Excellence in Patient-Centered Laboratory Medicine:

Challenges for Academia, Industry and Government

David E. Bruns, MD

3 July 2006

Durban, South Africa

Focus Today

- Analytical performance and patient care.
- Diagnostic accuracy of tests
- Outcomes studies

Characterization of Medical Tests

- 1. Analytical Performance: Accuracy, precision..
- 2. Nonanalytical Factors: Biologic variation...
- 3. Diagnostic Accuracy: LR, ROC…
- 4. Clinical Usefulness: Outcomes, added info...
- 5. Cost-benefit Analysis: Cost/QALY...

Key Analytical Characteristics of Tests

- **Linearity**
- **Precision** ("reproducibility")

  CV = SD/mean
- **Accuracy** (term includes precision in Europe)

  - bias (non "trueness") - difference from truth
  - interferences
  - "protocol-specific bias" (e.g.,carryover)
- **Detection Limit** (not = "sensitivity")

Does Analytical Quality Matter?

- **Medical schools** do not address the question.
- **Medical authors** do not indicate analytical quality of evaluated tests.
- **Medical journal editors** are only beginning to require information on test methods and analytical performance.
- **Medicare**: "A glucose is a glucose."

Not surprisingly, physicians rarely think about differences among test methods.

“Glucoses” Are Not Created Equal

- Reducing sugar methods, o-toluidine, glucose oxidase, hexokinase
- Spectrophotometric, electrochemical, etc.
- Interferences, bias, turnaround time
- Imprecision (CV) can be 1.0 – 1.5% (clinical laboratories) to 5- 20% (POCT).

How Accurate and Precise Must Glucose ***Meters*** Be for Adjusting Insulin Doses?

- Published analytical goals (quality specifications) are not patient-centered or evidence-based.
- Proposed goals for imprecision (CV) range from 1% to 20 %.

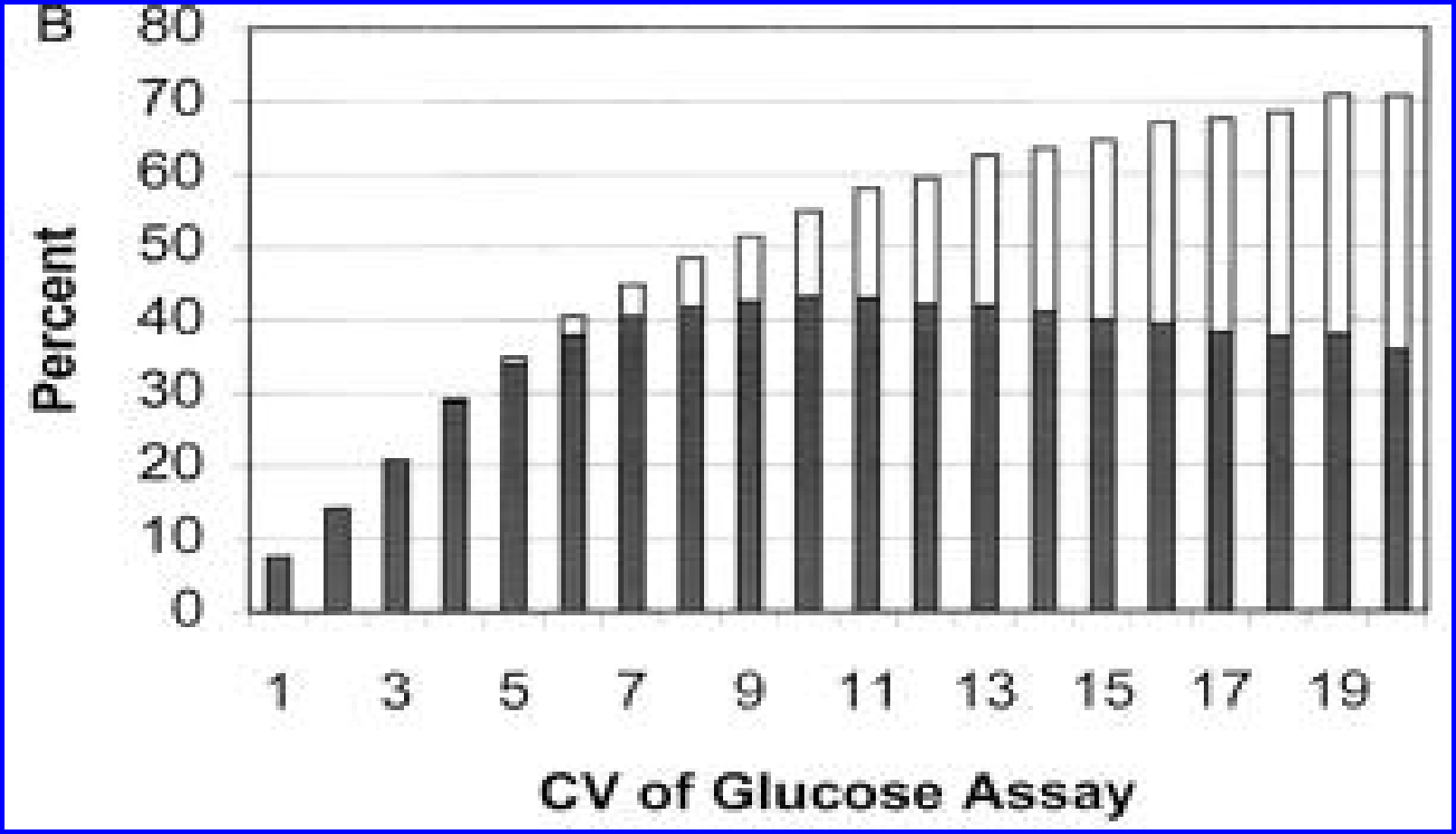
Effect of Meter Error on Selected Insulin Dose

