IOM Genomics Advancement
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Advancing utility and adoption of clinical genomic diagnostics

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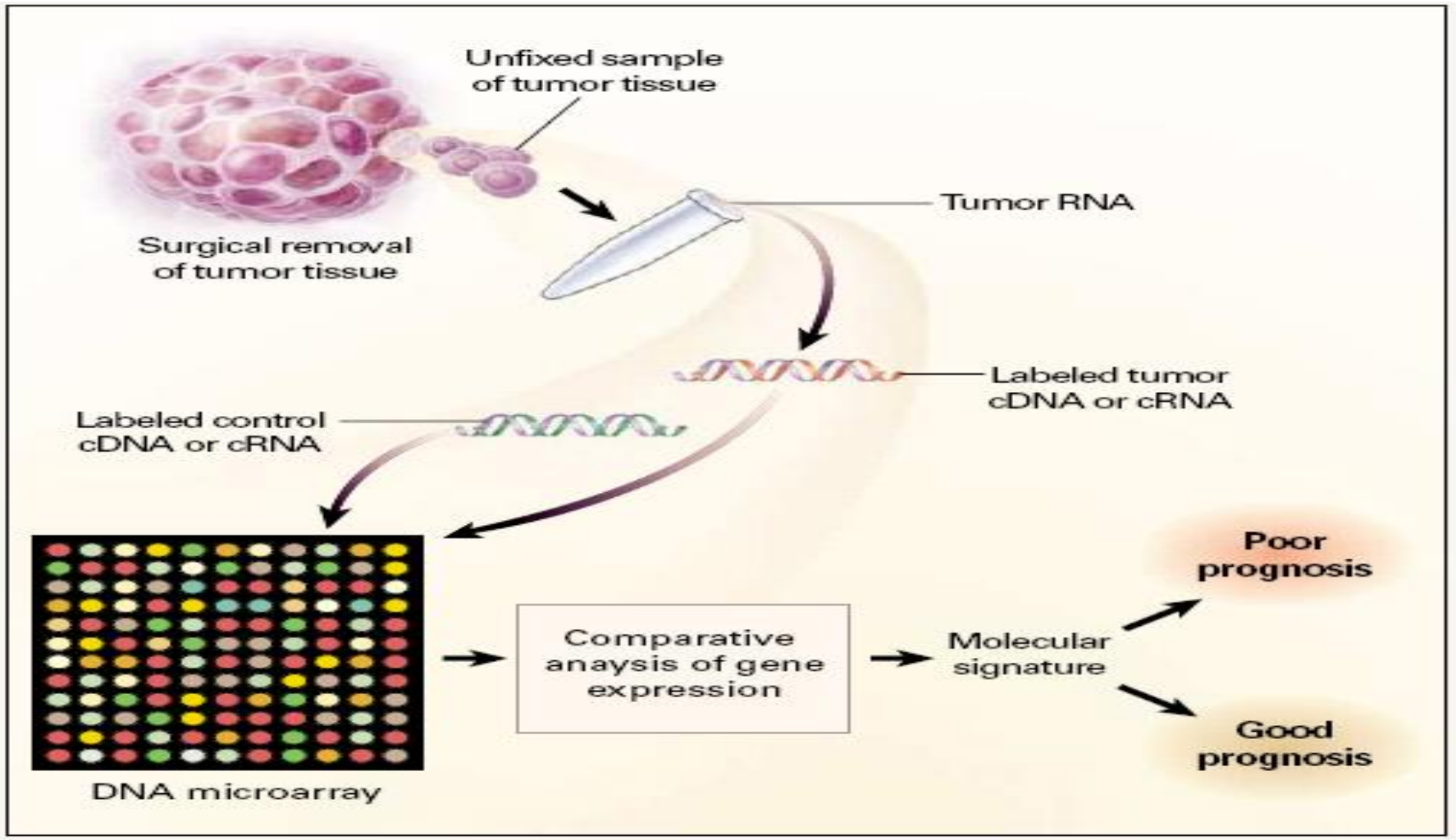
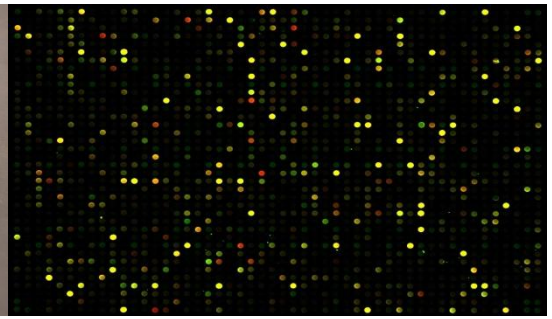
Genomics in Clinical Practice:

