Lost on planet biomarker?
Standards, pathways, carrots and sticks for diagnostic development in the post-genomic era
Precision Medicine meeting, Hong Kong 2016

Stuart Hogarth, Department of Social Science, Health and Medicine,

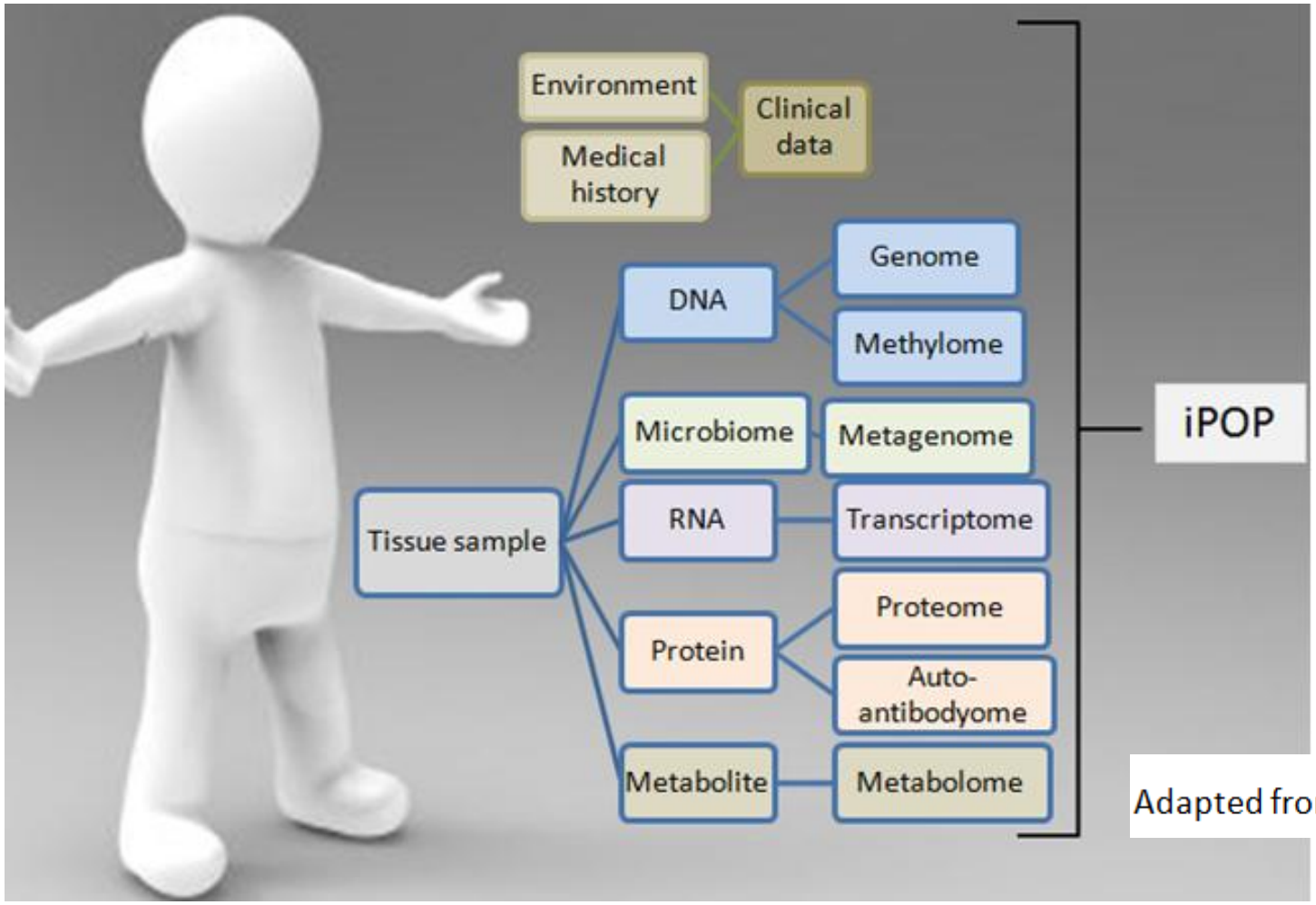
King's College London

Talking about a revolution?

"Today, one of our biggest goals is to cut the cost of sequencing an entire human genome to $1,000 or less ... leading to a revolution in the practice of medicine. ... I expect that within the next decade or so, most people living in developed nations will have their genomes sequenced as part of their medical record ...

Dr. Francis Collins, NIH Director,

Yale Journal of Medicine and Law April 2011



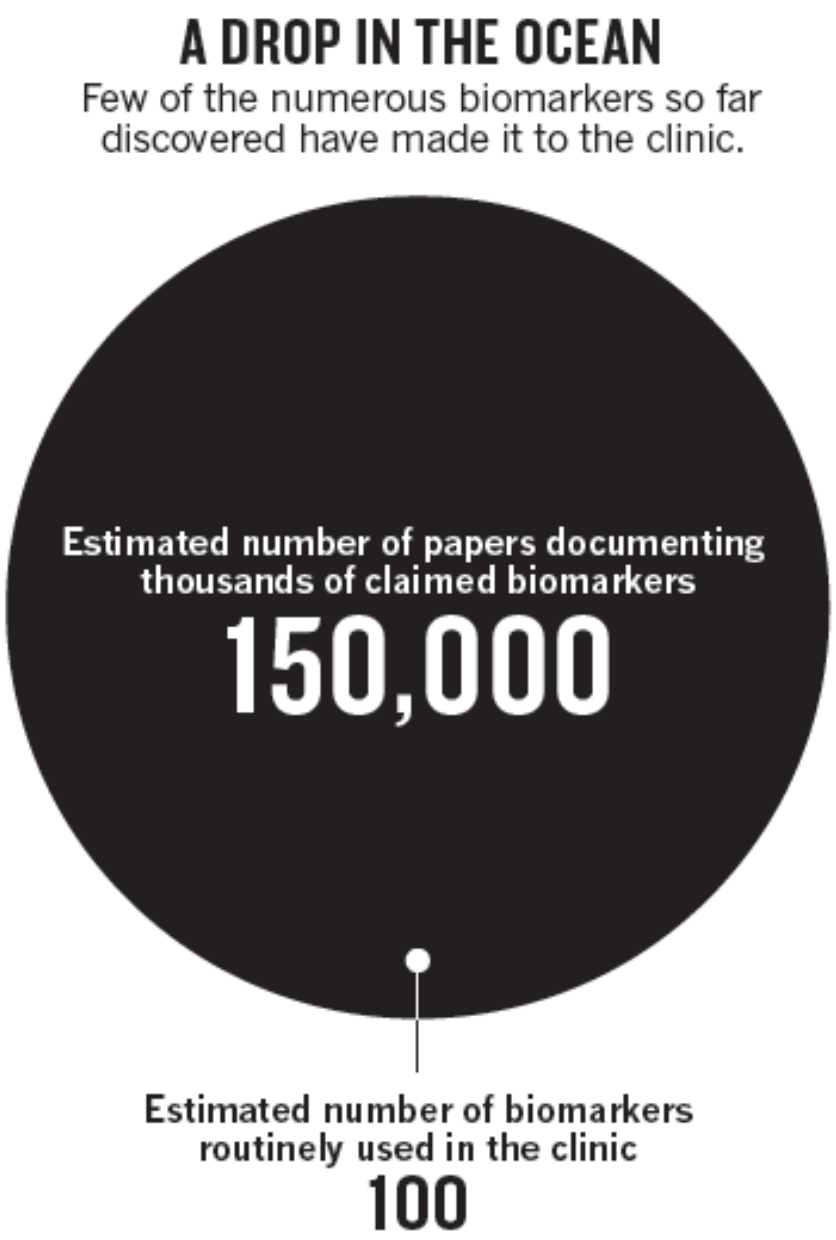
A growing proportion of diagnostic tests will be based upon the assessment of numerous markers drawn from many molecular classes (e.g. genetic, proteomic and metabolomic), the interpretation of which will require mathematical algorithms able to identify signatures characteristic of different disease strata. (MRC *Molecular Pathology Review*, London, 2014)

Not just DNA ...

