promoter mutations each in thyroid cancer, it was speculated and demonstrated that this mutation duet was a robust genetic background for the most severe aggressiveness of PTC, hence predicting the worst clinicopathological outcomes of PTC.⁴⁵ In this study, when the cohort was divided into four groups—no mutation, *BRAFV600E*, *TERT* promoter mutations, and the genetic duet of coexisting mutations, each mutation alone had a modest adverse effect while the mutation duet had a robust effect on the poor clinicopathological outcomes of PTC, including extrathyroidal invasion, lymph node metastasis, distant metastasis, and disease recurrence (Figure 1).⁴⁵ This pattern of the effects of the genetic duet of *BRAFV600E* and *TERT* promoter mutations was similarly observed with PTC-related patient mortality,⁴⁴ which was fully confirmed in an expanded large study on 1,051 patients with PTC, showing a robust

synergistic adverse effect of the genetic duet on PTC-specific patient survival; the mortality was virtually zero in the absence of either mutation, slightly increased with either mutation alone, and robustly increased with the genetic duet (Figure 2).³⁹ Many subsequent studies demonstrated a similarly robust synergistic adverse effect of the genetic duet of *BRAF* V600E and *TERT* promoter mutations on clinicopathological outcomes of thyroid cancer.^{15,37,42,47,48} This remarkable clinical finding of the genetic duet was beautifully explained by a novel molecular mechanism described recently.⁴⁹ In this mechanism, the *BRAF* V600E constitutively activates the MAP kinase pathway, causing the phosphorylation and activation of FOS, which, as a novel transcriptional factor for the *GABPB* gene, binds and activates the promoter of *GABPB* and up-regulates its expression. *GABPB*, at elevated level, drives the formation of *GABPA/GABPB* complex, which in turn selectively binds and activates the mutant *TERT* promoter and robustly promotes the expression of *TERT*, conferring strong *TERT* oncogenicity. This represents a robust molecular mechanism underpinning the synergism between the *BRAF*V600E and *TERT* promoter mutations in driving the aggressiveness and poor clinical outcomes of thyroid cancer.

4) RAS Mutation and Its Genetic Duet with TERT Promoter Mutation in Thyroid Cancer

RAS mutations are common in follicular thyroid neoplasms, occurring in about 20–25% follicular thyroid adenoma, 30–45% FVPTC, 30–45% FTC, 20–40% PDTC and ATC, and rarely in CPTC and virtually none in TCPTC.¹ A significant association between *RAS* and *TERT* promoter mutations in thyroid cancer was reported in a number of studies, particularly in FTC and FVPTC.^{15,42,48} This genetic duet of *RAS* and *TERT* promoter mutations was also shown to be associated with poor clinical outcomes of thyroid cancer, including robustly increased disease recurrence and patient mortality.^{15,42,48} Some previous studies showed an association between *RAS* mutation and poor clinicopathological outcomes in FTC⁵⁰ and PDTC.^{51,52} It is possible that this effect of *RAS* mutation was actually the effect of the genetic duet of *RAS* and *TERT* promoter mutations since *RAS* mutation alone often occurs in benign follicular adenoma and low-risk DTC. *TERT* promoter mutations are fairly common in FTC and very common in PDTC and ATC.^{8,11,15} The genetic duet of *RAS* and *TERT* promoter mutations is thus probably common and constitutes an important genetic background for the aggressiveness of these cancers. In fact, the duet of *RAS* and *TERT* promoter mutations were shown to be highly concordant between primary and matched metastatic FTC and associated with ominous clinical outcomes.¹⁵ The molecular mechanism for this synergism between *RAS* and *TERT* promoter mutations in driving thyroid cancer aggressiveness remain to be elucidated, but it likely involves also the MAP kinase/ROS/GABP/*TERT* pathway used by the duet of *BRAF*V600E and *TERT* promoter mutations since *RAS* can also activate the MAP kinase pathway albeit less robustly. As *RAS* and *BRAF* mutations are mutually exclusive,^{1,13} their synergism with *TERT* promoter mutations represents a complementary mechanism of the two mutations to each other in driving the aggressiveness of thyroid cancer.

5) Other Oncogenic Genetic Alterations in Thyroid Cancer

There are some other oncogenic genetic alterations that play a role in thyroid cancer aggressiveness and may potentially have prognostic values. Among them are *TP53*, *EIF1A* and *β-catenin* mutations, which occur commonly in PDTC and ATC, but very rarely in DTC.

