Association of British Clinical Diabetologists Autumn Meeting

Blood glucose meter accuracy – what it is, measurement and interpretation.

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Objectives

To explain and discuss ACCURACY of blood glucose meter systems

To show/discuss:

- The basics of accuracy and performance, and why accuracy is important.
- Not all systems are the same, why systems give different results.
- How to measure, analyze and display accuracy
- Current minimum accuracy regulatory requirements
- How to assess/interpret the validity of publications evaluating accuracy
- Common questions or statements relating to accuracy

What is accuracy and why it is important

- Accuracy – “closeness of the agreement between the results of a measurement and a true value of the ‘thing’ being measured”
- Accuracy is the basis of correct therapy decisions and allows reliable monitoring.
- Accuracy applies to system CE marking (launch minimum requirements), day to day results, and comparative publications.
- Accuracy is one part of blood glucose meter system performance and clinical utility, and is determined by a balance of multiple criteria.

Point of care blood glucose testing

The evolution of POC blood glucose tests

- No Wiping
- No Timing
- Small sample volumes (<1µl)
- Capillary fill
- Insufficient sample detection
- Quicker (<5 secs)
- Meter features

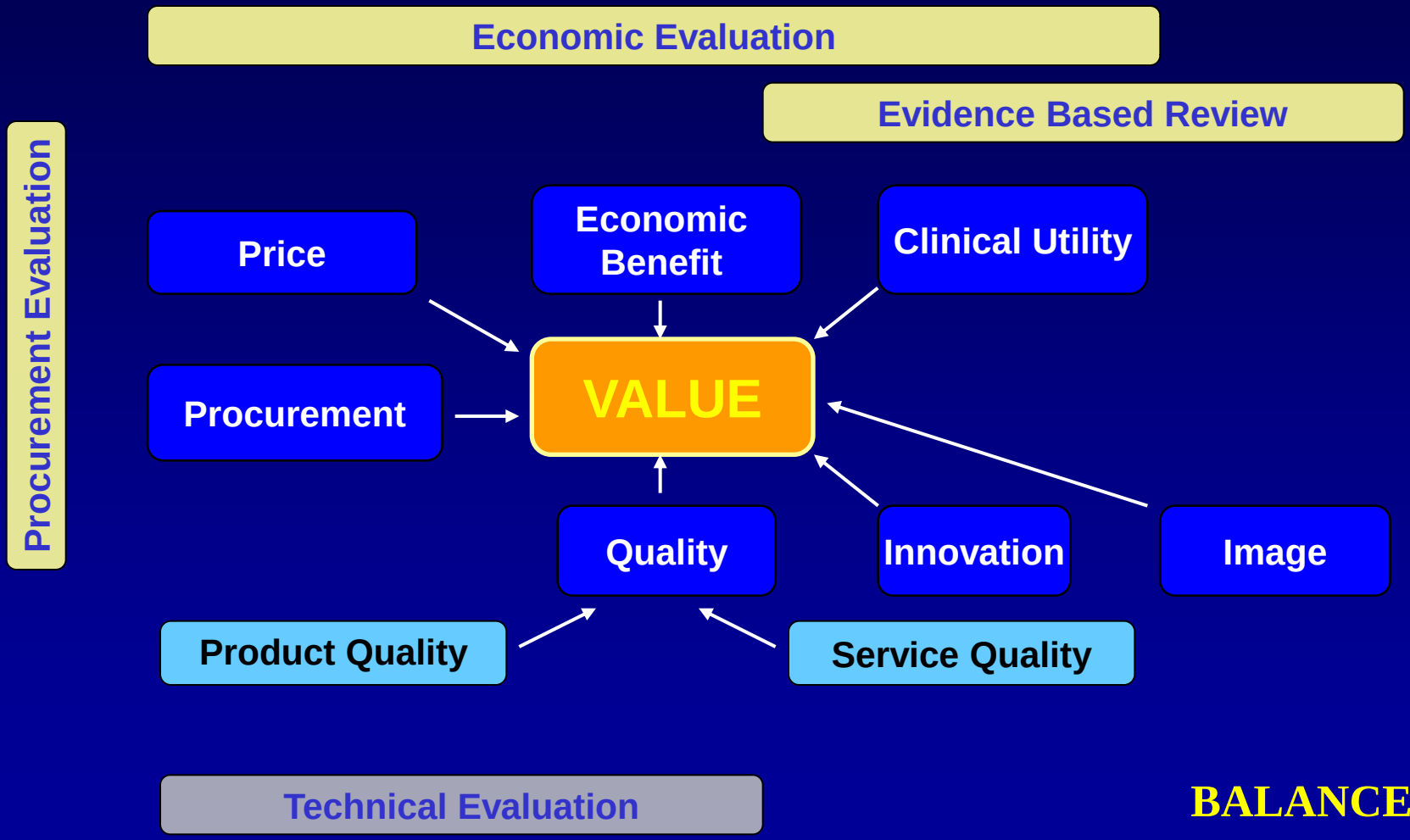
- Automatic or no calibration
- Simpler operation
- Fewer operator dependent steps
- Error messages and procedural controls
- Memory/connectivity

Glucose meter systems: important selection features

- Accuracy and precision COST !!
- Ease to use, operator dependent steps
- What does the healthcare professional recommend

- Sample volume, under dose protection
- Speed
- Calibration
- Interferences
  - effects of haematocrit, and oxygen,
  - effects of drugs, other sugars, and reducing substances
- Stability and test strip presentation
- Complexity - set up, size of memory, ease of access to results, data presentation
- Customer support, training, instructions for use
- Quality control **BALANCE !**

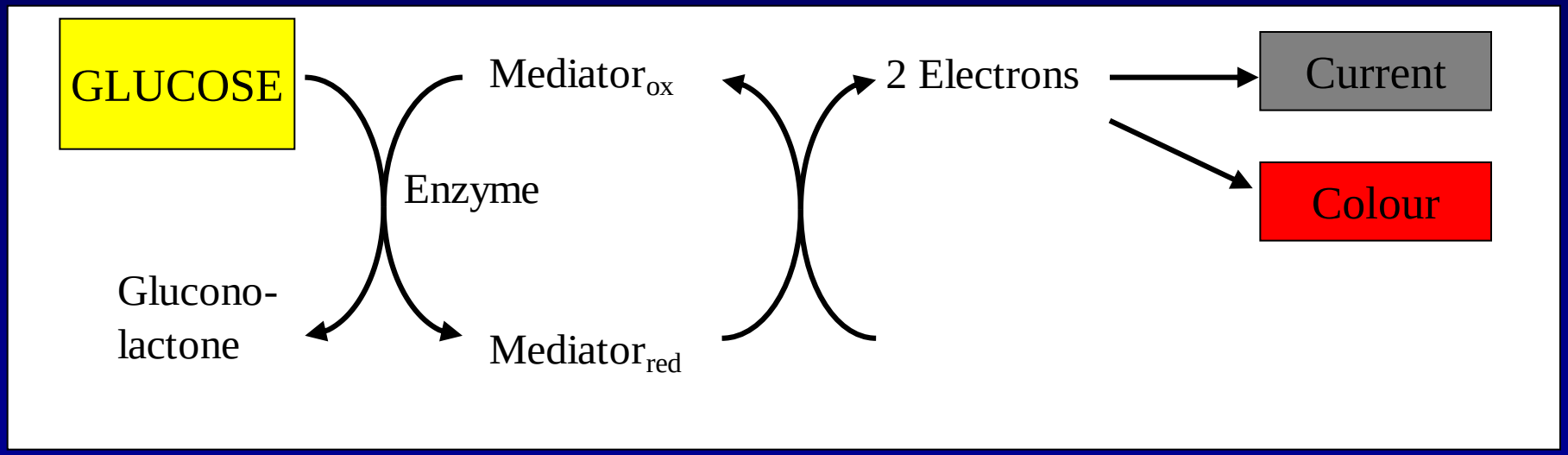
Considerations in blood glucose meter testing



BALANCE !

Why meters and strips have different characteristics

Reactions occurring in modern glucose strip technologies



Strips are based on the enzymes Glucose Oxidase (GO) or Glucose dehydrogenase (GDH) Different characteristics of enzymes, cofactors, reactions, mediators, strip constituents and architecture, diffusion etc
Many different mediator systems used.

