

amC 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

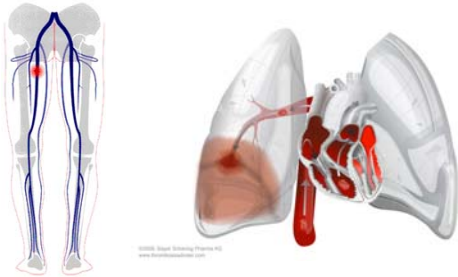
Wikipedia

A parable

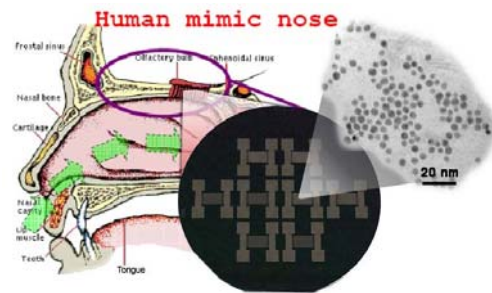
Visit 1



Pulmonary Embolism



Artificial Nose



Artificial Nose - PE-Sensor




In God we trust.
All others must
bring data.

A parable

Visit 2

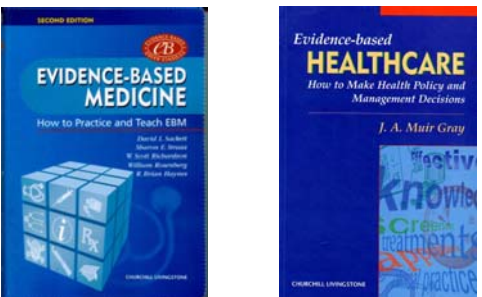
Certificate




CE mark

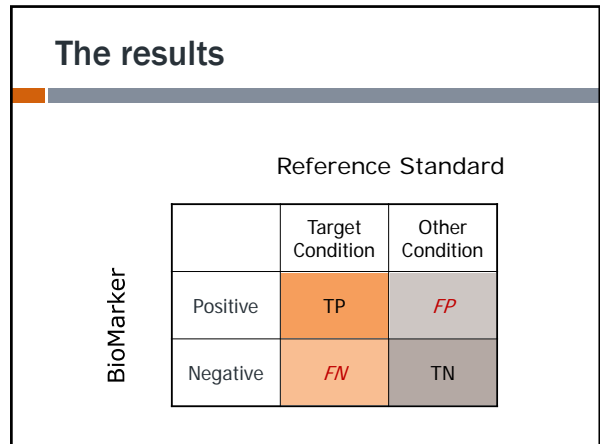
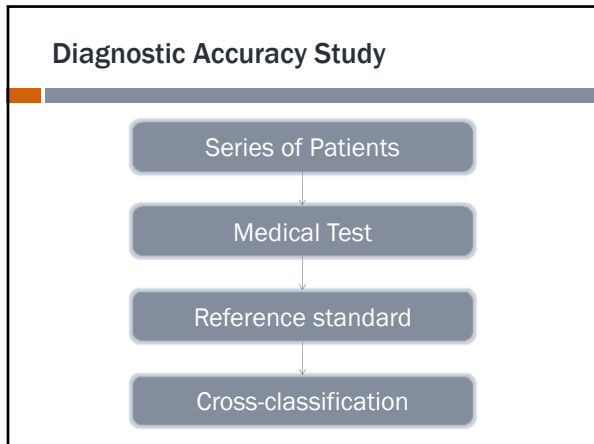
- Directive 98/79/EC
- Declaration of conformity
- Four risk categories:
 - Annex II List A (HIV I and II, Hepatitis B, C and D, ...)
 - Annex II List B (rubella, toxoplasmosis and phenylketonuria)
 - IVDs for self-testing
 - Other IVD

Evidence-based medicine



A parable

Visit 3



D-dimer Cardiovascular

Clearview Simplify D-dimer

Clearly different

- **Rapid Results** - Test easy, clean, results in 10 minutes.
- **Simple** - Easy to use test requires no expensive instrumentation and specialized training.
- **Flexibility** - Built-in control ensures accuracy.
- **Flexibility** - Faster results while the patient waits.

