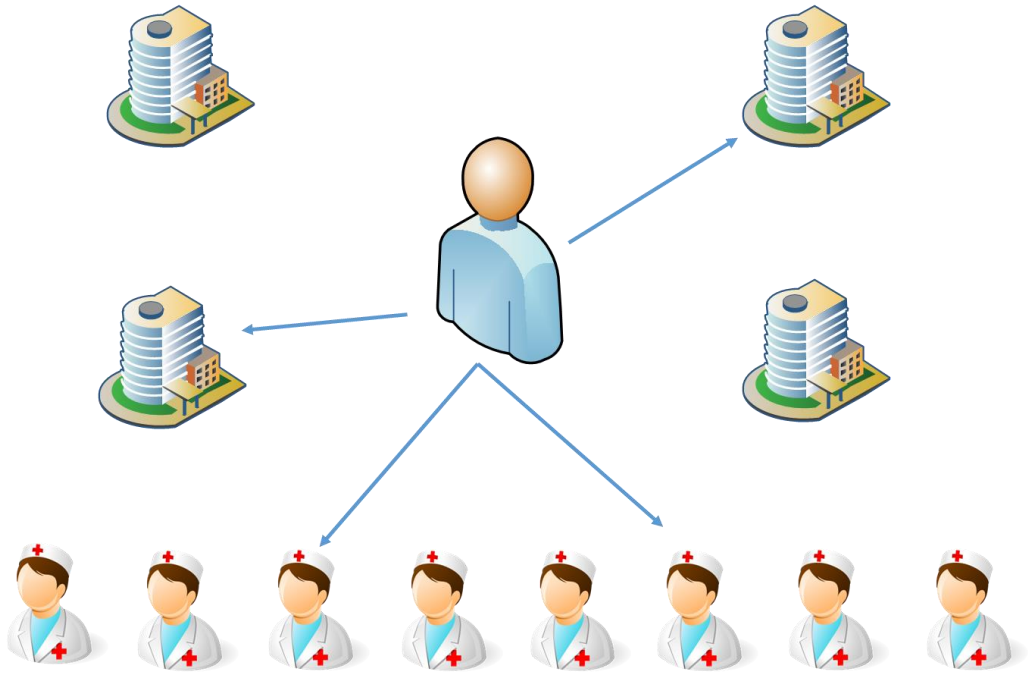
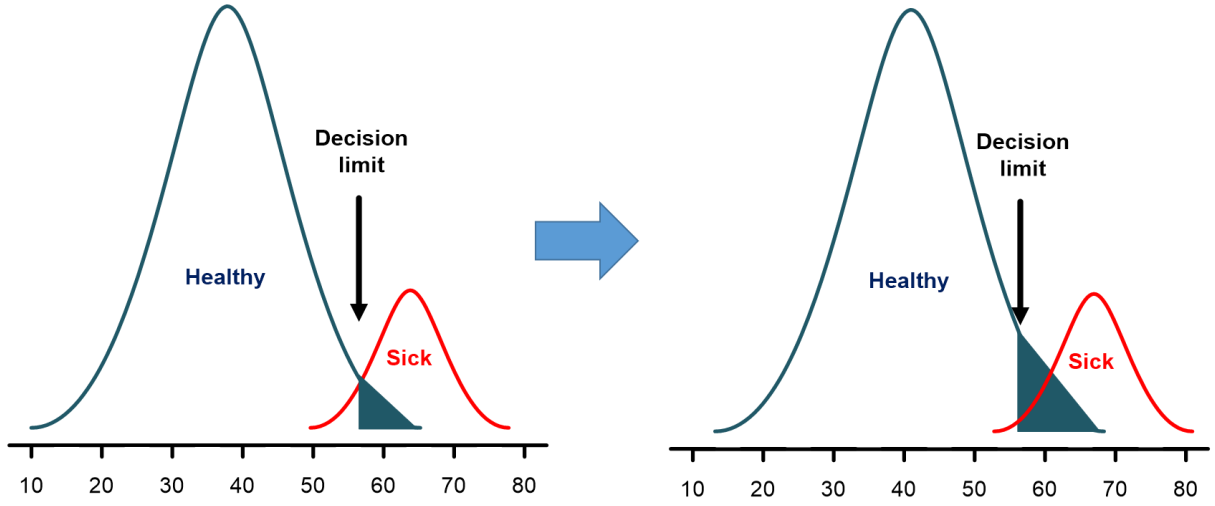
Verifisering av referansegrenser, beslutningsgrenser og rapporteringsintervall

Elvar Theodorsson

Importance of consistent results measured in the same sample geographically and over time