(Boyd and Bruns, *Clin Chem*)

- Some meter errors lead to errors in insulin dose, i.e., the insulin dose will not be appropriate for the patient's glucose.
- Simulation modeling (in a computer) can quantify rates of errors in insulin dose.

Percent of Insulin Doses in Error

(One-step errors in black, >1-step in white)



Errors in Glucose Meters and Errors in Insulin Dose - Results

(Boyd and Bruns, *Clin Chem*)

- With imprecision of current meters, 16% to >45% of insulin doses are in error.
- Worse when bias and interferences are considered.
- For 95% of insulin doses to be as intended, bias and imprecision must each be < 1.0% – 1.5%, assuming no interferences.
- No existing meters and no published goals for meters approach this target.

Glucose Measurements to Adjust Insulin Doses

Is an imprecision (CV) of 1.5% attainable?

--**No**, if there is no understanding of the relation between analytical quality and clinical decisions.

--**Perhaps**, if potential value in disease management is understood

Analytical Errors Affect Patient Management in All Areas

- Heart markers, cholesterol, HIV viral load
- Same type of problem as with glucose meters, but usually simpler
- As CV or bias increase at concentrations near the cutpoint, the proportion of patients who are misclassified, and thus may be mistreated, increases.

Misclassification rates for treatment with statin drugs: Cholesterol, 240 mg/dL

(G Klee et al, Scand J Clin Lab Invest 1999, and fax, 2002)

Bias	Percent Misclassified, N = 20,000
10 % (CLIA PT)	79 %
3 % (NCEP)	20 %
1 %	6 %

Analytical ***Interferences*** Also Affect Patent Care

- **False-positive cardiac troponin**

  Result: Unwarranted cardiac catheterization
- **False-positive hCG**

  Causes: Anti-animal antibodies

  Results: Erroneous diagnosis of carcinoma and then unnecessary surgery, chemotherapy and radiation therapy

Human Anti-Ig Antibodies

- Interference in assays known since 1971.
- Two-site assay interference described in 1980s.
- Problem for all cardiac marker tests – cTnI, CKMB, BNP, tHcy, hsCRP...
- Awareness outside the laboratory is poor.

Analytical Performance of Tests Affects Patient Care

- Imprecision
- Bias
- Interferences
- … and add your own favorites

Analytical Performance of Tests Affects Patient Care: Challenges

- **Industry:** To develop improved testing systems, available at affordable costs
- **Academia:** To provide objective evaluation of new test systems
- **Government:** To identify funds for support of research and for purchase of the best, cost-effective testing systems

Characterization of Medical Tests

- 1. Analytical Performance: Accuracy, precision..
- 2. Nonanalytical Factors: Biologic variation...
- 3. **Diagnostic/Prognostic Accuracy**: LR, ROC…
- 4. Clinical Usefulness: Outcomes, added info...
- 5. Cost-benefit Analysis: Cost/QALY...

