Clin. Lab. 2017;63:XXX-XXX

ORIGINAL ARTICLE

Uncritical Request of Thyroid Laboratory Tests May Result in a Major Societal Economic Burden: Results from a Large Population Study in Spain

Maria Salinas [1, 2], Maite López-Garrigós [1], Emilio Flores [1, 3], Carlos Leiva-Salinas [4]

[1] *Clinical Laboratory, Hospital Universitario de San Juan, San Juan de Alicante, Spain*
[2] *Department of Biochemistry and Molecular Pathology, Universidad Miguel Hernández, Elche, Spain*
[3] *Department of Clinical Medicine, Universidad Miguel Hernández, Elche, Spain*
[4] *Department of Radiology, University of Virginia, Charlottesville, VA, USA, (On Behalf of The Pilot Group of The Appropriate Utilization of Laboratory Tests (REDCONLAB) working group)*

SUMMARY

Background: **Our aim is to study the regional variability in the request of thyroid laboratory tests from primary care facilities in Spain and to investigate a potential inappropriate request and its economic societal impact.**
Methods: **Spain is divided into 17 autonomous communities (AACCs) which are in turn divided in Health Departments that cover a geographic area and its population and a laboratory that attends the needs of every inhabitant. Each participating laboratory was required to report the number of thyroid tests requested from primary care during year 2014 and to provide organizational data. The request of every test per 1000 inhabitants and ratio of related tests (free thyroxine (FT4)/thyrotropin (TSH), triiodothironine (FT3)/TSH, antithyroglobulin antibody (ATG)/antiperoxidase antibody (TPO)) were calculated and compared in different AACCs with more than 4 participants. The economic costs taking into account reagent cost were calculated.**
Results: **110 laboratories participated (27,798,262 inhabitants). Close to 6 million TSH tests were requested, representing an expense of more than 10 million euros. That corresponds to 18 million euros when extrapolating for the whole Spanish population, only in reagent cost. The number of TSH requests per 1000 inhabitants in the different AACCs ranged from 198 to 289. FT4 was ordered more than twice as frequently in some regions compared to others. TPO request per 1000 inhabitants ranged from 0.2 to 11.2.**
Conclusions: **There was a significant over-request and regional variability of thyroid laboratory tests in primary care in Spain, resulting in a high economic impact on society.**
(Clin. Lab. 2017;63:xx-xx. DOI: 10.7754/Clin.Lab.2017.170101)

Correspondence:
María Salinas, PhD
Hospital Universitario de San Juan
Carretera Alicante-Valencia, s/n
03550 San Juan de Alicante
Alicante
Spain
Phone: +34 965938877
Fax: +34 965938383
Email: salinas_mar@gva.es

Manuscript accepted February 6, 2017

KEY WORDS

thyroid laboratory tests, appropriateness, clinical laboratory, variability

LIST OF ABBREVIATIONS

TSH - thyrotropin
FT4 - free thyroxine
AACC - autonomous communities
HD - Health Department
FT3 - free triiodothyronine
TPO - anti-thyroid peroxidase antibodies

ATG - anti-thyroglobulin antibodies
GP - general practitioner
LIMS - Laboratory Information System

INTRODUCTION

Thyroid diseases are common and most can be safely and effectively managed in primary care [1]. The request of thyroid laboratory tests from primary care has increased in recent years [2], in part due to aging [3]. Various published guidelines recommend serum thyrotropin (TSH) as a first thyroid test and the subsequent implementation of a thyroid test ordering cascade [4]. Indeed, TSH has become the main test for the evaluation of thyroid function in most circumstances [5]. A TSH value within the reference range excludes overt primary thyroid disease [4]. Only if TSH is out of range, the measurement of free thyroxine (FT4) is needed.

Routine thyroid function testing is not recommended in asymptomatic adults [6,7]. It may just be indicated when non-specific signs and symptoms are present in patients at risk for thyroid disease, such as personal or family history of thyroid disease or autoimmune disease, past history of neck irradiation, intake of certain drugs such as lithium and amiodarone, or in women over age 50 or elderly patients [6]. However, the request of TSH from primary care has progressively and dramatically increased in Spain [8-10].