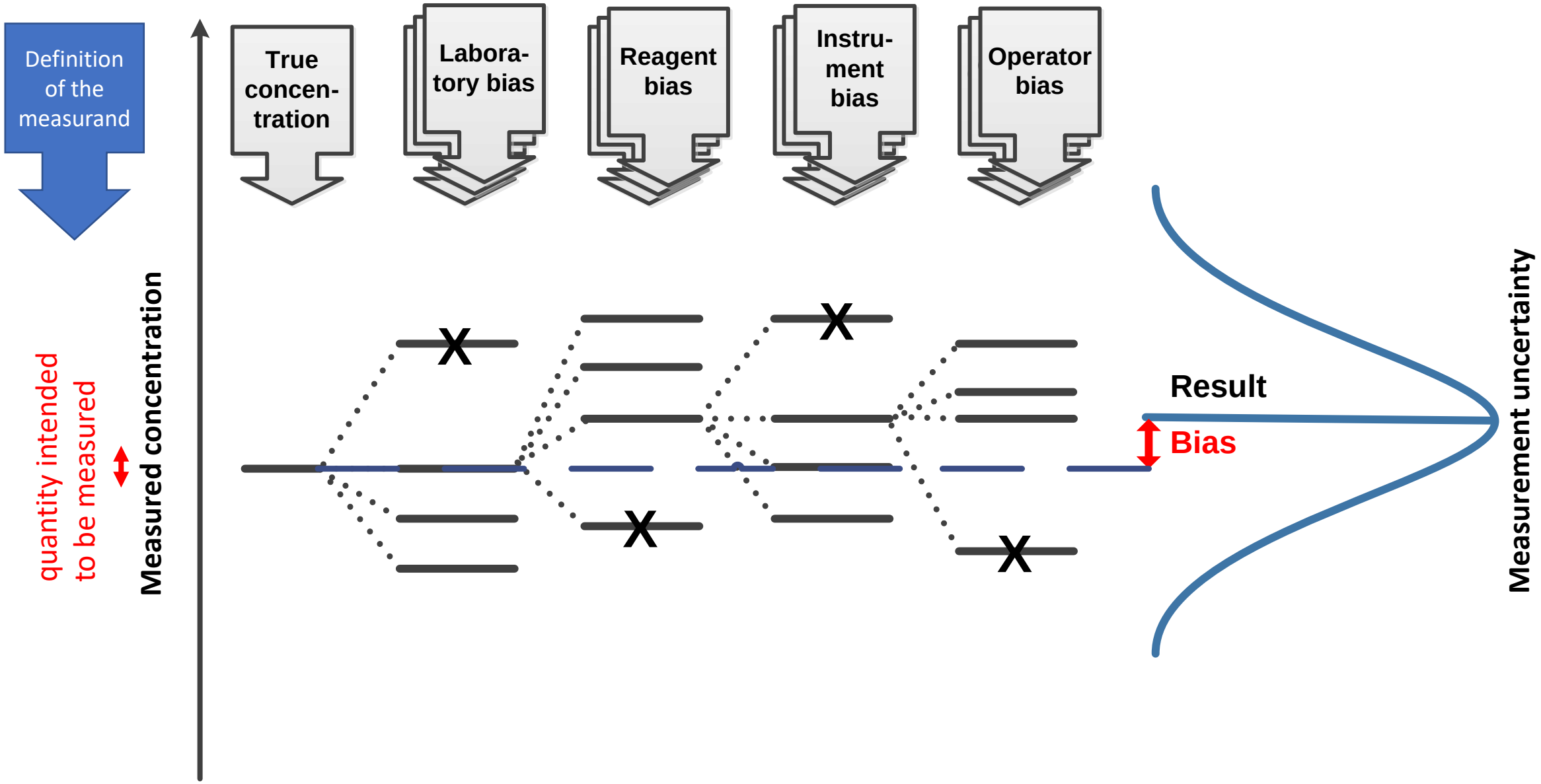


Patient perspective



A bias of + 5 units means that healthy persons are diagnosed sick

From the perspectives of healthcare-, research-, reference intervals-, decision limits and guidelines


Definition of the measurand
True concen-tration
Labora-tory bias
Reagent bias
Instru-ment bias
Operator bias
quantity intended to be measured
Measured concentration
Result
Bias
Measurement uncertainty

If different measurements systems result in different results for the same patient sample

- Physicians and patients will become confused
- Clinical guidelines will become less useful
- Suboptimal treatments and monitoring practices may be implemented

Ulysses syndrome

- The ill effects of too extensive diagnostic investigations conducted because of a false-positive result when performing routine laboratory screening, diagnostic and monitoring procedures

Clinical validation and verification

- **IVDR** - Regulation (EU/EES) 2017/746 allocates the responsibility of clinical validation to the manufacturers of measuring systems
- As long as a measuring system is validated and has appropriate traceability and practically no bias, the reference intervals, decision limits and reporting intervals provided by the producers do NOT need do be verified

