

# A View of Clinical Biochemistry Through *Clinical Chemistry*

David E. Bruns

4 July 2006

Durban, South Africa

Dear Sir or Madman:

Please send us the forms for  
your vapid communications.

I have received no ... support for this work. In fact, the article was written on a Sunday afternoon, and my wife was not very supportive of this effort.

# Manuscript (Methods Section)

Transfer the supernatant to a  
conical tube.

# Reviewers' Comments

There are many  
misspelled works.



[Anonymous reviewer]:  
My name is misspelled in Ref  
14.

- Reviewer: The authors should use unpaired t-test.
- Response: We used paired and unpaired t test.

Reviewer 1 has given us food  
for thought.

Re-review

I have examined the revision of manuscript 15-XXX and find that the changes are exclusively changes in the distance between the left and right margins.

# A View of Medicine Through *Clinical Chemistry*

David E Bruns, MD

July 2006

South Africa

# What is *Clinical Chemistry*?

- Subtitle: International Journal of Molecular Diagnostics and Laboratory Medicine
- Paper and electronic ([www.clinchem.org](http://www.clinchem.org))
- Electronic access free 12 months after publication. Always-free access in developing countries
- Full text of all papers is on-line from Vol. 1, No. 1 (1955) to present.

www.clinchem.org  
No. of Distinct Hosts Served per Week

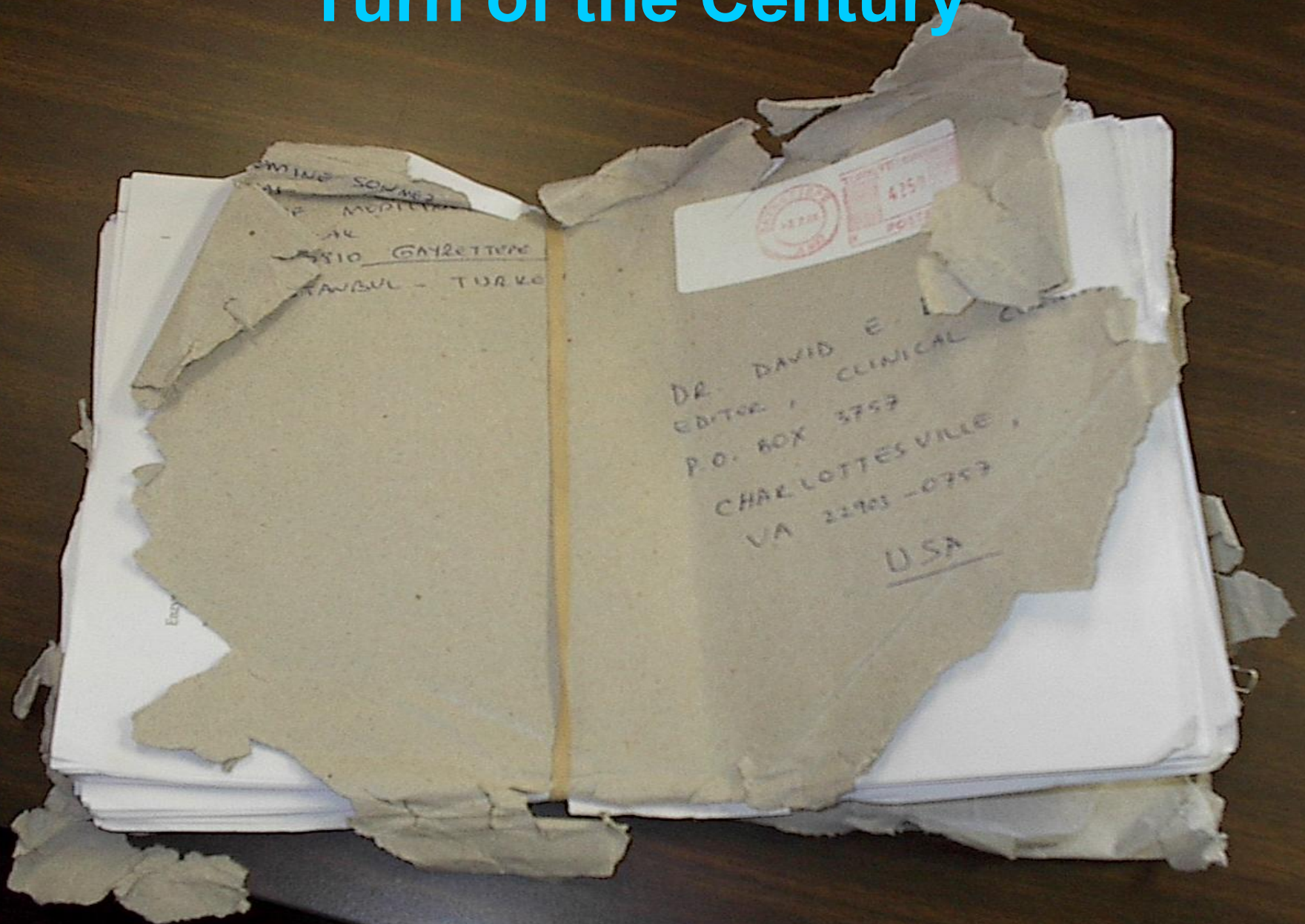




# Weekly Activity at [www.clinchem.org](http://www.clinchem.org)

	<u>2003</u>	<u>2006</u>
Hosts served (e.g., Medunsa)	4,000	30,000
No. of distinct files requested	20,000	100,000
Total completed requests	30,000	300,000
Mbytes transferred	3,000	20,000

