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Clinical implications of changing thyroglobulin and antithyroglobulin antibodies analytical methods in the follow-up of patients with differentiated thyroid carcinoma

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ABSTRACT

Background and aims: Patients' response to treatment in differentiated thyroid cancer (DTC) is classified according to serum thyroglobulin concentrations (Tg), usually using the American Thyroid Association guidelines and considering potential interfering anti-thyroglobulin antibodies (Ab-Tg). We aim to evaluate the clinical implications of changing Tg and Ab-Tg quantification method.

Material and methods: Tg and Ab-Tg were quantified in 82 serum samples (60 from DTC patients) by Elecsys and Access immunoassays.

Results: Elecsys immunoassay rendered higher values of Tg than Access: mean bias 5.03 ng/mL (95%CI:-14.14–24.21). In DTC patients, there was an almost perfect agreement for response classification (kappa index = 0.833). Discrepancies appeared in patients with undetermined response, with a more tendency to subclassification with Access. Ab-Tg showed a poor correlation (r = 0.5394). When Elecsys cut-off was reduced to 43 IU/mL, agreement for positive/negative classification improved from a kappa index of 0.607 to 0.650. Prospective study with personalized follow-up showed that only 6.3% of Tg results required an analytical confirmation, being confirmed 93% of them.

Conclusions: Despite the biases observed, clinical impact of an analytical change is minimal in patients' management. However, cautious and personalized follow-up period after the change is still mandatory, especially in patients with Tg levels between 0.2 and 1 ng/mL.

1. Introduction

Differentiated thyroid cancer (DTC) comprises>90% of all thyroid cancers, whose incidence has increased over the last decades mainly due to the improvement of diagnostics tools [1]. DTC presents good prognosis, being the routine treatment surgical resection of the tumour (lobectomy or total thyroidectomy) and, when necessary, radioactive iodine ablation. To evaluate treatment efficacy and risk of recurrence assessment of these patients, the follow-up comprises imaging studies and thyroglobulin (Tg) quantitation [2].

Tg, a high molecular weight glycoprotein of the colloid that act as substrate for thyroid hormones synthesis, is the tumor marker of election in DTC patients monitoring [3]. Based on serum Tg concentrations during follow-up, the American Thyroid Association (ATA) guidelines classifies the patient responses to treatment in three categories: excellent, indeterminate and incomplete [2]. Consequently, Tg measurement should be standardized and robust. A critical factor affecting Tg measurement is the interference by potential presence of anti-thyroglobulin

Abbreviations: Ab-Tg, anti-thyroglobulin antibodies; ATA, American Thyroid Association; CI, confidence interval; DTC, differentiated thyroid cancer; Tg, thyroglobulin.

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autoantibodies (Ab-Tg), whose prevalence is estimated in up to 10% in general population and up to 20% in DTC patients [4]. The presence of these antibodies can provoke falsely diminished Tg levels in immunoassays with "sandwich" configuration and, if this interference is not detected, patients' response might be wrongly classified. To avoid this, in the management of these patients, Ab-Tg must be simultaneously measured to Tg. Ab-Tg are also usually measured with automated immunoassays, and when positive, Tg reported value is not reliable and Ab-Tg can be considered themselves as a surrogate marker: declining or stable Ab-Tg in the absence of structural disease correspond to indeterminate response, while increasing Ab-Tg correspond to biochemical incomplete response [2].

Most laboratories assess Tg concentrations with automated immunoassays that should be standardized against the CRM-457 international standard [5], to reduce analytical variability. In the case of Ab-Tg quantitation, even after the introduction of the International Reference Preparation (IRP) MRC 65/93, there is still high variability among analytical methods that limits their interchangeability [6], probably due to the heterogeneity of Tg structure. Related to this high variability, it is crucial that longitudinal analysis of Tg and Ab-Tg during patient follow-up would be performed always with the same analytical method. Consequently and prior to any analytical method change, a comparative analysis is mandatory in order to evaluate the potential analytical differences among them.

