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Weqas | GLOBAL PROVIDER OF QUALITY IN DIAGNOSTIC MEDICINE

EXTERNAL QUALITY ASSESSMENT

INTERNAL QUALITY CONTROL

REFERENCE MEASUREMENT SERVICES

EDUCATION & TRAINING

How are we ensuring the accuracy of our calculated parameters?

Ceri Parfitt

In this talk…

- Overview of calculated parameters in Clinical Biochemistry
- Role of EQA in assessing accuracy of calculated parameters
- Review of recent data analysis of calculated parameters
  - Estimated GFR
  - Adjusted calcium

Calculated Parameters – why?

- Calculated parameters are values derived from measured biochemical analytes using mathematical formulas
  - Either standardised or lab-derived

- Provide useful information that cannot be measured directly, or would be time-consuming, costly or invasive to measure

- Examples:
  - eGFR
  - Adjusted calcium
  - LDL-cholesterol
  - Transferrin saturation/TIBC
  - Albumin/creatinine ratio
  - pH

Calculated Parameters – why?

- How do we ensure that formulas used give accurate and appropriate results?
    - Validation against gold standards
    - Population-based calibration
    - Awareness of limitations of each formula
    - Updated according to recently published data/guidelines
    - Calculations embedded in software or LIMS
    - Participation in EQA schemes that assess calculated parameters

EQA and calculated parameters

- EQA supports the accuracy of calculated parameters by:
    - Ensuring input measured values are correct
    - Directly assessing use of calculations by flagging formula issues
    - Identifying use of outdated formulas
    - Encouraging consistency across laboratories
    - Supporting ongoing education

Glomerular filtration rate (GFR)

- Glomerular filtration rate is assessed in investigation of early renal disease and to stage and monitor chronic kidney disease

- Creatinine measurement alone does not reliably reflect renal function on an individual basis
    - Creatinine increases with muscle mass
    - Higher concentrations expected in males and younger individuals
    - Creatinine may remain within reference range despite impaired kidney function

- GFR is a standardised value and can be compared between patients
    - Used in clinical guidelines

Glomerular filtration rate (GFR)

- GFR cannot be measured directly
- Gold standard for measurement of GFR is plasma/urinary clearance of an exogenous filtration marker (e.g. inulin, iohexol, ^{51}Cr-EDTA)
- This is not appropriate for routine practice
- Various equations have been proposed to calculate an estimate of GFR, using combinations of creatinine concentration, patient age, gender, ethnicity…