Clearly better

- **Full in the diagnosis of deep vein thrombosis (DVT), pulmonary embolism (PE), and disseminated intravascular coagulation (DIC).**
- **Utilizes the patented 3B222 Monoclonal Antibody, specific only to D-dimer, which minimizes the false positives that can be seen with competitive tests.**
- **Reduces the cost for test results.**
- **Any staff member can perform, eliminating the need for instrumentation and specialized training.**

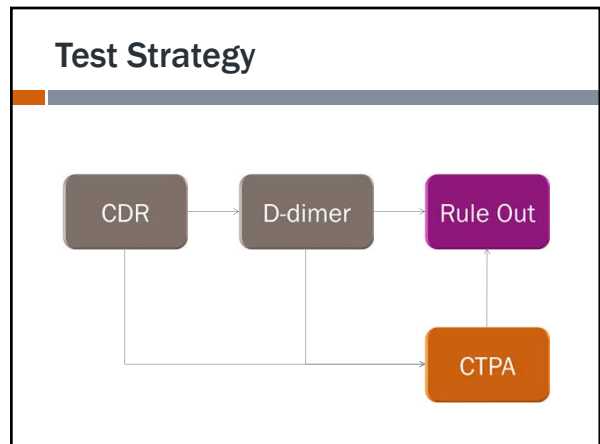
TABLE 4
Wells' criteria for predicting the probability of pulmonary embolism

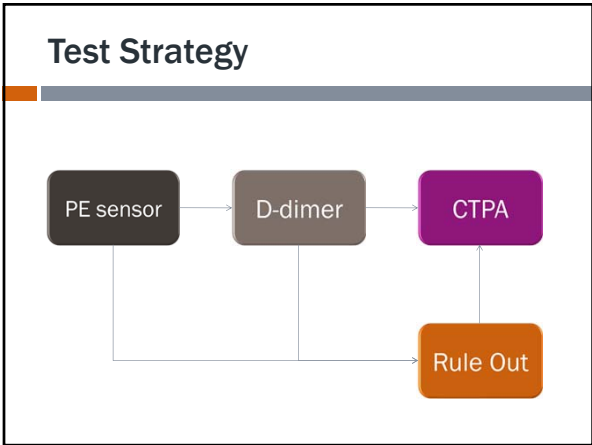
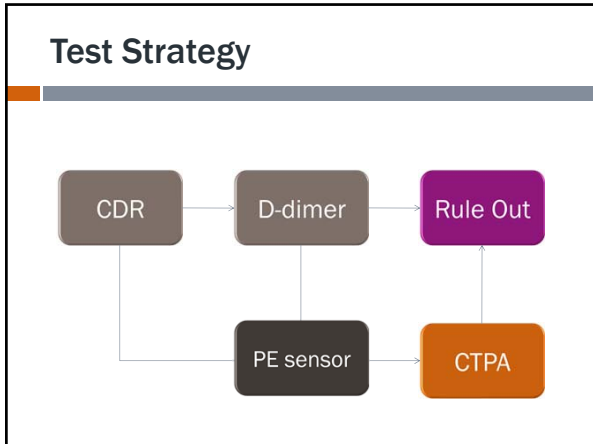
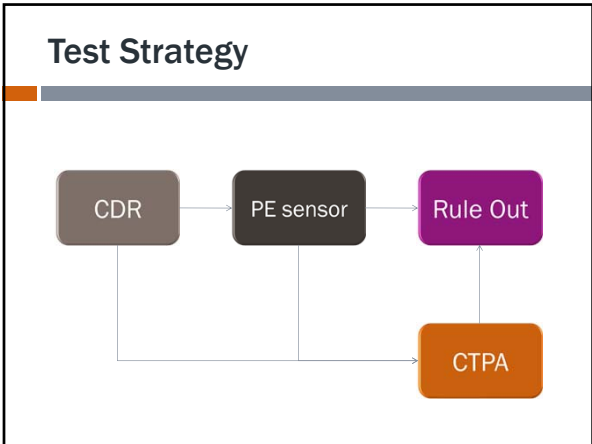
Variable risk factors	No. of points
Clinical signs and symptoms of DVT	3
An alternative diagnosis deemed less likely than PE	3
Heart rate >100 beats/min	1.5
Immobilization or surgery in the previous 4 wk	1.5
Previous DVT or PE	1.5
Hemoptysis	1
Cancer (receiving treatment, treated in past 6 mo, or palliative 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 Simplified D-dimer. *Thromb Haemostasis*. 2000;83:416-420, as presented in Fricko PE, Tapson VF. Clinical practice: the evaluation of suspected pulmonary embolism. *N Engl J Med*. 2003;349:1251-1256.





