Thyroglobulin (Tg) testing revisited: Tg assays, TgAb assays and correlation of results with clinical outcomes.
B·R·A·H·M·S anti-Tgn KRYPTOR / B·R·A·H·M·S hTg sensitive KRYPTOR
J Clin Endocrinol Metab 2015;Jun 16: jc20151967.
CONTEXT: Measurement of thyroglobulin (Tg) by mass spectrometry (Tg-MS) is emerging as a tool for accurate Tg quantification in patients with anti-Tg autoantibodies (TgAb). OBJECTIVE: To perform analytical and clinical evaluations of two Tg-MS in comparison to immunometric Tg assays (Tg-IA) and Tg radioimmunoassays (Tg-RIA) in a cohort of thyroid cancer patients. METHODS: 589 samples from 495 patients, 243 TgAb-/252 TgAb+, were tested by Beckman, Roche, Siemens-Immulite and Thermo-Brahms Tg and TgAb assays, two Tg-RIAs and two Tg-MS assays. RESULTS: The frequency of TgAb+ was 58%, 41%, 27% and 39% for Roche, Beckman, Siemens-Immulite and Thermo-Brahms, respectively. In TgAb- samples, clinical sensitivities and specificities of 100% and 74-100%, respectively, were observed across all assays. In TgAb+ samples, all Tg-IA demonstrated assay-dependent Tg under-estimation ranging from 41-86%. In TgAb+ samples, the use of a common cut-off (0.5ng/mL) for the Tg-MS, 3 Tg-IA and USC-RIA, improved the sensitivity for the Tg-MSs and Tg-RIAs when compared to the Tg-IAs. In up to 22% of TgAb+ cases, Tg-IAs failed to detect Tg that was detectable by Tg-MS. In Tg-RIAs false-high biases were observed in TgAb+ samples containing low Tg concentrations. CONCLUSIONS: Tg-IA remains the method of choice for Tg quantitation in TgAb- patients In TgAb+ patients with undetectable Tg by IA, Tg-MS will detect Tg in up to 22% additional cases. Tg-RIA will detect Tg in approximately 35% cases, but a significant proportion of these will be clinical false positives. The undetectable Tg-MS seen in approximately 40% of TgAb+ cases in patients with disease need further evaluation. PMID[26079778]

Evaluation of a new thyroglobulin sensitive assay in patients with differentiated thyroid cancer.
Thermo Scientific B·R·A·H·M·S hTg sensitive KRYPTOR
PMID[25153604]

Thyroglobulin autoantibodies as surrogate biomarkers in the management of patients with differentiated thyroid carcinoma.
Differentiated thyroid cancer is a rare malignancy, but leaves numerous survivors for life-long follow-up. The cornerstone in current guidelines for follow-up is by measuring the thyroid specific tumour marker, thyroglobulin in serum. Most patients can be followed by this method, but some thyroid cancer patients have antithyroglobulin antibodies in serum, both at diagnosis and after treatment, where follow-up is commenced. These antibodies interfere technically in the immunological methods for measuring thyroglobulin, and the antithyroglobulin antibody positive patients are thus eliminated from following current guidelines. In recent years studies have indicated that following the concentration of antithyroglobulin antibodies in serum may be a surrogate marker for recurrence of the thyroid carcinoma. This has recently resulted in publication of an expert position paper, providing a flow scheme for these particular patients. The current review summarises the literature which is the basis for the paper. PMID[25174917]

Thyroglobulin measurement using highly sensitive assays in patients with differentiated thyroid cancer: a clinical position paper.
Eur J Endocrinol 2014;171 (2),Aug: R33-46. OPEN ACCESS
Differentiated thyroid cancer (DTC) is the most common endocrine cancer and its incidence has increased in recent
decades. Initial treatment usually consists of total thyroidectomy followed by ablation of thyroid remnants by iodine-131. As thyroid cells are assumed to be the only source of thyroglobulin (Tg) in the human body, circulating Tg serves as a biochemical marker of persistent or recurrent disease in DTC follow-up. Currently, standard follow-up for DTC comprises Tg measurement and neck ultrasound combined, when indicated, with an additional radioiodine scan. Measurement of Tg after stimulation by endogenous or exogenous TSH is recommended by current clinical guidelines to detect occult disease with a maximum sensitivity due to the suboptimal sensitivity of older Tg assays. However, the development of new highly sensitive Tg assays with improved analytical sensitivity and precision at low concentrations now allows detection of very low Tg concentrations reflecting minimal amounts of thyroid tissue without the need for TSH stimulation. Use of these highly sensitive Tg assays has not yet been incorporated into clinical guidelines but they will, we believe, be used by physicians caring for patients with DTC. The aim of this clinical position paper is, therefore, to offer advice on the various aspects and implications of using these highly sensitive Tg assays in the clinical care of patients with DTC. PMID[24743400]