^{53–60} This distribution pattern suggests that these genetic alterations are involved in the development of aggressiveness of thyroid cancer and their occurrence, if ever, in DTC likely has a strong prognostic power for poor prognosis. However, the rareness of these mutations in DTC suggests that their clinical utility in the risk stratification of DTC is practically limited.

Genomic and large-scale genetic studies in recent years have unveiled overwhelming new findings in thyroid cancer.^{54,59,60} Large-scale epigenetic studies have similarly uncovered tremendous molecular information in thyroid cancer, such as aberrant miRNA and methylation.^{23,54,61} These are now bringing in a potentially exciting opportunity for discovering new prognostic molecular markers in thyroid cancer. Nevertheless, the biological functions of the new genomic/genetic/epigenetic molecular changes in thyroid cancer are largely undefined. Unlike *BRAF*V600E and *TERT* promoter mutations, most of these new molecular markers have limited clinical prognostic potential in thyroid cancer. Some of the common genetic rearrangements, such as *RET/PTC* and *PAX8/PPAR γ* , have no apparent impact on the development of aggressiveness of thyroid cancer and thus have a limited prognostic value.^{1,13}

CLINICAL APPLICATION OF PROGNOSTIC GENETIC MARKERS IN THYROID CANCER

Given the strong association of some of the oncogenic genetic markers, particularly *BRAF* V600E and *TERT* promoter mutations, with poor clinical outcomes and their relatively common occurrence, their prognostic application in thyroid cancer has robust clinical utility. However, depending on the genetic type and clinical setting, these mutations do not necessarily always herald ominous outcomes of thyroid cancer. Therefore, their prognostic use should not be indiscriminate but should be tailored to meet individualized need in specific clinical settings. A good utility of prognostic genetic markers is that they can be “tiebreaker” when a physician is faced with ambiguity from conventional clinicopathological risk assessment in treatment decision making for thyroid cancer. In this context, it is also important to emphasize that the high negative predictive values (NPVs) of these genetic markers for poor prognosis of thyroid cancer make a negative genetic test equally valuable. The following specific clinical settings exemplify the clinical application of prognostic genetic markers, particularly *BRAF*V600E and *TERT* promoter mutations, in thyroid cancer.

1) General Consideration of Clinical Application of High-risk Prognostic Genetic Markers

From the above discussion on the robust oncogenic role of the high-risk genetic alterations in the aggressiveness of thyroid cancer, including high patient mortality, it is reasonable to recommend that their existence in DTC should generally favor more aggressive treatment. These include the genetic duet of *BRAF*V600E and *TERT* promoter mutations, the genetic duet of *RAS* and *TERT* promoter mutations, and the rare *TP53*, *EIF1A* and *β -catenin* mutations. Specifically, it is reasonable to recommend total thyroidectomy for all patients with DTC harboring such genetic markers, even in cases of PTMC. Therapeutic and prophylactic neck dissections and RAI ablation will be usually reasonable in such patients.

As only 7.7% of PTC on average harbor the genetic duet of *BRAF*V600E and *TERT* promoter mutations,¹¹ if guided by this genetic duet, less than 10% of patients with PTC overall will be treated relatively aggressively. As high-risk genetic alterations are very rare in PTMC, only a small number of patients with PTMC will be treated aggressively based on them. In PTC >1.0–2.0 cm, particularly tumors >2.0 cm, prophylactic central neck dissection may be reasonable given the fact that large tumors are associated with increased disease recurrence⁶² and the high-risk genetic alterations are often associated with RAI refractoriness of recurrent disease,^{1,24,63} thus making initial elimination of metastatic lymph nodes particularly important. Patients with FTC harboring high-risk genetic alterations, such as *TP53*, *EIF1A*, and *β-catenin* mutations as well as the genetic duet of *RAS* and *TERT* promoter mutations, similarly favor aggressive treatments.