Commercial colorectal cancer screening tests

Firm	Test	Type of biomarker
Epigenomics	EpiProColon	DNA methylation
Exact Sciences	ColoGuard	DNA, DNA methylation and hemoglobin
Exiqon	miRSIGN	miRNA
GeneNews	ColonSentry	RNA
Metabolomic Technologies	Colo Dx	Metabolomics
Signature Diagnostics	Oncodetect-CRC	RNA
Volition Rx	NuQ	Nucleosomics

Biomarkers: the low-hanging fruit of genomic medicine



Poste, G . Bring on the biomarkers

Nature 2011


LOST ON PLANET
BIOMARKER

In the absence of international standards ... manufacturers, laboratory professionals, researchers and regulators are equally confused on what studies to do or accept as evidence for the clinical performance and effectiveness of medical tests

Horvath et al. ‘From Biomarkers to Medical Tests: The Changing Landscape of Test Evaluation’. *Clinica Chimica Acta;* 2014

A catalogue of errors

Commonly cited problems in diagnostic research

- underpowered studies
- various types of bias (e.g. verification, spectrum)
- insufficient research on clinical outcomes
- over-fitting of data in retrospective analyses
- a lack of prospective controlled studies

theguardian
website of the year

politics sport football opinion culture business lifestyle fashion environment tech

FDA orders genetics company 23andMe to cease marketing of screening service

Agency is 'concerned about the public health consequences of inaccurate results from the PGS device'

MIT Technology Review

Biomedicine

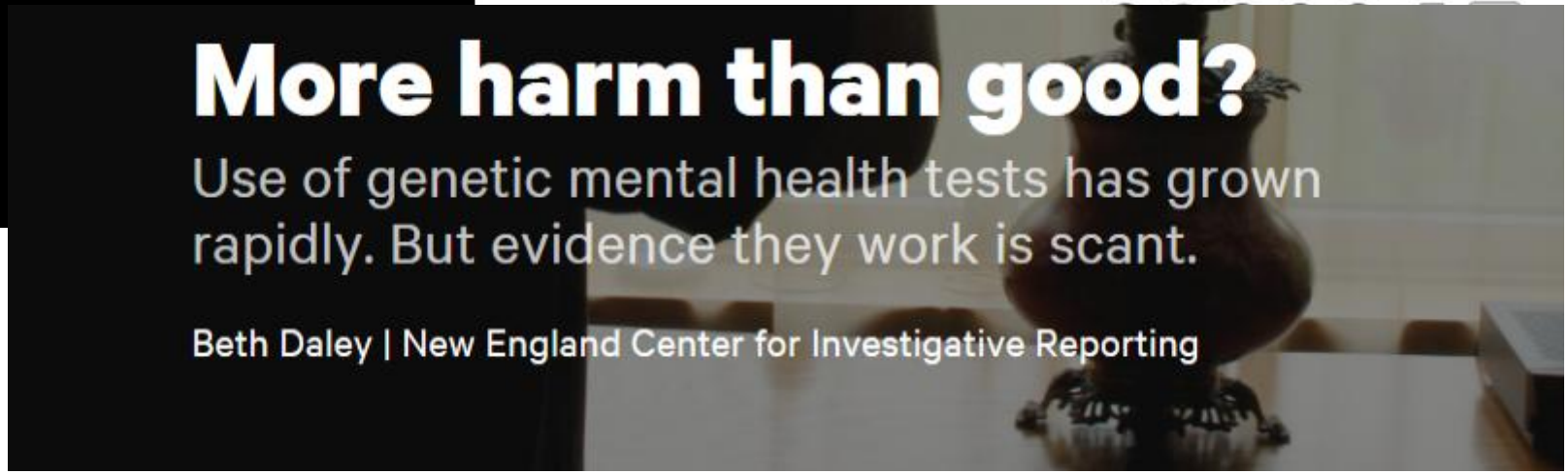
Theranos Promised a Revolution, but Delivered Dangerous Errors

The New York Times

SUBSCRIBE

RESEARCH

How Bright Promise in Cancer Testing Fell Apart



More harm than good?

Use of genetic mental health tests has grown rapidly. But evidence they work is scant.

Beth Daley | New England Center for Investigative Reporting

Diagnostic error

In the USA diagnostic errors are implicated in

- approximately 10% of patient deaths,
- 6 to 17% of hospital adverse events
- Most common source of medical malpractice claims

NAS. 2015. *Improving diagnosis in health care.*

Slow down, you move too fast ?

"[There has been] a noticeable lack of consensus within the genetics community about exactly when a test for a new marker was sufficiently validated for it to enter into clinical service.

Some labs rushed to provide testing after the first publication, while others waited until the result had been replicated in multiple studies or multiple ethnic groups."

Emily Winn-Deen, Cepheid

IVD Technology December 2003

Major policy reports

USA

1975 – *Genetics screening programmes, principles and research* (National Academy of Sciences)

1994 - *Assessing genetic risks* (Institute of Medicine)

1999 - *Promoting safe and effective genetic testing in the United States* (Task Force on Genetic Testing)

2000 - *Enhancing the oversight of genetic tests: recommendations of the Secretary's Advisory Committee on Genetic Testing* (SACGT)

2008 - *Recommendations on the U.S. System of the Oversight of Genetic Testing* (SACGHS)

UK

1994 - *Genetic screening – ethical issues* (Nuffield Council on Bioethics)

2000 - *Genetics and health – policy issues for genetic science and their implications for health and health services* (Nuffield Trust)

2000 - *NHS Laboratory services for genetics* (Report for the Department of Health)

2003 - *Genes direct. Ensuring the effective oversight of genetic tests supplied directly to the public* (HGC)

EU

2000 - *Report of European Parliament's Temporary Committee on Human Genetics and New technologies in modern medicine*

2003 - *Towards quality assurance and harmonisation of genetic testing services in the EU* (IPTS)

2004 - *Ethical, legal and social aspects of genetic testing: research, development and clinical applications* (EC Expert Group)

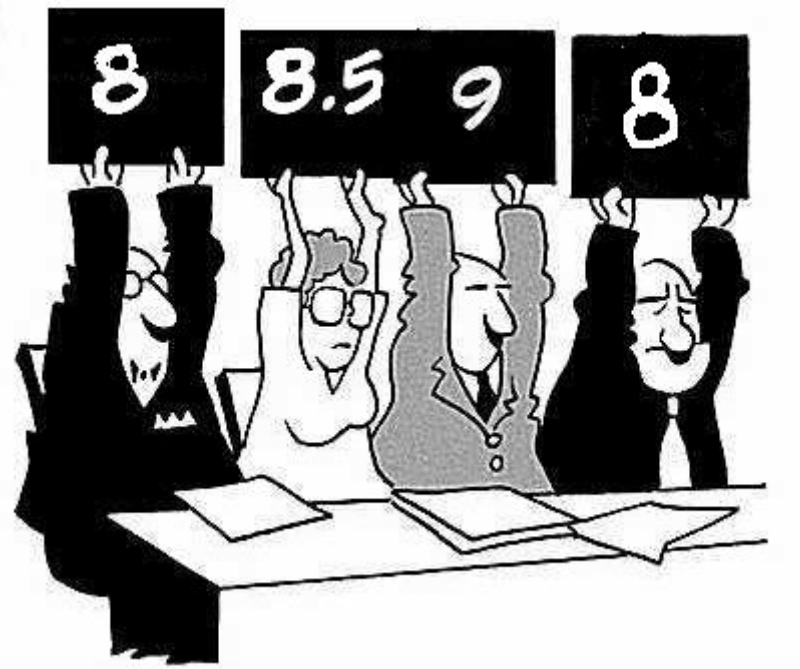
International

2001 - *Genetic testing: policy issues for the new millennium* (OECD)

2005 - *Quality assurance and proficiency testing for molecular genetic testing: survey of 18 OECD member countries* (OECD)

A policy consensus?

Genetic tests should not enter routine clinical practice without thorough independent evaluation



Where are the gaps?

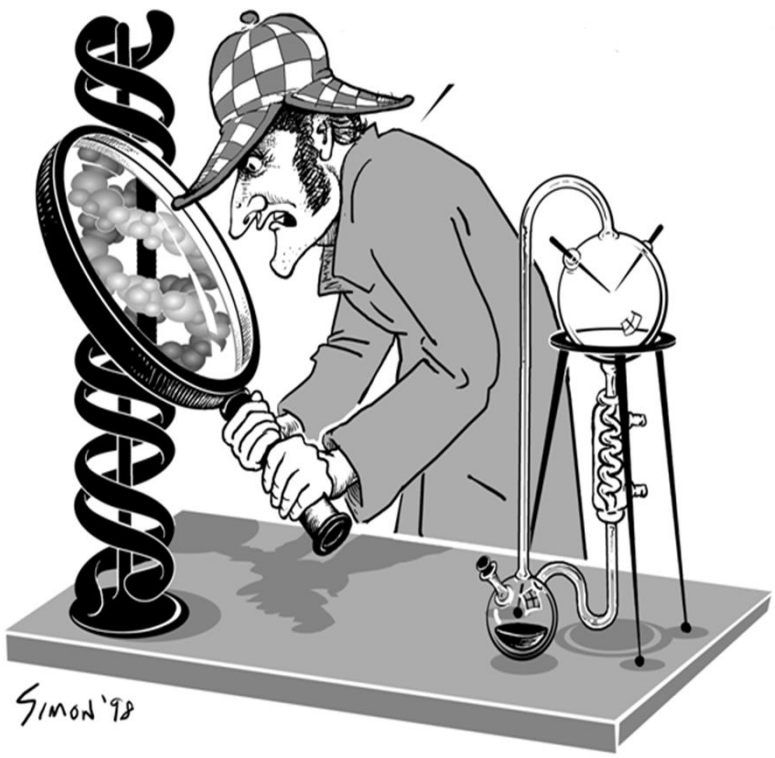
Failures in our medical device regulations

- Europe – nearly all tests are classed as low-risk, so are not subject to independent pre-market review
- USA – until very recently Laboratory Developed Tests (LDTs) have not been subject to FDA authority

In the absence of international standards ... manufacturers, laboratory professionals, researchers and regulators are equally confused on what studies to do or accept as evidence for the clinical performance and effectiveness of medical tests,

Horvath et al Clin Chem, 2014

Not a new problem



"Everyone would admit that we have not had adequate clinical trials for diagnostics in the past; the question is what constitutes enough evidence?