# Turn of the Century



SWINE SORE  
MURKIN

AK  
1810 GARRETT  
Istanbul - TURKEY

425  
POSTAGE

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# *Clinical Chemistry*

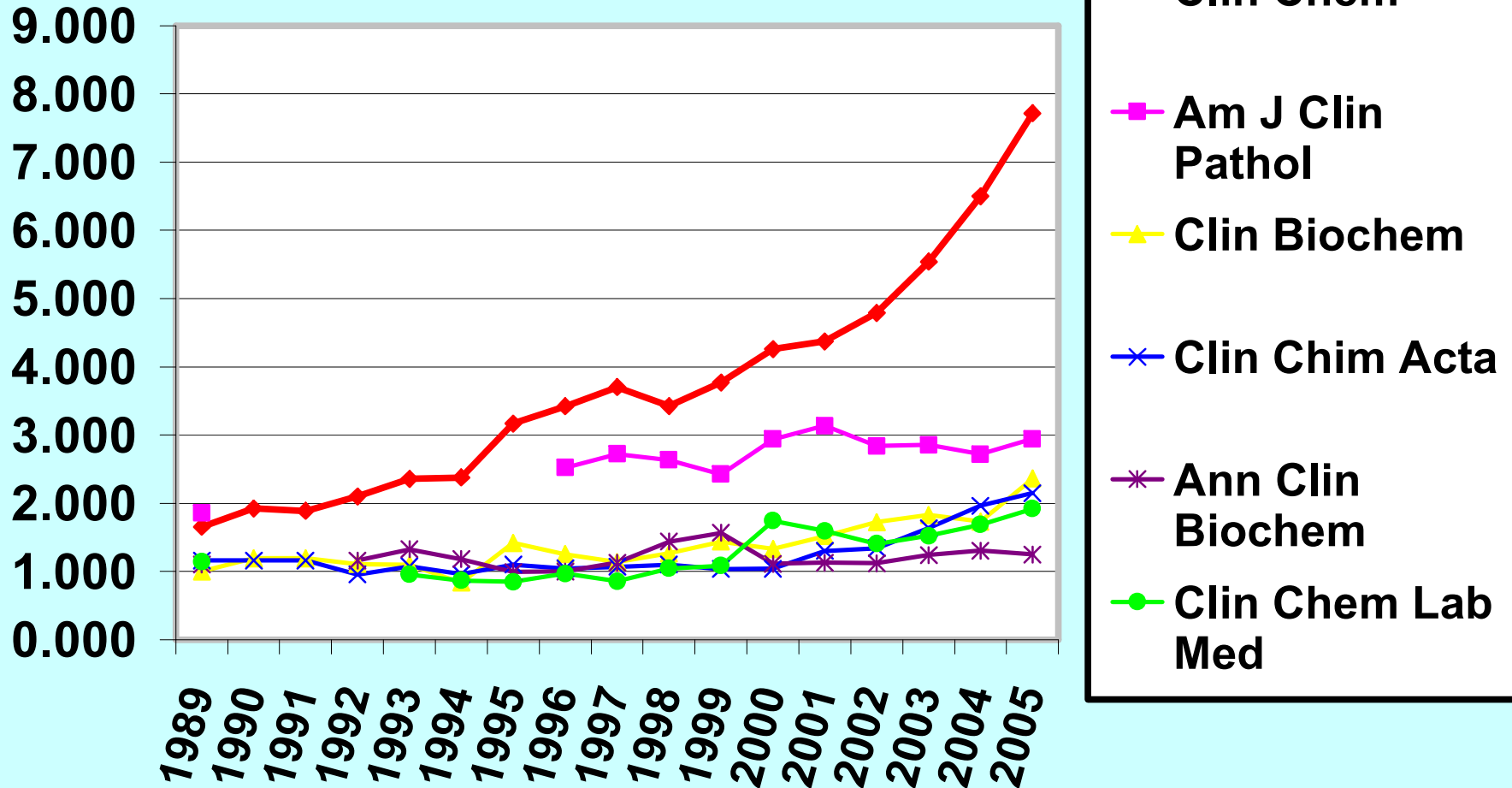
## International Journal of Molecular Diagnostics and Laboratory Medicine

- Submissions on line ([submit.clinchem.org](http://submit.clinchem.org))
- No fees to authors
- Mean time to decision: 23 calendar days
- Accepted papers are published on-line 3 weeks after acceptance.
- Papers printed in regular issue 7 weeks later.

# Acceptance Rates at *Clinical Chemistry*, 2002-2005

■ Articles	25%
■ Review articles	52%
■ Technical Briefs	52%
■ Letters to the Editor	61%
■ History	72%
■ Replies to Letters to Editor	84%
■ Editorials	89%

# ISI Impact Factor



# 2005 Impact Factors of Other Journals in Pathology and Laboratory Medicine

<b><u>CLIN CHEM</u></b>	<b><u>7.717</u></b>
<b>AM J PATHOL (top)</b>	<b>5.796</b>
<b>AM J SURG PATHOL (top)</b>	<b>4.377</b>
<b>J CLIN MICROBIOL (top)</b>	<b>3.537</b>
<b>MODERN PATHOL</b>	<b>3.426</b>
<b>TRANSFUSION (top)</b>	<b>3.160</b>
<b>AM J CLIN PATHOL</b>	<b>2.942</b>
<b>J MOL DIAGN (top)</b>	<b>2.885</b>
<b>J CLIN PATHOL (top)</b>	<b>2.170</b>
<b>ADV CLIN CHEM</b>	<b>1.867</b>
<b>ARCH PATHOL LAB MED</b>	<b>1.587</b>

# 2005 Impact Factors of Some Related Non-Pathology Journals

<b><u>CLIN CHEM</u></b>	<b><u>7.717</u></b>
<b>J CLIN ENDO METAB (top)</b>	<b>6.020</b>
<b>J BIOL CHEM</b>	<b>5.584</b>
<b>ANAL CHEM (top)</b>	<b>5.635</b>
<b>J LIPID RES</b>	<b>3.909</b>
<b>BIOTECHNIQUES</b>	<b>2.286</b>

# Clinical Chemistry

Clinical chemistry and *Clinical Chemistry* are  
alive and well.



