From promising biomarkers to medical tests
under the current EU IVD Directive 98/79/EC

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Zon-MW PM symposium
Content

• Introduction on diagnostic testing in medical labs
• From promising biomarkers to useful medical tests
    • Explaining Test Evaluation and Scenario with PE-nose
• Future practice under the new IVD Regulation 2017/746
• Conclusions
  • Future directions for PM & predictive biomarkers
70% of medical decisions are based on laboratory results
I. Introduction: Total Test Process

75% Pre-analytical phase

Outside the laboratory
- Patient identification
- Blood/specimen collection
- Specimen identification
- Specimen transport

Within the laboratory
- Time of specimen arrival
- Check-in
- Centrifugation, decapping
- Aliquoting, and labeling of secondary specimen

15% Analytical phase

- Accuracy
- Reproducibility
- Turnaround time
- Internal quality control
- External quality assessment

10% Post-analytical phase

Outside the laboratory
- Utilization of laboratory data in patient management
- Reaction to the results
- Interpretation of results
- Reception of reports

Within the laboratory
- Transmission of results
- Interpretation comments
- Reference range or decisional limits
- Medical validation
- Technical validation

Notifications/Meldingen
Diagnostic Uncertainty & Measurement Uncertainty

- Biological variation
- Preanalytical variation
- Analytical variation
- Postanalytical variation
- Diagnostic uncertainty
Determinants of DIAGNOSTIC UNCERTAINTY

“Medicine is a science of uncertainty and an art of probability” claimed William Osler. History, physical examination, imaging, electrocardiogram, and laboratory investigations are all fraught with uncertainties, frequently prompting further investigations, including laboratory methods, which usually reduce the diagnostic uncertainty.

However, in extreme cases, numerous investigations may be expensive, painful, and lead nowhere; aptly coined the Ulysses syndrome. Medical diagnosis must therefore rest on knowledge and skills in medicine combined with aptitude in the handling of uncertainties.

Elvar Theodorsson, CCLM 2017
II. From promising biomarker(s) to medical test(s)

“a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”

Biomarkers Definition Workgroup, NIH, 1998
Where to look for biomarkers?

Biofluids

- Cerebrospinal fluid

Tissue

- Connective tissue
- Skeletal muscle
- Cardiac muscle
- Epithelial tissue
- Smooth muscle

Spinal needle is inserted, usually between the 3rd and 4th lumbar vertebrae.
Clinical need for Biomarker discovery

Sensitivity 78% >50 jr
Sensitivity 40% <50 jr

Sensitivity 65%

Imaging 85-90%
Biomarker -to- test development pipeline

Drug Development Pipeline Flow

- Target Validation
- Lead Optimization
- Translational Medicine
- Phase I & II
- Phase III
- Commercial

Laboratory → Clinic

Biomarker Evolution

- Biomarker Identification
- Exploration
- Demonstration
- Characterization
- Surrogacy
- Diagnostic

Degree of evidence required

- Identify candidate markers
- Research and development tool (Find best candidate + Best assay)
- Probable or emerging biomarker (scientifically validated: Define assay performance + Sensitivity + Reproducibility)
- Known or established biomarker (Qualify in defined clinical populations)
- Biomarker can substitute for a clinical endpoint (Acceptance by regulators)
- General medical and research use
Lifecycle of the prostate cancer biomarker PSA

**PSA evolution**

- **1977:** Food and Drug Administration (FDA) approves PSA for patients already diagnosed
- **1996-1997:** Four new chemical entity therapeutics approved for prostate cancer
- **2002-2004:** Period and retrospective analyses on survival
- **1994:** PSA approved as predictive indicator
- **2007:** “220 therapeutics emerging;” 100 in Phase II; 20 on market

**Biomarker development**

- Preclinical exploratory
- Clinical assay and validation
- Retrospective longitudinal
- Prospective screening
- Cancer control

**Theme #1:** Early stages of development, PSA was informative
- PSA discovered 1971
- 1974: prostate cancer studied through imaging
- Focus on understanding underlying disease