Why laboratory assays and BGMs are different.

Laboratory based assays

- Centrifuged sample (red cells removed), diluted
- Minutes
- Liquid phase, fully buffered coupled reagents,
- Reactions at equilibrium, not diffusion limited
- Temperature controlled
- Accurate, volume pipetting

Glucose meter systems

- Whole blood sample, neat, <1ul
- Seconds
- Dry phase regents
- Non equilibrium, diffusion limited reactions
- Temperature corrected
- Volumes determined by disposable strips/electrodes

Implications of inaccuracy and imprecision

- An accurate & precise system is of no use unless actually, and correctly, used by the patient.
- Glucose monitoring is of no use unless something is done with the result and it leads to appropriate management

Accuracy relates to possible better treatment and outcome.

Accuracy & imprecision potentially influence:

- dosing errors in treatment
  - (insulin levels, hypoglycaemic and hyperglycaemic episodes)
- incidence of long term complications
- value and healthcare economics

Frequency of insulin dosing errors as a function of glucose measurement error

	Total glucose meter analytical error allowed		
	10%	15%	20%
Error in insulin dose			
Moderate	0.2%	2.0%	6.1%
Large	0.0%	0.02%	0.3%

Karon et al. Clinical Chemistry July 2010

Standards dealing with blood glucose meter system performance and accuracy

- ISO 15197: In vitro diagnostic test systems—requirements for blood glucose monitoring systems for self-testing in managing diabetes mellitus.

- POCT12-A3: Point-of-Care Blood Glucose Testing in Acute and Chronic Care Facilities; Approved Guideline— Third Edition (Formerly C30-A2). From the Clinical and Laboratory Standards Institute

- Two FDA discussion documents 2014 a) OTC b) POC healthcare professionals.

In vitro diagnostic test systems – Requirements for blood glucose monitoring systems for self testing in managing diabetes mellitus (ISO 15197:2013)

- EN ISO 15197:2013, Published on 30th June 2013, Supersedes BS EN ISO 15197:2003 which is withdrawn
- A 36 month transition period is recommended preceding mandatory compliance (Many glucose meters on the market at the time of publication were developed under the previous edition and may not meet the new requirements). ISO 15197 revision in force 2016.
- FDA discussion document May 2014 suggests tighter accuracy criteria.

The new ISO 15197:2013 standard and major differences from ISO 15197:2003

- Minimum system accuracy performance criteria

- Hematocrit evaluation
- Other interfering substances
- User performance evaluation

Accuracy criteria
CE marking and ISO 15197 2013

- ISO 15197 defines accuracy by the percentage of results within +/- 0.83 mmol/L (15 mg/dL) for glucose values < 5.55 mmol/L (<100 mg/dL), and within +/- 15% for glucose concentrations ≥ 5.55 mmol/L.

Freckmann et al, J Diabetes Science Technology 6, Sept 2012

- 20% of CE marked systems do not conform to 2003 ISO std, 50% do not meet new 2013 std
- Low cost systems; 37% do not conform to 2003 ISO std, 73% do not meet new 2013 std

Definitions: Analytical and clinical accuracy

- Analytical accuracy – "How closely the blood glucose measurement matches the true value"
- Clinical accuracy – "How well blood glucose measurements enable correct therapy decisions"

- Accuracy, trueness and precision.
- A system is accurate if it exhibits both 'trueness' and 'precision'.

- Trueness – "The closeness of the average of single results to the true value"
- Precision – "The closeness of agreement between single results" ie how closely individual measurements cluster.

Differences in meter accuracy and imprecision

Accuracy - perceived as a given

Imprecision - related to system and number of operator dependent steps

The more operator dependent steps the more potential for error

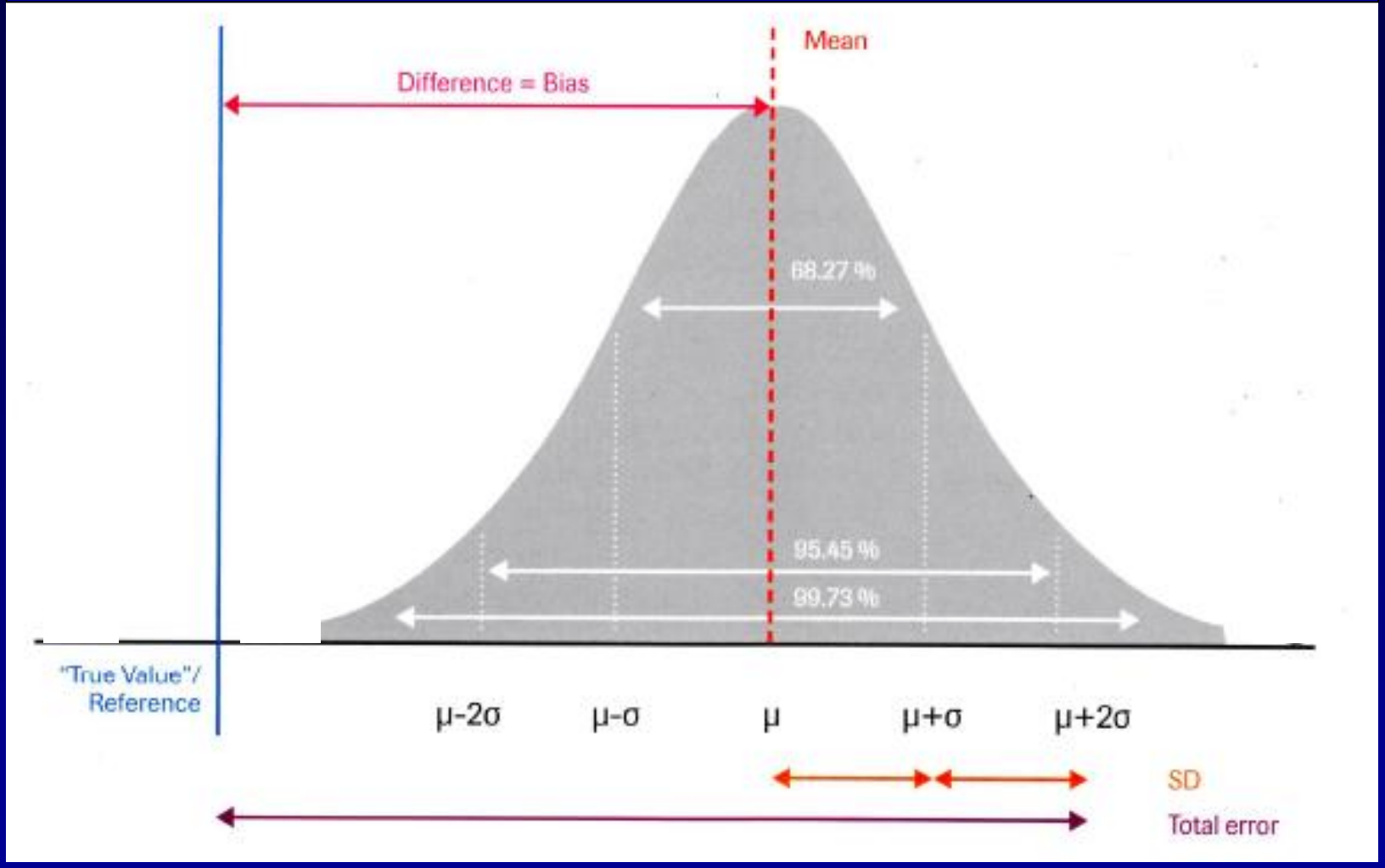
CE marking does not mean systems have the same or consistent performance

Accurate and precise

Precise but not accurate

Not accurate or precise

Trueness, precision and accuracy



Trueness	Systematic Error	Bias
Precision	Random Error	Standard Deviation
Accuracy	Total Error	Bias + 2x Standard Deviation

