Biobanking in Biomedical Research

Part 1

Introduction to biobanking: formats, international developments, challenges

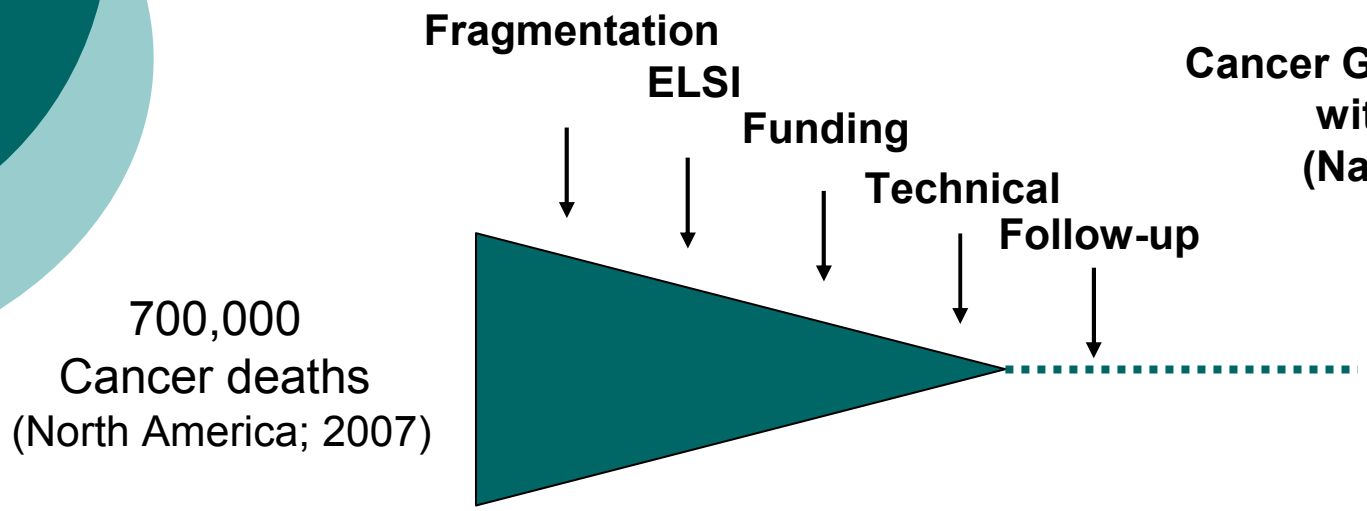
Kurt Zatloukal, Medical University of Graz, Austria

Siena, April 2009

Agenda

- Introduction
- Why biobanks?
- Different biobank formats
- Why biobank networks?
- International developments
- Evidence-based standards
- Special aspects of clinical biobanks

Biobanks in Medical Research



Cancer Genome Project struggels with sample shortage (Nature Medicine 2007)

Mainframephotographics.com

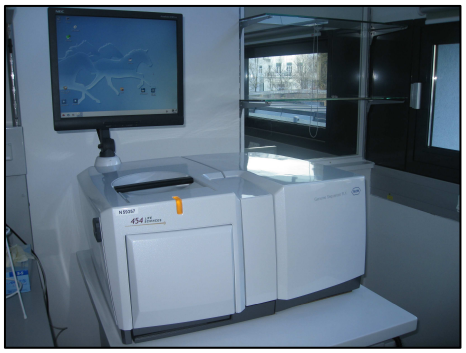
Long haul: The Lung Cancer Tissue Bank has only 20 of the 500 samples required.

- NCI: Biological sampels are #1 roadblock

Progress in Sequencing Technologies

Sequencing of the human genome:

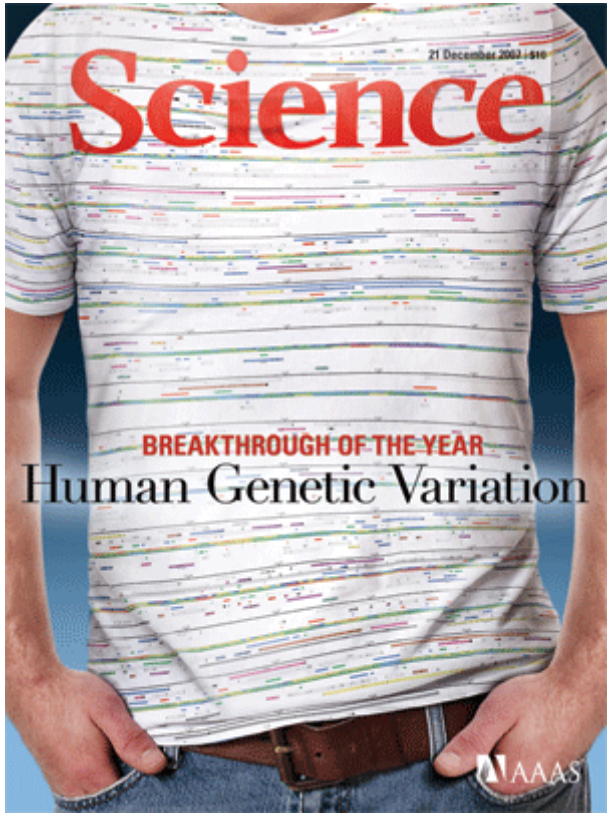
2000: Human Genome Project
10 years - 3 bio. USD

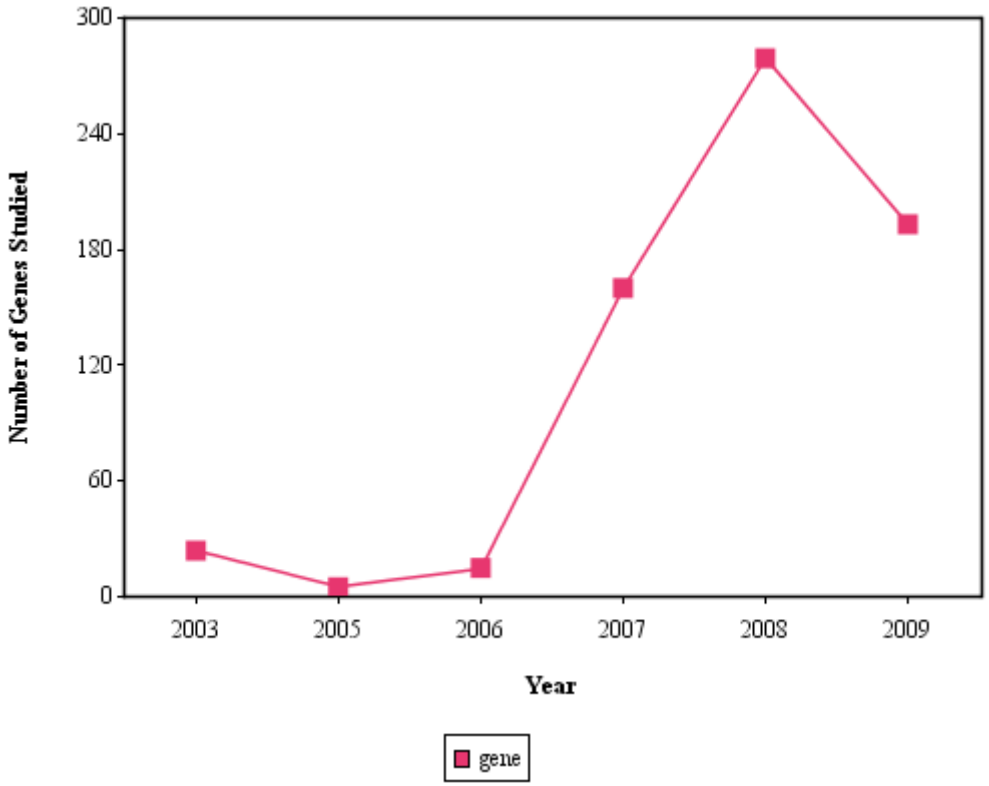


2008: Next generation sequencing
10 hrs - 50,000.- USD

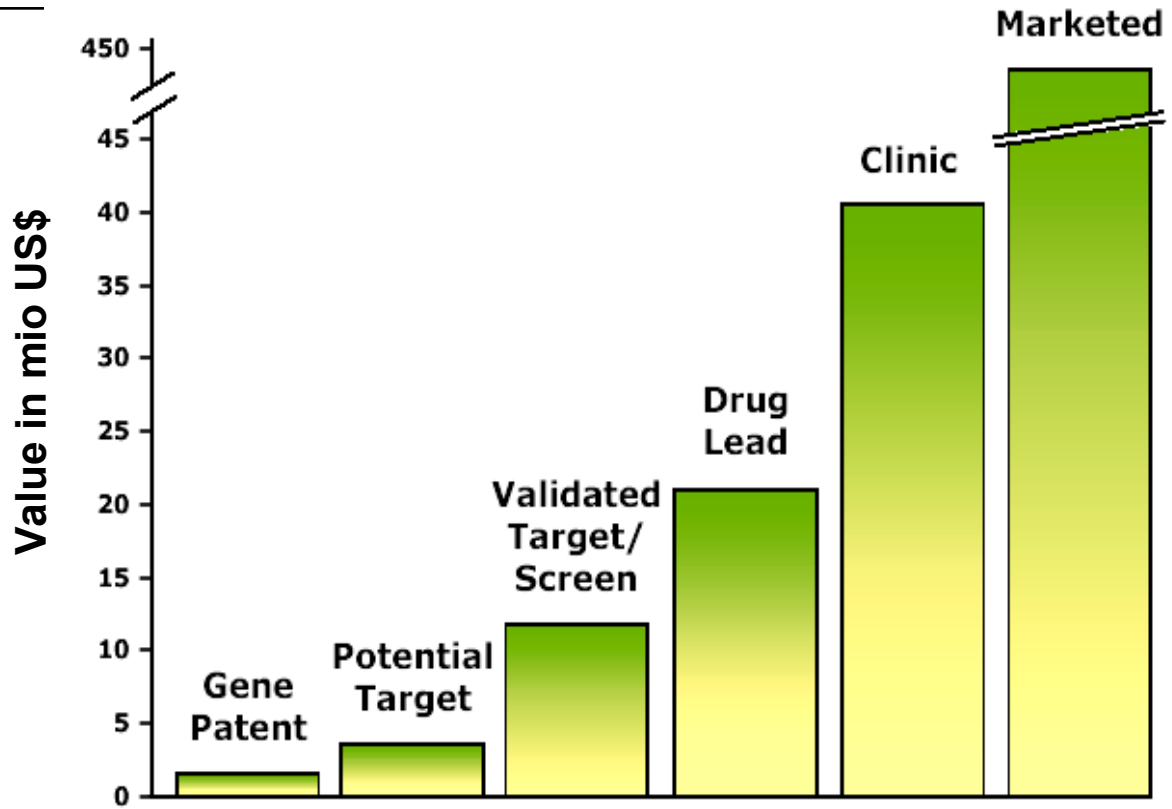
Shifts bottleneck from technologies
to biological samples and data/knowledge management