We can't have the same standards as pharmaceuticals - that is too high a barrier and the safety issues are not the same – so what should the standards be and what is the pathway to develop the evidence?"

US IVD industry executive, 2006

Road to nowhere?

"... there is currently no well defined structure or common terminology for the biomarker development process as, for example, there is for the development of a new drug."

Cancer Research UK 2008

Biomarker R&D

Traditional open source model

- Academic discovery of a biomarker
  - First tests with poor analytical validity
- Use at academic/clinical interface explores clinical relevance
  - Laboratories “home brew” test systems
  - Industry may start to commercialize reagents
  - Increase in analytical validity
- Clinical relevance established
  - Industry may start to commercialize test kits
  - As tests becomes widely used industry may start to sell systems or even offer testing services
  - Automation of tests and decrease in cost per test


The progress
of diagnostic
reform

Standards for screening

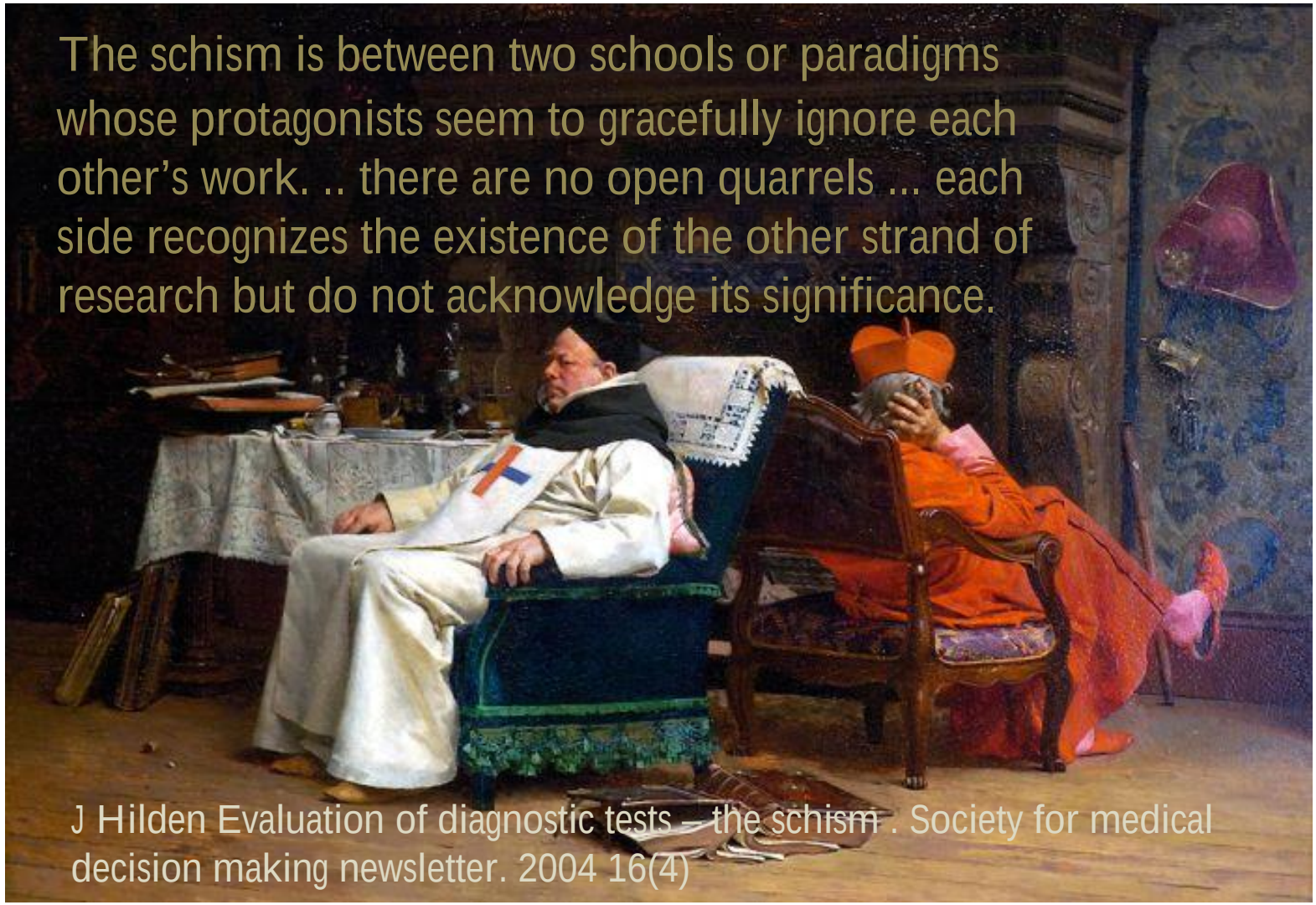
1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a "once and for all" project.

1968 - WHO-commissioned Wilson and Jungner report on screening establishes evaluative criteria for screening tests

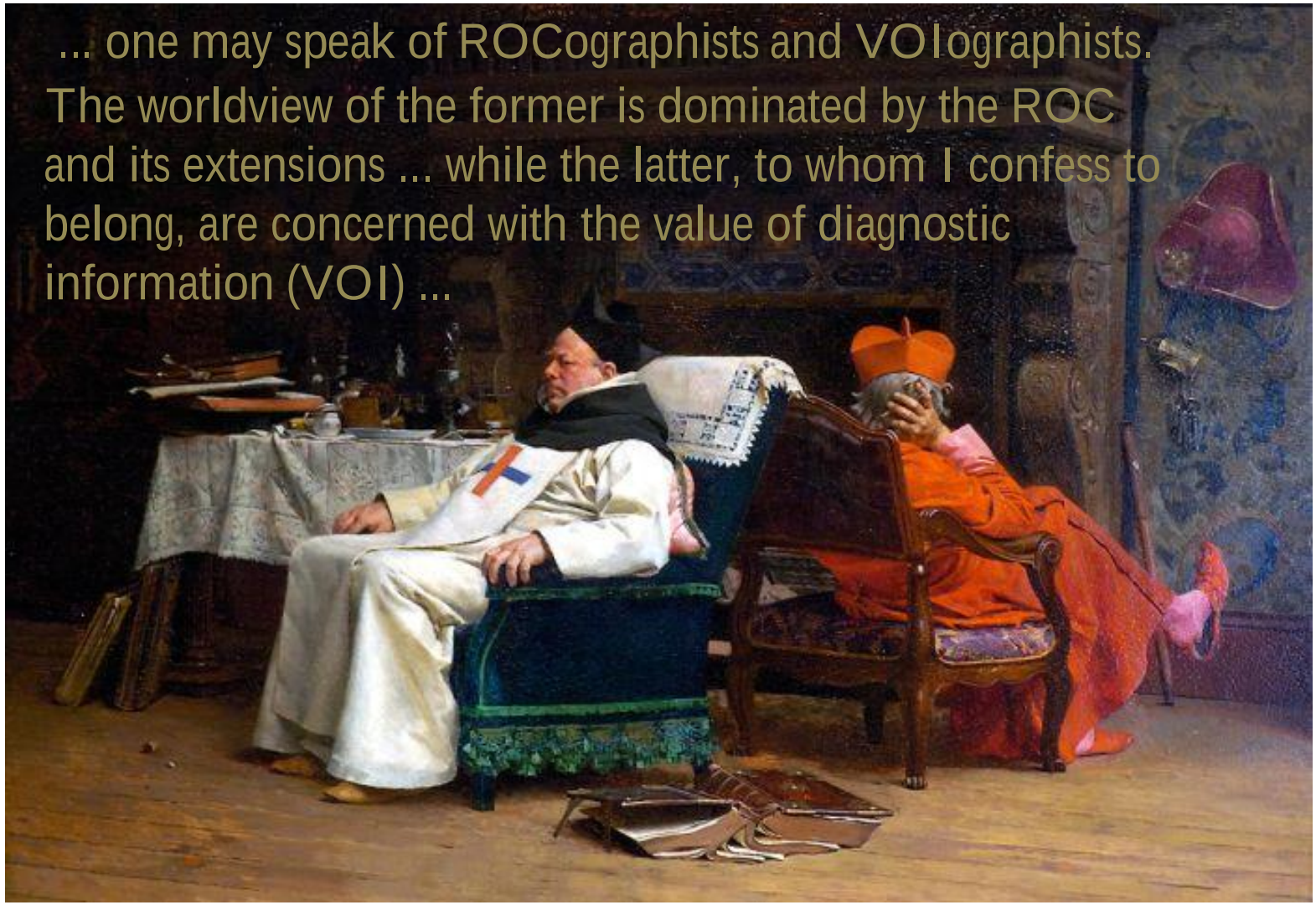
Health Technology Assessment

- CT scanning introduced in USA 1973
- Controversy over rapid clinical adoption
- Sceptics question benefits

