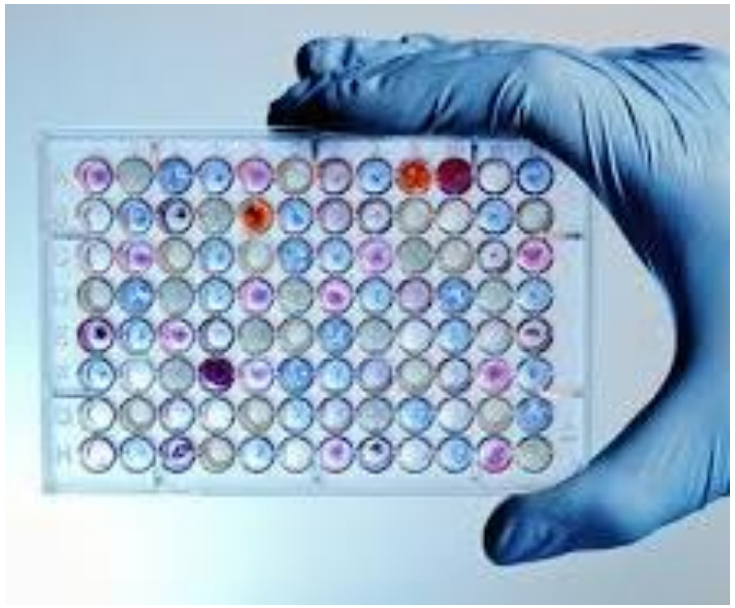
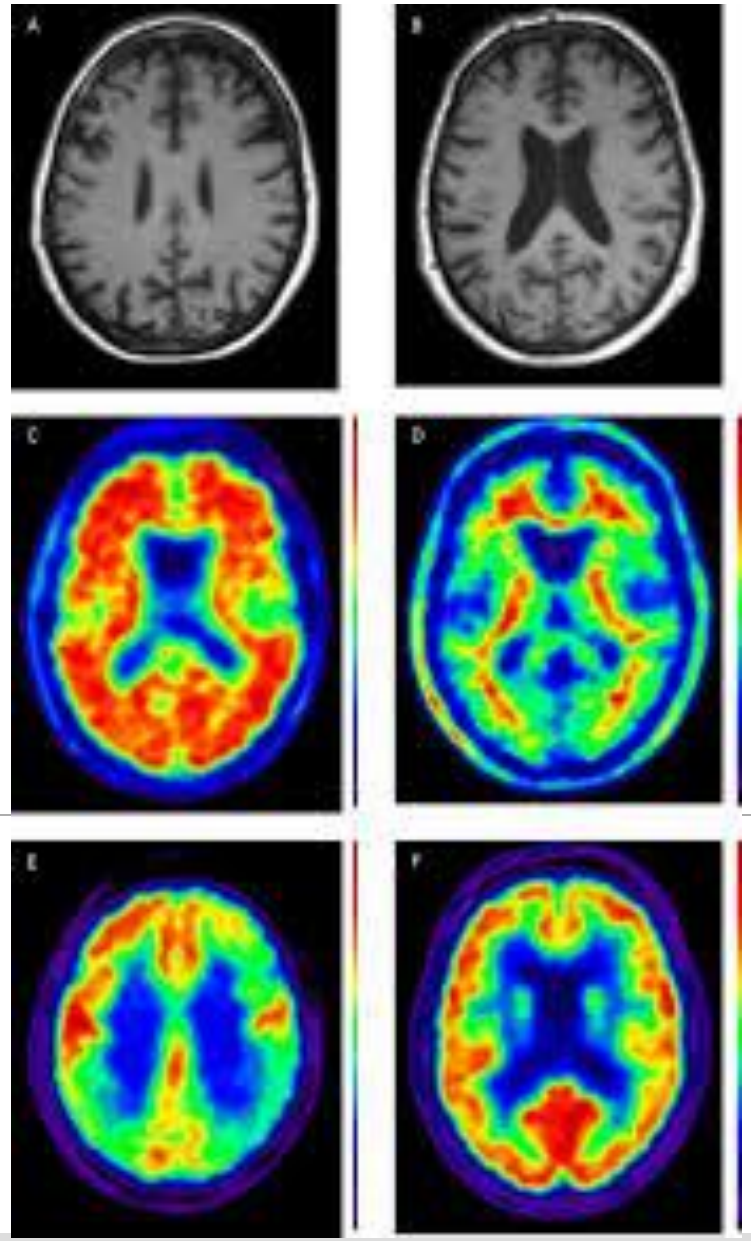