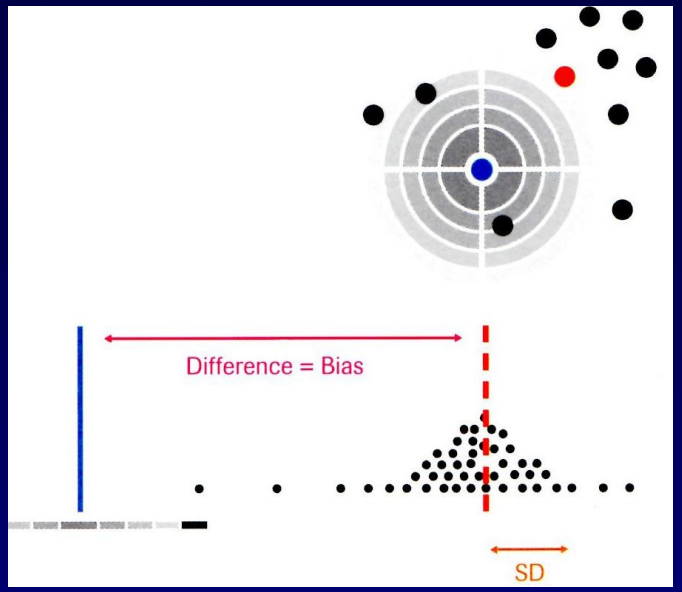
Accuracy, trueness and precision

Dependent on:

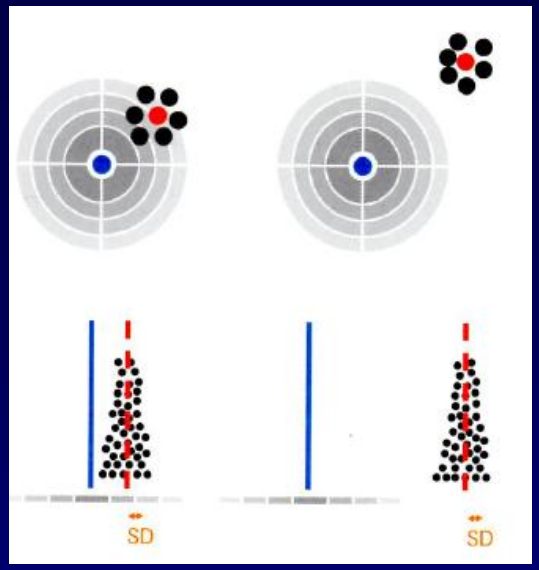
Systematic error - bias - Manufacturer meter system calibration and coding

Random error – imprecision - quality of strip design, chemistry, manufacture, operator dependency

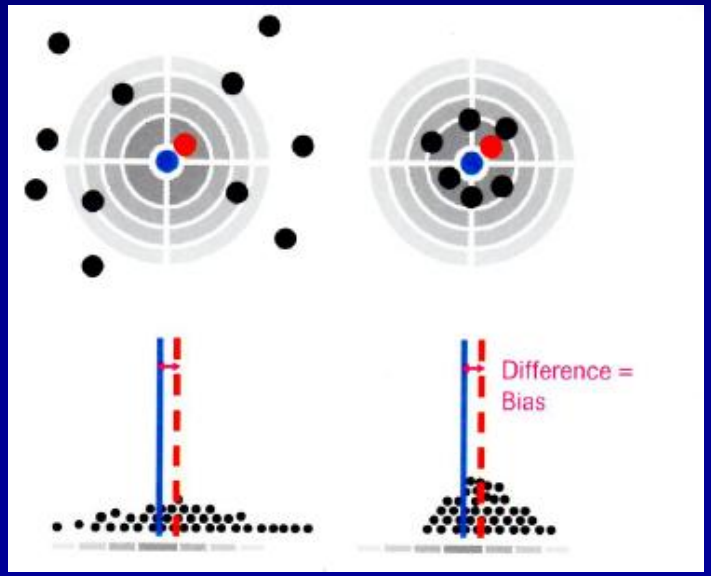
Consistency of manufacture, calibration and strip lot to lot variability



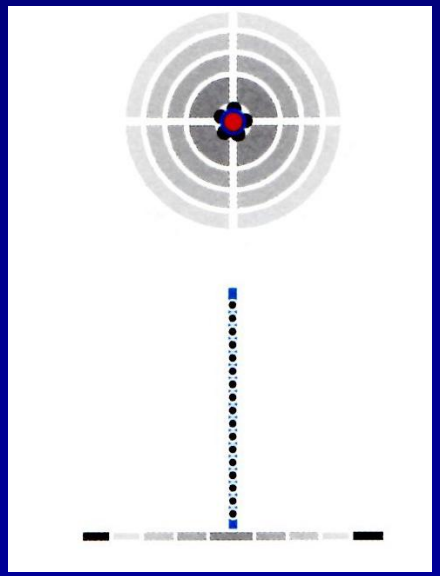
High systematic and high random error



High systematic and low random error



Low systematic and high random error



Low systematic and low random error

Influence of calibration on accuracy and bias

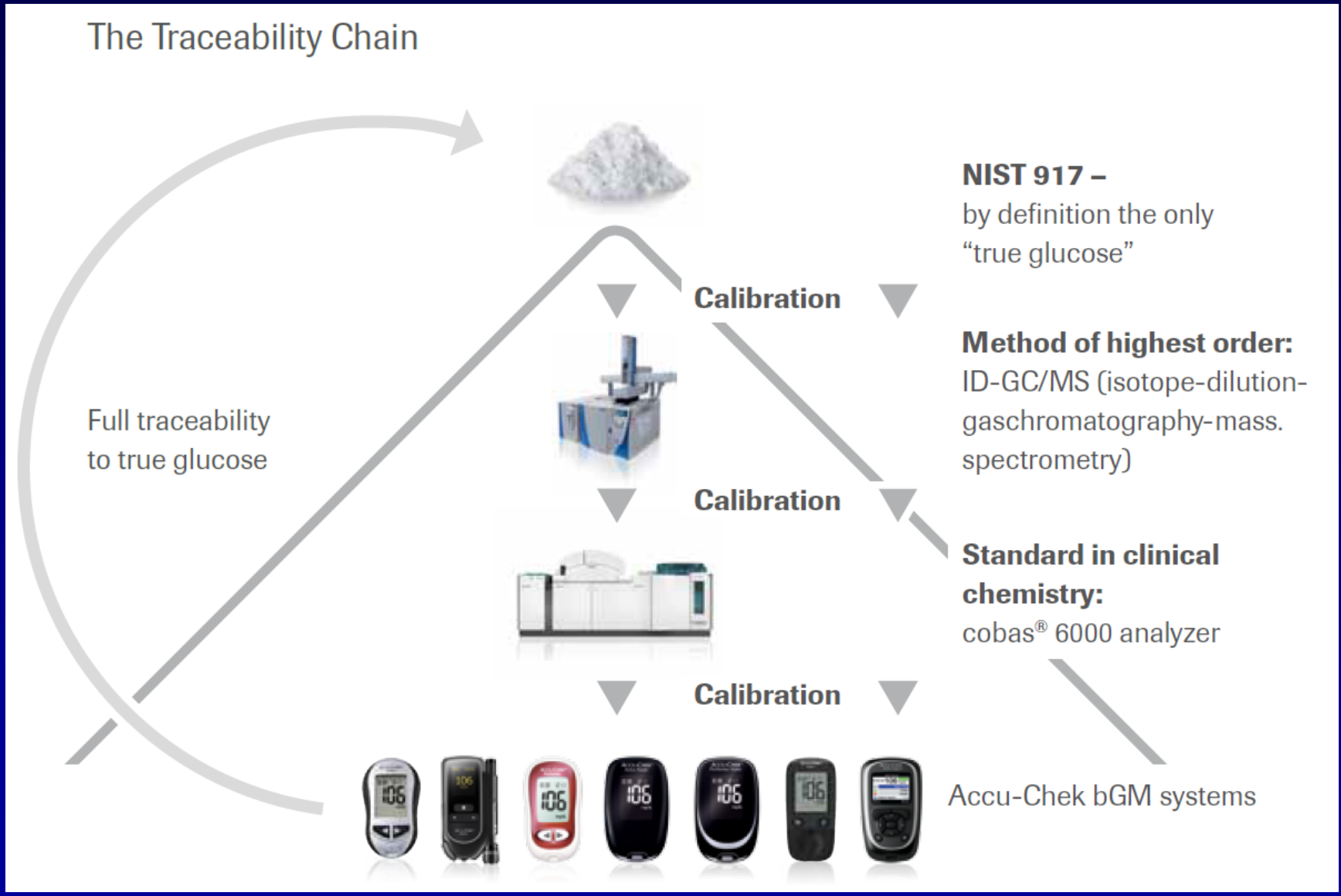
- What is calibration
- Conversion of the meter system response to a glucose concentration
- correlation of the meter system's readings with those of a 'standard' to ensure accuracy