Previous studies have compared multiple Tg and Ab-Tg immunoassays [7–9]. Most of these studies have been focused on correlations and analytical biases among them. However, these comparative studies should go beyond, and evaluate the clinical impact of those differences in DTC patients' management according to ATA classification [10]. For that reason, the aim of this study was to perform a comparative study for both Tg and Ab-Tg measurement between two methods, Access (Beckman Coulter) and Elecsys (Roche Diagnostics) immunoassays, focusing not only on the analytical biases but also in the potential clinical implications for the patients management. We will specially focus on concentrations of Tg below 1 ng/mL, which have the most important clinical implications for patients classification [2].

2. Materials and methods

2.1. Subjects and sample collection

A comparative study was performed with 82 serum samples in whom Tg and Ab-Tg were simultaneously quantified by an Access autoanalyzer and a Cobas autoanalyzer with the corresponding Elecsys immunoassay. Sixty of those samples were selected from the collection C. 0,003,132 from the Spanish National Biobank Registry and correspond to DTC patients (56 with previous total thyroidectomy and 4 with lobectomy). Additionally, 22 samples from patients with benign thyroid diseases were also included. All samples were kept at −80 °C until their simultaneous analysis with both methods.

Subsequently, a prospective study was performed after the analytical method change, with DTC patients in which Tg or Ab-Tg were discrepant with the clinical situation or previous reported concentrations.

The study was approved by the research local ethics board (Ref: 2023.017).

2.2. Laboratory measurements

Tg measurement by Access autoanalyzer (Beckman Coulter, USA) employs a one-step immunoenzymatic assay in a sandwich configuration using a biotinylated mixture of four monoclonal anti-Tg antibodies as capture antibodies and a monoclonal anti-Tg antibody conjugated to alkaline phosphatase as detection antibody. The detection limit is 0.10 ng/mL. In the case of Elecsys, the electrochemiluminiscent sandwich assay employed a biotinylated monoclonal antibody for capture and another monoclonal antibody with ruthenium complexes for detection. Manufacturer stated 0.04 ng/mL as detection limit and 0.10 ng/mL as quantitation limit. Elecsys assay is calibrated against the CRM-457 international standard, but not information about this issue is declared related to Access.

Regarding Ab-Tg measurements, Access autoanalyzer employs a two-step sandwich enzimoimmunoassay with Tg- coated beads and Tg conjugated to alkaline phosphatase. Detection limit is 0.9 IU/mL whereas the cut-off for positivity is 4 IU/mL. In the case of Cobas autoanalyzer, the Elecsys electroluminescent assay presents a competitive configuration for biotinylated Tg, between Ab-Tg of the sample and exogenous ruthenium-complexed Ab-Tg. Manufacturers establish 10 IU/mL as the detection limit and 115 IU/mL as the cut-off for positivity. Cut-offs for Ab-Tg positivity were established by the corresponding manufacturer based on healthy populations data and not in their capability to interfere in Tg quantification. Elecsys assay is calibrated against the 65/93 international standard from the National Institute for Biological Standards and Control (NIBSC), but not information about this issue is declared related to Access.

2.3. Statistical analysis

The analysis of Tg and Ab-Tg quantitative results comprised Passing-Bablok regression and Bland-Altman analysis. In addition, in the 56 samples from DTC patients with total thyroidectomy, Tg levels were classified in three groups according to ATA guidelines cut-offs: excellent response for Tg < 0.2 ng/mL, indeterminate response for Tg ≥ 0.2 and $<$ 1 ng/mL and incomplete biochemical response for Tg $\geq$ 1 ng/mL. Agreement among the classification resulting from Access and Elecsys results was evaluated with Cohen's kappa index and classified as: slight (0–0.2), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) and almost perfect (0.81–1.00). In the case of Ab-Tg, concordance was evaluated in all samples ($n = 82$), with Ab-Tg results classified based on the cut-off value for positivity established by each manufacturer. Additionally, an alternative bibliographic cut-off value for Ab-Tg measurement with Elecsys assay was also evaluated [6]. McNemar's test was performed to analyze the change in negative/positive proportions. Statistical analysis was performed with GraphPad v6.