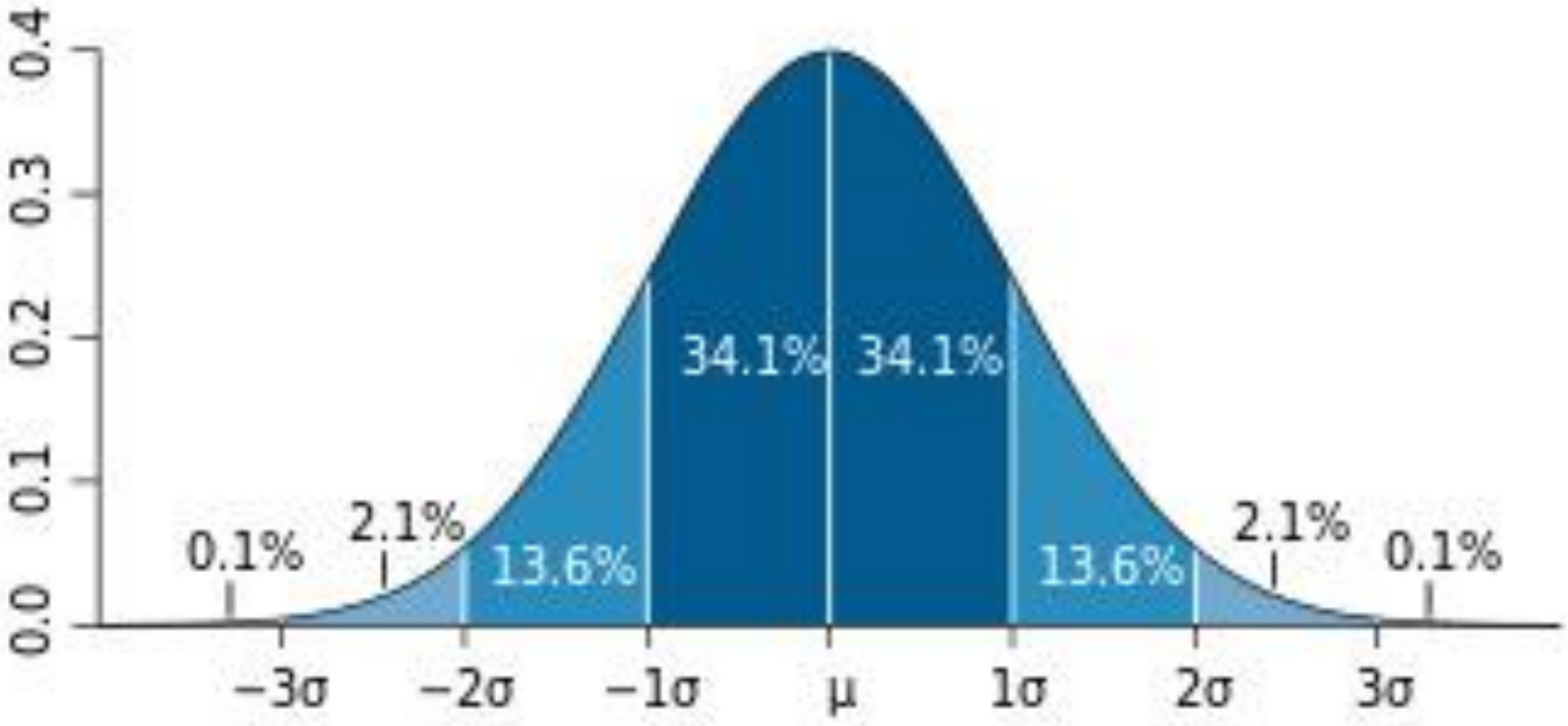
Need for clinical verification

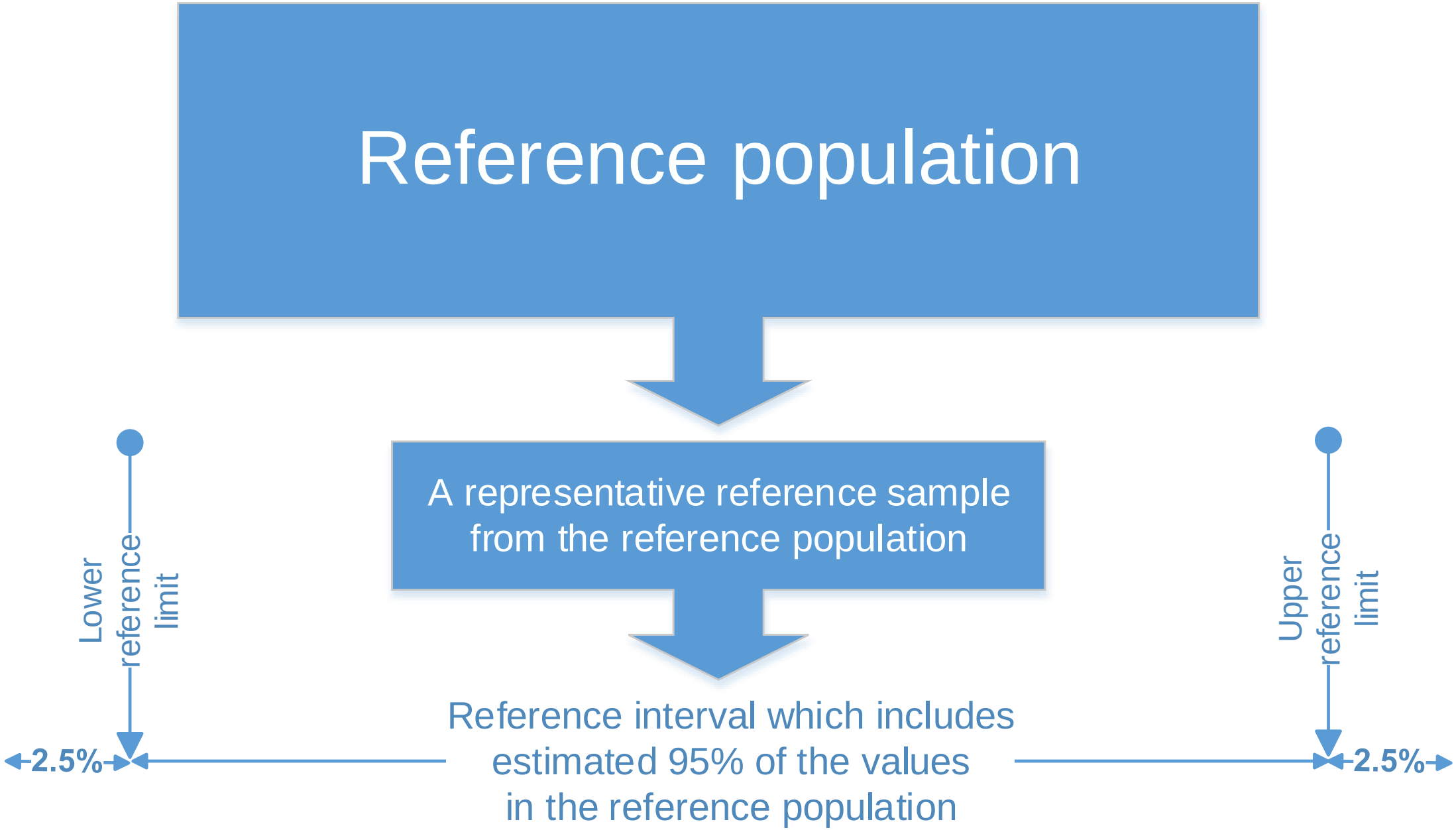
- Maintain open communication channels to the users of the laboratory
- Make sure they give you feedback on deficiencies in reference intervals, decision limits and reporting intervals
- Decisions to perform clinical verifications should be based on medical criteria and not on conceived demands of standards or accreditation authorities

