

How is Least significant change defined by the attached paper? How is the constant 2.77 derived

Based on the attached research paper, the **Least Significant Change (LSC)** is defined as the smallest difference between two consecutive measurements of serum 25-hydroxyvitamin D [25(OH)D] that can be considered a **real, non-random change** with 95% probability. It accounts for measurement precision errors to distinguish clinically significant changes from analytical variability^[1].

Key Definition from the Paper:

- **LSC Calculation:**

$$\text{LSC} = \text{Precision Error (CV)} \times 2.77$$

- **Precision Error (CV):** The root mean square standard deviation (absolute) or coefficient of variation (percentage) derived from triplicate measurements of 25(OH)D concentrations^[1].
- **Constant 2.77:** Derived statistically to achieve **95% confidence** that a difference exceeding LSC is non-random^[1].

Derivation of the Constant 2.77:

The factor 2.77 is based on:

1. **Z-score for 95% Confidence:** The z-value for a two-tailed 95% confidence interval is 1.96.
2. **Accounting for Two Measurements:** Since LSC compares two results (e.g., baseline and follow-up), the standard error is scaled by $\sqrt{2}$:

$$1.96 \times \sqrt{2} \approx 2.77$$

^[1].

3. **Statistical Basis:** This ensures that if the difference between two measurements exceeds LSC, there is $\geq 95\%$ probability that the change is real and not due to analytical imprecision^[1].

Contextual Findings:

- The study calculated an **absolute LSC of 4.0 ng/mL** (13.2% relative) for the IDS-iSYS 25(OH)D assay^[1].
- LSC varied with 25(OH)D concentration:

| 25(OH)D Range (ng/mL) | Absolute LSC (ng/mL) | Relative LSC (%) | |
|-----------------------|----------------------|------------------|--|
| <20 (Deficiency) | 2.2 | 14.7 | |
| 20–30 (Insufficiency) | 3.7 | 14.2 | |

| 25(OH)D Range (ng/mL) | Absolute LSC (ng/mL) | Relative LSC (%) | |
|-----------------------|----------------------|------------------|------------------|
| 30–50 (Optimal) | 4.1 | 10.9 | |
| >50 (High) | 11.8 | 16.9 | ^[1] . |

Practical Application:

Clinicians should interpret changes in serial 25(OH)D results using LSC:

- A difference **>4.0 ng/mL** (absolute) or **>13.2%** (relative) indicates a clinically significant change with 95% confidence^[1].
- Example: If a patient's 25(OH)D rises from 18 ng/mL to 23 ng/mL ($\Delta 5$ ng/mL > LSC 4.0 ng/mL), this reflects a true improvement beyond analytical noise^[1].

This approach standardizes interpretation of longitudinal vitamin D testing, reducing misclassification due to assay variability^[1].

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1. least-significant-change.pdf