# Views of Medicine

- Blurring of Boundaries
- Molecular Diagnostics
- Influence of Clinical Epidemiology and Evidence-Based Medicine

# Views of Medicine from *Clinical Chemistry*

- Blurring of Boundaries
  - Between and among disciplines in medicine
  - Between and among nations
- Molecular Diagnostics growing still
- Influence of Clinical Epidemiology and Evidence-Based Medicine

# New and Nontraditional Topic Areas in Clinical Chemistry

(From [www.clinchem.org](http://www.clinchem.org), 19 June 2006)

- **Infectious Disease** (New category) (>17 Articles)
- **Molecular Diagnostics and Genetics** (1172)
- **Evidence Based Laboratory Medicine** (386)
- **Hemostasis and Thrombosis** (127)
- **Proteomics and Protein Markers** (1173)
- **Hematology** (254)
- **Clinical Immunology** (273)
- **Nutrition** (219)
- **Cancer Diagnostics** (New category) (128)
- **Point-of-Care Testing** (New category) (>14)

# What's [Not] in a Name?

Just as

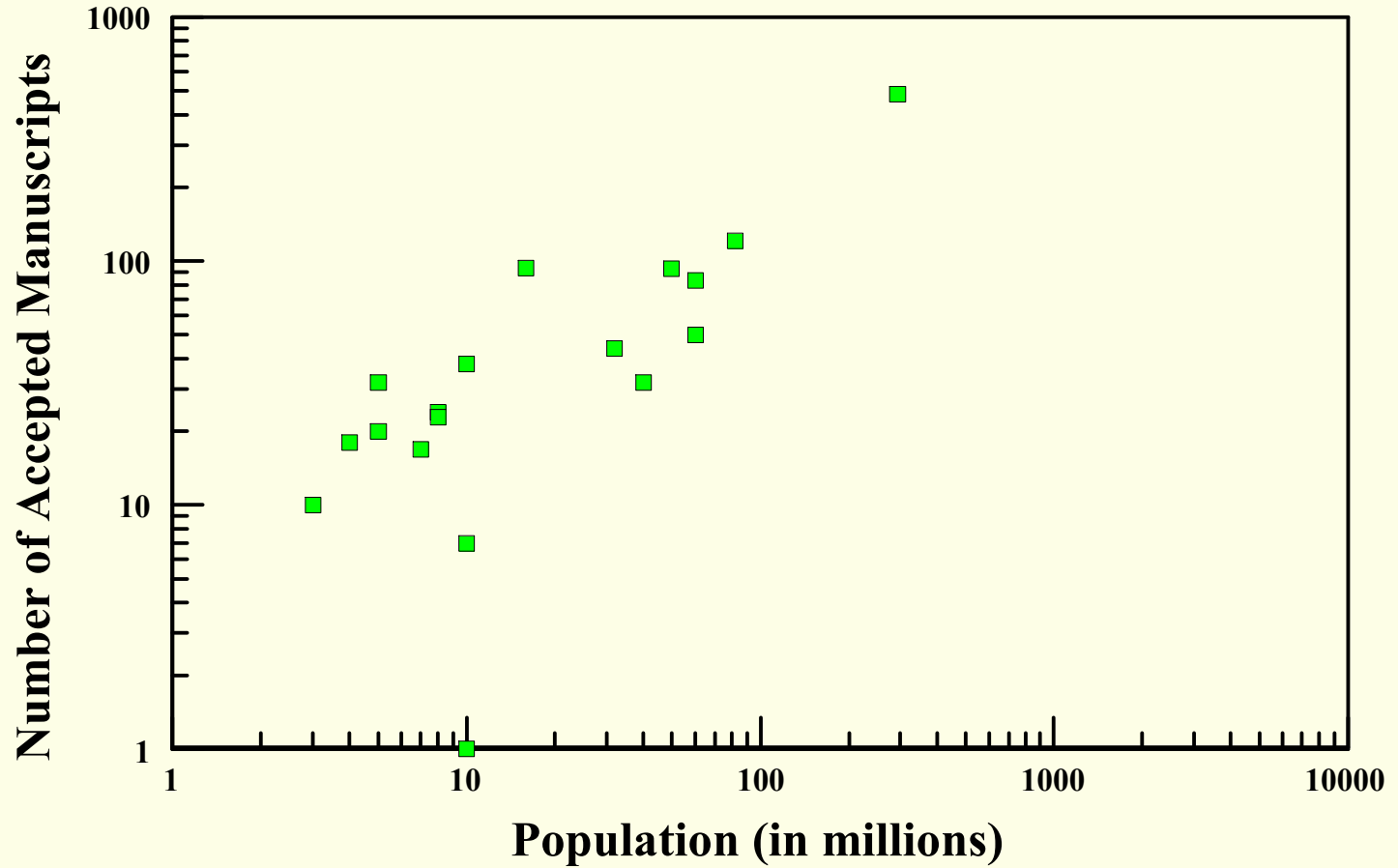
- *The Lancet* is not just about lancets, and
- *The New England Journal of Medicine* is not about medicine in New England,
- *Clinical Chemistry* is not just about the clinical chemistry of 1950s-1980s that remains in the minds of some. It is about the clinical biochemistry and molecular biology of the 21<sup>st</sup> century that crosses old lines between disciplines.