Verification of reference intervals etc.

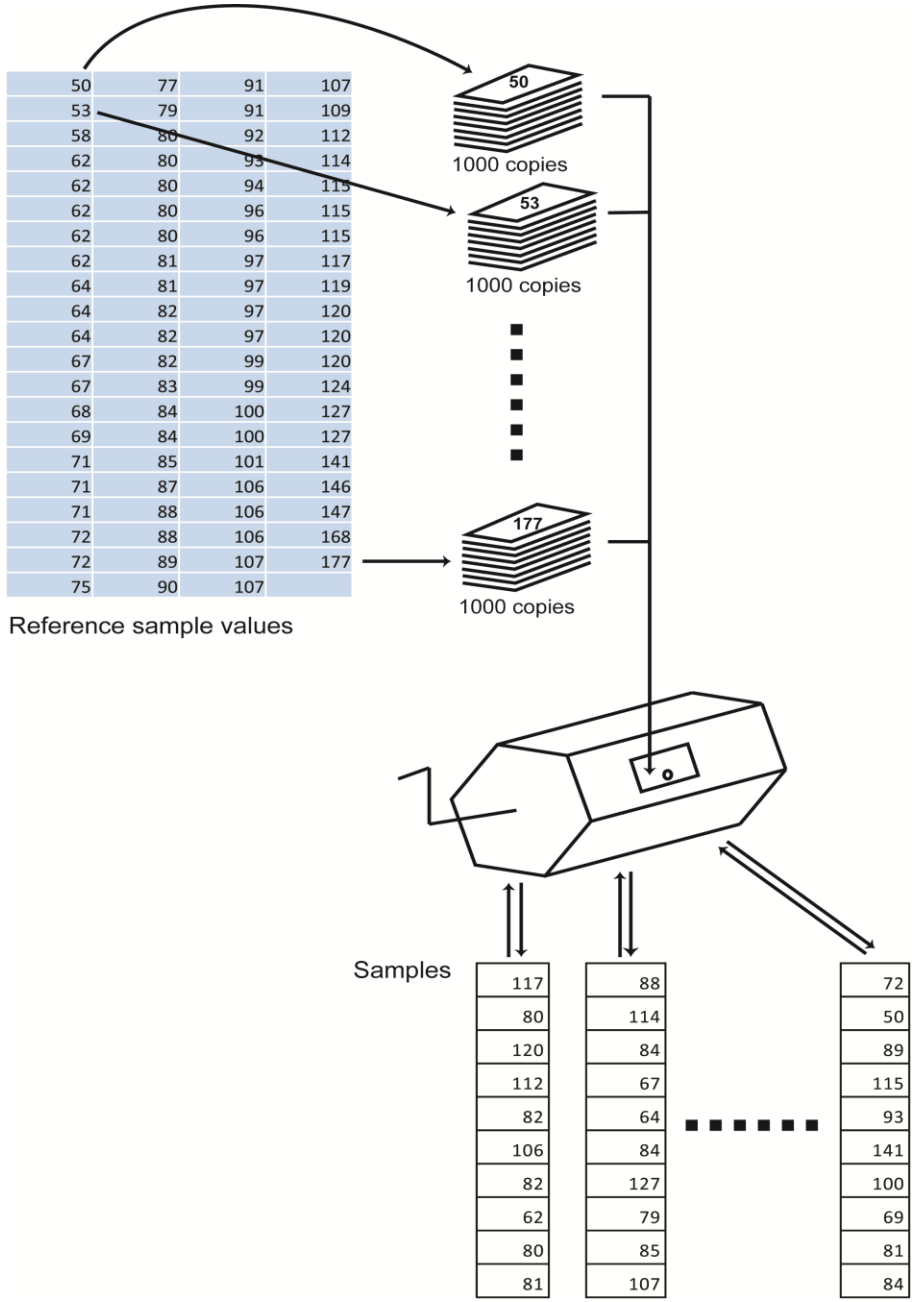
- Using (preferably random) samples from the population of interest
  - Preferably at least 120 samples
  - Minimum 40 samples
- Using big data
  - Select as many patient results from the laboratory database as you can
  - Remove probable outliers
    - Nephrology
    - Endocrinology
    - Oncology
    - Intensive care
  - Prefer results from primary care or hospital reception