eGFR calculations

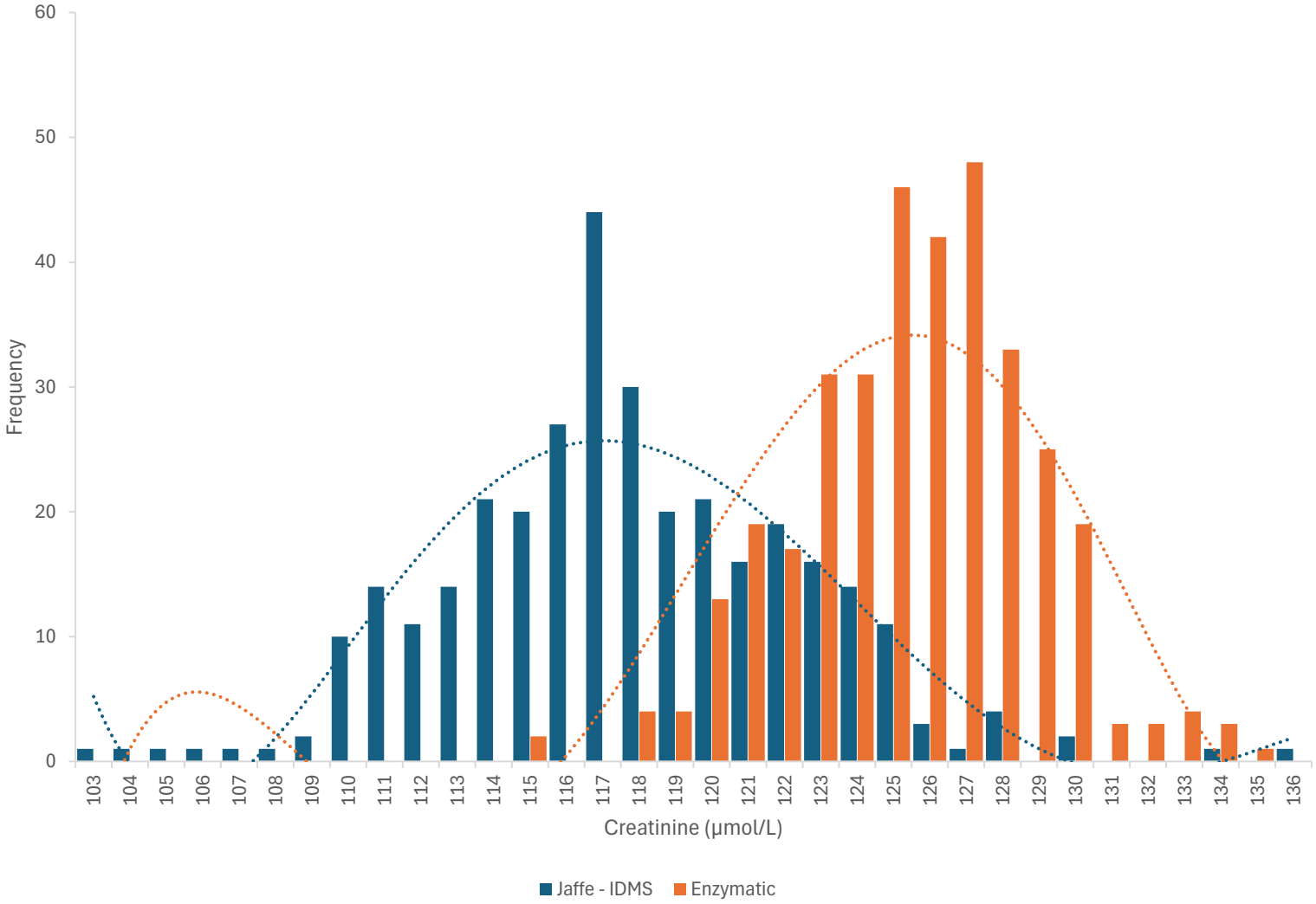
- Cockcroft-Gault (1978)
  - Serum creatinine, age, sex, weight
- MDRD study (1999/2005)
  - Serum creatinine, age, sex, race
- CKD-EPI (2009)
  - Serum creatinine, age, sex, race
- CKD-EPI (2021)
  - Serum creatinine, age, sex
  - More accurate than MDRD at higher GFR values
  - Currently recommended for clinical use

- Changing eGFR calculation equation is a challenge, and many labs will still be using older equations

Analysis of Weqas data

- Creatinine and eGFR results from a single pool of samples was examined
  - Comprised 676 results from 52 sites over a 12-month period
  - Creatinine approximately 120 µmol/L
  - Creatinine measured by either Jaffe or enzymatic methods
  - eGFR calculated by either CKD-EPI or MDRD equations
    - Specific equation used not supplied

