

甲状腺ホルモン検査の 国際標準化

日本臨床検査医学会
標準化委員会

IFCC (International Federation of Clinical
Chemistry and Laboratory Medicine)
Committee for Standardization of Thyroid
Function Tests (C-STFT)

The International Federation of Clinical Chemistry and Laboratory Medicine



The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) is a worldwide, non-political organization for clinical chemistry and laboratory medicine. As such it has a range of roles that include (1) global standard setting in collaboration with other international organizations, (2) supporting its members through scientific and educational endeavour, and (3) providing a series of congresses, conferences and focussed meetings in order for laboratory medicine specialists to meet and present original findings and best practice.

Scientific Division

SD Committees



SD Working Groups



SD Minutes

Reference Materials

SD Committees

- Nomenclature, Properties and Units (C-NPU) in collaboration with IUPAC
- Molecular Diagnostics (C-MD)
- Traceability in Laboratory Medicine (C-TLM)
- Reference Intervals and Decision Limits (C-RIDL)
- Standardization of Thyroid Function Tests (C-STFT)
- Harmonization of Autoimmune Tests (C-HAT)

Scientific Division

SD Committees

SD Working Groups

SD Minutes

Reference Materials

Project Proposal Form

SD Yearly Publications of Interest

Participation in External Programs

Standardization of Thyroid Function Tests (C-STFT)

Membership

Name	Position	Country	Term	Time in Office
L. Thienpont	Chair	BE	2nd	2015 01 - 2017 12
B. Das	Member	IN	2nd	2015 01 - 2017 12
J.D. Faix	Member	US	2nd	2015 01 - 2017 12
F. MacKenzie	Member	UK	2nd	2015 01 - 2017 12
M.M. Patru	Member/OCD	US	1st	2015 07 - 2017-12
F. Quinn	Consultant	US		
M. Rottmann	Consultant	DE		
K. Van Uytfanghe	Consultant	BE		

List of Corresponding Members, nominated by National Societies

Name

Paul Williams

Pierre Carayon

M. Reza Bakhtiari

Akira Hishinuma

Simeon Adebisi

Jens Berg

Lakminda Thilakarathna

Sevgi Eskiocak

David Halsall

Full and Affiliate Member Societies

Australasian Association of Clinical Biochemists (AACB)

Société Française de Biologie Clinique (SFBC)

Iranian Association of Clinical Laboratory Doctors

Japan Society of Clinical Chemistry (JSCC)

Association of Clinical Chemists Nigeria (ACCN)

Norwegian Society of Medical Biochemistry

Association for Clinical Biochemistry, Sri Lanka

Turkish Biochemical Society (TBS)

Association for Clinical Biochemistry (ACB) - UK

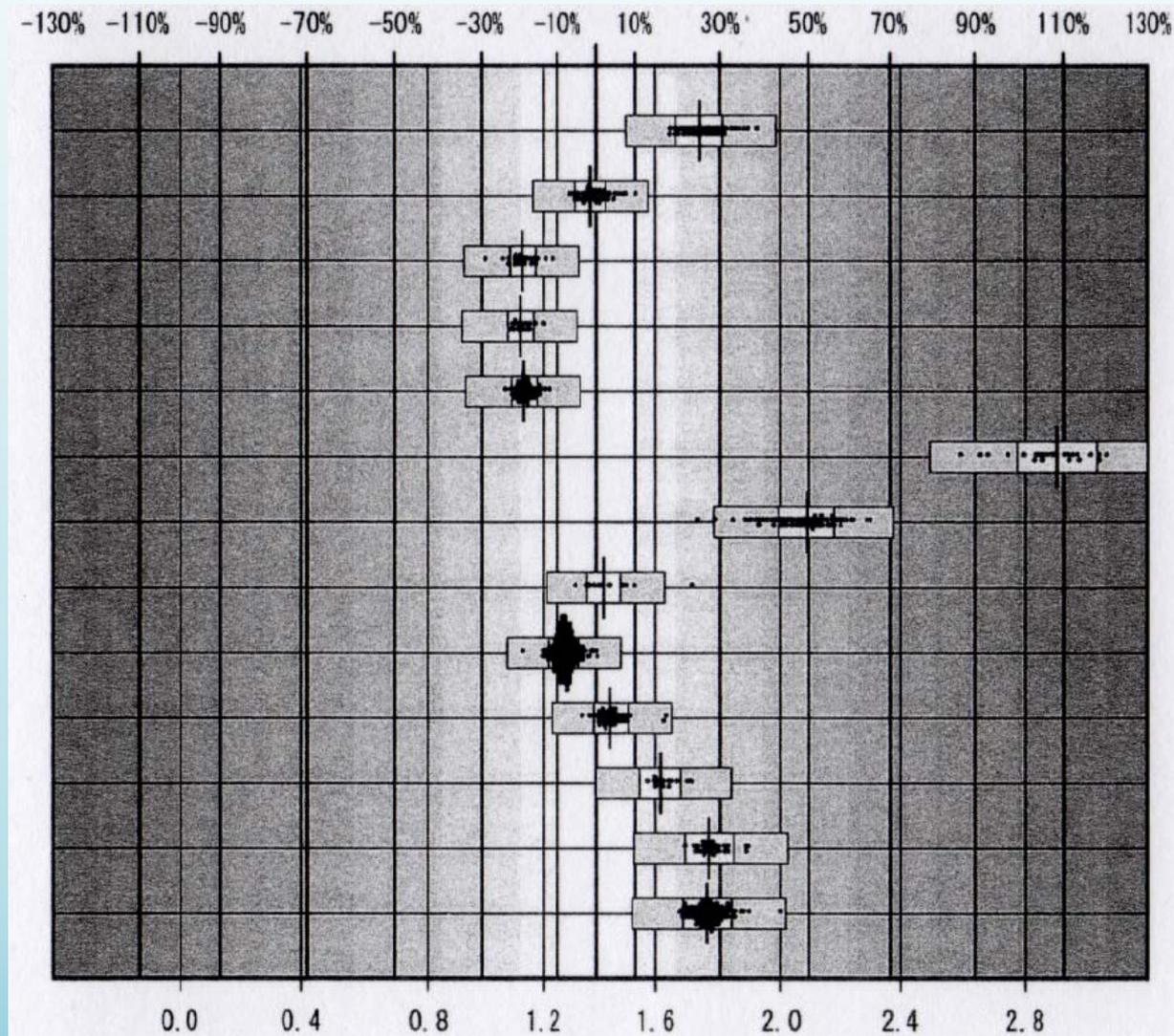
現状の問題点 方法間CVが大きい

平成26年度日本医師会
第48回臨床検査精度管理調査結果報告書

	測定平均値	方法間CV	方法内CV
FT4	1.391	26.97	2.85
	2.092	28.54	2.82
	2.834	27.97	2.88
TSH	3.053	8.84	2.88
	10.344	9.11	2.56
	16.178	9.84	2.75