- Which 'glucose assay' to calibrate against
- calibration against reference method
- listed in the Joint Committee for Traceability in Laboratory Medicine database
- isotope dilution gas chromatography mass spectrometry, YSI 'controversial'

- Traceability
- trueness of the reference method must be established by traceability to National Institute of Standards and Technology (NIST) materials or methods of higher order.
- certified reference materials for glucose in whole blood are not yet available

Traceability:

Meters to Lab comparison method to reference method to NIST std glucose



How to measure, analyse and display/represent accuracy

Analytical performance

- Measurement range, linearity
- Accuracy and imprecision
- Accuracy to which reference method
  - (hexokinase, glucose oxidase; plasma, whole blood)
- Bias, total error, imprecision, clinical error grid analysis

How to display meter analytical and clinical accuracy

a) A plot of the difference between individual results from meters against the mean of specific comparison values plotted as the dependent variable.

b) Tables of degree of meter results difference compared to the comparison method. For comparison glucose values

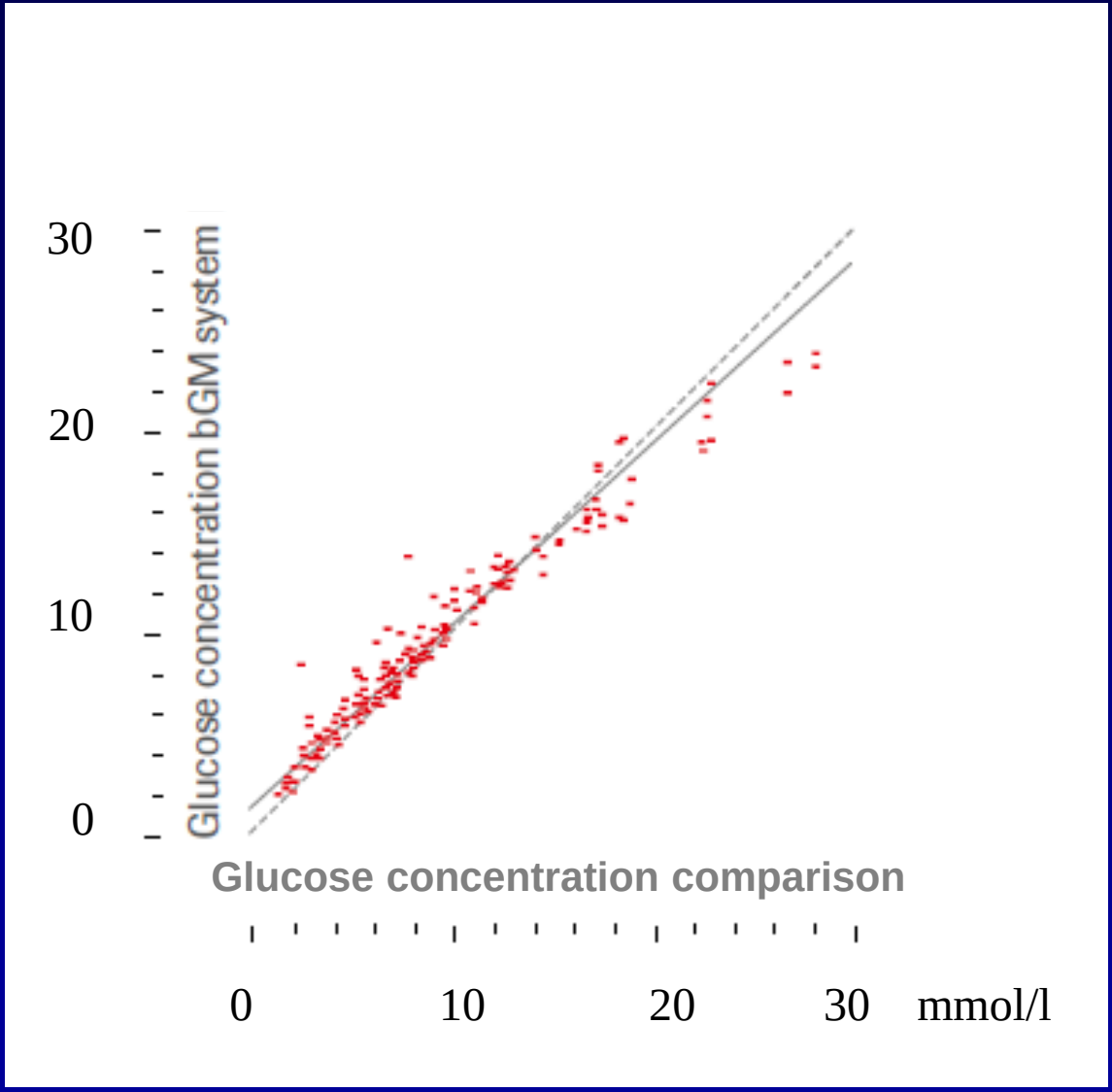
(i) < 5.55 mmol/L (100 mg/dL) showing the number of meter samples (%) within +/- 0.28 mmol/L (5 mg/dL), +/-0.56 mmol/l (10 mg/dL), +/- 0.83 mmol/L (15 mg/dL) of the comparison method.

(ii) ≥ 5.55 mmol/L providing the number of samples (%) within +/- 5%, 10%, 15%, 20% of the comparison method.

c) A summary of results identified as acceptable using current acceptance guidelines. 95% of results need to fall within acceptance criteria

d) A clinical accuracy assessment such as by Parkes or consensus error grid analysis. (outliers)