'Multigene index assay' MammaPrint identifies risk of recurrence for Breast Cancer Patients



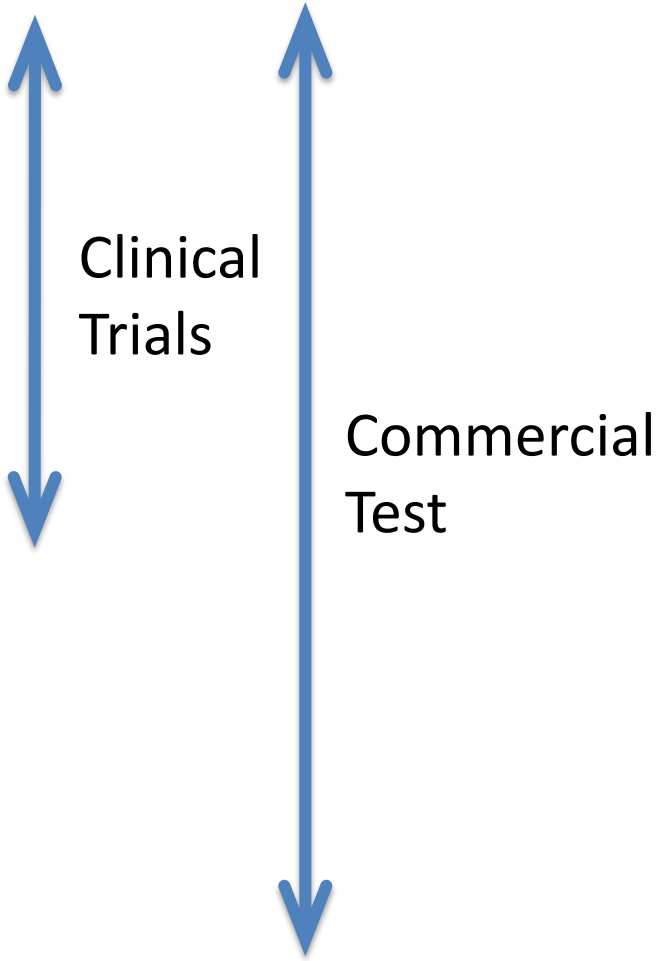
MammaPrint from Research to Diagnostics

• Retrospective validation	- Completed
• Prospective Technology assessment	- Utility & Cost-effectiveness EU & US
• Diagnostic test	- International CE marked
• Laboratory	- CLIA registered
• Diagnostic test	- ISO17025 certified
• Diagnostic test	- CAP accredited
• Diagnostic test and clinical use	- FDA approved, IVDMIA feb07
• Clinical Trials treatment ‘assignment’	- EU MINDACT, US I-SPY
• MammaPrint on 44K	- FDA IDE (Investigational Device Exempt)
• Clinical Trials implementation	- 8 countries, incl US and Japan
• Treatment Recommendations	- Dutch Guidelines 08
• Treatment Recommendations	- StGallen International Guidelines 09
• Reimbursement Insurance	- Netherlands, Italy, US



From Research Finding to Diagnostics: Clinical Trial / Commercial Test

- Discovery
- Research Confirmation
- Independent Validation
- Quality Assurance
- Regulatory Oversight
- Clinical Trial Group
- Technology Assessment
- Guideline Recommendation
- Cost Effectiveness
- Health Care Reimbursement