平成26年度日本医師会 第48回臨床検査精度管理調査結果報告書

FT4:1.391ng/dL



そもそも免疫検査を
標準化できるか？

日本臨床検査医学会 標準化委員会

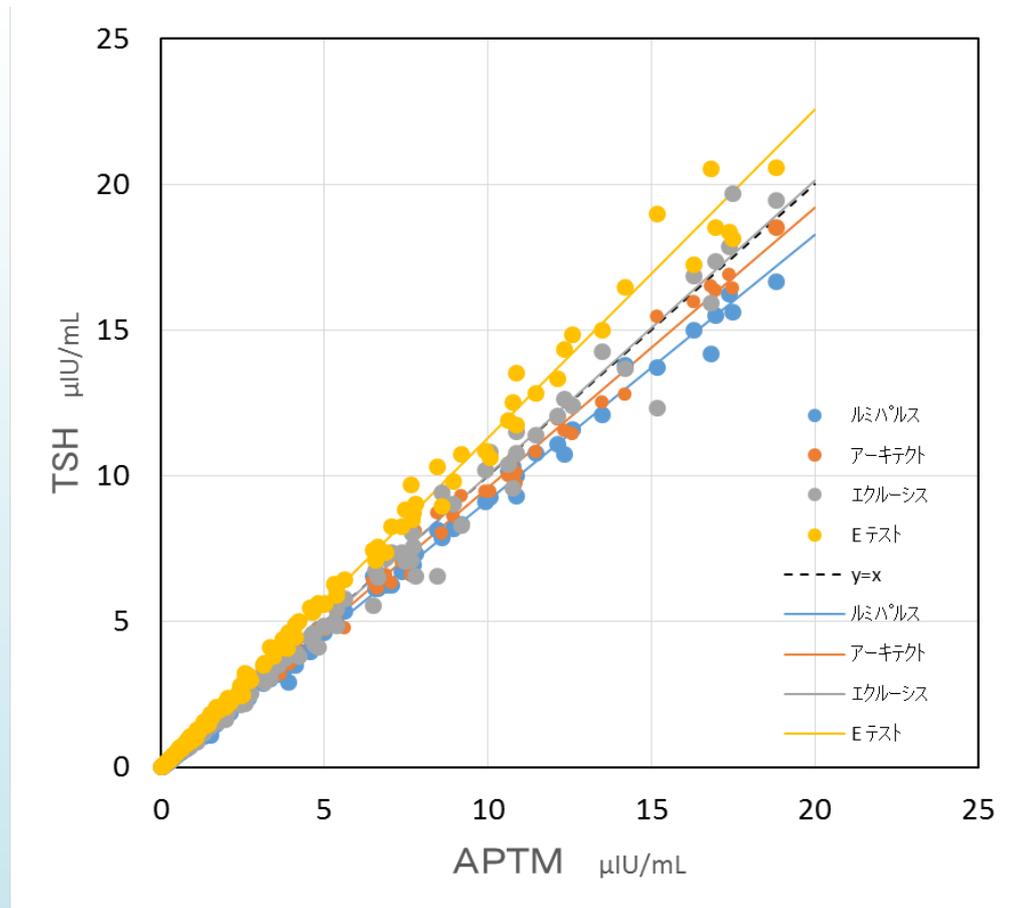
竹岡敬子、日高 洋、菱沼 昭、池田勝義、大久保滋夫、
土屋達行、橋口照人、吉田 耕、堀田多恵子、松下一之、
松本祐之、村上正巳、前川真人 (2016)

甲状腺刺激ホルモン(TSH)のハーモナイゼーション
臨床病理 64(4): 375-379.

日本医師会の2013年度臨床検査精度管理調査結果報告書

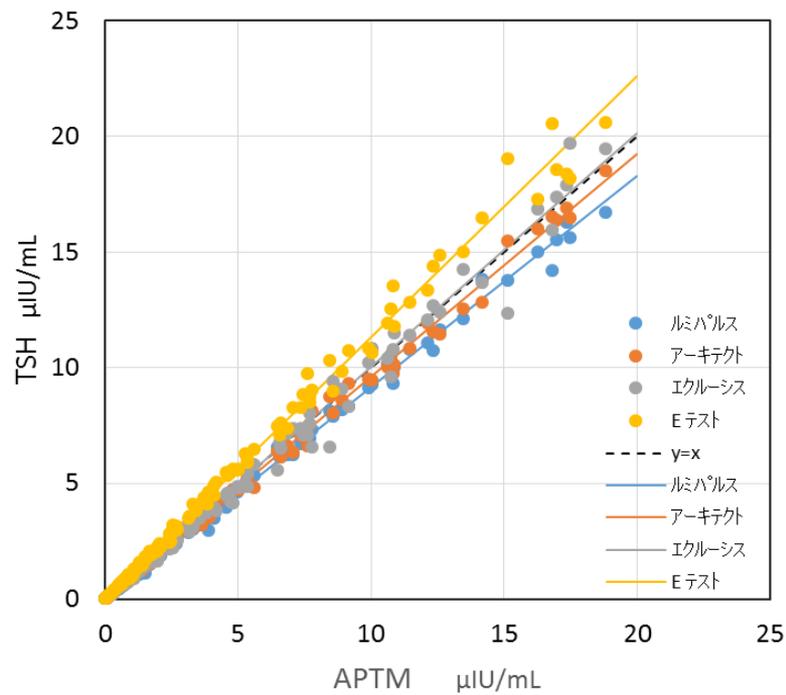
(測定対象試薬の参加施設数:1688施設)

- 677施設 アーキテクト[®]・TSH
- 308施設 エクルーシス[®]試薬TSH
- 155施設 ルミパルス[®] TSH-Ⅲ
- 118施設 Eテスト「TOSOH」Ⅱ (TSH)

