Challenges of TSH Measurement, Reporting and Interpretation

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Challenging TFTs

Definition:

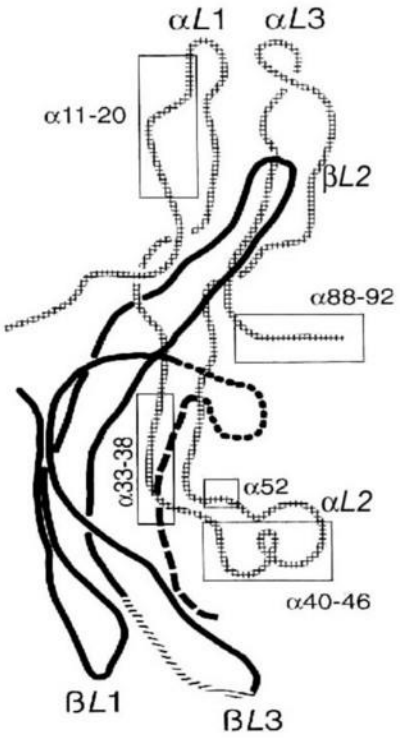
TFT Result vs. Clinical Picture

And / or

Inharmonious Results

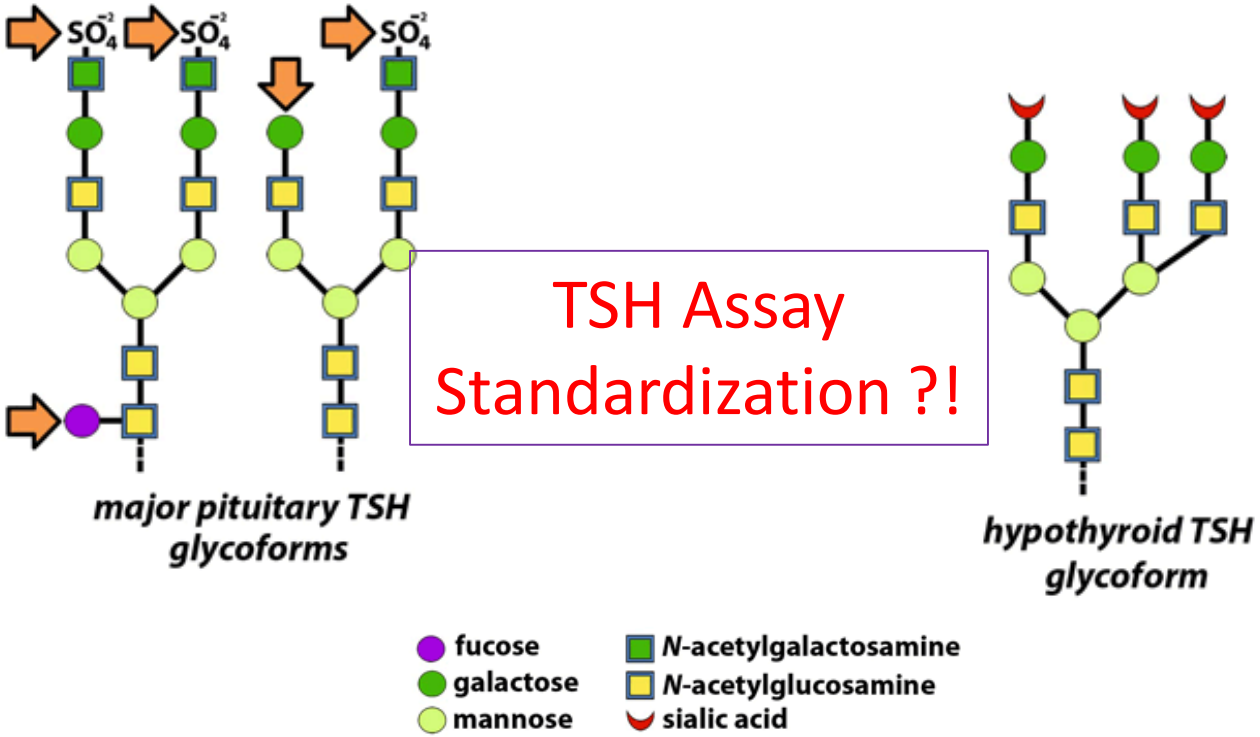
Thyroid Stimulating Hormone
(TSH, Thyrotropin)