# Blurring of Boundaries Between and Among Countries

# Countries of Origin of Papers in Clin Chem

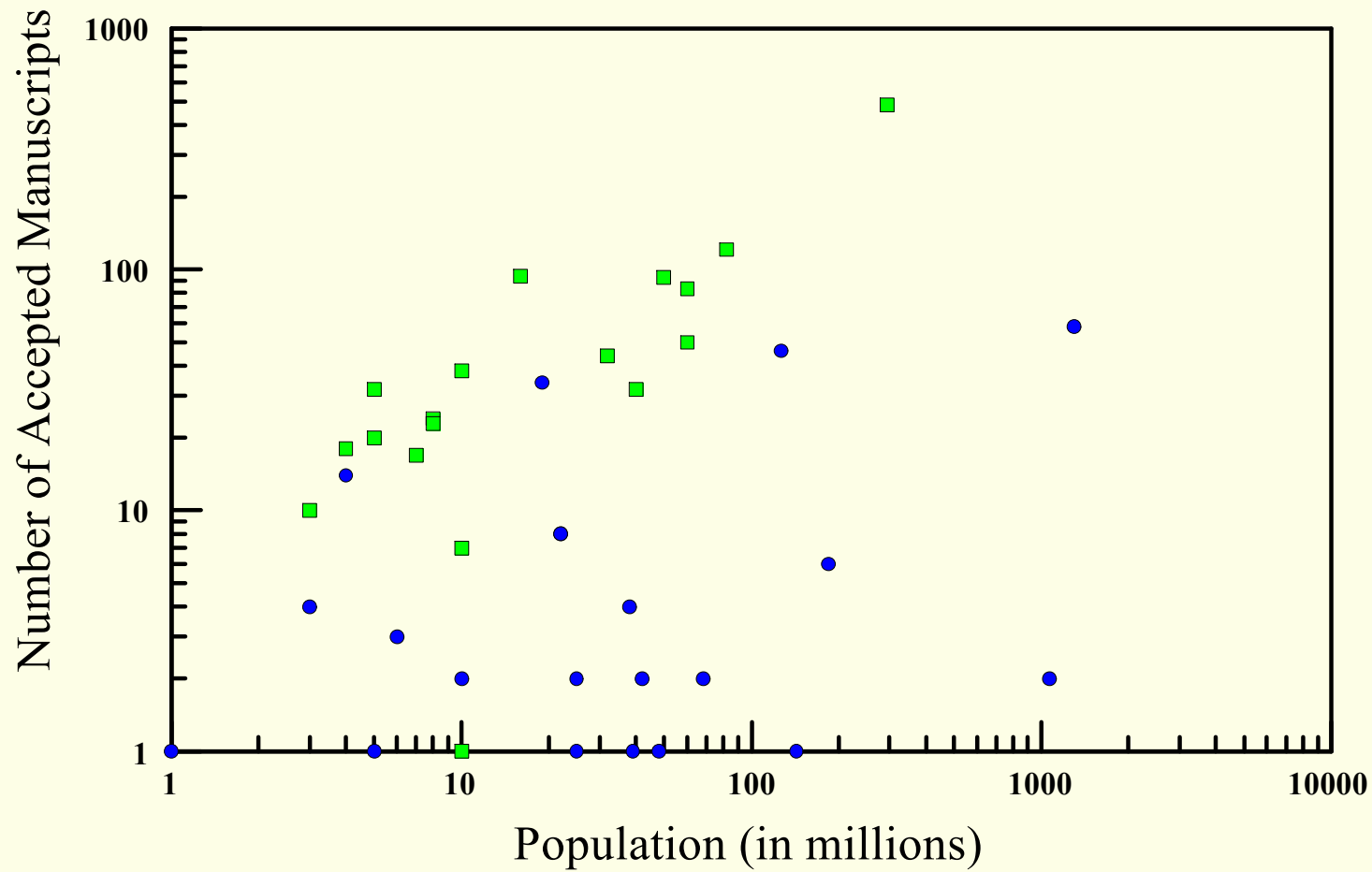
- 25 % of papers from US, 75% non-US

**Accepted Manuscripts and Populations  
Western Europe and North America  
January 1, 2002 - December 31, 2004**



# Accepted Manuscripts and Populations

January 1, 2002 - December 31, 2004

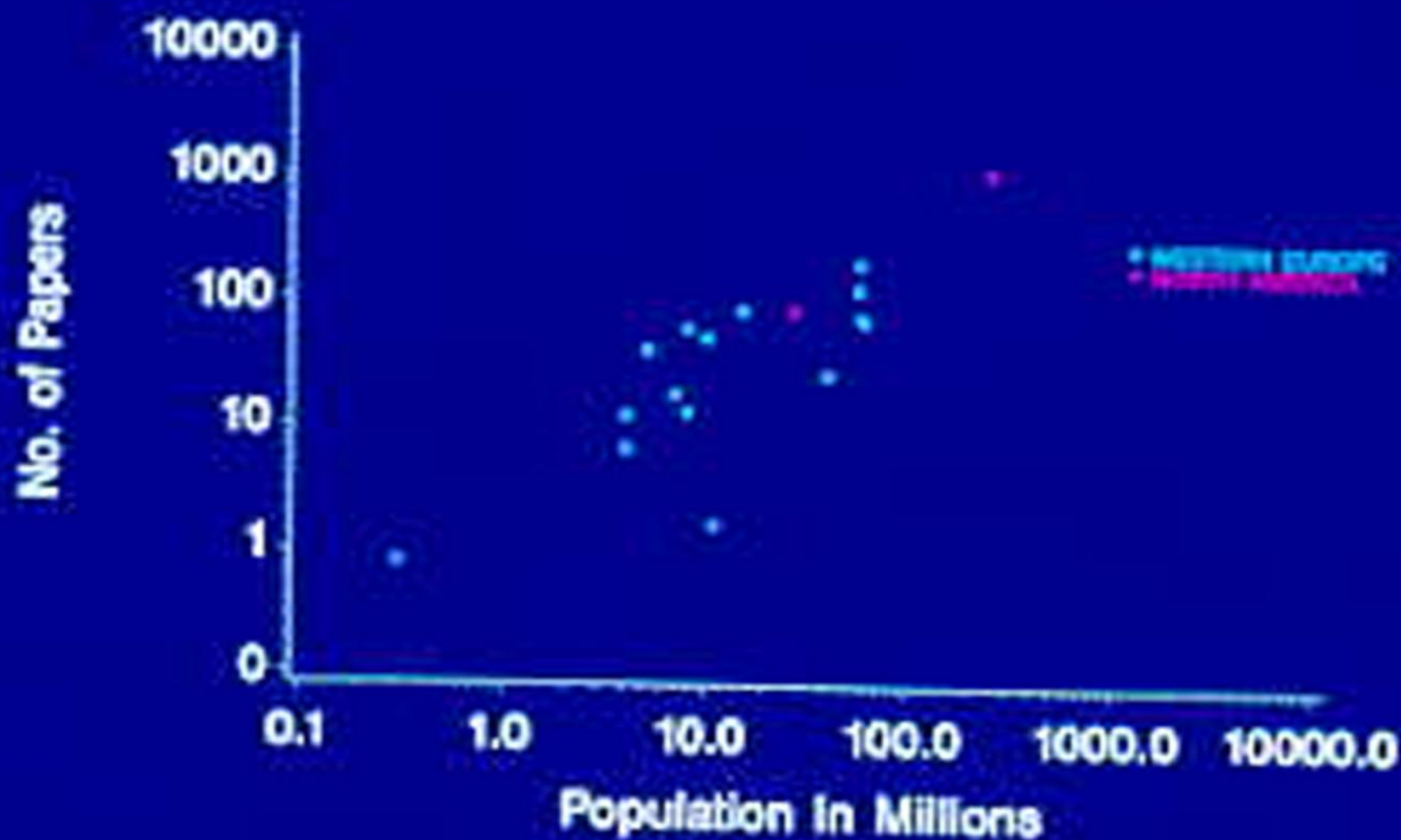




# Additional Findings

- The acceptance rates for papers from the various countries are similar. The acceptance rate for US papers is at the median.
- The correlation of number of published papers with population is at least 20 years old.

Publications 1962 - 1969  
By Country of Origin



# MY CONCLUSIONS

1. The boundaries between and among disciplines are being lowered.

**Presumption:** Molecular approaches are used in all disciplines, and all disciplines must address real clinical issues.

2. *Clinical Chemistry* publishes papers without regard to their country of origin,

**but** some countries remain underrepresented.

# Views of Medicine

- Blurring of Boundaries
  - Technical
  - Geographic
- Growth of Molecular Diagnostics
  - Plasma DNA and RNA – new discovery
  - Real-time, rapid-cycle PCR and genotyping
- Influence of Clinical Epidemiology and Evidence-Based Medicine

# Most Common Keywords for Submissions at *Clin Chem*

## 2004

1. Genotyping (96)
2. RT-PCR (67)
3. Immunoassay (65)
4. Mass Spec. (58)
5. Coronary (55)
6. BNP (45)
7. Troponins (37)
8. HPLC (26)
9. Hcy (24)