Jaffe vs enzymatic creatinine



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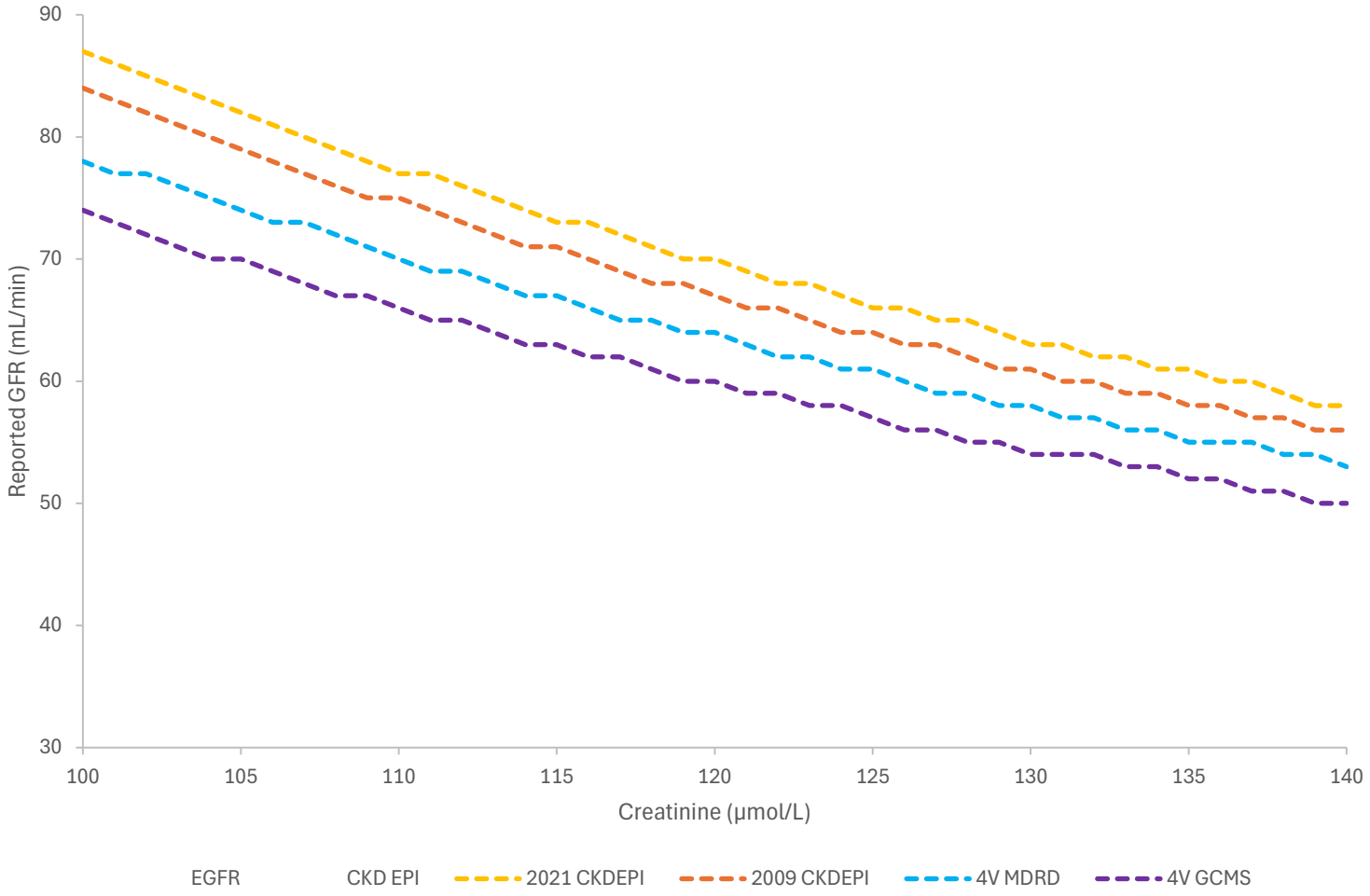
- Patient information supplied to participants:
  - Caucasian male, DOB 1/4/1989

- Patient information used to calculate 'correct' eGFR value for creatinine between 100 – 140 µmol/L
  - Allows direct comparison of eGFR results, irrespective of creatinine method used