Thyroglobulin measurement by highly sensitive assays: focus on laboratory challenges.
Abstract Differentiated thyroid cancer (DTC) is the most common endocrine cancer and its incidence has increased in recent decades. The initial treatment consists of total thyroidectomy followed by ablation of thyroid remnants by radioiodine in most cases. As thyroid cells are the only source of thyroglobulin (Tg), circulating Tg serves as a biochemical marker of persistent or recurrent disease in the follow-up of DTC. Due to the suboptimal clinical detection rate of older Tg assays endogenous or exogenous thyrotropin (TSH) stimulations are recommended for unmasking occult disease. However, the development of new Tg assays with improved analytical sensitivity and precision at low concentrations now allows detection of very low Tg concentrations, reflecting minimal amounts of thyroid tissue, even without the need for TSH stimulation. Even if the use of these assays still has not found its way in current clinical guidelines, such assays are now increasingly used in clinical practice. As serum Tg measurement is a technically challenging assay and criteria to define a 'highly sensitive' assay may differ, a good knowledge of the technical difficulties and interpretation criteria is of paramount importance for both clinical thyroidologists, laboratory physicians and scientists involved in the care of DTC patients. PMID[25355247]

Evaluation of a new ultrasensitive thyroglobulin assay in the follow-up of patients with differentiated thyroid cancer.
Thermo Scientific B·R·A·H·M·S hTg sensitive KRYPTOR
2013;
BACKGROUND: Basal and stimulated serum thyroglobulin (Tg), combined with neck ultrasound, is the main tool used in the follow up of patients with differentiated thyroid cancer (DTC). In the last few years ultrasensitive (US) methods for the measurement of serum Tg have been devised with the goal of avoiding the time-consuming and expensive rhTSH-stimulated Tg test.
OBJECTIVE: Aim of this study was to evaluate the clinical performance of a new assay if Tg (BRAHMS hTg sensitive KRYPTOR, Analytical Assay Sensitivity (AAS) = 0.09 ng/ml, Functional Sensitivity (FS) = 0.15 ng/ml) in patients with hDTC treated with total thyroidectomy (TTx) and radioiodine (RI) ablation of thyroid residues. METHODS: Results of basal serum Tg by BRAHMS hTg sensitive KRYPTOR were compared with those obtained by Immulite Tg (AAS = 0.2 ng/ml, FS 0.9 ng/ml) in 152 patients with DTC and in 58 normal controls (NC). RESULTS: Both in NC and DTC patients the results of BRAHMS hTg sensitive KRYPTOR showed a strong correlation with those by Immulite Tg (r 0.84 and 0.9, respectively – figures 1 and 2). When the results of basal serum Tg by BRAHMS hTg sensitive KRYPTOR were evaluated in relation to the clinical evidence of recurrent/metastatic disease, ROC curve identified a cut-off ≤ 0.2 ng/ml (AUC = 0.99 – figure 3). The same cut-off was obtained when only the results of rhTSH-stimulated Tg test were considered (figure 4). This cut-off had 100% sensitivity and negative predictive value (CI 95%) for free of disease status.

Evaluation of the BRAHMS Kryptor(R) Thyroglobulin Minirecovery Test in patients with differentiated thyroid carcinoma.
Thermo Scientific B·R·A·H·M·S hTg sensitive KRYPTOR
Abstract Background: The present study was undertaken to evaluate a new sensitive thyroglobulin (Tg) minirecovery test (Tg-mrec) for the detection of potential interferences in sera from patients with differentiated thyroid carcinoma (DTC) and low Tg levels. Methods: 167 DTC patients with serum Tg <2 mug/L were enrolled. Both TgAb and Tg-mrec measurements were performed on the automated Kryptor(R) platform. Serum pretreatment in proprietary blocking tubes was perfomed to screen for heterophile antibody interferences. The concordance rates between tests were evaluated. Results: One case of over-recovery occurred in a patient with discordant Tg results respectively. The concordance rate between the Tg-mrec test and the TgAb assay was