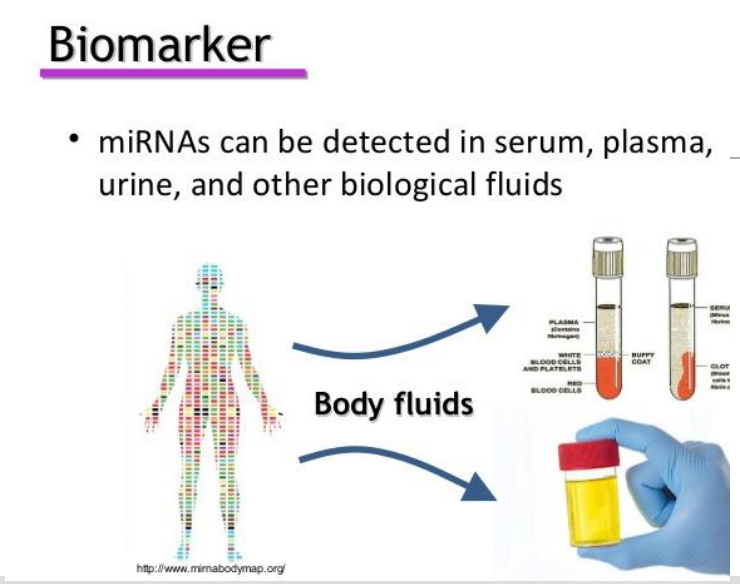






