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Measurement Uncertainty in Specific Hormone Tests

Spesifik Hormon Testlerinde Ölçüm Belirsizliği

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ABSTRACT

Aim: Quality improvement studies in clinical laboratories play a vital role in achieving accurate and reliable patient results. Measurement uncertainty is important for the quality and reliability of test results. Since laboratory results inherently involve uncertainty, ISO 15189 Accreditation Standards recommend reporting patient results accompanied by measurement uncertainty. The aim of our study is to determine the measurement uncertainty and compare it with the total allowable error (TEa%) values determined by international organizations in order to increase the accuracy and reliability of the specific hormone tests studied in our laboratory.

Material and Methods: Our study was conducted at the Medical Biochemistry Laboratory of Health Sciences University İzmir Tepecik Training and Research Hospital. To determine the measurement uncertainties of adrenocorticotropic hormone (ACTH), growth hormone, insulin-like growth factor-1 (IGF-1), C-peptide, thyroglobulin, 25-hydroxy vitamin D, and parathormone (PTH) parameters, the 3-month period from October to December 2022 internal quality control data and 12-month external quality control data from January to December 2022 were used. The measurement uncertainty of the tests was calculated according to the Nordtest guideline. These values were evaluated based on TEa% criteria established by three different international organizations.

Results: The measurement uncertainties of ACTH, growth hormone, IGF-1, C-peptide, thyroglobulin, 25-hydroxy vitamin D, and PTH tests were 11.53, 14.83, 12.35, 7.91, 18.18, 20.95, 15.69 for level 1 at 95% confidence interval; for level 2, it was calculated as 10.99, 13.65, 13.15, 5.87, 17.24, 17.05, 16.56 respectively. The measurement uncertainties of the C-peptide, thyroglobulin, and PTH tests for level 3 were 6.98, 16.03, and 15.51, respectively.

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Conclusion: While the expanded measurement uncertainties of growth hormone and C-peptide were determined below the TEa% values determined by international organizations, the measurement uncertainties of the ACTH and IGF-1 tests were found to be borderline high compared to the Royal College of Pathologists of Australasia (RCPA) TEa% values at both levels. While the measurement uncertainties of thyroglobulin, 25-hydroxy vitamin D, and PTH parameters were higher than the RCPA TEa% values at both levels, they were found below the TEa% values determined by other international organizations.

Key Words: Measurement uncertainty, Hormone, Quality, Total allowable error

ÖZET

Amaç: Klinik laboratuvarlarda yapılan kalite iyileştirme çalışmaları, doğru ve güvenilir hasta sonuçlarına ulaşılmasında hayati bir rol oynamaktadır. Ölçüm belirsizliği test sonuçlarının kalitesi ve güvenilirliği için önem arz etmektedir. Laboratuvar sonuçları doğal olarak belirsizlik içerdiğinden, ISO 15189 Akreditasyon Standartları, hasta sonuçlarının ölçüm belirsizliği ile birlikte rapor edilmesini önermektedir. Çalışmamızın amacı, laboratuvarımızda çalışılan spesifik hormon testlerinin doğruluk ve güvenirliğini arttırmak için ölçüm belirsizliğini belirleyip uluslararası kuruluşlar tarafından belirlenen toplam izin verilen hata (%TEa) değerleriyle karşılaştırmaktır.

Materyal ve Metod: Çalışmamız Sağlık Bilimleri Üniversitesi İzmir Tepecik Eğitim ve Araştırma Hastanesi Tıbbi Biyokimya Laboratuvarında gerçekleştirildi. Adrenokortikotropik hormon (ACTH), büyüme hormonu, insülin benzeri büyüme faktörü-1 (IGF-1), C-peptit, tiroglobulin, 25-hidroksi vitamin D ve parathormon (PTH) parametrelerinin ölçüm belirsizliklerini belirlemek için, Ekim - Aralık 2022 arasındaki 3 aylık iç kalite kontrol verileri ve Ocak - Aralık 2022 arasındaki 12 aylık dış kalite kontrol verileri kullanıldı. Testlerin ölçüm belirsizliği Nordtest kılavuzuna göre hesaplandı. Bu değerler, üç farklı uluslararası kuruluş tarafından belirlenen %TEa kriterlerine göre değerlendirilmiştir.