The Breakthrough of GWAs





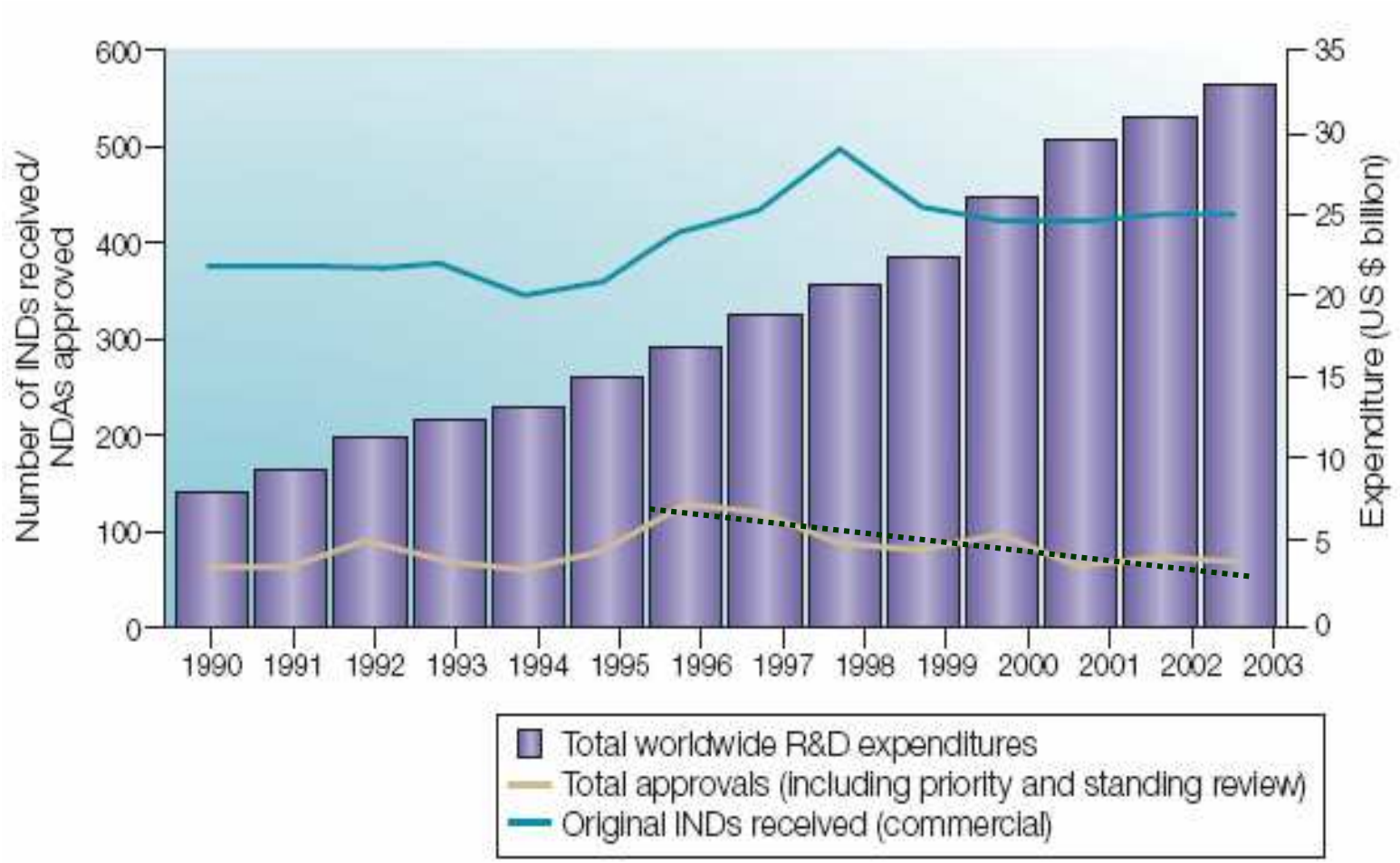
Attrition in Drug Development



Years to market	**14**	**12**	**8**	**6**	**4**	**0**
Attrition	**120**	**80**	**25**	**15**	**8**	**1**
Value (mio US$)	**2**	**3**	**12**	**21**	**41**	**440**

