



Knowledge Providers for Decision Makers

Industry strategies and biomarker business models

Arsia AMIR-ASLANI, PhD

**OECD WORKSHOP ON POLICY ISSUES FOR THE DEVELOPMENT AND USE OF
BIOMARKERS IN HEALTH**

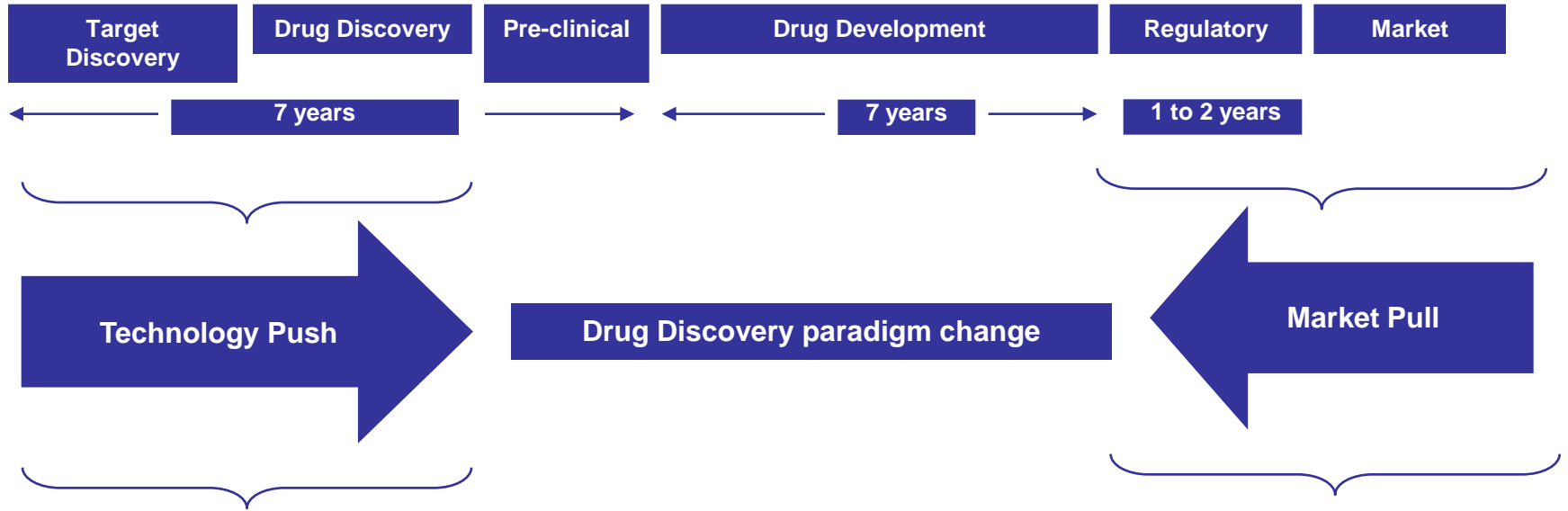
6&7 October, 2008

Wellcome Trust conference center, Hinxton, UK



Driving forces of drug discovery paradigm change

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Developments in biotechnology have allowed the drug discovery industry to move from serendipity-based research towards rational, evidence-based approaches. The wide range of technologies belong to one of the following fields:

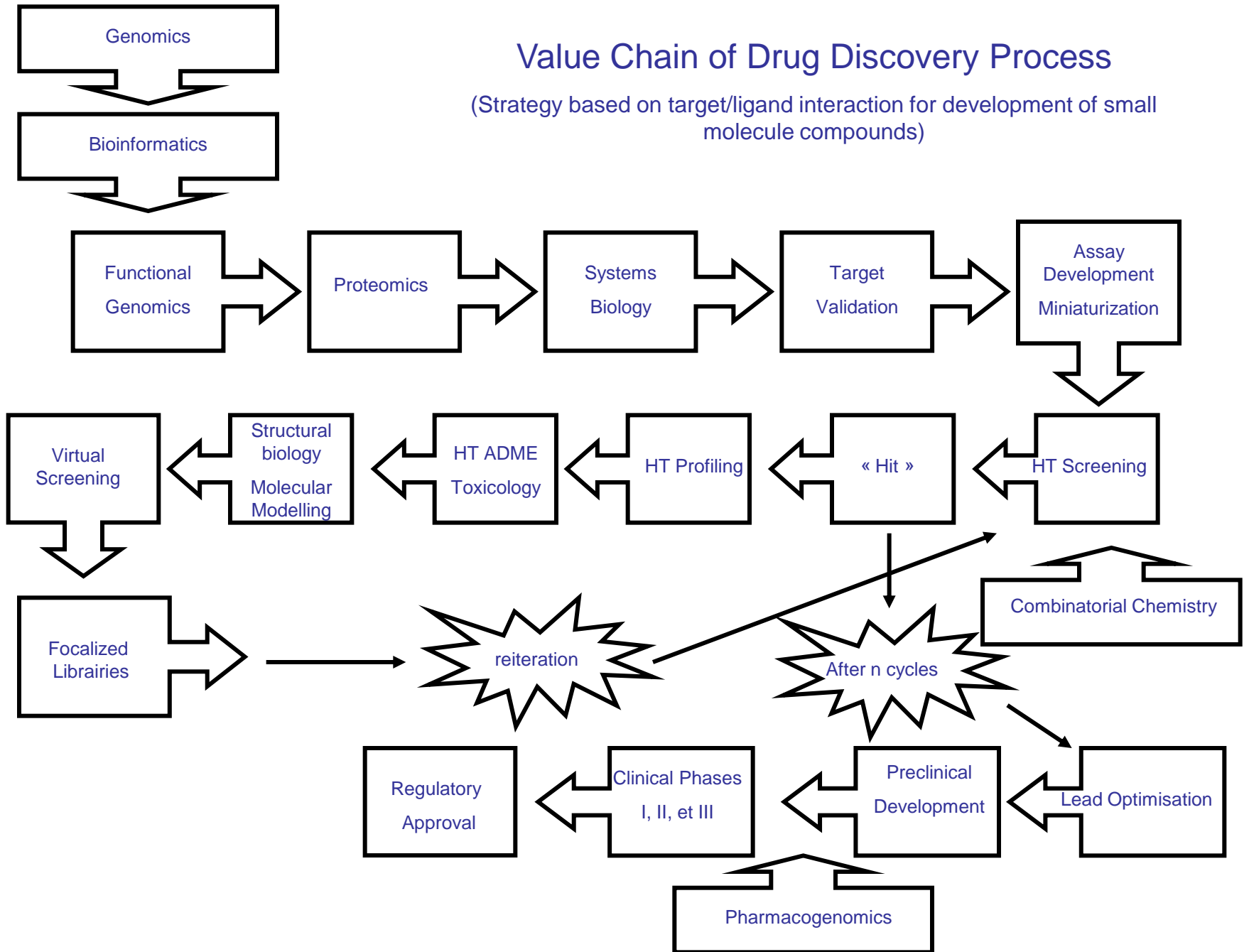
- Informatics
- Chemistry
- Biology

A successful therapeutic compound needs to fulfill fundamental requirements, such as:

- Satisfies an unmet medical need
- Exhibits superiority over existing treatments
- Provides specific advantages in terms of pharmacokinetics and metabolism
- Safe with low adverse drug reactions

Value Chain of Drug Discovery Process

(Strategy based on target/ligand interaction for development of small molecule compounds)