- ### 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

By JAH 599562 on Feb 22, 2012



Instrumentation Laboratory (IL), Bedford, MA, announced the release of their new HemosIL AcuStar HT Panel assay that is also now a European CE Marked product. The 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. Each 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 with tabs as a intuitive interface. Several hemostasis assays are already available on the AcuStar like D-Dimer testing and an Anti-platelet/platelet 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, potentially resulting in severe and/or fatal thrombocytopenia.

164 Technical report

Analytical performance of the new ACL AcuStar HemosIL D-Dimer

Giuseppe Lippi^a, Luigi Ippolito^a, Tania Russello^a, Valeria Pozzo^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 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 16200 ng/ml (r = 1.00; P < 0.001), and optimal between 224 and 6800 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, -12% to -49%). The analytical accuracy assessed against Vidas D-dimer also yielded an area under the curve of 0.999 (P < 0.001). As regards, the preliminary definition of cutoff value, optimal

sensitivity (100%) and specificity (98%) were found at a diagnostic threshold of 486 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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Correspondence to: Professor Giuseppe Lippi, U.O. Diagnostica Ematologica, Azienda Ospedaliera Università di Parma, Via Dimentici, 14, 43126 Parma, Italy (e-mail: giuseppe.lippi@unipr.it)

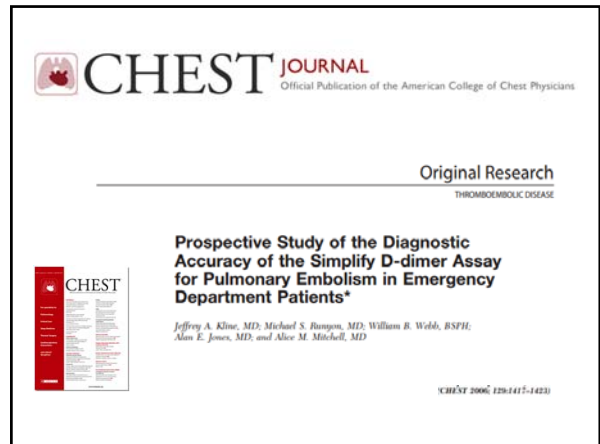
Received 5 September 2011; Revised 24 October 2011; Accepted 4 November 2011

2. Clinical Performance

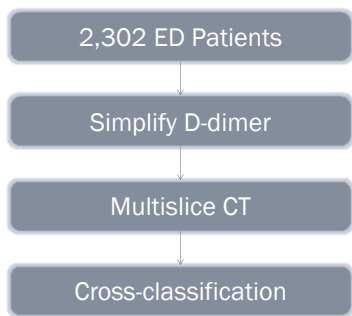
Is this test meaningful?