Introduction to Biomarker Research

BIOMARKER MODULE

AUG 8, 2019

SLIDES BY CAROLINE BELTRAN, PHD

Lecture Objectives

1. Define what a biomarker is
2. Explain the characteristics of a good biomarker
3. Define different biomarker types
4. Describe the properties of anatomical and molecular biomarkers
5. Explain the differences between single and panel biomarkers
6. Describe the biomarker discovery pipeline
7. Identify possible pitfalls in biomarker discovery

What is a Biomarker?

"Characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"- NIH Biomarkers Definitions Working Group

"any substance, structure, or process that can be measured in the body or its products, and influence or predict the incidence of outcome or disease"- WHO

Measurable biological component that can be analyzed and indicates a given disease state

Characteristics of a good Biomarker

Specific to disease

High sensitivity

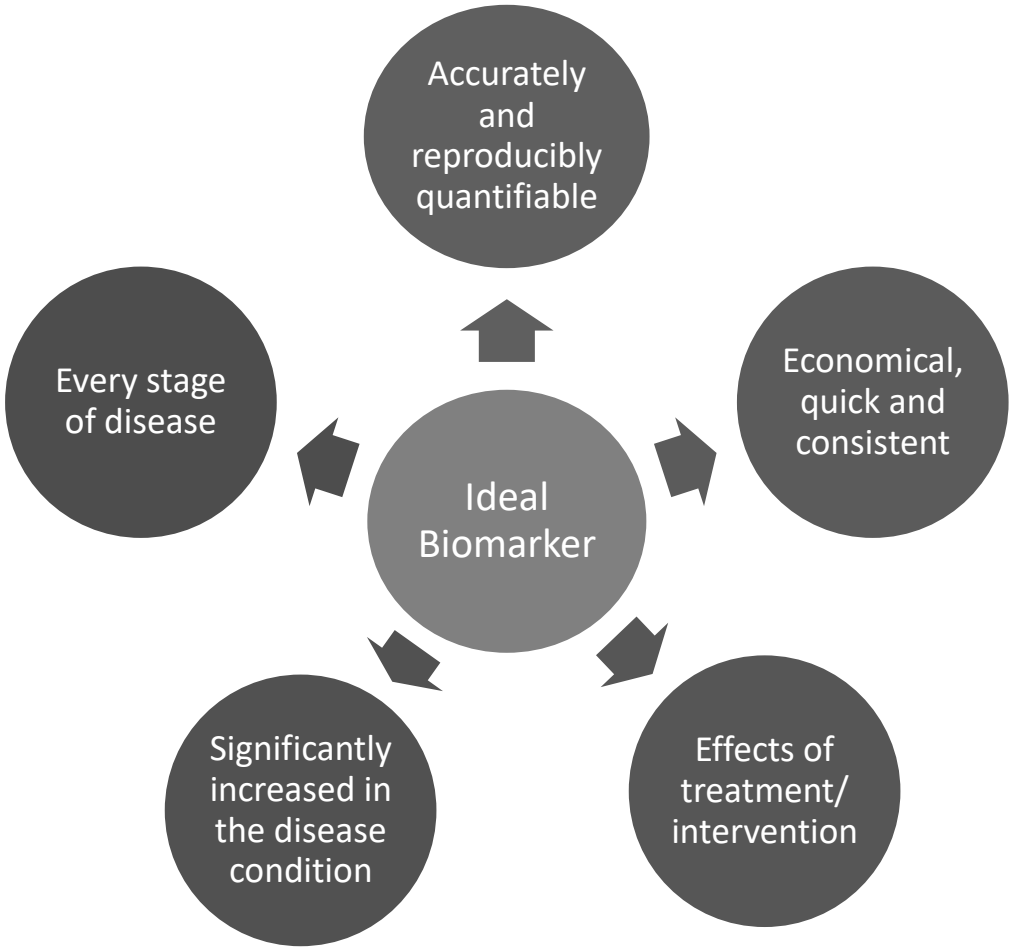
Safe and easy to measure

Rapid for fast diagnosis

Cheap

Consistent

Able to differentiate different states



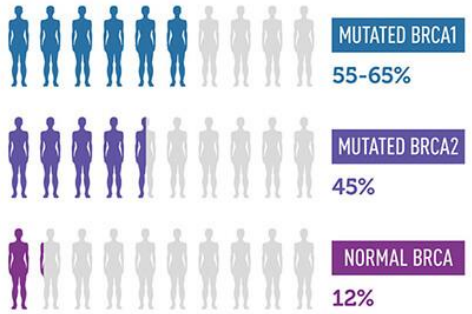
Types of Biomarkers

Predisposition Biomarkers:	Diagnostic Biomarkers:	Prognostic Biomarkers	Predictive Biomarkers	Treatment Response Biomarkers
• Risk/Genetic Susceptibility biomarker • Predisposition developing disease/condition • Screening	• Trait biomarkers • Determine/confirm presence of disease/disorder • Facilitate early detection	• Predict risk/outcome of disease • Intrinsic factors (patient, disease) • Likelihood of a clinical event, disease recurrence or progression in patients	• Predict effect of therapeutic intervention- how well will treatment work? • Determine which patients are most likely to benefit • Stratify patients into responders and non-responders	• Monitor disease recurrence • Therapeutic response

Types of Biomarkers: Metastatic breast cancer

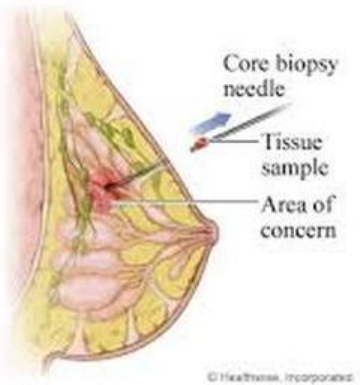
Predisposition Biomarkers:

- BCRA 1 & 2 Gene mutation



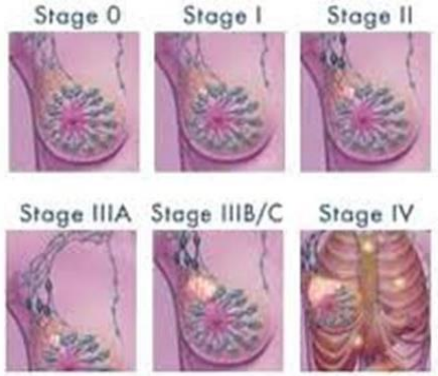
Diagnostic Biomarkers:

- Mammogram
- Tissue biopsy
- Protein blood-based test



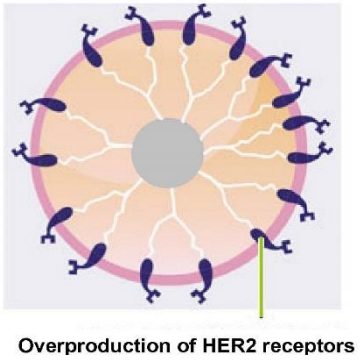
Prognostic Biomarkers

- Tumour size
- Tumour grade
- Lymph node metastases



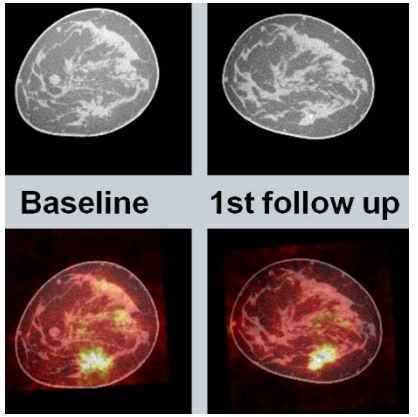
Predictive Biomarkers

- Estrogen and progesterone receptors



Treatment Response Biomarkers

- PET CT to monitor change in tumour size and metabolic activity



Biomarker Properties: Physiological/anatomical

Functional processes in the body

- Blood flow in the brain after stroke as measure of treatment success

Usually based on imaging techniques

- PET CT of tumors following treatment
- MRI scans

Typically non-invasive