Drug Discovery, Development and Approval Process

Research/Preclinical Testing



6.5 years

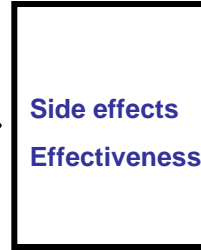
IND

Phase I



1.5 years

Phase II



2 years

Phase III



3.5 years

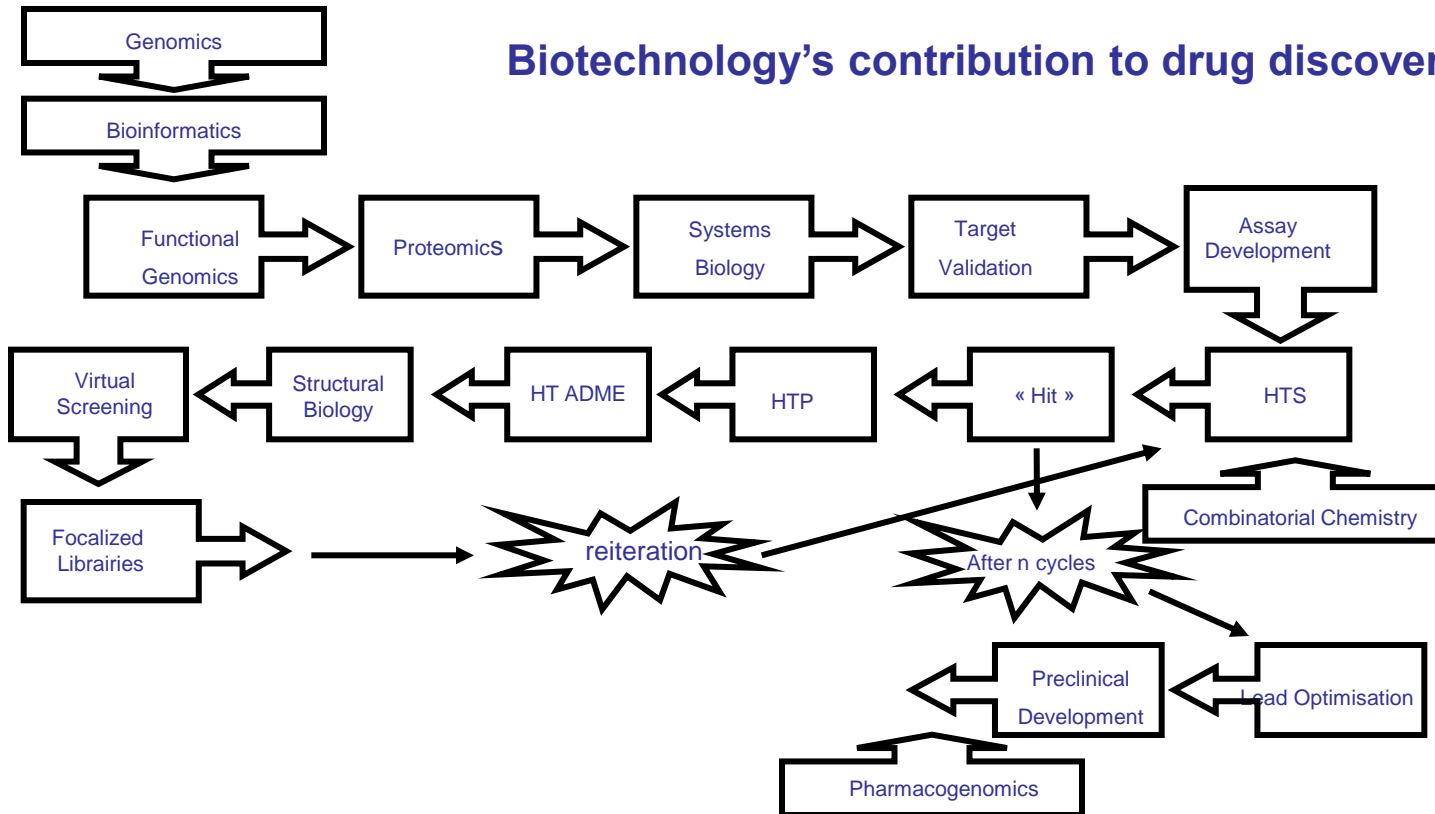
NDA

FDA



1.5 years

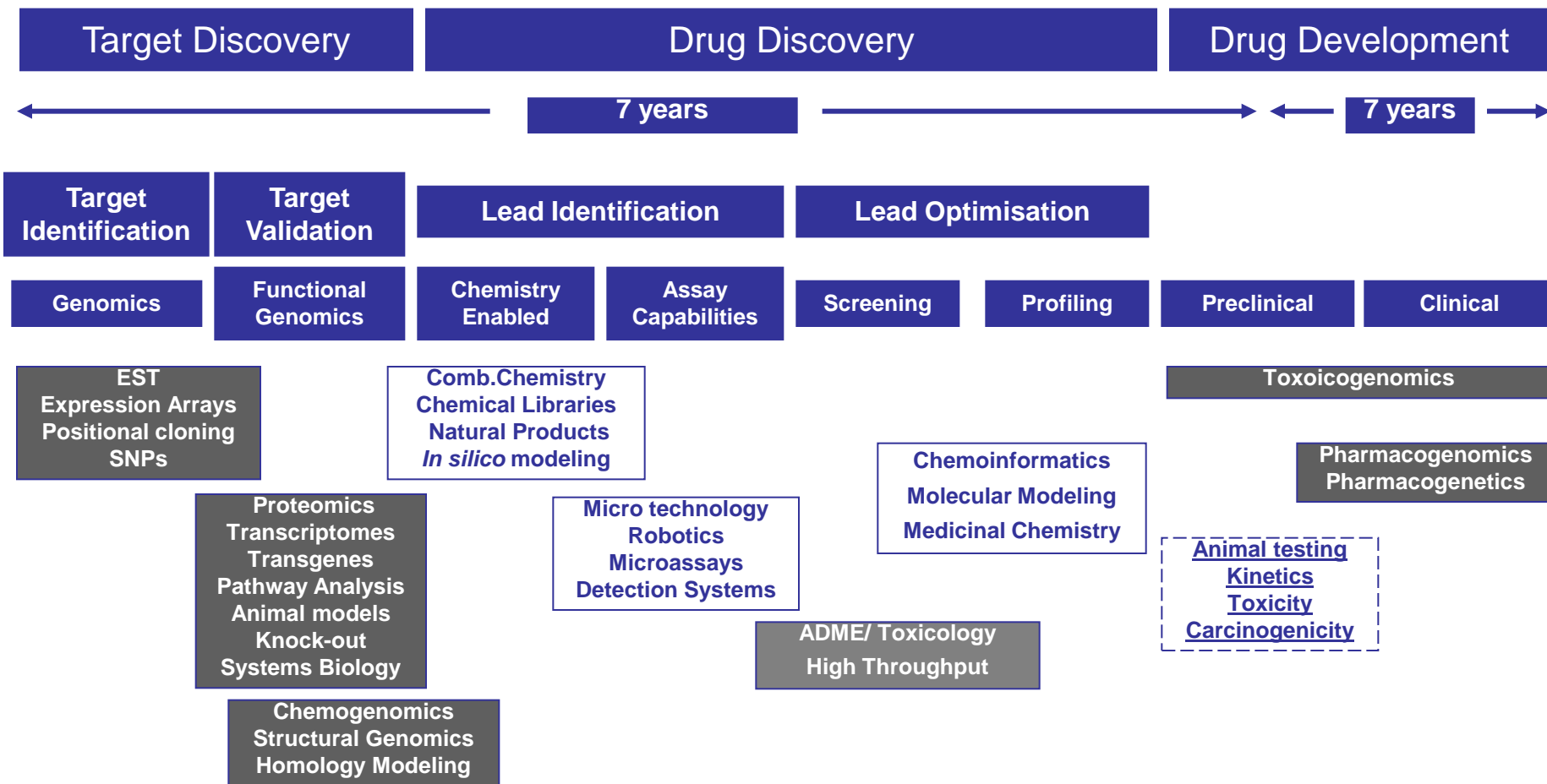
Biotechnology's contribution to drug discovery