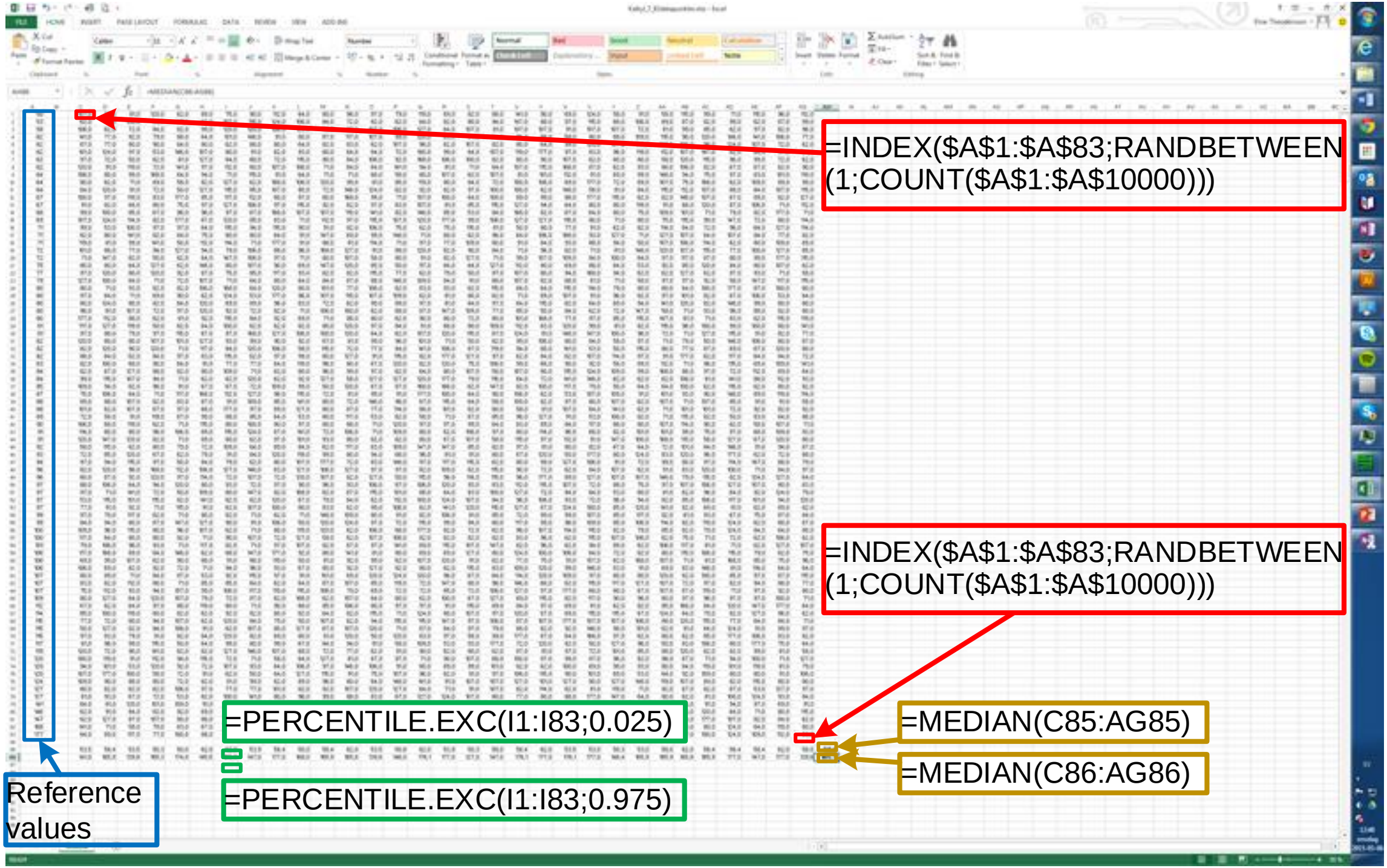
Normal distribution

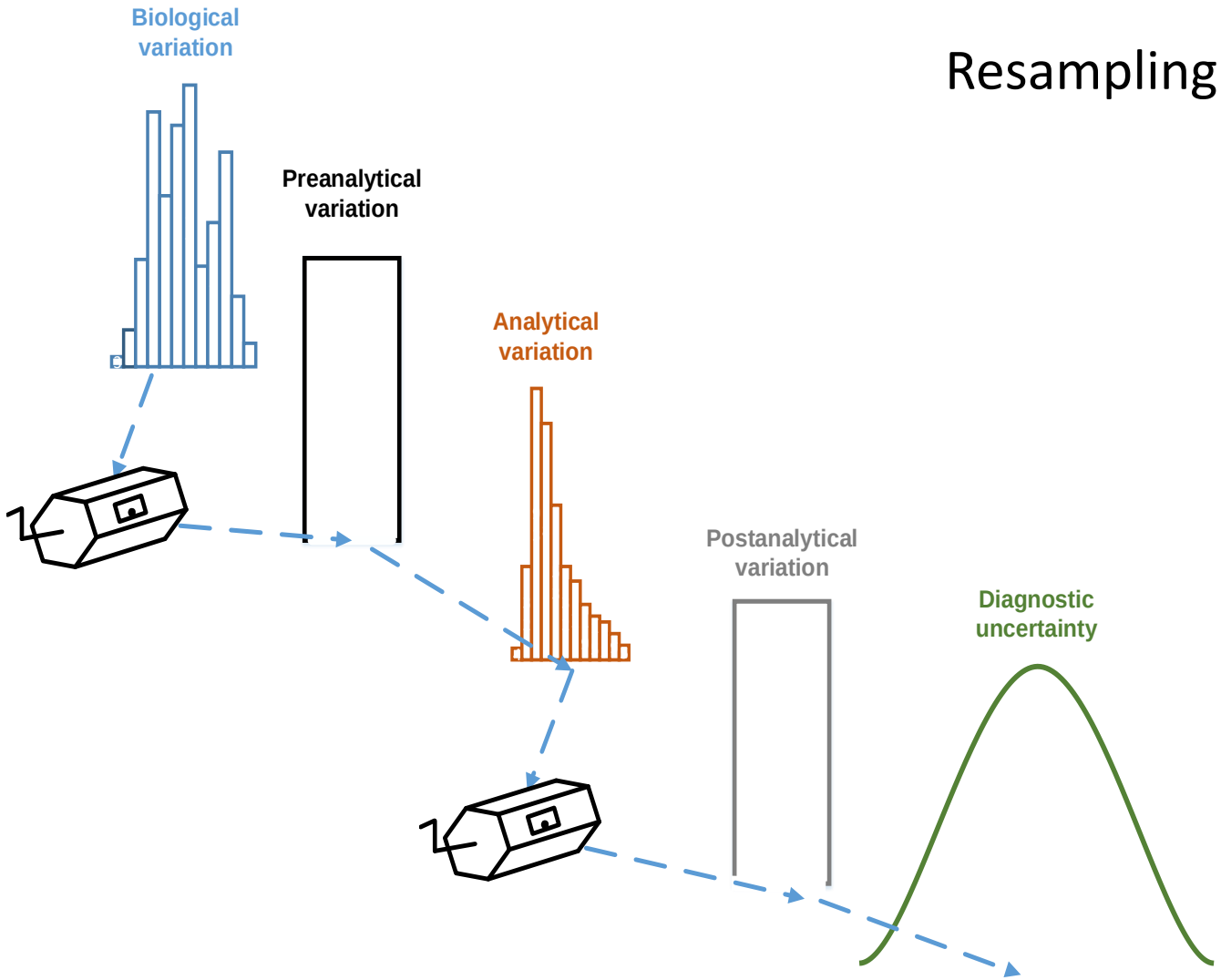



Reference population
A representative reference sample from the reference population
Lower reference limit
Upper reference limit
2.5%
Reference interval which includes estimated 95% of the values in the reference population
2.5%