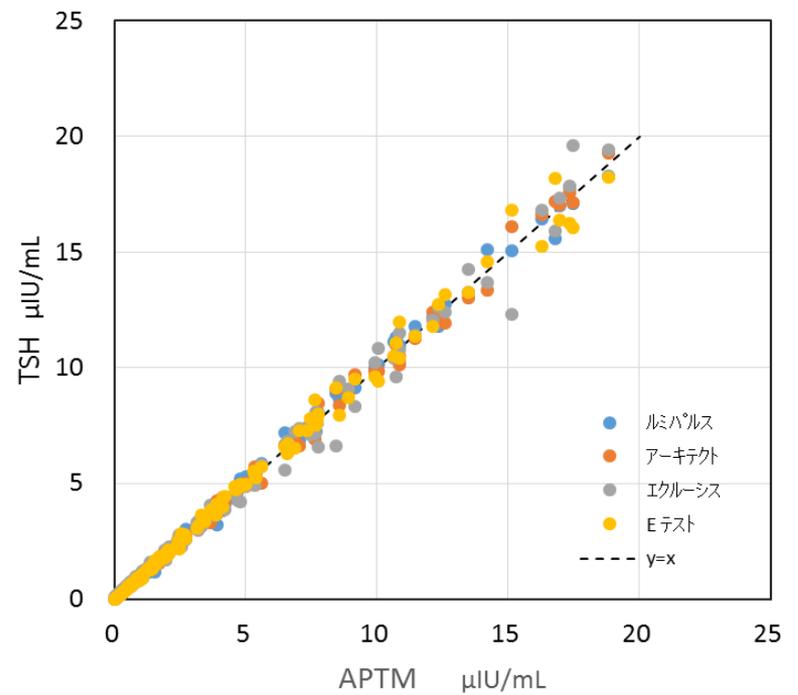


標準主軸回帰 x: APTM		相関係数
ルミパルス	$y=0.913x+0.013$	0.9988
アーキテクト	$y=0.961x-0.010$	0.9987
エクルーシス	$y=1.007x-0.079$	0.9951
Eテスト	$y=1.130x+0.015$	0.9972

換算前



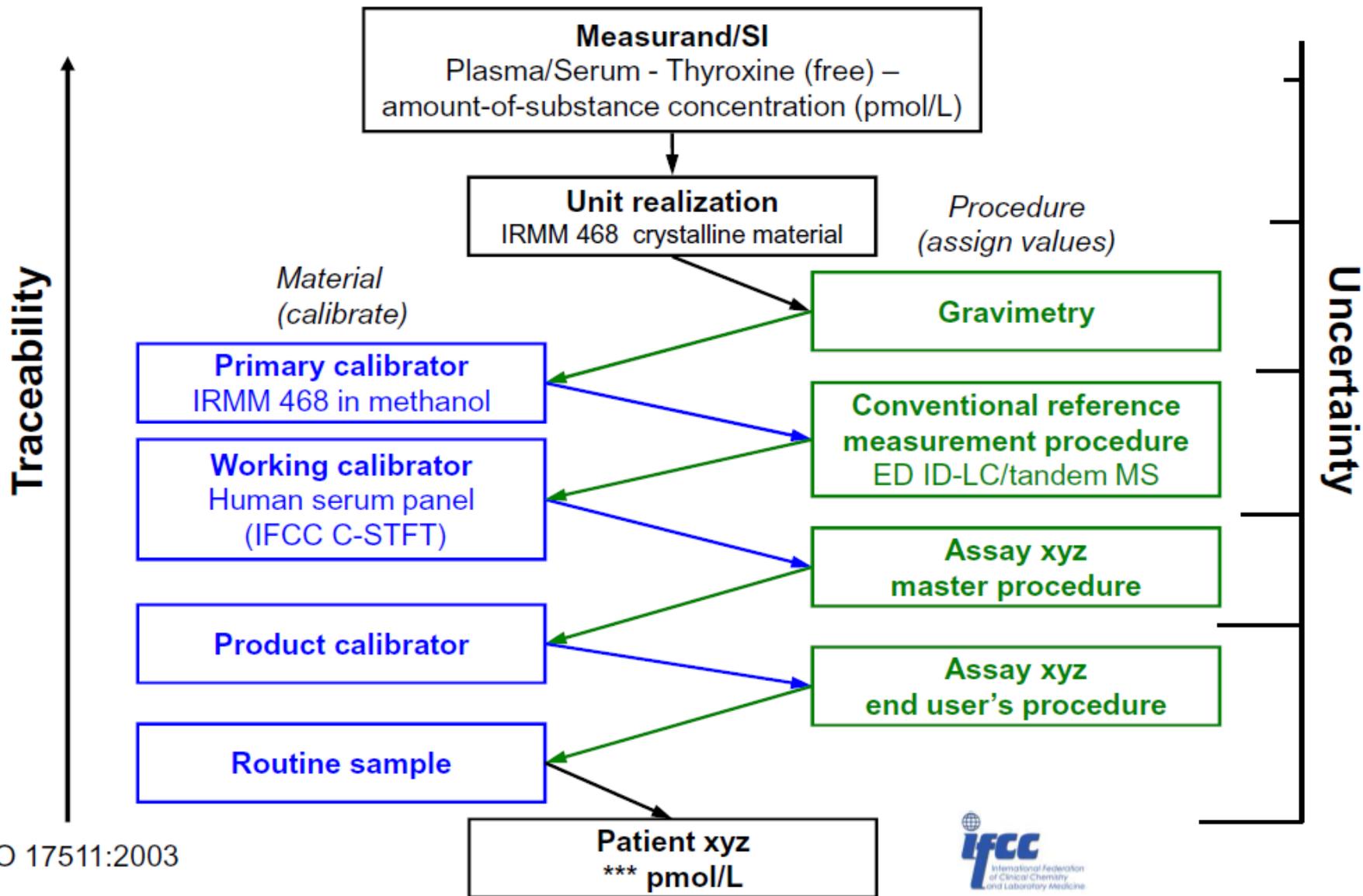
換算後



IFCC: C-STFT

	FT4	TSH
コンセプト	標準化(standardization)	ハーモナイゼーション (harmonization)
基準化法(RMP: Reference Measurement Procedure)	平衡透析—液体クロマトグラフ同位体希釈タンデム質量分析法 (ED ID-LC/tandem MS: equilibrium dialysis isotope dilution—liquid chromatography/tandem mass spectrometry)	全方法間平均法 (APTM: all-procedure trimmed mean)
値付け物質(CRM: Certified Reference Material)	IRMM468/469	WHO IRP80/558 & 81/565
問題点	市販全測定キットは低値である	血中TSHは単一物質でない

