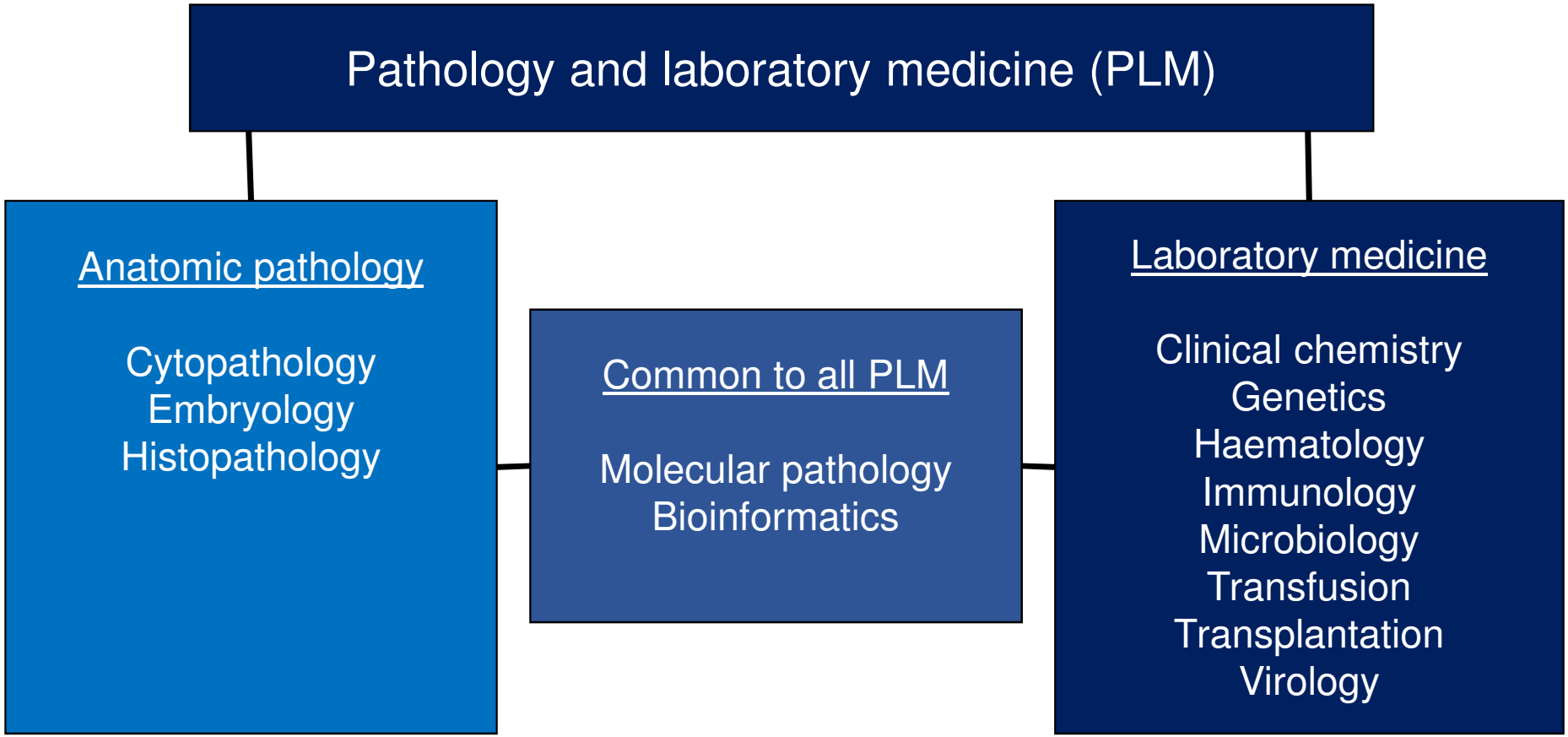
Traceability in laboratory medicine: a driver for accurate results for patient care

20 questions and answers for trainees in laboratory medicine

Prepared by the Joint Committee for Traceability in Laboratory Medicine (JCTLM)

www.jctlm.org

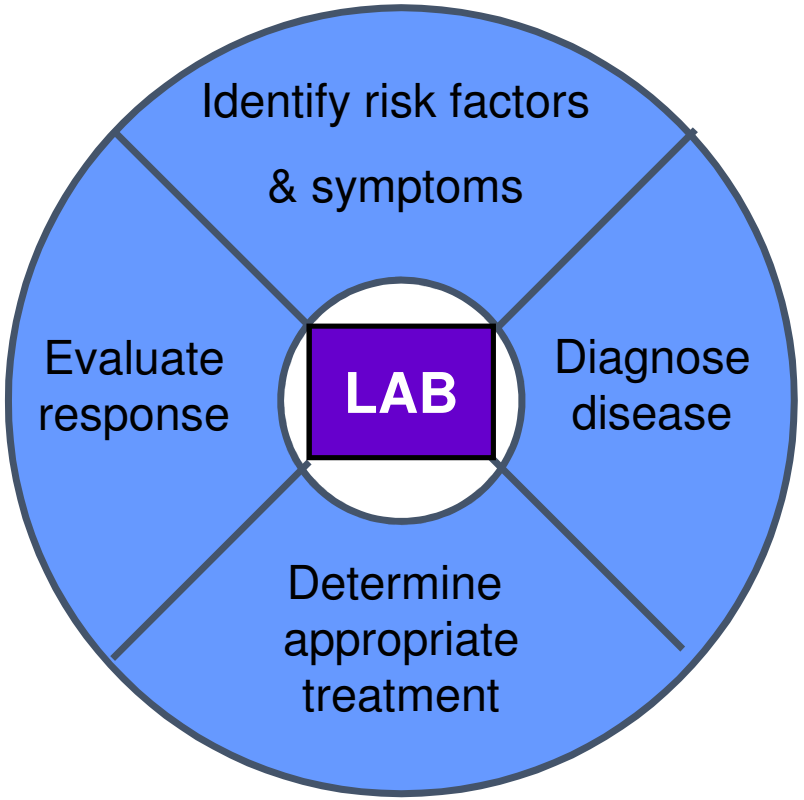
Q1. What is laboratory medicine?