Variation in eGFR data



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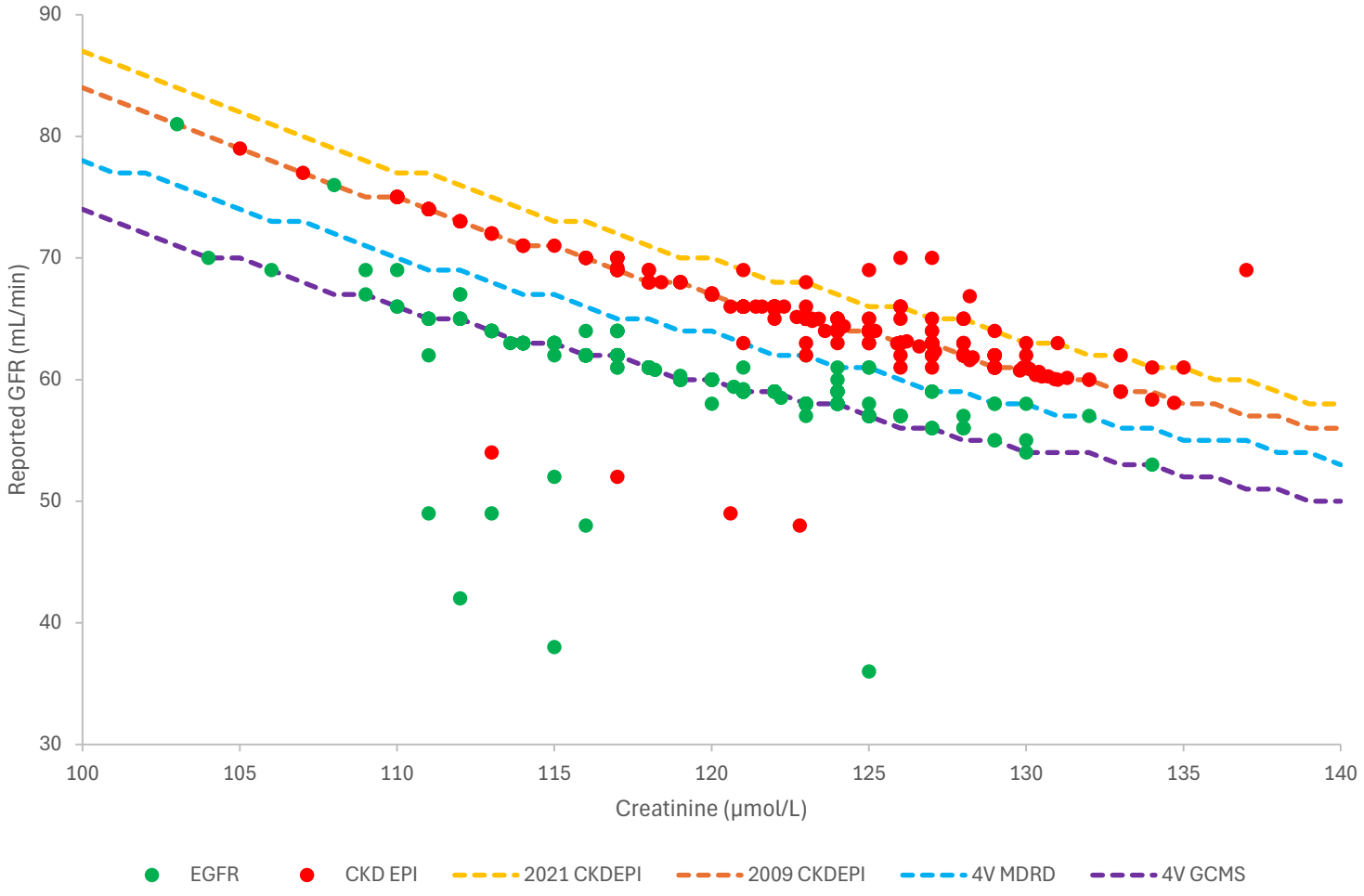
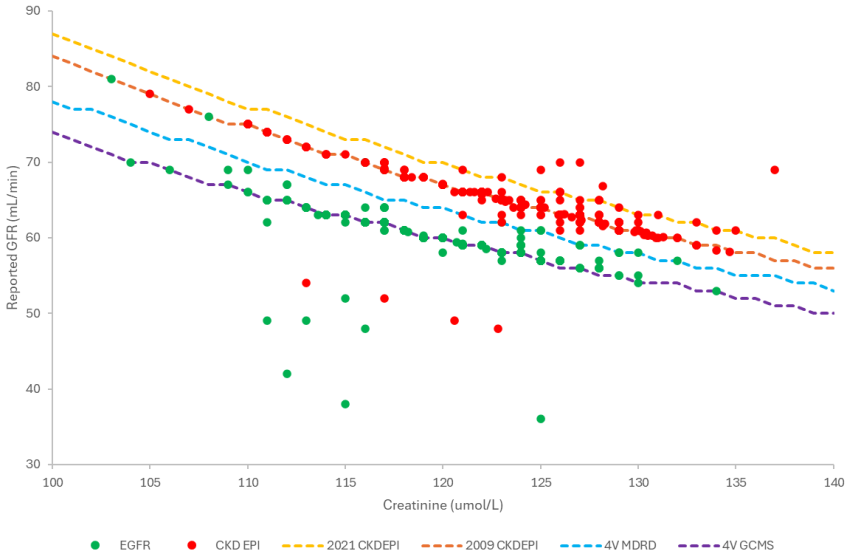


Variation in eGFR data

- Majority of points fit along lines corresponding to eGFR equations
- Several points are significantly displaced from target lines
- Points falling in between target lines
- Points corresponding to MDRD calculation falling on CKD-EPI lines



Variation in eGFR data

- Possible issues:
  - Transcription errors
    - Entering patient demographics
    - Reporting eGFR values to Weqas
  - Rounding errors
    - May result in minor variation in eGFR values
  - Participant in incorrect group
    - Changed equation in laboratory, but not updated with Weqas
  - Equation incorrect in LIMS/middleware

Summary – eGFR calculations

- Most labs are calculating and reporting eGFR values correctly
- Relatively few labs are using the recommended CKD-EPI (2021) equation
  - This is a complex change, so expected
- There is evidence of inaccuracy in calculating eGFR values, whatever equation is used
  - Ensure correct patient demographics entered
  - Check eGFR result makes sense compared to creatinine

Calcium

- Calcium measurement is essential in diagnosis and monitoring of a wide range of clinical conditions
- Approximately 40 % of calcium in plasma is bound to albumin and is biologically inactive
- Ionised calcium is the gold standard for assessing calcium status
- Measures the amount of biologically active (‘free’ calcium) available in plasma
  - Requires access to blood gas analyser
  - Samples must be analysed within 30 minutes of venepuncture
  - Frequently used in critical care units
  - Not ideal for primary care/routine outpatient work

Laboratory measurement of calcium

- Laboratory assays measure total calcium
  - Includes free- and protein-bound calcium
- Two main methods for calcium measurement in this dataset
  - Arsenazo III
  - NM-BAPTA (Roche instruments)
- Both colorimetric methods
- Laboratory total calcium results are typically adjusted for albumin concentration

Why adjust for albumin?

