Reporting Estimated GFR from Serum Creatinine

Recommendations from the Laboratory Working Group of the National Kidney Disease Education Program

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What is the NKDEP

Public health program to promote early detection and treatment of chronic kidney disease to prevent or slow disease progression.

- **National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, USA**
- **www.nkdep.nih.gov**

The Laboratory Working Group

Formed to address creatinine measurement issues and provide recommendations to implement reporting estimated GFR

Members representing:

- **Clinical laboratories**
- **IVD manufacturers**
- **Pharmacists**
- **Regulatory and public health agencies**
- **National metrology institute**
- **Proficiency testing (EQA) organizations**
- **International representation; cooperation with IFCC**

Laboratory working group recommendations

- Clinical Chemistry 2006; 52: 5-18
- www.nkdep.nih.gov/labprofessionals/index.htm
  - Updated regularly
- AACC Clinical Laboratory News, April 2006
- www.bloodgas.org, recent brief article

NKDEP

Reasons for a National Kidney Disease Education Program

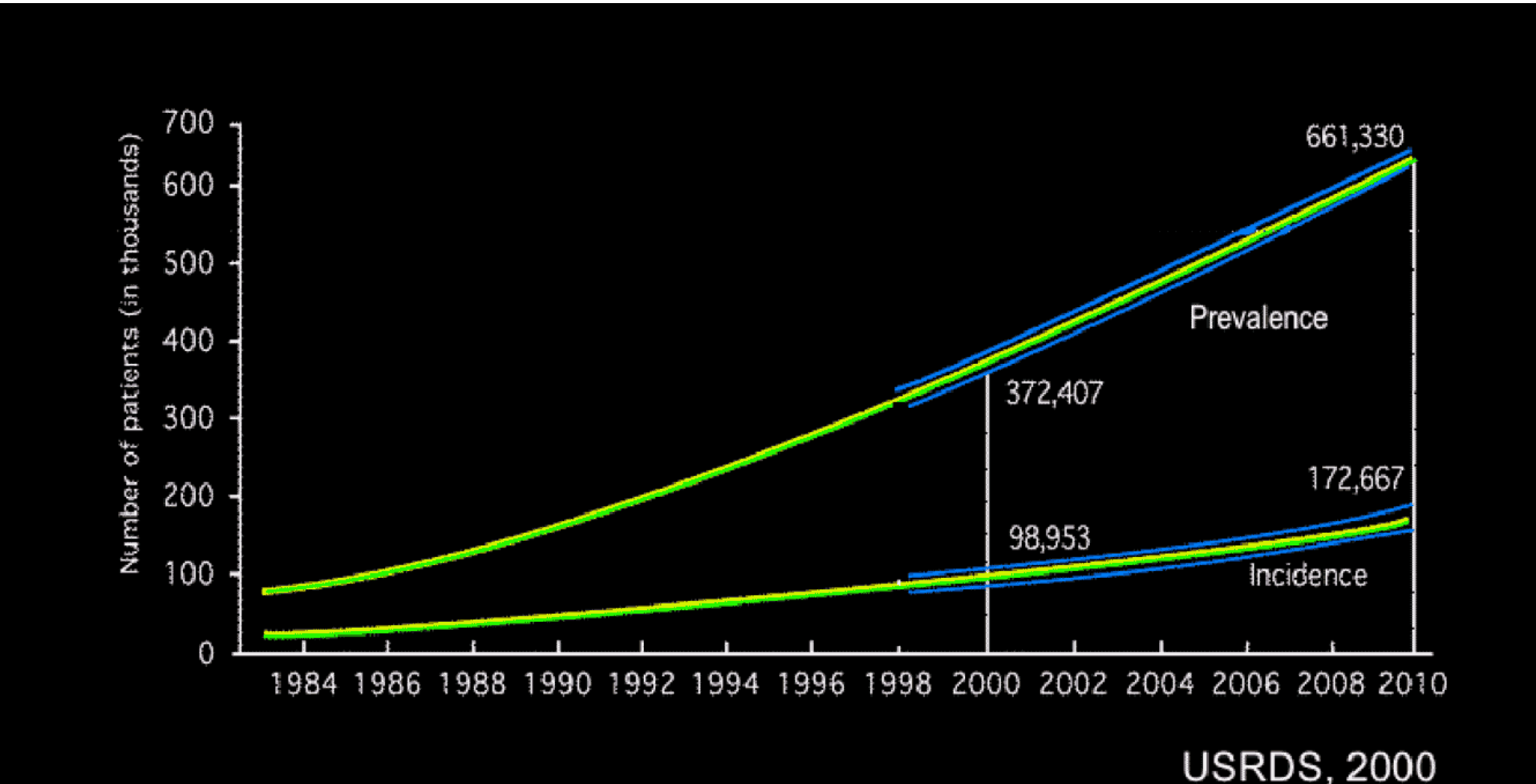
1) Kidney failure is a public health problem