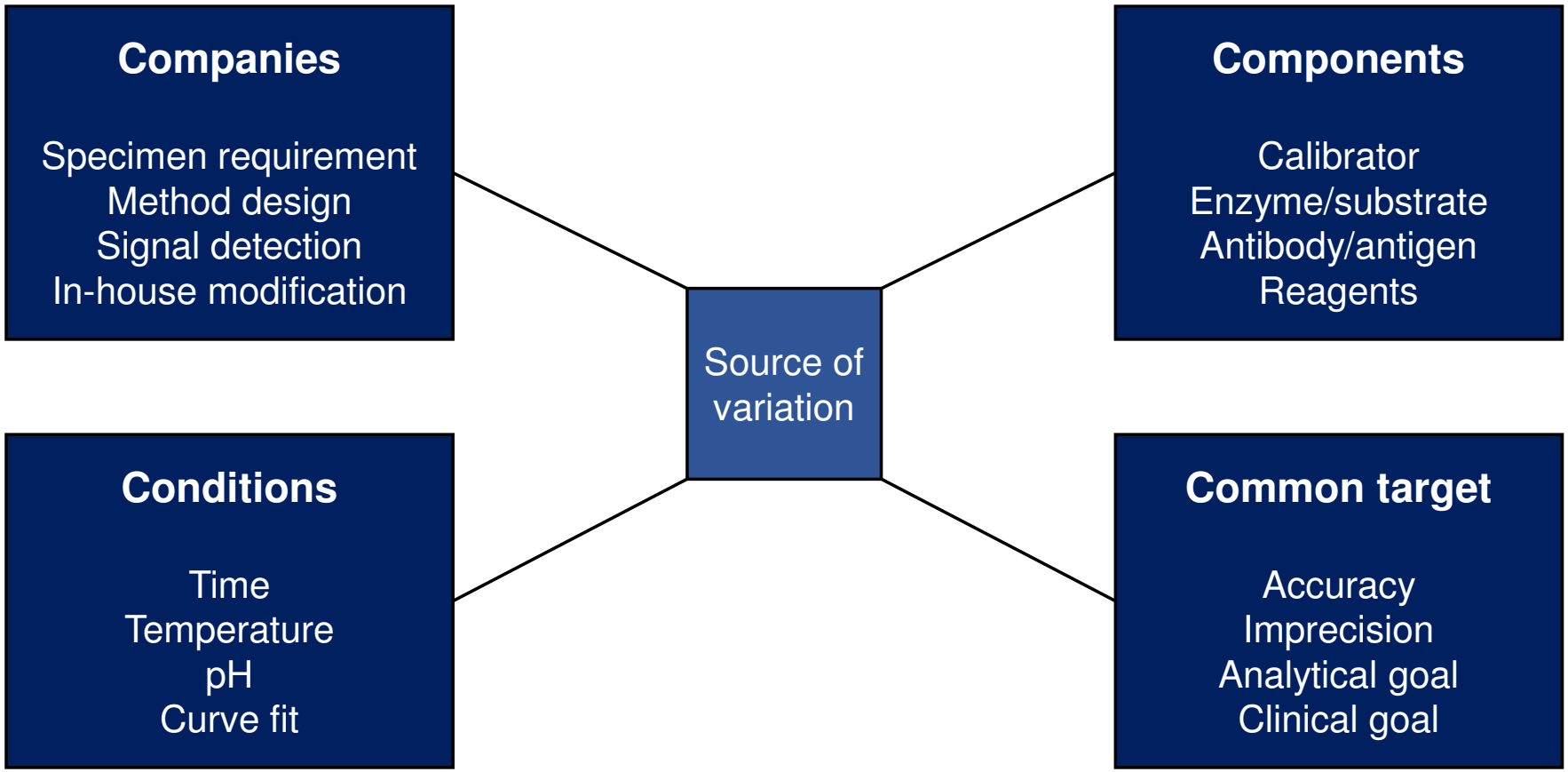
Q2. Why is laboratory medicine important?

A high percentage of all clinical decisions are influenced by laboratory medicine results

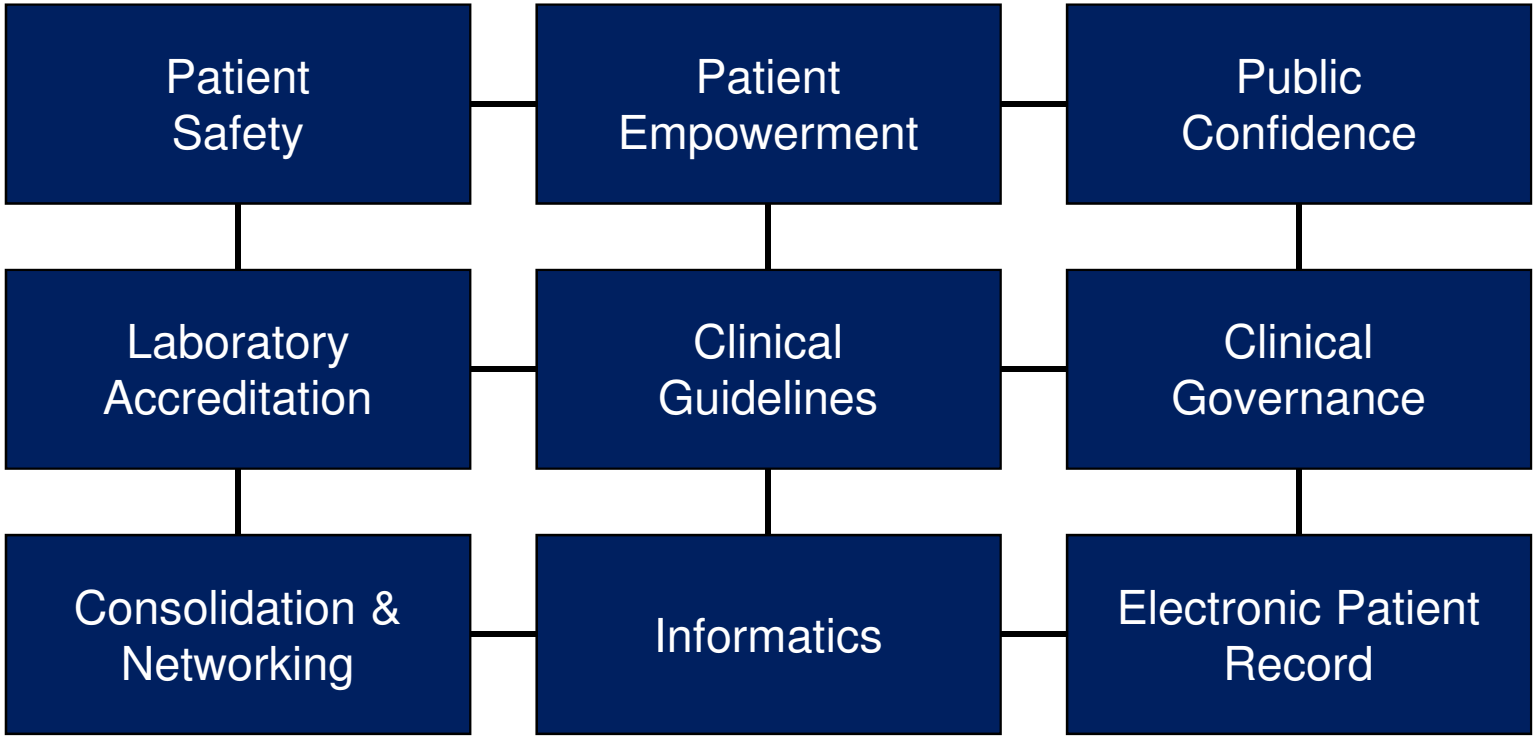
Laboratory medicine is part of the multi-disciplinary team at the centre of healthcare