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Implications of thyroglobulin antibody positivity in patients with differentiated thyroid cancer: a clinical position statement.
Thyroid 2013;23 (10),Oct: 1211-25.
BACKGROUND: Even though the presence of antithyroglobulin antibodies (TgAbs) represents a significant problem in the follow-up of patients with differentiated thyroid cancer (DTC), the current guidelines on the management of DTC that have been published in recent years contain no text concerning the methods to be used for detecting such antibody-related interference in thyroglobulin (Tg) measurement or how to manage TgAb-positive patients in whom Tg cannot be used reliably as a tumor marker. AIM: An international group of experts from the European Thyroid Association Cancer Research Network who are involved in the care of DTC patients met twice to form a consensus opinion on how to proceed with treatment and follow-up in TgAb-positive DTC patients based on the available evidence in the literature. Here we will report on the consensus opinions that were reached regarding technical and clinical issues. RESULTS: This clinical opinion article provides an overview of the available evidence and the resulting consensus recommendations. The current literature does not provide sufficient data for giving evidence-based answers to many questions arising in the care of TgAb-positive DTC patients. Where insufficient evidence was available, a thorough discussion by a group of physician-scientists, all of whom have a distinguished track record in thyroid cancer care, was held to arrive at a consensus expert opinion. The questions and answers discussed were then summarized into an algorithm for the management of TgAb-positive patients. CONCLUSION: We were able to define 26 consensus expert recommendations and a resulting algorithm for the care of TgAb-positive DTC patients. PMID[23095203]

Large discrepancy in the results of sensitive measurements of thyroglobulin antibodies in the follow-up on thyroid cancer: a diagnostic dilemma.
Thermo Scientific B·R·A·H·M·S GmbH
Thermo Scientific B·R·A·H·M·S hTg KRYPTOR
Thermo Scientific B·R·A·H·M·S Tg PlusS RIA/LIA
During follow-up on patients treated for differentiated thyroid cancer, thyroglobulin (Tg) antibodies can interfere with the Tg assay, making the use of Tg less reliable as a tumor marker. PURPOSE: To compare Tg and Tg autoantibodies (Tg-Ab) methods used in Denmark, regarding the number of patient samples being accepted for evaluating the result of a serum thyroglobulin (s-Tg) measurement. DESIGN: 95 consecutive blood samples drawn from patients in 2006 in one center were selected according to the following criteria: s-Tg <1 μg/L and accepted by the manufacturers of the assay were used. When using the detection limit to the cutoff seen in epidemiological studies the number increased to 40%. CONCLUSION: We found large discrepancies in acceptable patient samples for s-Tg evaluation, thus illustrating a diagnostic dilemma. PMID[24783019]

New insight in the follow-up strategies of differentiated thyroid cancer.
F. Pacini and M. G. Castagna.
Differentiated thyroid carcinoma (DTC), either papillary or follicular, has usually a very good prognosis with an overall mortality of less than 10%. In recent decades, the clinical presentation of DTC has been changing from advanced cases requiring intense treatment and surveillance to cancer detected by fortuitous neck ultrasonography requiring less aggressive treatment and follow-up. Given the changing presentation of DTC in the last years, the aim of DTC follow-up is to ensure the most effective and less invasive follow-up for a disease that nowadays is mostly cured just with surgery and is rarely fatal. The concept of "Ongoing Risk Stratification" which better define the patient risk based on the results of the initial treatment, can maximize the benefical effects of aggressive therapy in patients with DTC who are likely to benefit from it, while minimizing potential complications and side effects in low-risk patients who will achieve complete remission. PMID[23014072]
Evaluation of the BRAHMS KRYPTOR thyroglobulin "mini-recovery" test in thyroid healthy subjects.
Thermo Scientific B·R·A·H·M·S hTg KRYPTOR
The aim of the work was to compare the automated thyroglobulin (Tg) assay on the automated BRAHMS KRYPTOR platform (hTG KRYPTOR) to the established BRAHMS Tg Plus immunoradiometric assay for the measurement of Tg levels and regular Tg recovery rates and to assess a recovery test using a low Tg concentration of 10 mug/l ("mini-recovery") in samples with a native Tg level of <10 mug/l. Tg levels and recovery rates, as well as the mini-recovery, were determined in 208 serum samples from thyroid-healthy patients using both assays. The reference ranges for the Tg-Plus assay are 2.0-51.0 mug/l for Tg levels and 81.5-108% for recovery rates at 100 mug/l. The reference ranges for hTG KRYPTOR are 2.4-47.8 mug/l for Tg, 83.3-110.4% for a conventional recovery with 80 mug/l in Tg levels >/= 10.0 mug/l (n=121) and 94.4-122.9% for the mini-recovery with Tg <10.0 mug/l (n=87). The correlation between the Tg-Plus and hTG KRYPTOR is excellent for Tg (r2=0.95; p<0.001), but not significant for recovery rates. Tg levels determined using the KRYPTOR Tg assay are clinically comparable to the conventional Tg-Plus assay. New features of the KRYPTOR assay such as the ability to perform a "mini-recovery" still require further study before clinical use. PMID[22689210]