- Measurement of total calcium does not give an accurate representation of calcium status
    - In patients with low albumin concentrations, total calcium concentration will also be low – however 'free' calcium may be within reference range – no treatment required
    - Relying on total calcium measurements may result in inappropriate investigation/treatment for hypocalcaemia
- To combat this, total calcium is adjusted for albumin concentrations

Adjusted calcium equations

- In 1973, the Payne equation was proposed:

$$[Ca]_{adj} = [Ca]_{tot} + (40 - [Alb]) \times 0.02$$

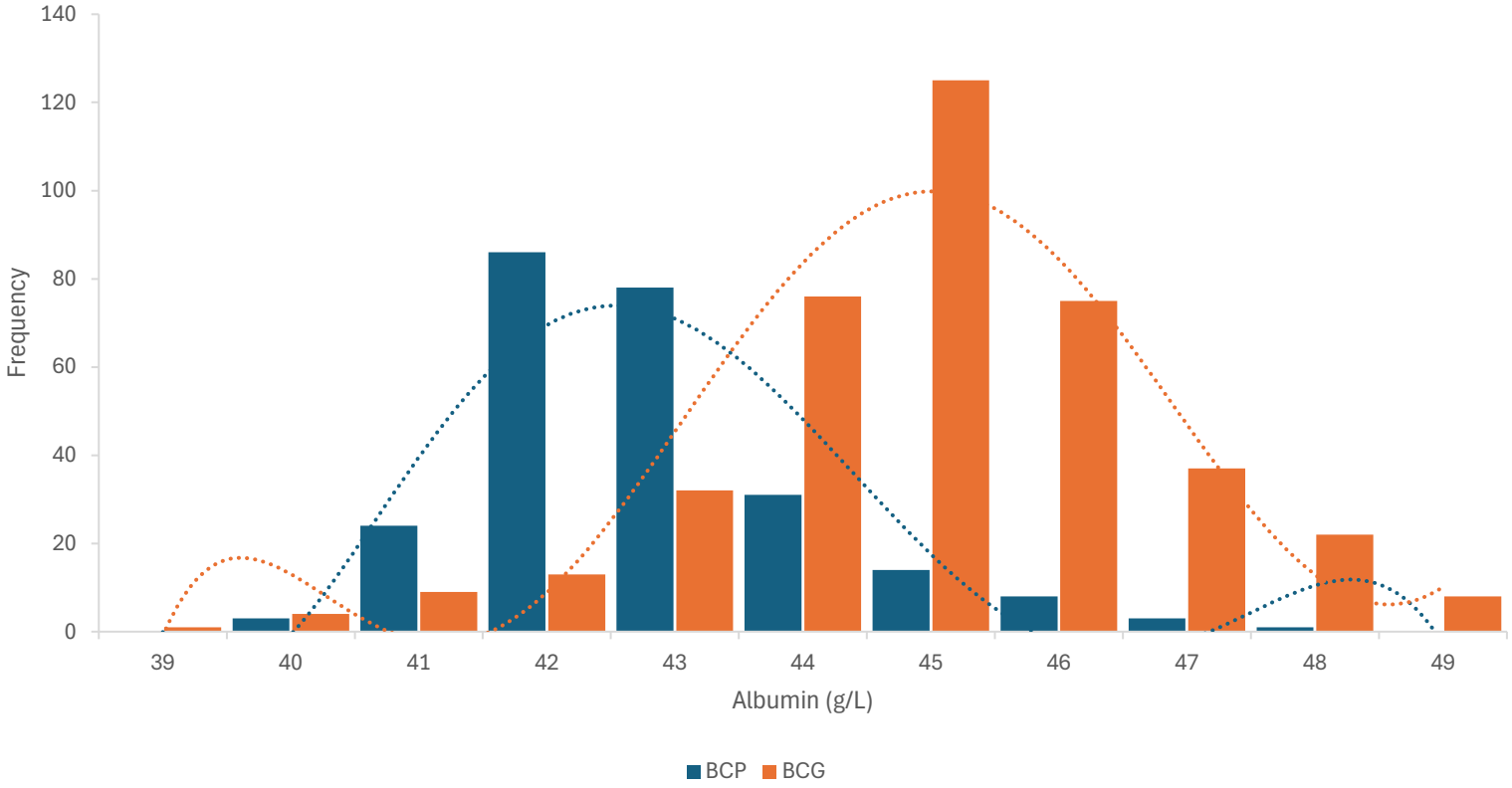
- Limitations include
  - Derived using CPC/BCP methods for calcium and albumin
  - Assumes mean normal albumin concentration is 40 g/L
  - Assumes 1 g albumin binds 0.02 mmol calcium
  - Can miss cases of hypercalcaemia