- ✓ A heterodimeric glycosylated peptide (92+118)
- ✓ Major role: Regulates the growth and function of thyroid gland
- ✓ MW ~ (28- 30) kDa
- ✓ Synthesized & secreted from thyrotrophs of the anterior pituitary
- ✓ Turnover: 40-150 mU/day
- ✓ Half Life: 1 hour (Variable)



Grossmann, M., Weintraub, B.D.& Szkudlinski, M.W.. Novel insights into the molecular mechanisms of human thyrotropin action: structural, physiological, and therapeutic implications for the glycoprotein hormone family. Endocr Rev , 18 , 476-501. (1997)

Thyroid Stimulating Hormone
(Glycobiology)



TSH Assay Standardization ?!

https://www.aacc.org/publications/cln/articles/2013/may/tsh-harmonization. Last seen: 01/17/2022

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Clinical Research Article

Clinical Research Article

Thyrotropin N-glycosylation and Glycan Composition in Severe Primary Hypothyroidism

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Abbreviations: AMS, anionic monosaccharide; FT4, free thyroxine; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SA, sialic acid; sPH, severe primary hypothyroidism; SU, sulfonated N-acetylgalactosamine; TSH, thyrotropin (thyroid-stimulating hormone); TSHdi, TSH with 2 N-glycans; TSHtri, TSH with 3 N-glycans.

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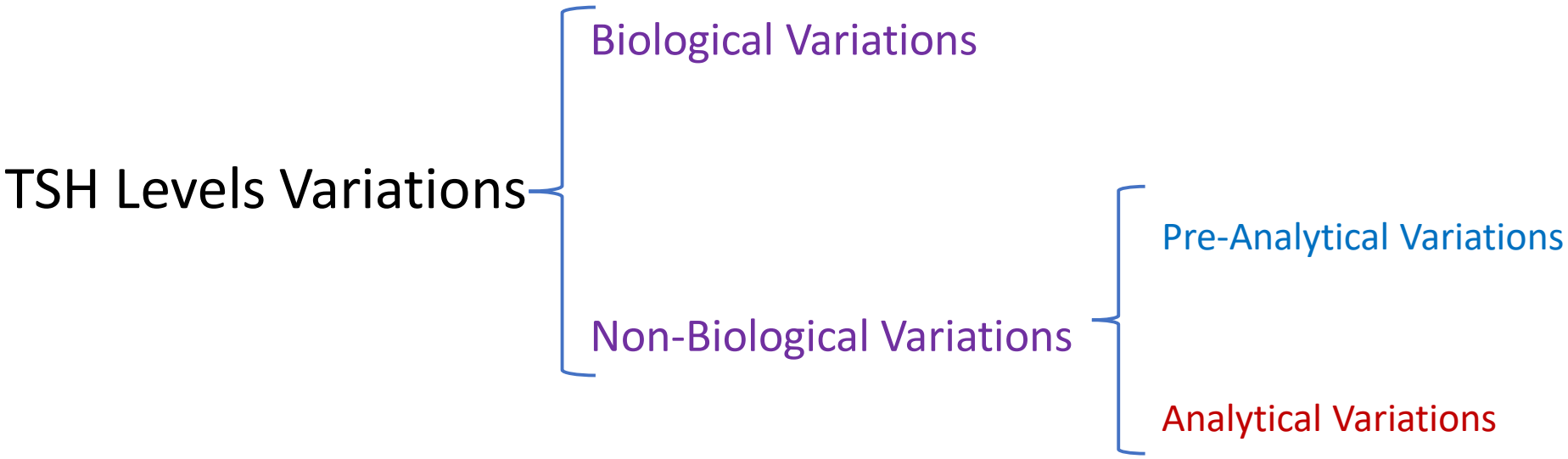
Abstract