Results from prior REDCONLAB initiatives show an increase in the ratio of TSH requests per 1000 inhabitants from 140 in 2009 to 187.4 in 2012. In the earlier studies, not enough collaborators were available to compare the regional differences in the request between the Spanish autonomous communities (AACCs).

The aim of this new REDCONLAB project with a higher number of participant laboratories is precisely to study the regional variability in the requests of thyroid laboratory tests from primary care in Spain and to investigate a potential inappropriate request and its economic societal impact.

MATERIALS AND METHODS

Setting

Spain is divided in 17 AACCs. Every Spanish citizen has the Individual Health Care Card, which allows access to public health services as a healthcare user throughout the National Health System. The Health System in every AACC is divided into Health Departments (HDs). Each HD covers a geographic area and its population. It is composed by several primary care centers and usually a unique hospital. The laboratory located at the hospital attends the needs of every HD inhabitant.

Data collection

A call for data was posted via email. The dissemination of the questionnaire was also addressed to the participants of previous studies of the REDCONLAB group that recommended other laboratories to join the current study and a LinkedIn (https://www.linkedin.com/in/redconlab-grupo-a5663bb7) group was created. Spanish laboratories willing to participate in the study were invited to fill out an enrollment form and submit their results online. Production statistics for 2014 were obtained from laboratories from diverse regions across Spain. Numbers of the thyroid tests [TSH, FT4, and free triodothyronine (FT3), anti-thyroid peroxidase antibodies (TPO) and anti-thyroglobulin antibodies (ATG)] requested by all of the general practitioners (GPs) from laboratories at different hospitals from diverse HDs across Spain were used. Every patient seen in any primary care center, regardless of the reason for consultation, gender, or age, was included in the study. Participating laboratories were required to be able to obtain patient data from local Laboratory Information System (LIMS) Patients' databases and to provide organizational data. Each participant reported the request of thyroid laboratory tests during 2014 from primary care. A call for data was sent to every participant asking for the price of a TSH test (reagent).

Data processing

After collecting the data, test-utilization rates were calculated by standardization with the population attended by each laboratory. Rates were expressed as tests per 1000 inhabitants. Also, a ratio of requests of related tests (FT4/TSH, FT3/TSH, ATG/TPO) was calculated and compared between the different AACCs. FT4/TSH was compared with its indicator target (0.25) [11].

Taking into account TSH test prices reported by REDCONLAB participants, the average price and the amount of money spent in this parameter measurement were calculated. The expenses were extrapolated to the entire Spanish population. Laboratories were grouped in the different AACCs, when there were more than 4 participants the additional participants were included in a group joining the results of the other groups. AACCs were codified by numbers to maintain confidentiality.

Statistical analysis

All analyses were performed using SPSS for Windows, Version 16.0 (Chicago, IL, USA; SPSS Inc.). Descriptive statistics were generated for test-utilization rates and for related indicators. The differences in the indicators between AACCs were calculated by way of the ANOVA or Kruskal-Wallis test analyses, as appropriate. A two-sided $p \leq 0.05$ rule was utilized as the criterion for rejecting the null hypothesis of no difference.

Table 1. Number of tests, descriptive analysis of every test rate per 1000 inhabitants, and the ratio of related tests.

	Number of tests	Tests/1000 inhabitants [median (IQR)]
TSH	5923116	221.80 (61.70)
FT4	1644350	51.10 (46.70)
FT3	141988	3.20 (5.45)
TPO	258451	6.70 (7.30)
ATG	152769	3.20 (6.90)
Ratio of related tests [median (IQR)]		
FT4/TSH	0.23 (0.19)	
FT3/TSH	0.02 (0.02)	
ATG/TPO	0.72 (0.90)	

IQR - Interquartile range, TSH - thyrotropin, FT4 - free thyroxine, FT3 - free triiodothyronine, TPO - anti-thyroid peroxidase antibodies, ATG - anti-thyroglobulin antibodies.

Table 2. Tests per 1000 inhabitants and ratio of related tests in every AACC.