Follow-up in patients with antibody interference in Tg measurement: A consensus statement.
Eur Thyroid J 2012;1 179. OPEN ACCESS
BACKGROUND: Even though the presence of antithyroglobulin antibodies (TgAbs) represents a significant problem in the follow-up of patients with differentiated thyroid cancer (DTC), the current guidelines on the management of DTC that have been published in recent years contain no text concerning the methods to be used for detecting such antibody-related interference in thyroglobulin (Tg) measurement or how to manage TgAb-positive patients in whom Tg cannot be used reliably as a tumor marker.
AIM: An international group of experts from the European Thyroid Association Cancer Research Network who are involved in the care of DTC patients met twice to form a consensus opinion on how to proceed with treatment and follow-up in TgAb-positive DTC patients based on the available evidence in the literature. Here we will report on the consensus opinions that were reached regarding technical and clinical issues.
RESULTS: This clinical opinion article provides an overview of the available evidence and the resulting consensus recommendations. The current literature does not provide sufficient data for giving evidence-based answers to many questions arising in the care of TgAb-positive DTC patients. Where insufficient evidence was available, a thorough discussion by a group of physician-scientists, all of whom have a distinguished track record in thyroid cancer care, was held to arrive at a consensus expert opinion. The questions and answers discussed were then summarized into an algorithm for the management of TgAb-positive patients.
CONCLUSION: We were able to define 26 consensus expert recommendations and a resulting algorithm for the care of TgAb-positive DTC patients.

The use of ultrasensitive thyroglobulin assays reduces but does not abolish the need for TSH stimulation in patients with differentiated thyroid carcinoma.
J Endocrinol Invest 2011;34 (8), Sep: e219-23.
Measurement of serum Tg using ultrasensitive assays is proposed to replace TSH-stimulated Tg measurement in the follow-up of differentiated thyroid cancer (DTC). Aim of our study was to verify this possibility using two ultrasensitive Tg assays. We selected 215 DTC patients with undetectable (<1 ng/ml) basal serum Tg at the time of a recombinant human TSH (rhTSH) stimulation. According to standard criteria, 173 (80.4%) patients were considered free of disease, 17 (7.9%) had documented disease and 25 (11.7%) had no evidence of disease but detectable serum rhTSH-stimulated Tg (biochemical disease). The sera of these patients were re-assayed with two commercial ultrasensitive assays and the results were compared with the clinical data. Basal Access and E-Iason Tg assays were able to distinguish patients with persistent disease or free of disease with a sensitivity of 82.3 and 82.3%, specificity of 85.5 and 86.1%, positive predictive value (PPV) of 35.8 and 36.8%, negative predictive value (NPV) of 98 and 96.6%, respectively. With both assays the addition of neck ultrasound to basal Tg increased the sensitivity and the NPV to 100% and decreased the false negative rate to 0%. In patients with detectable basal Tg without evidence of disease, serum Tg converted from detectable to undetectable in about 80% of the cases during 2-yr follow-up. Our study indicates that the combination of neck ultrasound and basal ultrasensitive Tg allows to identify all patients free of disease and can decrease the need for rhTSH stimulation in nearly 80% of the patients. PMID[21399390]
Risk-adapted management of differentiated thyroid cancer assessed by a sensitive measurement of basal serum thyroglobulin.