2) Clinical Application of BRAF V600E in Solitary Intrathyroidal PTC

It is generally acceptable to treat clinically apparent invasive/metastatic thyroid cancer with relatively aggressive approaches, such as total thyroidectomy and, in appropriate settings, therapeutic/prophylactic neck dissections and radioiodine ablation. However, how to treat intrathyroidal PTC—PTC without extrathyroidal invasion, lymph node metastasis, and distant metastasis—is not completely agreeable among physicians. The current American Thyroid Association (ATA) guidelines recommend lobectomy as an alternative option to total thyroidectomy for solitary intrathyroidal PTC (SI-PTC) of 1–4 cm in size.⁵ This recommendation is somehow controversial as it may not be a straightforward effort to decide lobectomy versus total thyroidectomy in an individual patient as such apparently clinically low-risk thyroid cancer may not uniformly turn out to be free of poor clinical outcomes. A recent multicenter study shed promise on tackling this dilemma using *BRAF*V600E as a prognostic genetic marker to guide better risk stratification in such patients.⁶² In this study, the recurrence rates of SI-PTC >1.0 cm, particularly tumors >2.0 cm, were 20–30% versus recurrence rates of only 2–3% in matched wild-type *BRAF*SI-PTC, with NPVs of *BRAF* V600E for recurrence being 97–98% or 100% if only structural recurrence was considered. Remarkably, this was true even in SI-PTC >4.0 cm. For intrathyroidal PTMC, recurrence rates were both low in *BRAF*V600E patients and wild-type *BRAF* patients, being only 1–2%. Given these findings, decision making on SI-PTC can now be more accurate if *BRAF* status is included in prognostic consideration: it is reasonable to treat wild-type *BRAF*SI-PTC of any tumor size, even tumor >4.0 cm, with thyroid lobectomy; *BRAF*V600E-positive SI-PTC >1.0 cm, particularly tumors >2.0 cm, should be treated aggressively—with total thyroidectomy and prophylactic neck dissection, followed by RAI ablation if indicated. *BRAF* mutation-positive SI-PTC >1.0 cm and <4.0 cm account for 23.1% and mutation-positive SI-PTC >2.0 cm and <4.0 cm account for 8.3% of all cases of SI-PTC. Thus, only a small minority of SI-PTC need to be treated aggressively. Given the low recurrence rates, SI-PTC <2.0 cm, particularly tumors <1.0 cm (i.e., low-risk PTMC), may be treated with lobectomy regardless of the *BRAF* status. With this *BRAF* status-guided strategy, the vast majority of SI-PTC patients can be treated with thyroid lobectomy only, which is associated with fewer surgical complications and a good chance of patient staying euthyroid, obviating the need for life-long thyroid hormone replacement.

3) Clinical Application of BRAF V600E in Clinically Low-risk PTMC

It is widely agreeable that clinically aggressive PTMC should be generally treated as for large PTC. Controversy exists, however, on how to treat clinically low-risk PTMC— PTMC without extrathyroidal extension, lymph node metastasis, distant metastasis and other aggressive features. Most physicians currently favor surgery as a preferred treatment option for such PTMC, usually lobectomy.⁵ In recent years, non-surgical active surveillance has become an alternative option acceptable to some physicians for clinically low-risk PTMC.⁵ This is primarily based on several prospective Japanese studies showing that clinically low-risk PTMC in the vast majority of patients remained indolent without serious clinical consequence after active surveillance for an average of 5–6 years.^{64–66} Yet, it has been well known that a small percentage of cases of PTMC present with significant tumor aggressiveness and even patient mortality and all large PTC have grown from PTMC. A major challenge is that no clinical features can reliably differentiate the relatively small number of patients with PTMC with disease destined to progress from the larger population of patients harboring inherently indolent PTMCs. Thus, there is concern on whether indiscriminate active surveillance of all clinically low-risk PTMC, particularly for long term (e.g., decades), is a reasonable strategy as serious disease progression, such as metastasis, may occur even if tumor size may remain relatively stable.