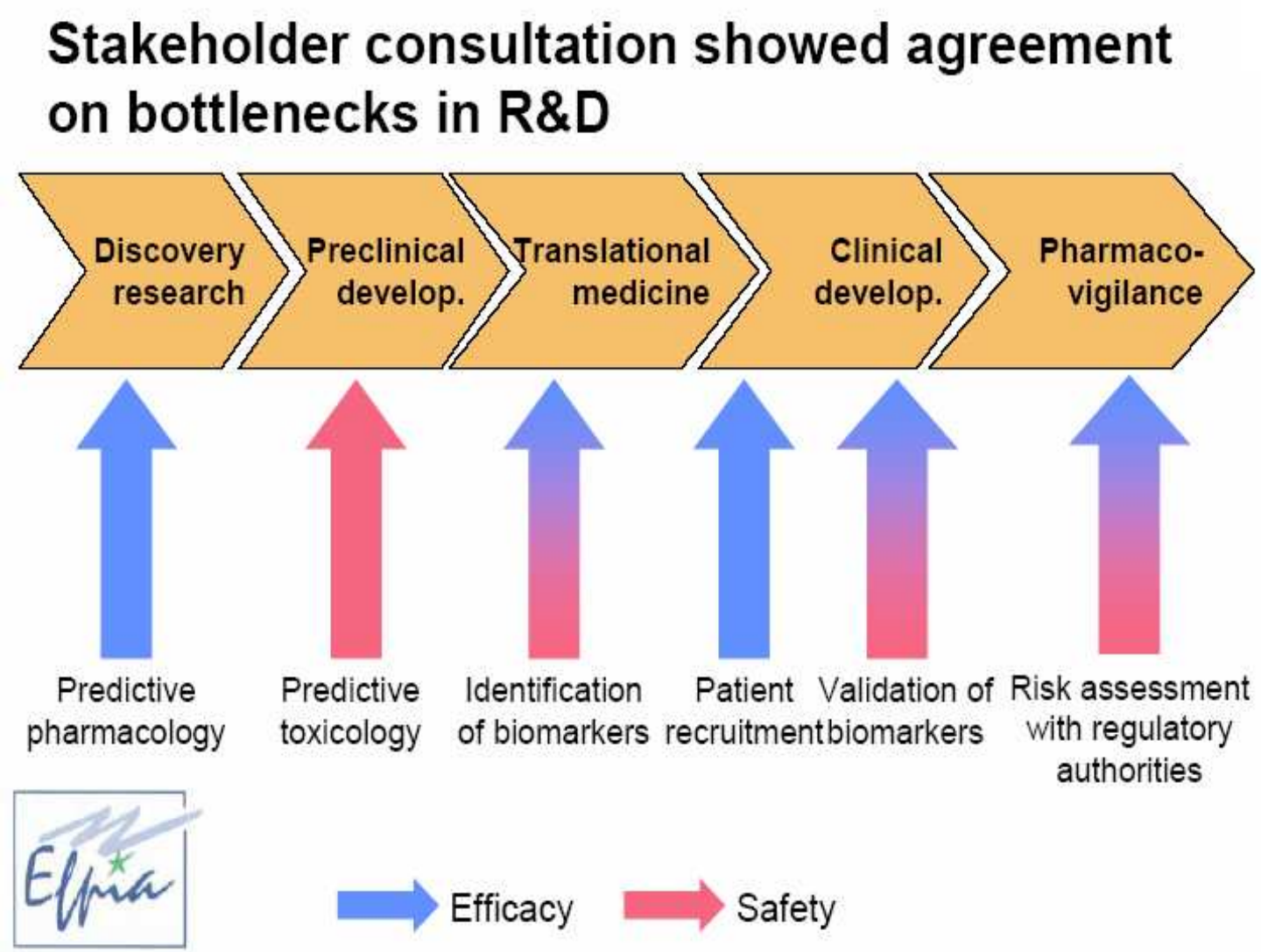
Adapted from Celgene

Dicrepancy Between R&D Expenditures and New Approved Drugs

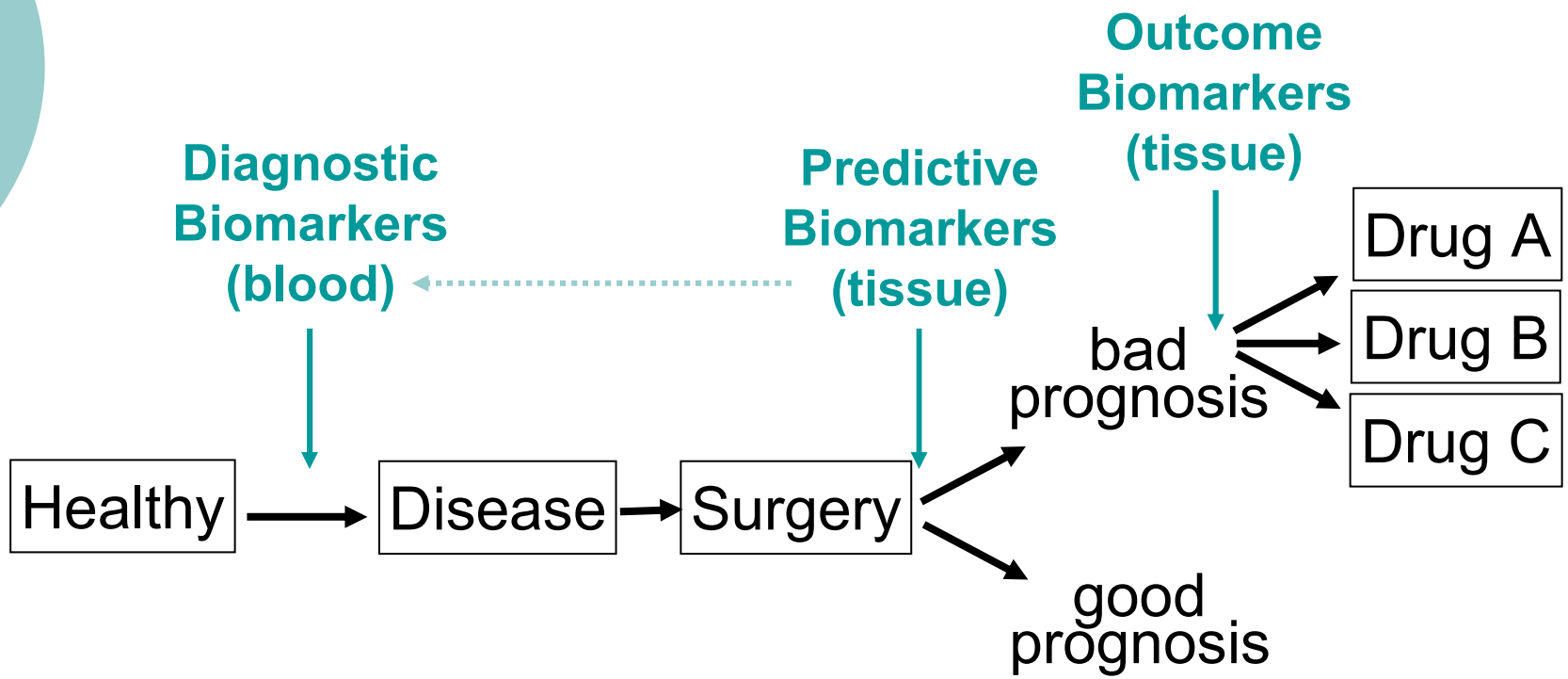


From Ashburn and Thor, Nature Rev Drug Disc, 2004

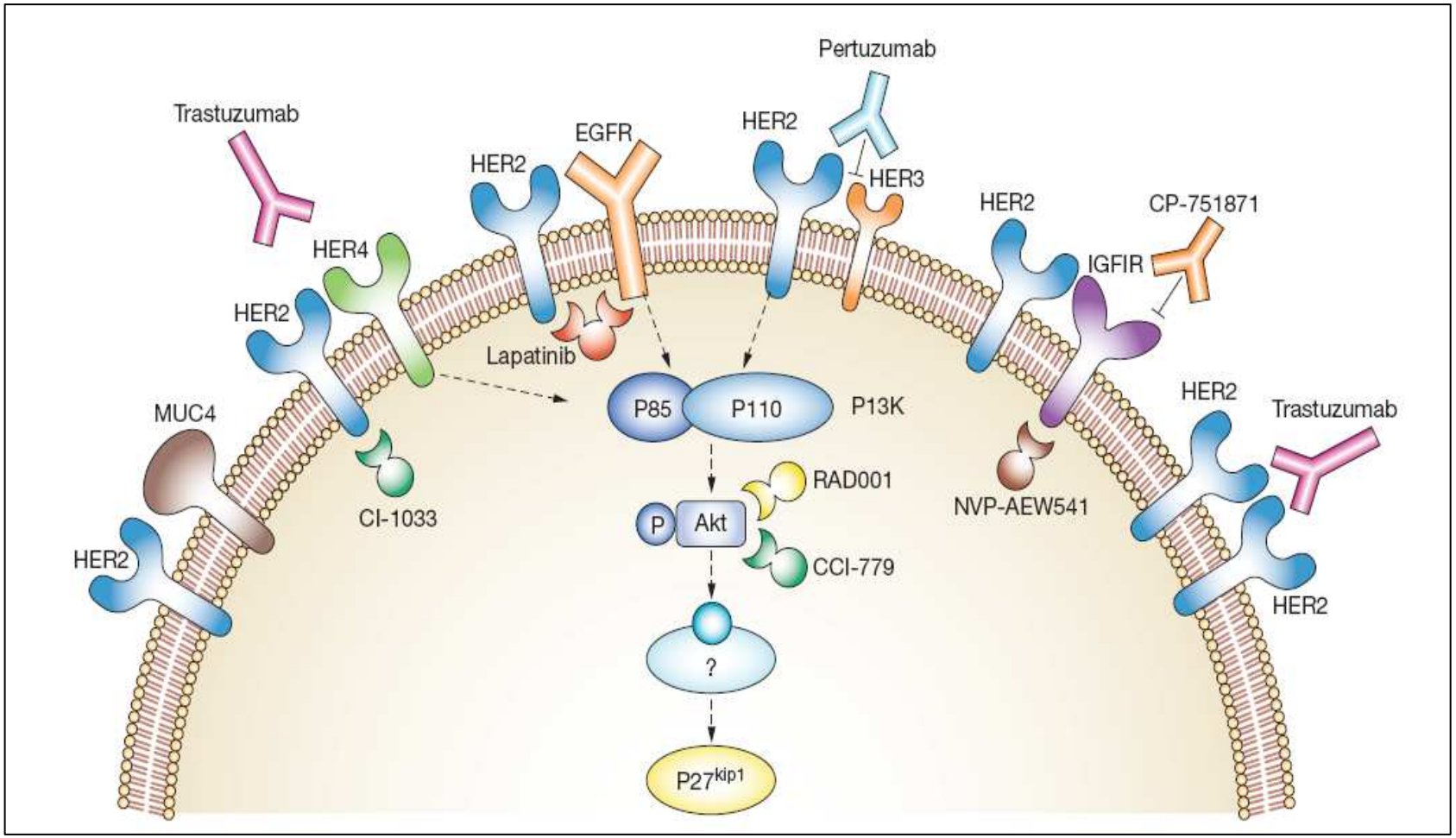
IMI Strategic Research Agenda: EFPIA needs