Q3. Why do methods give different results on a patient sample?

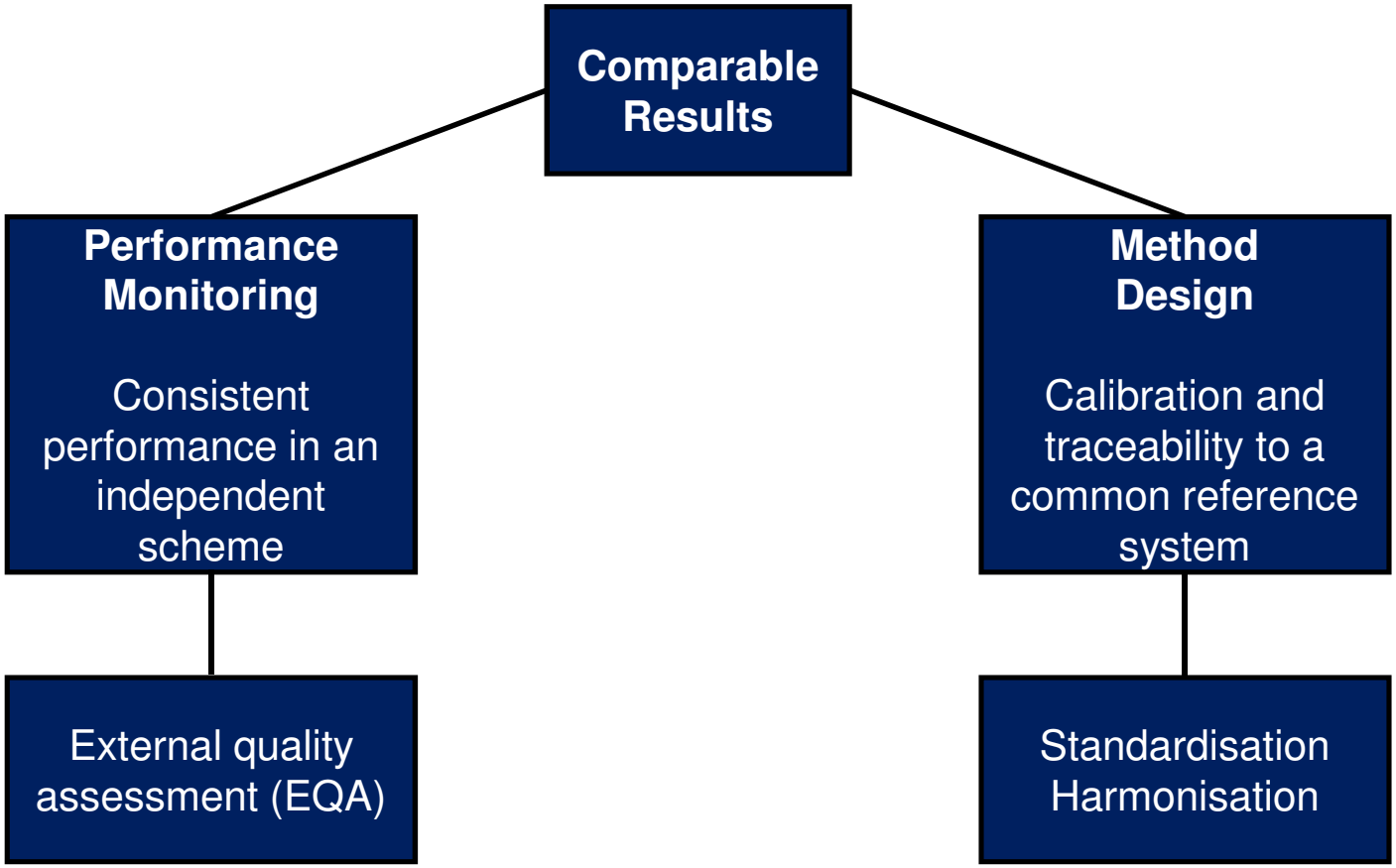


Q4. Why is reducing between-method variability important?



Adapted from Plebani, *Clin Chem Lab Med* 2013; **51**: 741-51

Q5. How can we reduce between-method variability?



Q6. What can we learn from EQA method performance?