Indicator [median (IQR)]	Autonomous communities (CODE; number of centers)										p-value
	1; 20	2; 16	3; 10	4; 10	5; 11	6; 5	7; 5	8; 6	9; 6	10; 5	11; 14	
TSH	233.4 (71.6)	235.2 (57.7)	209.8 (53.2)	216.9 (91.1)	211.2 (51.7)	289.0 (13.1)	251.9 (32.9)	215.2 (127.0)	241.2 (92.0)	187.0 (42.6)	197.8 (41.1)	**0.009**
FT4	56.4 (48.8)	61.7 (71.2)	65.4 (44.0)	44.3 (14.1)	38.5 (27.3)	55.8 (25.1)	81.5 (46.4)	42.6 (27.2)	97.8 (60.2)	33 (20.7)	62.5 (53.6)	0.191
FT3	2.0 (4.2)	5.3 (5.5)	4.3 (8.3)	1.3 (4.7)	0.7 (3.1)	3.8 (3.3)	6.4 (5.0)	5.7 (9.3)	4.4 (6.8)	3.5 (2.2)	2.9 (4.7)	0.073
TPO	6.3 (5.1)	7.7 (7.6)	9.8 (16.1)	13.9 (10.5)	3.7 (2.6)	7.3 (2.9)	13.8 (18.8)	3.9 (4.8)	10.9 (12.9)	10.2 (2.2)	3.6 (2.8)	**0.001**
ATG	1.1 (3.4)	3.3 (5.5)	6.6 (9.2)	11.2 (8.0)	1.2 (2.5)	6.5 (3.8)	2.5 (12.6)	1.2 (4.6)	10.9 (8.8)	0.2 (1.0)	2.9 (4.5)	**0.006**
FT4/TSH	0.21 (0.22)	0.29 (0.32)	0.30 (0.18)	0.20 (0.11)	0.18 (0.07)	0.19 (0.05)	0.30 (0.17)	0.19 (0.03)	0.36 (0.14)	0.24 (0.05)	0.31 (0.33)	0.144
FT3/TSH	0.01 (0.02)	0.03 (0.02)	0.02 (0.04)	0.01 (0.02)	0.00 (0.02)	0.01 (0.01)	0.02 (0.01)	0.03 (0.05)	0.02 (0.02)	0.02 (0.01)	0.02 (0.03)	0.086
ATG/TPO	0.27 (0.89)	0.51 (0.94)	1.00 (0.82)	0.83 (0.22)	0.54 (0.92)	1.00 (0.14)	0.74 (0.67)	0.59 (0.43)	0.94 (0.36)	0.03 (0.08)	0.98 (0.90)	0.230

IQR - Interquartile range, TSH - thyrotropin, FT4 - free thyroxine, FT3 - free triiodothyronine, TPO - anti-thyroid peroxidase antibodies, ATG - anti-thyroglobulin antibodies.

RESULTS

One hundred ten laboratories from 15 different AACCs participated in the study, corresponding to a catchment total of 27,798,262 inhabitants (59.8% of the Spanish population). Table 1 shows the request of each test in absolute numbers and the descriptive analysis of every test rate per 1000 inhabitants and, also, the ratio of request of related tests. As an average, FT4/TSH reached the indicator target (0.25); however, in an individualized evaluation, 47 of the 110 laboratories still did not reach the 0.25 indicator goal.

Ten AACCs had more than four participants. An eleventh group includes the results of the other 5 AACCs; Table 2 shows the demographic data and the ratio results in every group. TSH request per 1000 inhabitants