- Pathology Harmony (2020) proposes that labs should generate regression equations from individual lab data and that equations are normalised to calcium value of 2.40 mmol/L
  - In 2015, 42 % of labs still using Payne equation

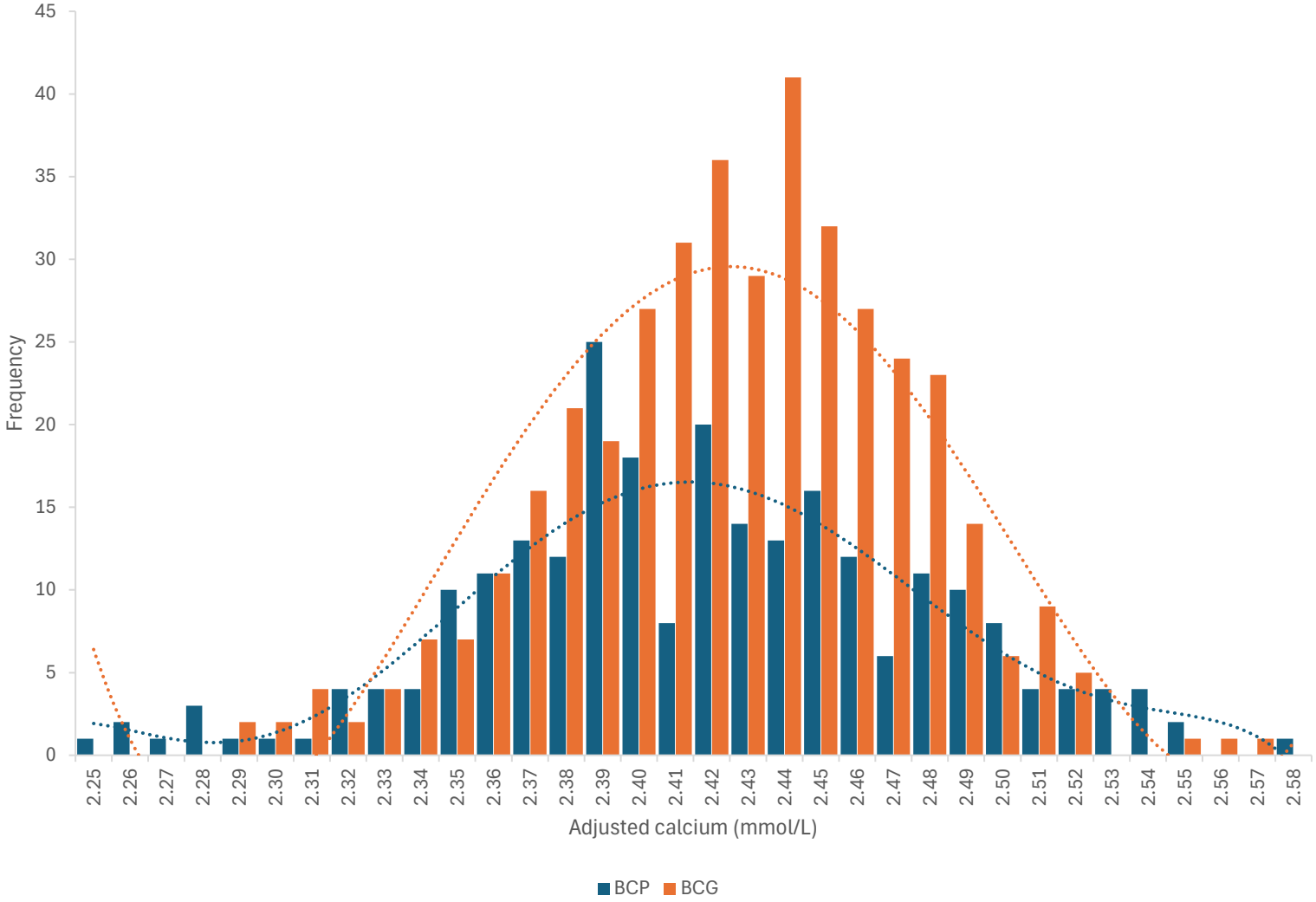
Analysis of Weqas data

- Calcium, albumin and adjusted calcium results from a single pool of samples was examined
    - Comprised 650 results from 50 sites over a 12-month period
    - Calcium measured by either NM-BAPTA or Arsenazo III methods
    - Albumin measured by either BCP or BCG methods
    - No information provided on equation used to calculate adjusted calcium