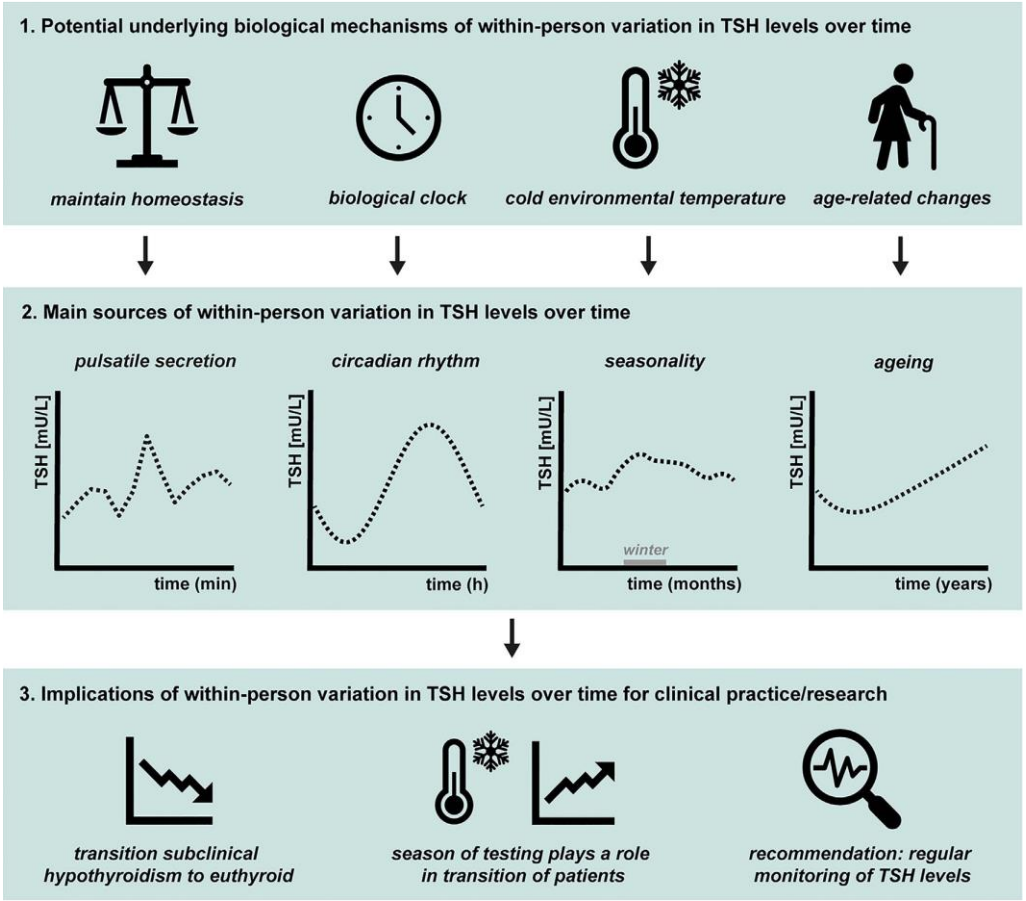
Context: In severe primary hypothyroidism (sPH), the serum thyrotropin (TSH) levels are elevated with an increased degree of sialylation. The circulating TSH comprises 2 different TSH glycoforms: TSHdi with 2 and TSHtri with 3 N-glycans and methods have developed to determine their contents of anionic monosaccharides (AMS), that is, sialic