FT4 reference measurement system*



*ISO 17511:2003

IFCC conventional RMP listed in the Joint Committee On Traceability in Laboratory Medicine (JCTLM)

Bureau
International des
Poids et
Mesures

Database of higher-order reference materials,
measurement methods/procedures and services



JCTLM Database
Laboratory medicine and *in vitro* diagnostics

> You are here : [JCTLM-DB](#) > [Reference measurement methods/procedures](#) > List T+ T T-

Result of the search: list of reference measurement methods/procedures

➤ JCTLM Database

- [Search Form](#)
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- [List of reference measurement methods no longer listed in the JCTLM database](#) 
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➔ **Your search criteria:** Reference measurement methods/procedures; Analyte: free thyroxine; Analyte category: Non-peptide hormones; Matrix category: Blood serum

➤ [Save as PDF file](#) ➤ [Modify your selection](#)

➤ Results of the search

Isotope dilution mass spectrometry method for free thyroxine in blood serum

▸ University of Ghent reference measurement procedure for free thyroxine in serum

Applicable matrice(s)	lyophilized, fresh, or frozen serum
Full description of technique(s)	equilibrium diaysis ID/LC/MS
Quantity	Amount-of-substance concentration
Applicable range	1.8 pmol/L to 80 pmol/L
Expected uncertainty (level of confidence 95%)	6.9 %
Reference(s)	Clin. Chem. Lab. Med., 2011, 49(8), 1275 - 1281
JCTLM DB identification number	C8RMP1

➤ JCTLM Newsletters

- [Issue 2 - March 2015](#)
- [Issue 1 - April 2014](#)

➤ JCTLM

- [Preamble](#) 
- [Joint Committee for Traceability in Laboratory Medicine \(JCTLM\)](#)
- [Leaflet](#) 

Reference services by ISO 17025 & 15195 accredited lab listed in the JCTLM database

Bureau
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Mesures

Database of higher-order reference materials,
measurement methods/procedures and services



JCTLM Database
Laboratory medicine and *in vitro* diagnostics

> You are here : [JCTLM-DB](#) > [Reference measurement services](#) > List

T+ T T-

Result of the search: list of reference measurement services

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➔ **Your search criteria:** Reference measurement services; Analyte: free thyroxine; Analyte category: Non-peptide hormones; Matrix category: Blood serum

➤ [Save as PDF file](#) ➤ [Modify your selection](#)

↘ Results of the search

UGent, Belgium	
Phone: +32 (0)9 264 81 04	Contact person: Prof. Dr. L. Thienpont
Fax: +32 (0)9 264 81 98	Email: linda.thienpont@Ugent.be
Analyte	free thyroxine
Material or matrix	blood serum
Applicable material or matrix	lyophilized, fresh, or frozen serum
Quantity	Amount-of-substance concentration
Service measurement range	1.8 pmol/L to 80 pmol/L
Expanded uncertainty (level of confidence 95%)	6.9 % The expanded uncertainty is calculated for measurement protocol n = 6
Measurement principle	equilibrium dialysis - ID/LC/MS
JCTLM reference measurement method/procedure	University of Ghent reference measurement procedure for free thyroxine in serum

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- [Issue 2 - March 2015](#)
- [Issue 1 - April 2014](#)

↘ JCTLM

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- [Joint Committee for Traceability in Laboratory Medicine \(JCTLM\)](#)
- [Leaflet](#)

TSH はハーモナイゼーション

問題点: TSH は分子的に1種ではない

非共有結合2分子体

分子的多様性

アミノ酸配列/アイソフォーム

糖化

TSH はハーモナイゼーション

WHO IRP 80/558 & 81/565: 死体下垂体抽出物
従って、血清中に存在するTSHと分子的に異なる
“便宜的”にIUが定義されている

Surrogate Reference Method Procedure (代替RMP)

統計的手法

“all-procedure trimmed mean” (APTM)

- フェーズI: 現メーカー法の質の確認。
- フェーズII: 各製造メーカー内での標準化実現可能性の検証。
- フェーズIII: 病的血清サンプルを用いた検査の質保証の検証。
- フェーズIV: 最終段階の基準値測定試験。

FT4はED ID-LC/tandemMSで値付けされた濃度範囲
4~202pmol/Lの約100サンプルを血清パネルとして利用:
standardization (n = 91) and follow-up panel (n = 95)

TSHはAPTМにより値付けされた濃度範0.002~193mIU/L
の約100サンプルを血清パネルとして利用:

harmonization (n = 101) and 1st follow-up panel (n = 95)

Standardization of Free Thyroxine Measurements Allows the Adoption of a More Uniform Reference Interval

Linde A.C. De Grande,¹ Katleen Van Uytfanghe,² Dries Reynders,³ Barnali Das,⁴ James D. Faix,⁵
Finlay MacKenzie,⁶ Brigitte Decallonne,⁷ Akira Hishinuma,⁸ Bruno Lapauw,⁹ Paul Taelman,¹⁰
Paul Van Crombrugge,¹¹ Annick Van den Bruel,¹² Brigitte Velkeniers,¹³ Paul Williams,¹⁴ and
Linda M. Thienpont,^{1,15*} on behalf of the IFCC Committee for Standardization of Thyroid Function
Tests (C-STFT)

Harmonization of Serum Thyroid-Stimulating Hormone Measurements Paves the Way for the Adoption of a More Uniform Reference Interval

Linda M. Thienpont,^{1,2*} Katleen Van Uytfanghe,³ Linde A.C. De Grande,¹ Dries Reynders,⁴ Barnali Das,⁵
James D. Faix,⁶ Finlay MacKenzie,⁷ Brigitte Decallonne,⁸ Akira Hishinuma,⁹ Bruno Lapauw,¹⁰
Paul Taelman,¹¹ Paul Van Crombrugge,¹² Annick Van den Bruel,¹³ Brigitte Velkeniers,¹⁴ and Paul Williams¹⁵
on behalf of the IFCC Committee for Standardization of Thyroid Function Tests (C-STFT)