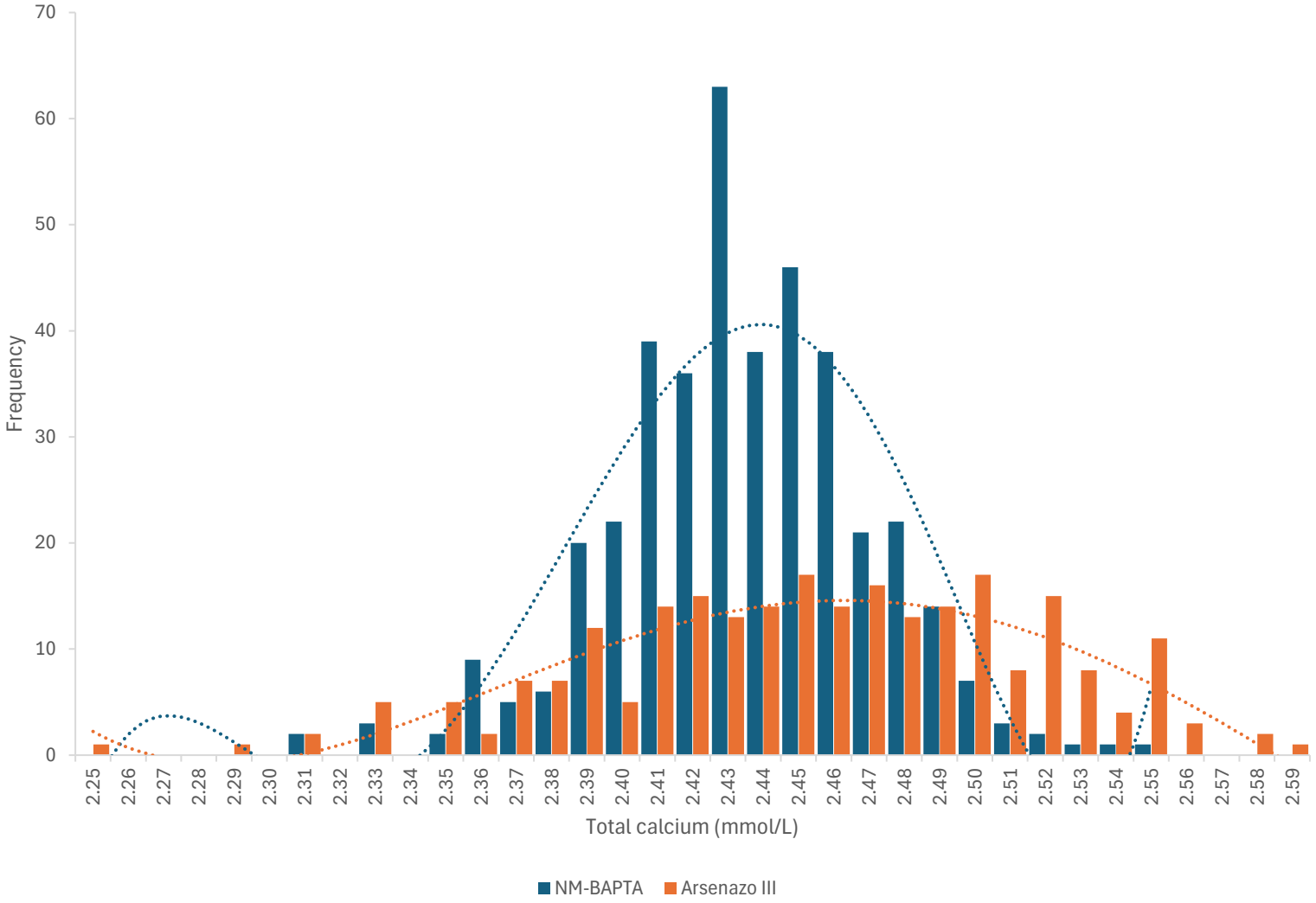
Effect of different methods on albumin concentration