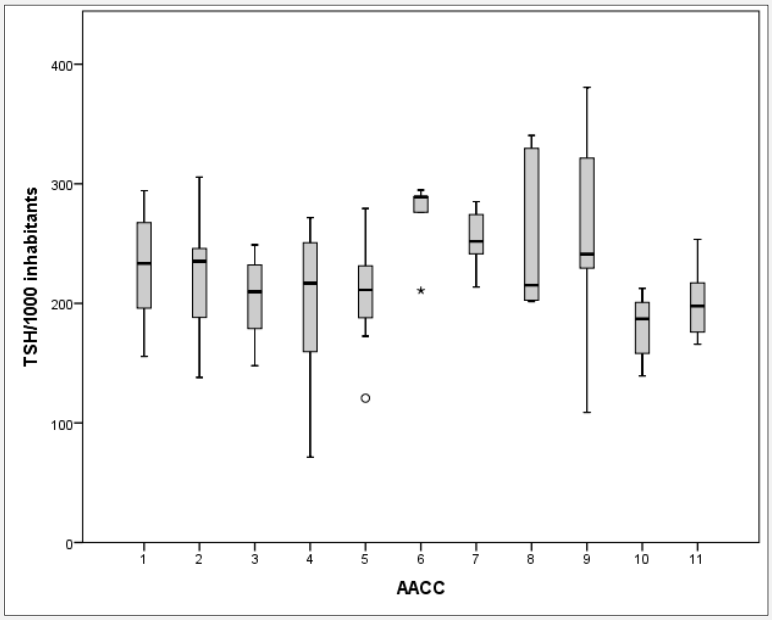

Figure 1. TSH/1000 inhabitants indicator in different autonomous communities.

Legend: Boxplot for thyrotropin (TSH)/1000 inhabitants in different autonomous communities (AACC)
O - Outlier, * - Extreme values.

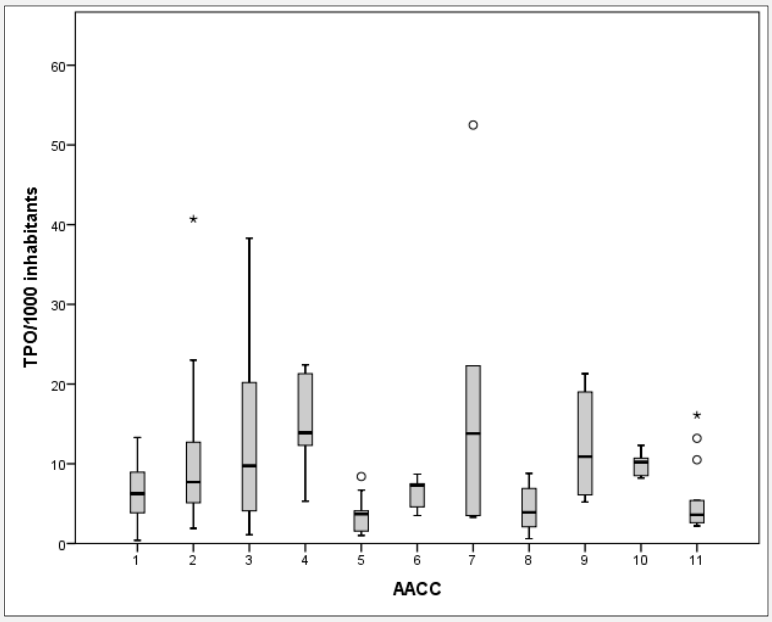

Figure 2. TPO/1000 inhabitants indicator in different autonomous communities.

Legend: Boxplot for anti-thyroid peroxidase antibodies (TPO)/1000 inhabitants in different autonomous communities (AACC)
O - Outlier, * - Extreme values.

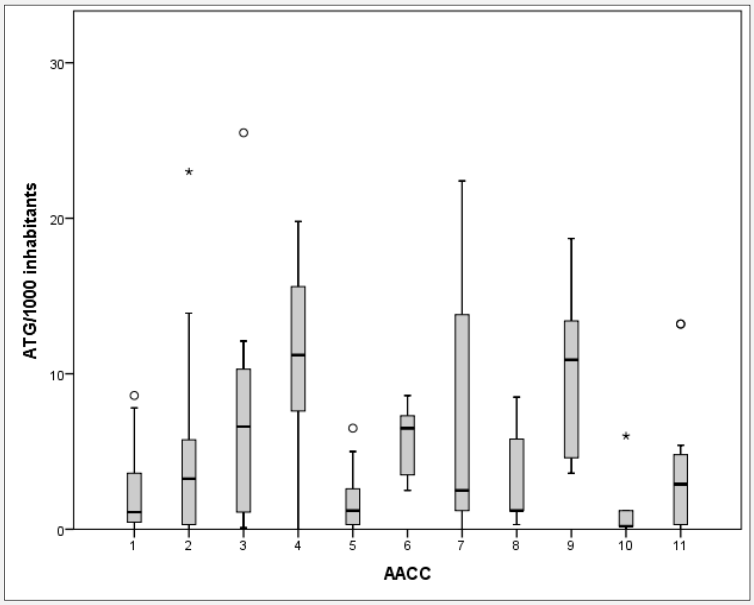

Figure 3. ATG/1000 inhabitants indicator in different autonomous communities.