Bulgular: ACTH, büyüme hormonu, IGF-1, C-peptid, tiroglobulin, 25-hidroksi D vitamini ve PTH testlerinin ölçüm belirsizlikleri %95 güven aralığında seviye 1 için sırasıyla 11,53, 14,83, 12,35, 7,91, 18,18, 20,95, 15,69; seviye 2 için sırasıyla 10,99, 13,65, 13,15, 5,87, 17,24, 17,05, 16,56 olarak hesaplanmıştır. Seviye 3 için C-peptid, tiroglobulin ve PTH testlerinin ölçüm belirsizlikleri sırasıyla 6,98, 16,03 ve 15,51 idi.

Sonuç: Büyüme hormonu ve C-peptidin genişletilmiş ölçüm belirsizlikleri uluslararası kuruluşlar tarafından belirlenen %TEa değerlerinin altında tespit edilirken, ACTH ve IGF-1 testlerinin ölçüm belirsizlikleri her iki seviyede de Avustralya Kraliyet Patologlar Kurulu (RCPA) %TEa değerlerine kıyasla sınırda yüksek bulundu. Tiroglobulin, 25-hidroksi vitamin D ve PTH parametrelerinin ölçüm belirsizlikleri her iki seviyede de RCPA %TEa değerlerinden yüksek olmakla birlikte, diğer uluslararası kuruluşlar tarafından belirlenen %TEa değerlerinin altında saptandı.

Anahtar Kelimeler: Ölçüm belirsizliği, Hormon, Kalite, Toplam izin verilen hata

INTRODUCTION

Clinical laboratories play a crucial role in various clinical decisions, including facilitating early and accurate diagnoses, guiding appropriate treatment selection, preventing treatment delays, and reducing the necessity for long-term care (1,2). Surveys conducted among clinicians in Germany and the USA have revealed that laboratory test results impact approximately 60-70% of clinical decisions (3). Clinical laboratories are focused on improving and maintaining quality using existing quality assurance tools. Reporting laboratory test results in a way that facilitates clinical actions increases the clinical value of the test. It is a requirement for clinical laboratories to provide consulting services that understand and act with clinicians in both the selection and interpretation of tests. Therefore, it is extremely important for laboratory specialists to share information that will benefit the clinic through face-to-face meetings, phone calls, and reports with clinicians to increase the clinical value of the tests (4). Laboratory tests contain many potential "uncertainties" that can significantly affect results (eg, incorrect collection or transport of the sample, biological variation, drug use,

recording, and reporting errors, etc.) (5). The uncertainty values of the tests are very important in the interpretation of test results, diagnosis of diseases, and treatment follow-up. In addition, the ISO 15189 Accreditation Standard recommends calculating the measurement uncertainty of tests and reporting them together with the patient test results (6).

Two main approaches are used in the calculation of measurement uncertainty: bottom-up and top-down. In the bottom-up approach, all factors and impact ratios are individually included in the calculation of uncertainty. On the other hand, in the top-down approach, existing analytical performance data obtained from quality control materials are used (7,8). For the calculation of measurement uncertainty; The International Vocabulary of Metrology (VIM2), Guide to Expression of Uncertainty in Measurement (GUM1), International Organization for Standardization / International Electrotechnical Commission (ISO/IEC), and VIM3 guides present metrological techniques. However, there is no consensus yet on how the calculation will be made (9). While the ISO 15189 Accreditation Standards recommend calculating the measurement uncertainty, they do not impose any restrictions on the guideline (6). The Nordtest guide, which makes measurement uncertainty calculations with the top-down method, aims to provide an understandable and practical application (10). Our study aims to determine the measurement uncertainty of the specific hormone parameters studied in our laboratory according to the Nordtest guideline and to compare the calculated values with the total allowable error (TEa%) values determined by international organizations.

