

Unstimulated Highly Sensitive Thyroglobulin in Follow-up of Differentiated Thyroid Cancer Patients: A Meta-Analysis

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Context: Serum thyroglobulin (Tg) is an indicator of differentiated thyroid cancer (DTC) relapse.

Objective: Our objective was to conduct a meta-analysis of published data about the diagnostic performance of highly sensitive serum Tg (hsTg) during levothyroxine therapy in DTC follow-up.

Data Sources: We performed a comprehensive literature search of PubMed/MEDLINE and Scopus for studies published until July 2013.

Study Selection: Studies investigating the diagnostic performance of basal hsTg in monitoring DTC were eligible. Exclusion criteria were 1) articles not within the field of interest; 2) reviews, letters, or conference proceedings; 3) articles evaluating serum Tg measurement with a functional sensitivity >0.1 ng/mL; 4) overlap in patient data; and 5) insufficient data to reassess diagnostic performance of basal serum hsTg.

Data Extraction: Information was collected concerning basic study data, patient characteristics, and technical aspects. For each study, the number of true-positive, false-positive, true-negative, and false-negative findings for basal hsTg, considering stimulated Tg measurement as a reference standard, were recorded.

Data Synthesis: Pooled data demonstrated that the negative predictive value of hsTg was 97% and 99% considering a stimulated Tg measurement >1 ng/mL and >2 ng/mL as cutoffs for positivity, respectively. Despite the high pooled sensitivity of basal hsTg, the pooled specificity, accuracy, and positive predictive value were insufficient to completely substitute for a stimulated Tg measurement.

Conclusions: Basal hsTg measurement has a very high negative predictive value but an insufficient positive predictive value for monitoring DTC patients. Therefore, a Tg stimulation test can be avoided in patients with an undetectable basal hsTg, whereas a stimulated Tg measurement should be considered when hsTg levels are detectable. (*J Clin Endocrinol Metab* 99: 440–447, 2014)

The initial management of differentiated thyroid cancer (DTC) consists of total thyroidectomy (with or without cervical lymph node dissection) and ^{131}I administra-

tion (1, 2). With this approach, most DTC patients achieve excellent prognosis and a normal life expectancy, even if life-long regular follow-up is required (3, 4). Thyroglob-

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Abbreviations: DTC, differentiated thyroid cancer; FS, functional sensitivity; hsTg, highly sensitive Tg; NPV, negative predictive value; PPV, positive predictive value; rhTSH, recombinant human TSH; Tg, thyroglobulin; TgAb, anti-Tg autoantibody.