# Most Common Keywords for Submissions at *Clin Chem*

## 2002

1. Genotyping (91)
2. Coronary (53)
3. RT-PCR (44)
4. Immunoassay (43)
5. Mass Spec. (41)
6. Hcy (30)

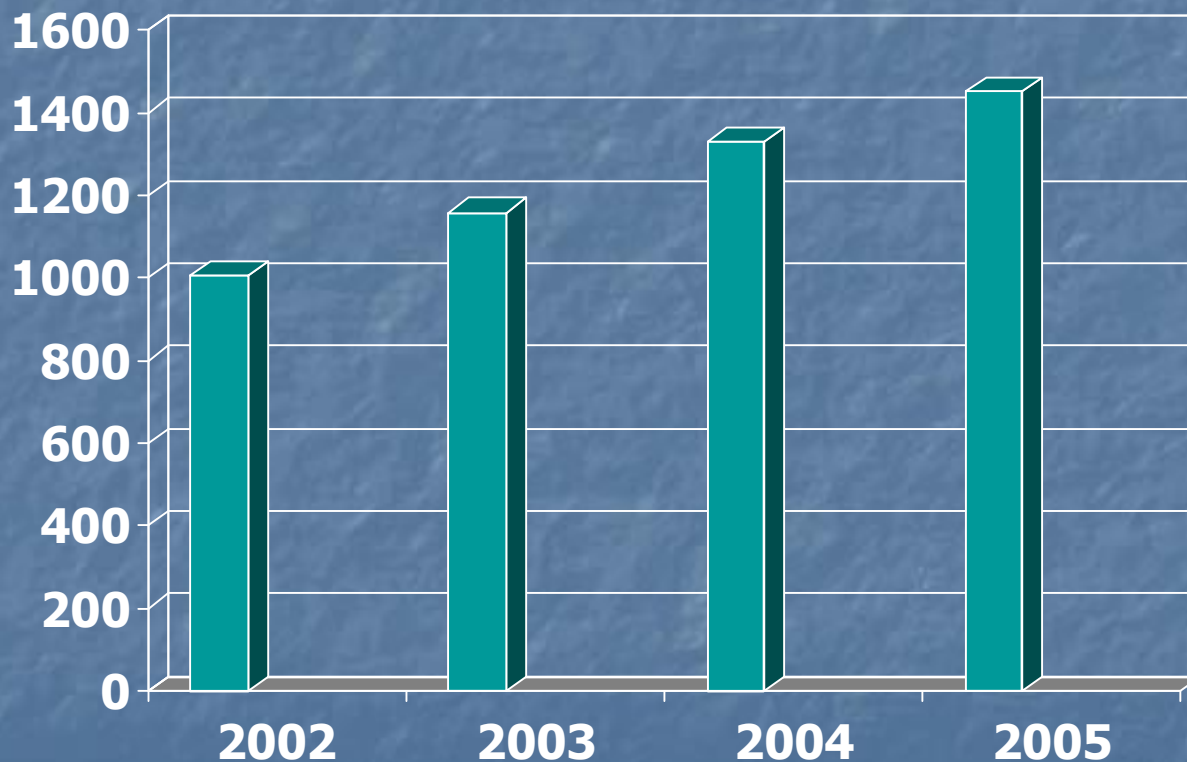
## 2003

1. Genotyping (118)
2. RT-PCR (82)
3. Immunoassay (54)
4. Mass Spec. (42)
5. Coronary (41)
6. Hcy (25)

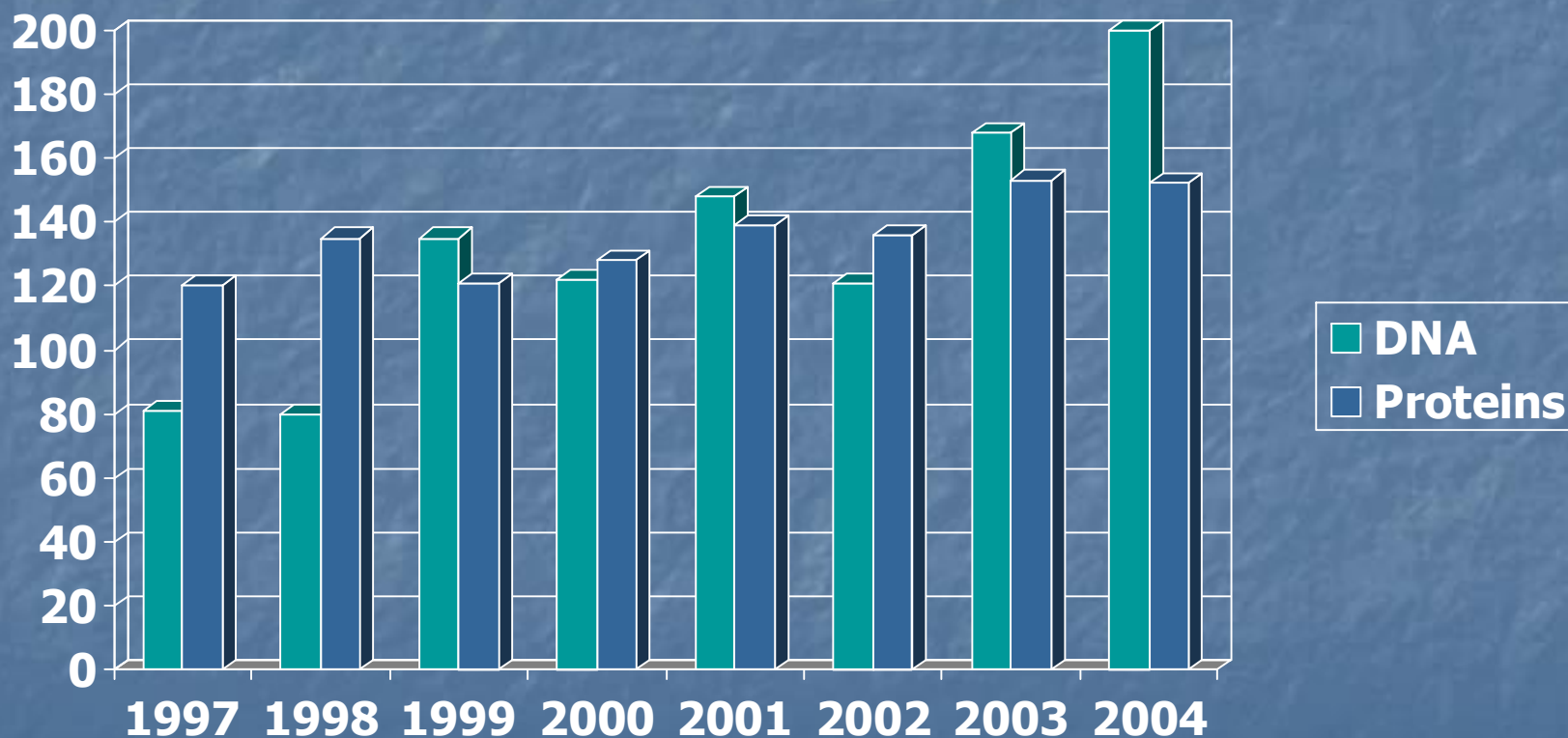
## 2004

1. Genotyping (96)
2. RT-PCR (67)
3. Immunoassay (65)
4. Mass Spec. (58)
5. Coronary (55)
6. BNP (45)
7. Troponins (37)
8. HPLC (26)
9. Hcy (24)

# Submissions of Manuscripts to *Clinical Chemistry* (N)



# Numbers of papers in *Clin Chem* on Molecular Diagnostics/Genetics (DNA) and Protein Markers/Proteomics





# Views of Medicine

- Blurring of Boundaries
- Molecular Diagnostics
- Influence of Clinical Epidemiology and Evidence-Based Medicine
  - STARD
  - Guideline on Clinical Guidelines

# Characterization of Medical Tests

1. Analytical Accuracy: Trueness and precision
2. Nonanalytical Factors: Biologic variation...
3. **Diagnostic Accuracy**: ROC Curves, Diagnostic Odds Ratios, Sensitivity-Specificity Pairs...
4. Clinical Usefulness: Outcomes...
5. Cost-benefit Analysis: Cost/QALY...

# Studies of Diagnostic Accuracy

Adherence to elementary principles of clinical epidemiology and EBM is abysmal.