Biomarkers in Oncology

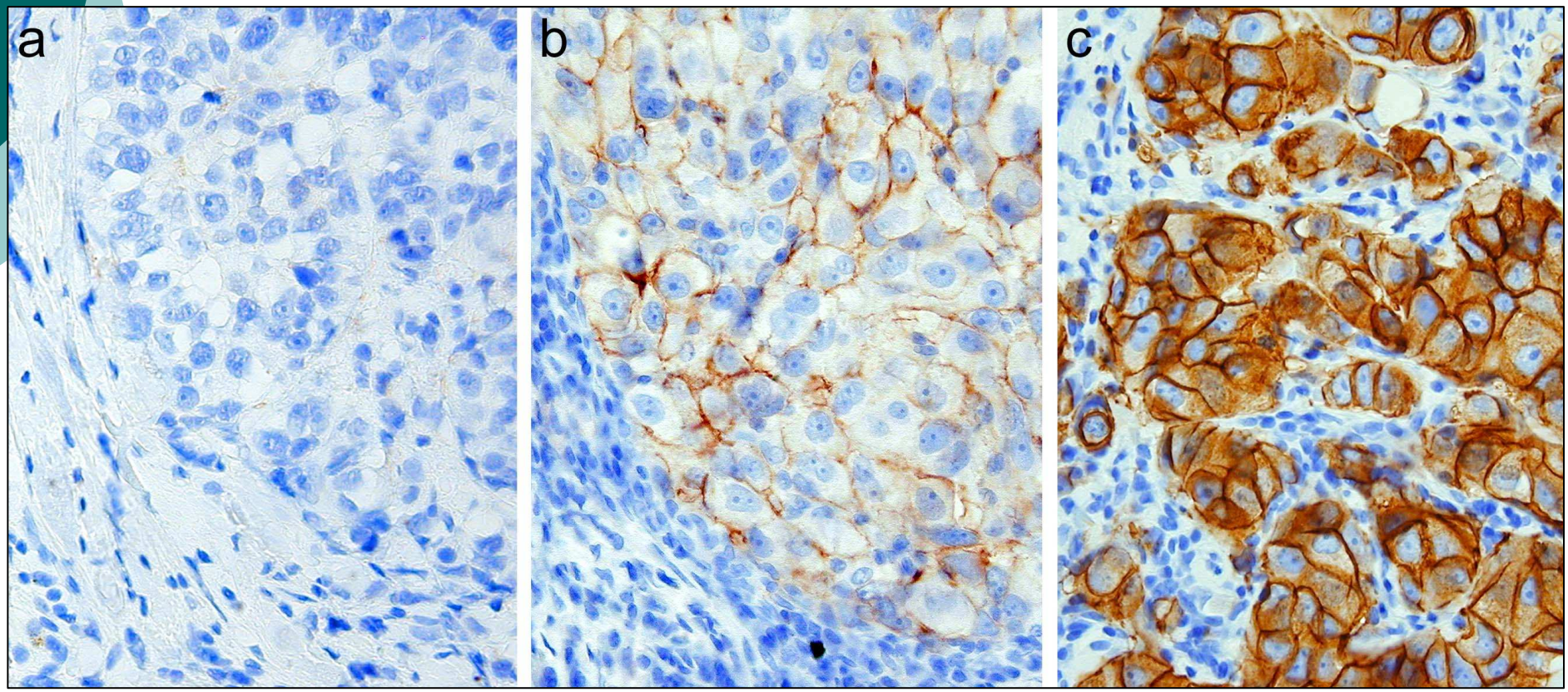


Mechanisms of Herceptin Resistence



Natha et al., Nature Clin Pract Oncol 2006

Her2 Expression in Mammakarzinomen

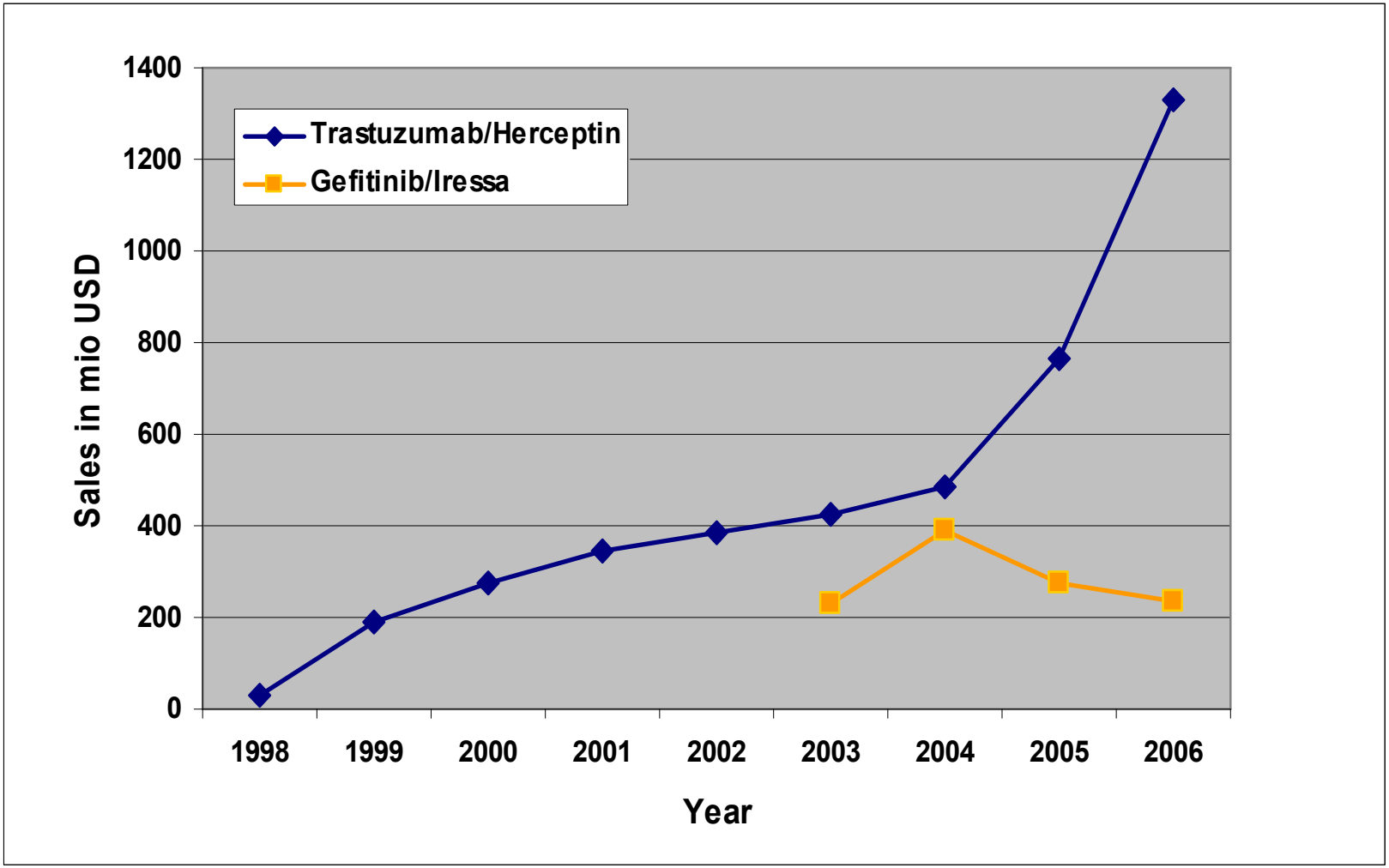


Impact of Biomarkers on Clinical Trials

case	cost reduction	patients screened	patients saved failure under treatment
trastuzumab Her2 IHC+ v. none	62,3%	3350	714
trastuzumab Her2 IHC+ PTEN+ v. Her2 IHC+	14,5%	991	56
trastuzumab Her2 FISH+ PTEN+ v. Her2 IHC+	29,5%	1002	111
erlotinib EGFR+ v. none	37,8%	994	158

David Wine Thesis MIT 2006

Sales of Targeted Therapies



Biobank: Definition

Collection of biological materials and associated dat

Different Types of Biobanks

- Human, microorganisms, animals, plants
- Biomedical research
- Medical archives
- Therapy
  - Blood banks
  - Bone marrow
  - Cord blood
  - Stem cells
  - Organs
- Forensic
- Museum

Differences: Archives vs Biobanks

- Access
  - Searchable databases
  - ELSI clearance
  - Access rules
  - Capacity
- Quality
  - Requirements of –omics technologies
  - International harmonization

Different Biobank Formats

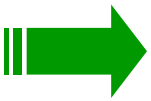
- Population-based
  - Random cohorts
  - Twin-registries
  - Population isolates
- Disease-oriented
  - Disease-specific cohorts
  - Tissue banks

Study Designs

- Cross sectional/longitudinal
- Retrospective/prospective
- Cohort studies
  - Risk ratio of exposed and non-exposed (e.g., smoking and lung cancer)
- Case-control studies
  - Odds ratio for diseased and non-diseased (e.g., SNP in T2D; 4 controls/1 diseased; also for rare diseases <5/10000)
- Nested case-control studies (same risks affected and non-affected)
- Matched case-control
  - Cancer tissue banks (tumor/non-affected of same individual)

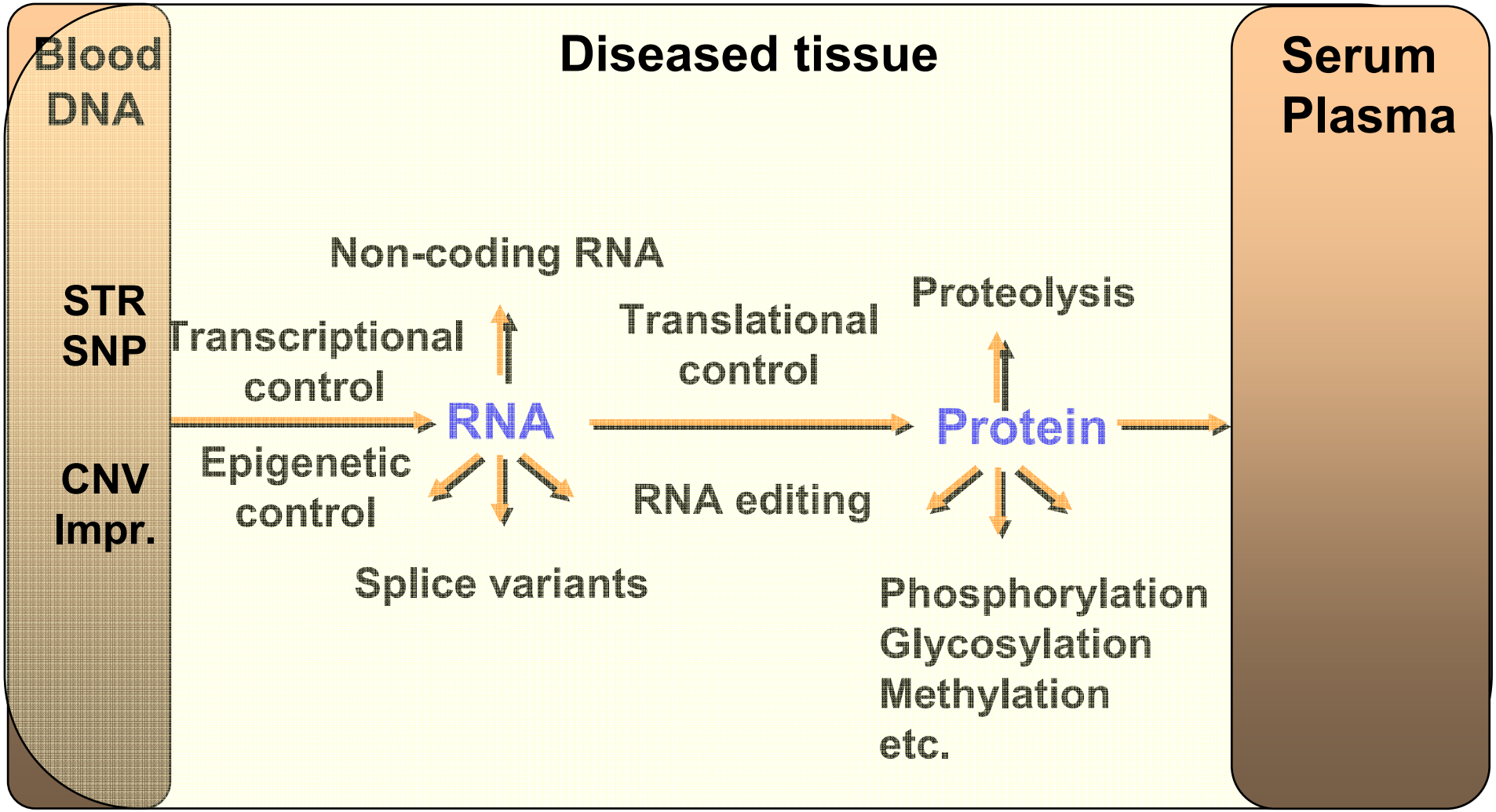
Clinical Samples: Opportunities

- Tissues, blood, urine, cells, DNA
  - Discovery of gene function
  - Identification of disease relevance of genes
  - Identification of new targets for drug discovery
  - Identification and validation of biomarkers for individualized therapy



Key resource for advancement of personalized medicine and improvement of attrition in drug development

From Gene to Function to Disease



Increasing Need for Biological Samples

- **Personalized medicine**
  - new patient subgroups
  - more biomarkers/mol. signatures
- **Drug development**
  - Biomarkers for toxicity/efficacy
- **Translational research**
  - Human disease relevance

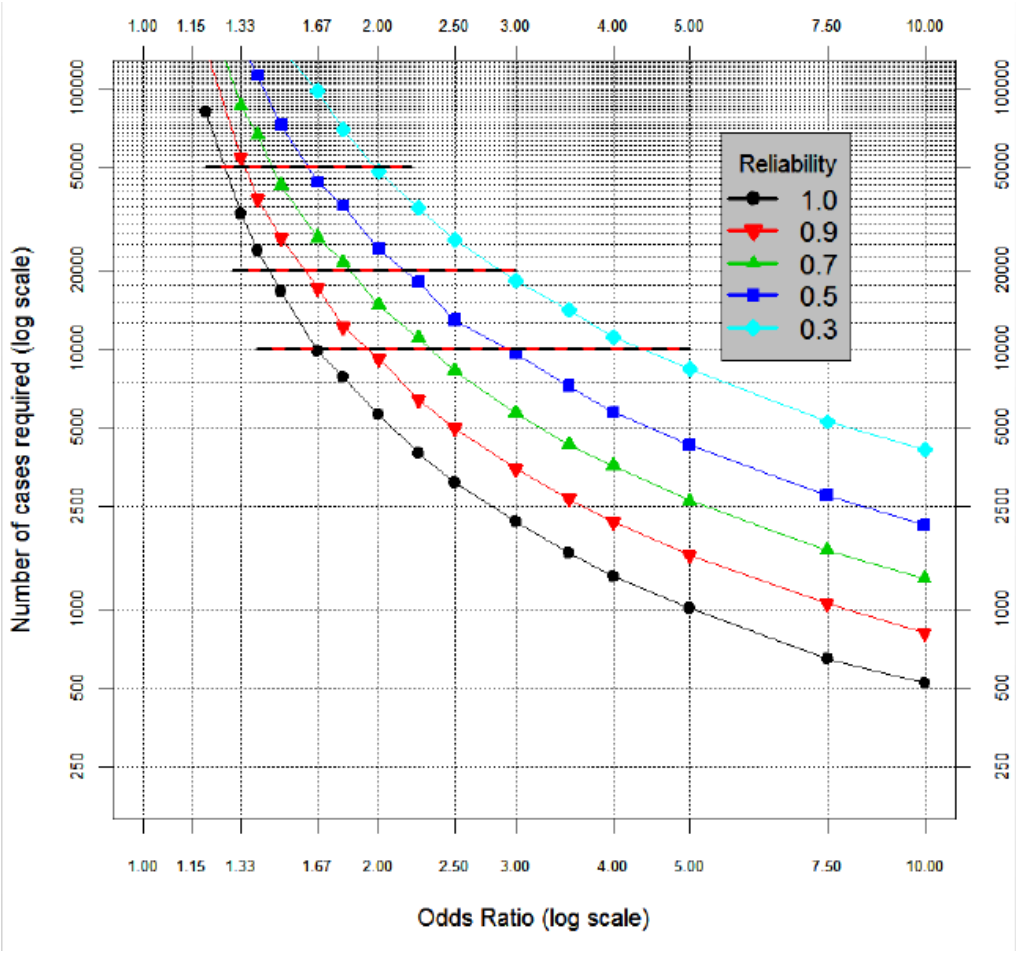
} more samples
larger cohorts
different ethnic groups

- **New technologies**
  - -omics technoloies
  - molecular tools

} specific sample quality

How Many Samples are Required?