IVD manufacturer Platform – Immunoassay (FT4/TSH)

Siemens Healthineers (USA) – Advia Centaur XP

Abbott Diagnostics (USA) – Architect i2000

Shenzhen Mindray Bio-Medical Electronics Co, Ltd (China) – CL-2000i

Ortho-Clinical Diagnostics (UK) – Vitros Eci

bioMérieux SA (France) – Vidas

Beckman Coulter Inc (USA) – Access 2

DiaSorin SpA (Italy) – Liaison® Analyser

Sichuan Maccura Biotechnology Co, Ltd (China) – IS1200

Roche Diagnostics GmbH Germany) – Elecsys (Cobas e 601)

Tosoh Corporation (Japan) – AIA-2000

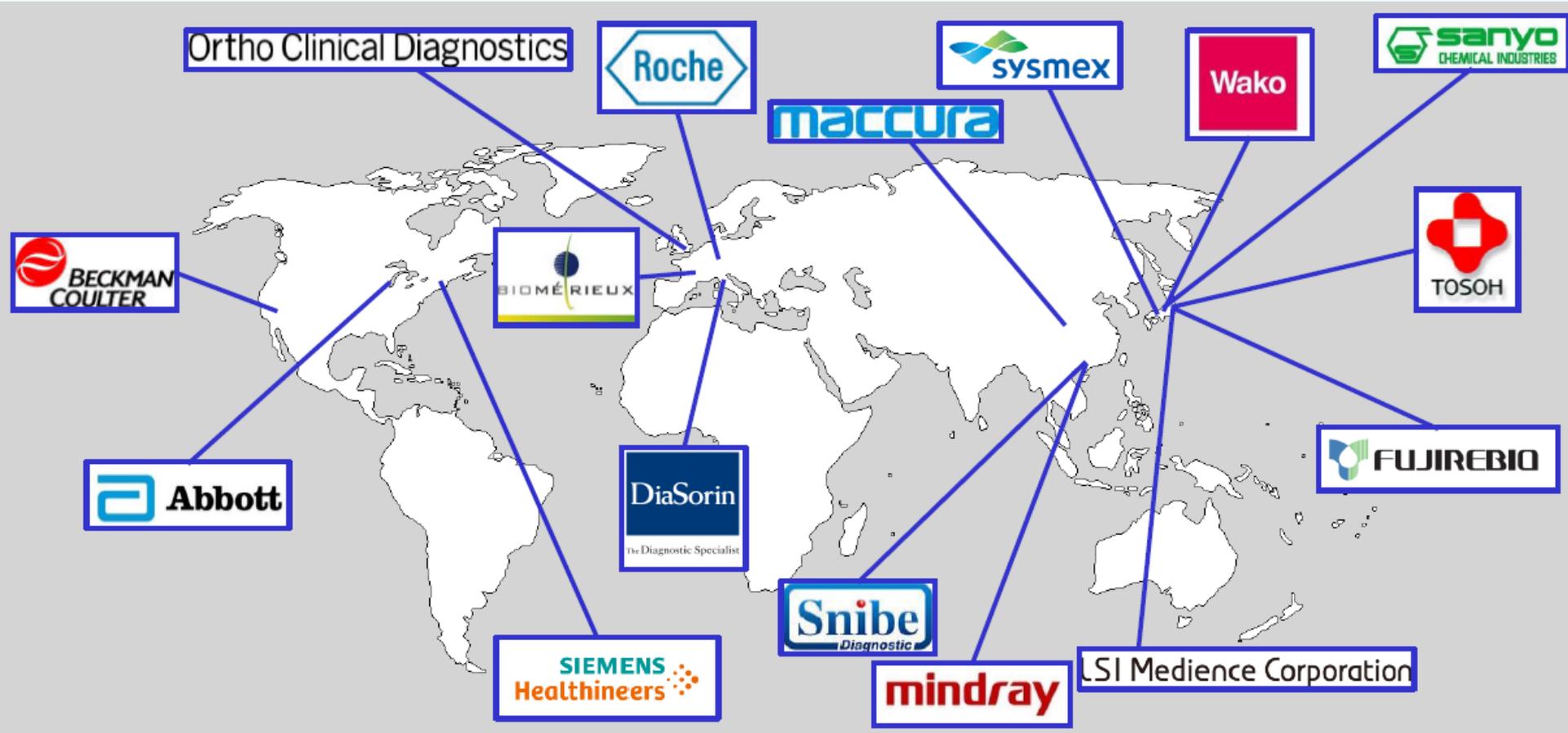
Snibe Co., Ltd. (China) – Maglumi 2000

Fujirebio Inc. (Japan) – Lumipulse G1200

LSI Medience Corporation (Japan) – STACIA