# Methodologic Standards in Test Research. Reid, Lachs and Feinstein. 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).
- 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 overestimate diagnostic accuracy

Lijmer et al. JAMA1999;282:1061-6

- Lijmer et al examined studies of diagnostic accuracy of selected tests.
- Compared studies that had acceptable study design with studies that did not.
- Calculated **relative** diagnostic odds ratio (**RDOR**) for poor vs good studies.

# Impact of Flawed Design

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

	RDOR	
■ 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		



# Lesson and Actions

- Poor reporting and poor study design precluded conclusions about the diagnostic accuracy of tests.
- Impact of poor design can be assessed only if reporting of study is complete.
- We needed to improve reporting of studies of diagnostic accuracy in journals.

# *Clinical Chemistry* 1997 Guidelines for Reporting Studies of Diagnostic Accuracy

Bruns, Huth, Magid, Young. *Clin Chem*, Nov 1997 & July 2000

- Reviewed by clinical epidemiologists, clinical chemists, statisticians, researchers and editors (NEJM, JAMA, Lancet, Ann Intern Med, et al.)
- First journal checklist for diagnostic accuracy.

# Selected Points in Checklist for Studies of Diagnostic Accuracy

- Masking of individuals performing tests
- Spectrum of disease
- Confidence intervals for measures of diagnostic accuracy (ROC areas, etc.)

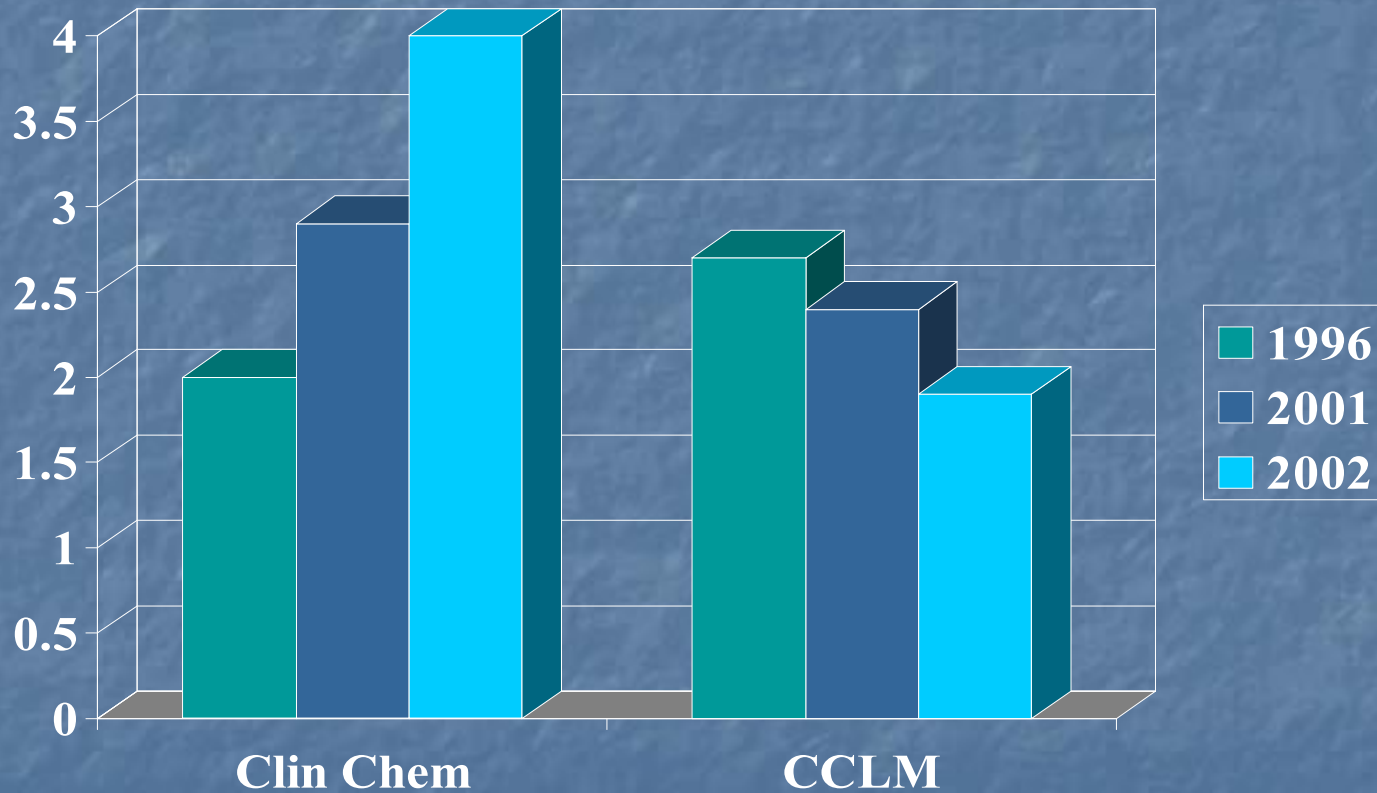
# Did Publication of Guidelines Improve Reporting?

(Lumbreras-Lacarra et al, Clin Chem 2004)

- Examined papers on diagnostic accuracy published in 1996 (before 1997 Checklist) and in 2001 and 2002.
- Compared *Clin Chem*, which used a checklist, with *CCLM*, which did not.
- Determined the number of the 7 criteria of Reid et al that were met in each paper.

# Mean Number of Criteria Met

(Lumbreras-Lacarra et al, 2004)



*(Clin Chem,  $p < 0.001$ ; CCLM,  $p = 0.7$ )*

Getting better,

But...