Knowledge of the *BRAF* status may now help facilitate decision making on such PTMC. As discussed above, mortality risk is extremely low in wild-type *BRAF* PTC in general regardless of tumor size and even lower in clinically low-risk PTMC. Even recurrence rate is extremely low in clinically low-risk wild-type *BRAF* PTC, including PTMC.⁶² Thus, active surveillance for clinically low-risk wild-type *BRAF* PTC seems to be reasonable and has the advantage of avoiding surgical complications and preserving normal thyroid functions. Given the lack of specific long-term prospective data, it is less clear, however, whether long-term active surveillance is reasonable for clinically low-risk but *BRAF* V600E-positive PTMC. The recent study on SI-PTC showed no significant impact of *BRAF* V600E on clinical outcomes of clinically low-risk PTMC treated with thyroidectomy.⁶² It is possible, however, that because surgical removal of PTMC at an early stage before *BRAF* V600E had sufficient time to exert adverse effects, there were no serious clinical consequences, even recurrence. The outcomes of increase in tumor size may potentially be problematic in the presence of *BRAF* V600E. As discussed above, in clinically low-risk SI-PTC, *BRAF* V600E was associated with robustly increased recurrence in tumors >1.0 cm, particularly tumors >2.0 cm, even after total thyroidectomy.⁶² Theoretically, if giving sufficient time, *BRAF* V600E may cause consequences, such as metastasis. Currently, there is no consensus on what is the appropriate size PTMC can be allowed to grow to before triggering thyroidectomy during active surveillance. If allowing *BRAF* V600E-positive but clinically apparent low-risk PTMC to grow to >2.0 cm, there may be a substantially increased risk of serious consequence, such as incurable RAI-refractory metastatic disease and even perhaps mortality. In contrast, some increase in tumor size (e.g., >3 mm), which could trigger a decision to operate PTMC in patients under currently suggested active surveillance,^{64–66} may not be as worrisome as currently believed if *BRAF* mutation is absent.

There is a well-known synergism between *BRAF*V600E and invasive tumor behaviors (e.g., extrathyroidal invasion, lymph node metastasis and distant metastasis) in adversely affecting PTC-related mortality.²⁷ Thus, surgical treatment rather than active surveillance of *BRAF* V600E-positive and clinically low-risk PTMC before the mutation has sufficient time to exert adverse actions seems to be reasonable. In such case, however, thyroid lobectomy may be just sufficient at this early stage of the disease when *BRAF*V600E does not exert adverse actions yet.⁶² This seems to be practical as only a small minority of thyroid cancers are clinically low-risk PTMC harboring *BRAF*V600E mutation.⁶² As discussed in the early section above, clinically low-risk PTMC, if ever found to harbor high-risk genetic alterations (e.g., duets of *BRAF*V600E/*RAS* and *TERT* promoter mutations, *TP53*, *EIF1A* and β -*catenin* mutations, etc), should be most reasonably treated relatively aggressively (e.g., total thyroidectomy).

4) Clinical Application of Prognostic Genetic Markers in FTC

Unlike PTC in which the prognostic value of *BRAF*V600E has been well characterized, molecular prognostication has been less well defined in FTC. Nevertheless, a few genetic markers are prognostically promising for FTC. *RAS* mutation was previously reported to be associated with aggressive behaviors of FTC.⁵⁰ *RAS* and *TERT* promoter mutations are both common in FTC and there is a significant association between them.^{11,15,42,48} In analogy with the robust prognostic value of the genetic duet of *BRAF*V600E and *TERT* promoter mutations in PTC, it is possible that the genetic duet of *RAS* and *TERT* promoter mutations may have an important prognostic value in FTC. In fact, this has been well demonstrated in DTC, including FTC, in several studies.^{15,42,48} Therefore, the duet of *RAS* and *TERT* promoter mutations is an important genetic background and prognostic genetic pattern for poor clinical outcomes of FTC. It is thus reasonable to aggressively treat FTC harboring the genetic duet of *RAS* and *TERT* promoter mutations, including, for example, total thyroidectomy and RAI ablation. Other high-risk genetic alterations, such as *TP53*, *EIF1A* and β -*catenin* mutations, if every found, should be treated as important genetic predictors for poor clinical outcomes of FTC and favor aggressive treatment.

5) Application of Prognostic Genetic Markers in Predicting Radioiodine Refractoriness of Thyroid Cancer