External quality assessment (EQA), often called proficiency testing (PT):

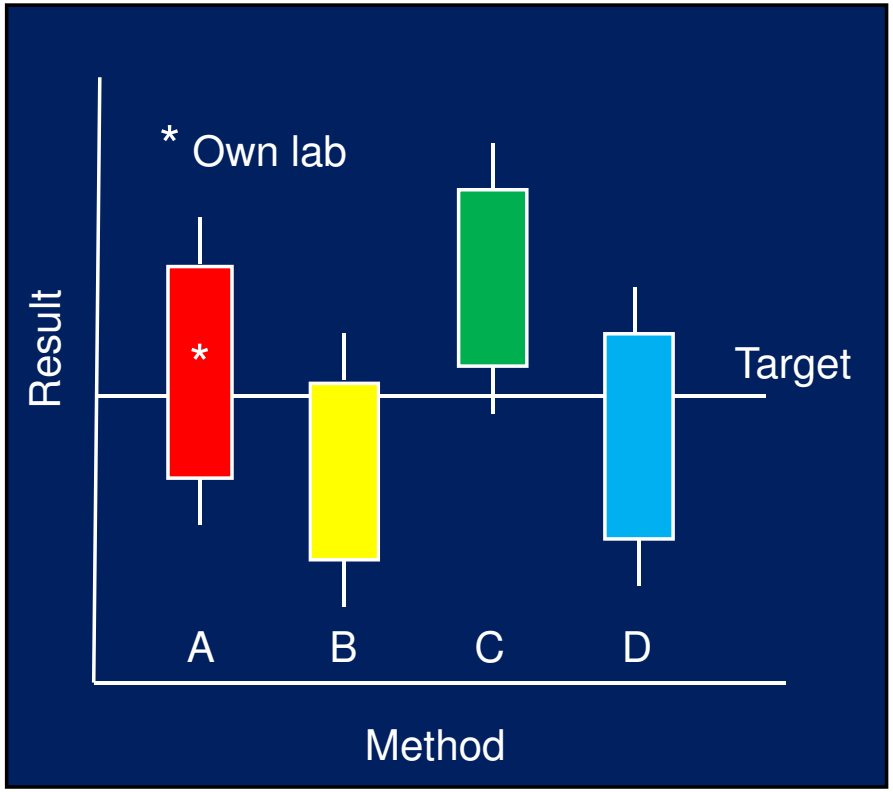
- Provides retrospective performance data
- Is focused on accuracy (trueness)

EQA enables an individual lab to assess :

- Own performance within own method
- Between method variability

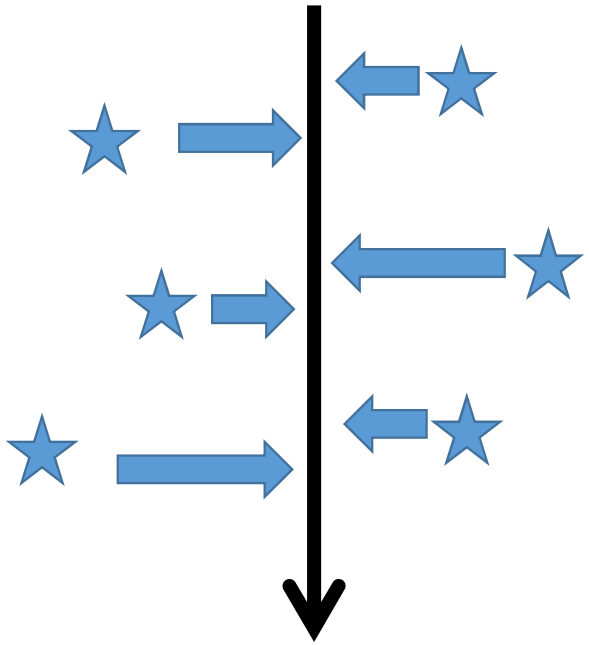
EQA may also enable:

- Method performance to be compared with a standard or target



Q7. How can method design reduce variability?

International reference system



- Laboratory medicine is a global activity:
  - IVD method manufacturers in many countries
  - Instant communication standards & procedures
- Method standardisation requires acceptance of an international reference system against which individual methods can be assessed
- An international reference system:
  - Defines measurand and SI units of measurement
  - Includes commutable reference materials
  - Is published and is capable of being reproduced
  - Is provided by an international reference lab
- Manufacturers modify assay design / components to align results with the international reference system

Q8. What is traceability in laboratory medicine?

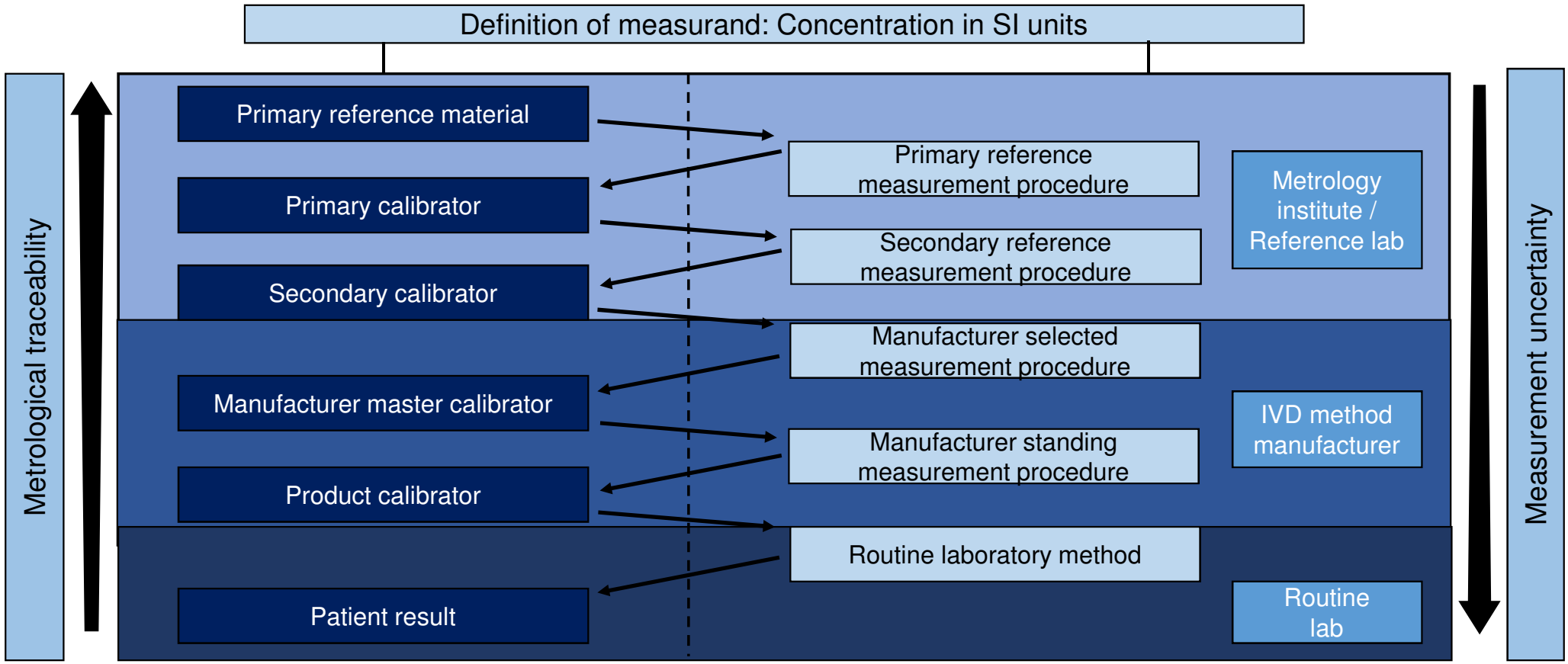
- Metrological traceability is the property of a measurement result, which can be related to a reference through a documented unbroken chain of calibrations
- Traceability requires both (certified) reference materials and the reference measurement procedures (methods) in which they are used
- For structurally simple measurands (analytes) it is possible to get pure substance primary reference materials . For more complex measurands pure substance may not be available
- Primary reference measurement procedures are often based on isotope dilution mass spectrometry