3. Results

3.1. Tg measurement and comparative study

When measuring Tg with Elecsys method, 28 samples (34%) had concentrations equal or below the quantitation limit established by manufacturer at 0.10 ng/mL and 24 of these (29%) presented values below the detection limit. However, 6 of the 28 samples had Tg concentrations quantifiable by Access, four of them near the quantification limit, and remarkably, one sample with a result of 4.6 ng/mL and another one with a result of 25 ng/. It is important to note that the last two samples presented high levels of Ab-Tg using both methods. Alternatively, when measuring Tg with Access method, 23 samples (28%) rendered Tg results equal or below the detection limit declared by manufacturer, of which all, except one with a Tg concentration of 0.11 ng/mL, were also undetectable in Elecsys.

When considering quantifiable results the median value of Tg with Access was 1.30 ng/mL (IQR: 0.13–6.50) and 4.27 ng/mL (IQR: 0.87–16.5) in the case of Elecsys assay. Passing-Bablok regression analysis of the 52 samples with quantifiable results for both methods, rendered a slope of 1.517 (95% CI: 1.388–1.603) and an intercept of −0.2617 (95%CI: −0.4245-(-0.1370), Fig. 1A). Bland-Altman test showed a higher values of Tg when measured by Elecsys in samples considered negative for Ab-Tg by both methods (mean bias: 5.98 ng/mL, 95%CI:-16.53–28.29) and also in those positive for Ab-Tg with one or the two assays (mean bias 3.69 ng/mL; 95%CI:-8.79–16.17). There was no difference in the bias between these two groups ($p = 0.885$) and the bias considering all these samples was 5.03 ng/mL (95%IC:-

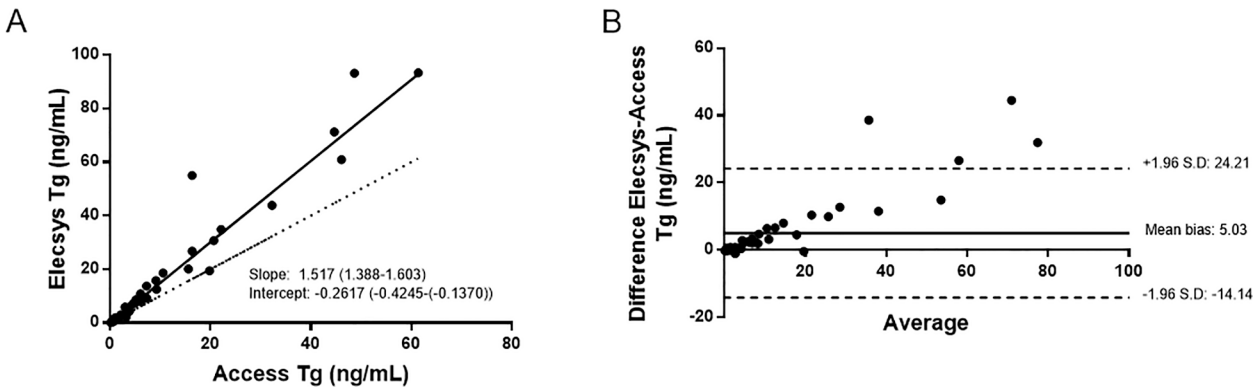

Fig. 1. (A) Passing-Bablok regression analysis between thyroglobulin (Tg) concentrations measured with Access and Elecsys immunoassays. Solid line corresponds to regression line while dashed one corresponds to 1:1 perfect fit. (B) Bland-Altman plot of the difference between Tg concentrations measured by Elecsys and Access immunoassays. Solid line represents bias and dashed lines the 95% confidence interval.

14.14–24.21, Fig. 1B). In the case of Tg concentrations between 0.1 and 1 ng/mL, where accuracy of the results is critical, the global bias was 0.09 ng/mL (95%IC:-0.44–0.62). No difference was found between samples considered negative for Ab-Tg by both methods (mean bias: 0.08 ng/mL, 95%CI:–0.44–0.61) and those positive for Ab-Tg with one or the two assays (mean bias 0.05 ng/mL; 95%CI:-0.42–0.52; p = 7263). Thus, there was a proportional and systematic bias between both immunoassays with higher Tg concentrations when measured by Elecsys.