Legend: Boxplot for anti-thyroglobulin antibodies (ATG)/1000 inhabitants in different autonomous communities (AACC)
O - Outlier, * - Extreme values.

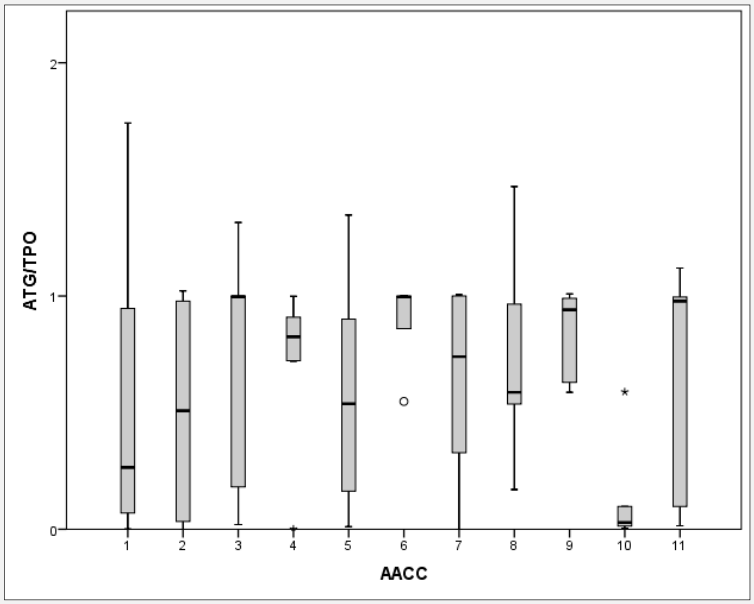

Figure 4. ATG/TPO indicator in different autonomous communities.

Legend: Boxplot for anti-thyroid peroxidase antibodies (TPO)/anti-thyroglobulin antibodies (ATG) in different autonomous communities (AACC)
O - Outlier, * - Extreme values.

ranged from 198 to 289. FT4 was ordered more than twice as frequently in some regions than others. FT3 was not requested at all in AACC 5; however, in AACC 7, it was 6 per 1000 inhabitants. TPO request per 1000 inhabitants ranged from 3.6 to 13.9 requests per 1000 inhabitants. Regarding FT4/TSH, 6 AACCs reached the 0.25 indicator target. Still in 4 AACCs, ATG and TPO requests were redundant or almost redundant as shown by an ATG/TPO indicator result above 0.9.

The significant difference in TSH, TPO, and ATG requests is also shown graphically in Figures 1, 2, and 3. The TSH demand was significantly different ($p < 0.05$) between AACCs 10 and 11 and AACCs 1, 2, 6, 7 and 8; between AACC 6 and AACCs 3, 4 and 5; and between AACC 7 and AACCs 3 and 5. Figure 4 shows that TPO and ATG were requested redundantly in 4 AACC (3, 6, 9, and 11) and that in AACC 10 the ATG request was ten times lower.

Forty-eight laboratories reported the reagent price of a test in its HD. The average price was 1.797€. In our patient cohort, 5,923,116 TSH tests were performed and 10,039,180 when extrapolated to the whole Spanish population. Taking into account this price, 10,643,840€ were spent during year 2014 in measuring TSH when ordered from primary care in 60% of the Spanish population; that corresponds to 17,672,610€ if extrapolated to the entire Spanish population (46,155,123 inhabitants).

DISCUSSION

This large population study shows that the request of thyroid laboratory tests from primary care was very heterogeneous and high overall.

Almost 6 million TSH tests were performed in the study during 2014, only from primary care. Close to 11 million euros were spent, only in reagent cost. The request of TSH is rapidly increasing and so will be the economic costs.

The request for thyroid tests showed a significant regional variability. In some regions, FT4 was ordered more than twice as frequently as others. The request of TPO was more than 4-fold higher in certain AACCs than others. Only 6 Spanish regions reached the FT4/TSH 0.25 indicator target. ATG and TPO requests were redundant in 4 AACCs.