P. Malandrino, A. Latina, S. Marescalco, A. Spadaro, C. Regalbuto, R. A. Fulco, C. Scillo, R. Vigneri and G. Pellegriti. J Clin Endocrinol Metab 2011;96 (6), Jun: 1703-9. OPEN ACCESS CONTEXT: Treatment and follow-up of patients thyroidecтомized for differentiated thyroid carcinoma (DTC) mainly depends on the identification of the patient’s risk of recurrence. Thyroglobulin (Tg) is the most important marker of persistent/recurrent disease. The recent introduction of a new, more sensitive Tg measurement allows for the early detection of the disease by measuring the basal (under L-T(4) therapy) serum Tg level without TSH stimulation. OBJECTIVE: The goal of this study is to identify the basal serum Tg threshold value that indicates recurrent disease by using a second-generation Tg assay. DESIGN AND PATIENTS: A continuous series of 425 DTC patients, all thyroidecтомized and treated with (131)I after surgery and having basal Tg of no more than 1.0 ng/mL, negative anti-Tg antibodies, and a recombinant human TSH-stimulated Tg measurement was retrospectively analyzed. SETTING: The study took place at an academic hospital. RESULTS: The most accurate basal Tg value for predicting the presence of recurrent/residual disease was more than 0.15 ng/mL (sensitivity 87%, specificity 91%, negative predictive value 98.6%, and positive predictive value 47.8%). When the basal Tg level was no more than 0.15 ng/mL, the risk of disease presence was very low, even in patients classified at an intermediate or high risk. In contrast, when the basal Tg level was more than 0.15 ng/mL, the percentage of recurrent disease was relatively high (12.5% or one in eight cases) in low-risk patients. CONCLUSIONS: Basal Tg, measured using a second-generation Tg assay allows for the identification of DTC patients who are likely to remain disease free with great accuracy. This simple measurement, therefore, may be sufficient to assess the risk-adapted management of DTC patients. PMID[21450986]

Current thyroglobulin autoantibody (TgAb) assays often fail to detect interfering TgAb that can result in the reporting of falsely low/undetectable serum Tg IMA values for patients with differentiated thyroid cancer. C. Spencer, I. Petrovic and S. Fatemi. J Clin Endocrinol Metab 2011;96 (5), May: 1283-91. CONTEXT: Specimens have thyroglobulin antibody (TgAb) measured prior to thyroglobulin (Tg) testing because the qualitative TgAb status (positive or negative) determines risk for Tg assay interference, and the quantitative TgAb concentration serves as a surrogate tumor marker for differentiated thyroid cancer. OBJECTIVE: This study assessed the reliability of four TgAb methods to detect interfering TgAb [as judged from abnormally low Tg immunometric assay (IMA) to Tg RIA ratios] and determine whether between-method conversion factors might prevent a change in method from disrupting TgAb monitoring. METHODS: Sera from selected and unselected TgAb-negative and TgAb-positive differentiated thyroid cancer patients had serum Tg measured by both IMA and RIA and TgAb measured by a reference method and three additional methods. RESULTS: The Tg IMA and Tg RIA values were concordant when TgAb was absent. Tg IMA to Tg RIA ratios below 75% were considered to indicate TgAb interference. Manufacturer-recommended cutoffs were set in the detectable range, and when used to determine the presence of TgAb misclassified many specimens displaying Tg interference as TgAb negative. False-negative misclassifications were virtually eliminated for two of four methods by using the analytical sensitivity (AS) as the detection limit for TgAb. Relationships between values for different specimens were too variable to establish between-method conversion factors. CONCLUSIONS: Many specimens with interfering TgAb were misclassified as TgAb negative using manufacturer-recommended cutoffs. It is recommended that assay AS limits be used to detect TgAb to minimize false-negative misclassifications. However, for two of four assays, AS limits failed to detect interfering TgAb in 20-30% of cases. TgAb methods were too qualitatively and quantitatively variable to establish conversion factors that would allow a change in method without disrupting serial TgAb monitoring. PMID[21325460]