Variations in TSH levels



Within-Person Variation in TSH levels over time

Biological Variations



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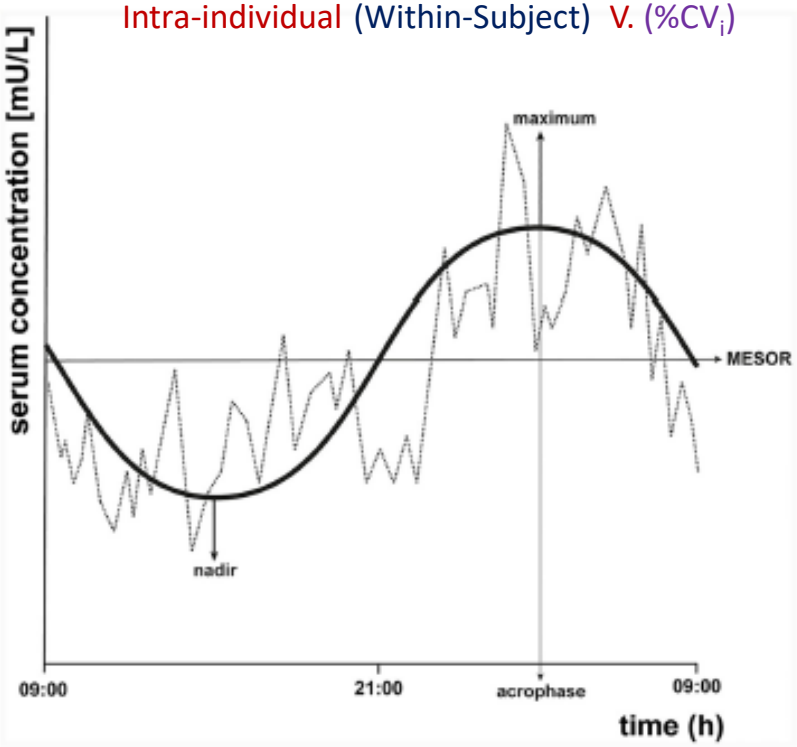
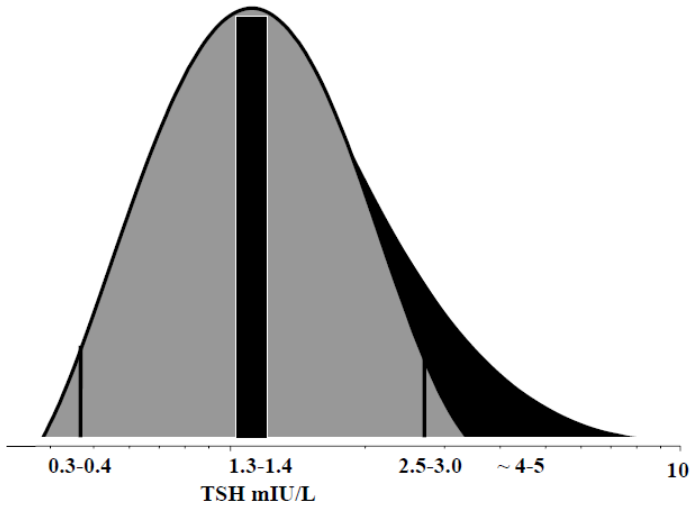
Variations in Serum Thyrotropin Concentrations

Intra-individual (Within-Subject) V. ($\%CV_i$)



Inter-individual (Within--Group) V. ($\%CV_G$)



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ASSESSMENT of CLINICAL SIGNIFICANCE of RESULTS

Clinically Significant Difference between Two Consecutive Patient Results		
Analyte		**Change**
Total T_4		2.2 µg/dL
Free T_4		0.5 ng/dL
Total T_3		35 ng/dL
Free T_3		0.1 ng/dL
TSH	**RR: (0.4 – 5.0)**	0.75 mIU/L
Thyroglobulin		1.5 ng/mL

Case Presentation

- Female
- 40 y/o
- Married with a 7 y/o Daughter
- An Office Employee
- CC: fatigue, weight gain & hair loss (Non-Specific)
- **Labs**:

TSH	**4 m before: 6.3**	**Current: 6.8**	**mU/L**	**RR: (0.4 – 5.0)**
fT4		**14**	**pmol/L**	**RR: (10 – 23)**
Anti-TPO Ab		**40**	**IU/mL**	**RR: (< 35)**

- PMH: NS
- Drugs: No
- Menses.: Normal No plan for pregnancy
- F/H: No thyroid diseases
- BMI: 27 kg/m^2
- C/E: a firm palpable thyroid (~25 g)
- **Questions:**
  1. **Are the lab results Reliable?**
  2. **Are the two TSH results significantly different?**
  3. **Why her TSH is above the RR but fT4 in the range?**

Proper Test Utilization

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1- Are the lab results Reliable?