Diagnostic Test Accuracy

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



Diagnostic Accuracy Study

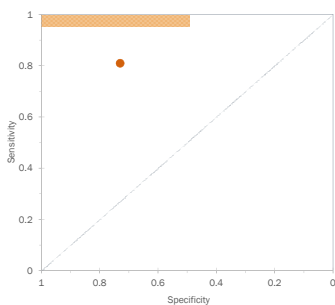


Measures of Diagnostic Test Accuracy

- 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

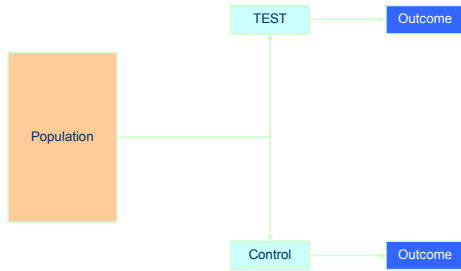
ROC space: Target Region



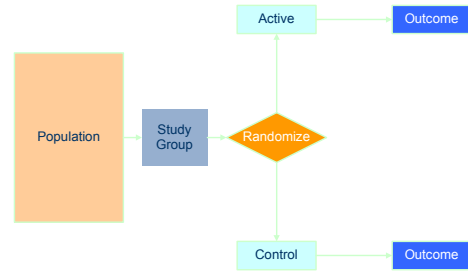
3. Clinical Effectiveness

Is this test useful?

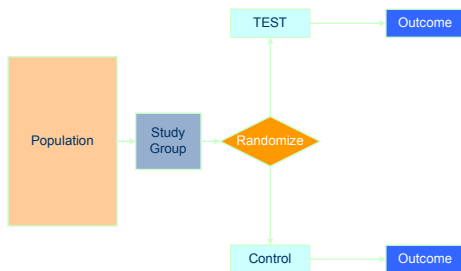
Consequences of Testing



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?

The screenshot shows the Cochrane Library homepage. At the top, it says 'THE COCHRANE LIBRARY' and 'Independent high-quality evidence for health care decision making'. Below this is a search bar with 'Title, Abstract, Keywords' and a 'GO' button. There are navigation links for HOME, SIGN UP, LEARN, ACCESS, and HELP. The main content area includes 'COCHRANE DATABASE OF SYSTEMATIC REVIEWS', 'SPECIAL COLLECTIONS' (with a 'toilet day' link), and 'EDITORIAL' (with a link to 'Measuring the performance of the Cochrane Library'). At the bottom, there are links for 'COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS (CENTRAL)' and 'WORKING OTHER REQUIREMENTS'.

Annals of Internal Medicine | ARTICLE

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

A Randomized Trial

Chen Kaewin, MB, MD; Jeffrey S. Ginsberg, MD; James Doucette, MD; Alexander C. Turpin, MB; Shannon M. Rubin, MD; Agnes Y. Lee, MD; Mark A. Crowther, MD; Jeffrey L. Witt, MD; Patrick Brill Edwards, MD; Philip Wells, MD; David B. Anderson, MD; Michael J. Krauss, MD; Lou Ann Lantieri, MD; Jim A. Julian, MEd; Laura K. Benfante, MD; and Michael Gerr, DSc, for the Canadian Pulmonary Embolism Diagnostic Study (CANPDES) Group*

Background: It may be safe to omit additional diagnostic testing in selected patients with suspected pulmonary embolism (PE) who have a negative d-dimer test, but this approach has never been evaluated in a randomized, controlled trial.

Objective: To determine if additional diagnostic testing can be safely withheld in patients with suspected PE who have negative erythrocyte agglutination d-dimer test results.

Design: Randomized comparison in 2 subgroups of a prospective multicenter study.

Setting: 7 university hospitals.

Patients: 1126 inpatients or outpatients with suspected PE, of whom 494 patients with negative erythrocyte agglutination d-dimer test results were randomly assigned to the intervention group. Patients were classified into 2 clinical probability groups: those with a low clinical probability of PE (low-probability group) and those with a moderate or high clinical probability of PE, a nondiagnostic ventilation-perfusion lung scan, and no evidence of proximal deep venous thrombosis on bilateral ultrasonographic moderate- or high-probability groups.