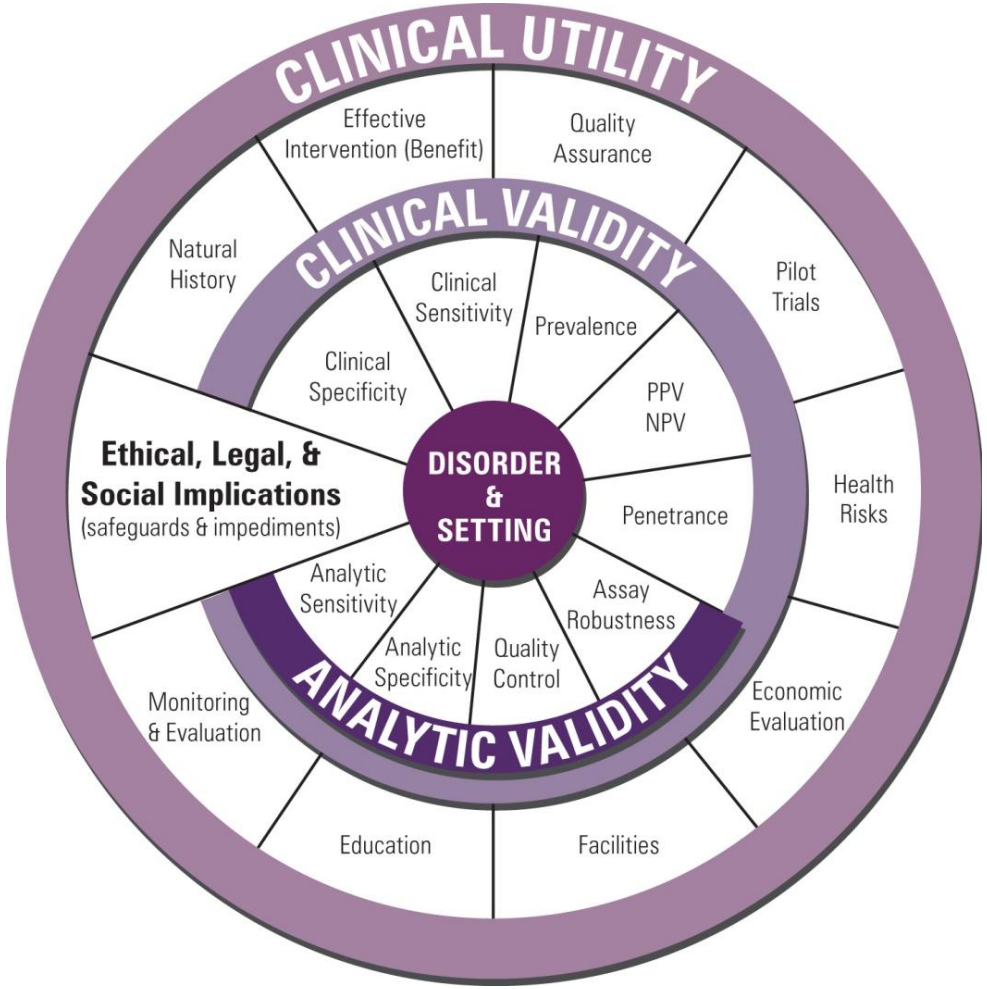
ROC v. VOI – a great schism?



ROC v. VOI – a great schism?



ACCE and the rise of public health genomics



- NOHPG, CDC in USA
- PHGF in UK
- CanGene Test in Canada
- European network

2003 - publication of STARD

Toward Complete and Accurate Reporting of Studies of Diagnostic Accuracy

The STARD Initiative

*Patrick M. Bossuyt, PhD, Johannes B. Reitsma, MD, PhD, David E. Bruns, MD, Constantine A. Gatsonis, PhD, Paul P. Glasziou, MBBS, PhD, Les M. Irwig, MBBch, PhD, Jeroen G. Lijmer, MD, PhD, David Moher, MSc, Drummond Rennie, MD, Henrica C.W. de Vet, PhD, for the STARD Group**

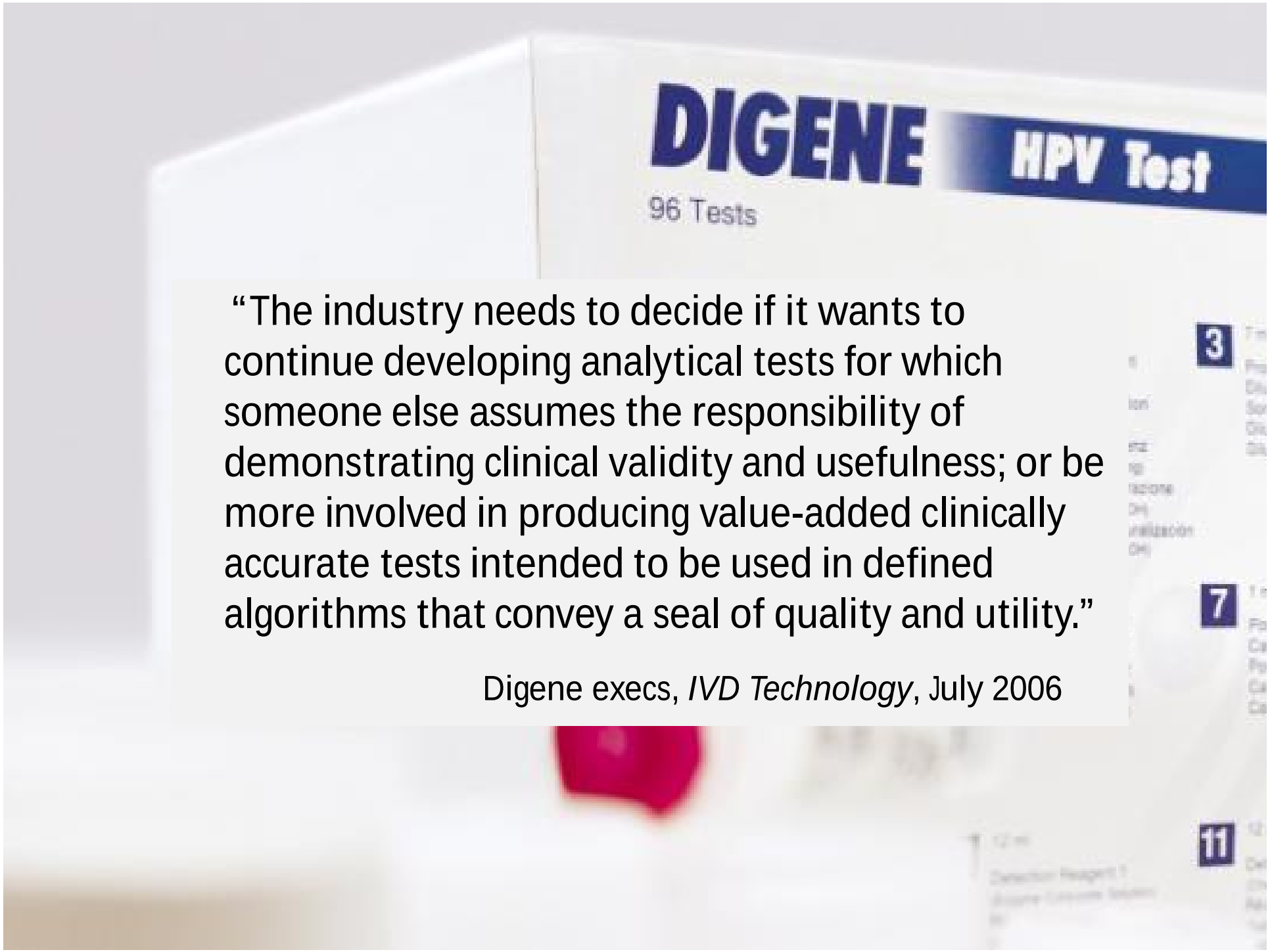
STARD endorsed by FDA

Guidance for Industry and FDA Staff

Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests

Document issued on: March 13, 2007

The draft of this document was issued on March 12, 2003.



"The industry needs to decide if it wants to continue developing analytical tests for which someone else assumes the responsibility of demonstrating clinical validity and usefulness; or be more involved in producing value-added clinically accurate tests intended to be used in defined algorithms that convey a seal of quality and utility."