2) Economical, effective testing and therapy exist

3) Testing and therapy are inadequately applied

NKDEP

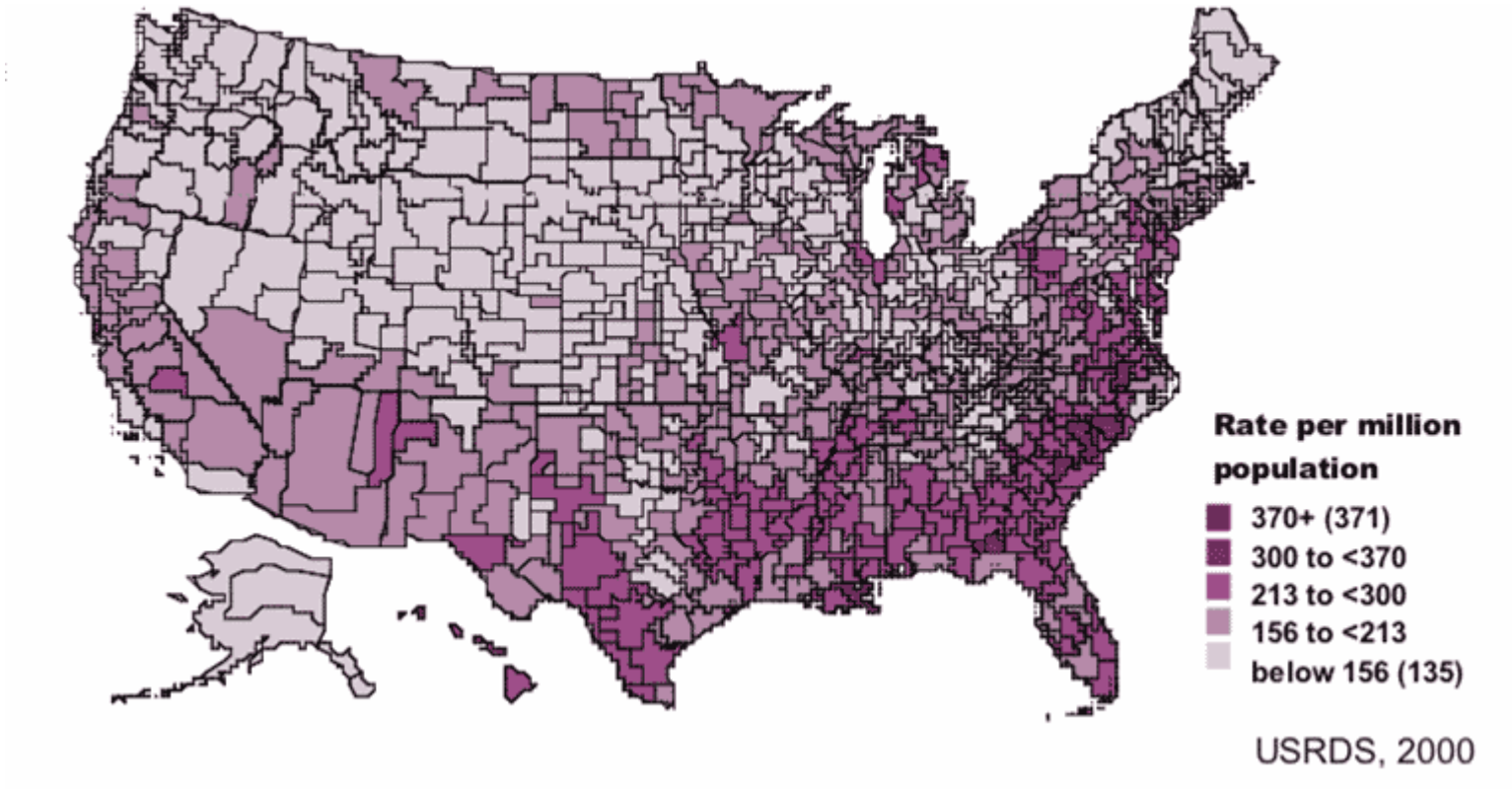
Kidney Failure Is a Rapidly Growing Problem



NKDEP

Incidence of Kidney Failure

per million population, **1990**, by HSA, unadjusted



NKDEP

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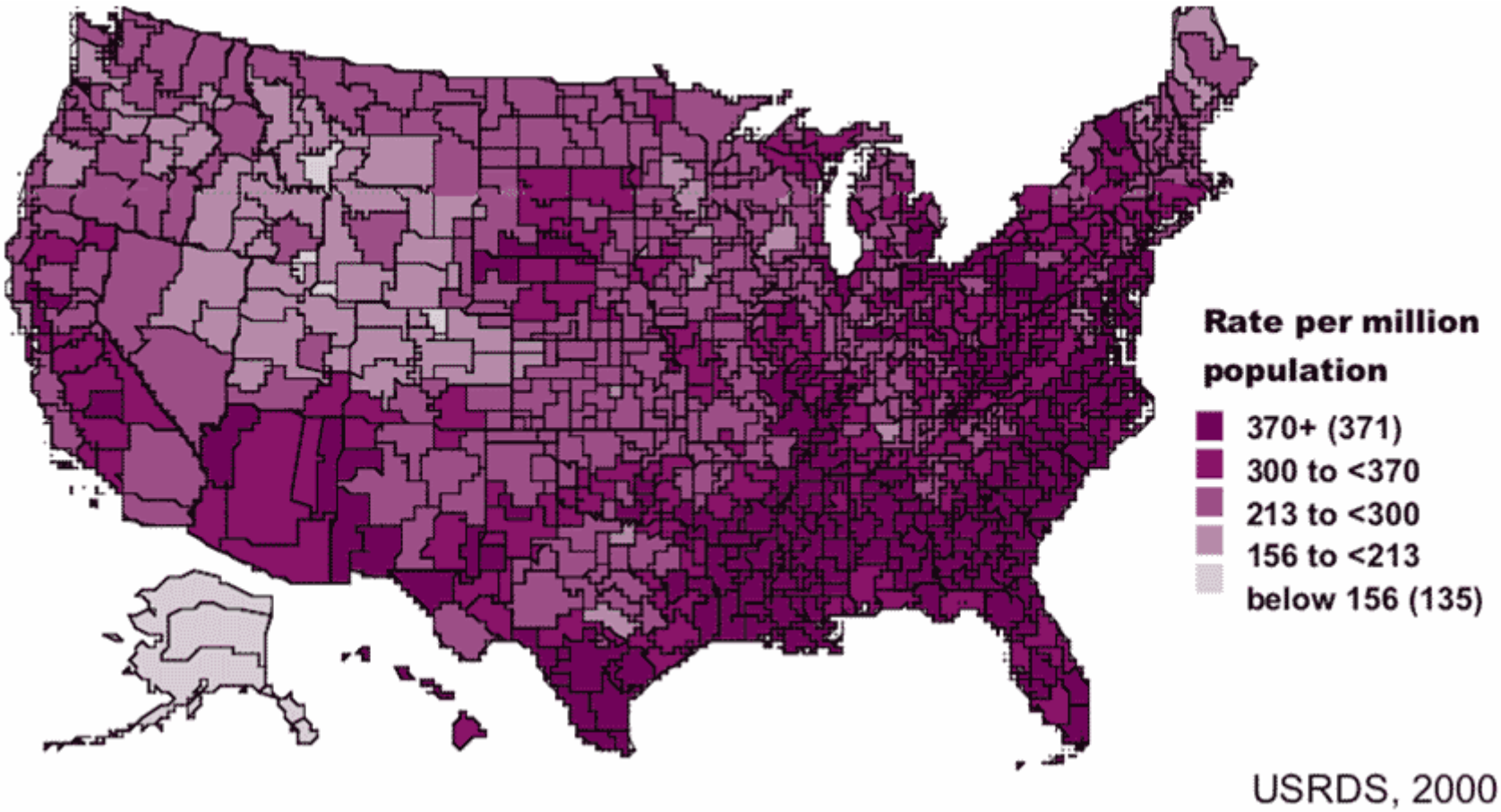

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Prevalence of Renal Insufficiency in U.S.