Opportunities for Implementation Efficiency

1. Validation Protocol

Independent validation
External Audits
Pre-defined statistical Protocol

J NCI, Buyse et al, 17, 1183-1192, 2006

TRANSBIG (EU 6th framework) Independent Validation Protocol

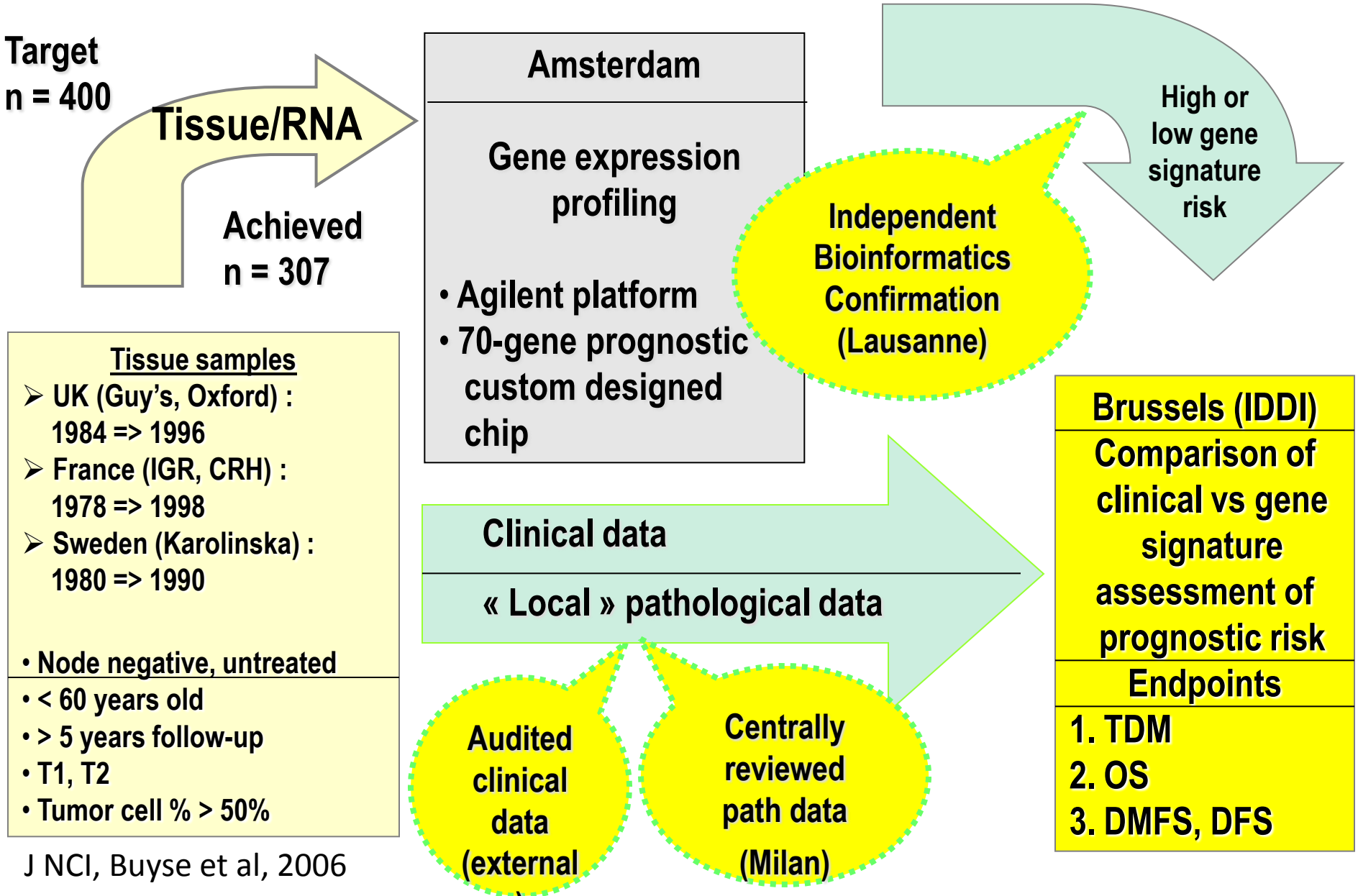
September 2004

AIM OF THE VALIDATION

- The purpose of the validation is to show the robustness of the genetic risk assessment across different patient samples, using the Agilent microarray platform at NKI/ Agendia (validation, robustness, reproducibility)
- This sets the background for the EORTC/TRANSBIG clinical microarray trial MINDACT to commence in the last quarter of 2005.