Sysmex Corporation (Japan) – HISCL-5000

Sanyo/Wako Chemical Industries Ltd (Japan) – Accuraseed



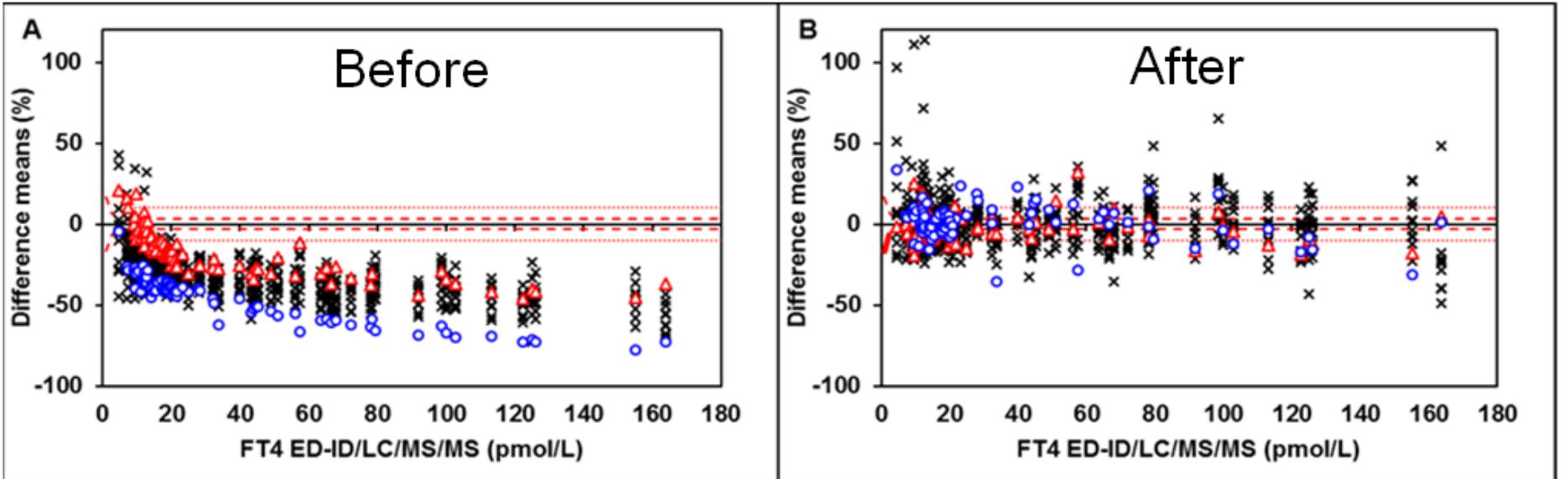
Status of standardization – FT4

Assay bias (% , average) vs ED ID-MS
(sorted by bias in the range 9 – 27 pmol/L)

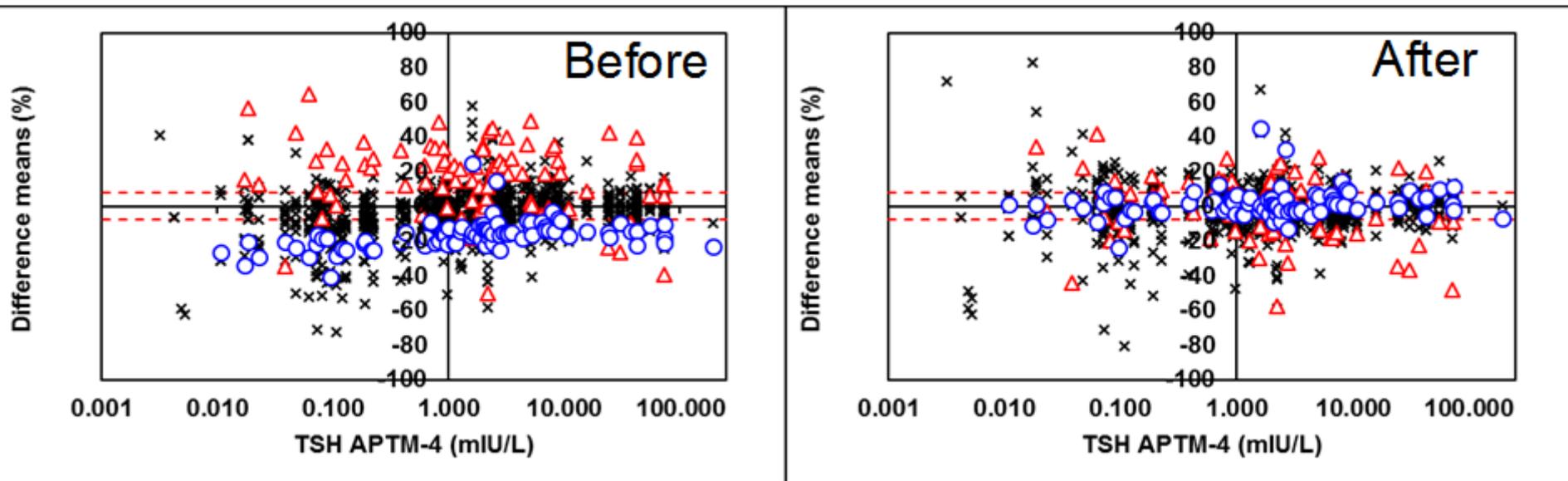
Assay	<9 pmol/L	9-27 pmol/L	>27 pmol/L
<u>M</u>	38.4	<u>-14.0</u>	-33.3
<u>E</u>	<u>61.6</u>	-17.5	-42.5
<u>G</u>	4.6	-20.2	-33.8
<u>B</u>	<u>-28.3</u>	-20.4	<u>-21.2</u>
<u>H</u>	22.5	-22.4	-42.0
<u>D</u>	26.0	-23.0	-40.9
<u>I</u>	-17.8	-24.3	-30.3
<u>C</u>	-10.2	-24.8	-37.1
<u>A</u>	-27.3	-26.3	-26.9
<u>L</u>	5.7	-28.2	-44.5
<u>J</u>	-9.3	-28.5	-36.8
<u>F</u>	-27.1	-36.7	<u>-47.7</u>
<u>K</u>	-15.2	<u>-42.4</u>	-45.1

