Biomarker & Test Evaluation Program

INTRODUCTION TO CLINICAL EVIDENCE AND MEASUREMENTS

Patrick MM Bossuyt

A parable in four visits

παραβολή

the name given
by Greek rhetoricians
to any fictive illustration
in the form of a brief narrative

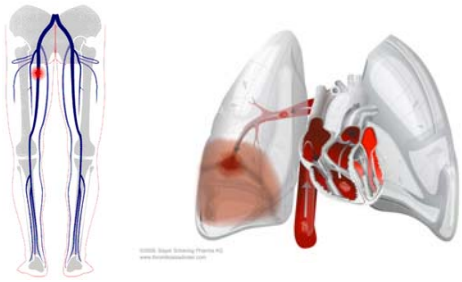
Wikipedia

A parable

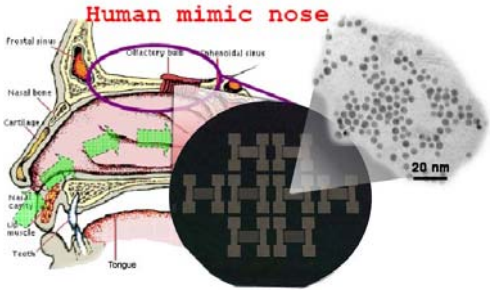
Visit 1

www.allergroup.com

Pulmonary Embolism



Artificial Nose



Artificial Nose – PE-Sensor

In God we trust.
All others must
bring data.

A parable

Visit 2

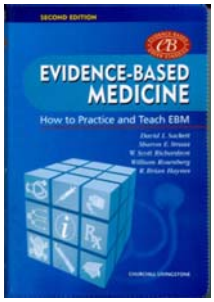
Certificate

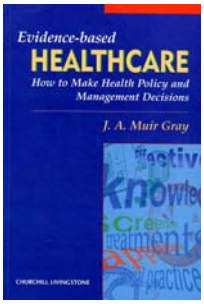
CE

CE mark

- Directive 98/79/EC
- Declaration of conformity
- Four risk categories:
  - Annex II List A
    (HIV I and II, Hepatitis B, C and D, ...
  - Annex II List B
    (rubella, toxoplasmosis and phenylketonuria)
  - IVDs for self-testing
  - Other IVD

Evidence-based medicine





A parable

Visit 3

Diagnostic Accuracy Study

Series of Patients

Medical Test

Reference standard

Cross-classification

The results

Reference Standard

BioMarker		Target Condition	Other Condition
	Positive	TP	*FP*
	Negative	*FN*	TN

TABLE 4
Wells' criteria for predicting the probability of pulmonary embolism

Variable risk factors	No. of points
Clinical signs and symptoms of DVT	3
An alternative diagnosis deemed less likely than PE	3
Heart rate >100 beats/min	1.5
Immobilization or surgery in the previous 4 wk	1.5
Previous DVT or PE	1.5
Hemoptysis	1
Cancer (receiving treatment, treated in past 6 mo, or palliative care)	1

Clinical probability	Total points
Low	<2
Intermediate	2-6
High	>6

Key: DVT, deep vein thrombosis; PE, pulmonary embolism.

Adapted from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer. *Thromb Haemost*. 2000;83:416-420, as presented in Feldin PF, Tapson VF. Clinical practice: the evaluation of suspected pulmonary embolism. *N Engl J Med*. 2003;349(13):1247-1256.