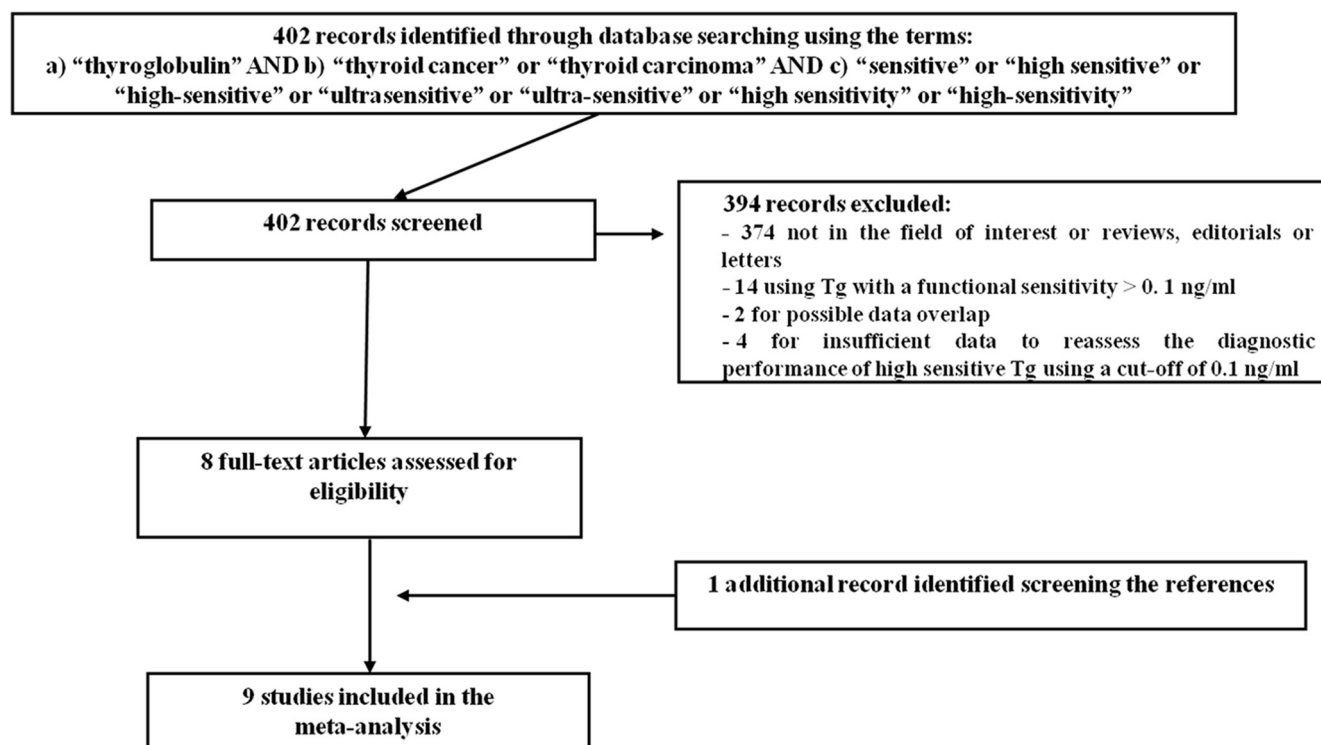


Figure 1. Flow chart of the search for eligible studies on the diagnostic performance of basal serum hsTg measurement (with an FS \leq 0.1 ng/mL) in monitoring patients with DTC.

ulin (Tg) is a glycoprotein produced by normal thyroid cells, and this property is maintained by well-differentiated thyroid cancer types. Therefore, after surgery and ^{131}I ablation, serum Tg measurement is eminently suitable for use as an indicator of DTC relapse and holds a leading role in the follow-up of DTC patients (5). In sera from athyreotic patients, Tg is expected to be undetectable, whereas detectable Tg levels are associated with recurrent or persistent disease. The diagnostic accuracy of Tg as a tumor marker is high during L-T₄ treatment and increases further after TSH stimulation obtained by L-T₄ withdrawal or exogenous administration of recombinant human TSH (rhTSH) (Thyrogen; Genzyme Corporation) (6, 7). The detection of Tg depends on the analytical sensitivity of the

assay used. The limit of quantitation of an assay as distinct from the clinical sensitivity of a test, which is defined as the probability that a test will correctly assert the presence of illness when it is indeed present, can be defined as the lowest concentration that can be reliably distinguished from 0 (eg, analyte-free serum). Currently, the functional sensitivity (FS) is widely used to define the clinical usability of Tg assays. It involves variation that is strictly due to measurement imprecision and not biological variation, and it is the variation that would be observed in many repeated measures of a single biologic sample under unchanging conditions. FS is defined as the concentration that results in an interassay coefficient of variation of 20% and is a measure of an assay's imprecision at lowest ana-

Table 1. Characteristics of the Studies Included in the Meta-Analysis

Ref.	Year	Country	Patients Evaluated	Mean Age, y	Gender, % Male	Type of DTC, %		Type of Highly Sensitive Tg Assay	Type of TSH Stimulation (Cutoff for Positivity of Stimulated Tg)
						PTC	FTC		
Zöphel et al (22)	2003	Germany/UK	126	52	16	57.1	42.9	EIASON TgCa	L-T ₄ withdrawal (>1 ng/mL)
Schlumberger et al (21)	2007	France	944	47	22	87.4	12.6	Access-Tg and EIASON TgCa	L-T ₄ withdrawal or rhTSH stimulated Tg (>2 ng/mL)
Smallridge et al (23)	2007	U.S.	194	NR	NR	NR	NR	Access-Tg	rhTSH stimulated Tg (>2 ng/mL)
Iervasi et al (24)	2007	Italy	160	51.2	34	77.5	22.5	Access-Tg	rhTSH-stimulated Tg (>1 and > 2 ng/mL)
Rosario et al (25)	2008	Brazil	178	48	19	83.1	16.9	Access-Tg	L-T ₄ withdrawal or rhTSH stimulated Tg (>1 ng/mL)
Spencer et al (9)	2010	U.S.	849	49	32	NR	NR	Access-Tg	rhTSH stimulated Tg (>1 and > 2 ng/mL)
Castagna et al (26)	2011	Italy	215	43.8	20	89	11	Access-Tg and EIASON TgCa	rhTSH stimulated Tg (>1 ng/mL)
Malandrino et al (27)	2011	Italy	425	43.6	22	95.5	4.5	Access-Tg	rhTSH stimulated Tg (>2 ng/mL)
Nakabashi et al (28)	2012	Brazil	87	40	10	90.8	9.2	Access-Tg	NR (>1 ng/mL)