Reference materials (calibrators)
- Primary reference material (pure substance)
- Primary calibrator (SI traceable)
- Secondary calibrator
- Product calibrator

Reference measurement procedures
- Primary reference measurement procedure
- Secondary reference measurement procedure
- Manufacturer selected procedure
- Routine laboratory procedure

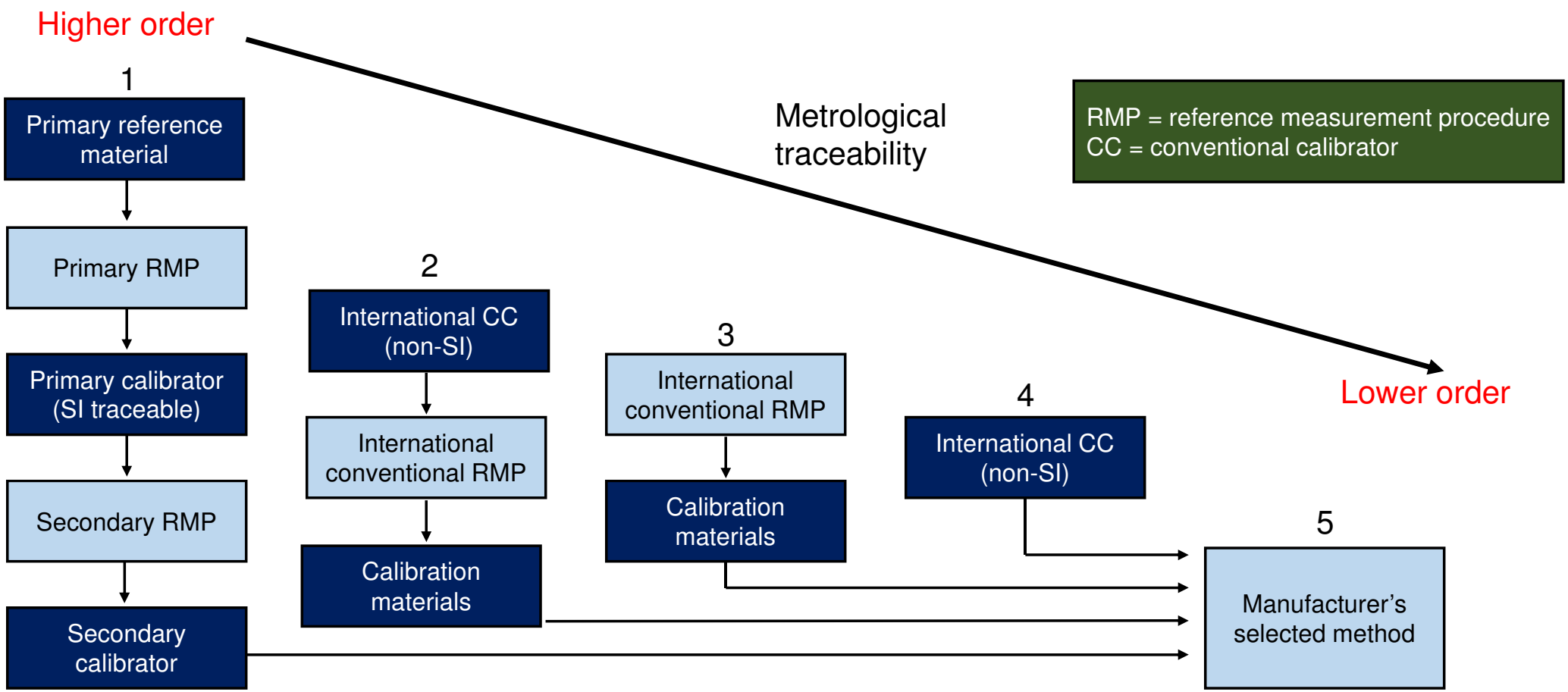
Hierarchy

Q9. What is a metrological traceability chain?



Adapted from EN ISO 17511 2003

Q10. What are ‘higher order’ materials and procedures?



Adapted from White GH Ann Clin Biochem 2011; 48: 393-408

Q11. What is method standardisation and harmonisation?