J NCI, Buyse et al, 17, 1183-1192, 2006

INDEPENDENT VALIDATION : DESIGN



J NCI, Buyse et al, 2006

Validation Protocol and Review

- Develop and establish

  outline of required validation protocol needed at time of clinical implementation

  will facilitate efficient development
- Include predefined acceptance criteria

Opportunities for Implementation Efficiency

2. Quality Control and Regulatory Oversight

Europe:	*IVD CE-marking*, Quality - ISO certification, (no EMEA oversight)*
US:	*CLIA*, FDA - IDE and 510K IVDMIA*

* by law

IVDMIA FDA guidance document 1610, July 26th 2007

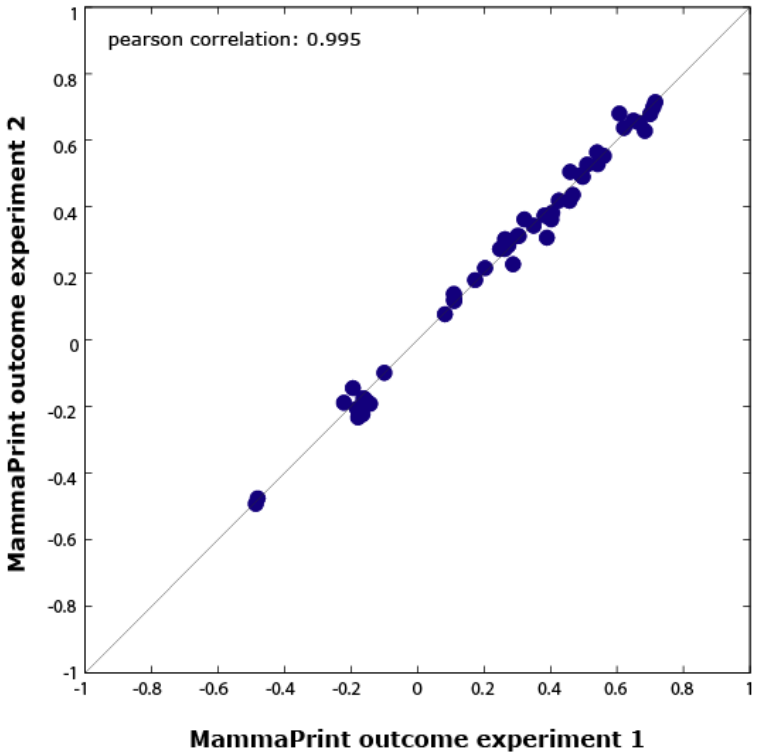
Quality Assessment for Clinical trials

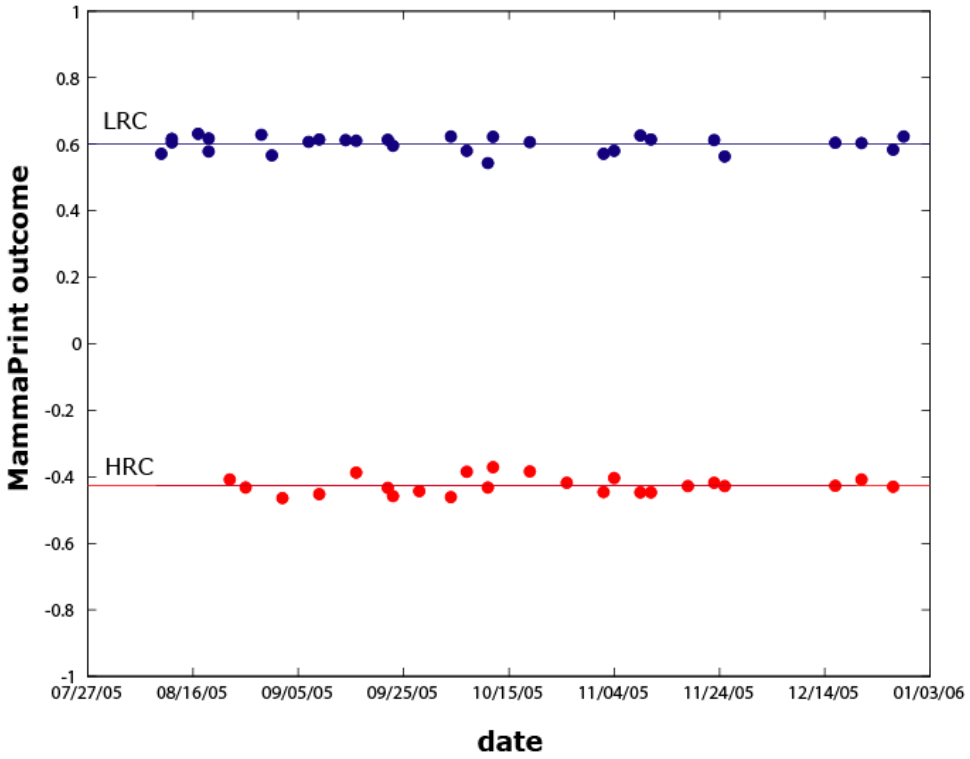
Technical Validation

- Precision
- Reproducibility
- Repeatability
- Accuracy
- Sensitivity
- Robustness

Software Validation

MammaPrint replicate & repeated experiments





Pearson correlation 0.995
ANOVA for 70 gene values per sample p=0.96

LRC: Cosine correl: 0.60, Stdev 0.023

HRC: Cosine correl: -0.43, Stdev 0.026

BMC Genomics, Glas et al, 7, 278, 2006

Quality control and regulatory oversight

- Genomics tests used in clinical trials should obtain IDE status
- For companion diagnostics IDE as part of IND

FDA guidance document 11723, June 1th 2011

Protocol Review

- IRBs need guidance how to review genomics tests
- Establish external party to review genomics tests in case of ‘local hospital trial’

FDA oversight Market Approval: 510K, PMA

Clinical Validation

- Clinical Claim (Intended Use)
  - Instruction for Use
  - Indication for Use

Technical Validation

(in compliance with NCCLS EP5-2A document)

- Precision
- Reproducibility
- Repeatability
- Accuracy
- Sensitivity
- Robustness

Software Validation

IDE: Investigational Device Exempt - ’skeleton’ for trials