Interventions: The experimental intervention for both probability groups was no further diagnostic testing for PE. The control intervention for the low-probability group was a ventilation-perfusion lung scan followed by ultrasonography of the proximal deep veins of the leg on the same day. If the lung scan was nondiagnostic, ultrasonography of the leg was repeated 7 and 14 days later. The control intervention for the moderate- or high-probability group was ultrasonography of the proximal deep veins of the leg after 7 and 14 days. In the control and experimental groups, anticoagulation was withheld or withdrawn if PE was not diagnosed.

Measurements: Symptomatic versus thromboembolism (VTE) during 6 months of follow-up.

Results: Prevalence of VTE was 15.3% in the 1126 enrolled patients. In the low-probability group, VTE occurred during follow-up in 0 of 182 patients who had no additional diagnostic testing and in 1 of 180 patients who had additional testing (difference, -0.5 percentage point [95% CI, -1.0 to 1.6 percentage points]). In the moderate- or high-probability group, VTE occurred during follow-up in 1 of 41 patients who had no additional diagnostic testing and in 0 of 41 patients who had additional testing (difference, 2.4 percentage points [95% CI, -0.4 to 12.6 percentage points]).

Limitations: The authors could not enroll 2000 patients as originally planned; 3 randomly assigned patients did not receive the allocated intervention, and 7 received inadequate follow-up. Personnel who performed follow-up evaluations were not blinded to the results of diagnostic testing at enrollment or to allocation group assignment.

Conclusion: In patients with a low probability of PE who have negative d-dimer results, additional diagnostic testing can be withheld without increasing the frequency of VTE during follow-up. Low clinical probability and negative d-dimer results occur in 10% of outpatients and in 20% of inpatients with suspected PE.

Ann Intern Med. 2006;144(10):821. doi:10.1213/00006123-200610000-00001

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

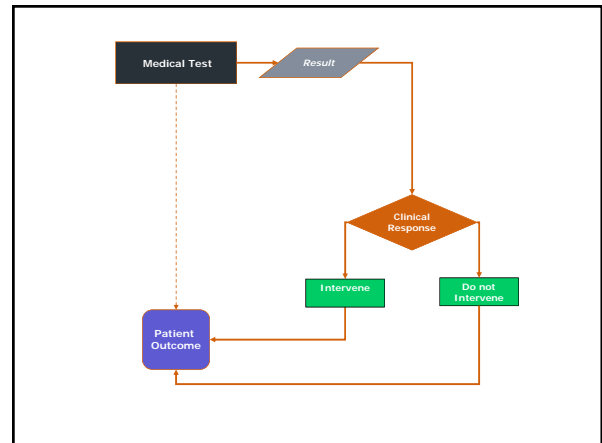
Consequentialism

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



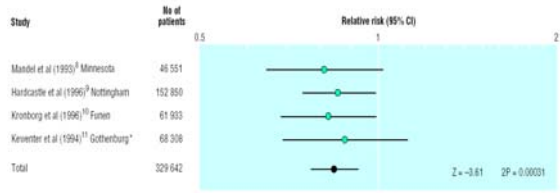
Clinical Effectiveness

Think RCT

Do not always perform an RCT



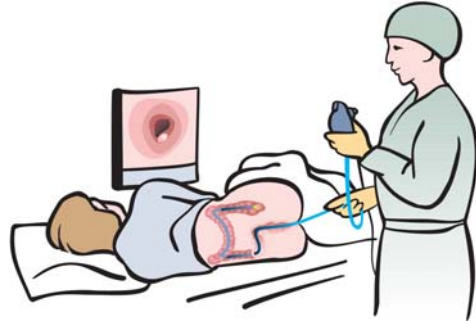
Meta-analysis CRC Screening RCT



Relative Risk CRC Mortality: 0.84
(95% CI: 0.77 to 0.93)