Regarding categorical classification of Tg concentrations of DTC patients with total thyroidectomy according the cut-offs from ATA guidelines, the concordance between Access and Elecsys immunoassays was 89% with a Cohen's kappa index of 0.833 (95%CI: 0.712–0.955), which corresponds to an almost perfect agreement (Table 1). All the samples with Tg concentrations by Access corresponding to an excellent (n = 21) or biochemical incomplete response (n = 21), were classified as well by Elecsys immunoassay. In the case of 14 samples with Tg concentrations by Access corresponding to an indeterminate response, 8 were similarly classified with an indeterminate response with Elecsys immunoassay, whereas 2 would have been classified with an incomplete response, with Tg < 1.5 ng/mL in both cases. The other 4 would have been classified with an excellent response, with 2 of them even with undetectable Tg levels according Elecsys immunoassay. In this case, two out of these 4 volunteers, had elevated Ab-Tg levels.

The agreement is similar when focusing on those samples considered negatives for Ab-Tg according both methods (n = 43), with a concordance of 91% and a Cohen's kappa index of 0.852 (95%CI: 0.719–0.986). In fact, from the 13 samples considered positive by at least one the Ab-Tg immunoassays, only 2 were not equally classified. Both cases had a Tg concentration of 0.2 ng/mL and were consequently classified as indeterminate response by Access immunoassay, whereas they corresponded to an excellent response by Elecsys immunoassay.

Table 1
Biochemical classification of patients according to ATA criteria based on serum thyroglobulin concentrations value quantified by Access and Elecsys methods. ATA, American Thyroid Association; Tg, thyroglobulin. Response classification: excellent: ≤0.2 ng/mL; indeterminate: 0.2–1 ng/mL; biochemical incomplete: >1 ng/mL.

Tg (ng/mL)		Elecsys			
		≤ 0.2	0.2–1	> 1	Total
Access	≤ 0.2	21	0	0	**21**
	0.2–1	4	8	2	**14**
	> 1	0	0	21	**21**
	Total	**25**	**8**	**23**	**56**

3.2. Ab-Tg measurement and comparative study

Regarding Ab-Tg, 41 samples (50%) presented undetectable levels in Access autoanalyzer and only 6 (7%) when analyzed with Elecsys. All of the latter except one, had also undetectable levels in Access autoanalyzer. Ab-Tg median concentration was 1.0 IU/mL (IQR: 0.9–43.4) in Access and 16.7 IU/mL (IQR: 12.8–246.1) with Elecsys.

Considering only the 40 samples with quantifiable results for Ab-Tg with both methods, Passing-Bablok analysis showed a slope of 2.277 (95% CI: 1.269–3.757) and an intercept of 17.739 (95%CI: 9.014–63.749; Fig. 2A).Bias analysis with Bland-Altman test showed a mean bias was 127 IU/mL (95%IC:-840–1095, Fig. 2B). Thus, there was a proportional and systematic bias with higher values of Ab-Tg when measured by Elecsys.

Regarding classification according Ab-Tg presence (Table 2) using the corresponding cut-offs, the concordance between both methods was 83% with a Cohen's kappa index of 0.607 (95%CI: 0.423–0.791), which corresponds to a substantial agreement. Access method considered 28 samples (34%) as positive. In the case of Elecsys method, considering the cut-off value recommended by the manufacturer (4 IU/mL), 24 patients (29%) were classified as positive for Ab-Tg presence. None of the samples with undetectable Ab-Tg for one method were considered positive with the other. Patients considered positive according Access immunoassay but not with Elecsys, rendered concentrations by Elecsys between 13 and 91 IU/mL. On the contrary, patients considered positive by Elecsys but not by Access, rendered concentrations by the latter that ranged between 1.1 and 3.9 IU/mL.

When the cut-off level indicated by the manufacturer for Ab-Tg for Elecsys was changed to 43 IU/mL, calculated by D'Aurizio et al. [6], 5 patients changed their classification from negative to positive. Interestingly, 3 of them were clearly positive according Access results (64, 248 and 605 IU/mL, respectively) whereas the other two had concentrations ≤ 0.9 IU/mL. The change observed in negative/positive proportion due to the Elecsys cut-off decrease was not significant (p = 0.0735), and the concordance only improved slightly, with 84% of agreement and a Cohen's kappa index of 0.650 (95%CI: 0.477–0.824).