FDA oversight -IVDMIA

Home Brew (CLIA) versus IVDMIA (FDA)	"Home Brew"	IVDMIA
CLIA laboratory (laboratory competency)	☑	☑
FDA Clearance (product safety and effectiveness)	☒	☑
Quality System Regulation (GMP) (procedural Quality)	☒	☑
Post Market Surveillance & **Medical Device Reporting** (adverse events)	☒	☑

Opportunities for Implementation Efficiency

3. Technology assessment

Uptake of new technology by patients and physicians; cost-effectiveness

Technology Assessment and Education

- Implementation needs review of logistical processes in hospitals
- Education about clinical use and clinical impact of new technology

Opportunities for Implementation Efficiency

4. Clinical Utility

Definition of clinical utility
Prognosis; Prediction
Retrospective; Prospective

Clinical Utility

- Guideline Committees and Regulatory Bodies have different requirements to show clinical utility
- Harmonize and differentiate

Prognosis – Prediction

Retrospective analysis on prospectively collected biospecimens

Randomized trials – Large Cohorts

Opportunities for Implementation Efficiency

5. process for future efficiency

Biomarkers in I-SPY 2

- When a drug leaves the trial, we learn the probability of success to predict response for
  - Established/Approved Biomarkers — FDA Cleared/Approved used for stratification/assignment
  - IDE Biomarkers — CLIA used for stratification/assignment
  - Qualifying Biomarkers — CLIA used for evaluation
  - Exploratory Biomarkers — Research Laboratories used for evaluation or discovery of new markers

1-3 Efficient Process to move to next trial
4 needs further development

Esserman et al; Nat Clin Pract Oncol 2010

Netherlands Cancer Institute
Agendia
EORTC Breast Group
TRANSBIG Breast International Group
ISO Accreditation
FDA
ISPY TRIAL GROUP
et al