MATERIALS AND METHODS

Our study was carried out in Health Sciences University İzmir Tepecik Training and Research Hospital Medical Biochemistry Laboratory. Adrenocorticotropic hormone (ACTH), growth hormone, insulin-like growth factor-1 (IGF-1), C-peptide, and thyroglobulin parameters were analyzed on the Immulite 2000XPI (Siemens, USA) device. 25-hydroxy vitamin D and parathormone (PTH) parameters were analyzed on the Advia Centaur XP (Siemens, ABD) device.

3-month internal quality control (IQC) data from October-December 2022 and 12-month external quality control (EQC) data from January-December 2022 were used to calculate measurement uncertainty. EQC data were obtained from Randox International Quality Assessment Scheme (RIQAS) (Randox Laboratories Ltd., Crumlin, UK) for the IGF-1 test and External Quality Assurance Services (EQAS) (Bio-Rad Laboratories Inc., Irvine, CA, USA) programs for other parameters. The measurement uncertainty of the tests was determined by following the guidelines outlined in the Nordtest guide (10), which includes a six-step calculation process (Figure 1).

The measurement uncertainties of the parameters were assessed based on the TEa% values established by international organizations; namely The Royal College of Physicians of Australasia Quality Assurance Program (RCPA), Desirable specifications for allowable total error based on biological variability (BV), and the New York State Department of Health Clinical Laboratory Evaluation Program (NYS) (11-13). Approval was obtained from the ethics committee of our institution within the Declaration of Helsinki, with the decision 2022/01-05, and dated January 17, 2022.