Since it was first reported in 2005 that *BRAF*V600E was associated with recurrence of PTC and RAI refractoriness and hence incurability of recurrent PTC,²⁴ numerous studies have confirmed this finding and demonstrated impaired or even absent expression of the thyroid iodide-metabolizing genes—genes for thyroid-stimulating hormone receptor (TSHR), sodium/iodide symporter, thyroperoxidase, thyroglobulin (Tg), thyroid transcription factor 1, and PAX8 transcription factor—in PTC harboring *BRAF*V600E.^{1,7,13,14} A direct functional link between *BRAF* V600E and the impairment of thyroid iodide-metabolizing gene expression was the demonstration that introduced expression of *BRAF* V600E in normal thyroid cells caused silencing of thyroid iodide-metabolizing genes; cessation of the expression of *BRAF* V600E or inhibition of the *BRAF*/MAP kinase pathway could restore the expression of thyroid genes.⁶⁷ This was later recapitulated in animal models⁶⁸ and even human patients—treatment of patients carrying RAI-refractory PTC with an inhibitor of the MAP kinase pathway could restore RAI avidity of the tumor.⁶⁹ Recent studies demonstrated

that *TERT* promoter mutations may also be associated with impairment or loss of RAI avidity and, in fact, the genetic duet of *BRAFV600E* and *TERT* promoter mutations was most robustly associated with RAI refractoriness of metastatic PTC.⁶³ Pediatric PTC is generally highly curable with RAI treatment, consistent with its low prevalence of *BRAFV600E*¹³ and very rare occurrence of *TERT* promoter mutations.⁷⁰ Since *BRAFV600E* is associated with increased risk of RAI refractoriness of recurrent disease of PTC, mostly recurrent metastatic lymph nodes, a positive test for *BRAFV600E*, particularly the genetic duet of *BRAFV600E* and *TERT* promoter mutations, favors thorough therapeutic neck dissection and, in appropriate cases, prophylactic neck dissection, to minimize the risk of the development of RAI-refractory recurrent disease. Prophylactic neck dissection is particularly applicable to *BRAF* mutation-positive PTC >2.0 cm as discussed in the above sections. However, even with impairment of RAI avidity, *BRAFV600E*-positive PTC still should be treated with RAI ablation when clinically indicated as RAI avidity loss is often partial. Also, as the mutation-positive cancer has an increased risk for disease recurrence and even mortality, patients need to be effectively monitored in the follow-up surveillance following total thyroidectomy. Thus, reliable specific Tg test is particularly important, which is made possible with RAI ablation of normal thyroid tissues. It is not clear at this time whether a higher dose of RAI may be beneficial to *BRAFV600E*-positive PTC given the impairment of RAI avidity in such cancer.

6) Application of Prognostic Genetic Markers in DTC Already with Clinically Apparent Aggressiveness

Genetic markers may even be prognostically useful in DTC that already shows clinically apparent aggressiveness, such as extrathyroidal invasion, lymph nodes metastasis and distant metastasis. Even though aggressive initial treatment is generally needed in such patients, the outcomes from the current standard treatments may be different depending on the genotype of *BRAF* and *TERT* in the tumor. In the absence of *BRAFV600E* and *TERT* promoter mutations, the mortality of PTC, particularly CPTC and FVPTC, is extremely low, while, in contrast, the genetic duet of *BRAFV600E* and *TERT* promoter mutations was associated with robustly high mortality in a manner independent of conventional clinicopathological risk factors.³⁹ The genetic duet of *RAS* and *TERT* promoter mutations has similar prognostic value.^{15,42,48} Also, as discussed above, these mutations are strongly associated with loss of RAI avidity and hence often treatment failure of recurrent disease. Thus, even the initial clinical presentation of the tumor aggressiveness is similar in patients, the disease prognosis can be different in such patients depending on whether there are these mutations. Therefore, these genetic markers still have values in assisting prognostic evaluation of clinically apparent aggressive DTC. Existence of these genetic markers implies increased risk of therapeutic failure of the current treatment and emphasizes the importance of complete eradication of the disease in the initial treatment and the need for subsequent vigilant active surveillance for disease recurrence.

7) Potential Prognostic Value of Genetic Markers in ATC and PDTC

Although ATC is generally an extremely aggressive cancer, its aggressiveness seems to be differentiable by certain genetic patterns. For example, *TERT* promoter mutation-positive ATC was found to be more commonly associated with distant metastasis,⁴³ which is likely to

be translated into accelerated mortality. The genetic duet of *BRAF*V600E and *TERT* promoter mutations are likely to represent a genetic background for more aggressiveness of ATC. *RAS* mutation was reported to be associated with increased aggressiveness of PDC. ^{51,52} It is likely that this effect of *RAS* mutation originates from the genetic duet of *RAS* and *TERT* promoter mutations. Therapeutically, *BRAF*V600E-positive ATC has recently been demonstrated to have a remarkable response to the combination treatment with BRAF V600E and MEK inhibitors,⁷¹ promoting an expedited approval by FDA of the combination use of the BRAF V600E inhibitor dabrafenib and the MEK inhibitor trametinib for the treatment of BRAF V600E-positive ATC. Thus, testing of certain genetic markers in ATC may have both prognostic and predictive values. This may likely become true also for PTC.