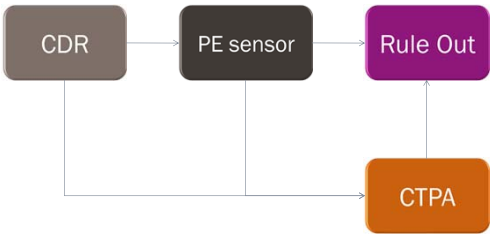
Jaapa.com

Test Strategy

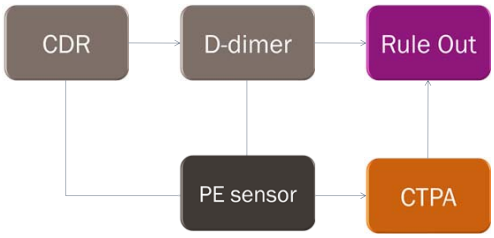
CDR → D-dimer → Rule Out

CDR → CTPA

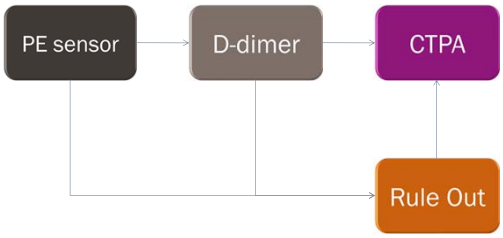
Test Strategy



Test Strategy



Test Strategy



Where is the benefit?

- for patients?
- for society?

Where is the evidence?

- to back up these claims.

A parable

Visit 4?

Evaluating Medical Tests

Three questions

Three questions

Question	Feature
Is the test trustworthy?	Technical Performance
Is the test meaningful?	Clinical Performance
Is the test useful?	Clinical Effectiveness

1. Technical Performance

Can I trust this test?

PATHOLOGY ARCHIVES

New Assay on AcuStar Hemostasis Testing System Receives CE Mark

Instrumentation Laboratory (IL), Bedford, MA, announced the release of their new HemosIL AcuStar HT Panel assay that is also now a European CE IVD Marked product.The ACL AcuStar is a fully automated device for chemiluminescent testing in the hemostasis laboratory. Ready to use cartridges with reagents can be kept stable up to six weeks refrigerated at 4°C onboard. One test takes around 30 minutes and one rack accommodates 30 samples, so 60 results can be produced per hour.

The system comes with an easy to use touchscreen and runs on a Windows interface. Several hemostasis assays are already available on the ACL AcuStar like D-Dimer testing and an Anti-phospholipids panel for diagnosis of Antiphospholipid syndrome (APS).

The new approved assay detects antibodies associated with Heparin-Induced Thrombocytopenia (HIT), a severe immunologic adverse reaction to Heparin, paradoxically resulting in venous and/or arterial

164 Technical report

Analytical performance of the new ACL AcuStar HemosIL D-Dimer

Giuseppe Lippi[a], Luigi Ippolito[a], Tania Russello[a], Valeria Ponzo[a], Gian L. Salvagno[b] and Gian C. Guidi[b]

Several lines of clinical evidence as well as guidelines and recommendations suggest that the overall diagnostic performance of D-dimer testing outstrips that of any other biomarker in the diagnostic approach of patients with venous thromboembolism or disseminated intravascular coagulation. Along with specific technical characteristics, the analytical performance of each D-dimer immunoassay should, however, be assessed before implementation in clinical practice. The aim of this study was to evaluate the analytical performance of HemosIL AcuStar D-Dimer immunoassay, a novel chemiluminescent immunoassay specifically designed for the instrument Instrumentation Laboratory ACL AcuStar. The within and between-run imprecision (n = 20) was comprised between 3.6 and 5.8%. The linearity was excellent up to 16 200 ng/ml ($r = 1.00$; $P<0.001$), and optimal between 224 and 69 900 ng/ml ($r = 0.992$; $P<0.001$). A significant agreement of values was observed between HemosIL AcuStar D-Dimer and HemosIL D-Dimer HS for ACL TOP ($r = 0.884$; $P<0.001$), as well as with Vidas D-Dimer ($r = 0.791$; $P<0.001$). Results of HemosIL AcuStar D-Dimer displayed a modest negative bias as compared with those of Vidas D-dimer (mean bias −22%; 95% Confidence Interval, −122% to 49%). The analytical accuracy assessed against Vidas D-dimer also yielded an area under the curve of 0.998 ($P<0.001$). As regards, the preliminary definition of cutoff value, optimal sensitivity (100%) and specificity (96%) were found at a diagnostic threshold of 466 ng/ml. The results of this investigation attest that the novel HemosIL AcuStar D-Dimer is characterized by remarkable accuracy and precision, optimal linearity and excellent agreement with the reference immunoassay. As such, its technical and analytical performance would make it a suitable method for the rapid and accurate quantification of D-dimer in clinical laboratories. *Blood Coagul Fibrinolysis* 23:164–167 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Blood Coagulation and Fibrinolysis 2012, 23:164–167

Keywords: D-dimer, diagnosis, disseminated intravascular coagulation, testing, venous thromboembolism

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Received 5 September 2011 Revised 26 October 2011
Accepted 4 November 2011

2. Clinical Performance

Is this test meaningful?