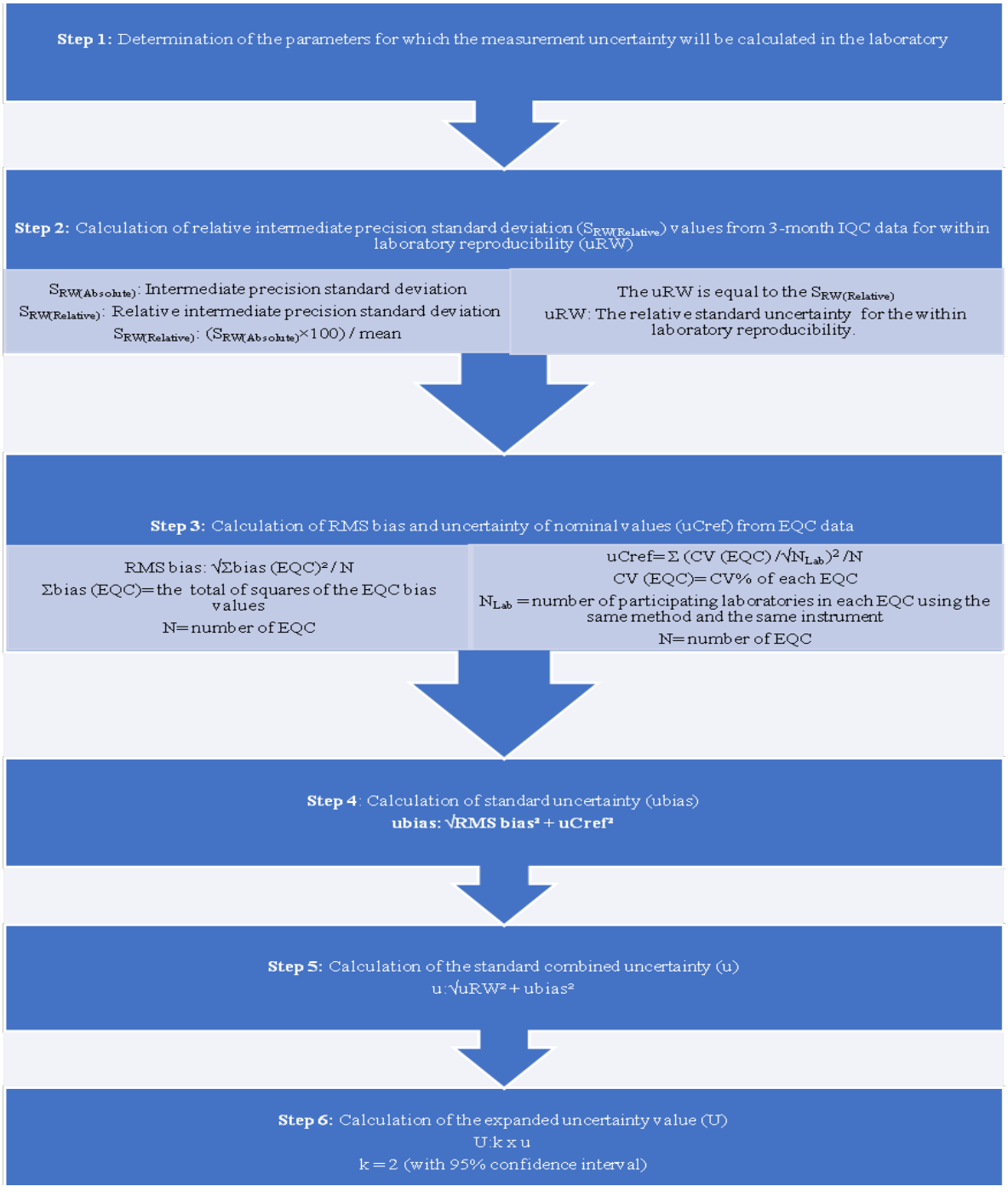

Figure 1. The measurement uncertainty calculation algorithm

RESULTS

The uRW, RMS bias, and uCref values of the parameters are shown in Table 1. The measurement uncertainties of ACTH, growth hormone, IGF-1, C-peptide, thyroglobulin, 25-hydroxy vitamin D, and PTH tests were 11.53, 14.83, 12.35, 7.91, 18.18, 20.95, 15.69 for level 1 at 95% confidence interval; for level 2, it was calculated as 10.99, 13.65, 13.15, 5.87, 17.24, 17.05, 16.56 respectively. The measurement uncertainties of the C-peptide, thyroglobulin, and PTH tests for level 3 were 6.98, 16.03, and 15.51, respectively. While the expanded

measurement uncertainties of growth hormone and C-peptide were determined below the %TEa values determined by international organizations at both levels, the measurement uncertainty of the ACTH test was found to be borderline high compared to the RCPA TEa% value at both levels. The measurement uncertainty of the IGF-1 test was borderline high compared to the RCPA TEa% value but below the BV TEa% value. While the measurement uncertainties of thyroglobulin, 25-hydroxy vitamin D, and PTH parameters were higher than the RCPA TEa% values at both levels, they were found below the TEa% values determined by other international organizations (Table 2).

Table 1. The uRW, RMS bias, and uCref values of parameters.

Test		Level 1			Level 2			Level 3			RMS bias	uCref
	N	Mean	SD	uRW	Mean	SD	uRW	Mean	SD	uRW		
ACTH (ng/mL)	66	21	1.6	3.84	289	17.3	3.42	-	-	-	4.02	1.54
Growth Hormone (ng/mL)	72	3.06	1.13	6.19	8.2	2.28	5.47	-	-	-	4.01	0.78
IGF-1 (ng/mL)	68	70.4	7.05	3.42	198	20	4.10	-	-	-	4.40	0.81
C-peptide (ng/mL)	44	0.76	0.09	3.86	2.8	0.24	2.80	6.1	0.52	3.38	2.56	0.77
Thyroglobulin (ng/mL)	46	1.75	0.22	6.45	9.6	0.72	5.77	56	4.3	4.83	6.21	1.52
25-hydroxy vitamin D (ng/mL)	70	19.7	9.2	8.67	95.2	20.8	6.17	-	-	-	5.81	0.95
PTH (ng/mL)	69	33.9	4.75	4.89	196	22	5.56	718	83.5	4.74	6.03	1.13

N: numbers of internal quality control data, SD: standard deviation, uRW:standard uncertainty component for the within-laboratory reproducibility, RMS: Root Mean Square, uCref: Uncertainty of nominal values.