When focusing on the 4 patients with lobectomy, two of them had undetectable Ab-Tg concentrations with Access, and near the quantification limit with Elecsys. The other two had Ab-Tg concentrations detectable but below the 4 ng/mL cut-off with Access, but were classified as positive with Elecsys assay even according Roche cut-off.

3.3. Effect of method change in the classification of treatment response

We performed a prospective study after changing the analytical method with 463 patients. We analyzed with both methods: a) samples with Tg and Ab-Tg results with a substantial change from the previous

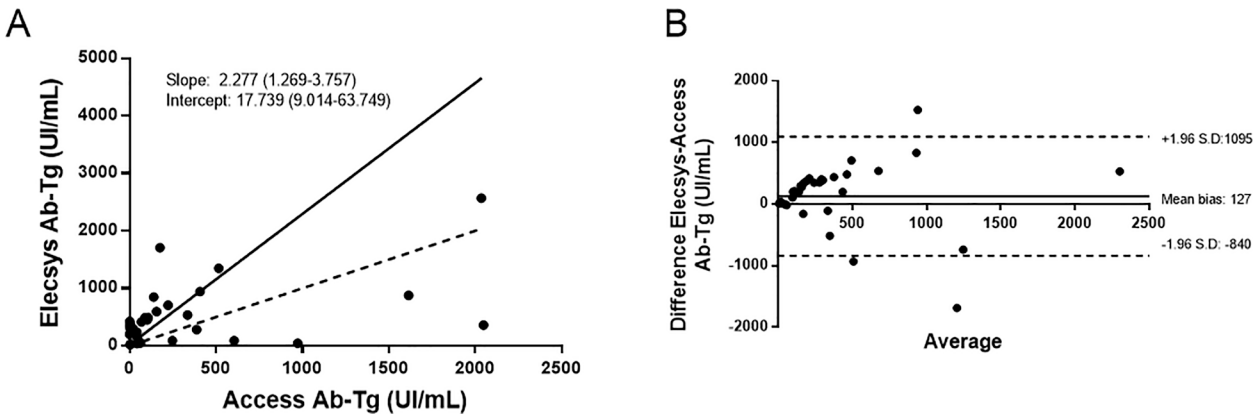

Fig. 2. (A) Passing-Bablok regression analysis between anti-thyroglobulin antibodies concentrations (Ab-Tg) measured with Access and Elecsys immunoassays. Solid line corresponds to regression line, while dashed line corresponds to 1:1 perfect fit. (B) Bland-Altman plot of the difference between Tg concentrations measured by Elecsys and Access immunoassays. Solid line represents bias and dashed lines the 95% confidence interval.

Table 2
Patients' classification related to anti-thyroglobulin antibodies (Ab-Tg) presence evaluated by Access and Elecsys methods.

Ab-Tg (IU/mL)		Cobas				
		Cut-off: 115		Cut-off: 43		
		Negative	Positive	Negative	Positive	Total
Access	Negative (<4)	49	5	47	7	**54**
	Positive (>4)	9	19	6	22	**28**
	Total	**58**	**24**	**53**	**29**	**82**

concentrations, that did not apparently agree with patient clinical situation, or b) samples with a change in Ab-Tg status (from previous negative to positive or the contrary, from previous positive to negative). The samples that required this type of confirmations during the prospective study were only 6.3%.

In the case of Tg, we checked Tg concentrations in 29 samples. Passing-Bablok analysis of 23 samples with quantifiable concentrations showed a slope of 1.515 (95% CI: 1.322–1.615) and an intercept of −0.050 (95%CI: −0.300–0.140. The concordance according the ATA classification between both methods was 93% with a Cohen's kappa index of 0.877 (95%CI: 0.716–1.000; Table 3). From 6 samples with undetectable Tg concentrations with Elecsys method, 5 were also undetectable with Access and the remaining had a concentration of 0.2 ng/mL. Interestingly, this sample with biochemical indeterminate response was positive for Ab-Tg with Elecsys but not with Access and imaging studies detected the presence of a thyroid remnant. Additionally, the other sample with discrepant classification had Tg concentrations of 1.1 and 0.9 ng/mL when measured with Elecsys and Access method respectively.