Abbreviations: FTC, follicular thyroid cancer; NR, not reported; PTC, papillary thyroid cancer; UK, United Kingdom.

Table 2. Methods and Positivity Cutoff Levels Adopted to Screen for Interfering Tg Autoantibodies in Different Studies

Ref.	Method	Cutoff
Spencer et al (9)	Kronus RIA	0.5 kU/L
Schlumberger et al (21)	Access TgAb (combined with Access Tg)	5 IU/mL
Schlumberger et al (21)	Recovery test (combined with EIASON TgCA)	<70%
Zöphel et al (22)	Medipan RIA	50 U/L
Smallridge et al (23)	NR	NR
Iervasi et al (24)	TgAb Immulite	2.2 IU/mL
Rosario et al (25)	Nichols Advantage	2 IU/mL
Castagna et al (26)	TgAb Immulite 2000	29 IU/mL
Malandrino et al (27)	Abbott AxSYM	34 IU/mL
Nakabashi et al (28)	NR	NR

Abbreviation: NR, not reported.

lyte concentrations. As a consequence, it is generally considered the lowest reportable value because the results below the FS, although not technically undetectable, cannot be quantified with acceptable precision. Nonetheless, because in clinical practice and many studies in literature the term undetectable is used colloquially for any value below the FS, we will use the term undetectable to indicate Tg results below the FS of the assay used.

Conventional Tg assays (ie, with an FS \sim 1.0 ng/mL) have limitations in clinical practice (1, 5–8). More recently, so-called highly sensitive methods (with an FS \sim 0.1 ng/mL) have been developed (5, 8, 9), with more reliable results for basal (eg, under L-T₄ therapy without TSH stimulation) Tg testing. In fact, if one defines a false-negative serum Tg measurement as an undetectable basal Tg (ie, below the FS of the assay) that is subsequently followed by a rise in serum Tg upon TSH stimulation to more than 1 to 2 ng/mL, the false-negative rate is somewhere between 5% and 20% for Tg assays with an FS of 1 ng/mL (1, 2, 4). There is considerable evidence that this rate is reduced substantially when assays with better FS are used (5, 8). Several studies in the literature have investigated the di-

agnostic performance of basal Tg measurement by highly sensitive Tg (hsTg) assays in the follow-up of DTC patients, reporting different values of sensitivity and specificity (8, 9). Based on data from recent literature (10), we considered Tg assays with an FS \leq 0.1 ng/mL as hsTg methods. The purpose of our study was to systematically review and meta-analyze published data on the diagnostic performance of hsTg assays in the follow-up of DTC patients and demonstrate whether and when basal hsTg measurement could replace stimulated Tg measurement in the follow-up of DTC patients.

Materials and Methods

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, which describes an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses (11).

Search strategy

A comprehensive computer literature search of the PubMed/MEDLINE and Scopus databases was conducted to find relevant published articles on the diagnostic performance of basal serum hsTg in monitoring DTC patients. We used a search algorithm that was based on a combination of the terms: 1) thyroglobulin; 2) thyroid cancer or thyroid carcinoma; and 3) sensitive, high sensitive, high-sensitive, ultrasensitive, ultrasensitive, high sensitivity, or high-sensitivity. No beginning date limit or language restriction was used; the search was updated until July 31, 2013. To expand our search, references of the retrieved articles were also screened for additional studies.