Category	Reference measurement procedure	Primary (pure substance) reference material	Secondary (value assigned) reference material	Examples
1	Yes	Yes	Possible	Glucose Creatinine
2	Yes	No	Possible	Enzymes
3	Yes	No	No	Hemostatic factors
4	No	No	Yes	Some proteins HIV
5	No	No	No	Some proteins Most viruses

Standardisation

Harmonisation

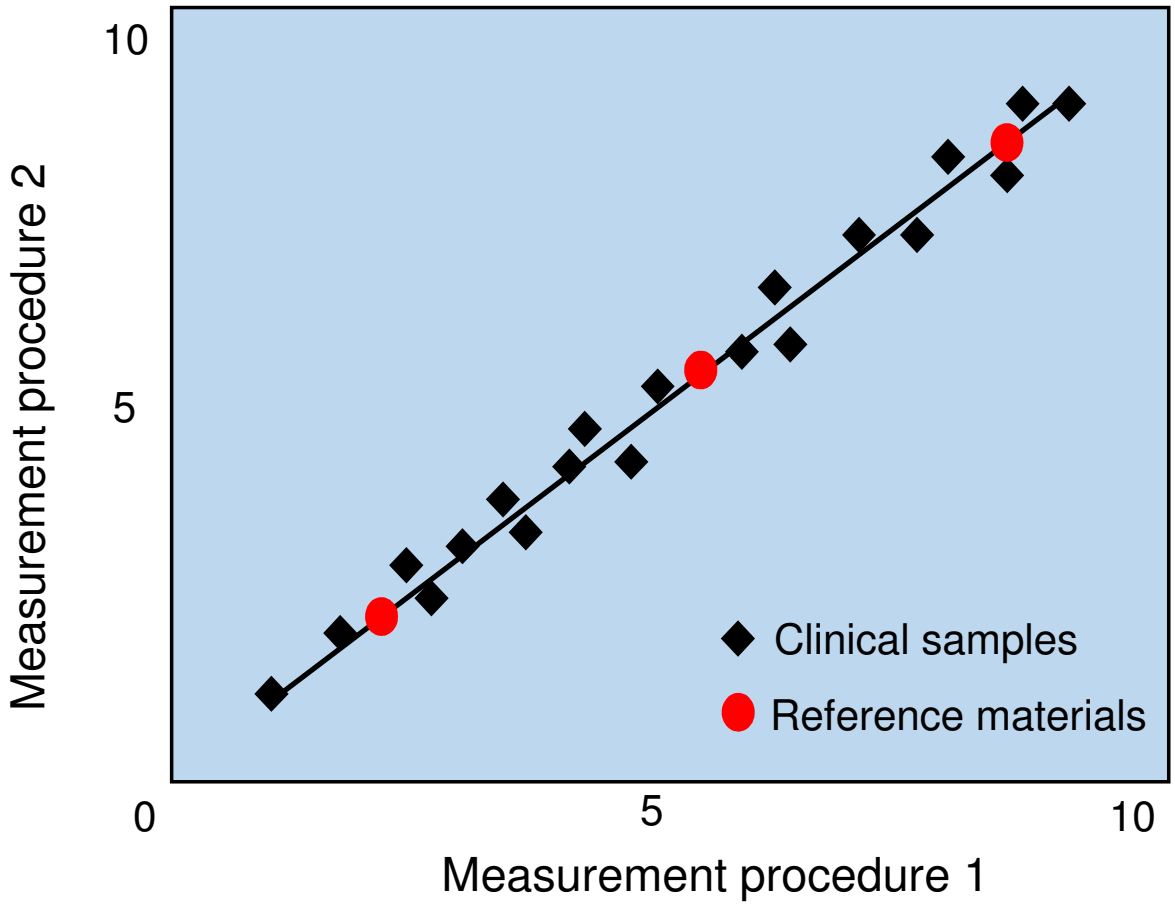
Adapted from EN ISO 17511 2003

Q12. Why can’t all methods be standardised?

- Standardisation requires a reference measurement procedure. This is achievable for chemically ‘simple’ measurands
- For complex measurands (e.g. some proteins, viruses etc.) it may not be possible to develop a reference measurement procedure

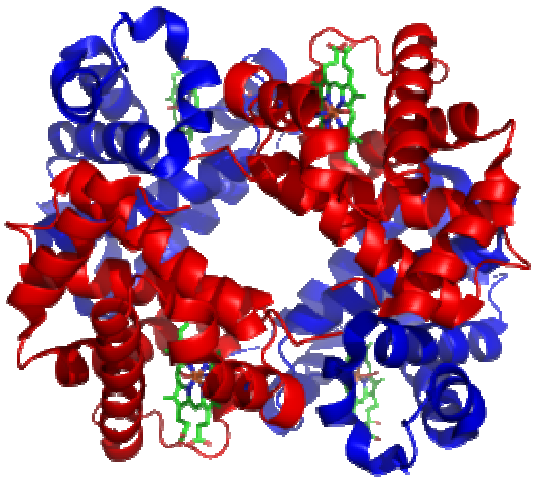
- While standardisation may not always be achievable it should be possible to achieve method harmonisation
- Manufacturers are able to harmonise their selected methods against ‘higher order’ entities including:
  - International conventional calibrator
  - Secondary (value assigned) reference material

Q13. What is a commutable reference material?



After Miller WG 2012

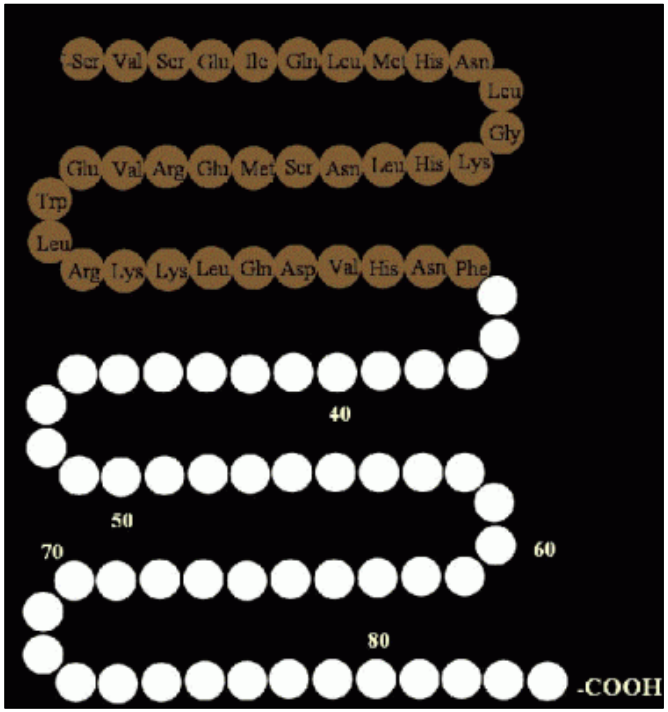
Q14. Why is HbA1c an example of good method standardisation?