# Proportion (%) of Studies that Met Standards in 4 Medicine Journals (Reid et al) and 2 Clinical Chemistry Journals (Lubreras-Lacarra et al)

<u>Standard</u>	<u>Medicine, 90-93</u>	<u>Chemistry, 1996</u>
Spectrum indicated	32%	22%
Patient subgroups	12	44
No verification bias	62	33
Masking	47	22
Conf. Intervals	24	22
Indeterminate results	38	0
Test reproducibility	32	83
<b>Mean (SD)</b>	<b>35 (16)%</b>	<b>34 (28)%</b>

**IF NEJM ET AL AREN'T "GOOD", WE AREN'T EITHER.**

# New Initiative

- Develop a checklist for studies of all types of diagnostic tests – clinical chemistry, radiology, anatomic pathology, etc.
- Builds on work of Lijmer and Bossuyt that documented that design flaws matter.
- Project is in its fifth year.



# ***STARD* Working Group**

## **(Laboratory Medicine in yellow)**

### **Researchers:**

William Black

Harry Buller

Kenneth Fleming

Myriam Hunink

**Erik Magid**

Barbara McNeil

**Christopher Price**

Sharon Straus

David Sackett

### **Methodologists:**

Doug Altman

Colin Begg

Patrick Bossuyt

Jon Deeks

Constantine Gatsonis

Afina Glas

Paul Glasziou

Gordon Guyatt

James Hanley

Les Irwig (**So African**)

Andre Knottnerus

Jeroen Lijmer

David Moher

Hans Reitsma

Riekje de Vet

Stephen Walter

### **Editors:**

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**David Bruns**

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**Andrew Onderdonk**

John Overbeke

Tony Proto

Drummond Rennie

(BMJ)

**(Clin Chem)**

(Ann Intern Med)

(Lancet)

**(J Clin Microbiol)**

(NtvG)

(Radiology)

(JAMA)

### **Professional organizations:**

**Gregory Campbell**

Jos Kleijnen

Harold Sox

**Matthew McQueen**

**Gerard Sanders**

Paul Dieppe

**(FDA)**

(CRD)

(ACP)

**(IFCC)**

**(IFCC)**

(HSRC)

# *STARD* Guidelines

- Similar to the *Clinical Chemistry* Checklist.
- Published in 14 journals, including Clin Chem, CCLM, Ann Clin Biochem, AJCP, Ann Intern Med, BMJ, Radiology, etc.
- Adopted by numerous additional journals.
- Referenced in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals

# STARD Checklist

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	
METHODS		Describe	
<i>Participants</i>	3	The study population: The inclusion and exclusion criteria, setting and locations where the data were collected.	
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in items 3 and 4? If not, specify how participants were further selected.	
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	
<i>Test methods</i>	7	The reference standard and its rationale.	
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	
	9	Definition of and rationale for the units, cutoffs and/or categories of the results of the index tests and the reference standard.	
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	
<i>Statistical methods</i>	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	
	13	Methods for calculating test reproducibility, if done.	
RESULTS		Report	
<i>Participants</i>	14	When study was done, including beginning and ending dates of recruitment.	
	15	Clinical and demographic characteristics of the study population (e.g. age, sex, spectrum of presenting symptoms, comorbidity, current treatments, recruitment centers).	
	16	The number of participants satisfying the criteria for inclusion that did or did not undergo the index tests and/or the reference standard; describe why participants failed to receive either test (a flow diagram is strongly recommended).	
<i>Test results</i>	17	Time interval from the index tests to the reference standard, and any treatment administered between.	
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	
	20	Any adverse events from performing the index tests or the reference standard.	
<i>Estimates</i>	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	
	22	How indeterminate results, missing responses and outliers of the index tests were handled.	
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	
	24	Estimates of test reproducibility, if done.	
DISCUSSION	25	Discuss the clinical applicability of the study findings.	

Section and Topic	Item #		On page #
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INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	
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<i>Statistical methods</i>	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	
	13	Methods for calculating test reproducibility, if done.	

# STARD Flow Diagram

General example



# Summary: Reporting of Studies of Diagnostic Accuracy

- Reporting is getting better, but still is not good.
- When writing or reading studies of diagnostic accuracy, use the STARD checklist to be sure that you have all the information that is needed to assess the diagnostic accuracy of the test.

# Views of Medicine

- Blurring of Boundaries
- Molecular Diagnostics
- Influence of Clinical Epidemiology and Evidence-Based Medicine
  - STARD
  - Guideline on Clinical Guidelines

# Clinical Practice Guidelines

- Guidelines are influential

NACB Guidelines published in Clin Chem:

- Cardiac (1999), cited 220 times, accessed >22,346 times
- Diabetes (2002), cited 103 times, accessed >54,437 times
- Difficult to do well
- Danger of harm as well as hope of doing good: Primum non nocere.



*Clinical Chemistry* 50:5  
806–818 (2004)

Special Report

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# Evidence-Based Guidelines in Laboratory Medicine: Principles and Methods

WYTZE P. OOSTERHUIS,<sup>1†</sup> DAVID E. BRUNS,<sup>2</sup> JOSEPH WATINE,<sup>3†</sup> SVERRE SANDBERG,<sup>4†</sup> and  
ANDREA R. HORVATH<sup>5†</sup>

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# What Can a Journal Do to Advance a Field?

- Information for Authors
  - How to describe an analytical method (1970s) or a clinical study (1990s)
- Foster new areas through special publications
  - Molecular diagnostics (San Diego Conf. Proceedings)
  - Plasma DNA and RNA (CNAPS Proceedings)
  - Evidence-based (laboratory) medicine: EB(L)M reviews, NACB guidelines, systematic reviews
- Guidance in new areas
  - Diagnostic accuracy: STARD
  - EBM: Guideline on Clinical Guidelines
  - What is needed next? Proteomics? Pharmacogenetics?

# Key Points

- *Clin Chem* is more than old clinical chemistry.
- The field is international.
- Evidence-based medicine affects the practice of medicine – STARD for us.
- Guidelines are highly cited and must be done well.
- What remains the same in *Clinical Chemistry* is clinical use of technology. We must emphasize the clinical as well as the “chemistry”.

Thank you for the opportunity to  
visit with you.