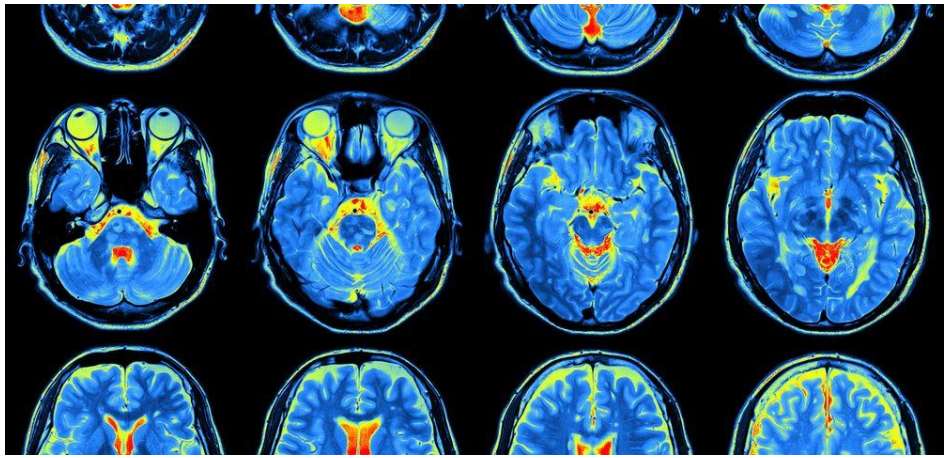


Image source: www.wsj.com

Biomarker Properties: Molecular

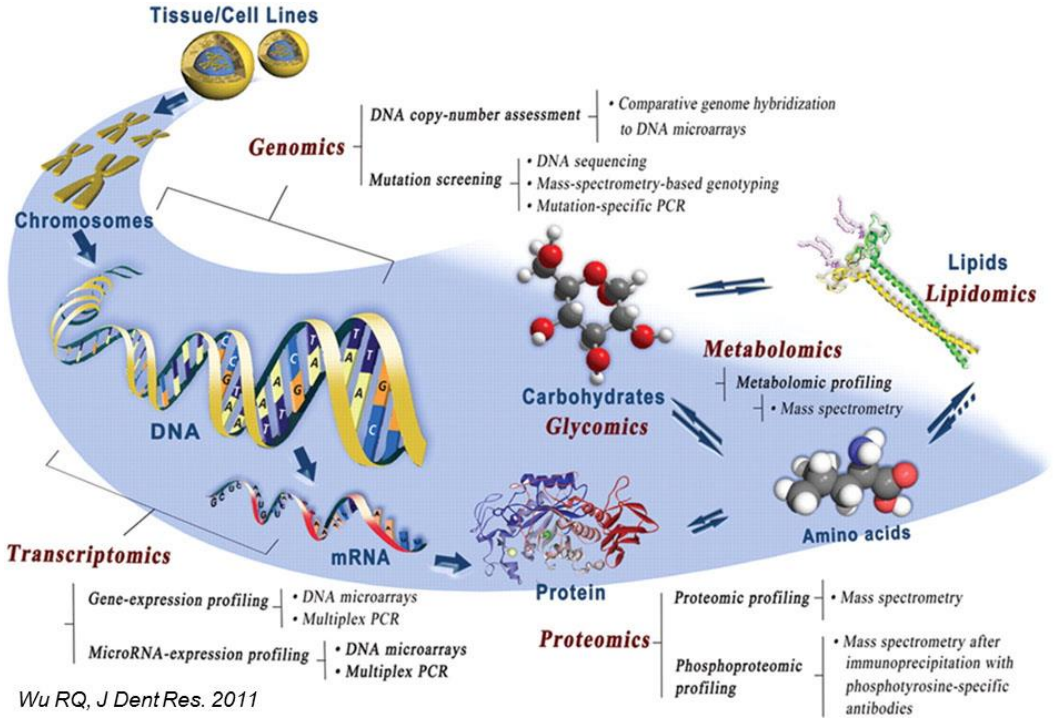
Genomic Biomarkers: BRCA1 and/or BRCA2 genes for breast cancer

Transcriptomic Biomarkers: multi-gene molecular patterns or ‘fingerprints’ for breast cancer survival

Proteomic Biomarkers: Prostate specific antigen in serum

Metabolomic Biomarkers: Sugar metabolites in the blood for diabetes

Cytometrics: Circulating Tumor Associated Cells



Single vs panel biomarkers: Single marker tests

Older methodologies
- Laborious to screen
- Based on pre-existing knowledge

Simple and low cost BUT:
- Variability of disease
- Heterogenous population
- Lower accuracy, sensitivity and specif
- Unlikely to discriminate all cases