bGM system results against comparison method results

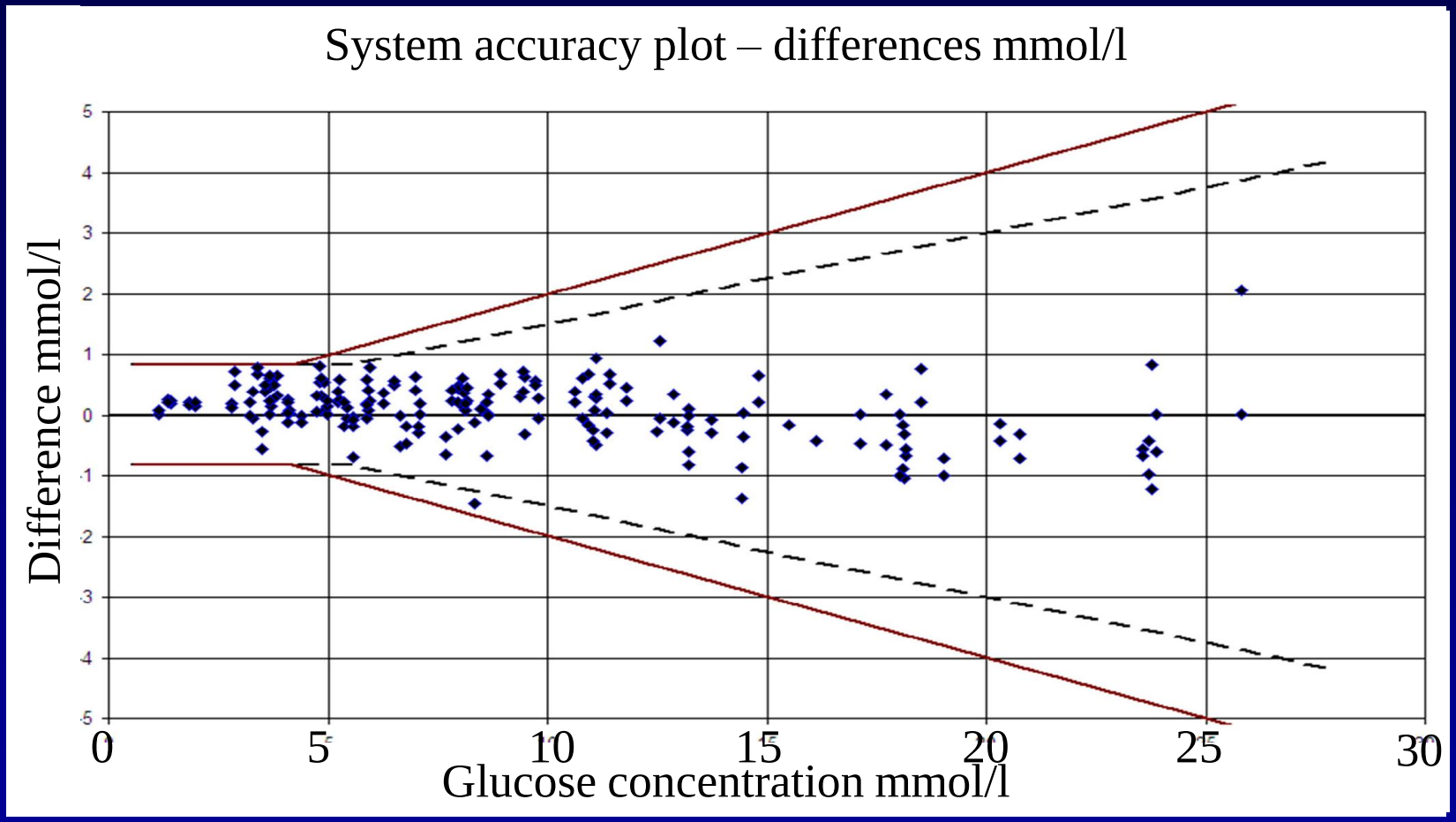


Number of samples and spread of glucose concentrations
(according to ISO 15197:2013)

- At least 100 fresh capillary samples, and 200 data points (for each of 3 lots of strips)
- Sufficient defined spread of results spanning the analytical range.
- % of results as in ISO 15197.
- Difficulty obtaining fresh samples with very high/low blood glucose concentrations

Percentage of samples	Glucose concentraion mmol/l (mg/dL)
5	≤ 2.77 (≤ 50)
15	> 2.77 – 4.44 (> 50 – 80)
20	> 4.44 – 6.66 (> 80 – 120)
30	> 6.66 – 11.10 (> 120 – 200)
15	> 11.10 – 16.65 (> 200 – 300)
10	> 16.65 – 22.20 (> 300 – 400)
5	> 22.20 (> 400)

Graphical analysis -minimum system accuracy performance criteria accuracy difference plot



Cut off: old 4.2 mmol/L (75 mg/dL) new 5.55 mmol/L (100 mg/dL)

Less than cut off: both ± 0.83 mmol/L (15 mg/dL),

Above cut off: old ± 20% new ± 15%

Meter results regarded as ‘acceptable’ by ISO 15197 2013

	‘acceptable’ results within
2 mmol/L	1.2 to 2.8
3 mmol/L	2.2 to 3.8
4 mmol/L	3.2 to 4.8
5 mmol/L	4.2 to 5.8
6 mmol/L	5.1 to 6.9
10 mmol/L	8.5 to 11.5
15 mmol/L	12.8 to 17.2
20 mmol/L	17.0 to 23.0

ISO 15197:2013 Presentation of results for system accuracy

Table 4 — System accuracy results for glucose concentration < 5,55 mmol/l (<100 mg/dl)

Within ± 0,28 mmol/l (Within ± 5 mg/dl)	Within ± 0,56 mmol/l (Within ± 10 mg/dl)	Within ± 0,83 mmol/l (Within ± 15 mg/dl)
68/150 (45,3 %)	105/150 (70,0 %)	143/150 (95,3 %)

Table 5 — System accuracy results for glucose concentration ≥ 5,55 mmol/l (≥100 mg/dl)

Within ± 5 %	Within ± 10 %	Within ± 15 %
221/450 (49,1 %)	383/450 (85,1 %)	439/450 (97,6 %)

Table 6 — System accuracy results for glucose concentrations between X,XX mmol/l (XX mg/dl) and YY,Y mmol/l (YYY mg/dl)

Within ±0,83 mmol/l or ±15 % (Within ±15 mg/dl or ±15 %)
582/600 (97,0 %)

NOTE X,XX mmol/l (XX mg/dl) represents the lowest glucose reference value and YY,Y mmol/l (YYY mg/dl) represents the highest glucose reference value

Tables 4,5,6 illustrate the presentation of results for an evaluation in which 100 subjects were enrolled. Three reagent lots were used, providing 600 measured values.

Clinical accuracy - Consensus Error Grid

Zone A: No effect on clinical action

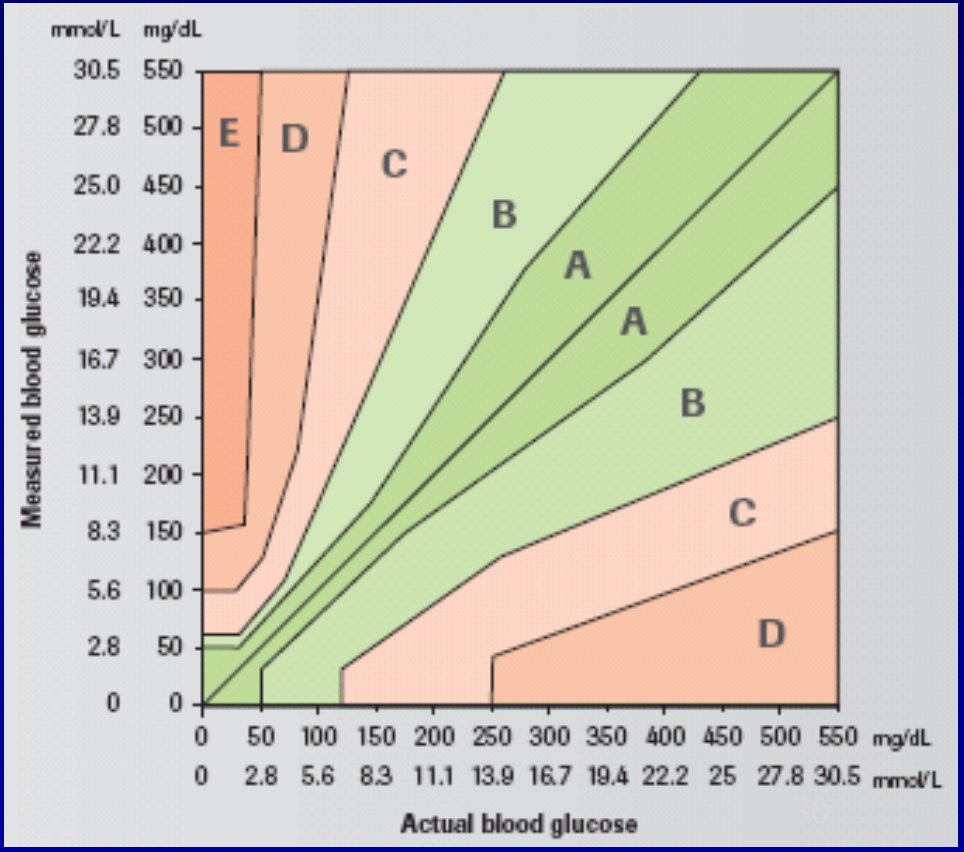
Zone B: Altered clinical action - little or no effect on clinical outcome

Zone C: Altered clinical action - likely to affect clinical outcome

Zone D: Altered clinical action - could have significant medical risk

Zone E: Altered clinical action - could have dangerous consequences

ISO 15197 2013: 99% of results in zones A and B of Consensus Error Grid for the pooled 3 strip lots (n = 600)



Major Differences between the 'new' ISO 15197:2013 and the 'old' ISO 15197:2003

6.3.3 minimum system accuracy performance criteria

'old' ISO 15197 2003

- 95% of results

± 0.83 mmol/L (15 mg/dL)
glucose < 4.2 mmol/L (75 mg/dL)

± 20% glucose > 4.2 mmol/L

'new' ISO 15197 2013

- 95% of results for each lot

± 0.83 mmol/L (15 mg/dL)
glucose < 5.55 mmol/L (100 mg/dL)

± 15% glucose > 5.55 mmol/L(100 mg/dL)

99% of results in zones A and B of Consensus Error Grid for type 1 diabetes for the **pooled lots** (~ ± 20%)

Precision and Accuracy experiments have to use 3 lots of strips instead of 1 lot.