In a cross-sectional study to identify the prevalence of thyroid testing and associations with a positive test result [12], 12% of the population had TSH testing for diagnostic purposes in a single year. The authors also showed that the diagnostic yield of thyroid disease was only 2.1%. They concluded that thyroid testing could be better targeted without missing diagnoses, and that there was significant room for improving the demand of TSH. In that investigation, the ratio of TSH/1000 inhabitants was 120, much lower than ours, which was 222. In some Spanish regions, the ratio was more than triple. If we could achieve a national TSH/1000 inhabitants ratio of 120 (still in the over-request), the public health system would save more than 8.5 million euros only in reagent costs.

This evidence should be a starting point to aggressively design and establish corrective measures through restrictive policies, as there are no recommendations to screen adults with TSH [13], just targeted screening as mentioned in the introduction.

The study had certain limitations. First, the possible existence of severe differences in iodine availability and content between the different regions and the different rate of management of patients with thyroid diseases in primary care among the different AACCs could theoretically contribute to the observed regional variability. Second, the calculated economic savings may not apply to other countries or settings, since our laboratories belong to the Public Health Network; in any case, they would be much higher and other expenses were not taken into account. And, finally, there are additional limitations as no information of the age and gender distribution and education of the population, age and experience of the requesting physicians, economic situation of the different regions or whether TSH, FT4, FT3 and antibodies were requested stepwise following a decision tree, that could promote more frequent or asking for more testing, more criticism in ordering thyroid tests or more wealthy population that may request more laboratory testing.

CONCLUSION

There is regional variability in the request of thyroid tests and a significant over-request of thyroid laboratory tests in primary care in Spain, resulting in a high economic impact to society. In all, it is imperative to design and establish strategies on a national scale for a better request of thyroid laboratory tests.

Acknowledgement:

Members of the REDCONLAB working group are the following: Vidal Pérez Valero (Hospital Regional Universitario de Málaga, Hospital Universitario Virgen de la Victoria, Málaga); Félix Gascón (Hospital Valle de los Pedroches, Pozoblanco); Isidoro Herrera Contreras (Complejo Hospitalario de Jaén); Maria Ángeles Bailen Garcia (Hospital Universitario Puerta del Mar de Cádiz); Cristóbal Avivar Oyonarte (Hospital de Poniente, El Ejido); Esther Roldán Fontana (Hospital La Merced, AGS Osuna); Fernando Rodríguez Cantalejo (Hospital Universitario Reina Sofía de Córdoba); José Ángel Noval Padillo (Hospital Universitario Virgen del Rocío); M Ángela González García (AGS Norte de Cádiz); Ignacio Vázquez Rico (Hospital Juan Ramón Jiménez de Huelva); Cristina Santos (Hospital Rio Tinto); Ángeles Giménez-Marín (Hospital de Antequera); Maria del Señor López Vélez (Hospital San Cecilio de Granada), José Vicente García Larios (Hospital Virgen de las Nieves, Granada); Federico Navajas Luque (AGS Este de Málaga-Axarquía); Amado Tapia (Hospital de Barbastro); Maria Esther Solé LLop (Hospital de Alcañiz); Juan José Puente (Hospital Clínico Universitario Lozano Blesa); Patricia Esteve (Hospital Ernest Lluch); Maria Teresa Avello López (Hospital San Agustín-Avilés, Hospital Valle del Nalon); Emilia Moreno Noguero (Hospital Can MIsses); Ana Maria Follana Vázquez (Hospital Mateu Orfila); Jose Luis Ribes Valles (Hospital de Manacor); Mª Luisa Fernández de Lis Alonso (Área de Salud de Fuerteventura); MC Martin-Fer-