In the case of Ab-Tg, we check 20 results with both methods and more discrepant classifications were found between them (Table 4) with a concordance was 60% and a Cohen's kappa index of only 0.2 (95%CI: −0.194–0.594). From the 3 samples with undetectable Ab-Tg with Elecsys immunoassay, when measuring with Access immunoassay 2 of them had also undetectable Ab-Tg concentrations, whereas the other was above the cut-off for positivity. In the other 7 samples with quantifiable Ab-Tg but below the reference range, only one of them resulted positive with Access, with a concentration of 10 IU/mL. In the rest of the 10 samples, that were positive according to Elecsys results, only 4 were positive with Access immunoassay. It is interesting to note that from the other 6 patients, negative with Access immunoassay, 3 presented hypothyroidism related to Hashimoto disease, one had been initially positive for Ab-Tg with Access assay, but later had become negative and in another case, Ab-Tg with Access assay had increased from previously undetectable concentrations to 2 IU/mL. The last patient with discrepant Ab-Tg results, positive with Elecsys and negative with Access, had progressively increasing Ab-Tg concentrations with Elecsys immunoassay, and there was remaining thyroid tissue in the imaging studies. In addition, this patient had presented after thyroidectomy a Tg concentration of 0.90 ng/mL that had decreased to 0.1 ng/mL as the Ab-Tg increased.

4. Discussion

The decision of changing an analytical method is of most importance in clinical laboratories, especially in the case of tumor markers, such as Tg. Although, this must not prevent us from exploring alternatives, it compels us to perform a cautious assessment of the consequences of the hypothetical change. Our comparative study between Access and Elecsys immunoassays showed a similar rate of samples with Tg concentrations below the detection limit with both methods. We found a proportional and systematic bias with higher Tg concentrations when analysed with Elecsys immunoassay, which agrees with previous studies [11]. Interestingly, those with greatest bias against Elecsys immunoassay, correspond to samples that according both methods, presented

Table 3
Concordance between Access and Elecsys methods in samples checked after analytical method change. ATA, American Thyroid Association; Tg, thyroglobulin. Response classification: excellent: ≤0.2 ng/mL; indeterminate: 0.2–1 ng/mL; biochemical incomplete: >1 ng/mL.

Tg (ng/mL)		Elecsys			
		≤ 0.2	0.2–1	> 1	Total
Access	≤ 0.2	5	0	0	**5**
	0.2–1	1	5	1	**7**
	> 1	0	0	17	**17**
	Total	**6**	**5**	**18**	**29**

Table 4
Patients classification related to anti-thyroglobulin antibodies (Ab-Tg) presence evaluated by Access and Elecsys methods in samples checked after analytical method change.

Ab-Tg (IU/mL)		Elecsys		
		Negative (<43)	Positive (>43)	Total
Access	Negative (<4)	8	6	**14**
	Positive (>4)	2	4	**6**
	Total	**10**	**10**	**20**

elevated concentrations of Ab-Tg, which are known interfering molecules in Tg measurement. However, in spite of that bias, we observed a high concordance between these two methods in the classification of patients' response according the ATA guidelines categories of response to treatment, even in samples positive for Ab-Tg. These results support the possibility of an analytical change for Tg measurement between these 2 immunoassays.