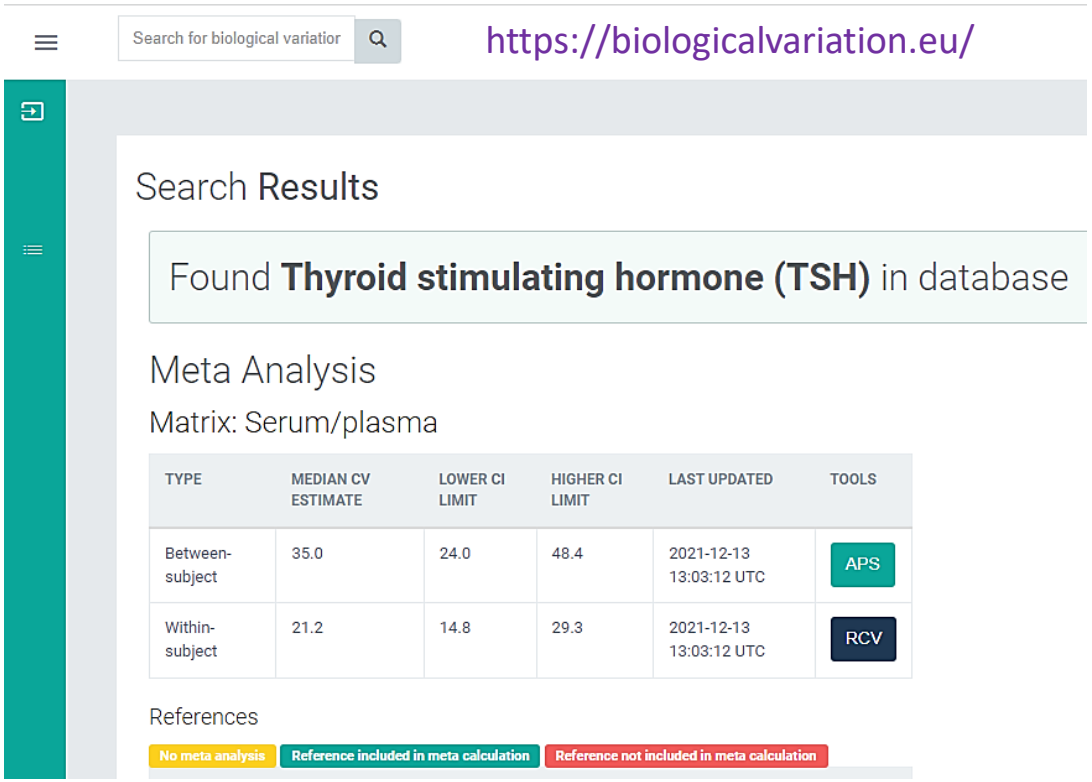
TSH	**4 m before: 6.3**	**Current: 6.8**	**mU/L**
fT4 pmol/L			**14**
Anti-TPO Ab		**40**	**IU/mL**

TSH Measurement Analytical V.

Imprecision: $CV_A < 0.5 \times CV_i$

Bias: $< 0.25 \times (CV_i^2 + CV_G^2)^{1/2}$

TE: $< 1.65 \times 0.5 \times CV_i + 0.25 \times (CV_i^2 + CV_G^2)^{1/2}$



1- Are the lab results Reliable?

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TE: $< 1.65 \times 0.5 \times CV_i + 0.25 \times (CV_i^2 + CV_G^2)^{1/2}$

Imprecision: CVA < 0,5 x CVI. The factor 0.5 refers to desirable APS. The factor for optimum and minimum performance specifications are 0.25 and 0.75 respectively

Bias: $< 0.25 \times (CVI^2 + CVG^2)^{1/2}$ The formula for bias is intended to be used for laboratories to be able to use the same reference limits. The factor 0.25 refers to desirable APS. The factor for optimum and minimum performance specifications are 0.125 and 0.375, respectively.

Total error: $TE < 0.1.65 \times 0.5\ CVI + 0.25\ (CVI^2 + CVG^2)^{1/2}$ The formula was developed for EQA organisers, but has been widely applied since it is easy to use. However, the theoretical basis for this formula is lacking since two "maximum" errors are added, and the total error concept should therefore be applied with cautions. Formulas based on other principles e.g. measurement uncertainty have been proposed and are under further development.