Haemoglobin A1c (HbA1c)

- A glycated form of haemoglobin, always present in blood
- Established as the key analyte for long-term monitoring of diabetes. Lowering HbA1c improves clinical outcomes
- Huge numbers of HbA1c measurements made using many different methods. Methods used to show great variability.
- IFCC reference measurement procedure introduced 2004. International consensus statement to use IFCC aligned methods
- Between method variability now ~5% in EQA schemes
- Improved method performance has led to WHO recommendation to use HbA1c to diagnose as well as monitor diabetes
- Quality targets for HbA1c methods now available to assess if they are fit for purpose

Q15. Why is PTH an example of bad method standardisation?



Intact parathyroid hormone (PTH)
84 AA peptide MW = 9500Da

- PTH is the key hormone in calcium homeostasis acting on bone, the kidney and the gut. PTH is a key biomarker in renal osteodystrophy, a condition associated with renal failure
- The biological activity resides in N-terminal 34 amino acids. Intact and N-terminal PTH have a short half life in plasma. C-terminal PTH fragments have a long half life and create assay interference issues, especially in renal patients
- Current methods for plasma/serum PTH show a ~300% variation in results, owing to calibration and interference issues
- Patient management depends on knowing the PTH assay used. It is unsafe to use results from a different method
- An international project has commenced on PTH method standardisation

Q16. What is the challenge facing laboratory medicine?

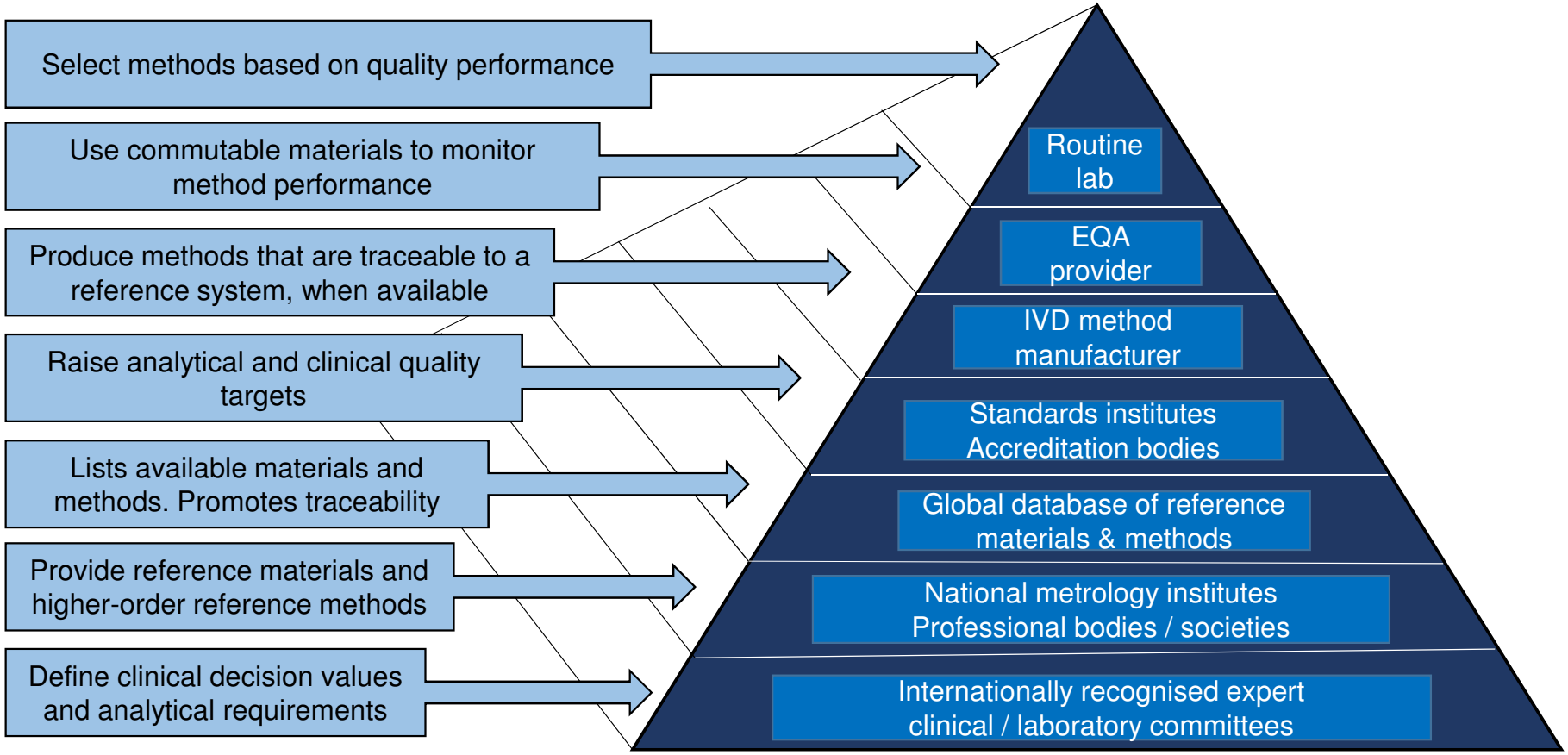
- There are ~4000 clinically relevant analytes measured across the scope of laboratory medicine (P Laitinen, Finland)
- The Joint Committee for Traceability in Laboratory Medicine (JCTLM) database holds 295 certified reference materials;170 reference measurement procedures www.bipm.org/jctlm/

JCTLM
Accurate Results for Patient Care

- The World Health Organisation (WHO) catalogue of blood products and related biological standards contains ~300 entries http://www.who.int/bloodproducts/catalogue/en/

World Health Organization

Q17. Who are the stakeholders in achieving traceability?