Diagnostic Test Accuracy

- How good is the test in correctly classifying patients as being diseased?

CHEST JOURNAL
Official Publication of the American College of Chest Physicians

Original Research
THROMBOEMBOLIC DISEASE

Prospective Study of the Diagnostic Accuracy of the Simplify D-dimer Assay for Pulmonary Embolism in Emergency Department Patients*

Jeffrey A. Kline, MD; Michael S. Runyon, MD; William B. Webb, BSPH; Alan E. Jones, MD; and Alice M. Mitchell, MD

(CHEST 2006; 129:1417–1423)

Diagnostic Accuracy Study

2,302 ED Patients

↓

Simplify D-dimer

↓

Multislice CT

↓

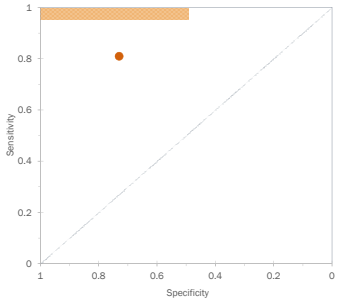
Cross-classification

Measures of Diagnostic Test Accuracy

Sensitivity & Specificity	81 %	73 %
Predictive Values	13 %	99 %
Likelihood Ratios	2.93	.27
Diagnostic Odds Ratio	10.9	

	PE	Non PE
Positive	87	603
Negative	21	1,591

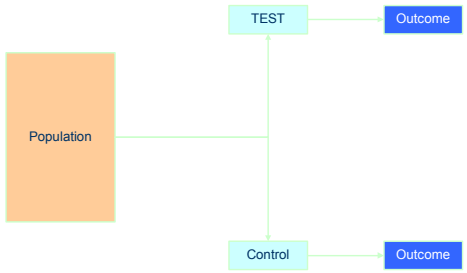
ROC space: Target Region



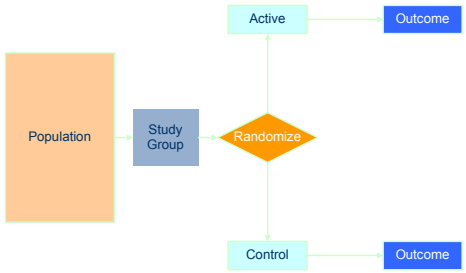
3. Clinical Effectiveness

Is this test useful?