GFR (ml/min/1.73 m^2)	59-30	29-15	< 15
Number of People	7.6 Million	360,000	> 300,000

More than 8 million Americans have substantial kidney impairment and 10 million more have albuminuria.

Coresh, Levey, et al. Am J Kid Dis 2003; 41: 1-12.

How to test for chronic kidney disease

- **Estimate GFR from serum creatinine**
- **Estimate GFR from creatinine clearance**
- **“Spot” urine albumin to creatinine ratio**

Why an emphasis on serum creatinine?

1) Serum creatinine is much more frequently ordered than quantitative urinary albumin

2) Serum creatinine is harder to interpret than albuminuria

3) Ordering urinary albumin presupposes concern for chronic kidney disease

4) Creatinine clearance is less accurate than eGFR, is difficult to perform correctly, and presupposes concern for CKD

NKDEP

At what level of creatinine does a 65-year-old diabetic, hypertensive white woman weighing 50 kilograms have chronic kidney disease (CKD)?

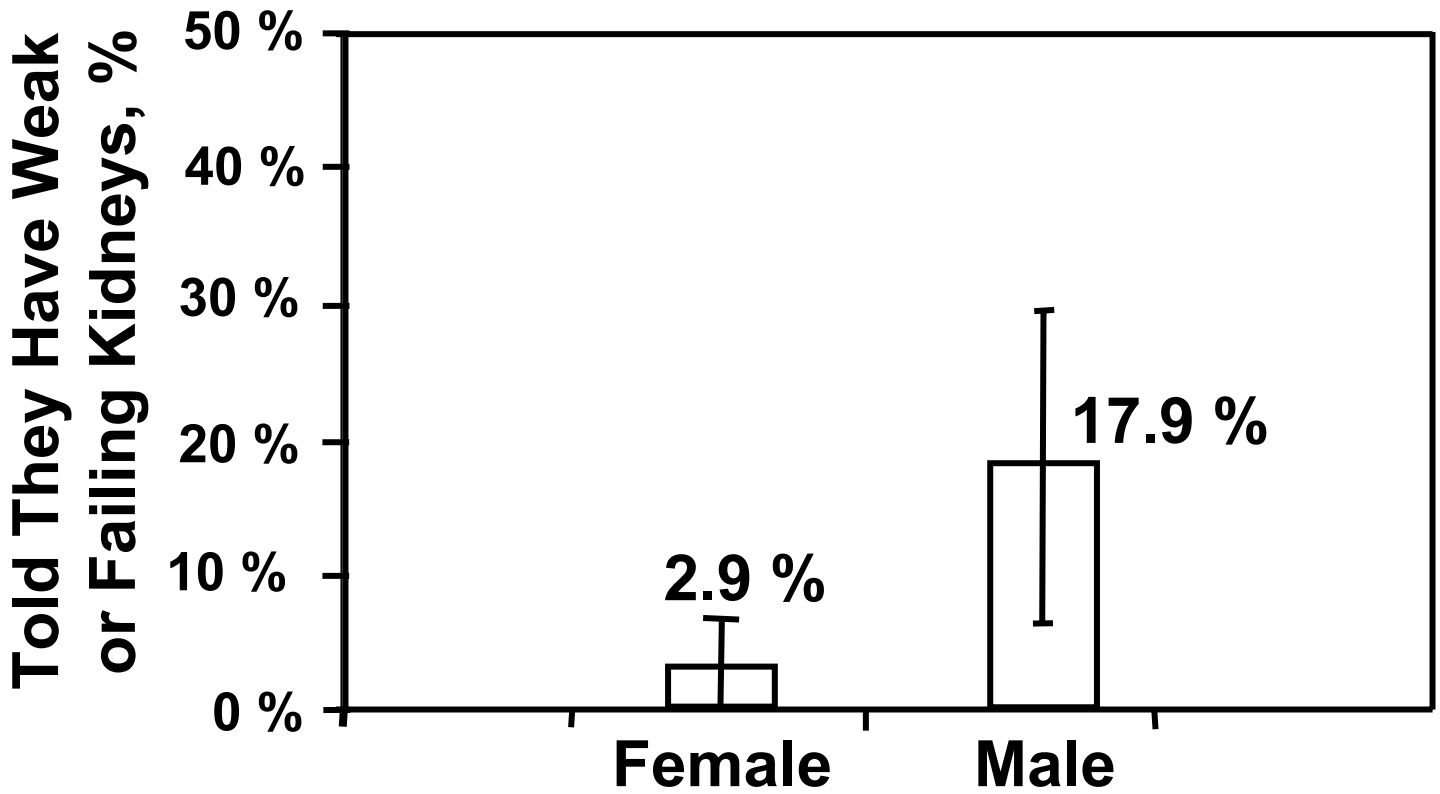
77% of physicians said:

Creatinine > 1.5 mg/dL

Actual eGFR at this creatinine = 37 mL/min/1.73m^2

Creatinine = 0.94 mg/dL when eGFR = 60 mL/min/1.73 m^2

Less than 20% of people with CKD are aware they have the disease



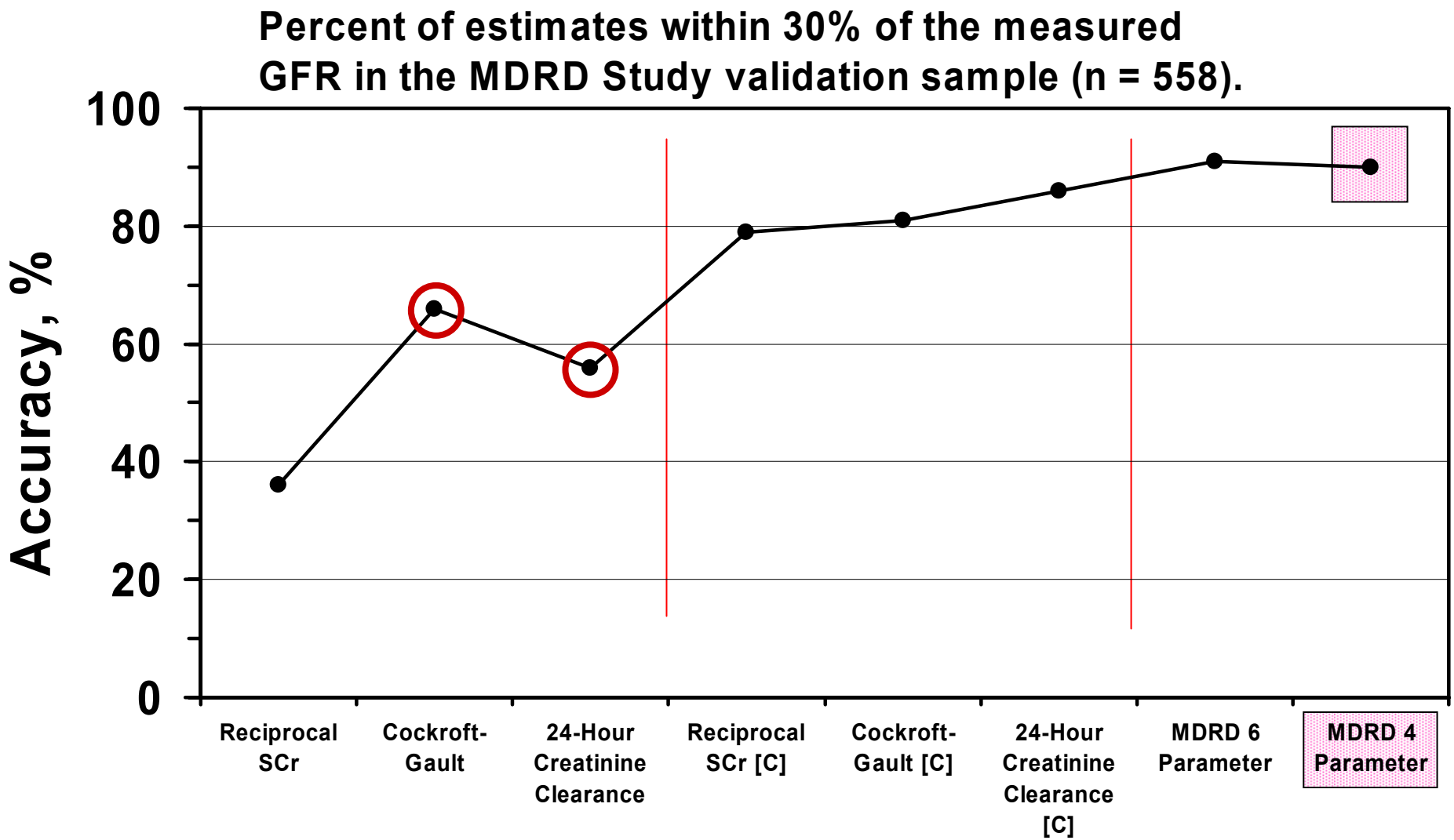
Coresh, 2003

Why?: creatinine reference interval does not easily correlate with GFR

GFR estimating equations

- **The next slide shows that creatinine clearance and estimated creatinine clearance using the Cockcroft-Gault equation have poorer accuracy at predicting GFR than do the MDRD equations.**
- **The middle section with [C] notation shows that applying correction factors can improve the accuracy of the procedures to predict GFR.**
- **The right section shows that the four parameter MDRD equation had as good performance as the six parameter version and is recommended because it is simpler to implement.**

GFR estimation



Redrawn from: K/DOQI Clinical practice guidelines for chronic kidney disease. Am J Kidney Dis 2002;39:S1-S266.

NKDEP recommends the MDRD four parameter estimation equation for adults age 18 and older

GFR (mL/min/1.73 m^2) =

186^{*} x Creatinine (serum) $^{-1.154}$

x Age $^{-0.203}$

x 0.742 (If Female)

x 1.210 (If African-American)

*** use 186 for conventional calibration;**

*** use 175 for calibration traceable to IDMS**

MDRD equation limitations

- Population was adult (18-70 years) white and African-American with chronic GFR <90 mL/min/1.73m^2
  - Acceptable performance for diabetics
- Agreement with measured GFR is poorer for:
  - Hospital inpatients
  - Acute renal failure
  - Normal renal function
- Validation is underway for additional ethnic groups, patient groups, and individuals with normal renal function

Creatinine measurement limitations for any GFR estimating equation

- **Conventional calibration has not been standardized among methods**
  - **Original MDRD equation was based on Beckman CX3 routine method results from Cleveland Clinic**
- **Jaffe method non-specificity influences on individual patient creatinine results**
- **Measurement bias and imprecision have a larger impact on result variability as creatinine values get lower (GFR gets higher)**

How does creatinine measurement performance impact calculated GFR

Critical serum creatinine values

- **Adults:**
  - **@ GFR = 60 mL/min/1.73m^2,**
  - **Creatinine is 1.0-1.6 mg/dL (88.4-141 µmol/L) for different demographic groups**
- **Pediatrics:**
  - **Lower creatinine values correspond to impaired kidney function**
  - **Performance of current creatinine methods is marginal to use an estimating equation**