Study selection

Studies or subsets of studies investigating the diagnostic performance of basal serum hsTg measurement in monitoring DTC patients treated with thyroidectomy with negative anti-Tg antibodies were eligible for inclusion. The exclusion criteria were 1) articles not within the field of interest of this review; 2) review articles, editorials, letters, comments, or conference proceedings; 3) articles evaluating the diagnostic performance of serum hsTg

Table 3. Study Design and Quality Assessment of the 9 Included Papers

Author	Study Design	Spectrum of Patients	Consecutive or Random Selection of Patients	Reference Standard
Zöphel et al (22)	Retrospective	TT, ¹³¹ I, neg WBS, neg TgAb	Yes	US, WBS, sTg
Schlumberger et al (21)	Prospective	TT, ¹³¹ I, neg WBS, neg TgAb	NA	US, WBS, sTg
Smallridge et al (23)	Retrospective	TT, ¹³¹ I, neg TgAb	Yes	US, WBS, PET, sTg
Iervasi et al (24)	NA	TT, ¹³¹ I, neg TgAb	Yes	US, WBS, sTg
Rosario et al (25)	Retrospective	TT, ¹³¹ I, neg WBS, Tg <1 ng/mL, neg TgAb	NA	US, WBS, sTg
Spencer et al (9)	Retrospective	TT, neg TgAb	Yes	sTg
Castagna et al (26)	Retrospective	TT and ¹³¹ I, undetectable Tg, neg TgAb	No	US, WBS, sTg
Malandrino et al (27)	Retrospective	TT, ¹³¹ I, Tg <1.0 ng/mL, neg TgAb	Yes	US, WBS, PET, sTg
Nakabashi et al (28)	NA	TT, ¹³¹ I, neg TgAb	NA	US, WBS, sTg

Abbreviations: NA, not available; neg, negative; PET, positron emission tomography; sTg, stimulated Tg; TT, total thyroidectomy; US, ultrasound; WBS, radioiodine whole-body scan.

with a functional sensitivity >0.1 ng/mL; 4) overlap in patient data (possible duplicate publication; in such cases, the most complete article was included); 5) insufficient data to reassess diagnostic performance of basal serum hsTg with a positivity cutoff of 0.1 ng/mL. Three researchers (G.T., R.S., and L.G.) independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. Articles were rejected if they were clearly ineligible. The same 3 researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved in a consensus meeting. All selected studies with sufficient data to reassess diagnostic performance of basal serum hsTg in monitoring DTC patients considering stimulated Tg measurement (using recombinant TSH or hormone withdrawal) as a reference standard were included in the meta-analysis.

Data extraction

For each included study, information was collected concerning basic study data (authors, journals, year of publication, country of origin, and study design), patient characteristics (mean age, gender, number of patients evaluated, and histology of DTC), technical aspects (hsTg assay method, Tg stimulation, and applied reference standard). For each study, the number of true-positive, false-positive, true-negative, and false-negative findings for basal serum hsTg in monitoring DTC patients, considering stimulated Tg measurement as a reference standard, were recorded. In some cases (see Supplemental Data, published on The Endocrine Society's Journals Online website at <http://jcem.endojournals.org>), we could not include all patients reported in the specific study because these patients did not meet the criteria for inclusion in the present analyses, eg, by having anti-Tg autoantibodies (TgAbs) (5). Furthermore, data reported in several studies (see Supplemental Data) were recalculated based on the unified criteria for evaluation reported below, because the data mentioned in those studies were based on different cutoffs (eg, as calculated using receiver operating characteristic analysis) (8).

We considered 2 different cutoff values for positivity (1 and 2 ng/mL, respectively) of serum stimulated Tg measurement, as adopted by the included studies, and a positivity cutoff ≥ 0.1 ng/mL for basal serum hsTg. Therefore, we defined as true positive a basal hsTg level ≥ 0.1 ng/mL in a DTC patient with a positive stimulated Tg and as true negative a basal hsTg level <0.1 ng/mL in a DTC patient with a negative stimulated Tg. We defined as false positive a basal hsTg assay ≥ 0.1 in a DTC patient

with a negative stimulated Tg and as false negative a basal hsTg assay <0.1 in a DTC patient with a positive stimulated Tg.

Quality assessment

The 2011 Oxford Center for Evidence-Based Medicine checklist for diagnostic studies was used for quality assessment of the included studies (12). This checklist has 5 major parts: representative spectrum of the patients, consecutive patient recruitment, ascertainment of the gold standard regardless of the index test results, independent blind comparison between the gold standard and index test results, and enough explanation of the test to permit replication.