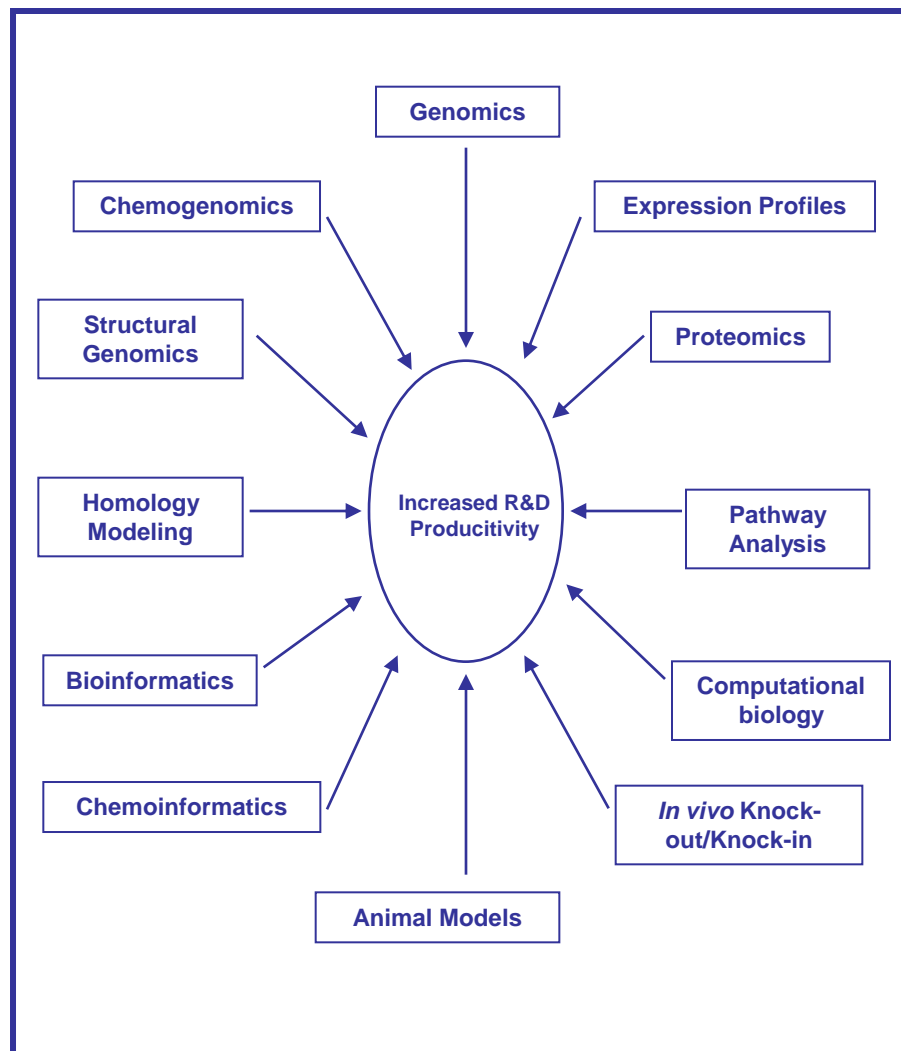
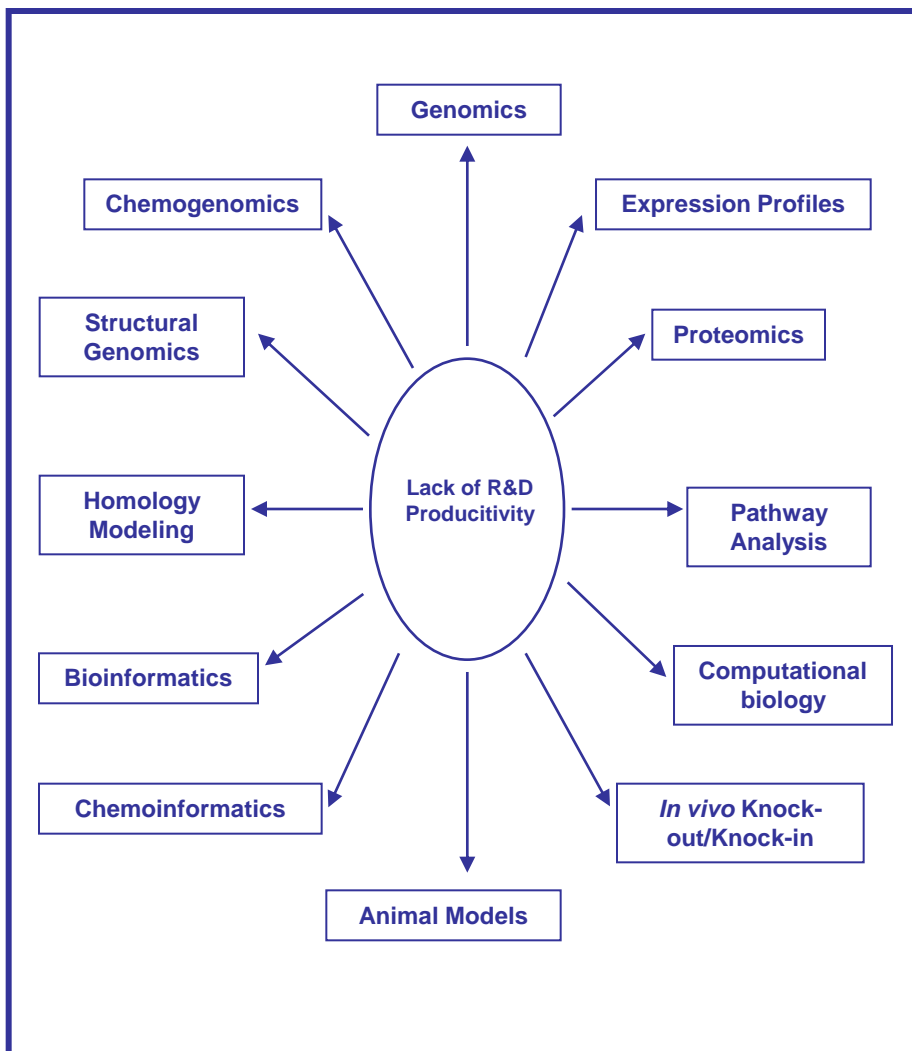