Case control sudy: 1 case 4 controls



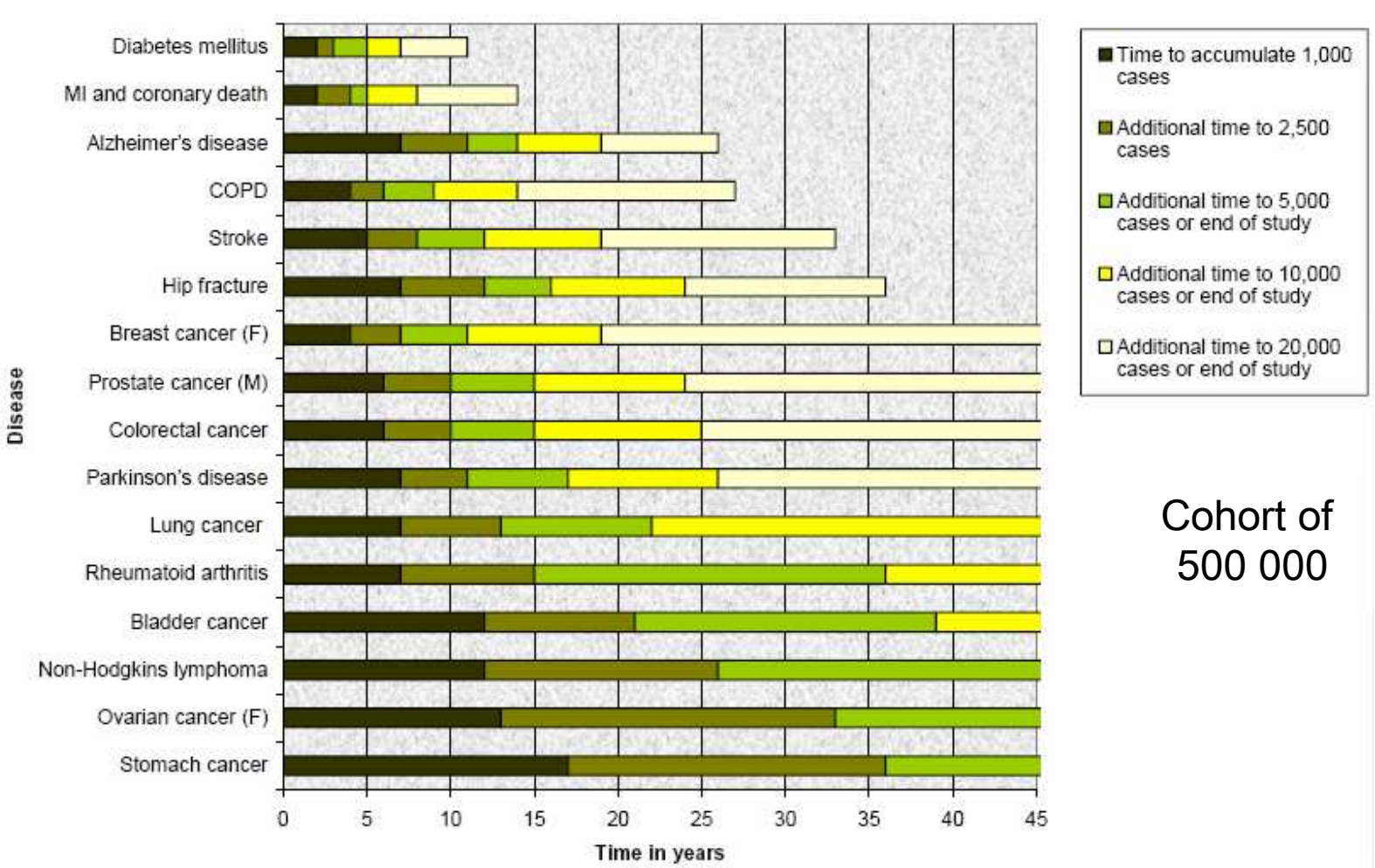
from P. Burton et al., Int J Epidemiol 2008

Impact of Parameter Reliability on Samples Size

Reliability of measurement	Lifestyle/environmental factor
$\geqslant 0.95$	Body mass index (BMI) calculated from measured height and weight in various studies[76]
~0.9	Measured hip or waist circumference[76,77]
~0.7	Blood pressure measurement in the Intersalt Study[78]
~0.5	Many nutritional components in a dietary recall study, mean of four 24 h assessments[79]
~0.3	Many nutritional components in a dietary recall study, a single 24 h assessment[79]

from P. Burton et al., Int J Epidemiol 2008

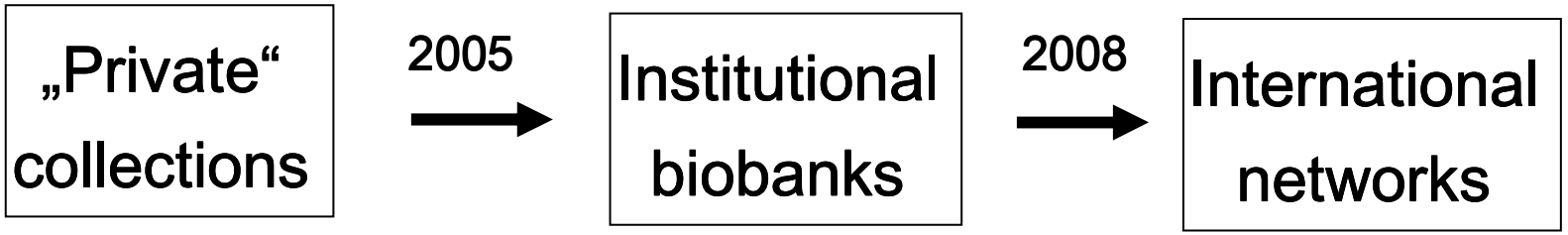
Time Required for Disease Cases



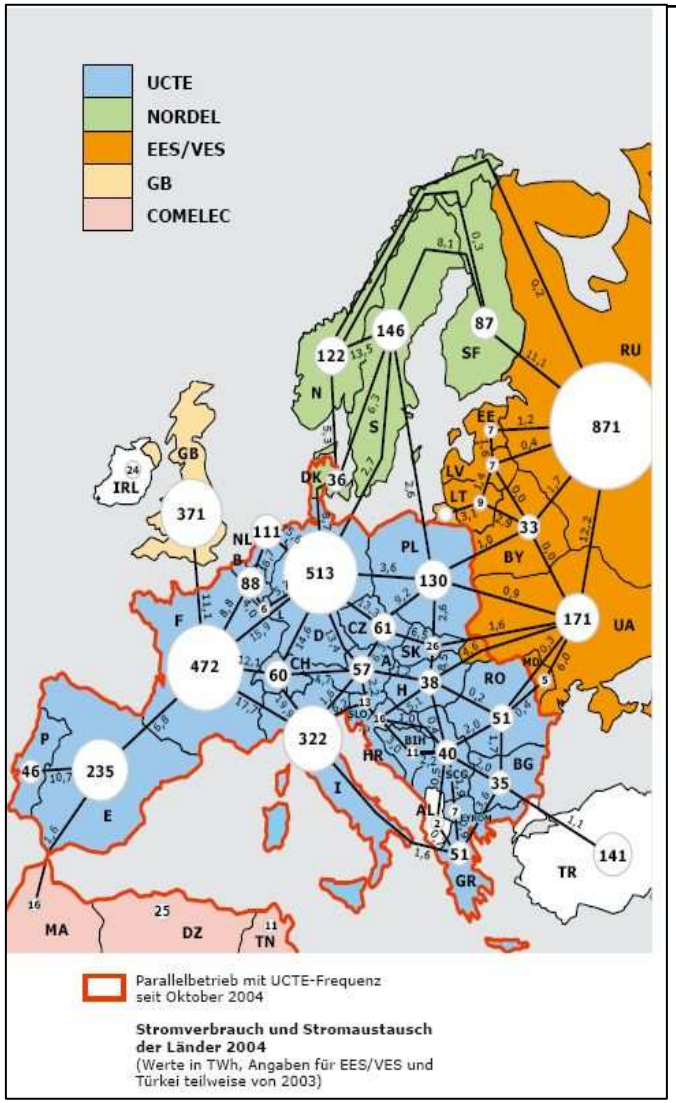
Cohort of 500 000

from P. Burton et al., Int J Epidemiol 2008

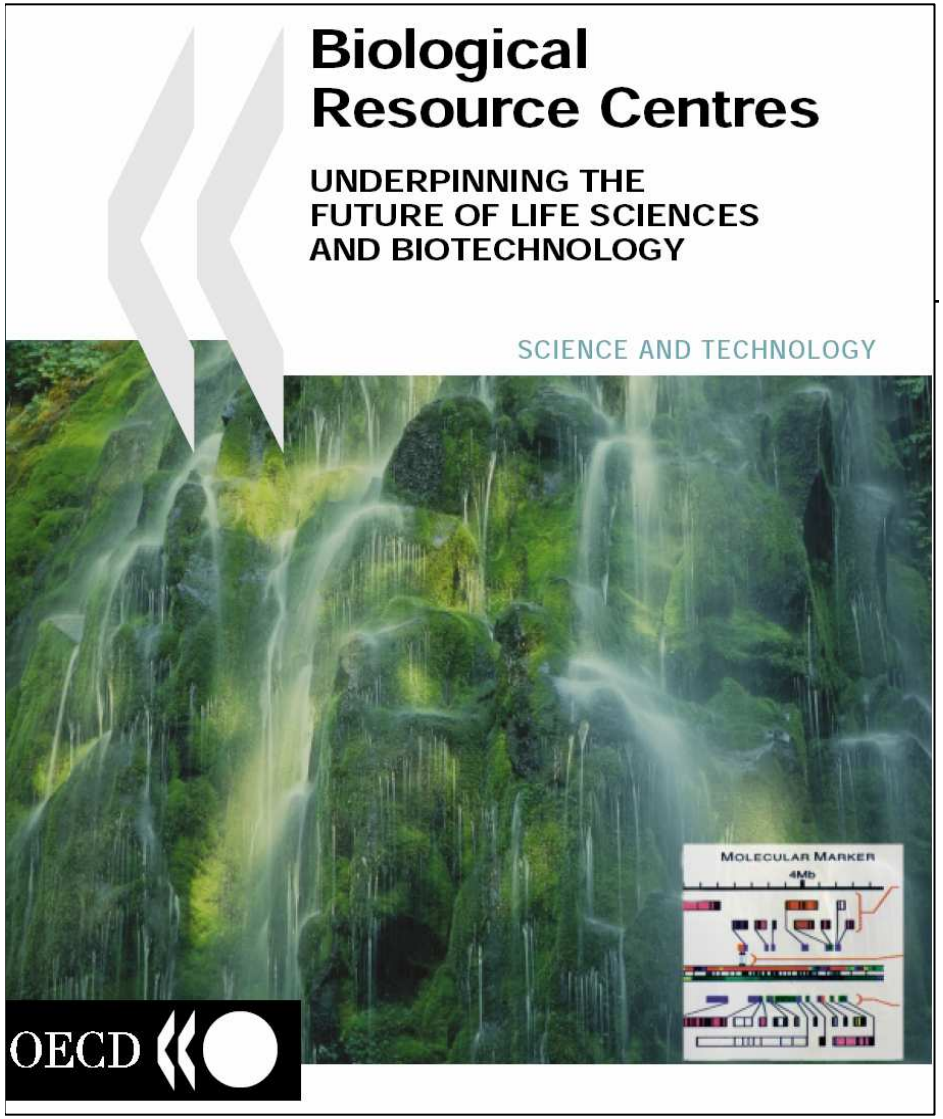
What Has Changed?