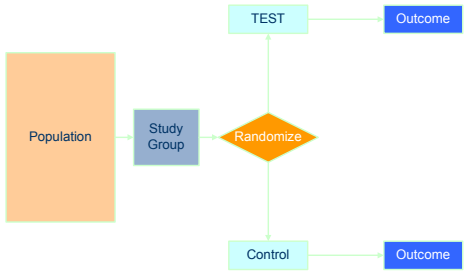
Consequences of Testing



Consequences of Testing



Medical Test RCT

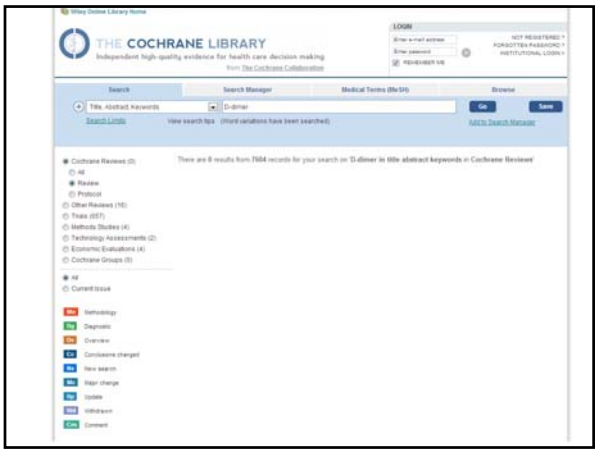


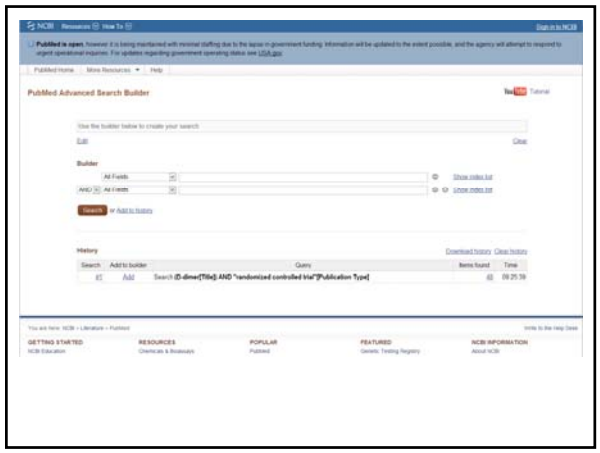
Clinical Effectiveness

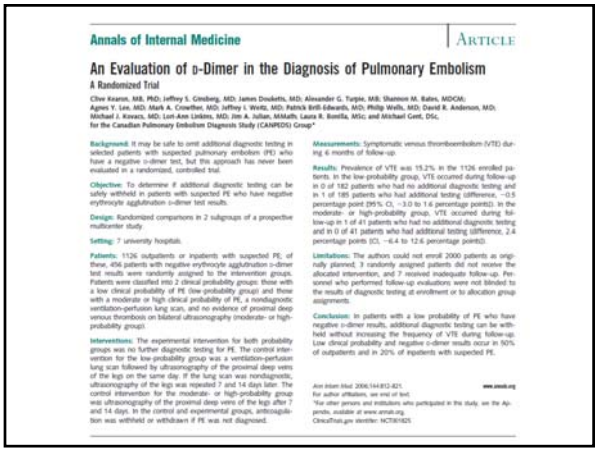
	Explanation
Health Outcome	Health outcomes that matter to patients and society: to prevent premature death, to restore or maintain functional health.
Probabilistic	Not all outcomes will be observed in everyone tested; evaluations will be made at the group level, and expressed in terms of a distribution of outcomes.
Comparative	Effectiveness is defined relative to a comparator strategy: current best standard practice.

Trials of Tests

Do they exist?






Annals of Internal Medicine | ARTICLE

An Evaluation of D-Dimer in the Diagnosis of Pulmonary Embolism

A Randomized Trial

Two views on medical tests

Value of Medical Tests

Essentialist

Consequentialist

Essentialism

the theory that
the value of a marker or a medical test
should be judged
by the 'trueness'
of its results

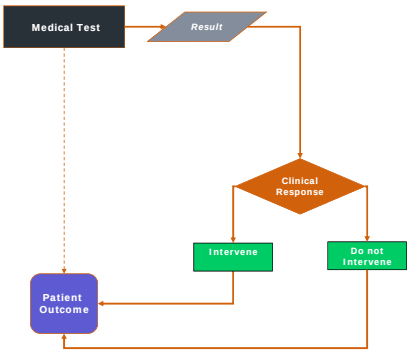
Consequentialism

the theory that
the value of a marker or a medical test
should be judged
by the value
of its consequences

Two views on tests

	Essentialism	Consequentialism
Key Value	Truth	Usefulness
Focus	Results	Consequences
Emphasis	Validity	Utility
Statistics	Accuracy	Health Outcomes

Consequences

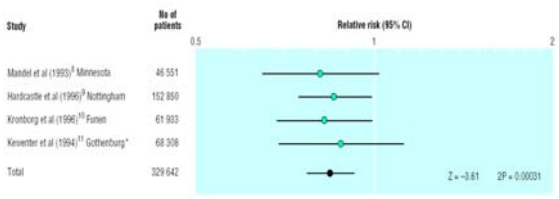


Clinical Effectiveness

Think RCT

Do not always perform an RCT

Meta-analysis CRC Screening RCT

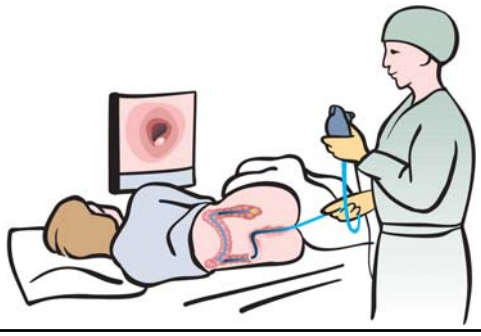


Relative Risk CRC Mortality: 0.84

(95% CI: 0.77 to 0.93)