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Biotechnology and Drug Discovery and Development



The need for data integration



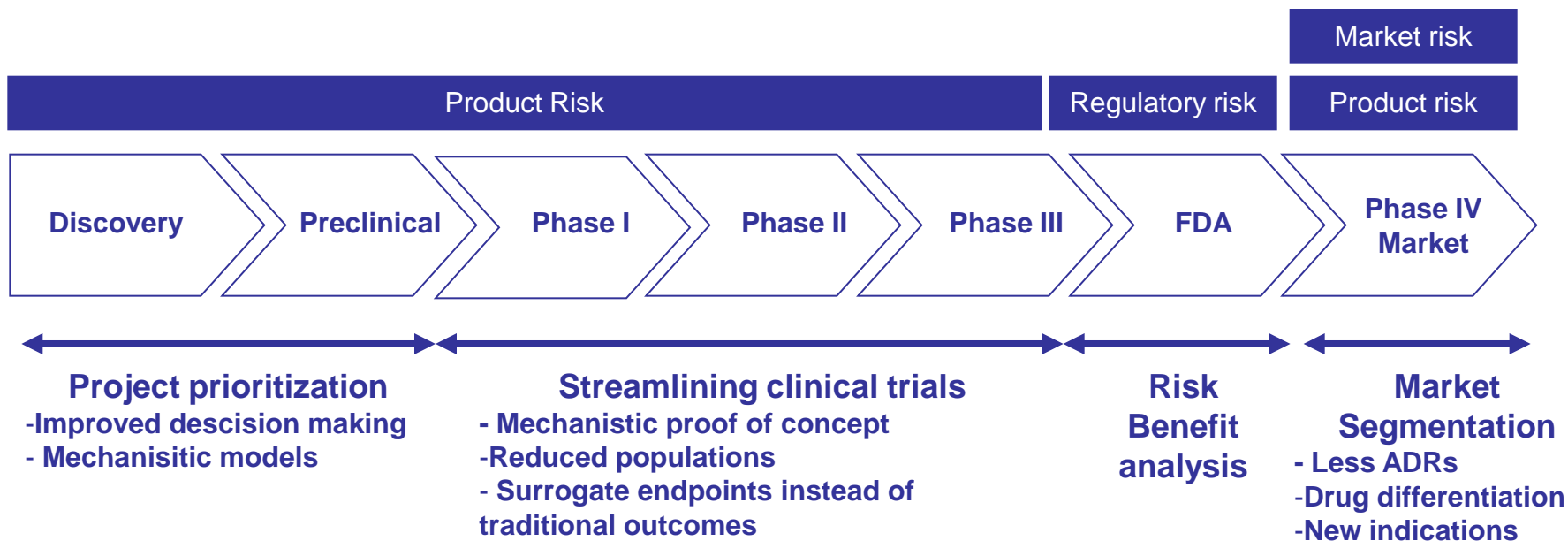


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Major Biomarker-related benefits

- 1. A better understanding of the molecular mechanisms of diseases and drug response**
- 2. A safer, faster and more efficient drug development process**
- 3. A safer utilisation of therapeutic drugs**
- 4. Increased efficiency**
- 5. Better post marketing surveillance**
- 6. Methods for differentiating competitors**
- 7. New indications for new and existing therapeutic drugs**

Integrating biomarkers into the drug discovery and development





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Drivers of diffusion

- 1. Nature of disease and intervention**
- 2. Regulation**
- 3. Value, coverage and reimbursement**
- 4. Ability to integrate diagnostics and pharmaceuticals**



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Nature of disease and intervention

- **Cancer**
- **Infectious Disease**



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Examples of FDA approved of valid genomic biomarkers for approved drug labels (www.fda.gov).