Table 2. Standard, combined, expanded uncertainty and Tea % values of parameters

		Standard Uncertainty	Combined Uncertainty	Expanded Uncertainty	TEa%
ACTH	**Level 1**	4.30	5.76	11.53	10[a]
	Level 2		5.49	10.99	
Growth Hormone	**Level 1**	4.08	7.41	14.83	15[a]
	Level 2		6.82	13.65	
IGF-1	**Level 1**	5.14	6.17	12.35	12[a] / 24[b]
	Level 2		6.57	13.15	
C-peptide	**Level 1**	0.87	3.95	7.91	12[a] / 20.8[b]
	Level 2		2.93	5.87	
	Level 3		3.49	6.98	
Thyroglobulin	**Level 1**	6.40	9.09	18.18	12[a] /21.9[b]
	Level 2		8.62	17.24	
	Level 3		8.01	16.03	
25-hydroxy vitamin D	**Level 1**	5.88	10.47	20.95	15[a] /25[c]
	Level 2		8.52	17.05	
PTH	**Level 1**	6.13	7.84	15.69	12[a] / 30.2[b] /30[c]
	Level 2		8.28	16.56	
	Level 3		7.75	15.51	

a: The Royal College of Physicians of Australasia Quality Assurance Program (RCPA) TEa% value
b: Desirable specifications for allowable total error, based on biological variability (BV) TEa% value
c: New York State Department of Health Clinical Laboratory Evaluation Program (NYS) TEa% value

DISCUSSION

The measurement uncertainty is a statistical parameter that is reported together with the measurement result and characterizes the distribution of values reasonably attributable to the measurable quantity (14). Medical laboratory results are extremely important in diagnosing diseases and monitoring treatment efficacy. It is essential to be aware of the possible uncertainties of laboratory parameters and to strive to minimize them (15). Although the expression "uncertainty" in its general meaning seems to be related to the concept of doubt; on the contrary, knowing the uncertainty means increased confidence in the validity of a measurement result (14). In our study, the expanded measurement uncertainties of growth hormone and C-peptide were determined below the %TEa values determined by international organizations. The measurement uncertainties of the ACTH and IGF-1 tests were found to be borderline high compared to the RCPA TEa% values at both levels. While the measurement uncertainties of thyroglobulin, 25-hydroxy vitamin D, and PTH parameters were higher than the RCPA TEa values at both levels, they were found below the %TEa values determined by other international organizations.

In the study of Van Eenoo et al. in which the measurement uncertainty of a quantitative method approved for the determination of human growth hormone abuse in doping control was investigated, the expanded uncertainty of growth hormone was reported as 26.08% and 23.12% for kit 1 and kit 2, respectively (16). In the study of Kos et al., the measurement uncertainty of the IGF-1 test was reported as 22% in 2017 and 16% in 2018 (17). In both studies, the measurement uncertainties of the growth hormone and IGF-1 test were found to be considerably higher than in our study. A heterogeneous analyte, GH consists of various forms and their detection differs between analyzers. When GH or IGF-I parameters are measured on different analyzers, they can give very different results because results differ depending on the epitope specificity of the antibodies used (18,19).

The National Metrology Institute of Japan has reported a measurement uncertainty of 6.20% for the certified reference material (SRM) developed for C-peptide (20). Furthermore, the candidate standard 13/146 for C-peptide was recommended as the 1st international standard by the WHO Biological Standardization Expert Committee in October 2015, with a measurement uncertainty of 4.98% (21).

In a study conducted by Cavalier et al., the measurement uncertainty was investigated for four different commercially available 25-hydroxy vitamin D analysis techniques (Diasorin RIA, Diasorin liaison, Roche Elecsys, and HPLC). To assess the measurement uncertainty, three serum pools with varying 25-hydroxy vitamin D levels were created. The mean relative uncertainties observed for 35.3 nmol/L, 79.5 nmol/L, and 126.1 nmol/L across all techniques were found to be 19.4%, 16.0%, and 11.3%, respectively. It was reported that these techniques exhibited relatively high measurement uncertainty for the measurement of 25-hydroxyvitamin D (22). Basat et al. conducted a study in which they determined the measurement uncertainty of the 25-hydroxy vitamin D test using liquid chromatography-tandem mass spectrometry (LC-MS/MS) to be 34.64% (23). In a study conducted by Lim et al., the measurement uncertainties of the 25-hydroxy vitamin D parameter were compared across three different immunoassay systems. The expanded uncertainty of the 25-hydroxy vitamin D test on the Architect system was 4.2%, which was lower than the Roche (8.2%) and Siemens (15.6%) immunoassay systems (24). While the values obtained in some of the studies investigating the 25-hydroxy vitamin D measurement uncertainty were higher than the TEa% values, they were lower in some. In our study, the measurement uncertainty of 25-hydroxy vitamin D was below the TEa%

value determined by NYS and above the TEa% determined by RCPA. The reasons for obtaining such different results about the same parameter in the studies may be that the devices and methods are different, the use of formulas belonging to different guides in the calculation of measurement uncertainty, or the use of TEa% values of different institutions.