Serum Basal thyroglobulin measured by a second-generation assay correlates with the recombinant human thyrotropin-stimulated thyroglobulin response in patients treated for differentiated thyroid cancer. C. Spencer, S. Fatemi, P. Singer, J. Nicoloff and J. Lopresti. Thyroid 2010;20 (6), Jun: 587-95. BACKGROUND: Recombinant human thyrotropin (rhTSH) stimulation is frequently used to assess the disease status of patients treated for differentiated thyroid cancer (DTC) when basal (unstimulated) thyroglobulin (b-Tg) is below the assay sensitivity limit. The objective of this study was to determine relationships between the b-Tg and the 72-hour rhTSH-stimulated Tg (rhTSH-Tg) using a second-generation immunochemiluminometric assay with a functional sensitivity of 0.05 ng/mL (microg/L). METHODS: Serum Tg was measured in paired b-Tg and rhTSH-Tg specimens from 1029 rhTSH tests performed on 849 TgAb-negative patients during long-term monitoring for DTC. RESULTS: Basal Tg correlated with rhTSH-Tg across b-Tg concentrations ranging from 0.05 to 1000 ng/mL (microg/L) (r = 0.85, p < 0.0001). The b-Tg concentration was unrelated to age, sex, basal TSH, 72-hour TSH, or the Tg fold response (rhTSH-Tg/b-Tg). Further, only 2/655 (0.3%) tests with b-Tg below 0.1 ng/mL (microg/L) had rhTSH-Tg above 2.0 ng/mL (microg/L). METHODS: Serum Tg was measured in paired b-Tg and rhTSH-Tg specimens from 1029 rhTSH tests performed on 849 TgAb-negative patients during long-term monitoring for DTC. RESULTS: Basal Tg correlated with rhTSH-Tg across b-Tg concentrations ranging from 0.05 to 1000 ng/mL (microg/L) (r = 0.85, p < 0.0001). The b-Tg concentration was unrelated to age, sex, basal TSH, 72-hour TSH, or the Tg fold response (rhTSH-Tg/b-Tg). Further, only 2/655 (0.3%) tests with b-Tg below 0.1 ng/mL (microg/L) had rhTSH-Tg above 2.0 ng/mL (microg/L). CONCLUSIONS: An rhTSH-Tg response above 2.0 ng/mL (microg/L) was
highly unlikely when b-Tg was below 0.1 ng/mL (microg/L). Second-generation b-Tg measurements correlated with the degree of rhTSH-Tg stimulation and thus the likelihood of having rhTSH-Tg above the customary cut-off of 2.0 ng/mL (microg/L), whereas b-Tg measured by a first-generation assay did not. Correlations between four different assays showed that the use of a fixed Tg cut-off was influenced by assay selection. Patients receiving repetitive rhTSH tests had highly reproducible rhTSH-Tg/b-Tg fold responses, suggesting that repetitive testing is unnecessary and that second-generation measurement of b-Tg trends without rhTSH stimulation would be satisfactory for the long-term monitoring of most patients with DTC. PMID[20470203]

Unstimulated high sensitive thyroglobulin measurement predicts outcome of differentiated thyroid carcinoma.
BACKGROUND: Thyroglobulin (Tg) measurement following thyrotropin (TSH) stimulation is used in the follow-up of patients with differentiated thyroid carcinoma (DTC). However, high-sensitive assays allow accurate measurement of serum Tg even without TSH stimulation. Here, we prospectively evaluated the impact of unstimulated high-sensitive Tg measurement in early and long-term outcome of patients with DTC. METHODS: One hundred and ninety five patients affected with DTC were evaluated. Six months after thyroid ablation (i.e., thyroidectomy plus radioiodine) serum Tg was measured during TSH-suppressive thyroxine (T4) treatment (onT4-Tg). Patients with undetectable onT4-Tg and negative neck ultrasound (US) were considered disease free and onT4-Tg was measured every 12 months for a mean follow-up of 6.8 (4.7-8.9) years. Patients with an increase in onT4-Tg underwent specific diagnostic work-up and appropriate treatment if necessary. RESULTS: Four patients showed recurrence at first follow-up visit with a corresponding increase in onT4-Tg concentrations (sensitivity 100%). Three patients had false positive onT4-Tg measurement (specificity 98%) with a spontaneous decrease within 3-6 months in all cases (specificity 100%). Three of 188 patients with undetectable serum onT4-Tg at first follow-up showed recurrence later with an increase in onT4-Tg as the first (n=2) or unique (n=1) sign of relapse (sensitivity 100%). Among 185 disease-free patients in a prolonged follow-up, 12 had a transient increase in onT4-Tg (specificity 91.6%). However, a spontaneous reduction within 3-6 months occurred in all cases (specificity 100%). CONCLUSIONS: Undetectable serum onT4-Tg using a high-sensitivity immunoradiometric assay 6 months after thyroid ablation predicts low-risk of DTC recurrence. When onT4-Tg became detectable during follow-up, the evaluation of Tg slope in a 3-6 months period accurately discriminated patients with DTC recurrence from those without recurrence. This helped avoid unnecessary diagnostic or therapeutic procedures. PMID[19589104]

Diagnosis and management of thyroid carcinoma: a focus on serum Thyroglobulin.