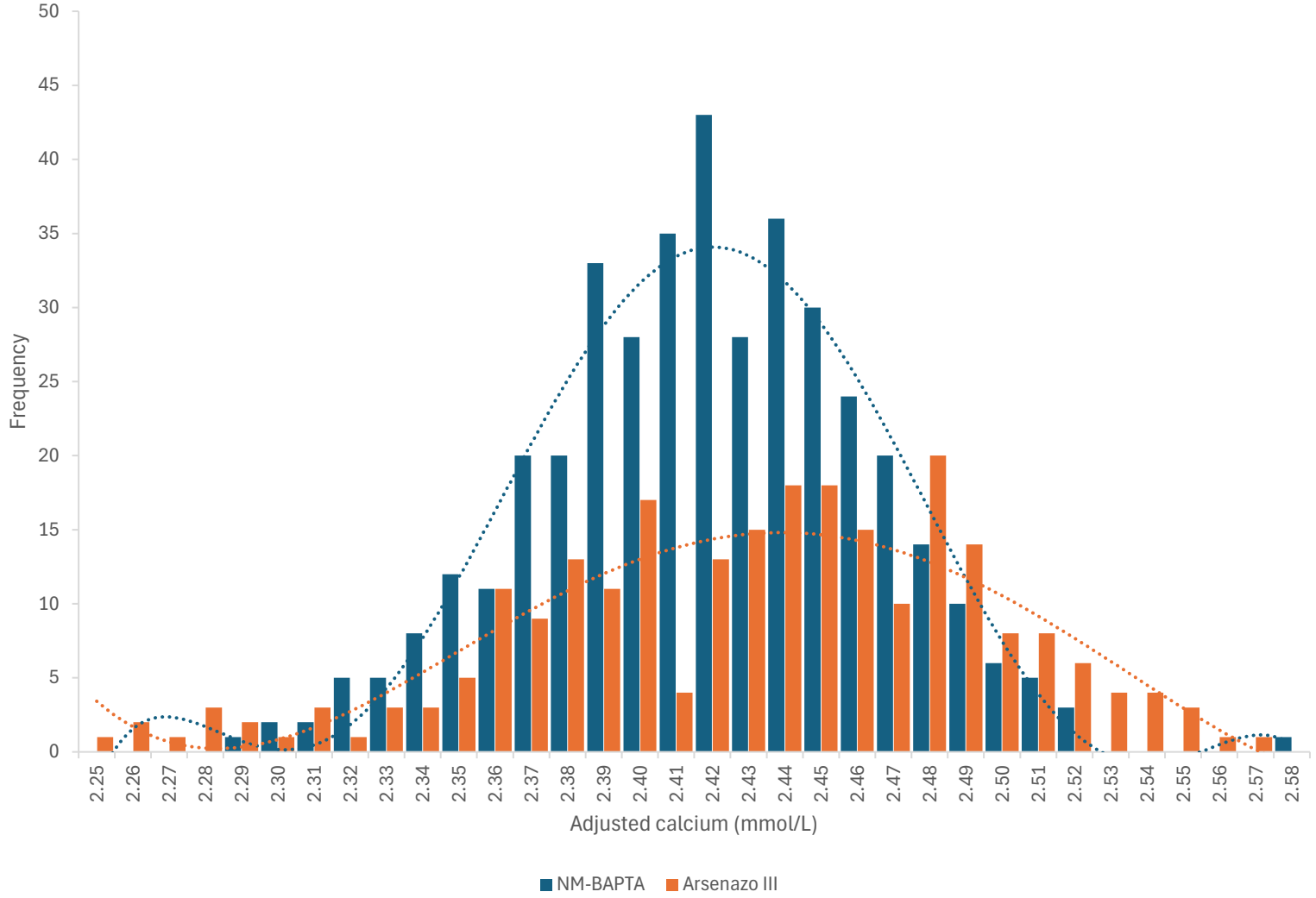
Effect of albumin methods on adjusted calcium values



Effect of different methods on total calcium concentration



Effect of calcium methods on adjusted calcium values



Summary - adjusted calcium calculations

- Although significant differences between albumin methods and calcium methods remain, there does not appear to be significant differences between adjusted calcium values
- Likely due to laboratories establishing appropriate specific equations for use with current assays and local population
- Our most recent questionnaire was in 2015, where 42 % of participants used the generic Payne equation
  - Has this changed?
  - We are intending to find out!

Conclusions

- Overview of calculated parameters in use in Clinical Biochemistry, and the role of EQA in assessing accuracy of reported values

- Estimated GFR
  - Majority of labs are accurately reporting eGFR results
  - Uptake of CKD-EPI (2021) appears relatively low at present
  - Potential issues in calculating eGFR highlighted

- Adjusted calcium
  - Despite differences in both albumin and creatinine methods, adjusted calcium is reported accurately
  - Specific equations in use not known

Thank you for listening!