**Theme #2:** Conundrum – What is the value of diagnostics for which there is no therapy?
- 1990’s debate on PSA’s usefulness in identifying disease with no drug therapy
- PSA use grew despite up to 75 percent false positives
- Biopsies continued on patients without cancer
- Used as a predictive marker to diagnose early enough to assess effectiveness

**Theme #3:** Perseverance can prevail, but innovation and collaboration must shorten timelines
- Reduce mortality in prostate cancer – long term Tyrol screening reduced mortality by 54 percent compared to Austria average
- Combine biomarker indicators
- Partner with other experts to improve clinical outcomes
- PSA velocity (rate of increasing concentration) is a better risk indicator than original PSA
Introduction of PSA-test in 1986

Prostate Cancer Diagnoses and Death Rates in the U.S.
1975-2007

Year


Diagnoses

Deaths

No. per 100,000
Increasing importance of medical tests!
Rationale: Value based and clinically effective healthcare!

Focusing on patients from research through clinical care.

**Biomarkers in clinical development help**
*Biopharma create more effective therapies*

- Shifts blockbuster model to more patient-focused development model
- Supports more efficient R&D methods
- Identifies risk groups and candidates of responders
- Identifies risk for toxicity
- Addresses expensive, slow-progressing diseases

**Biomarkers in medical practice help improve outcomes and reduce cost to society**

- Addresses diseases of aging population
- Assesses disease risk
- Helps diagnose patients early in disease process to reduce healthcare costs
- Provides prognostic tools

**Common value**
- Predicts safety
- Identifies risk and candidates of responders
- Monitors therapy

*Source: IBM Institute for Business Value.*
Recognition that doctors need to take individual variability into account is driving huge interest in Precision Medicine.

Imprecision Medicine and Prescription Roulette

Schork NJ, Nature, 2015; 520: 609-611
From imprecision medicine with prescription roulette to precision medicine with targeted Dx & Tx.
Scenario:
you as a doctor phone ...
...and you say:

“I just came back from a conference in the US and heard about PE Sensor® to be a much better test than Sniff-Sniff® (that you have been providing in the last 10 years). Can your lab move to this new test for me please TOMORROW?”
Artificial Nose – PE-Sensor
Breathomics as a diagnostic tool for pulmonary embolism

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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 composite nanosensor 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 [4,6].

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 [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 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...
Clearview Simplify D-dimer

**Clearly different**
Clearview’s patented innovative technology provide highly sensitive and specific tests for D-dimer.

- **Rapid Response**: Two easy steps, results in 10 minutes.
- **Simplicity**: Easy to use test requires no expensive instrumentation and specialized training.
- **Reliability**: Built-in control ensures accuracy.
- **Flexibility**: Faster results while the patient waits.

**Clearly better**
Clearview Simplify D-dimer offers important benefits for you and your patients.

- Aid in the diagnosis of deep vein thrombosis (DVT), pulmonary embolism (PE), and disseminated intra-vascular coagulation (DIC).
- Utilize the patented 3B6/22 Monoclonal Antibody, specific only for D-dimer, which minimizes the false positives that can be seen with competitive tests.
- Reduces the wait for test results.
- Any staff member can perform, eliminating the need for instrumentation and specialized training.
What questions do laboratory professionals & IVD-industry answer and what should they do before providing this test?
Is it value for money?

Laboratory tests have **clinical value** only if they are **clinically effective** and improve patient-centred, or organizational or economic outcomes; i.e., if they provide benefit to patients at acceptable costs.
How would you assess the value of a test before implementing it?

EVALUATING DIAGNOSTIC TESTS
Diagnostic Biomarkers: Are We Moving from Discovery to Clinical Application?