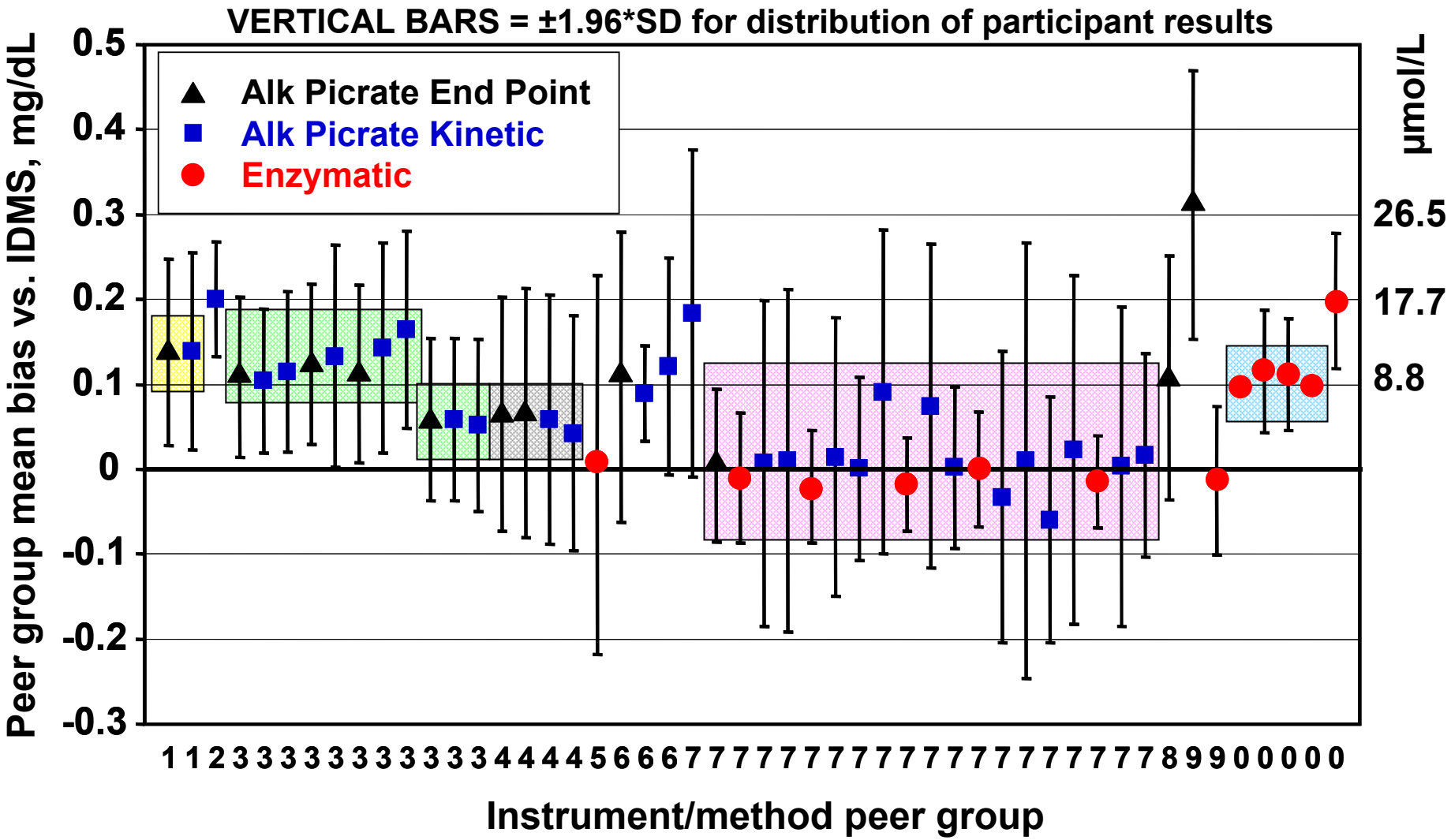
Commutable Material

- **A reference or control material that has equivalent mathematical relationships between the results of different measurement procedures to those observed for native clinical samples.**

- **The next two slides show results from PT/EQA Surveys that used a commutable serum specimen that had IDMS reference method target values assigned.**

CAP, 2003, Fresh Frozen Serum, N = 5624

Creatinine = 0.90 mg/dL (79.7 µmol/L)



Miller et al. Arch Pathol Lab Med 2005;129:297-304

Creatinine bias vs. IDMS over time

RMP value =	0.86 mg/dL (76 µmol/L) Bias 1994[a]		0.90 mg/dL (80 µmol/L) Bias 2003[b]	
Beckman CX	0.08	(7)	0.12	(11)
Dade Dimension	0.08	(7)	0.06	(5)
Roche 717/747	0.22	(19)	0.00	(0)
Olympus	0.13	(11)	0.11	(10)
Ortho Vitros	0.14	(12)	0.10	(9)

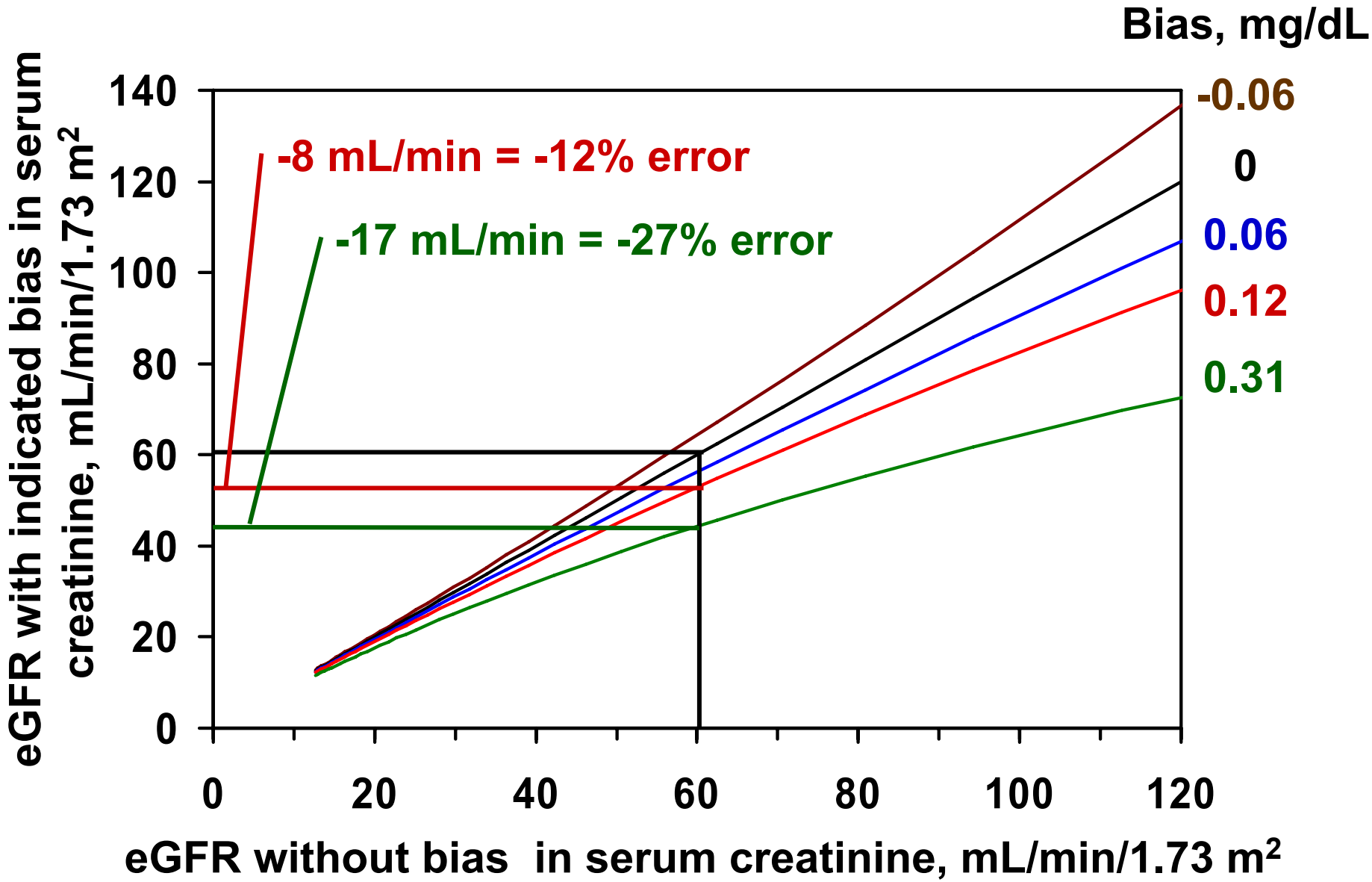
[a] Ross et al. Arch Pathol Lab Med 1998;122:587-608