nández de Basoa (Hospital Nuestra Señora de la Candelaria, Tenerife); Leopoldo Martin Martin (Hospital General de la Palma); Miguel Angel Pico Picos (Hospital Universitario de Canarias); Casimira Domínguez Cabrera (Hospital Universitario de Gran Canaria Dr Negrín); Marta Riaño Ruiz (Hospital Insular de Gran Canaria); Juan Ignacio Molinos (Hospital Sierrallana de Torrelavega); Luis Fernando Colomo (Hospital de Laredo); José Carlos Garrido (Hospital Universitario Marqués de Valdecilla); Enrique Prada de Medio (Hospital Virgen de la Luz de Cuenca); Pilar García Chico (Hospital General Universitario de Ciudad Real); Simón Gomez-Biedma (Hospital General de Almansa); Jesús Domínguez (Hospital Universitario de Guadalajara); Guadalupe Ruiz (Complejo Hospitalario de Toledo); Laura Navarro Casado (Complejo Hospitalario Universitario de Albacete); Fidel Velasco Pena (Hospital Virgen de Altagracia, Manzanares); Carolina Andrés Fernández (Hospital General de Villarobledo); Joaquín Domínguez Martínez y Oscar Herrera Carrera (Hospital General Mancha Centro y Hospital General de Tomelloso); Mª Carmen Lorenzo Lozano (Hospital de Santa Bárbara de Puertollano); Maria Teresa Gil (Hospital Nuestra Señora del Prado Talavera de la Reina); Mª Ángeles Rodríguez Rodríguez (Complejo Asistencial Universitario de Palencia (Hospital Rio Carrión); M. Victoria Poncela García (Hospital Universitario de Burgos); Luis Rabadan (Complejo Asistencial de Soria); Vicente Villamandos (Hospital Santos Reyes, Aranda del Duero); Nuria Fernández García (Hospital Universitario Rio Hortega-Valladolid); José Miguel González Redondo (Hospital Santiago Apóstol de Miranda de Ebro); Cesáreo García (Hospital Universitario de Salamanca); Luis Garcia Menendez (Hospital El Bierzo); Pilar Álvarez Sastre (Complejo Asistencial de Zamora); Ovidio Gómez (Hospital Clínico Universitario de Valladolid); Mabel LLovet (Hospital Universitario Verge de la Cinta (Tortosa); Nuria Serrat (Hospital Joan XXIII de Tarragona); Mª José Baz (Hospital de Llerena, Badajoz); Maria José Zaro (Hospital Don Benito-Villanueva); M Carmen Plata (Hospital Campo Arañuelo, Navalmoral de la Mata); Pura García Yun (Área de Salud de Badajoz (Hospital Infanta Cristina, Hospital Perpetuo Socorro y Hospital Materno Infantil); Milagrosa Macías Sánchez (Area de Salud de Cáceres (Complejo Hospitalario San Pedro de Alcántara); Javier Martin (Hospital Virgen del Puerto de Plasencia); Lola Máiz Suarez (Hospital Lucus Agustí, Lugo); Berta González Ponce (Hospital Da Costa, Burela); Aida Pérez Fuertes (Hospital Arquitecto Marcide, El Ferrol); M. Amalia Andrade Olivie (Hospital Xeral-Cies, CHU Vigo); Pastora Rodríguez (Hospital Universitario de A Coruña); M. Mercedes Herranz Puebla (Hospital General Universitario Gregorio Marañón); Antonio Buño Soto (Hospital Universitario La Paz, Madrid); Fernando Cava; Raquel Guillén Santos (BR Salud); Tomas Pascual (Hospital Universitario de Getafe); Carmen Hernando de Larramendi (Hospital Severo Ochoa de Leganés); Raquel Blázquez Sánchez (Hospital de Móstoles); Pilar Díaz (Hospital 12 de Octubre, Madrid); Ana Díaz (Hospital Universitario de La Princesa); Marta García Collía (Hospital Ramón y Cajal, Madrid); Maria Ángeles Cuadrado Cenzual (Hospital Clínico Universitario San Carlos); Santiago Prieto Menchero (Hospital Universitario de Fuenlabrada); María del Carmen Gallego Ramírez (Hospital Rafael Méndez, Lorca); José Luis Quilez Fernández (Hospital Universitario Reina Sofía de Murcia); Maria Dolores Albaladejo (Hospital Santa Lucia, Cartagena); Maria Luisa López Yepes (Hospital Virgen del Castillo de Yecla); Alfonso Pérez Martínez (Hospital Morales Meseguer); Antonio López Urrutia (Hospital de Cruces, Bilbao); Adolfo Garrido Chércoles (Hospital Universitario de Donostia); Carmen Mar Medina (Hospital Galdakao-Usonsolo); M Carmen Zugaza (Unidad de Gestión Clínica de Álava); Francisco Javier Aguayo Gredilla (Hospital Universitario de Basurto); Silvia Pesudo (Hospital La Plana); Carmen Vinuesa (Hospital de Vinaros); Julián Díaz (Hospital Francesc de Borja, Gandía); Marisa Graells (Hospital General Universitario de Alicante); Diego Benitez Benitez (Hospital de Orihuela); Arturo Carratala (Hospital Clinico Universitario de Valencia); Consuelo Tormo (Hospital General de Elche); Francisco Miralles (Hospital Lluis Alcanyis, Xativa); Amparo Miralles (Hospital de Sagunto); José Luis Barberà (Hospital de Manises); Juan Molina (Hospital Comarcal de La Marina, Villajoyosa); Martin Yago (Hospital de Requena); Mario Ortuño (Hospital Universitario de la Ribera (Alzira); Maria José Martínez Llopis (Hospital de Denia); Nuria Estañ (Hospital Dr. Peset); Ricardo Molina (Hospital Virgen de los Lirios, Alcoy); Juan Antonio Ferrero (Hospital General de Castellón); Begoña Laiz Marro (Hospital Universitario y Politécnico La Fe de Valencia); Goitzane Marcaida (Consorcio Hospital General Universitario de Valencia).