Self-monitoring blood glucose test systems for over-the-counter use
Draft guidance (2014)for industry and FDA staff

Distributed for comments 2014

- 95% of SMBG results within +/- 15% ref across claimed measuring range (at least 2.8 to 22.2 mmol/l, 50-400 mg/dL) 99% within +/- 20%

- Tables within +/- 5, 7, 10, 15 mg/dL, within +/- 5, 10, 15, 20%

- Single evaluation, 350 subjects, fresh capillary samples, intended users obtain samples and perform test using only IFUs. >10% users naïve to SMBGs
- 3 test strip lots, typical shipping and handling conditions
- Recommended 20-60% haematocrit range (30-55% unacceptable)

- POC hospital systems: 99% within +/- 10% of ref for glucose ≥ 3.9 mmol/l (70 mg/dl) and within +/- 7 mg/dL (0.39 mmol/l) at glucose < 3.9 mmol/l.

Assessing the quality of publications evaluating the accuracy of blood glucose monitoring systems

Hypothesis

"Assessing the quality of the numerous publications evaluating the accuracy of blood monitoring systems is NOT easy and it can be DIFFICULT to compare different systems and draw conclusions about their accuracy"

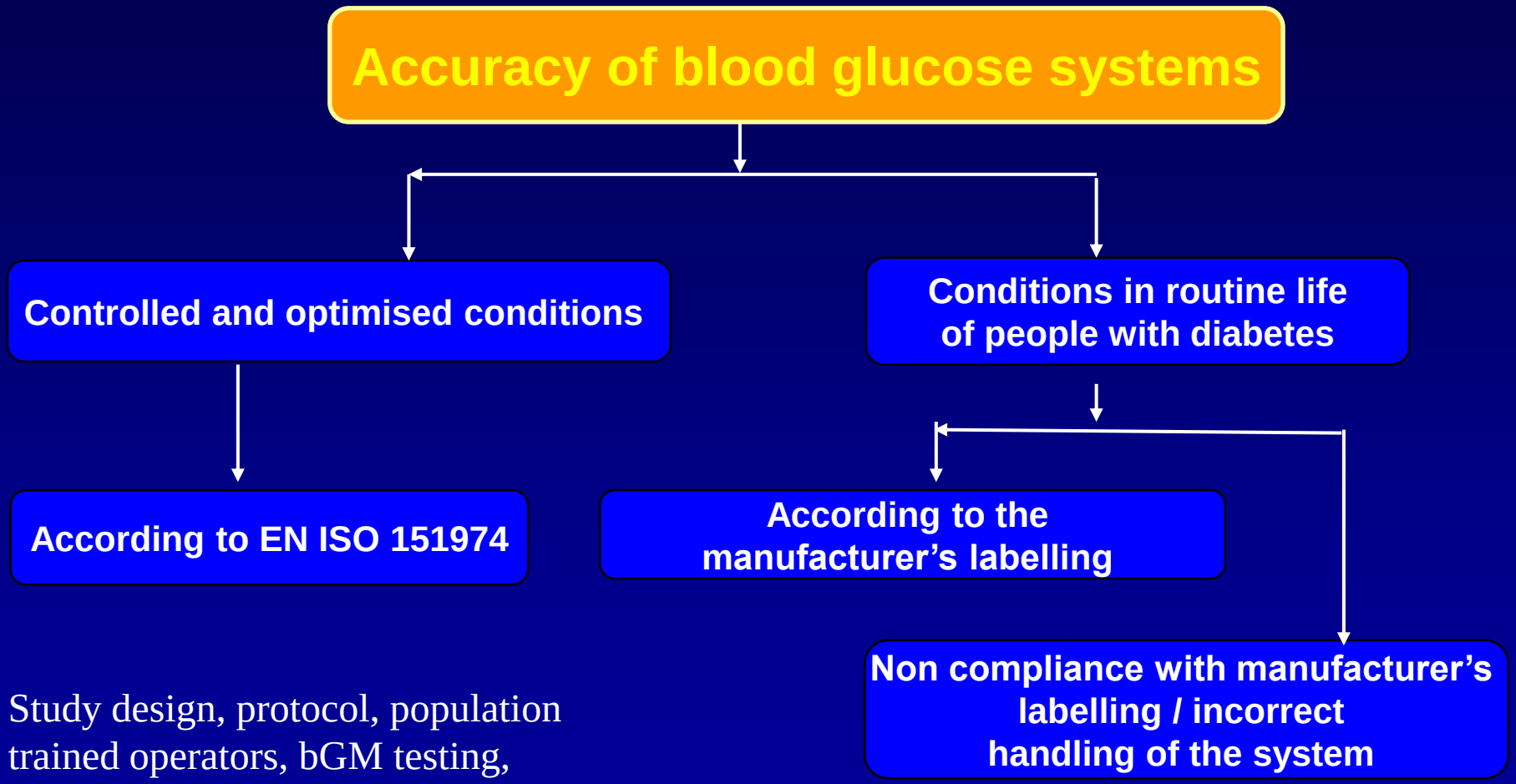
Thorpe GH: Diabetes Technology and Therapeutics : Assessing the quality of publications evaluating the accuracy of blood glucose monitoring systems. Diabetes Technol Ther 2013; Mar (15) 3, 253-9

Accuracy checklist components

- Comparison method
- Comparing like with like samples
- Number of samples, who is doing test
- Spread of glucose concentrations
- Accuracy criteria
- Number of strip lots

- Full details provided
- Independency
- Concordance ISO 15197 (FDA guidance)

Possible evaluation ‘protocols’ in blood glucose meter testing



Study design, protocol, population trained operators, bGM testing, duplicates, sample collection storage, time, stability of samples and methods, etc

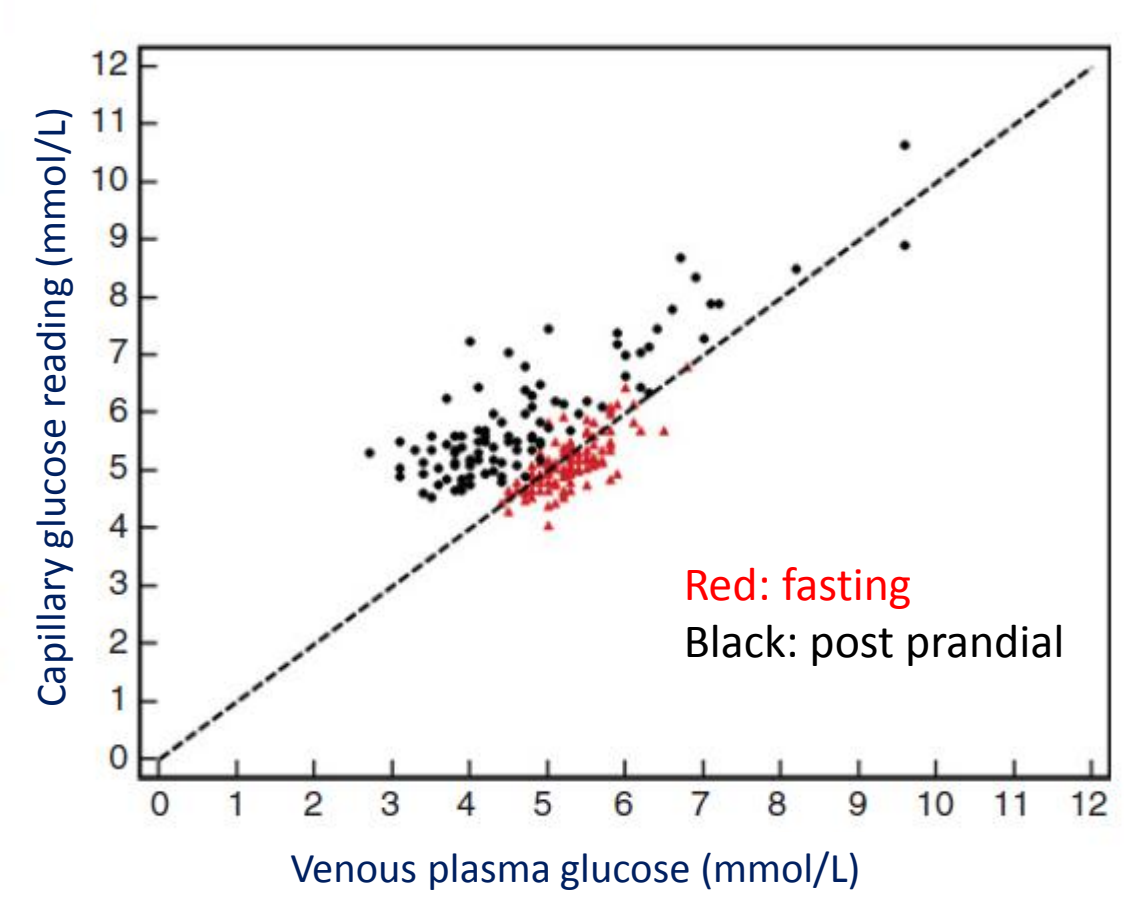
Comparison to what ?