Digene execs, *IVD Technology*, July 2006

Firm	Test	List price
Genomic Health	Oncotype Dx- 21-gene expression signature for breast cancer prognosis/ treatment response prediction	$4,175
Agendia	Mammaprint – 70-gene expression signature for breast cancer prognosis	$4,200
AssureRx	Genesight Psychotropic – 50-SNP pharmacogenetic test for antidepressant/antipsychotic drugs	$3,800
CareDx	AlloMap - prognostic gene expression signature for monitoring heart transplant patients	$2,821
Veracyte	Afirma – 167-gene miRNA expression signature to identify benign thyroid nodules prior to surgery	$4,875

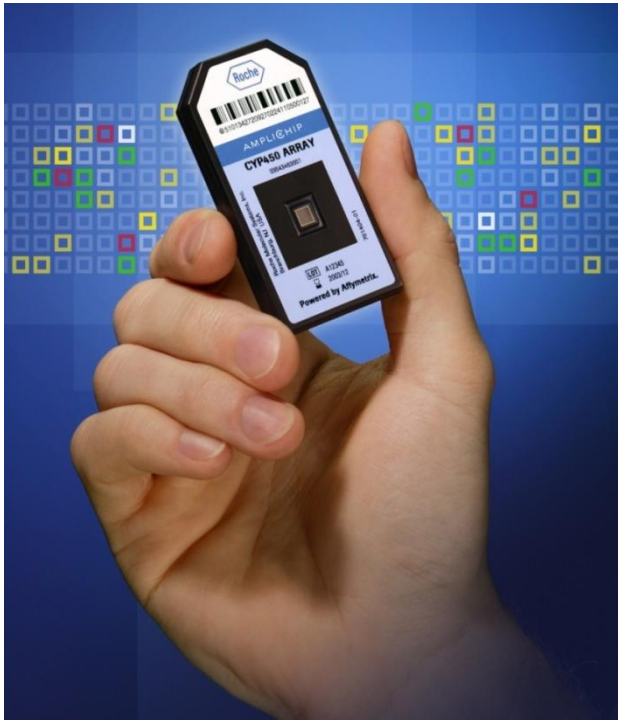
Regulatory expansion

- UK National Screening Committee
- NICE Diagnostics Assessment Programme
- UK Genetic Testing Network
- US Preventive Services Task Force
- EGAPP
- US Genetic Testing Registry

Payers get pushy

Roche Amplichip CYP450 Array

- First CYP450 test to gain FDA approval (2004)
- Tests for 31 polymorphisms in CYP450 genes
- Adopted by major US reference laboratories (LabCorp and Quest)



Payers get pushy

"Genotyping for cytochrome P450 polymorphisms to determine drug-metabolizer status is considered investigational/not medically necessary, including but not limited to, patients initiating therapy with warfarin, phenytoin, antidepressants or antipsychotics.

Clinical utility studies of genotyping for well-established brand name and generic drugs are in their infancy. A literature search did not indentify any published controlled studies that demonstrated that therapy directed by the results of genotyping resulted in improved patient management."

Blue Cross / Blue Shield Technology Evaluation Center, 2004

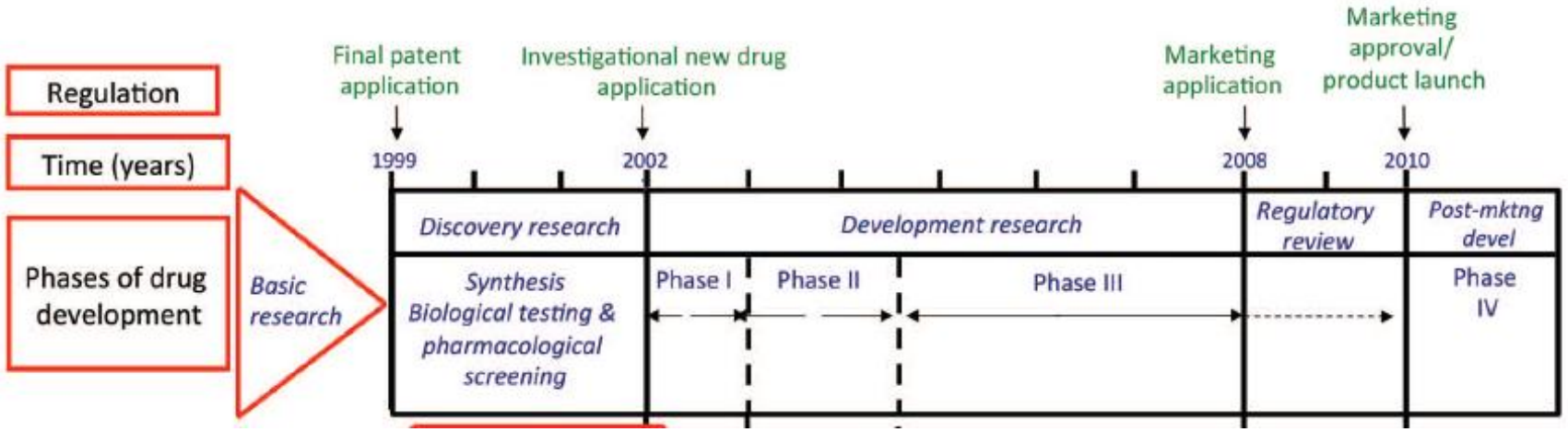
Biomarker development pathway models

Road to nowhere?

"... there is currently no well defined structure or common terminology for the biomarker development process as, for example, there is for the development of a new drug."

Cancer Research UK 2008

It’s just a phase I’m going through

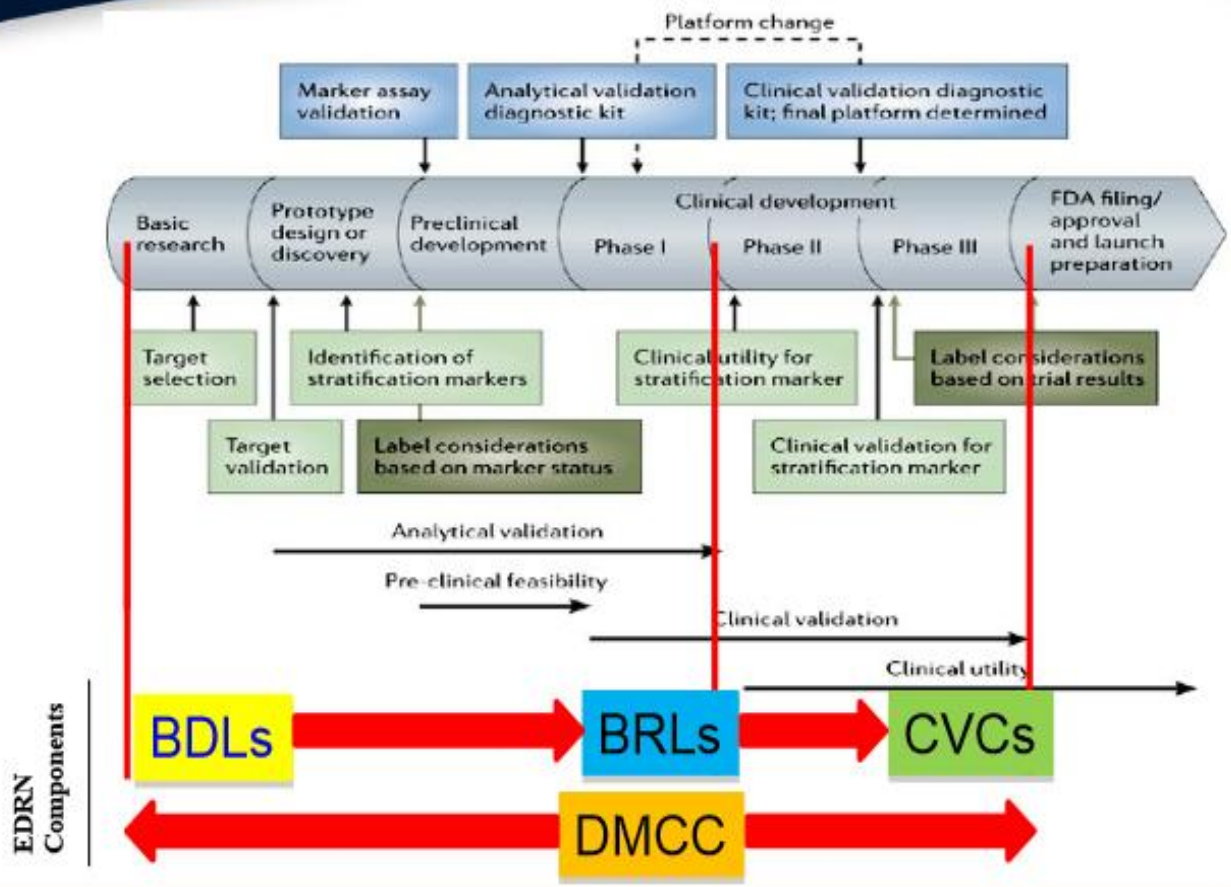


Office of Health Economics, 2012

Research funding agencies

EDRN Biomarker Pipeline:
Modeled After Drug Discovery Pipeline

Early Detection Research Network



BDLs= Biomarker Developmental Labs; BRLs= Biomarker Reference Labs; CVCs = Clinical Validation Centers; DMCC = Data Management and Coordinating Center.