Single biomarkers are of limited specific

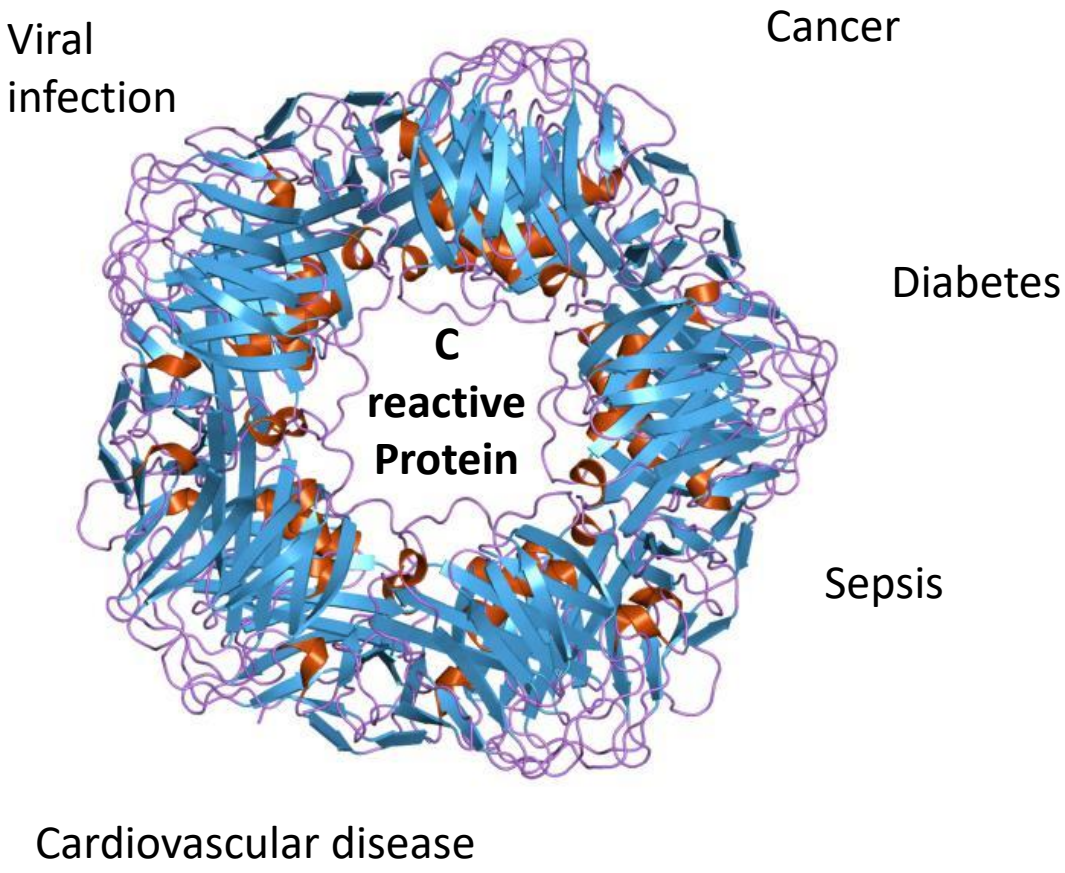


Image source: wikipedia

Single vs panel biomarkers: Multi-Biomarker panels

New methodologies

- “Omics era”: High throughput, 1000s of markers
- Computing power

Multiplex: multiple markers measured simultaneously

Bundled: multiple independent assays

Higher sensitivity and specificity

Quantitative information for large cohorts simultaneously

Personalised medicine

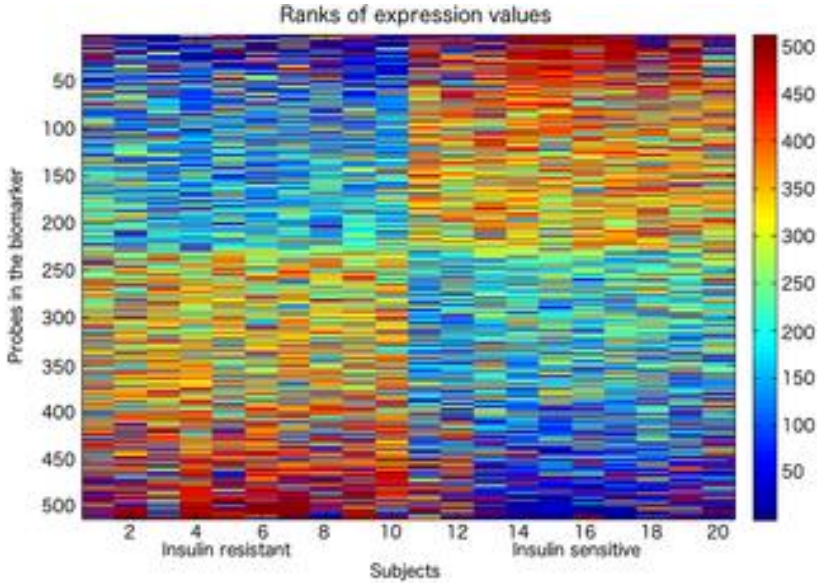


Image source: Matone et al., 2017

Biomarker Discovery Pipeline

1. Discovery:
   - Early exploration: candidate list (>1000)
2. Confirmation:
   - Viability of select candidates?
3. Validation:
   - Characterise specificity and sensitivity
   - Optimize assay, multiple time points
4. Clinical evaluation
   - High sample size (>1000)
   - <10 analytes