Within-subject %Biological Variation

21.2

Within-group %Biological Variation

35.0

Submit Close

https://biologicalvariation.eu/

1- Are the lab results **Reliable?**

TSH Measurement Performance Characteristics

Bias: $< 0.25 \times (CV_i^2 + CV_G^2)^{1/2}$

Imprecision: $CV_A < 0.5 \times CV_i$

TE: $< 1.65 \times 0.5 \times CV_i + 0.25 \times (CV_i^2 + CV_G^2)^{1/2}$

Uncertainty Reporting ?

Test Reliability Criteria

%BIAS Specifications

Minimum Specification	Desirable Specification	Optimum Specification
15.3	10.2	5.1

%CV Specifications

Minimum Specification	Desirable Specification	Optimum Specification
15.9	10.6	5.3

%Total Error Specifications

Minimum Specification	Desirable Specification	Optimum Specification
41.6	27.7	13.9

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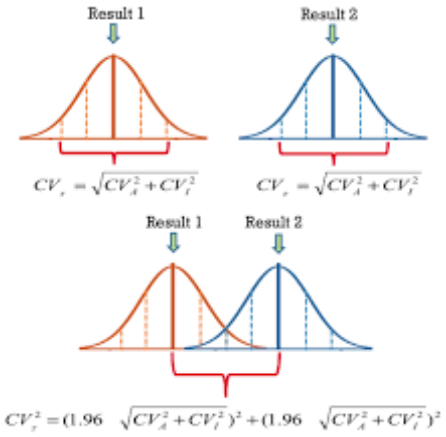
2- Are the two TSH results significantly different?

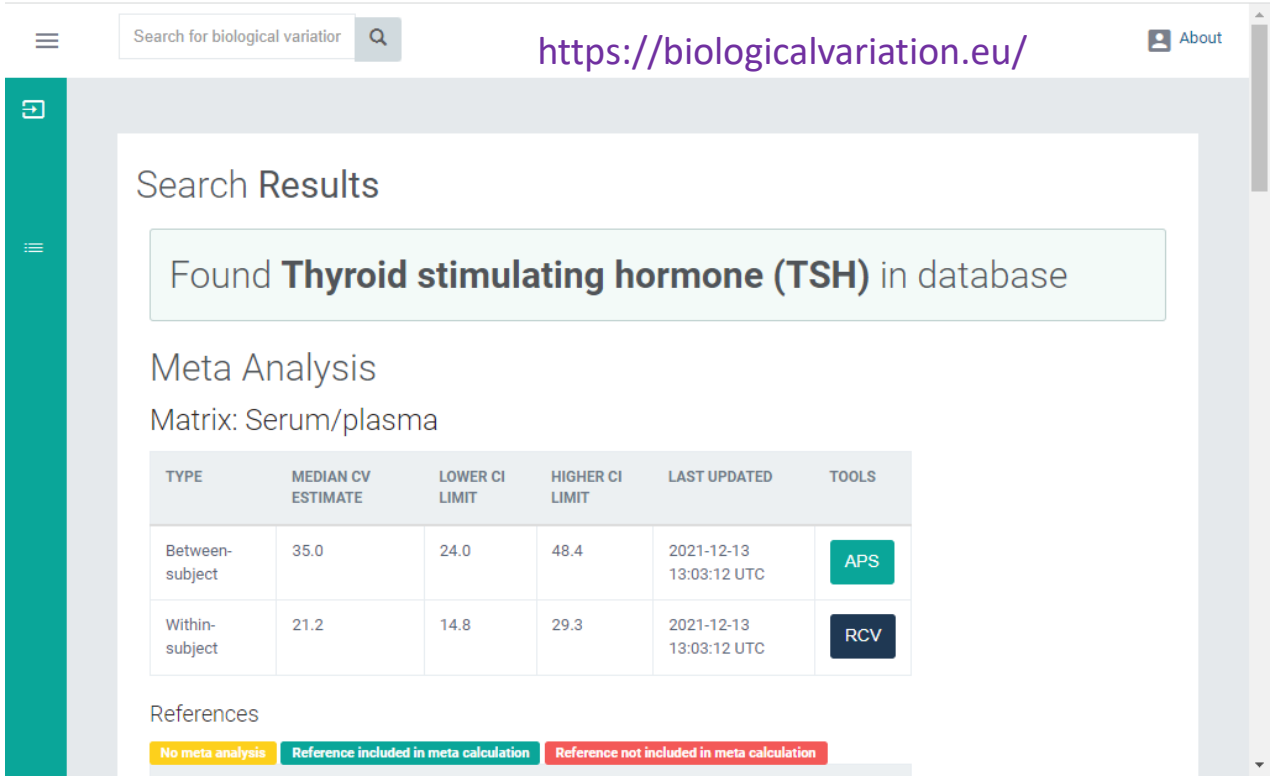
4 m before: 6.3 Current: 6.8 mU/L RR: (0.4 – 5.0)