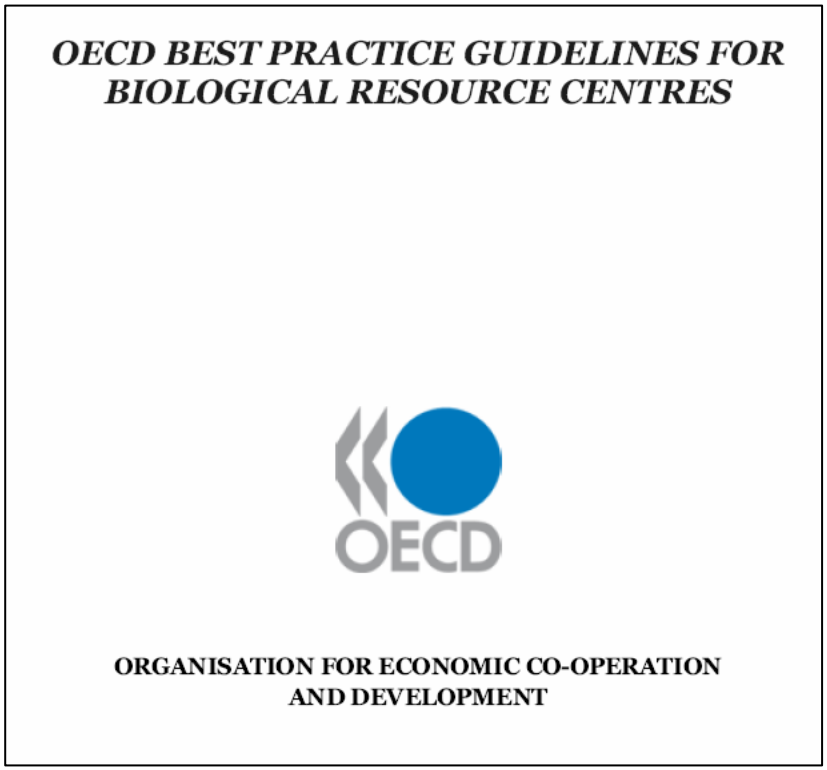


Sustained Energy Supply by a pan-European Network



- Many resource suppliers (oil, gas, uranium etc.)
- Integration of diff. types of power stations (caloric, water, nuclear, wind etc.)
- Common technical standards
- Environmental issues
- Rules for providers and users





Endorsed by CSTP in March 2007

"Biological resources – living organisms, cells, genes, and related information – are the essential raw material for the advancement of biotechnology, human health, and research and development in life sciences"

ESF Science Policy Briefing

Population Survey and Biobanking


EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

SCIENCE POLICY BRIEFING • May 2008 32

Population Surveys and Biobanking

Contents

Foreword

Rapid developments in medical research produce a continuous stream of new knowledge about disease processes. However, the possibilities for early detection or, preferably, prevention of disease remain limited. Population-based prospective studies investigating the interaction between genetic predisposition to a disease and exposure to environmental factors are a prerequisite to gain knowledge for the development of disease-preventing strategies. Increasingly, it is being realised that population surveys and biobanking – systematically assembling collections of genetic material and other relevant information about individuals – will play a key role in achieving the medical paradigm shift from "cure" to "prevention".

A multitude of national and regional population- and disease-oriented biobanks have been established in Europe. However, the exchange of data and materials within national legal frameworks is still difficult and European biobanking efforts are characterized by fragmentation.

The European Science Foundation's medical section, the European Medical Research Councils (EMRC), initiated this science policy activity because studies of complex diseases require population surveys directed at building a knowledge base to improve early detection techniques and ultimately develop primary preventive measures.

This report is the outcome of an ESF/EMRC Workshop on Population Surveys and Biobanking, involving an international high-level expert group, whose members made specific recommendations to stimulate co-ordinated activity in population surveys and biobanking across Europe. The recommendations, summarized at the end of this report, are intended to trigger targeted efforts by relevant stakeholders, including the ESF and its Member Organisations, governments, the European Commission, other international agencies, industry and academia.

To strengthen Europe's position in this scientific field, emphasis has to be put on increased collaboration to converge European biobanking activities, to address ethical issues and to prevent fragmentation by integrating parallel activities in this field. Sustained funding of biobanks is a prerequisite to fostering further development of this research area in Europe.

Professor Marja Makarow, Chief Executive, ESF

Professor Liselotte Højgaard, Chair, EMRC

www.esf.org

Scientific Organisers:

Professor Gertjan van Ommen [Co-Chair]
LUMC - The Netherlands
Professor Frank Skorpen [Co-Chair]
NTNU - Norway

Recommendations:

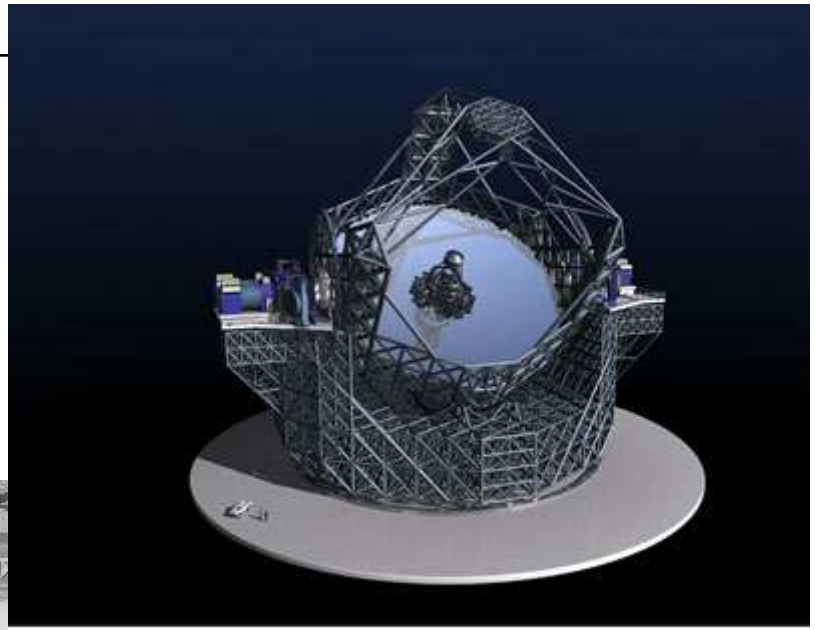
- **Pan-European biobanking infrastructure – integrated effort of multiple biobanking resources and interdisciplinary research centers**
- **Sustainable funding system based on cooperation between national and international funding partners**
- **Social, legal and regulatory framework that facilitates trans-national research and data exchange**

Status: **The Science Policy Briefing was released on 27 May 2008**

Research Infrastructures

Synchrotron

Supercomputers



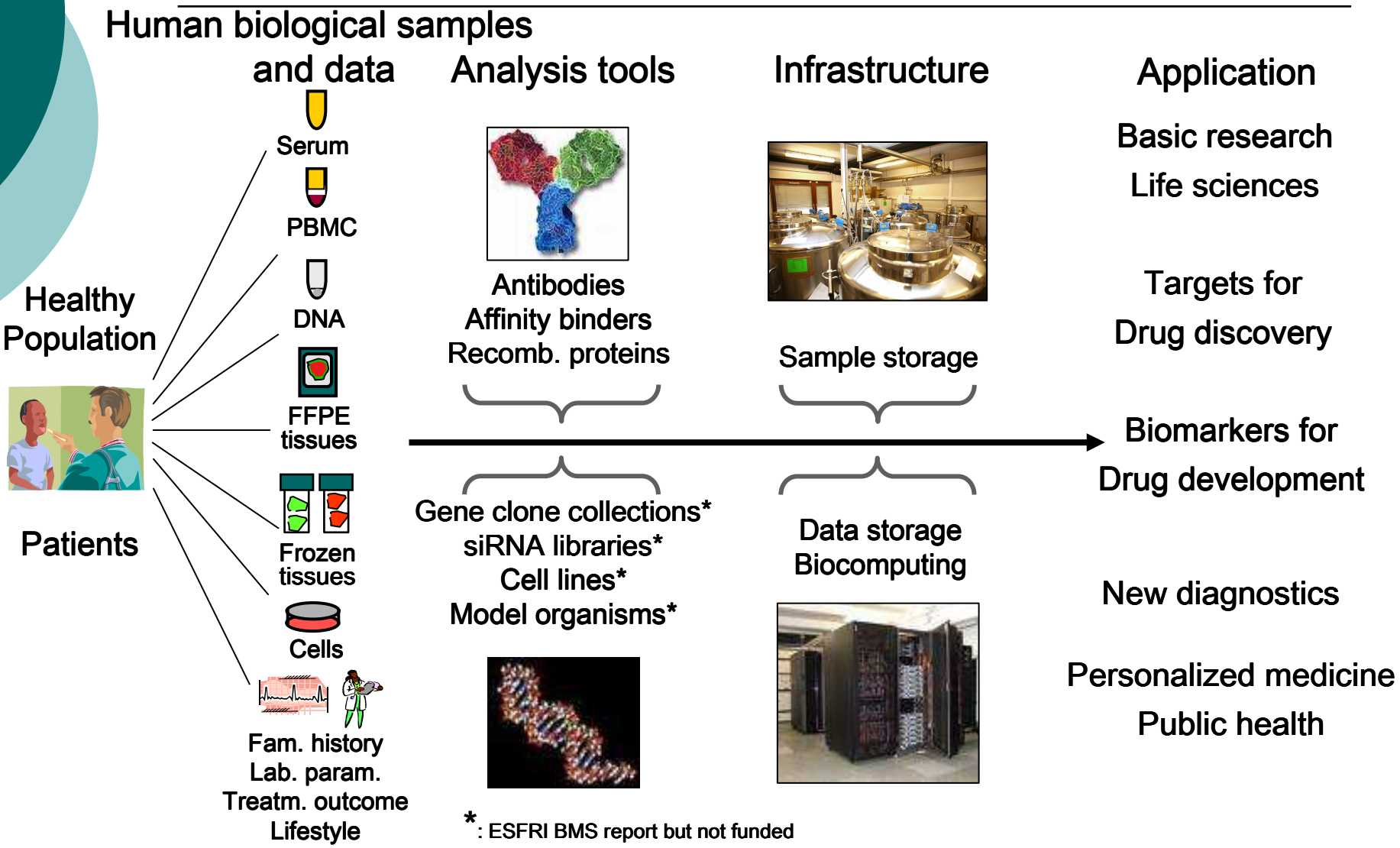
The European Extremely Large Telescope
(Artist's Impression)

ESO PR Photo 46/06 (11 December 2006) © ESO

The facility

A pan-European and broadly accessible network of existing and de novo biobanks and biomolecular resources. The infrastructure will include samples from patients and healthy persons, molecular genomic resources and bioinformatics tools to optimally exploit this resource for global biomedical research.