[b] Miller et al. Arch Pathol Lab Med 2005;129:297-304

Impact of creatinine method performance on estimated GFR (1)

- The next slide shows the impact of bias.
- As the GFR gets larger (less CKD), the creatinine gets smaller, and the impact of bias in creatinine value has a progressively greater impact on the variability in eGFR.
- The bias values illustrated are the typical, and the worst, observed in the 2003 CAP data in a previous slide.
- The goal of the creatinine standardization program is to reduce the bias among methods to low levels to improve the accuracy of estimated GFR.

Impact of creatinine bias on GFR

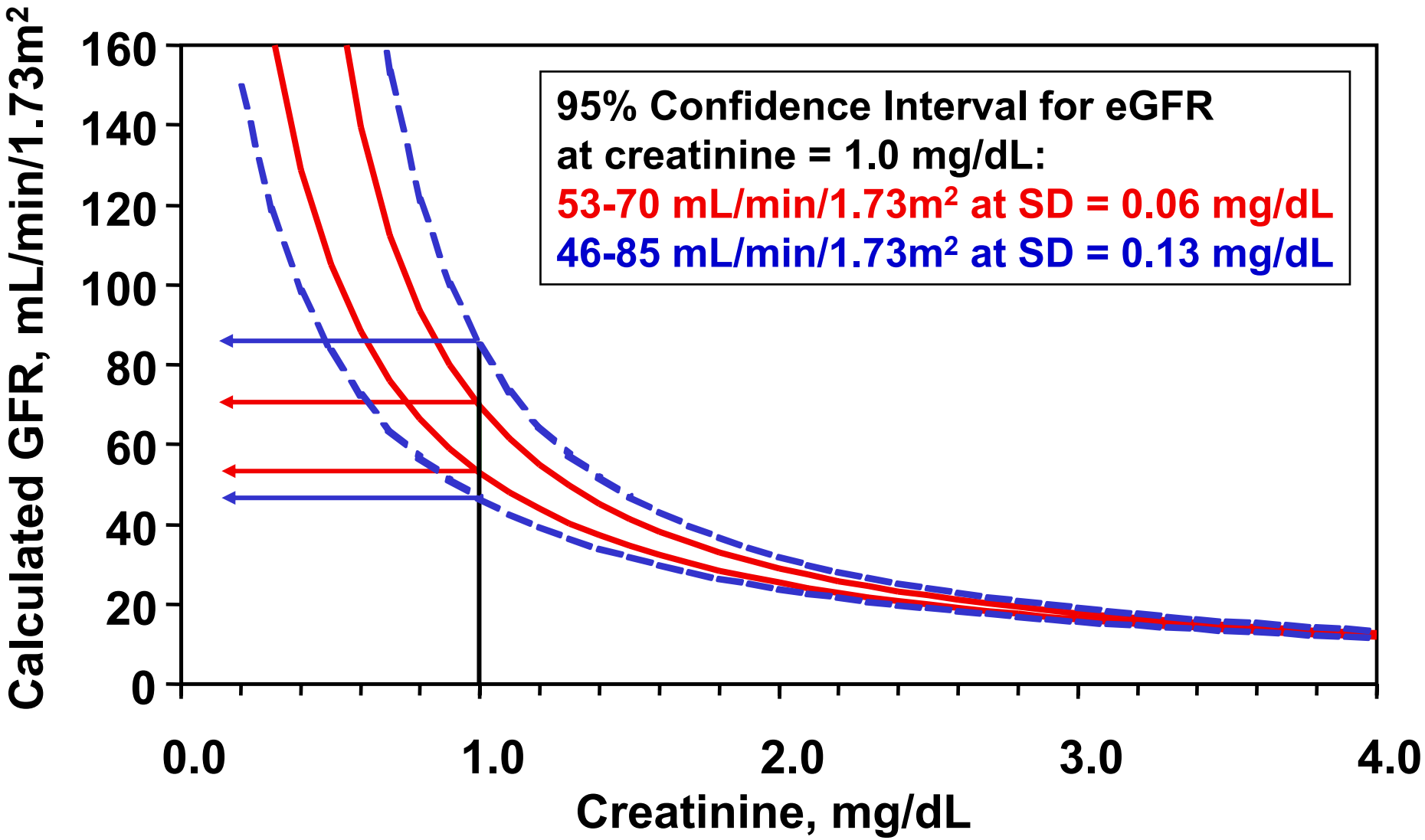


Myers et al. Clin Chem 2006;52:5-18

Impact of creatinine method performance on estimated GFR (2)

- The next slide shows the impact of imprecision.
- As the creatinine value gets smaller, the impact of imprecision has a progressively greater impact on the variability in eGFR.
- The SD values illustrated are the median, and the worst, observed in the 2003 CAP data in a previous slide.
- Both bias and imprecision adversely affect the variability in eGFR at lower creatinine values. These measurement limitations are part of the reason NKDEP recommends not to report eGFR values >60 mL/min/1.73m^2.
- At GFR <60 mL/min/1.73m^2 (higher creatinine) the bias and imprecision have less impact on the variability, and thus the clinical reliability, of eGFR.