A Tg isolated assessment has limited clinical utility since its measurement can be interfered by the presence of Ab-Tg, quite common in general population and even more in DTC with concurrent autoimmune thyroid disease [4]. For that reason, Tg quantitation should be always accompanied by Ab-Tg assessment and we have included them in this comparative study. In the case of Ab-Tg, we found indeed important differences in Ab-Tg concentrations between immunoassays. In fact, the cut-off values suggested by the corresponding manufacturers differ in orders of magnitude (4 vs 115 ng/mL). This clearly prevents the interchangeability of Ab-Tg results. We also found higher discrepancies in the classification of patients related to Ab-Tg presence. These discrepancies only improved slightly with alternative and lower cut-off of 43 IU/mL for Elecsys immunoassay, suggested by previous studies [6]. However, an even lower cut-off (22 IU/mL) suggested in another study [9] did not increase the concordance between both methods (data not shown). Nevertheless, our study did not reach the concordance observed by Algeciras-Schimnich et al. [9]. This can be due to their higher proportion of patients with high Ab-Tg levels (>10 IU/mL according Access method). It is well known that the heterogeneity in Tg structure provokes heterogeneity in the corresponding autoantibodies [12]. Given that Ab-Tg immunoassay are based in the binding of these autoantibodies to exogenous Tg, there is a high variability in the capability of the different commercial available immunoassays to detect and quantify Ab-Tg [7,13].

These discrepancies in patient classification related to Ab-Tg presence, may affect the validity of the corresponding Tg measured concentrations and, as a consequence, patient management. For that reason, the change in analytical method should be followed by a transition period with close and personalized scrutiny of both Tg and Ab-Tg results. Related to this, the guidelines suggest two options: a) simultaneous quantitation of all samples with both methods for a minimum period of 6 months, or b) to keep for a year the last sample of each patient prior the analytical change, to be simultaneously analyzed with the subsequent sample obtained after the analytical change [14]. Although these strategies clearly eliminate potential negative impacts in patients' management, both of them present important economical and/or logistical limitations. Given the good agreement observed for Tg measurement we decided for a more practical strategy; only checking against the previous method those samples with results that clearly differed from the previous results and/or are not consistent with clinical evolution.

After a reasonable period, we only needed a confirmation analysis in a small percentage of the samples. Most of those samples showed an agreement between both methods for Tg measurement, and the observed change from previous values was due to changes in patient status. This supports our strategy of reducing the confirmation process to carefully selected samples and not all them, which reduces material and staff costs. In the case of Ab-Tg, we found more discrepancies, with higher detection rates when using Elecsys immunoassays, which agree with previous studies where Elecsys presented higher detection rate than other immunoassays [7,15]. When examining the clinical situation of these patients considered positive for Ab-Tg by Elecsys but not by Access immunoassay, we found that most likely, they had been true positive for Ab-Tg that had not been detected until then. For example, they presented Hashimoto's thyroiditis, they had been previously positive or there were dynamic changes in Ab-Tg levels. All these situations reduce the probability of a false positive result with Elecsys immunoassay. Nevertheless, this newly detected positivity for Ab-Tg in these patients indicates the need for a closer follow-up of them, which it is only in patient interest.

Currently, Ab-Tg evaluation is essential when quantifying Tg by an immunometric method that is the most commonly used in routine practice. However, the potential presence of Ab-Tg would become irrelevant in the case of Tg quantification by mass spectrometry [16]. This methodology is not affordable by many clinical laboratories yet, but it would be desirable to spread its use because it would avoid interferences not only by Ab-Tg [16] but also by others confounding factors such as biotin [17]. However, recent studies suggest that when there are low Ab-Tg concentrations their interference in Tg quantifications by immunoassays in minimum and their results are still reliable and useful in the management of DTC patients [18].

In summary, we found that the analytical biases resulting from the analytical change between Access and Elecsys immunoassays do not turn out into substantial changes in patients' management. Nevertheless, a close and personalized follow-up should be performed as we propose here.

Policy and ethics

The study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and approved by the local Ethics Committee of University of Navarra (protocol code: 2023.017). Informed consent was obtained from DTC patients prior to their inclusion in the sample collection. The rest of clinical histories were anonymously consulted.

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CRediT authorship contribution statement

Sara Deza: Formal analysis. **Julia Maroto:** Investigation. **Olaia Tellechea:** Formal analysis. **Natalia Orbegozo:** Formal analysis. **Juan C Galofré:** Investigation. **Estibaliz Alegre:** Conceptualization, Methodology. **Álvaro González:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper: [Álvaro González has received support from Roche Diagnostics for attending Euromedlab 2023 and Sara Deza and Estibaliz Alegre for Spanish National Congress of Laboratory Medicine 2022].

Data availability

Data will be made available on request.

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