8) Special Consideration of RAS Mutation in Several Clinical Settings

As *RAS* mutations can occur in both benign and malignant thyroid neoplasms, its value as a diagnostic and prognostic marker by itself had been uncertain until recently.⁷² It has been recently demonstrated that long-term follow-up of cytologically benign but *RAS* mutation-positive thyroid nodules had no clinical consequence and *RAS* mutation alone in DTC was usually associated with low-risk disease with excellent clinical outcomes.⁷³ As discussed above, it is the genetic duet of *RAS* and *TERT* promoter mutations that is robustly associated with poor clinical outcomes of DTC.^{15,42,48} Given these and other studies, the following recommendations as recently proposed⁷² may be reasonable to consider for thyroid neoplasms that are negative for other high-risk genetic markers (e.g., *TERT* promoter mutation) unless clinically suggested otherwise: 1) Cytologically benign but *RAS* mutation-positive thyroid nodules can be non-surgically managed with long-term surveillance; 2) *RAS* mutation-positive thyroid nodules with cytological atypia of undetermined significance or follicular neoplasm may be treated surgically with limited extent (e.g., lobectomy); 3) Clinically low-risk but *RAS* mutation-positive DTC can be generally treated with limited extent (e.g., lobectomy).

SUMMARY

The value of prognostic genetic marker-based risk stratification and precision management of thyroid cancer is widely appreciated. Well characterized and clinically applicable prognostic genetic markers are best exemplified by *BRAF*V600E and *TERT* promoter mutations. The genetic duet of *BRAF*V600E/*RAS* and *TERT* promoter mutations has particularly robust prognostic power for poor clinical outcomes of DTC. The negative predictive values of these prognostic genetic markers are equally important clinically. Appropriate application of these prognostic markers can particularly improve the precision of management decision making for thyroid cancer in currently controversial areas, such as thyroid lobectomy versus total thyroidectomy, prophylactic neck dissection versus no neck dissection, RAI ablation versus no RAI ablation, and non-surgical active surveillance versus surgical treatment. A suggested approach for the clinical application of prognostic genetic markers in DTC is illustrated in Figure 3. In this approach, the best prognostic utility of the genetic markers in guiding the treatment of thyroid cancer can be achieved in a clinical risk level-based and genotype-individualized manner.

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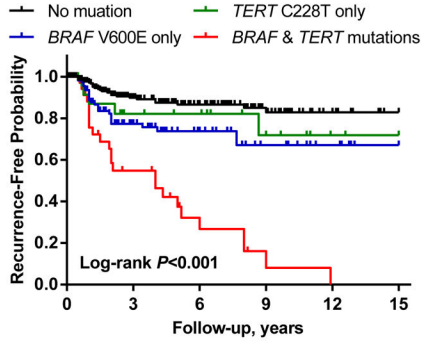
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KEY POINTS

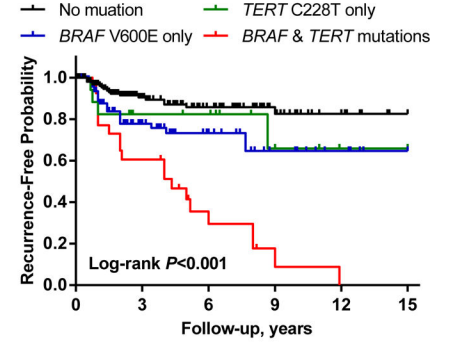
- 1) Controversies exist on how to optimally manage thyroid cancer as the prognosis is often uncertain based on clinical backgrounds.
- 2) Prognostic genetic markers in thyroid cancer, exemplified by *BRAFV600E* and *TERT* promoter mutations, have been well characterized and widely appreciated.
- 3) The genetic duet of *BRAFV600E/RAS* and *TERT* promoter mutations are most robust prognostic genetic patterns for poor prognosis of differentiated thyroid cancer.
- 4) The high negative predictive values of the prognostic genetic markers are equally valuable.
- 5) The best prognostic value of genetic markers in thyroid cancer is achieved through a clinical risk level-based and genotype-individualized manner.