Diff.% = (6.8 - 6.3)/6.3

Diff.% = 7.93 ~8 %

$$CV_T = RCV = 2.77 \times \sqrt{CV_A^2 + CV_I^2}$$





2- Are the two TSH results significantly different?

Reference Change Value (RCV)

Please note that this formulae is developed for the use of analytical and biological variation estimates quantified in units of SD. The calculator will therefore not provide fully correct RCVs, especially if CVI and CVA estimates are high.

Assymetrical RCV calculation, which is designed for the use of estimates quantified as CVs, will be included in the near future.

When calculating RCV, the local long-term CVA from your own laboratory should be used, incorporating variable bias and calibration effects. The ΔB is therefore usually set to "0".

Analytical %CV

10

Within-subject %Biological Variation

21.2

Probability

95

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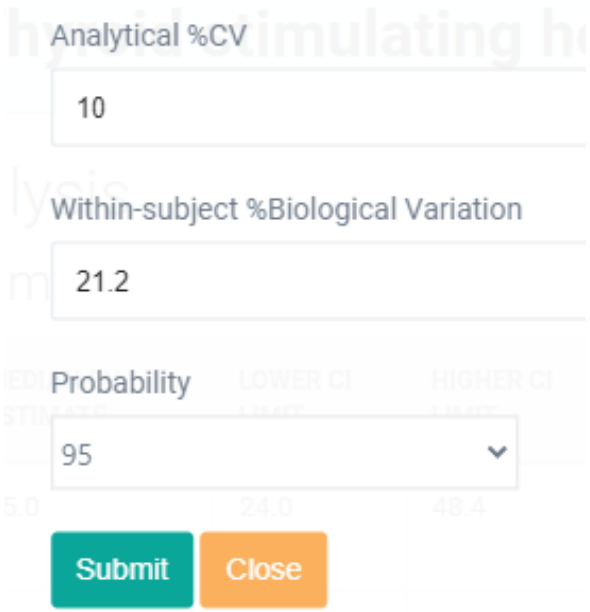

Diff.% = (6.8 - 6.3)/6.3

Diff.% = 7.93 ~8 %

two TSH results not significantly different

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Causes:

1. **Subclinical Hypothyroidism ?**
   - Prevalence (3 – 15 %)
   - Gender & Age ?
   - Anti-TPO ? Autoimmunity?
   - Signs & Symptoms ? (T. Palpation, Dry Skin, Poor Memory, Slow Thinking, Fatigue, Muscle Weakness / Cramps, Cold Intolerance, Puffy Eyes, constipation, bradycardia and neurocognitive deficits)
   - Persistence of TFTs profile
   - Optimum TSH Range ? (0.4 – 2.5)

2. **Recovering from Non-Thyroidal Illness (NTI)**
3. **Drugs interfering with thyroid function**
4. **Transient Thyroiditis**
5. **Extreme Obesity**
6. **Adrenal Insufficiency**

7. **Interference in TSH assay**
   - Heterophil Abs
   - RF
   - Macro TSH

8. **TSH Resistance**
   - Family history

Thank you for your Attention

- *M Reza Bakhtiari, DCLS, PhD*

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QR Code of Telegram Thyroidology Group