Biomarker	Test utilization	Drug	Drugs associated with this biomarker	Label
C-KIT expression	Information	Imatinib mesylate		Gastrointestinal stromal tumor <i>c-Kit</i> expression.
CYP2C19 variants	Information	Voriconazole	Omeprazole, pantoprazole, Esomeprazole, diazepam, nelfinavir, Rabeprazole	Poor Metabolizers and Extensive Metabolizers with genetic defect leads to change in drug exposure.
CYP2C9 Variants	Information	Celecoxib	Warfarin	Poor Metabolizers and Extensive Metabolizers with genetic defect leads to change in drug exposure.
CYP2D6 variants	Information	Atomoxetine	Venlafaxine, Risperidone, Tiotropium bromide inhalation, Tamoxifen, Timolol Maleate	People with reduced activity in this pathway have higher plasma concentrations of atomoxetine compared with people with normal activity.
DPD Deficiency	Information	capecitabine	Fluorouracil	Unexpected, severe toxicity has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity.
EGFR expression with alternate Context	Required	Cetuximab (Colorectal cancer)	Gefitinib	Patients enrolled in the clinical studies were required to have immuno-histochemical evidence of positive EGFR expression using the DakoCytomation EGFR pharmDx™ test kit.”
Her2/neu Over-expression	Required	Trastuzumab		Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy
Protein C deficiencies (hereditary or acquired)	Recommended	Warfarin		Hereditary or acquired deficiencies of protein C or its cofactor, protein S, has been associated with tissue necrosis following warfarin administration.
TPMT variants	Recommended	Azathioprine	Thioguanine, Mercaptopurine	Thiopurine methyltransferase deficiency or lower activity due to mutation at increased risk of myelotoxicity.
UGT1A1 Variants	Recommended	Irinotecan		UGT1A1 mutation in patients, exposure to drug and hence their susceptibility to toxicity.



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Major drug withdrawals between 1997 and 2005

Drug	Date of approval	Date of withdrawal	Adverse Drug Reactions
Pondimin (Fenfluramine)	1973	1997	Risk of heart valve abnormalities
Redux (Dexfenfluramine)	1996	1997	Risk of heart valve abnormalities
Seldane (Terfenadine)	1985	1998	Risk of fatal heart rhythm abnormalities
Duract (Bromfenac)	1997	1998	Severe hepatic reactions, potentially fatal fulminant hepatitis and liver failure, with some cases requiring transplantation.
Posicor (Mibefradil)	1997	1998	Heart conditions including arrhythmias and low blood pressure.
Raxar (Grepafloxacin)	1997	1999	Severe cardiovascular events among patients
Hismanal (Astemizole)	1998	1999	Serious cardiac side effects, involving changes in heart rhythm
Lotronex (Alosetron)	2000	2000	Intestinal damage resulting from ischemic colitis, severely obstructed or ruptured bowels, and death.
Propulsid (Cisapride)	1993	2000	Heartbeat interruption and cause an arrhythmia
Rezulin (Troglitazone)	1997	2000	Severe liver toxicity has been known to occur
Baycol (Cerivastatin)	1997	2001	Fatal rhabdomyolysis, a severe muscle adverse reaction
Raplon (Rapacuronium)	1999	2001	An inability to breathe normally that can lead to permanent injury or death
Vioxx (Rofecoxib)	1999	2004	Increased risk of heart attack and stroke
Palladone (Hydromorphone)	2004	2005	Potential fatalities when taken with alcohol
Bextra (Valdecoxib)	2001	2005	Increased risk of heart attack and stroke



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Assessing Value

- **Cost-effective Analysis**
- **reimbursement**



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Ability to integrate diagnostics & Pharmaceuticals

- **Herceptin**
- **CYP450**



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Defining a Business Model

A representation of a firm's underlying core logic and strategic choices for creating and capturing value within a value network (Shafer et al., 2005)



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Competitive Environment

- **Healthcare companies manufacturing tests and analyzers**
- **Diagnostics/Pharmaceutical companies**
- **Molecular services businesses**
- **Companies developing drug discovery technologies**
- **Companies developing molecular diagnostics and genetics tests**
- **Companies developing POC and genetic tests**
- **Laboratory Services**
- **CROs**



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Publicly listed companies with commercial interest in biomarkers (As of May 30, 2008)