Declaration of Interest:
None declared.

Funding:
None declared.

References:

1. Sheehan MT. Biochemical Testing of the Thyroid: TSH Really is the Best and, Oftentimes, Only Test Needed - A Review for Primary Care. Clin Med Res 2016;14:83-92 (PMID: 27231117).

2. Hardwick R, Heaton J, Griffiths G, et al. Exploring reasons for variation in ordering thyroid function tests in primary care: a qualitative study. Qual Prim Care 2014;22:256-61 (PMID: 25887650).

3. Boucai L, Hollowell JG, Surks MI. An approach for development of age-, gender-, and ethnicity-specific thyrotropin reference limits. Thyroid 2011;21:5-11 (PMID: 21058882).

4. Ladenson PW, Singer PA, Ain KB, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. Arch Intern Med 2000;160:1573-5 (PMID: 10847249).

5. Dufour D. Laboratory Tests of Thyroid Function: Uses and limitations. Endocrinol Metab Clin North Am 2007;36:579-94 (PMID: 17673120).

6. Baloch Z, Carayon P, Conte-Devolx B, et al; Guidelines Committee, National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 2003;13:3-126 (PMID: 12625976).

7. Association of Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation. UK Guidelines for the Use of Thyroid Function Tests. 2006. http://www.btf-thyroid.org/images/documents/tft_guideline_final_version_july_2006.pdf

8. Salinas M, López-Garrigós M, Pomares FJ, et al; on behalf of REDCONLAB. [Request of thyroid function tests from Primary Care in Spain]. Endocrinol Nutr 2016;63:19-26 (PMID: 26548629).

9. Salinas M, López-Garrigós M, Díaz J, et al. Regional variations in test requiring patterns of general practitioners in Spain. Ups J Med Sci 2011;116:247-51 (PMID: 22066972).

10. Salinas M, López-Garrigós M, Tormo C, Uris J. Primary care use of laboratory tests in Spain: measurement through appropriateness indicators. Clin Lab 2014;60:483-90 (PMID: 24697126).

11. Larsson A, Palmer M, Hultén G, Tryding N. Large differences in laboratory utilisation between hospitals in Sweden. Clin Chem Lab Med 2000;38:383-9 (PMID: 10952220).

12. Werhun A, Hamilton W. Thyroid function testing in primary care: oversed and under-evidenced? A study examining which clinical features correspond to an abnormal thyroid function result. Fam Pract 2015;32:187-91 (PMID: 25782692).

13. Summaries for Patients. Screening for Thyroid Dysfunction: U.S. Preventive Services Task Force Recommendation. Ann Intern Med 2015;162:1-32 (PMID: 26146668).