Statistical analysis

Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of basal serum hsTg in monitoring DTC patients considering serum stimulated Tg measurement as a reference standard (by using 2 positivity cutoff values of 1 and 2 ng/mL, respectively) were obtained from individual studies. A random-effects model was used for statistical pooling of the data. Pooled data were presented with 95% confidence intervals and obtained individually for each different assay method. An I^2 index was used to test for heterogeneity between studies. I^2 index is the inconsistency index and represents how much of the heterogeneity among the included studies is real and cannot be attributed to sampling error. For publication bias, evaluation of Egger's regression intercept (13) was used. Statistical analyses were performed using Meta-DiSc statistical software version 1.4 (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain) and CMA version 2 (Biostat) (14).

Results

The comprehensive computer literature search revealed 402 articles. Reviewing the titles and abstracts, 394 articles were excluded because they did not focus on the field of interest or were review articles, editorials, letters, comments, or conference proceedings ($n = 374$ articles) or were excluded due to Tg FS >0.1 ng/mL ($n = 14$), possible overlap in patient data ($n = 2$) (15, 16), or insufficient data

Table 3. Continued

Application of Reference Standard Regardless of Indexed Test	Enough Explanation of the Index Test to Ensure Reproducibility	Independent Blind Comparison Between Index Test and Reference Standard	Level of Evidence
Yes	Yes	NA	3
Yes	Yes	Yes	3
Yes	Yes	NA	3
Yes	Yes	NA	3
Yes	Yes	NA	3
Yes	Yes	NA	4
Yes	Yes	NA	3
Yes	Yes	NA	3
Yes	Yes	NA	3

to reassess diagnostic performance of basal Tg with the positivity cutoff of 0.1 ng/mL ($n = 4$) (17–20). One additional study was found by screening the references in other articles (21). Finally, 9 articles including 3178 DTC patients were eligible for the meta-analysis (10, 21–28) (Figure 1).

The main clinical characteristics of the studies are summarized in Table 1. There was a predominance of female subjects; mean age of subjects ranged from 40 to 52 years, and papillary thyroid cancer was more frequent than the follicular one. Eight studies used the automated immunochemiluminometric Tg Access assay (Beckman Coulter) (10, 21, 23–28) and 3 studies the manual ELISA EIASON TgCa (IASON GmbH) (21, 22, 26). Of these, 2 papers compared the 2 methods (21, 26). Heterogeneous aspects between the different studies concerning Tg stimulation (eg, L-T₄ withdrawal vs rhTSH) and the cutoff for positivity of stimulated Tg were found (Table 1). In particular, 2 possible positivity cutoffs for stimulated Tg were reported (>1 and >2 ng/mL) in the 9 articles, reflecting differences in the American (1) and European (2) clinical guidelines, respectively. Different methods were also used to screen for the presence of interfering TgAbs (29) (Table 2).

Study designs are summarized in Table 3. The cases in all studies included DTC subjects treated by total thyroidectomy; adjuvant radioiodine ablation therapy was performed in most cases. Six studies were retrospective (10, 22, 23, 25–27), and 1 was prospective (21), whereas the study design was not clearly described in the remaining 2 (24, 28).

According to the 2011 Oxford Center for Evidence-Based Medicine checklist for diagnostic studies, the quality of the 9 included studies was moderate. In particular, only 5 studies reported the consecutive recruitment of the patients, and only 1 study reported independent blind

comparison between the index test and the reference standard.

Tables 4 and 5 illustrate the diagnostic performance characteristics of basal hsTg from each of the included studies. Pooled data were available considering different hsTg assays and different reference standards (ie, cutoff of stimulated Tg >1 or >2 ng/mL). Pooled data on the Access Tg assay resulted in a sensitivity of 91%, a specificity of 87%, an accuracy of 88%, a PPV of 70%, and an NPV of 97% when using the value of >1 ng/mL as a cutoff for positivity of stimulated Tg (Table 4) and a sensitivity of 97%, a specificity of 77%, an accuracy of 80%, a PPV of 42%, and an NPV of 99% when using a positivity cutoff of >2 ng/mL (Table 5). For the EIASON TgCa assay, we found a sensitivity of 88%, a specificity of 85%, an accuracy of 86%, a PPV of 58%, and an NPV of 97% using a positivity cutoff value for stimulated Tg of >1 ng/mL cutoff (Table 4); the values of the same indices were 91%, 82%, 83%, 32% and 99%, respectively in the only one study using a positivity cutoff value for stimulated Tg of >2 ng/mL (Table 5). The included studies were statistically quite heterogeneous in their pooled estimates as demonstrated by the I² index. Using Egger's regression intercepts, no significant publication bias was found for sensitivity, specificity, accuracy, PPV, or NPV of basal hsTg.