Lucy A. Parker,1,2 Elisa Chilet-Rosell,1,2 Ildefonso Hernández-Aguado,1,2 María Pastor-Valero,1,2 Sonia Gea,1 and Blanca Lumbreras1,2*

RESULTS: In the 10-year period analyzed, 4257 articles cited the 107 diagnostic studies; 118 (2.8%) were diagnostic studies of the same test, and of these papers, 25 (21.2%) did not constitute progress toward validation of the test for use in clinical practice (potential research waste). Of the 107 molecular- or “omics”-based tests described in 2006, only 28 (26.2%) appeared to have made progress toward clinical application. Only 4 (9.1%) of 44 proteomics-based tests had made progress toward clinical application.
EFLM Test Evaluation Framework: a consequentialist approach

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

Andrea R. Horvath a,b,*, Sarah J. Lord b,c,1, 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
European Federation of Laboratory Medicine (EFLM) Working Group on Test Evaluation developed a comprehensive framework & tools for test evaluation

 colaboration between:
 – laboratory medicine professionals
 – epidemiologists and evidence-based medicine experts
 – diagnostic industry.

 informed decisions on:
 – adoption of new tests
 – existing tests and practices

 impact on:
 – patient-related, organisational and economic outcomes

https://www.eflm.eu/
https://www.eflm.eu/site/page/a/1203 (resources and educational material)
https://elearning.eflm.eu/course/view.php?id=43 (elearning clinical needs)
The Test Evaluation Cycle

Is there an unmet clinical need and is there an effective intervention?
<table>
<thead>
<tr>
<th>Step</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Identify unmet need</td>
</tr>
<tr>
<td>2</td>
<td>Verify unmet need</td>
</tr>
<tr>
<td>3</td>
<td>Validate intended use</td>
</tr>
<tr>
<td>4</td>
<td>Assess feasibility</td>
</tr>
</tbody>
</table>

**Is there an existing solution?**
- Could the problem be solved by optimising current practice?
- Could these solutions be effective?
- Could these solutions be cost effective?
- Are there any barriers for these solutions?

**Would the biomarker contribute to the solution?**
- How could the biomarker alter and improve current practice?
- What are the expected outcomes of test results?
- How do these outcomes compare to the desired outcomes defined in STEP1?

**Is the biomarker solution feasible in practice?**
- Under what conditions would the new biomarker be feasible?
  - Commercially?
  - Economically?
  - Technically?
  - Organisatorially?
- Are there any other barriers?
Waste, Leaks, and Failures in the Biomarker Pipeline

John P.A. Ioannidis\textsuperscript{1*} and Patrick M.M. Bossuyt\textsuperscript{2}

\textbf{Current situation}

**SUMMARY:** The current biomarker pipeline is too prone to failures. Consideration of clinical needs should become a starting point for the development of biomarkers.
Data only become evidence within the context of a decision framework

- A test is a procedure that makes use of an assay in the context of a particular disease, in a particular population for a particular purpose, followed by action.

- Before a new test is fully evaluated:
  - its intended purpose (screening, diagnosis, monitoring, etc.)
  - its role (add on, replacement, triage),
  - the clinical pathway
Test Role

Clinical decision rule → D-dimer → Rule Out

CTPA → CT Pulmonary Angiography
Test Role: replacement test

Clinical decision rule ➔ PE-sensor ➔ Rule Out ➔ CTPA

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Test Role: add on test

Clinical decision rule ➔ D-dimer ➔ Rule Out

PE sensor ➔ CTPA
Test Role: triage test

PE sensor → D-dimer → CTPA

Rule Out
Key messages

Before a new test is fully evaluated, the
- unmet clinical needs,
- intended purpose (screening, diagnosis, monitoring, etc.),
- role (add on, replacement, triage),
- population,
- healthcare setting in which the test is intended to be used,
- condition that is intended to be managed with the use of the test,
- procedures for evaluating these, and
- potential final outcomes of testing

must be clearly defined.

All the above are best mapped out by drawing the clinical pathway

Bossuyt, 2010
The Test Evaluation Cycle

The ability of an assay to conform to predefined TECHNICAL specifications and to correctly detect or measure a particular analyte/measurand.

- preanalytical considerations
- analytical sensitivity/specificity
- limit of detection/quantitation,
- measurement range
- linearity
- metrological traceability,
- imprecision and trueness
Proteomic Discovery and Validation of the Confounding Effect of Heparin Administration on the Analysis of Candidate Cardiovascular Biomarkers

Hans C. Beck,1,2* Lisette O. Jensen,3,4 Charlotte Gils,1 Albertine M.M. Ilondo,1 Martin Frydland,5 Christian Hassager,5 Ole K. Møller-Helgestad,3,4 Jacob E. Møller,3,4 and Lars M. Rasmussen1,2,4

BACKGROUND: Several plasma proteins have been suggested as markers for a variety of cardiovascular conditions but fail to qualify in independent patient cohorts. This may relate to interference of medication on plasma protein concentrations.