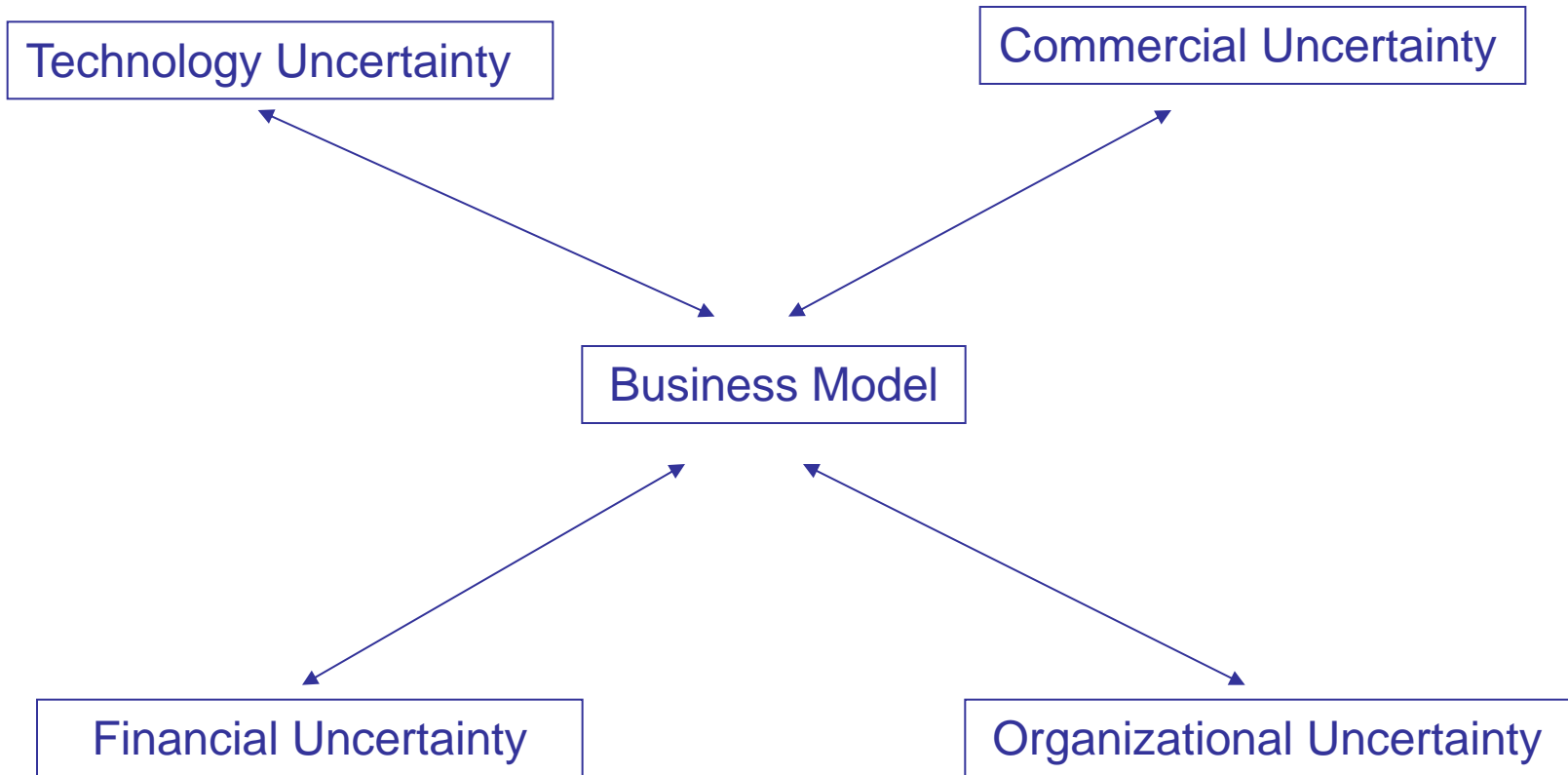
Company	Market Capitalization	Activity	Location	2007 Revenues
Avalon	USD 28.8 M	Technology platform	USA	USD 0.81 M
Bio-reference labs	USD 337 M	Clinical and genetic testing	USA	USD 250 M
Clinical data	USD 393 M	Pharmacogenomics	USA	USD 63.7 M
Combimatrix	USD 58 M	Technology platform	USA	USD 6.03 M
Curidium	UK£ 47 M	Companion diagnostics	UK	No revenue
Diagnocure	CAN\$ 98	Diagnostics and lab services	Canada	CAN\$ 3.5 M
DNA Print genomics	USD < 1M	Genetic testing, SNP analysis	USA	NA
Epigenomics	€ 54 M	DNA Methylation biomarkers	Germany	€ 2.6 M
Exact Sciences	USD 49 M	DNA testing	USA	USD 1.8 M
Gene News Ltd	CAN\$ 55 M	Molecular diagnostics	Canada	CAN\$ 2.17 M
Genomic Health	USD 487 M	Molecular diagnostics	USA	USD 64 M
Genetic Technologies	USD 38 M	Genetic testing and services	Australia	USD 11.7 M
Genoptix	USD 460 M	Laboratory service provider	USA	USD 59.3 M
Helicos Biosciences	USD 99 M	Genetic testing	USA	USD 0.58 M
IVAX Diagnostics	USD 20.8 M	Diagnostics	USA	USD 20 M
Imaging diagnostics systems	USD 13 M	Molecular imaging	USA	USD 0.07 M



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Publicly listed companies with commercial interest in biomarkers (As of May 30, 2008)

Company	Market Capitalization	Activity	Location	2007 Revenues
Interleukin Genetics	USD 48 M	Genetic tests	USA	USD 9.7 M
Medtox	USD 129 M	Lab services and diagnostics	USA	USD 80 M
Monogram Biosciences	USD 155.6	Lab services and diagnostics	USA	USD 43.2M
Nanogen	USD 24 M	Technology platform	USA	USD 38.2 M
Nanosphere	USD 211 M	Technology platform	USA	USD 1.2 M
Orchid Cellmark	USD 90.8 M	DNA testing	USA	USD 60 M
Ore Pharmaceuticals	USD 11 M	Drug repositioning	USA	USD 1.6 M
Oncomethylome	€ 112 M	Cancer detection tests	Belgium	€ 2.6 M
Pacific biometrics	USD 7.6 M	Lab service for clinical research	USA	USD 8.5 M
Radnet	USD 223 M	Diagnostics imaging	USD	USD 425 M
Rosetta Genomics	USD 52M	MicroRNA diagnostics	Israel	No revenue
Transgenomic	USD 39 M	Genetic testing	USA	USD 23 M
Vermillion	USD 14 M	Diagnostics	USA	USD 0.04 M



Biotechnology R&D challenges

Increasing complexity
Low R&D productivity
High R&D expenditures
Information over-load
Technology integration
New technologies

Pharmaceutical industry dynamics

Mainly focused on small molecules
Intense M&A activity
Need for late-stage compounds
Low innovative capability
Management of numerous Strategic alliances

M&A driving forces

Industry and capital market challenges

Decreasing number of Pharmaceutical partners
Rising expectations from pharmaceutical partners
Volatile financing through capital markets
Increasing investor demand for value
Favorable government policies
Blockbuster model no longer valid
High-patient expectations

Organizational challenges

Resource allocation
Critical mass
Organizational models
Portfolio management
Sustainable business model



**Araxes
Associates**

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Acquirer

Clinical Data

Clinical Data

Clinical Data

Clinical Data

Qiagen

Qiagen

Siemens

Siemens

Quest Diag.