A. PTC (all types)



No. at risk	0	3	6	9	12	15
No mutation	287	130	85	42	14	5
<i>BRAF</i> V600E only	159	55	32	20	12	5
<i>TERT</i> C228T only	26	15	13	8	3	2
<i>BRAF</i> & <i>TERT</i> mutations	35	14	6	2	0	0

B. PTC (conventional type)

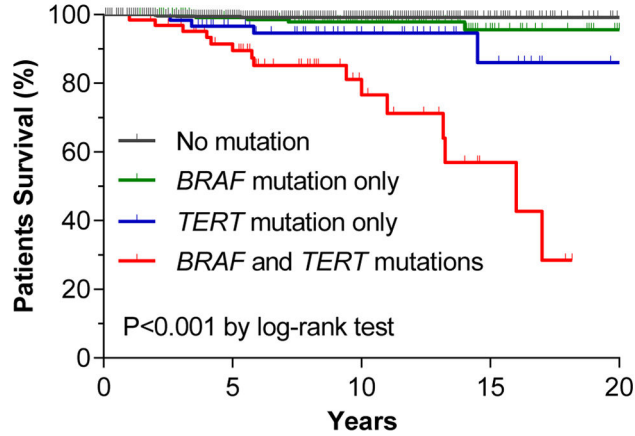


No. at risk	0	3	6	9	12	15
No mutation	200	92	56	30	12	4
<i>BRAF</i> V600E only	136	46	26	15	9	5
<i>TERT</i> C228T only	19	11	10	5	2	2
<i>BRAF</i> & <i>TERT</i> mutations	28	14	6	2	0	0

Figure 1. Impacts of *BRAF* V600E or *TERT* promoter mutation alone or their coexistence on disease-free survival of patients with papillary thyroid cancer (PTC).

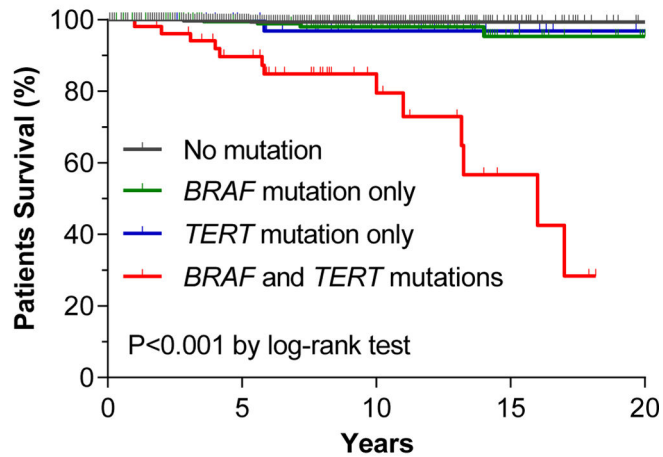
Kaplan-Meier analyses of 507 patients with PTC were performed. **Panel A** shows the analysis results of patients with PTC of all types and **Panel B** shows the analysis results of patients with conventional-variant PTC only. Four groups of patients were included in each panel, including patients with neither mutation (black line), *TERT* mutation only (green line), *BRAF*V600E mutation only (blue line), and the genetic duet of the two coexisting mutations (red line). Adapted from Xing et al. *J Clin Oncol.* 2014;32(25):2718–26 (Reference 45) with permission.