Impact of imprecision on GFR



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What creatinine method performance is needed

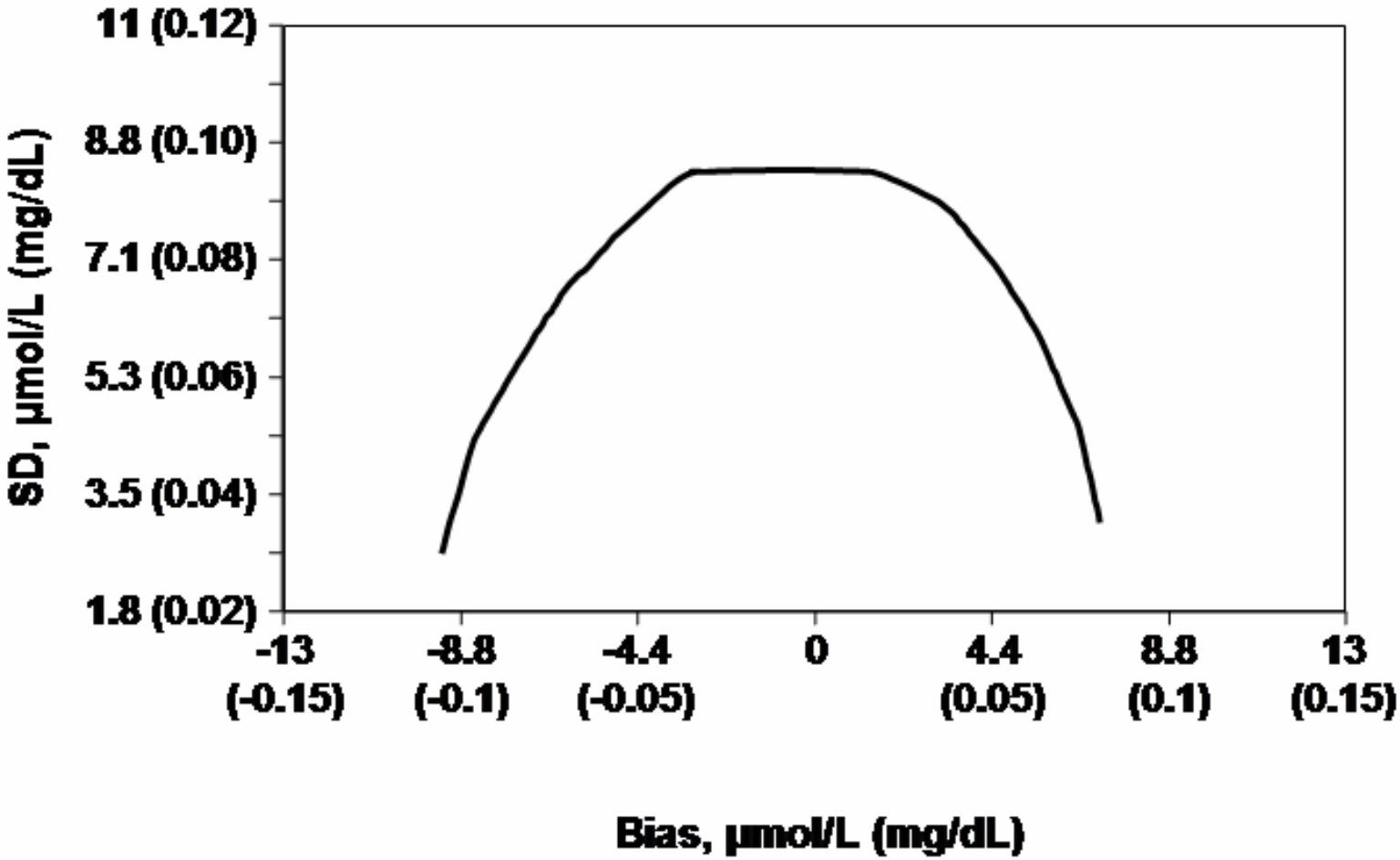
Total error in creatinine measurement is not to increase the variability in eGFR more than 10% in the critical creatinine range 1.0-1.5 mg/dL (88-133 µmol/L)

- **Comparable performance is needed in the 0.6-1.0 mg/dL (53-88 µmol/L) range for pediatric patients and to extend eGFR to higher values**
- **Method non-specificity also needs to be addressed**

Required creatinine method performance

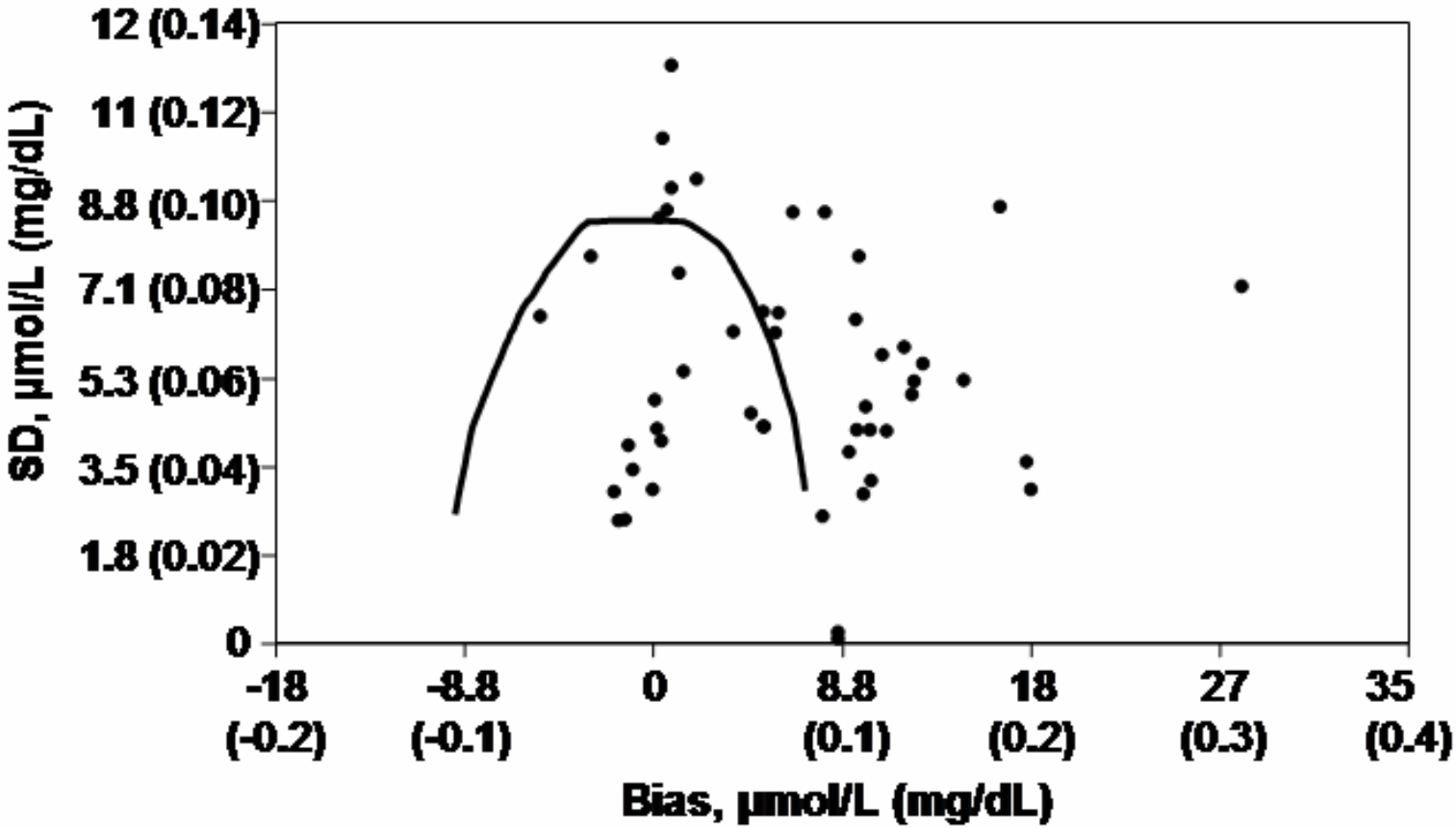
- The next slide shows a figure that defines the total error limits, as a combination of bias and imprecision, that will meet the criteria in the previous slide. A method that has bias and imprecision within these boundaries will have acceptable performance to allow standardized use of the MDRD equation.
- The following slide shows the combinations of bias and among laboratory SDs for the methods represented in the 2003 CAP Survey in a previous slide. Most methods had adequate imprecision to meet the total error goal if the bias could be reduced to low values.
- The creatinine standardization program is intended to provide IVD manufacturers with appropriate tools to allow them to achieve calibration traceability to IDMS reference measurement procedures.