Resampling techniques

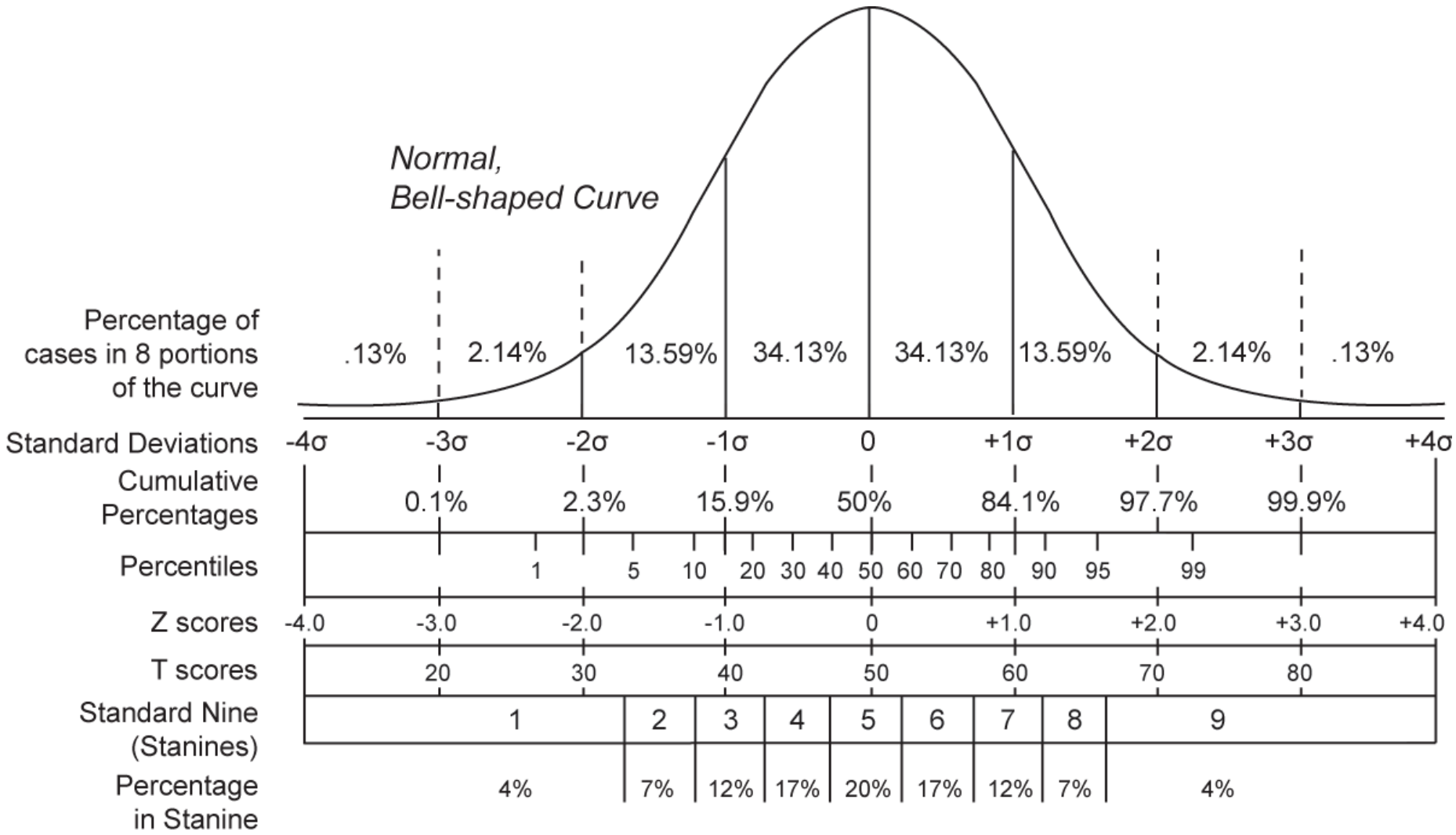



=INDEX($A$1:$A$83;RANDBETWEEN(1;COUNT($A$1:$A$10000)))
=INDEX($A$1:$A$83;RANDBETWEEN(1;COUNT($A$1:$A$10000)))
=PERCENTILE.EXC(I1:I83;0.025)
=PERCENTILE.EXC(I1:I83;0.975)
=MEDIAN(C85:AG85)
=MEDIAN(C86:AG86)
Reference values