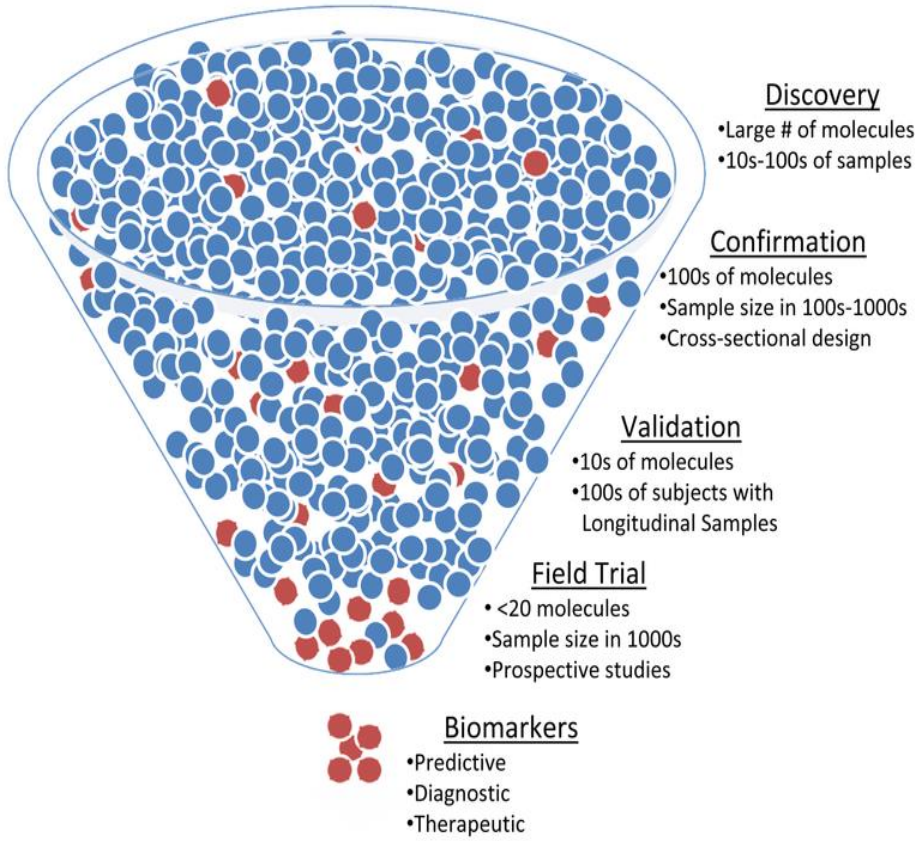


Image source: Carey et al., 2010

Biomarker Discovery Pipeline: Pitfalls

Discovery to implementation failure

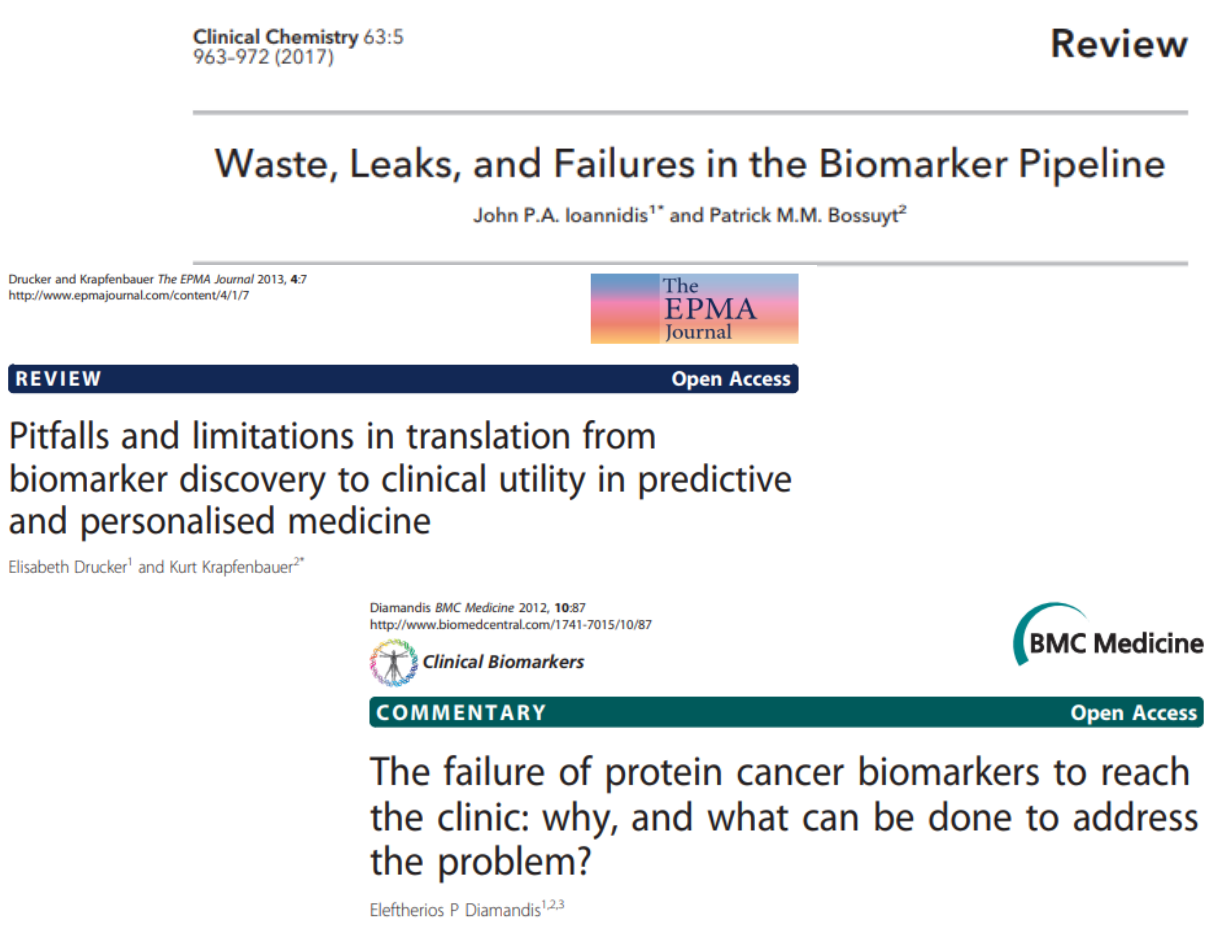
No small feat

Expensive

Time consuming

Confounding factors

- Intra and inter individual variation
- Tissue localization
- Persistence of the biomarker
- Confounding factors: failure to identify factors that may alter the measurement of the biomarker
- Bias



Clinical Chemistry 63:5
963-972 (2017)

Review

Waste, Leaks, and Failures in the Biomarker Pipeline

John P.A. Ioannidis[1*] and Patrick M.M. Bossuyt[2]

Drucker and Krapfenbauer *The EPMA Journal* 2013, **4**:7
http://www.epmajournal.com/content/4/1/7

The EPMA Journal

REVIEW Open Access

Pitfalls and limitations in translation from biomarker discovery to clinical utility in predictive and personalised medicine

Elisabeth Drucker[1] and Kurt Krapfenbauer[2*]

Diamandis *BMC Medicine* 2012, **10**:87
http://www.biomedcentral.com/1741-7015/10/87

Clinical Biomarkers

BMC Medicine

COMMENTARY Open Access

The failure of protein cancer biomarkers to reach the clinic: why, and what can be done to address the problem?

Eleftherios P Diamandis[1,2,3]

Take home message

A biomarker is a measurable characteristic indicating a biological state or condition

An ideal biomarker should be specific to the condition, sensitive, easily measurable and able to differentiate different states

Biomarkers can be classified based on their application

Biomarkers can be either anatomical or molecular

Panels offer improved sensitivity and specificity over single biomarkers

The biomarker discovery pipeline begins with many candidates and ends with a few validated markers