BMJ 1998;317:559–65

Colonoscopy



Fecal hemoglobin testing

Informative Performance

Clinica Chimica Acta 427 (2014) 49–57

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Special report

From biomarkers to medical tests: The changing landscape of test evaluation

Andrea R. Horvath [a,b,*], Sarah J. Lord [b,c,], Andrew StJohn [d], Sverre Sandberg [e], Christa M. Cobbaert [f], Stefan Lorenz [g], Phillip J. Monaghan [h], Wilma D.J. Verhagen-Kamerbeek [i], Christoph Ebert [j], Patrick M.M. Bossuyt [k], For the Test Evaluation Working Group of the European Federation of Clinical Chemistry Laboratory Medicine

Diagnostic Test Accuracy

- How good is the test in correctly classifying patients as being diseased?

Diagnostic Test Accuracy

- How good is the test in correctly classifying patients as having the target condition?


Target practice: choosing target conditions for test accuracy studies that are relevant to clinical practice

BMJ 2011;343:d4684 doi: 10.1136/bmj.d4684

A parable

Coda

Artificial Nose – PE-Sensor

Artificial Nose – SensorFreshQ

SensorFreshQ

Breathomics as a diagnostic tool for pulmonary embolism

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To cite this article: Fens N, Douma RA, Sterk PJ, Kamphuisen PW. Breathomics as a diagnostic tool for pulmonary embolism. J Thromb Haemost 2010; 8: 2801–3.

Pulmonary embolism (PE) remains a serious and frequent disease, with an incidence of 1–2 per 1000 per year in western society [1]. Adequate diagnosis is mandatory to prevent PE-related mortality and morbidity on the one hand, and unnecessary treatment on the other. Individual signs and symptoms have low accuracy, and additional tests are also not sensitive or specific enough to rule PE in or out [2]. Preferably, exclusion of the diagnosis should be performed with safe, efficient and non-invasive diagnostic methods.

A breath test is certainly a candidate to fulfill these conditions. Exhaled breath has been demonstrated to contain hundreds of volatile organic compounds (VOCs), derived from various metabolic pathways in the airways and elsewhere in the body. Samples of exhaled breath can be analyzed by high-throughput assessment and pattern metabolomic recognition of molecular mixtures [3]. By means of electronic noses (eNoses), the sampling of exhaled breath and its VOCs has become readily available, owing to their ability to discriminate biomarker profiles or 'breathprints' with comparable nanosecond

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DOI: 10.1111/j.1538-7836.2010.04044.x
Received 20 August 2010; accepted 14 September 2010

arrays (breathomics). Currently available eNoses include handheld devices using on-board pattern recognition software that is suitable for diagnostic classification without identification of the individual molecular components [3,4]. This provides the potential option of 'on the spot' diagnosis of diseases, as has been investigated in lung cancer [5], chronic obstructive pulmonary disease and asthma [6,8].

The combination of a clinical decision rule (CDR) and D-dimer testing excludes PE in about 20–30% of patients [7]. This implies that the majority will undergo imaging tests, such as computed tomography (CT) scan. As a minority of these latter patients will have PE, an increase in the number of patients in whom PE can be excluded without additional imaging is mandatory. The eNose is an interesting diagnostic tool in patients with suspected PE, especially in those without comorbidity [9–11].

We hypothesized that exhaled breath molecular fingerprinting by eNose could differentiate between PE and absence of PE in patients with suspected acute PE who have a likely CDR or elevated D-dimer level, and that this differentiation would be more pronounced in patients without relevant comorbidity.

The study was a prospective proof-of-principle study in patients with suspected PE. Patients with a diagnosis of PE were compared with patients in whom this diagnosis was excluded. Suspected PE was defined as sudden onset of dyspnea, deterioration of existing dyspnea, and/or sudden onset of pleuritic chest pain in combination with a high clinical probability according to Wells or a d-dimer level