Total Error budget for creatinine measurement in the range 1.00-1.50 mg/dL



Myers et al. Clin Chem 2006;52:5-18

Performance of routine methods compared to the TE limit for creatinine



Myers et al. Clin Chem 2006;52:5-18

NKDEP Laboratory working group recommendations

- **Clinical Chemistry 2006; 52:5-18**
- **www.nkdep.nih.gov/labprofessionals/index.htm**
  - **Updated regularly**

Implement calculated GFR now

- **Use the conventional calibration MDRD equation for methods not calibrated to IDMS**
  - **Many routine methods have a calibration bias that is similar to that of the routine method used in the MDRD study.**
- **Use the IDMS-traceable MDRD equation for methods calibrated to IDMS**
- **Use creatinine reported to two decimals (mg/dL), or nearest whole number (µmol/L), in the MDRD calculation**

Reporting calculated GFR

- **Report GFR with all creatinine results**

  (Consider if appropriate for inpatients)

- **Report two values:**
  - **GFR_{est} if African-American**
  - **GFR_{est} if not African-American**

- **If value is $\leq$ 60, report rounded to a whole number (e.g. 53 mL/min/1.73 m^2)**

- **If value is > 60, report as ">60 mL/min/1.73 m^2"**
  - **Limited by calibration variability, imprecision, and MDRD equation accuracy**

Creatinine calibration standardization program

- **Eliminate the bias between different methods**
  - **Make calibration traceable to IDMS reference measurement procedure (gold standard)**
- **Improve the accuracy and consistency of estimated GFR**
- **Creatinine results for most methods will be 10-20% lower after standardization**
- **IVD manufacturers expect two years to implement recalibration of existing methods**

How to standardize

- **Collaborate with a reference laboratory that offers IDMS measurements**
  - **JCTLM has approved 3 methods submitted by 3 labs**
  - **New LC-IDMs method expected in 2006**
- **NIST will release SRM 967 in 2006**
  - **Off-the-clot fresh frozen serum material**
  - **Two concentrations approx. 0.8 and 4.0 mg/dL**
  - **Commutability will be validated for many routine methods**

For clinical laboratories

- **Coordinate introduction of calibration traceable to IDMS with use of the correct MDRD equation**
- **Communicate clinical issues associated with IDMS-traceable calibration (even if a method is already IDMS-traceable)**
  - **To clinical care providers**
  - **To prescribers of medications**
  - **To pharmacists**

Clinical issues to communicate

- **Creatinine reference interval change**
  - **Creatinine clearance change if urine and serum calibrations are affected differently**
- **IDMS-calibrated creatinine results will affect decision algorithms used to adjust drug doses**
  - **Cockcroft-Gault estimation of creatinine clearance is commonly used by pharmacists (mfr. claims)**
  - **Criteria based only on serum creatinine concentration**
  - **Pediatrics: recommend a measured GFR or creatinine clearance for critical and potentially toxic drug effects**

For IVD manufacturers

- Implement calibration traceability to IDMS
- Provide guidance to labs per previous slides
- Provide the relationship between results from the IDMS-calibrated method compared to results for a previous conventionally calibrated method
  - Critical for drug dose adjustment algorithms that are based on algorithms that used creatinine methods with conventional calibration
- Communicate with PT/EQA providers
- Address imprecision and non-specificity

For PT/EQA providers

- **Accommodate grading of results from participants during the transition from conventional to IDMS-traceable calibration**
  - **A bimodal distribution of results may occur**
- **Communicate with IVD manufacturers regarding timing of calibration standardization**
- **Introduce programs that use commutable serum materials**

For pharmacists and the pharmaceutical industry

- Drug dose adjustment procedures may need to be modified when creatinine is calibrated to be traceable to IDMS because manufacturer claims are based on algorithms that were developed using creatinine methods with conventional calibration.
- Lab needs to inform pharmacy and clinical providers of the magnitude of the change in creatinine results when a method with calibration traceable to IDMS is used.
- Transition to using the MDRD estimating equation in product labeling.

For software providers

- **Support the MDRD equation**
- **Allow adjustment of the creatinine value used in the Cockcroft-Gault equation in pharmacy packages**

Summary

- **Report eGFR with creatinine results using the correct MDRD equation**
- **Coordinate use of a creatinine method with IDMS-traceable calibration with use of the IDMS-traceable MDRD equation**
- **Communicate the clinical issues associated with IDMS-traceable creatinine results**