METHODS:
- proteomic approach to quantify several hundred proteins in a discovery study using individual plasma samples after an AMI before and after heparin administration
- validated findings in 500 patients with suspected STEMI at admission, of whom 363 were treated with heparin before admission.

RESULTS: In the discovery study, 25 of 653 identified plasma proteins displayed a changed concentration after heparin administration; 14 proteins changed significantly among heparin-treated patients in the validation study.

CONCLUSIONS: Medications such as heparin administration given before blood sampling may confound biomarker discovery and should be carefully considered in such studies.
Key messages

Analytical performance specifications

- should reflect clinical needs
- can be based on 3 different models:
  1/ outcomes
  2/ biological variation
  3/ state-of-the art;
- should be set at a level that achieves net health benefit for patients at reasonable costs;
- should be tailored to the purpose and role of the test in a well defined clinical pathway;
- should be commensurate with the impact of the laboratory test on subsequent medical decisions and actions

High quality analytical performance does not guarantee high quality clinical action or patient compliance or that the chosen treatment will be effective.

The opposite is also true; poor analytical performance of a test that plays a small part in a complex clinical pathway may not necessarily lead to adverse or unfavourable outcomes.
The Test Evaluation Cycle

- the ability of a biomarker to conform to predefined CLINICAL specifications in detecting patients with a particular clinical condition or in a physiological state.

- How well does it work in practice?
- In what subset of patients?
- Is it really better than Sniff-Sniff®?
- How do alternative tests compare?
Comparative diagnostic accuracy
In symptomatic patients is PE Sensor® better than Sniff-Sniff® to rule in/out PE?

Consecutive patient series suspected for target condition

Index test

Comparator index test

Reference standard

Blinded cross-classification

- Patients with SOB
- PE Sensor
- Sniff-Sniff
- Pulmonary angiography
- PE

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Graphics adapted from Patrick Bossuyt, Amsterdam
The Test Evaluation Cycle

The ability of a test to improve OUTCOMES

- How does the test result affect patient’s health and quality of life?
- What are the benefits and harms and risks of testing?
Diagnostic RCT to assess clinical effectiveness

Do patients who undergo the new test fare better (in terms of health outcomes) than those who have the old test?

Patients with suspected target condition

PE Sensor

Sniff-Sniff

Outcome

Outcome

Treatment

Control

Treatment

Control

R
Key messages

- The link between testing and health outcomes is indirect and is dictated by the clinical pathway.

- Improved diagnostic or prognostic accuracy of a test or the effects of the test on medical decisions are not necessarily indicative of patient benefit.

- Direct evidence of clinical effectiveness would be ideal but, under specific circumstances, indirect evidence is sufficient for the clinical use of a new biomarker.
The Test Evaluation Cycle

Assessment of changes of costs in relation to changes in outcomes
The Test Evaluation Cycle

- organisational
- social
- psychological
- ethical
- legal consequences

PSA!

effectiveness

Clinical Performance
Analytical Performance
Impact
Cost
Clinical Effectiveness
Pathway
Test evaluation ...but who should do this?

“The burden of proof falls on whoever makes a positive claim”...
Problem description

- No/insufficient proofs that lab tests impact health outcomes
- No feedback from clinicians on the clinical use and performance of laboratory tests and how they influence medical decisions
- Collecting clinical information is hard
- There is too much variation in practice
- Assessing all consequences of test results is difficult
- There is no time to do this
- We do not know how to do this
- I do not think it is the lab’s responsibility
- Etc, etc…
Legislation and Certificates

Under the current IVDD:
CE mark does not guarantee clinical effectiveness nor safety, except for class A tests!
From biomarkers to medical tests requires collaboration and interdisciplinary alliances among all stakeholders of the biomarker-medical test pipeline.

The wheels are rolling on...

- Clinicians
- Laboratory professionals
- Regulators & Policy makers
- Epidemiologists and methodologists
- Researchers
- Industry &
Time for questions