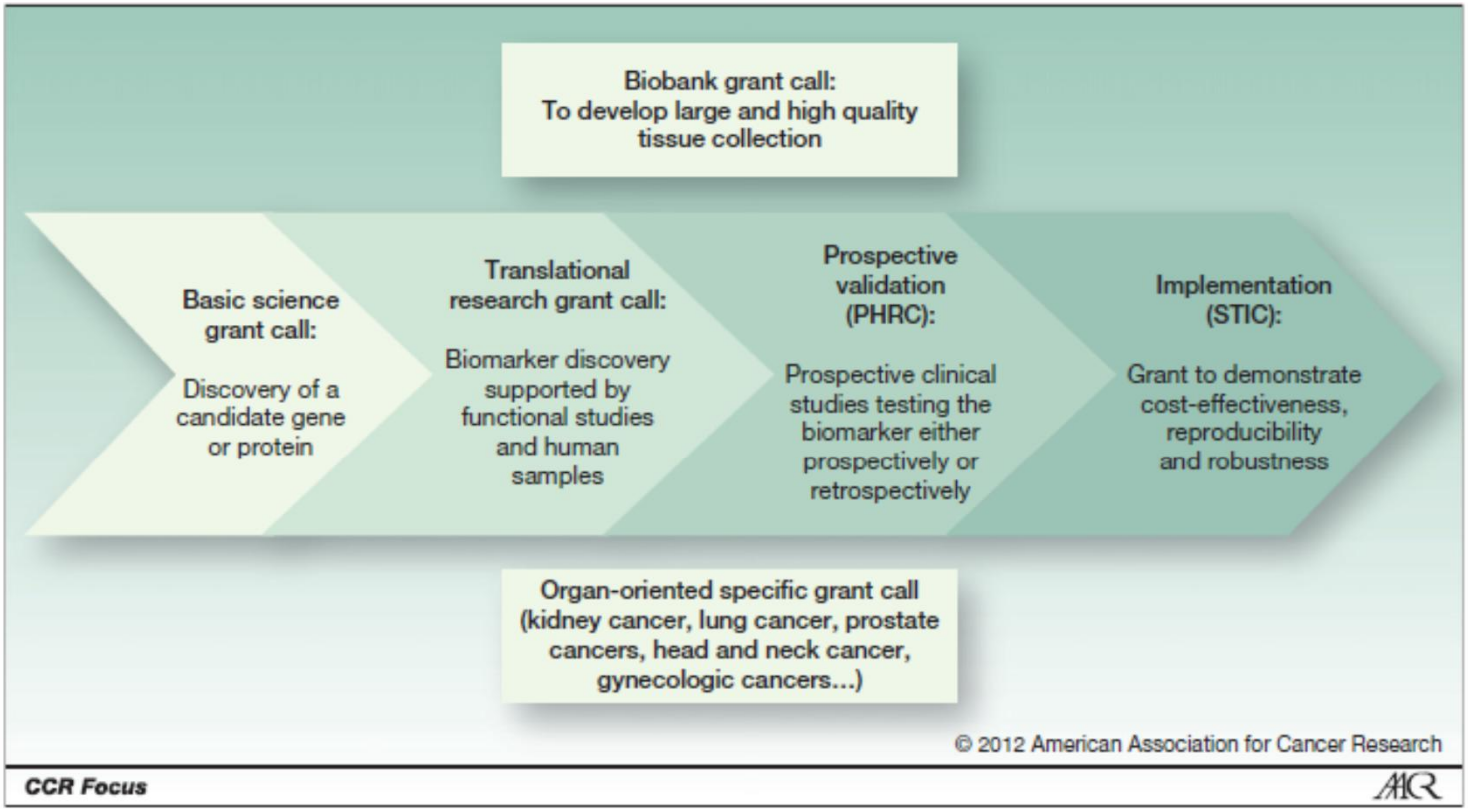
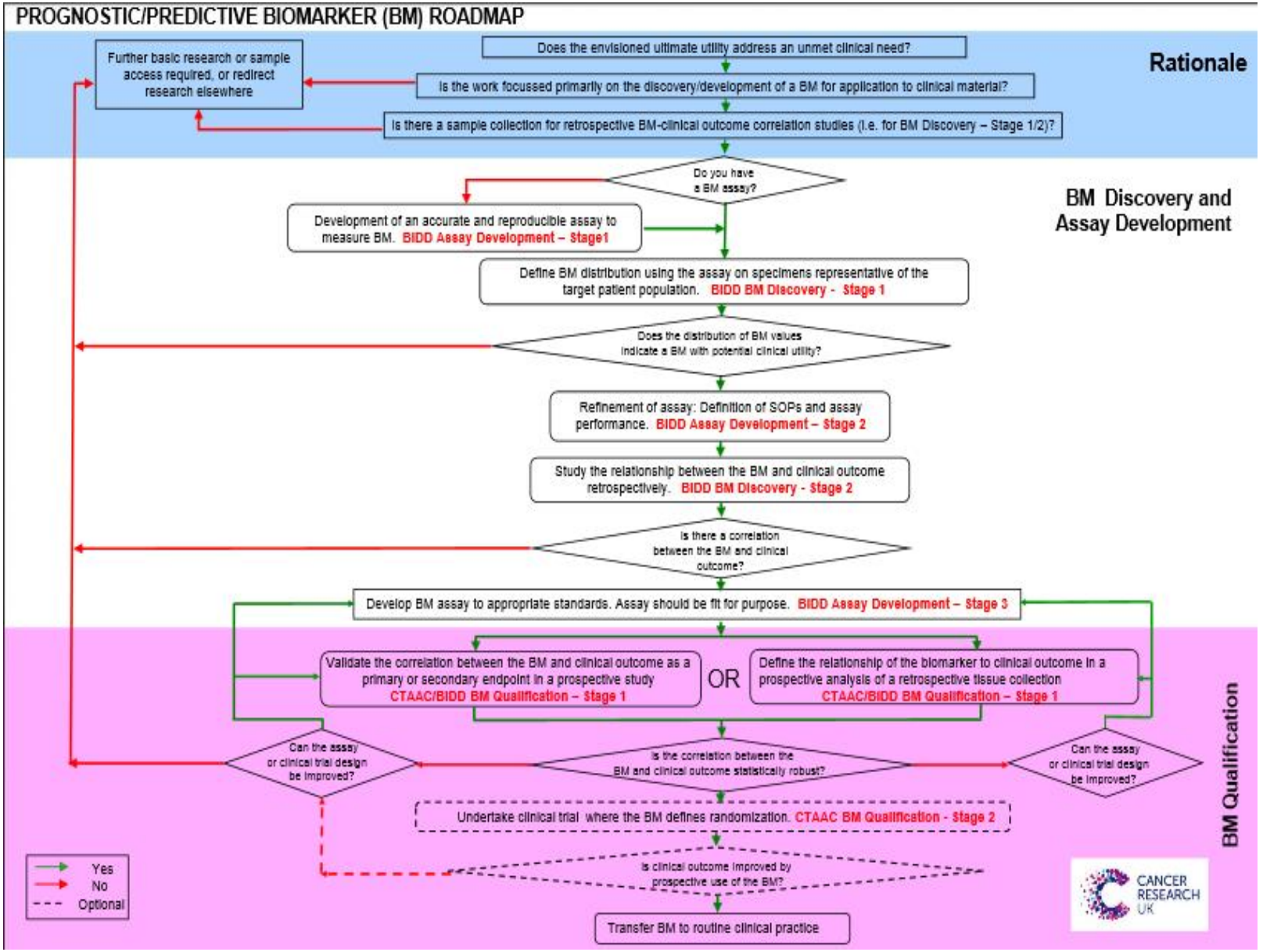
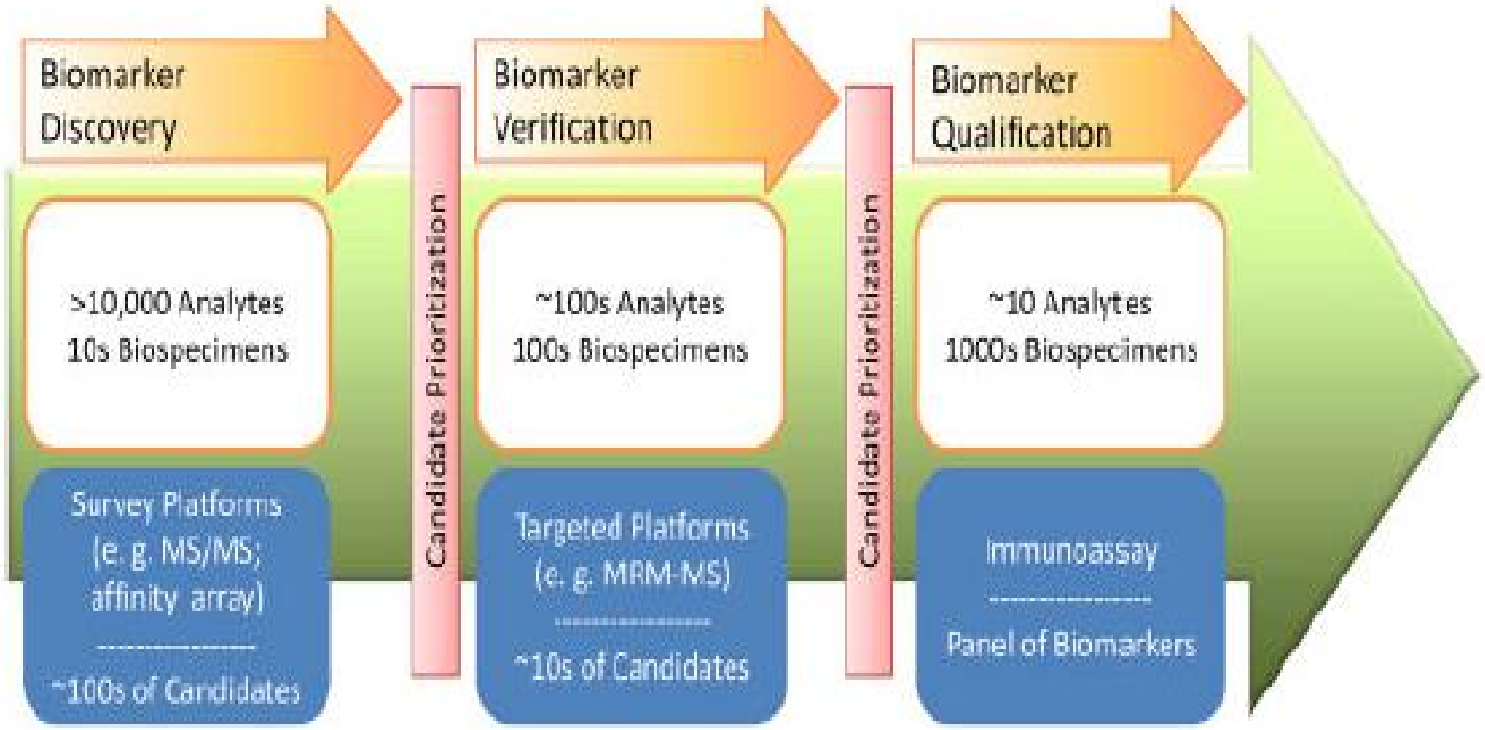