A All PTC patients



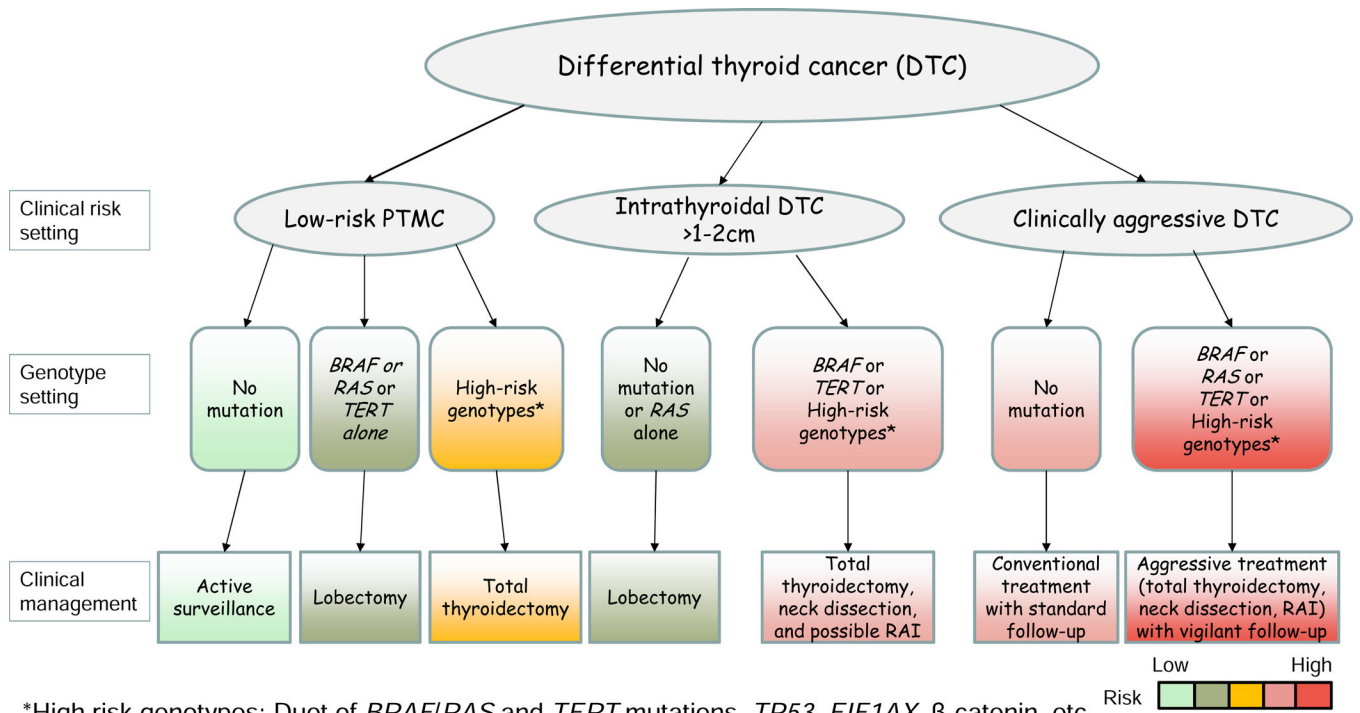
No. at Risk					
No mutation	629	415	225	66	17
<i>BRAF</i> mutation only	292	188	98	29	8
<i>TERT</i> mutation only	64	50	27	10	2
<i>BRAF</i> and <i>TERT</i> mutations	66	48	18	4	0

B Patients with Conventional PTC



No. at Risk					
No mutation	442	288	155	50	15
<i>BRAF</i> mutation only	256	165	82	22	8
<i>TERT</i> mutation only	41	33	19	8	2
<i>BRAF</i> and <i>TERT</i> mutations	54	39	16	4	0

Figure 2. Impacts of *BRAF* V600E or *TERT* promoter mutation alone or their coexistence on disease-specific survival of patients with papillary thyroid cancer (PTC). Kaplan-Meier analyses of 1,051 patients with PTC were performed. Panels **A** and **B** show the analysis results of patients with PTC of all types and only patients with conventional-variant PTC, respectively. In each panel, the patients were divided into four genotype groups — no mutation (black line), *BRAF* V600E only (green line), *TERT* promoter mutation only (blue line), and genetic duet of the two coexisting mutations (red line). *Adapted from Liu R et al. JAMA Oncol. 2017;3(2):202–208 (Reference 39) with permission.*



*High risk genotypes: Duet of *BRAF/RAS* and *TERT* mutations, *TP53*, *EIF1AX*, β -catenin, etc.

Figure 3. Summary of the clinical application of major prognostic genetic markers in thyroid cancer.

The diagram shows how thyroid cancer at different clinical risk levels in various clinical settings can be appropriately treated with the guidance of specific individual genotypes. DTC, differentiated thyroid cancer; PTMC, papillary thyroid microcarcinoma; RAI, radioactive iodine. *High-risk genotypes include the duet of *BRAFV600E/RAS* and *TERT* promoter mutations, *TP53*, *EIF1A*, β -catenin mutations, etc.