- Comparison method
  - the manufacturer's standing measurement procedure should be used for method comparison (ISO 15197) ,
  - traceable to methods of higher order
  - Comparison method's imprecision, bias, total error, quality assurance
  - 5% differences are common if inappropriate comparison methods are used
  - Avoids the negative biases of approximately 4% reported for whole blood samples between YSI and ID/GC/MS
  - Comparative assays and standing measurement procedures are not generally reference methods
  - For Roche systems the standing measurement procedures is perchloric acid precipitation and consecutive measurement with hexokinase on a cobas 6000 which has been calibrated against isotope dilution gas chromatography (ID/GC/MS. YSI used by some other manufacturers.

Meter and comparison method samples

- Blood sample type and comparing ‘like with like’ samples
- Comparisons of ‘like’ fresh whole blood specimens. Ideally capillary versus capillary and split sample analysis
- Correct collection with minimal delay in analysis and post collection control of sample handling time
- Capillary and venous blood glucose levels should not be assumed to be equivalent, they may show differences of about 2% but there can be up to 30% differences in the postprandial state

Comparing capillary against venous samples

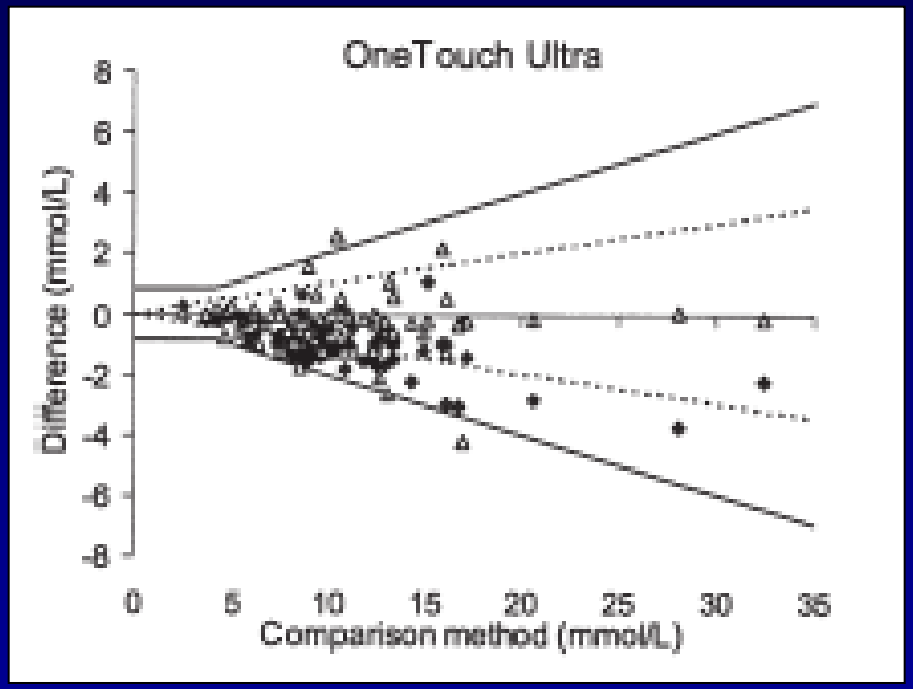


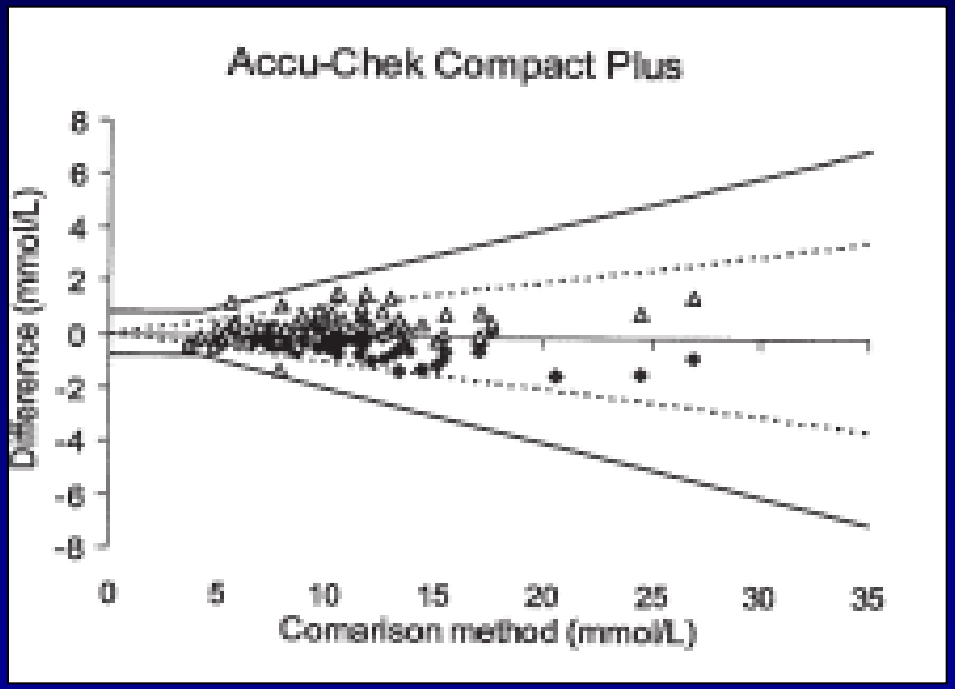
For fasting samples, there is some correlation between the two different sample types, deviations in the order of 1 mmol/L (18 mg/dL).

For post-prandial samples, the correlation is much worse and deviations up to 3 mmol/L (54 mg/dL) are typical.

Swaminathan et al. Ann Clin Biochem 2013; 50: 6–12.

Correlation of meter results with a laboratory comparison method





Provides a quick visual indication and comparison of accuracy over a range of glucose concentrations

Degree of meter results differences compared to the comparison method

Table 4 — System accuracy results for glucose concentration < 5,55 mmol/l (<100 mg/dl)