Quest Diag.

Becton Dickson

Fisher Scientific

Celera

Celera

Sequenom

Target

Genaissance Pharma Oct/05

Icoria Dec/05

Genome Express March/06

Epidauros Biotech Aug/07

Digene June/07

Genaco Oct/06

Bayer Diagnostics Jun/06

DiagnosticsProducts Apr/06

LabOne Aug/05

Focus Diagnostics May/06

GeneOhm Sciences Jan/06

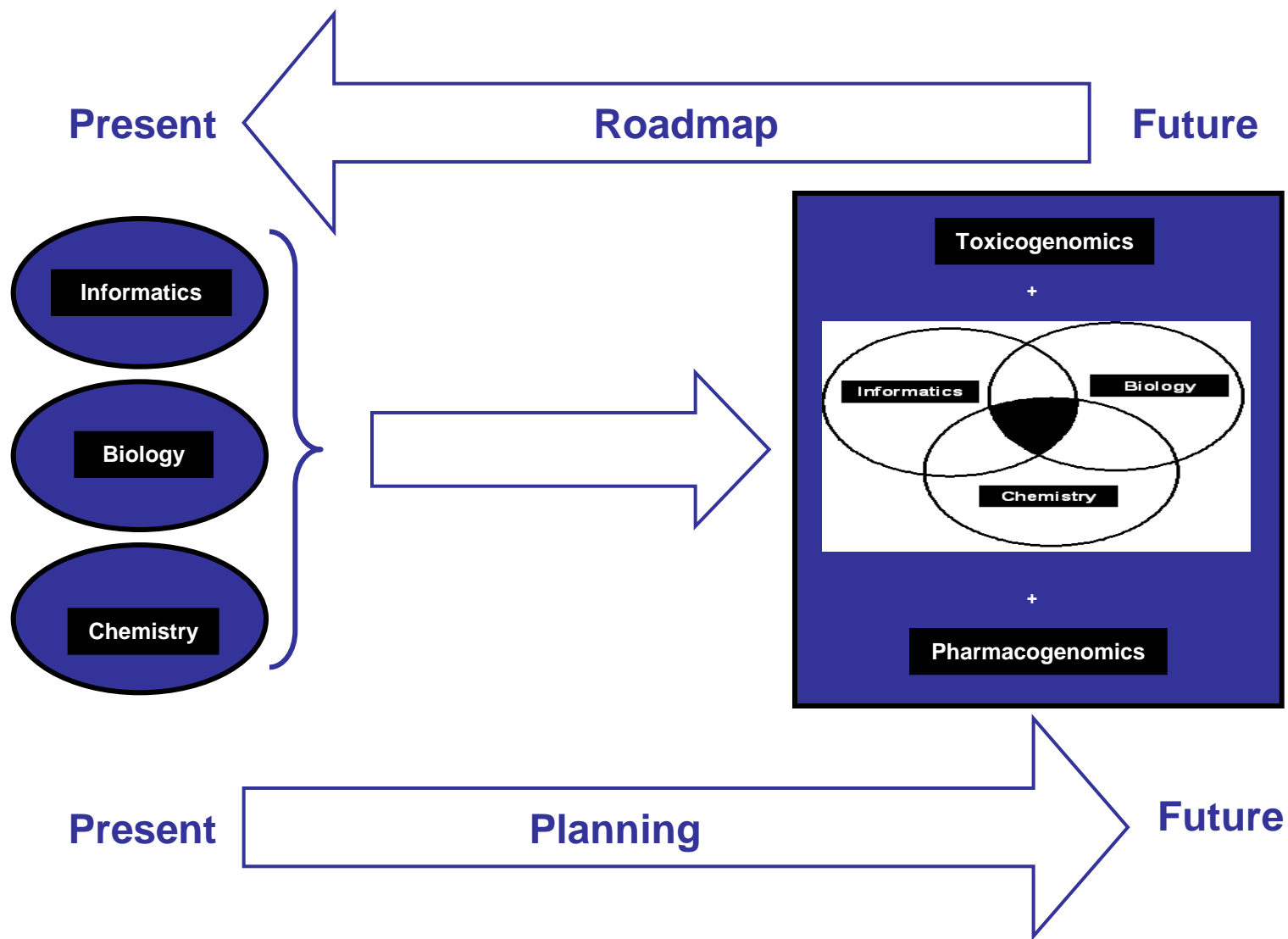
Athena Diagnostics Mar/06

Berkely Hearthlab Oct/07

Atria Genetics Oct/07

Michigan CLIA Sep/08

The benefits technology roadmapping in drug discovery and development





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Thank You