BMJ 1998;317:559-65

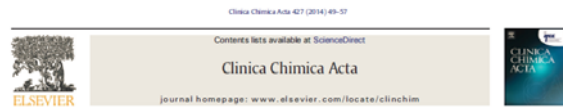
Colonoscopy



Fecal hemoglobin testing



Informative Performance



Special report

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

Andrea R. Horvath^{a,b}, Sarah J. Lord^{b,c,d}, Andrew Sjödin^e, Sverre Sandberg^f, Christa M. Cobbaert^g, Stefan Lorenz^h, Philip J. Monaghan^h, Wilma D.J. Verhagen-Kamerbeekⁱ, Christoph Ebert^j, Patrick M.M. Bossuyt^k

For the Test Evaluation Working Group of the European Federation of Clinical Chemistry Laboratory Medicine

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

Andrea R. Horvath^a, Sarah J. Lord^{b,c,d}, Andrew Sjödin^e, Sverre Sandberg^f, Christa M. Cobbaert^g, Stefan Lorenz^h, Philip J. Monaghan^h, Wilma D.J. Verhagen-Kamerbeekⁱ, 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

Clinicians should share information about how well a new test correctly diagnoses that will benefit from clinical intervention rather than simply the presence of any disease.

S. J. Lord research fellow¹, L. P. Stuck PhD candidate¹, P. M. M. Bessink professor of clinical epidemiology¹, L. M. Irving professor of epidemiology²

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

A parable

Coda



Artificial Nose – PE-Sensor



Artificial Nose – SensorFreshQ



Breathomics as a diagnostic tool for pulmonary embolism

N. FENS*, R. A. DOUMA, F. J. STERK* and P. W. KAMPHUIS*
 *Department of Respiratory Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, and †Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

To cite this article: Fens N, Douma RA, Sterk FJ, Kamphuis PW. Breathomics as a diagnostic tool for pulmonary embolism. *J Thorac Dis* 2016; 8: 2016-4.

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 morbidity and mortality on the one hand, and unnecessary treatment on the other. Individual signs and symptoms have low sensitivity, and additional tests are also not sensitive or specific enough to rule PE in or out [2]. Probably, inclusion of the diagnosis should be performed with well-defined and non-invasive diagnostic methods.

A breath test is certainly an ideal way to fulfil 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-molecular recognition of molecular vibrations [3]. By means of electronic, laser-based methods, the sampling of exhaled breath and its VOCs has become readily available, owing to their ability to discriminate molecular profiles or 'fingerprints' with computer-assessment

software. Breathomics. Clearly, available eNose-like handheld devices using on-board pattern-recognition software that is suitable for diagnostic classification without identification of the individual molecular components [4,6]. This provides the potential option of 'on the spot' diagnosis of disease, as has been investigated in lung cancer [5], chronic obstructive pulmonary disease and asthma [6].

The combination of a clinical decision rule (CDR) and D₂ laser sensing includes PE in about 20-30% of patients [7]. This implies that the majority will undergo imaging tests, such as computed tomography (CT) scans. As a majority of these latter patients will have PE, as mentioned in the number of patients in whom PE can be excluded without additional imaging is mentioned. The eNose is an interesting diagnostic tool in patients with suspected PE, especially in those without comorbidity [8-11].

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 high CDR or absent D-dimer level, and that this differentiation would be more pronounced in patients without relevant comorbidity.

The study was a prospective, parallel, pilot study in patients with suspected PE. Patients with a diagnosis of PE were compared with patients in whom the diagnosis was excluded. Suspected PE was defined as a positive result of duplex ultrasonography of existing duplex, and/or evidence of plethoric distal pain in combination with a high initial probability according to Wells or a D-dimer level

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DOI: 10.1111/jth.1269

Received 20 August 2015, accepted 18 September 2015

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