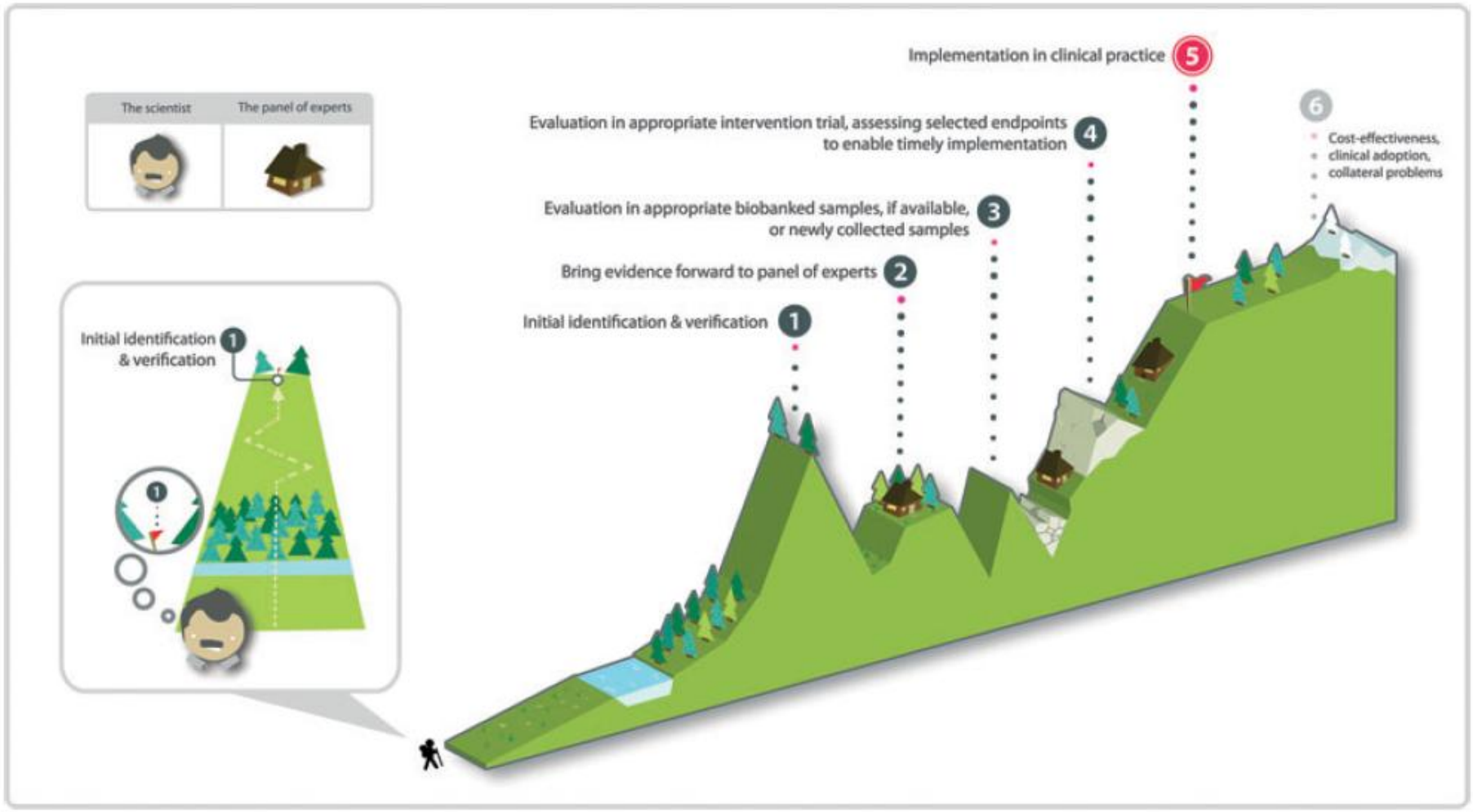
Figure 3. Grant calls from the French NCI to support biomarker research in France. PHRC, Programme Hospitalier de Recherche Clinique; STIC, support for extensive and innovative technologies.


PROGNOSTIC/PREDICTIVE BIOMARKER (BM) ROADMAP
Rationale
Does the envisioned ultimate utility address an unmet clinical need?
Is the work focussed primarily on the discovery/development of a BM for application to clinical material?
Is there a sample collection for retrospective BM-clinical outcome correlation studies (i.e. for BM Discovery – Stage 1/2)?
Further basic research or sample access required, or redirect research elsewhere
BM Discovery and Assay Development
Do you have a BM assay?
Development of an accurate and reproducible assay to measure BM. BIDD Assay Development – Stage1
Define BM distribution using the assay on specimens representative of the target patient population. BIDD BM Discovery - Stage 1
Does the distribution of BM values indicate a BM with potential clinical utility?
Refinement of assay: Definition of SOPs and assay performance. BIDD Assay Development – Stage 2
Study the relationship between the BM and clinical outcome retrospectively. BIDD BM Discovery - Stage 2
Is there a correlation between the BM and clinical outcome?
Develop BM assay to appropriate standards. Assay should be fit for purpose. BIDD Assay Development – Stage 3
Validate the correlation between the BM and clinical outcome as a primary or secondary endpoint in a prospective study CTAAC/BIDD BM Qualification – Stage 1
OR
Define the relationship of the biomarker to clinical outcome in a prospective analysis of a retrospective tissue collection CTAAC/BIDD BM Qualification – Stage 1
BM Qualification
Can the assay or clinical trial design be improved?
Is the correlation between the BM and clinical outcome statistically robust?
Can the assay or clinical trial design be improved?
Undertake clinical trial where the BM defines randomization. CTAAC BM Qualification - Stage 2
Is clinical outcome improved by prospective use of the BM?
Transfer BM to routine clinical practice
Yes
No
Optional
CANCER RESEARCH UK

NCI CPTC


Biomarker Discovery
>10,000 Analytes
10s Biospecimens
Survey Platforms (e. g. MS/MS; affinity array)
~100s of Candidates
Candidate Prioritization
Biomarker Verification
~100s Analytes
100s Biospecimens
Targeted Platforms (e. g. MRM-MS)
~10s of Candidates
Candidate Prioritization
Biomarker Qualification
~10 Analytes
1000s Biospecimens
Immunoassay
Panel of Biomarkers

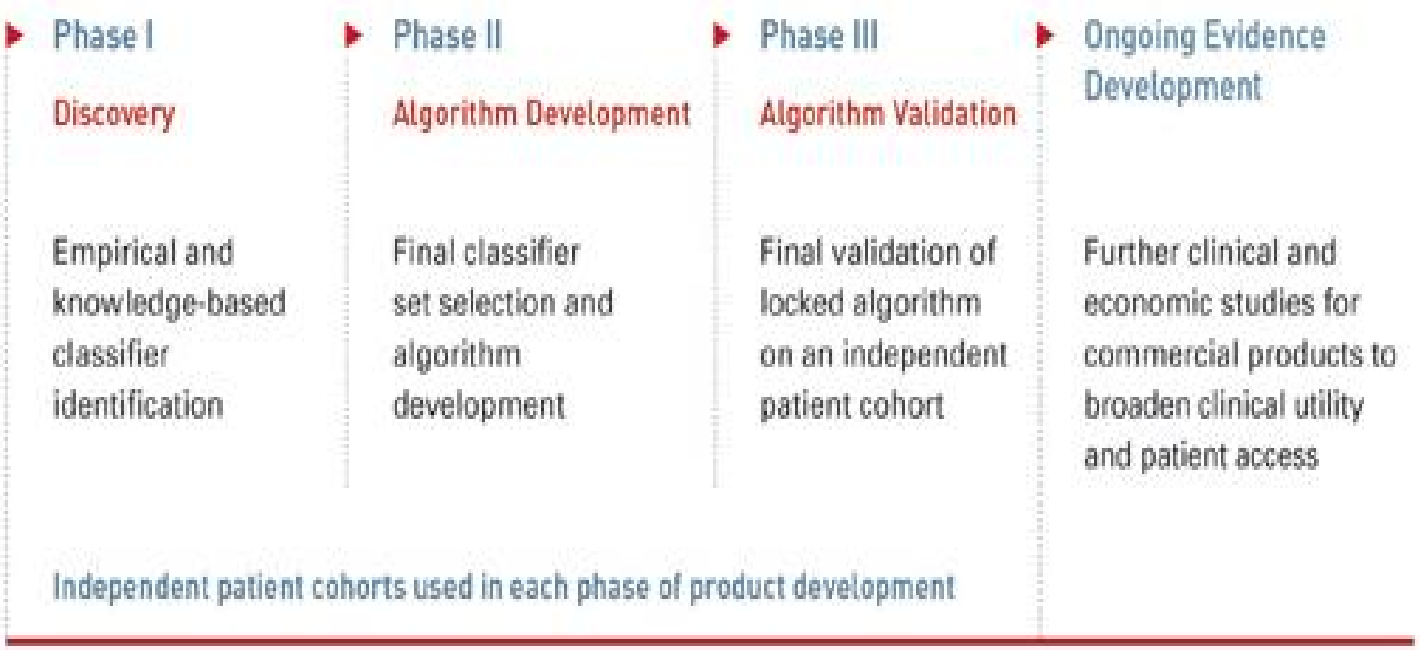
Academia



Miscack et al 2012

Industry

CardioDx


Phase I
Discovery
Empirical and knowledge-based classifier identification
Phase II
Algorithm Development
Final classifier set selection and algorithm development
Phase III
Algorithm Validation
Final validation of locked algorithm on an independent patient cohort
Ongoing Evidence Development
Further clinical and economic studies for commercial products to broaden clinical utility and patient access
Independent patient cohorts used in each phase of product development

AND YET ....