Monitoring thyroglobulin in a sensitive immunoassay has comparable sensitivity to recombinant human tsh-stimulated thyroglobulin in follow-up of thyroid cancer patients.
CONTEXT: Most thyroglobulin (Tg) assays have a sensitivity of 0.5-1 ng/mL. A minority of patients with undetectable T4-suppressed Tg levels have a recombinant human TSH (rhTSH)-stimulated Tg above 2 ng/mL and identifiable residual disease. OBJECTIVE: The objective was to determine whether a Tg assay with improved sensitivity could eliminate the need for rhTSH stimulation when baseline Tg is below 0.1 ng/mL. DESIGN: A retrospective study of two academic endocrine practices was conducted. POPULATION: A total of 194 patients undergoing rhTSH stimulation participated in the study. RESULTS: Of the 80 patients with Tg below 0.1 ng/mL, two (2.5%) had rhTSH-stimulated Tg above 2 ng/mL. One other patient with stimulation to 0.3 ng/mL and negative 123I scan had an ultrasound-detected malignant lymph node resected. None had 131I/123I imaging after rhTSH stimulation suggestive of local recurrence or distant metastasis. If T4-suppressed Tg was 0.1-0.5 or 0.6-2.0 ng/mL, rhTSH Tg was above 2 ng/mL in 24.2 and 82.4%, respectively. CONCLUSIONS: Patients with differentiated thyroid carcinoma and a T4-suppressed serum Tg below 0.1 ng/mL rarely have a rhTSH-stimulated Tg above 2 ng/mL, and none of these patients had 131I or 123I imaging after rhTSH stimulation suggestive of local recurrence or distant metastasis. We recommend monitoring such patients with a T4-suppressed Tg level and periodic neck ultrasonography. An increase in T4-suppressed serum Tg to a detectable level or the appearance of abnormal lymph nodes by physical or ultrasound exam should prompt further investigation. PMID[17077133]

Management guidelines for patients with thyroid nodules and differentiated thyroid cancer.

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European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium.
Eur J Endocrinol 2006;154 (6),Jun: 787-803. OPEN ACCESS
PMID[16728537]

Serum thyroglobulin measurements with a high sensitivity enzyme-linked immunosorbent assay: is there a clinical benefit in patients with differentiated thyroid carcinoma?
Thyroid 2003;13 (9),Sep: 861-5.
Serial serum thyroglobulin (Tg) measurements with a highly sensitive enzyme-linked immunosorbent assay (ELISA; functional sensitivity 0.03 ng/mL) in 126 patients (Tg autoantibody negative) with treated differentiated thyroid cancer (DTC) are described. At the beginning of the retrospective study, all 126 patients were in remission and Tg was detectable by ELISA in 92 (73%; range, 0.03-0.8 ng/mL). Over the following 4-year period, Tg levels remained essentially unchanged (i.e., any increases were less than 2 times the Tg level at the start of the study) in 121 of 126 (96%) and all 121 patients remained well. In 5 patients, Tg levels increased to more than 2 times the starting Tg level over the study period and in 4 of these 5, there was recurrence of DTC. The fifth patient in this group remains well as evidenced by extensive diagnostic imaging, although his serum Tg level continues to increase and can be stimulated by thyrotropin (TSH). Our results suggest that serial measurements of low levels of Tg by ELISA in treated patients with DTC enable detection of recurrence (without using TSH stimulation) 6-12 months earlier than would have been possible using a conventional Tg immunoradiometric assay (IRMA). A prospective study is now needed to confirm these observations. PMID[14588100]