In a study aimed at determining the measurement uncertainty of the PTH test and interpreting PTH levels in hemodialysis patients, the PTH levels of 149 hemodialysis patients and 240 individuals with 25-hydroxyvitamin D levels >75 nmol/L and estimated glomerular filtration rate >60 mL/min/1.73m^2 were analyzed using DiaSorin IRMA and Abbott Architect instruments. Only 8% of patients were classified differently, according to the measurement uncertainty calculated with DiaSorin IRMA and Abbott Architect to determine the grey area around the threshold, using the 5% analytical CVs specified by the respective manufacturers for PTH level >50 pg/mL (25). In the study conducted by Farré-Segura et al., the development and validation of the LC-MS/MS method for PTH analysis were undertaken due to cross-reactivity and standardization issues observed in PTH immune tests available on the market. The method was validated across a range of 5.7-872.6 pg/mL, and the measurement uncertainty of the PTH test using LC-MS/MS was determined to be <5.6% (26). In our study, the measurement uncertainty of the PTH test was higher than the RCPA TEa% values at both levels, it was lower than the BV and NYS TEa% values.

In some of the studies, the measurement uncertainty of the test kits was investigated, but in some studies, the measurement uncertainty of the test standard was reported by international organizations. We could not compare our study results because we could not find any publications in the literature on the measurement uncertainty of ACTH, C-peptide, and thyroglobulin test kits. Since it is the first study in which the measurement uncertainty of these parameters is investigated, we think that our study can make an important contribution to the literature.

The lack of publication in the literature on the measurement uncertainty of these parameters may be due to difficulties in the preanalytical and/or analytical stages. For example; since ACTH can undergo proteolytic degradation by enzymes in blood cells at room temperature, strict procedures are followed after sample collection. In the preanalytical phase, blood should be collected in a pre-chilled tube, transferred to the laboratory via a cold chain, and its plasma separated in a refrigerated centrifuge (27,28). In Tg measurement, standardization cannot be achieved due to the heterogeneity of the analyte and the use of various monoclonal antibodies with different TG epitopes in immunoassays (29).

The limitation of our study is that the analysis of C-peptide and thyroglobulin tests is not performed every day of the week in our laboratory, so more than sixty IQC results recommended in the Nordtest guideline cannot be obtained.

CONCLUSION

The uncertainty of measurement is a numerical indicator that can also include possible inconsistencies that may belong to the relevant test. Therefore, explaining the measurement uncertainty to clinicians in detail and giving it together with patient results can both enable physicians to make more accurate decisions in diagnosis and treatment and increase confidence in laboratory results. If the calculated uncertainty of measurement is less than the target limit value for the test, we conclude that the measurement is suitable for the intended use and the uncertainty should be stated in the report, but if the uncertainty is high, the analytical performance characteristics should be reviewed and possible sources of error should be investigated. The target values suggested by various organizations for the same

parameter are quite different from each other, and one of the most important reasons for this difference is the methods used in target setting. It is necessary to strike a good balance between the applicability of the objectives and the analytical reliability. While strict targets can cause difficulties in terms of applicability, broad targets can cause problems with analytical reliability. In our study, the institution with the strictest target is RCPA, and we think that it is very difficult to meet these targets considering the preanalytical and analytical problems in specific hormone tests. We think that determining the quality targets according to their applicability based on parameters on the scale of strict and broad targets can be more effective in laboratory applications.

Ethical Approval Approval was obtained from the ethics committee of our institution with the decision numbered 2022/01-05 and dated January 17, 2022.

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Conflict of interest

None

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