全キットがマイナスにシフトしている。

FT4

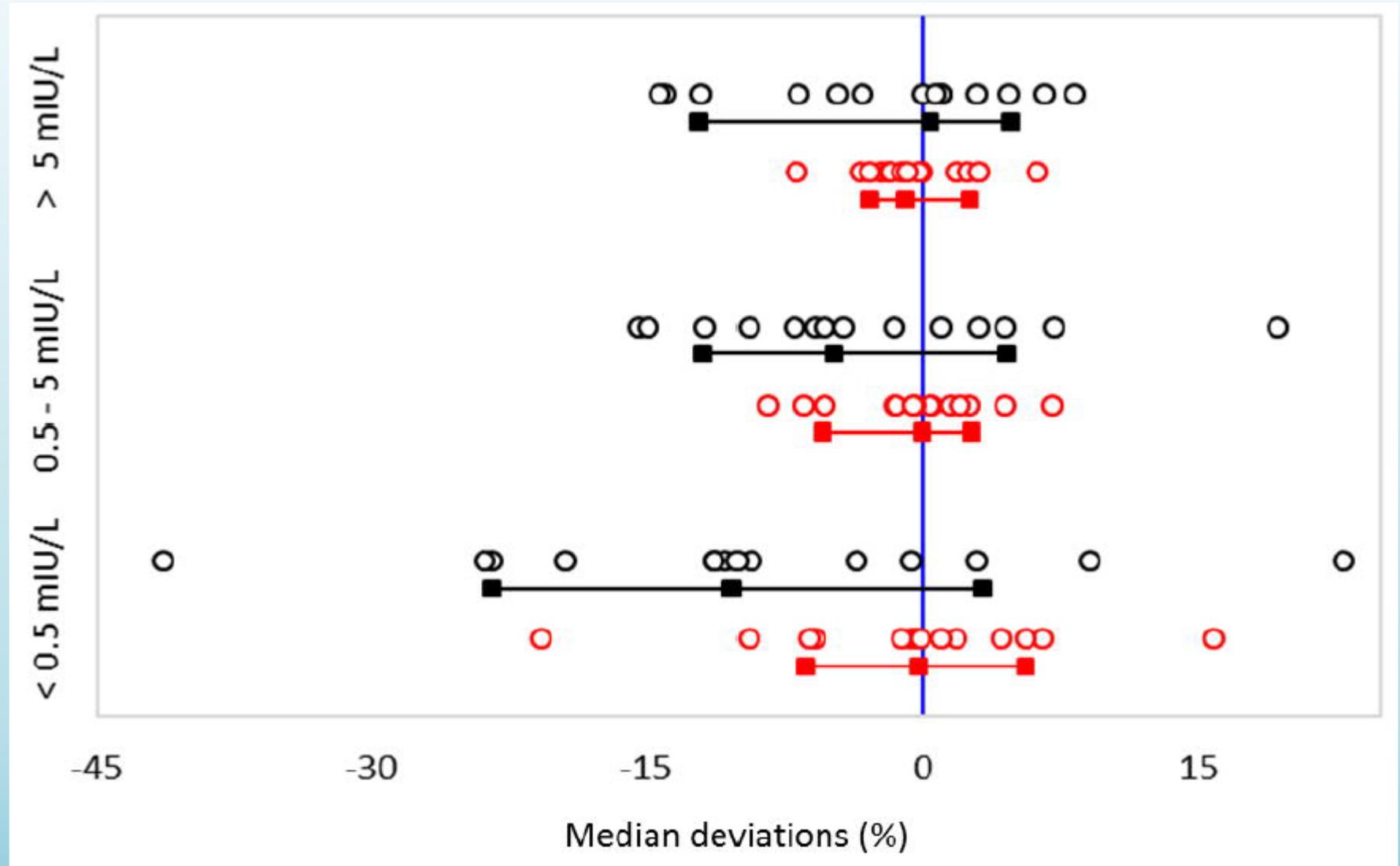


TSH



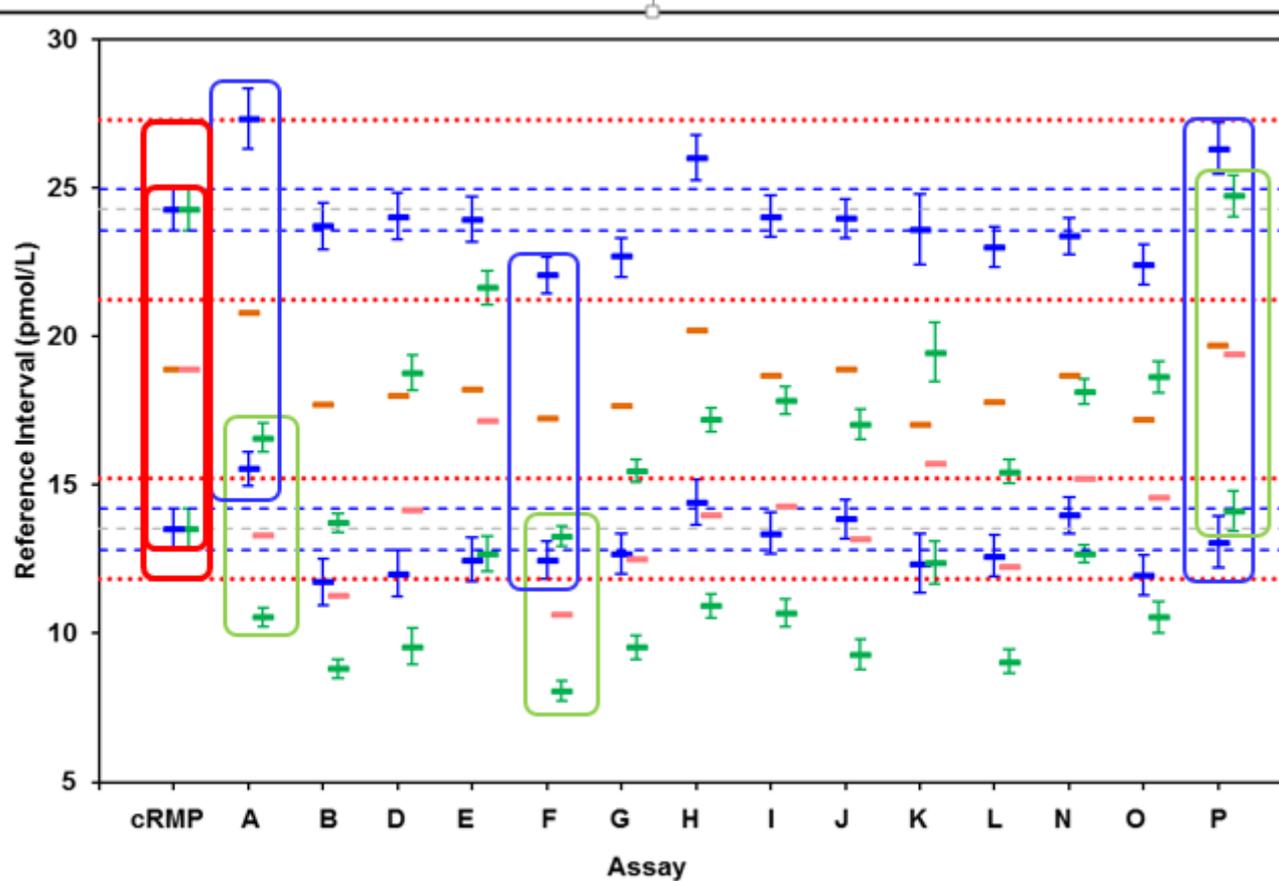
All-Procedure Trimmed Mean (APT_M)

Median deviations (%) of the assays to the APTM-4 before and after recalibration in 3 concentration intervals