Discussion

Current guidelines state that serum Tg measurement is the pivotal tool in DTC management (1, 2). A detectable/elevated Tg has to be considered as a marker of cancer persistence or recurrence in patients without TgAbs (29). Tg detection depends strongly on the functional sensitivity of

Table 4. Diagnostic Accuracy of Data of Unstimulated Tg (Positive if ≥ 0.1 ng/mL) Considering Stimulated Tg as Reference Standard (Positive if >1 ng/mL)^a

Assay, Ref.	Cases, n					Sensitivity, %	Specificity, %	Accuracy, %	PPV, %	NPV, %
	All	TP	FP	TN	FN					
Access hsTg										
Castagna et al (26)	215	35	25	148	7	83	86	85	58	95
Iervasi et al (24)	160	15	8	133	4	79	94	92	65	97
Nakabashi et al (28)	74	24	2	40	8	75	95	86	92	83
Rosario et al (25)	178	20	28	125	5	80	82	81	42	96
Spencer et al (9)	1029	278	96	643	12	96	87	89	74	98
Pooled data						91 (88–94), I ² = 80%	87 (85–89), I ² = 70%	88 (86–90), I ² = 70%	70 (66–74), I ² = 80%	97 (95–98), I ² = 80%
EIASON hsTg										
Castagna et al (26)	215	37	24	149	5	88	86	87	61	97
Zöphel et al (22)	14	1	3	10	0	100	77	79	25	100
Pooled data						88 (75–96), I ² = 0%	85 (80–90), I ² = 0%	86 (81–90), I ² = 0%	58 (45–71), I ² = 50%	97 (93–99), I ² = 0%

Abbreviations: FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

^a The number of cases may be different from the number of enrolled patients stated by different authors (see Table 1 and the Supplemental Data) because patients with positive TgAb or those without a Tg-stimulation test were not included in the meta-analysis. For pooled data, 95% confidence intervals are shown in parentheses.

Table 5. Diagnostic Accuracy of Data of Basal hsTg (Positive if ≥ 0.1 ng/mL) Considering Stimulated Tg as Reference Standard (Positive if >2 ng/mL)^a

Assay, Ref.	Cases (n)					Sensitivity, %	Specificity, %	Accuracy, %	PPV, %	NPV, %
	All	TP	FP	TN	FN					
Access hsTg										
Iervasi et al (24)	160	8	15	137	0	100	90	91	35	100
Malandrino et al (27)	425	33	61	328	3	92	84	85	35	99
Schlumberger et al (21)	831	77	233	516	5	94	69	71	25	99
Smallridge et al (23)	130	22	28	78	2	92	74	77	44	97
Spencer et al (9)	1029	214	160	653	2	99	80	84	57	100
Pooled data						97 (94–98), $I^2 = 60\%$	77 (75–79), $I^2 = 90\%$	80 (78–82), $I^2 = 90\%$	42 (38–45), $I^2 = 90\%$	99 (98–100), $I^2 = 40\%$
EIASON hsTg										
Schlumberger et al (21)	810	63	131	610	6	91	82	83	32	99

Abbreviations: FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

^a The number of cases may be different from the number of enrolled patients stated by different authors (see Table 1 and the Supplemental Data) because patients with positive TgAb or those without a Tg-stimulation test were not included in the meta-analysis. For pooled data, 95% confidence intervals are shown in parentheses.