High-sensitivity human thyroglobulin (hTG) immunoradiometric assay in the follow-up of patients with differentiated thyroid cancer.
L. Giovanella and L. Ceriani.
Circulating human thyroglobulin (hTG) measurement has a pivotal role in the management of patients affected by differentiated thyroid cancer (DTC). Generally, hTG serum concentration less than 1 ng/mL is considered a marker of complete remission after total thyroid ablation. Recently, high-sensitivity immunoradiometric assays (IRMA) have been developed to detect very low hTG serum concentrations. The present study was undertaken to test a newly developed high-sensitivity hTG IRMA and to evaluate its diagnostic performance and reproducibility in the follow-up of patients affected by DTC. We retrospectively selected 156 patients without signs of recurrence and 39 patients with DTC recurrence. Serum samples were collected during L-thyroxine (T4) suppressive therapy (ONT4) and 4 weeks after T4 withdrawal (OFFT4), and hTG was measured by a specific high-sensitivity IRMA (DYNOtest Tg-plus, BRAHMS Diagnostica GmbH, Berlin, Germany). Sera showing the presence of antibodies against hTG (AbhTG) or hTG-recovery less than 80% were excluded from the study. The receiver operator characteristic (ROC) curve analysis was performed to select the best cut-off levels, and diagnostic performance of the marker was evaluated. By using ONT4 cut-off level of 0.2 ng/mL and OFFT4 cut-off level of 0.5 ng/mL we obtained a sensitivity/specificity/accuracy profile of 0.92/0.98/0.97 and 0.97/0.98/0.98, respectively. We found false-negative results in three (12%) and one (4%) out of 24 patients with cervical recurrence by using 0.2 and 0.5 ng/mL cut-off levels, respectively. However, we found false-negative results in 13 (54%) and six (25%) patients when 1.0 ng/mL cut-off level was used. Finally, DYNOtest Tg-plus showed a very satisfactory intra- and inter-assay reproducibility in the very low hTG concentration range. Based on our data, we conclude that DYNOtest Tg-plus assay is effective and accurate in evaluation of patients with DTC. PMID[12113292]

High-sensitive 2nd generation thyroglobulin immunoradiometric assay. Clinical application in differentiated thyroid cancer management.
L. Giovanella, L. Ceriani and S. Garancini.
BACKGROUND: Circulating human thyroglobulin (hTG) measurements have a pivotal role in the management of patients affected by differentiated thyroid cancer (DTC). The present study was undertaken by employing a new developed high-sensitivity hTG immunoradiometric assay to evaluate its diagnostic performance in patients affected by radically cured and relapsing DTC and to set the most appropriate cut-off point for DTC management.
METHODS: We retrospectively selected 172 patients without signs of recurrence after primary treatment and 45 patients with recurrences from DTC. Serum samples were collected during L-thyroxine (T4) suppressive therapy (ONT4) and 4 weeks after T4 withdrawal (OFFT4) and hTG measured by a specific high-sensitivity IRMA (DYNOtest Tg-plus, BRAHMS Diagnostica GmbH, Berlin, Germany). Sera showing the presence of AbhTG or hTG-recovery less than 80% were excluded from the study. ROC curve analysis was performed to select the best cut-off levels and diagnostic performance of the marker evaluated. RESULTS: By using ONT4 cut-off level of 0.2 ng/mL and OFFT4 cut-off level of 0.5 ng/mL we obtained a sensitivity/specificity/accuracy profile of 0.91/0.98/0.96 and 0.98/0.97/0.97, respectively. We found ONT4-hTG false-negative results in 4 patient with local recurrence (n=2) or cervical lymph-node metastasis (n=2) while only 1 patient with local recurrence showed negative OFFT4-hTG.
However, onT4 and offT4-hTG false-negative results were observed in 9 and 5 patients when 1.0 ng/mL cut-off level was employed. CONCLUSIONS: On the basis of our data, we conclude that DYNOtest Tg-plus assay is very effective and accurate in the evaluation of patients with DTC. PMID[12411872]

Epitope mapping of human thyroglobulin reveals a central immunodominant region.
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Thyroglobulin is the thyroid hormone precursor and the major antigen frequently involved in autoimmune diseases. The primary structure of human thyroglobulin is known but the spatial structure remains largely undetermined. By using fusion protein produced in prokaryotic system we have characterized seven short immunoreactive peptides carrying at least one epitope. None of them includes hormonogenic sites, but five are concentrated in the central part of the monomeric molecule, which thus emerges as the major immunogenic region of this protein. PMID[1705895]