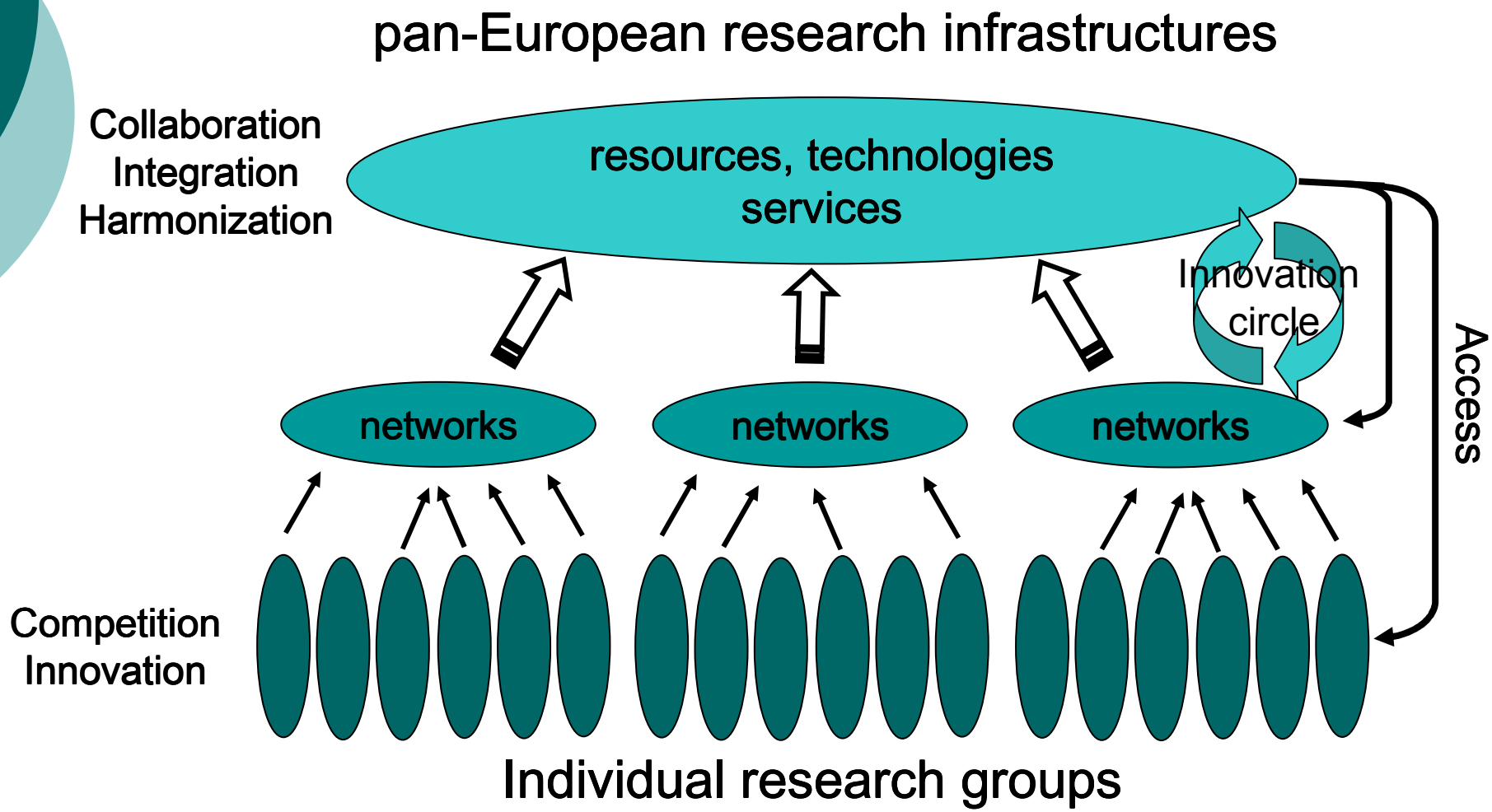
Key Components of BBMRI



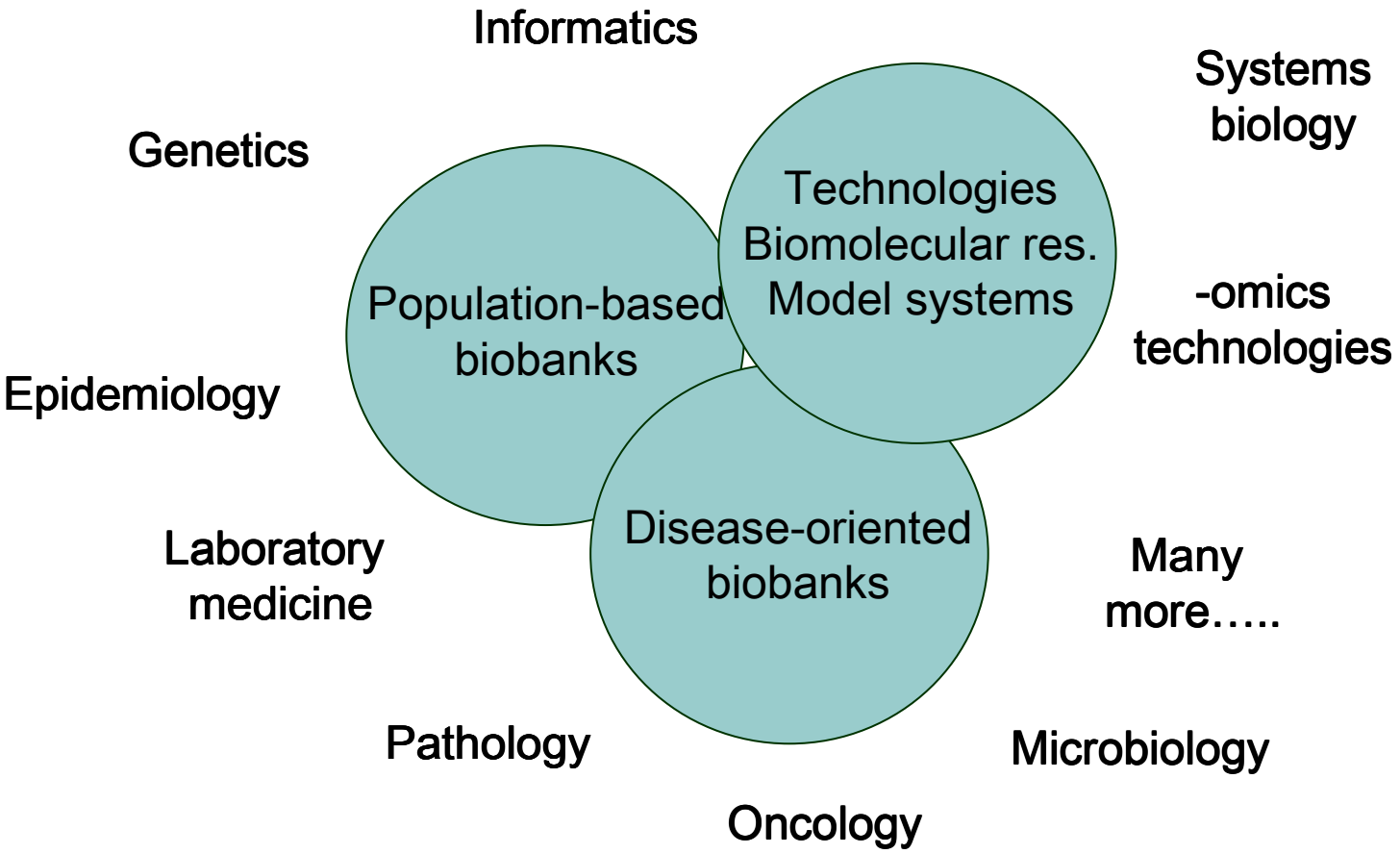
Features of Research Infrastructures

- Pan-European
- Agreement on long-term strategy
- Colaboration
- Access
- Power of scale
- Sustainability