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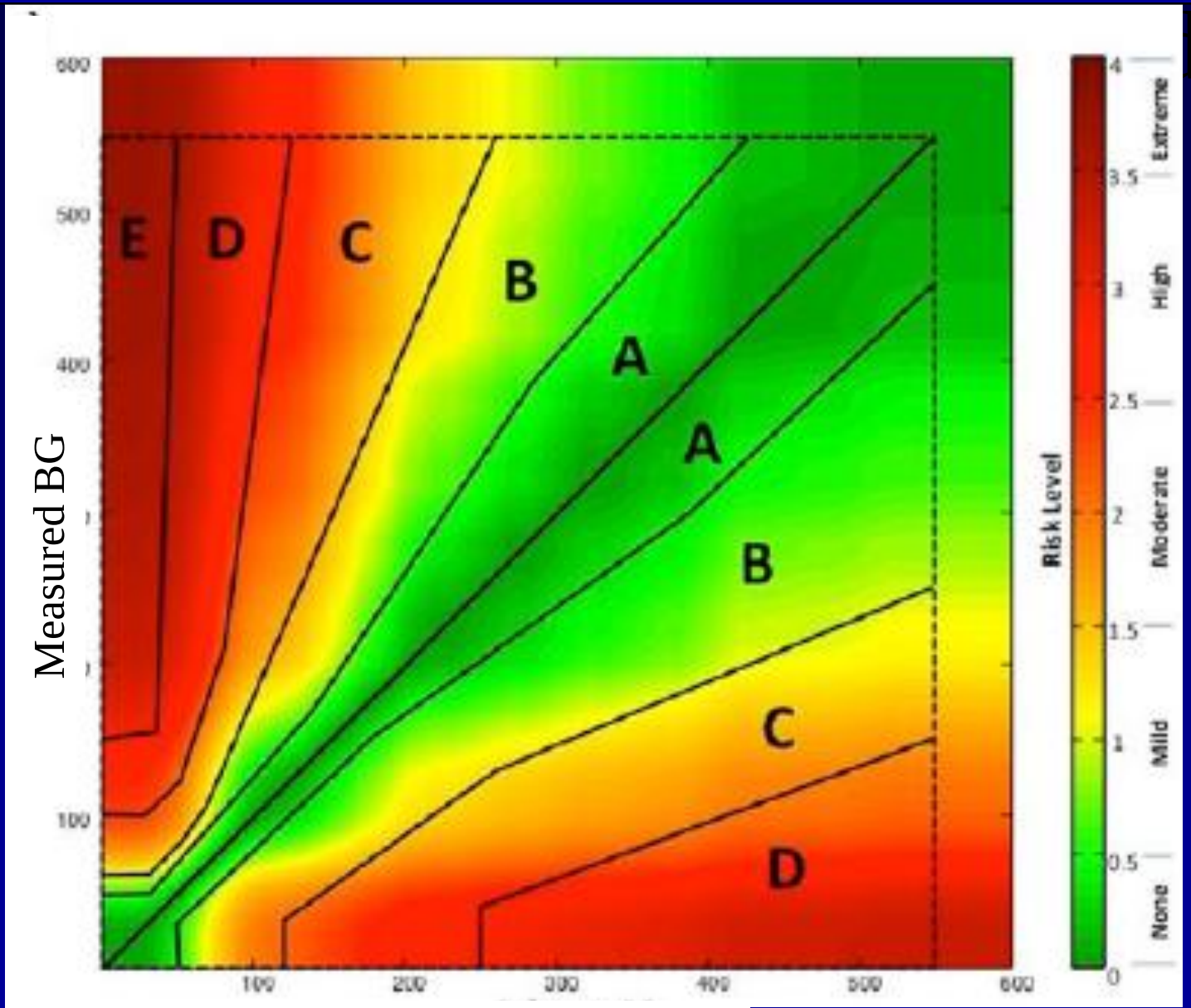
NOTE X,XX mmol/l (XX mg/dl) represents the lowest glucose reference value and YY,Y mmol/l (YYY mg/dl) represents the highest glucose reference value

Enables %s within stricter limits than existing standard (eg 5%/5mg/dl) to be compared FDA also 7 mg/dl and 20%

Computing the Surveillance Error Grid analysis

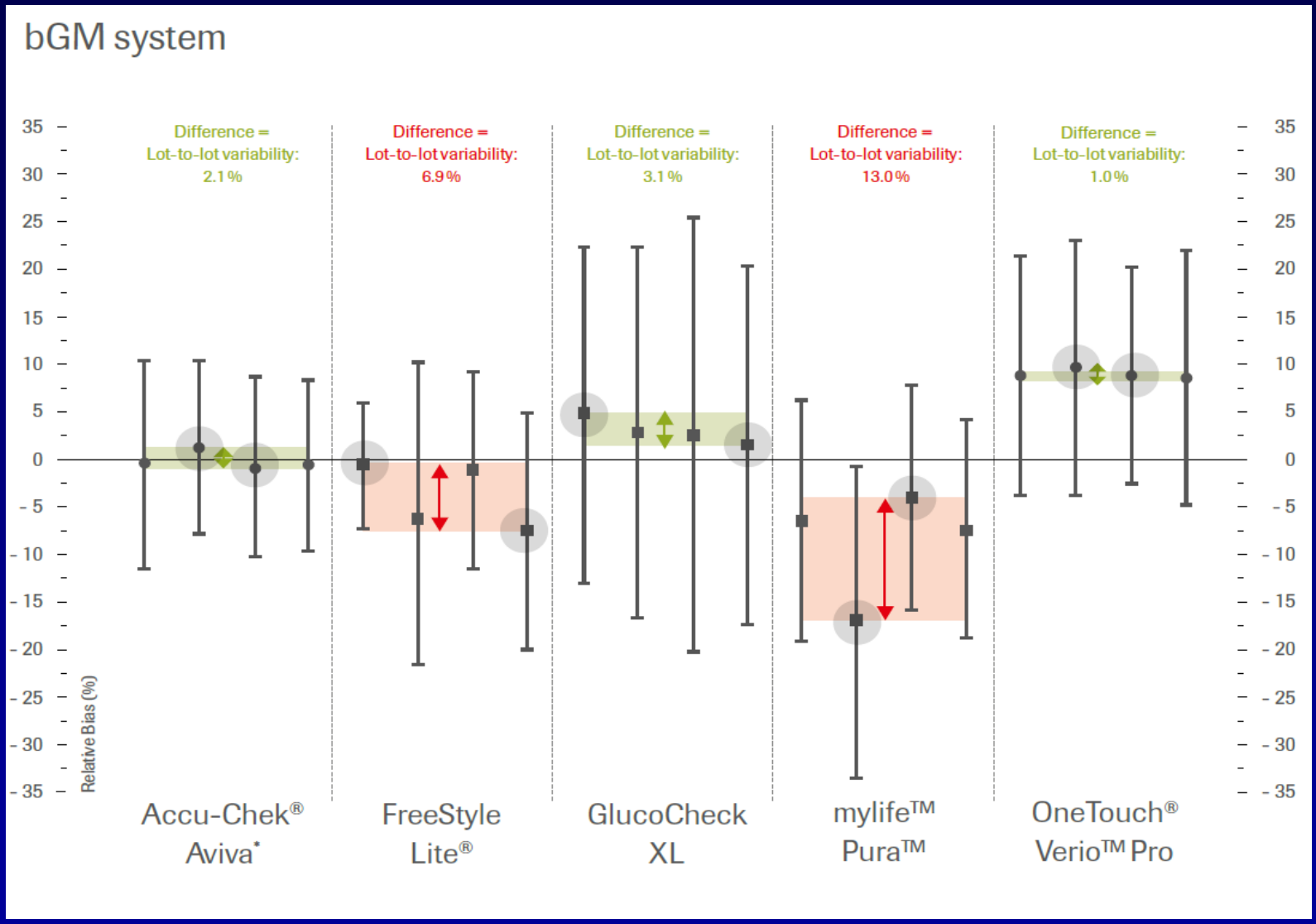


J Diabetes Sci Technol 2014 8: 673

Number of strip lots
(lot-to-lot variability)

- Use of several different lots, ideally 3. Low variability indicates robustness, reliability and consistency of accuracy
- Indicative of strips supplied via general supply chain / distribution channel. Representative of routine production and real world patient use. Not a snap shot of one lot supplied under special conditions (CE mark
- Lot to lot variability can be as big as differences between systems, >5% varying biases found in some systems lot to lot. Determined by the quality of production and quality checks/assurance
- Need for awareness of existence and magnitude of lot to lot variation. Important in CE marking, post launch surveillance and evaluation
- Constant bias can be dealt with. Strongly varying bias can present as an unknown factor and have a negative effect on blood glucose control as accommodation is not possible

Accuracy of different ‘lots’ of strips (lot to lot variability)



Baumstark A et al. J Diabetes Sci Technol. 2012 Sep 1;6(5):1076-86.

Understanding accuracy answers to questions/statements.

- “All blood glucose meter systems are accurate – they are all CE marked and performance won’t vary”.

- “When I repeat a test on my meter I don’t get exactly the same result!”
- “Testing the same sample on different meter systems gives different results. One meter is therefore giving the wrong result”.

- “How accurate is this meter system?” “ Is this system more accurate than that one”
- “Studies comparing the accuracies of different blood glucose meter systems give contradictory results - why is this and which do I believe?

- “Local laboratories can do quick small evaluations to determine accuracy”.
- “We’ll test this meter system against the one we already use to see if it’s accurate”.

Conclusions

- Accuracy is a very important part of blood glucose meter system performance
- Accuracy is complex and influenced by many factors
- Accuracy and its determination is often incompletely understood

- Checklists help raise awareness of important issues involved, aiding readers' examination of studies in more detail and drawing clear and valid conclusions from the increasing number of bG system evaluation publications

- A full understanding of accuracy provides an important perspective to correctly interpret differences between meter systems

- Blood glucose meter system accuracy studies should be interpreted with caution. Protocol differences and limitations explain why comparative accuracy studies can yield differing results.