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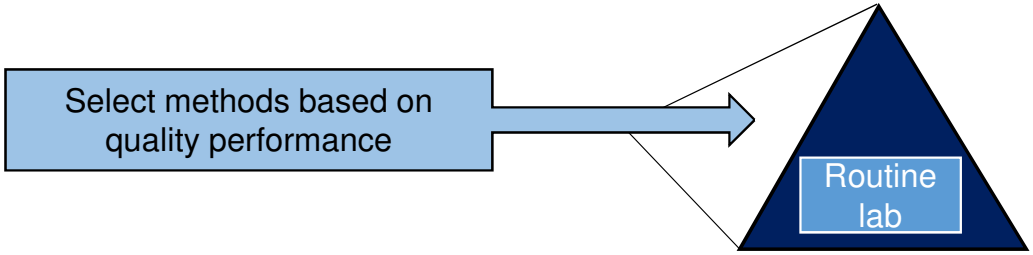
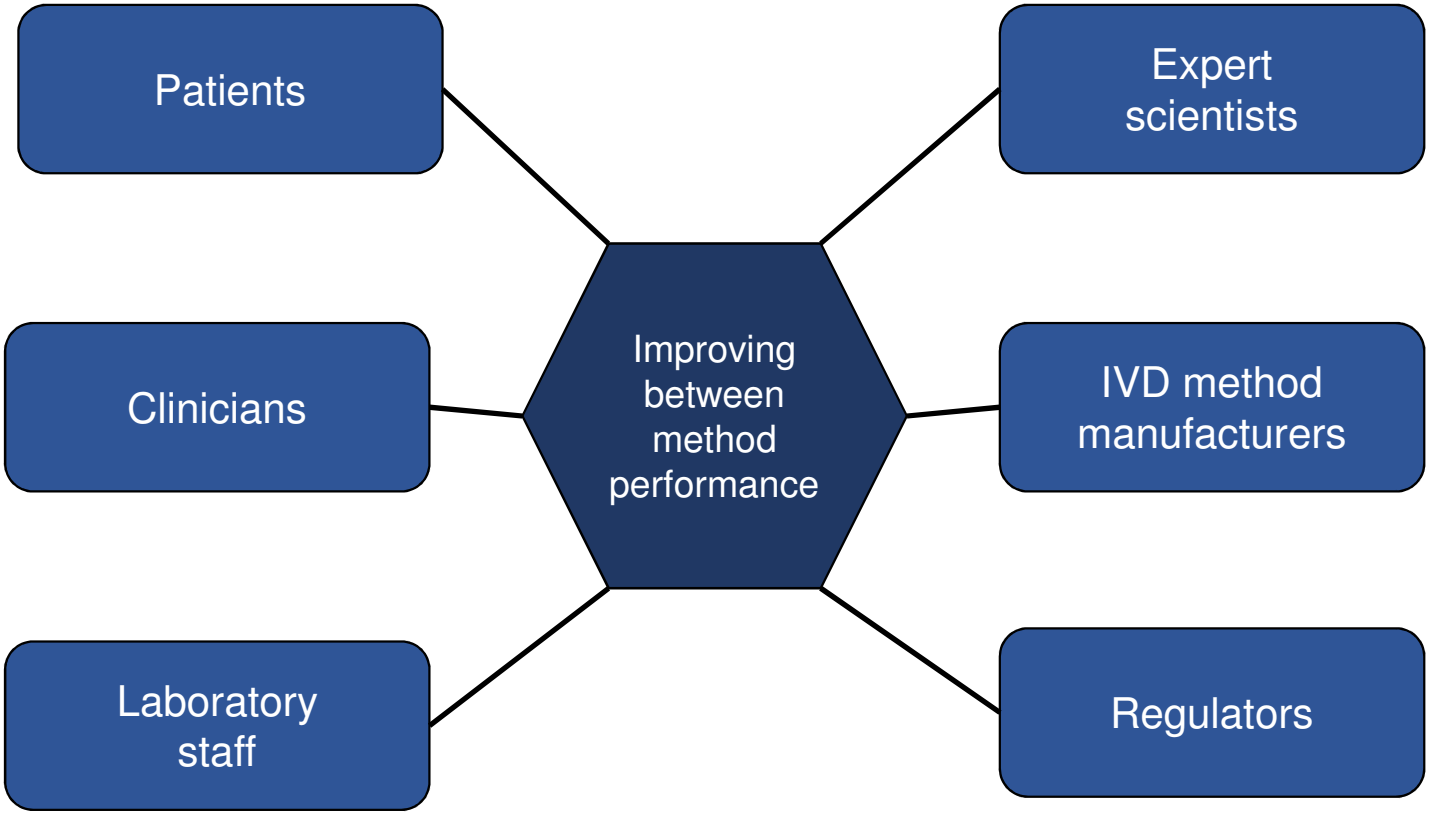
Q18. What can I do in my lab to assure method quality?



1. Check the traceability status of the methods that you use. If uncertain check with your supplier
2. Encourage key colleagues to learn more about traceability in laboratory medicine
3. Check whether your EQA scheme provider is using commutable materials
4. Analyse your EQA performance critically to assess the extent to which traceability issues may be influencing the results obtained

Q19. Who are the interested parties in assuring patient results?



Q20. Where can I find more information?

Websites

- Joint Committee for Traceability in Laboratory Medicine (JCTLM): www.jctlm.org
- JCTLM database of reference materials and measurement procedures www.bipm.org/jctlm/
- International Consortium for Harmonization of Clinical Laboratory Results www.harmonization.net
- WHO catalogue of blood products and biological standards http://www.who.int/bloodproducts/catalogue/en/

References

- White GH. Metrological traceability in clinical biochemistry. Ann Clin Biochem 2011; 48: 393-408
- Greenberg N. Update on current concepts and meanings in laboratory medicine - standardization, traceability and harmonization. Clin Chim Acta 2014; 432: 49–54
- Miller WG Myers GL. Commutability still matters. Clin Chem 2013; 59: 1291-1293

Documents

- ISO 17511:2003. In vitro diagnostic medical devices -- Measurement of quantities in biological samples -- Metrological traceability of values assigned to calibrators and control materials
- ISO 15194:2009. In vitro diagnostic medical devices -- Measurement of quantities in samples of biological origin -- Requirements for certified reference materials and the content of supporting documentation