the assay used, which is defined as the Tg concentration that can be measured with a 20% interassay coefficient of variation (30). The literature shows that there is a considerable degree of discordance between different Tg assays (21). Lack of a reliable gold standard thus far has prevented any conclusion on the question of whether such an assay is better than others. In the last decade, hsTg has been investigated in DTC, because ideally, this would lead to more accurate patient management. However, differing results of the diagnostic accuracy of hsTg under L-T₄ therapy were reported, and more robust estimates of the performance of basal hsTg are therefore necessary. In the present study, we systematically reviewed published studies using hsTg in DTC follow-up and many potential selection biases were avoided. To the best of our knowledge, this is the first meta-analysis evaluating the diagnostic performance of basal hsTg measurement in follow-up of DTC patients. The studies included in the present meta-analysis used either the Access Tg or the EIASON TgCa assay for the follow-up of DTC patients. Unfortunately, the data from the included studies were inadequate for performing a receiver operating characteristic curve analysis to establish the optimal basal hsTg cutoff for the presence of recurrent or persistent disease (19, 21). Therefore, a positivity value of ≥ 0.1 ng/mL was chosen because this value was adopted in most the studies analyzed here. Pooled results from the present analysis demonstrate that hsTg measured under L-T₄ therapy has an insufficient specificity, accuracy, and PPV to eliminate TSH-stimulated Tg measurement from the follow-up of DTC. However, a very high pooled sensitivity (from 88%–97%) and NPV (from 97%–99%) were found for hsTg, indicating that a Tg stimulation test can be avoided in DTC patients with undetectable basal hsTg, provided no TgAbs are present. This is strongly corroborated by many papers, several of

which were ineligible for inclusion in the present analysis, reporting a very low rate of cancer persistence/recurrence in DTC subjects who had undetectable hsTg during T₄ therapy (9, 17, 18, 20, 23, 24, 27, 31, 32). Most of these papers, and those included in our meta-analysis, adopted stimulated Tg values as the reference standard for a patient's disease status. However, stimulated Tg measurement also is an imperfect measure of a patient's DTC status and serves only as a surrogate for the ideal reference standard, which is a long clinical follow-up.

Chindris et al (18) reported on 163 low- and high-risk DTC patients with an undetectable basal hsTg, and during a median 9.6 years follow-up, only 4% had recurrent disease detected by ultrasound or chest x-ray. This study is an extension of the study by Smallridge et al (23), and both studies demonstrate that rhTSH testing does not change the management of patients with undetectable highly sensitive Tg. The latter was also demonstrated prospectively by Rosario et al (17). These authors reported on 122 DTC patients with a negative neck ultrasound and a basal hsTg <0.1 ng/mL using the Access assay as assessed 6 months after thyroidectomy and ¹³¹I ablation. After a median follow-up of 56 (range 24–78) months, at the end of the study, 117 patients still had no apparent disease and an undetectable Tg. Serum Tg was slightly detectable with a stable or decreasing trend over time in another 4 disease-free patients. Finally, serum Tg was detectable in subsequent measurements and a lymph node metastasis was detected by neck ultrasound in 1 patient. These results demonstrate that rhTSH testing does not change the management of patients with undetectable basal hsTg, which should be taken into account for the development of clinical practice.

Some potential limits of this meta-analysis should be discussed. First, it could be argued that taking an FS value

and using it to define high or low sensitivity is an oversimplification. In fact, what is clinically important is the precision at a range of low concentrations. It is theoretically possible that one assay with an FS of 0.3 ng/mL has a worse precision at 1 ng/mL than another assay with an FS of 0.5 ng/mL. Consequently, it is important when comparing the performance of different assays to carefully evaluate the exact details of the experimental protocol because otherwise any comparison of assays is futile.

Second, different methods (eg, direct immunoassay or recovery test) were employed to screen sera from interfering TgAbs resulting in different criteria adopted to exclude TgAb-positive patients in different studies.

All in all, the series were statistically inhomogeneous for most of the diagnostic performance indices evaluated. This heterogeneity is likely to have arisen through differences with regard to important methodological aspects of the different studies included, and here it was accounted for using a random-effects model. Also, the baseline differences between the patients in the included studies and the study quality might affect the heterogeneity of the results. To limit these effects, we pooled the published studies according to the hsTg assay method or the different positivity cutoff of stimulated Tg used as a reference standard. Finally, the present results could be limited by the small number of included papers. Speaking against this potential limitation, however, is the very large number of patients included in most of these studies as well as the exclusion of a publication bias by Egger's regression and the fact that the quality of the included studies was at least moderate.

Conclusions

Unstimulated basal hsTg measurement using assays with an FS ≤ 0.1 ng/mL has a very high NPV but a suboptimal PPV in monitoring DTC patients. Therefore, a Tg stimulation test can be avoided in patients with basal hsTg values below the FS, provided TgAbs are not present, whereas a stimulated Tg measurement should be considered when hsTg levels are above the FS value.

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