Good science

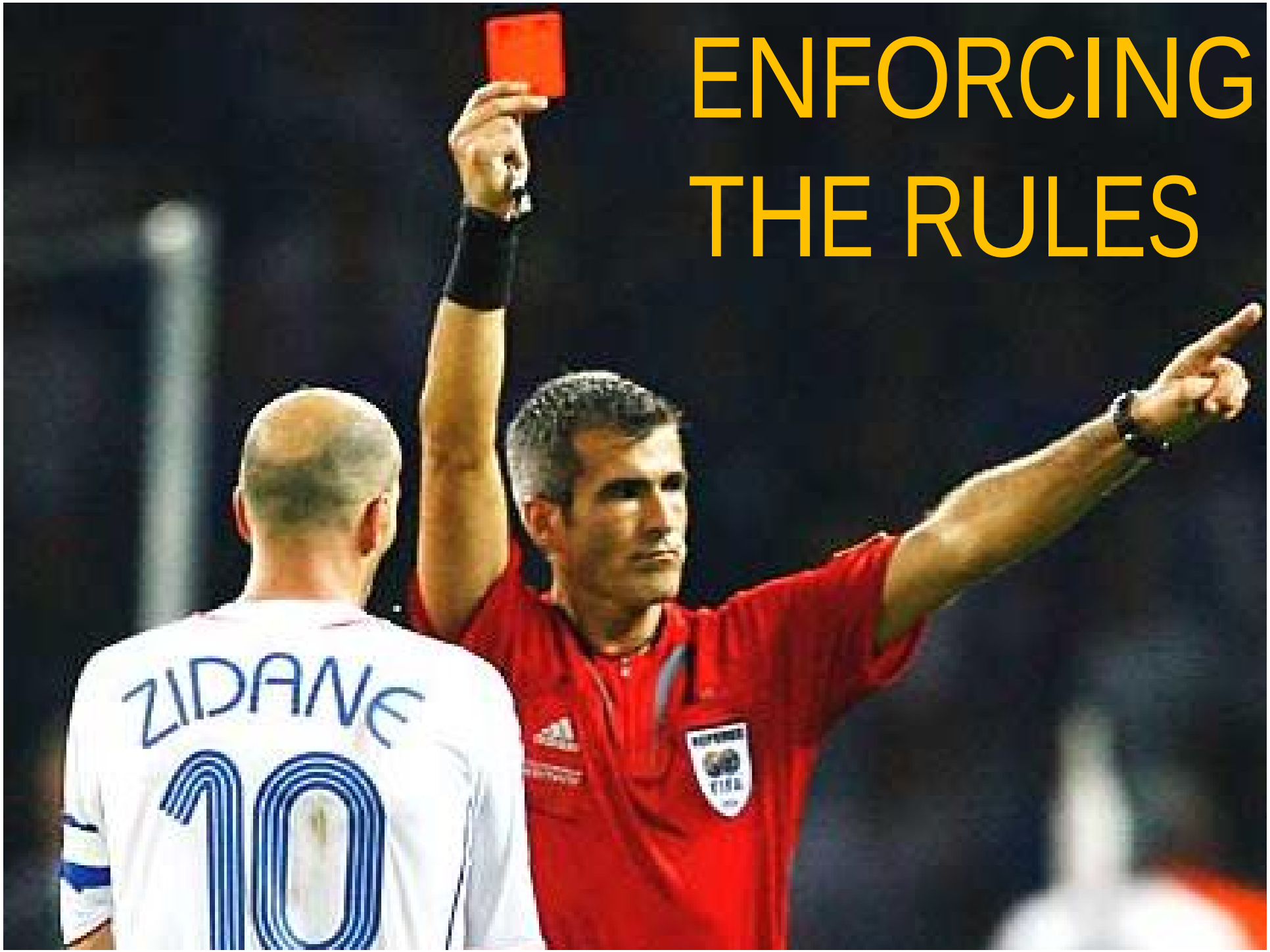
... over the last century, the scientific community has developed very strict criteria for scientific discovery and reporting of both basic laboratory research and clinical trial investigations ...

Hayes, BMC Medicine 2013

Bad science

For a variety of reasons, investigators who translate putative biomarkers from basic research to clinical studies have often ignored some of these fundamental principles of the scientific process.

Hayes, BMC Medicine 2013


ENFORCING
THE RULES
ZIDANE
10

History lesson

Defining development

Linked to Malformed Babies

'Heroine' of FDA Keeps Bad Drug Off of Market

By Morton Mintz
Staff Reporter

This is the story of how the skepticism and stubbornness of a Government physician prevented what could have been an appalling American tragedy, the birth of hundreds or indeed thousands of armless and legless children.

The story of Dr. Frances Oldham Kelsey, a Food and Drug Administration medical officer, is not one of inspired prophesies nor of dramatic research breakthroughs.

She saw her duty in sternly simple terms, and she carried it out, living the while with insinuations that she was a bureaucratic nitpicker, unreasonable — even, she said, stupid. That such attributes could have been ascribed to her is, by her own acknowledgement, not surprising, considering all of the circumstances.

What she did was refuse to be hurried into approving an application for marketing a new drug. She regarded its safety as unproved, despite considerable data arguing that it was ultra safe.

It was not until last April, 19 months after the application was filed with the FDA, that the terrible effects of the drug abroad were widely reported in this country. What remains to be told is how and why Dr. Kelsey blocked the introduction of the drug before these effects were suspected by anyone.

Dr. Kelsey invoked her high standards and her belief that the drug was "peculiar" against these facts:

The drug had come into widespread use in other countries. In West Germany, where it was used primarily as a sedative, huge quantities of it were sold over the counter before it was put on a prescription basis. It gave a prompt, deep, natural sleep that was not followed by a hangover. It was cheap. It failed to kill even the would-be suicides who swallowed massive doses.

And there were the reports on experiments with animals. Only a few weeks ago the American licensee told of giving the drug to rats in doses 6 to 60 times greater than the comparable human dosage. Of 1518 offspring, none was delivered with "evidence of malformation."

In a separate study, one rat did deliver a malformed offspring, but the dosage had been 1200 times the usual one. Rabbits that were injected with six times the comparable human dose also were reported to have produced no malformed births.

Recently, the FDA publicly

See DRUG, A8, Col. 1

The Washington Post

DR. FRANCES O. KELSEY
. . . skepticism wins

Thalidomide scandal

1962 Kefauver Amendments

- Three phases of drug development
- Randomised control trials
- Proof of safety and efficacy

FDA and Laboratory Developed Tests

- 2000 SACGT recommendations
- Data template piloted in nine labs, plans for lab registry
- ‘Election’ of Bush, neoliberal turn at FDA
- SACGT disbanded, FDA retreat
- FDA intervene on ad-hoc basis:
  - 2004 - Correlogic / Ovacheck
  - 2006 - LabCorp / PreGenPlus
  - 2006 - Genomic Health / Oncotype Dx
  - 2006 - InterGenetics / OncoVue

FDA and LDTs

- 2006 / 2010 - Congressional hearings on DTC genetics
- 2006 / 2010 - FDA writes warning letters to DTC companies
- 2007 - FDA issues IVDMIA draft guidance
- 2008 - SAGHS report
- 2010 - FDA holds public meeting on LDT regulation
- 2014 - FDA LDT draft guidance

EU regulatory reform

- New IVD regulation due for completion 2016
- New risk classification system
  - More tests subject to premarket review
  - Still some issues
- Greater emphasis on clinical evaluation

Conclusions

- Significant progress in process of diagnostic reform
- Diagnostics companies facing greater demands for clinical evidence from both licensing authorities and payers
- Regulatory standards and pathways still need clearer definition
- Regulatory reforms in USA and EU may herald new era but will require additional guidance and standards to clarify the new regulatory paradigm

Thanks for listening

Contact:

Stuart Hogarth, Department of Social Science, Health and Medicine, King’s College London

Email: stuart.hogarth@kcl.ac.uk