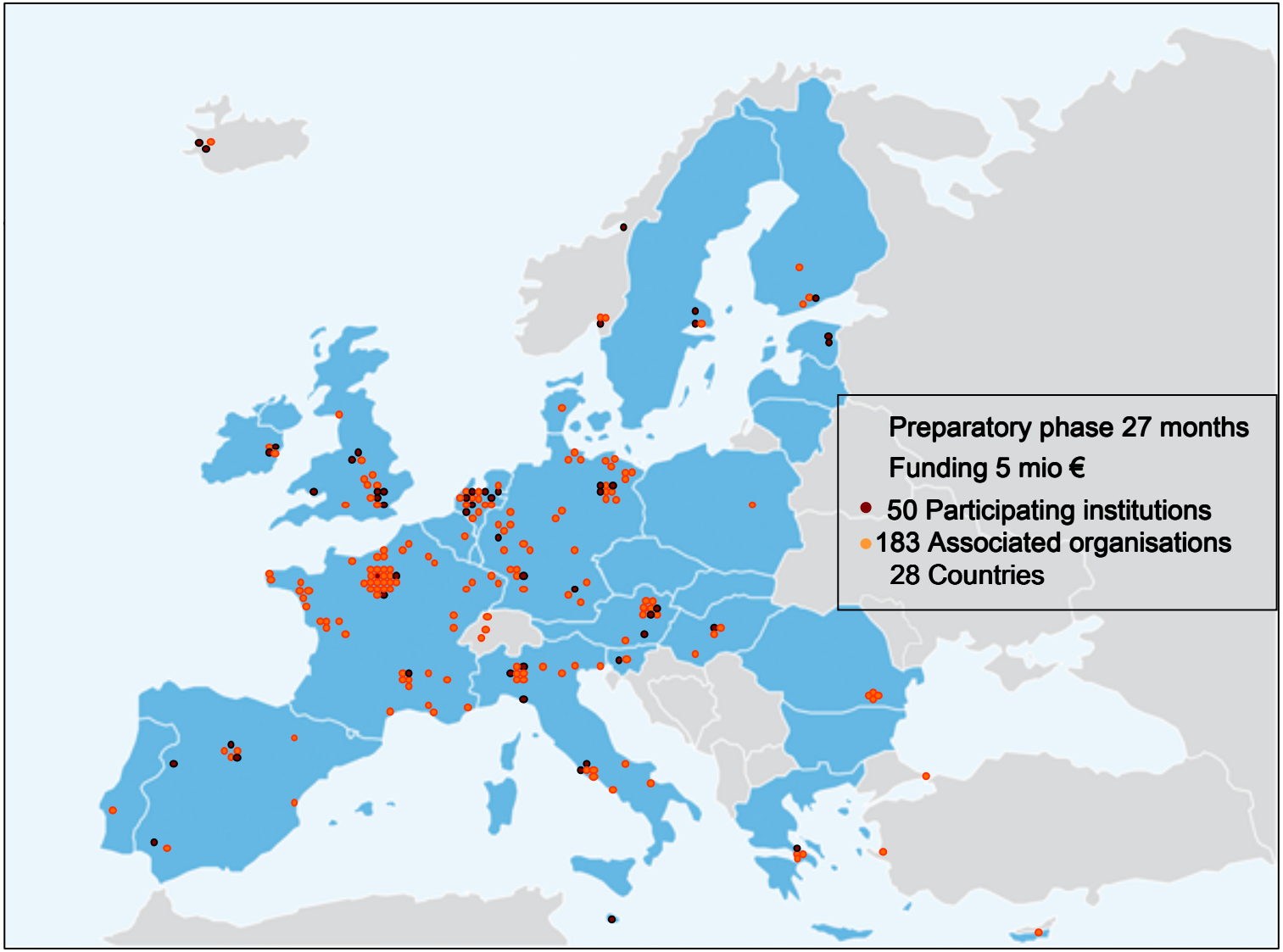
The New Dimension in Life Sciences Research



The Added Value of Collaboration



The Starting Point for a pan-European BBMRI



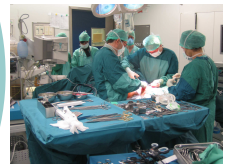
Specific Challenges for International Networking

- Harmonization of guidelines and standards
- Guidance through the heterogeneous ethical and legal frameworks of European Member States
- Implementation of harmonized data protection and informed consent standards

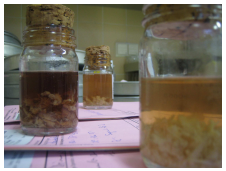
Clinical Samples: Critical Issues

- Collected in routine medical service
  - Limited possibilities for standardization
    - Processes are directed by patient needs (surgery, pathology etc.)
    - Differences in European health care
    - Modifications are difficult and expensive
- Many stakeholders
  - Patients
  - Health care funders
  - Medical professionals (surgeons, pathologists, radiologists, lab.medicine, internist etc.)
- Incentives for Contributors
- Finite resource (access rules)

Samples Quality: Critical Issues



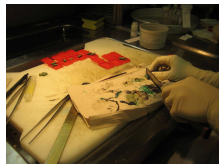
Medication
Surgical procedure
Warm ischemia



Fixation
Fixative
Time

Transport
Temperature
Cold ischemia

Embedding
Temperature

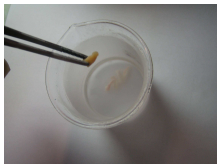


Sample processing
Mech. alteration
Selection+annotation

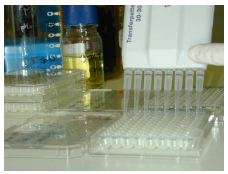
Diagnosis
Disease codes

Aliquotting

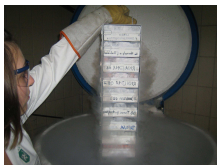
Storage
Time
temperature



Freezing
Freezing rate
Temperature



Sample preparation



Cryostorage
Temperature
Temp. shifts

Analysis

Sample Quality is defined by the Use

- Morphology
- Antigenicity
- Biomolecules
  - DNA
  - Protein
    Protein modifications
  - RNA
  - Metabolites
- Interactomes

Need for Evidence-Based Standards

- Basis for harmonization of guidelines
- Requires global cooperation
- Implementation by journals
- Implementation by funders
- Integral part of good scientific practice

Caveat: misuse of standards to generate competitive advantage

Reproducibility Depends on Quality

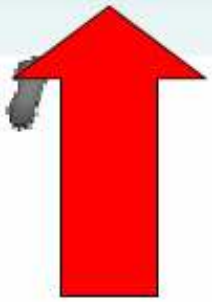
OBBR Office of Biorepositories and Biospecimen Research

GARBAGE IN ⇒ GARBAGE OUT

Many SOPs Around the World: Which are the Best?

OBBR Office of Biorepositories and Biospecimen Research

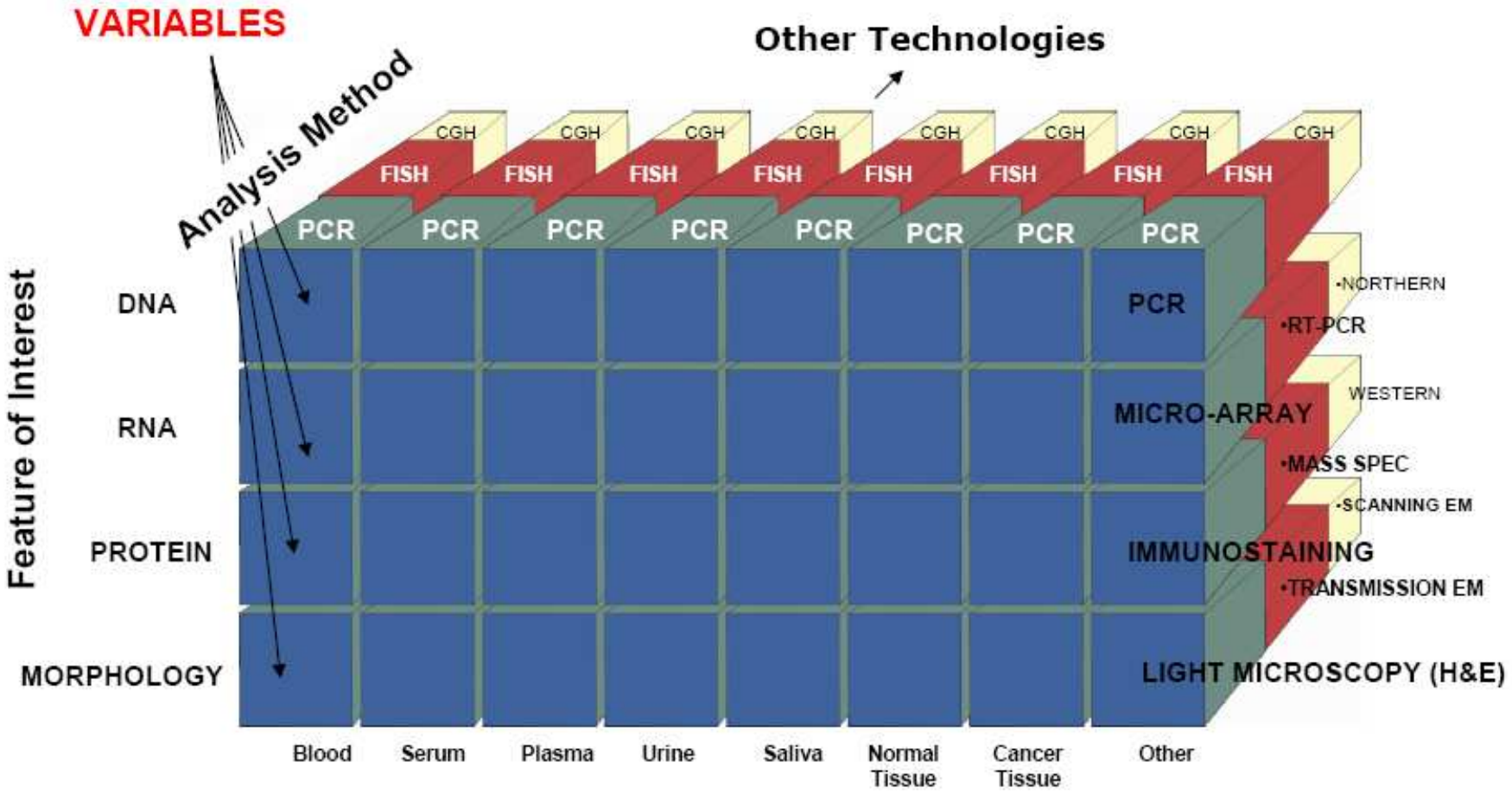
- Impossible to call any one "best" (even NCI's)
  - All have strengths and weaknesses
  - No single set of SOPs are applicable to all clinical and research analytical platforms
  - Very few SOPs are based on scientific evidence



Where we need to go

Framework for Development of Evidence-Based Standards Operating Procedures

OBBR Office of Biorepositories and Biospecimen Research



Forum for International Biobanking Organisations (FIBO)

International Agency for Research on Cancer
Centre International de Recherche sur le Cancer

Office of Biorepositories
and Biospecimen Research


ISBER says …
P3G says …
IARC says …
BBMRI says .
ISBER says …
BBMRI says .
IARC says …
OBBR says …
P3G says …
OBBR says …


FIBO says …

Harmonization: The Adaptor Model

- Define criteria
  - Which samples and data can be combined?
  - Need for evidence-based standards
- Develop tools
  - Data exchange
  - Sample transport

Building the Resources for the Future
Can we really do this?

- How to foresee the sample and data requirements for projects performed in 20 years?
- Several new preservation methods
  - How to do stability testing?
  - Good experience for DNA and RNA
  - Little experience for proteins, protein modifications, protein complexes, metabolites

What is the Best Strategy?

- Very high sample quality criteria
  - Outmost scientific value
  - Only few samples fulfill criteria
  - Strong selection bias
  - Not relevant for medical routine
  - Very expensive
- Samples from health care
  - Variable quality
  - Available in sufficient quantity
  - Required for biomarker validation
  - Affordable

Emerging Challenges

- Integrating population-based and disease-oriented biobanks
- Disease phenotype description
- Biomarkers for environmental exposure
- Evidence-based standards
- Knowledge management
- Socio-economic impact
- Communication strategy