Methodologic Standards in Test Research Reid et al JAMA 1995

- Examined 112 test evaluations published in Lancet, NEJM, JAMA, and BMJ, 1978-93.
- Over 50 % of tests were clinical laboratory procedures (32 % radiological).
- Reid et al evaluated adherence to 7 elementary standards of clinical epidemiology.

Proportion of 112 Studies that Met 7 Specific Standards

- Spectrum indicated 27 %
- Subgroup analyzed 8 %
- No verification (work-up) bias 46 %
- No review bias (masking) 38 %
- CI for indices of test accuracy 11 %
- Indeterminate test - N and use 23 %
- Test reproducibility 23 %

» Reid et al JAMA 1995

Does Poor Study Design Matter?

Poorly designed studies => overly-optimistic assessments of the diagnostic accuracy of tests

Lijmer et al. JAMA1999;282:1061-6

- Examined studies of diagnostic accuracy of selected diagnostic tests.
- Compared studies that had acceptable study design with studies of the same test that did not.
- Calculated relative diagnostic odds ratio: RDOR > 1 indicates overestimation of test accuracy when design/reporting is poor.

Relative Diagnostic Odds Ratios

(RDOR > 1.0 indicates overestimation of test accuracy when design or reporting of study is poor)

- Case-control vs series 3.0 (2.0 - 4.5)
- Verification bias present 2.2 (1.5 - 3.3)
- Test poorly described 1.7 (1.1 - 1.7)
- Patients poorly described 1.4 (1.1 - 1.7)

» Lijmer et al. JAMA 1999

Initiatives to Improve Reporting

- STARD Initiative 2003 – present
- Clinical Chemistry Checklist 1997, 2000

(July 4 in Durban)

Proportion (%) of Studies that Met Standards in 2 Chemistry Journals (Lubreras-Lacarra et al)

Standard	1996	2001	2002
(N)	(18)	(27)	(34)
Spectrum indicated	22%	37%	71%
Patient subgroups	44	26	38
No verification bias	33	48	71
Masking	22	37	44
Conf. Intervals	22	44	65
Indeterminate results	0	15	6
Test reproducibility	83	81	68
Mean (SD)	**32%** **(26)**	**41%**(21)	**52%**(24)

Studies of Diagnostic Accuracy

- Reporting: Improvement has begun, but much room for improvement remains.
- Study design: Still requires attention

Studies of Diagnostic Accuracy: Challenges Are Shared by Academia, Industry and Government

To design, fund, perform and report improved studies of diagnostic accuracy of tests

To educate physicians in the use of the best tests and to not waste money on poor tests

Characterization of Medical Tests

- 1. Analytical Performance: Accuracy, precision..
- 2. Nonanalytical Factors: Biologic variation...
- 3. Diagnostic/Prognostic Accuracy: LR…
- 4. **Clinical Usefulness: Outcomes**, added info...
- 5. Cost-benefit Analysis: Cost/QALY...

What Are "Outcomes"?

- **Outcomes** are results of medical interventions in terms of health or cost.
- **Patient outcomes** are results that are perceptible to the patient.

M.G.Bissell, 2000, AACC Press

Examples of Outcomes

- Mortality
- Length of stay (in hospital or clinic, etc.)
- Rate of hospital-acquired infection
- Cost of care
- Patient satisfaction

Test Attributes That Are Amenable to Outcomes Studies

- Availability/non-availability of a test(s)
- Method for a test
- Quality of test performance
- Turnaround time
- Method of reporting of test results,

  e.g., interpretive reporting vs data only

Outcomes Studies. Reimbursement, and JCAHO

- Outcomes evidence is demanded by payers – governments, HMOs, insurance carriers.
- The US Joint Commission on Accreditation of Health Organizations (JCAHO) **defines** quality in health care as increased probability of desired **outcomes** and decreased probability of undesired **outcomes**.