		TSH RI	FT4 RI
Age (year)	Median	53	55
	Range	19-84	19-84
Gender	Female	59	58
	Male	61	62
Ethnicity	African American	16	10
	Caucasian	102	108
	Native American	0	1
	Hispanic	1	1
	Asian American	1	0
Medication	Yes	43	60
	No	77	57
	Unknown		3
Smoker	Yes	37	24
	No	83	96
Body Mass Index	Median	29	29
	Range	20-49	14-55
TSH screening	Median	1.9 mIU/L	1.8 mIU/L
	Range	0.5-6.8 mIU/L	0.5-6.8 mIU/L

FT4基準値



RI by the RMP
(parametric)

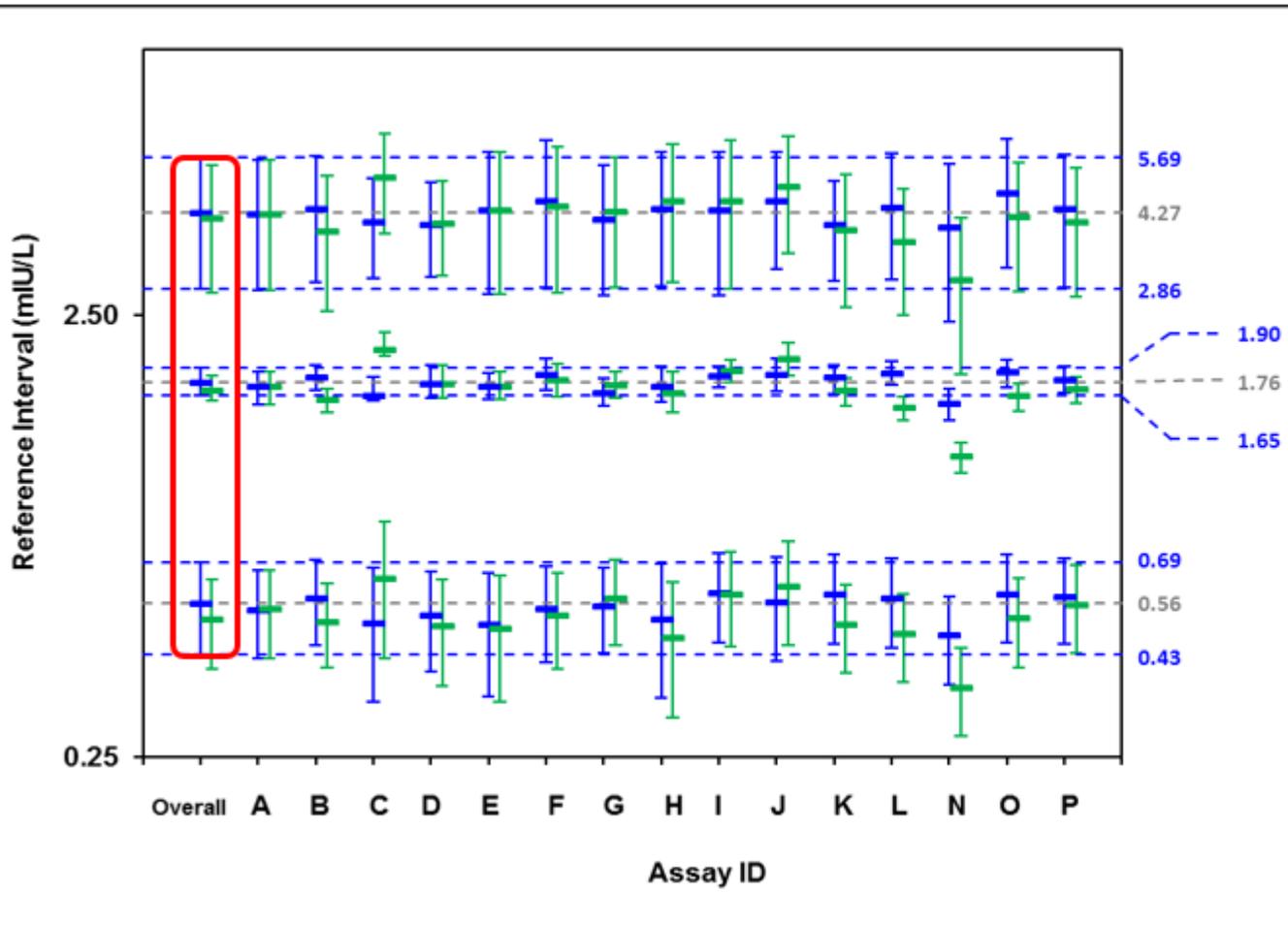
Mean: 18.9 pmol/L
Width: 10.7 pmol/L

2.5 Percentile (90% CI): 13.5 pmol/L
(12.8 - 14.2 pmol/L)

97.5 Percentile (90% CI): 24.3 pmol/L
(23.6 - 25.8 pmol/L)

13.5~24.3 pmol/L 1.05~1.89ng/dL

TSH基準値



“Overall” RI after recalibration (non-parametric)

Median: 1.76 mIU/L
Width: 3.72 mIU/L

2.5 Percentile (90% CI): 0.56 mIU/L
(0.43 – 0.69 mIU/L)

97.5 Percentile:
4.27 mIU/L
(2.86 – 5.69 mIU/L)

0.56~4.27 mIU/L

- 今後の課題

- ① 実現に向けてメーカーの協力を継続してもらうこと。
日本国内で同一日に実行、世界一斉には無理
海外メーカー、日本メーカー
薬事申請の手続きの内容？ 届出、承認
換算式による値の変更or試薬システムor標準品の値付けの変更
- ② 学会主導で厚生労働省に要望書を提出する。
甲状腺学会、臨床化学会、臨床検査医学会、臨床検査標準協議会
- ③ 単位の変更 $\text{ng/dL} \Rightarrow \text{pmol/L}$
換算式 各メーカーの標準化前 \Rightarrow 標準化後
- ④ 基準値の設定
共通基準値(ED-ID-LC/MS)、IFCC論文のキット別の値
日本人？
特殊な状態 妊娠、、、
- ⑤ 関係者、関係団体などへの周知をどのように行うか？
パブコメ募集？
移行期間？

メリット or 必要性

- ① 研究成果の互換性
- ② ガイドラインの作成
- ③ カルテのIT化