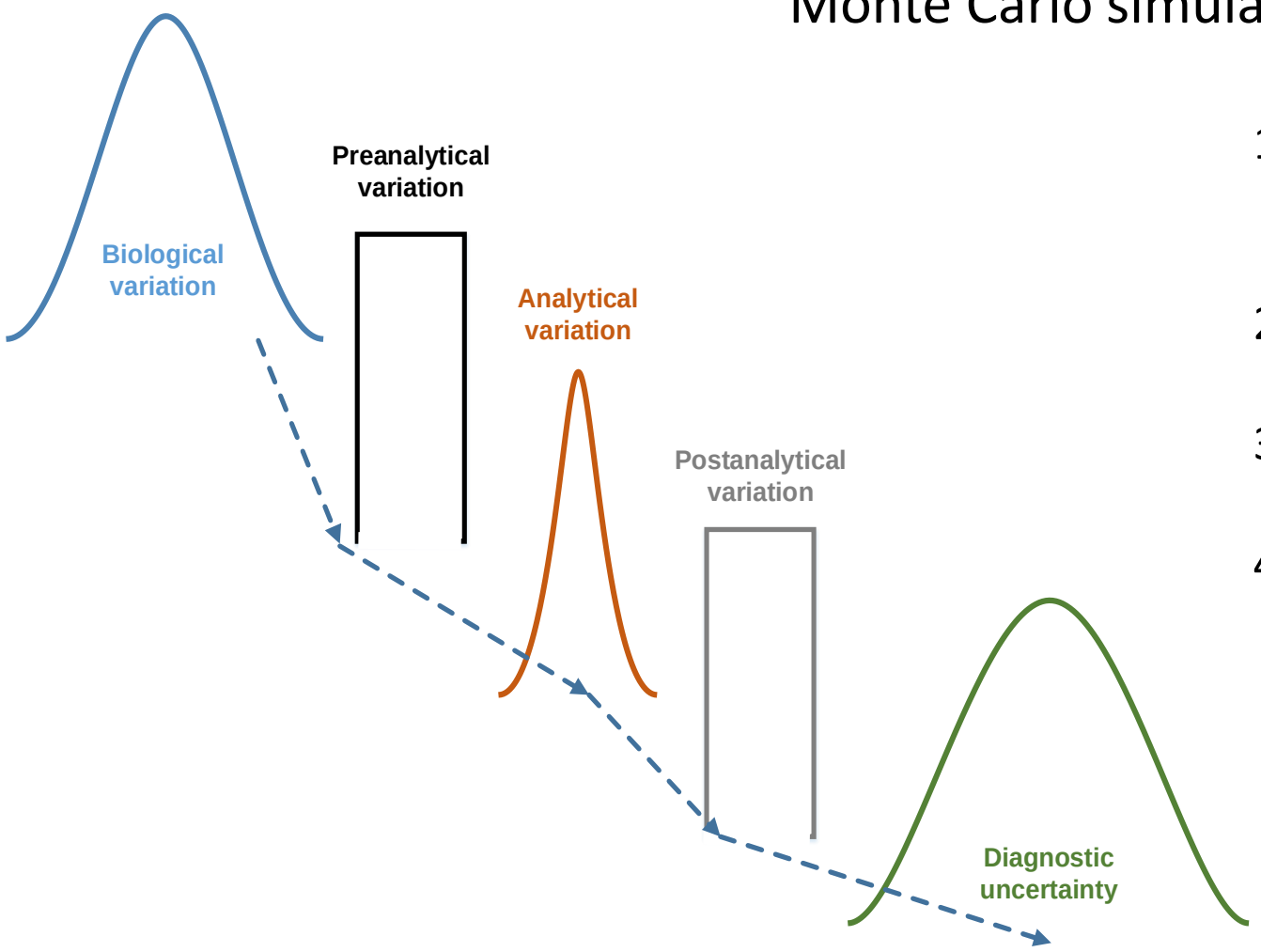


Resampling estimation of **diagnostic uncertainty**

1. No mathematical function (output function) is needed to evaluate the diagnostic uncertainty
2. No assumptions about the input quantities is needed in addition to the assumption that they follow a Gaussian distribution
3. There is no need to calculate partial derivatives
4. It is unaffected by partial derivatives that vanish when estimating input quantities


Normal,
Bell-shaped Curve
Percentage of cases in 8 portions of the curve
.13%
2.14%
13.59%
34.13%
34.13%
13.59%
2.14%
.13%
Standard Deviations
-4σ
-3σ
-2σ
-1σ
0
+1σ
+2σ
+3σ
+4σ
Cumulative Percentages
0.1%
2.3%
15.9%
50%
84.1%
97.7%
99.9%
Percentiles
1
5
10
20
30
40
50
60
70
80
90
95
99
Z scores
-4.0
-3.0
-2.0
-1.0
0
+1.0
+2.0
+3.0
+4.0
T scores
20
30
40
50
60
70
80
Standard Nine (Stanines)
1
2
3
4
5
6
7
8
9
Percentage in Stanine
4%
7%
12%
17%
20%
17%
12%
7%
4%

Monte Carlo simulation of **diagnostic uncertainty**



1. Gaussian distribution is needed to evaluate the diagnostic uncertainty
2. The input quantities are assumed to follow a Gaussian distribution
3. Calculation of partial derivatives needed
4. Affected by partial derivatives that vanish when estimating input quantities