Outcomes Studies in Laboratory Medicine

- Difficult to design and difficult to perform
- Outcomes of testing occur only after other steps:
  - A test leads to prompt and correct diagnosis only if result is interpreted by the patient's physician promptly and correctly.
  - A correct diagnosis leads to improved outcome only if an effective intervention (such as a drug) is available and is provided.

Outcomes Studies of Laboratory Testing: Examples

- **Fecal occult blood testing to detect polyps**

  - Decreased incidence of colon cancer
- **Rapid PCR testing of spinal fluid for enterovirus meningitis in children**

  - Shortens length of hospital stay for meningitis (saves money, decreases parents' anxiety)

Demonstrating Improved Outcomes

- Academia, manufacturers and private laboratories must identify how our work improves health outcomes and lowers costs.
- Demonstrating improved outcomes will require collaboration with clinicians who depend on the laboratory and thus need to see the laboratory supported.

Summary

- **Analytical quality** affects patient-management decisions.
- Studies of **diagnostic/prognostic accuracy** are getting better, but room for improvement remains in study design and reporting.
- **Outcomes studies** are needed.

How To Fund Medically Valuable Analytical Quality in a Time of Limited Resources?

- Base quantitative analytical goals on medical uses of tests, not on expert opinion.
- Quantify effects of analytical errors on clinical uses.
- Perform outcomes studies to quantify effect of improved analytical quality on patient outcomes.

Goals for Analytical Quality: Policy Implications

Policy must consider:

- Not: How much analytical error is OK?

  But: How much error in patient management is allowable?

- Not: What is the value of better precision (or detection limit, etc.)?

  But: What is the value of improved clinical management?

Excellence in Patient-Centered Laboratory Medicine

- Important
- Presents challenges for
  - Academia
  - Industry
  - Government
- Cooperation and new ideas are needed.

Thank you for the opportunity to discuss these ideas with you.

Simulation Modeling of Glucose Meters – Methods (1)

- Computer generated 10,000 numbers representing “true” glucose concentrations within chosen intervals.
- “Measured” the glucose with a virtual meter of known imprecision and bias.

Simulation Modeling of Glucose Meters – Methods (2)

- Used a rule to determine the insulin doses for the "true" glucose and "measured" glucose values.
- Tallied the number of errors in insulin doses.
- Repeated the process for meters with CV = 0 – 20% and bias = 0 – 20%, and for various distributions of true glucose and for two rules (scales) for adjusting insulin dose.

Intensive Insulin Therapy in SICU

van den Berghe et al, NEJM 2001

- RCT, 1548 patients
- Glucose measured hourly to adjust insulin infusion rate according to a schedule (rule).
- Target glucose = 80 - 110 mg/dL

  [4.4 - 6.1 mmol/L]
- Mortality decreased from 8.0 % to 4.6 %

Intensive Insulin Therapy in SICU

van den Berghe et al, NEJM 2001

- "For such strict BG control goals a good technical precision/accuracy is vital."*
- CVs 3 % (2.8 & 3.5 at 90 & 220 mg/dL)*
- In US, ICUs are using bedside glucose meters with CVs > 10%.

---

*Personal Communication, Roger Bouillon, March 16, 2002.

Intensive insulin therapy in the surgical intensive care unit.

van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R.

N Engl J Med 2001 Nov 8;345(19):1359-67

High hCG Without a Pregnancy

First Reactions:

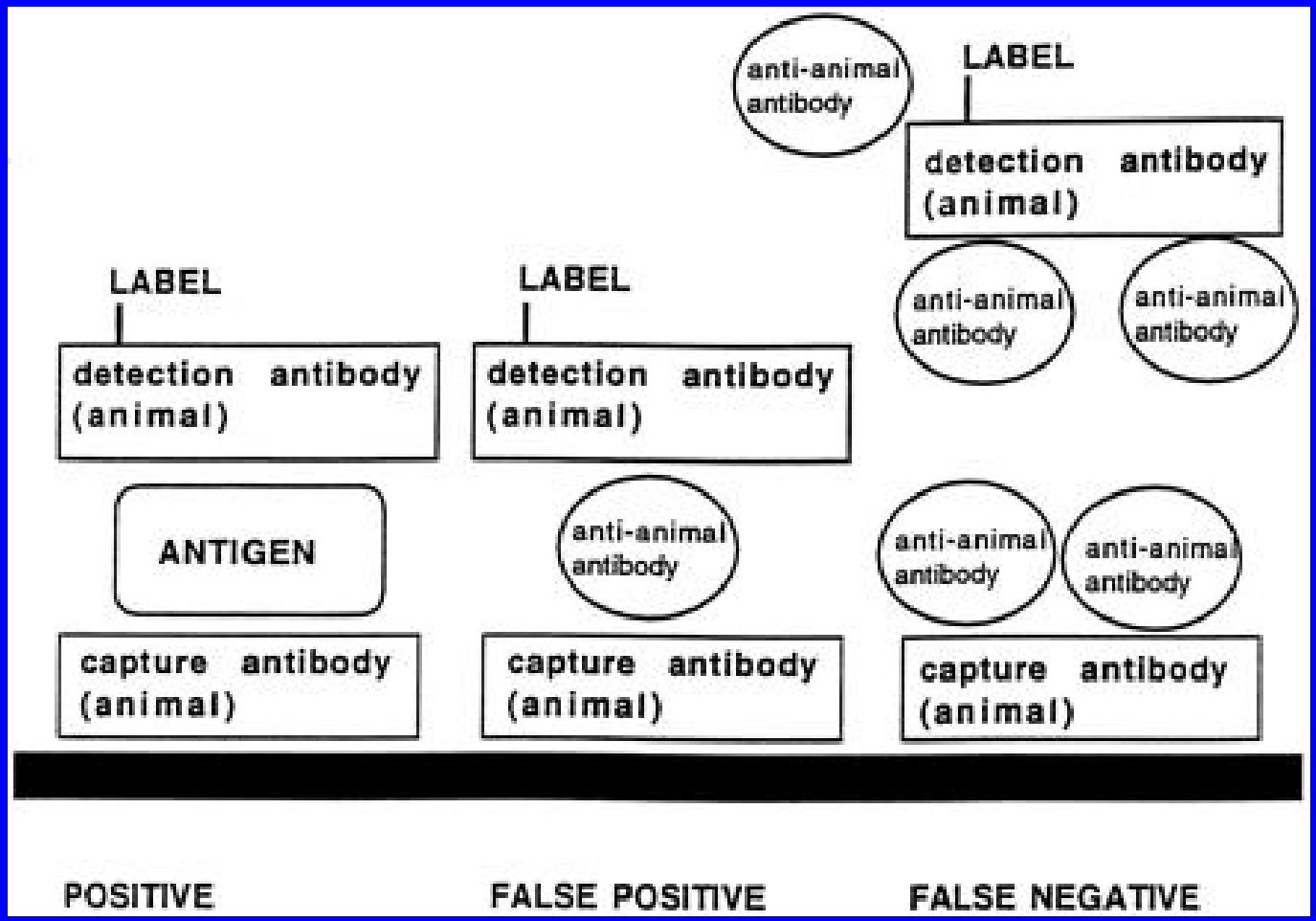
- Obstetricians: Cancer
- Clinical chemists: HAMA

HAMA

- **HAMA**: **H**uman **A**nti-**M**ouse **A**ntibody
- Patient's antibody binds reagent (mouse) antibody
- Similar phenomena with rabbit or goat or other antibodies.

Mechanism of Interference

(Kricka LJ. Clin Chem 1999)



Outcomes Studies Related to Laboratory Medicine

- **D-Dimer in suspected pulmonary embolism to decrease use of expensive imaging tests**
  - **Increases costs if D-dimer testing is misused**
- **POCT to decrease length of stay in emergency (A&E)**
  - **Controversial**
- **POCT and LOS in clinic**
  - **May help, but only if part of redesigned patient flow**
- **Preoperative testing and complication rates after cataract surgery**
  - **No effect**
- **Discontinuation of bleeding time test (bleeding time)**
  - **No effect on mortality rate or other measures**

How Might Clinicians Learn about Laboratory Tests?

- Bring clinical residents into laboratory.
- Train pathology residents in the relationship of analytical quality to outcomes so that they can communicate to other residents.
- Improve reporting of studies of idagnostic accuracy.
- Foster collaborative research of clinicians and laboratory-based physicians and scientists. Learn the questions that physicians really ask.