The Feasibility of Integrating Pharmacogenetics/Biomarkers into Drug Development from an Economic Perspective

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Industry view of biomarkers

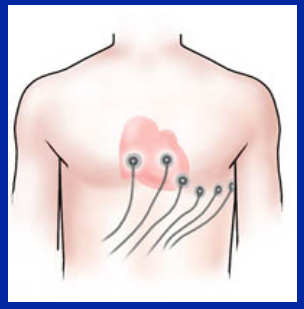
Broad definition

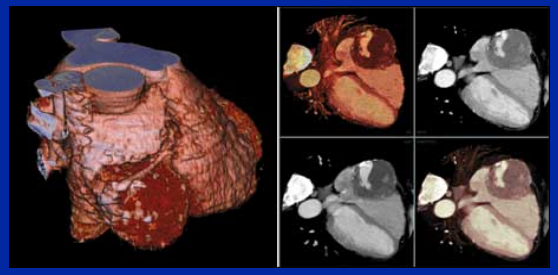
- An objective measure or evaluation of normal biologic processes, pathogenic processes, pharmacologic responses to a therapeutic intervention or responses to preventative or other healthcare interventions
- Biomarkers may or may not be dynamically modulated
- Biomarkers can increase our understanding of drug metabolism, action, and efficacy and/or safety, facilitate therapy response prediction, expand the molecular definition of disease, and inform about the course of disease

Industry view of biomarkers

Broad definition

- The broad definition includes all diagnostic tests, imaging technologies and any other objective measure of a person's health status and all pharmacodiagnostic tests.





- Remarks are focused on **novel** markers – either newly discovered markers or markers which are being validated for novel applications.

Biomarkers/Pharmacodiagnostics and drug development – what is changing?

- Genetics, genomics, proteomics, modern imaging techniques and other technologies allow us to measure many more markers than before
- Improved understanding of targets, signaling pathways, metabolism and mechanisms of toxicity and action allow us to make more sense of biomarker data
- Biostatistics and bioinformatics are allowing us to collect, store and interpret data more effectively

Biomarkers/Pharmacodiagnostics and drug development – what is changing?

- These new marker data are allowing us to make considerably richer decisions in late research and early development - essentially an evolution of the current paradigm
- There are, as yet, few validated surrogate markers which allow us to run considerably shorter trials
- There are, as yet, very few highly informative “response” markers which allow us to run smaller / shorter trials enriched for potential responders
- Steady evolution of the drug development process, rather than revolution

Biomarker utilities in drug development

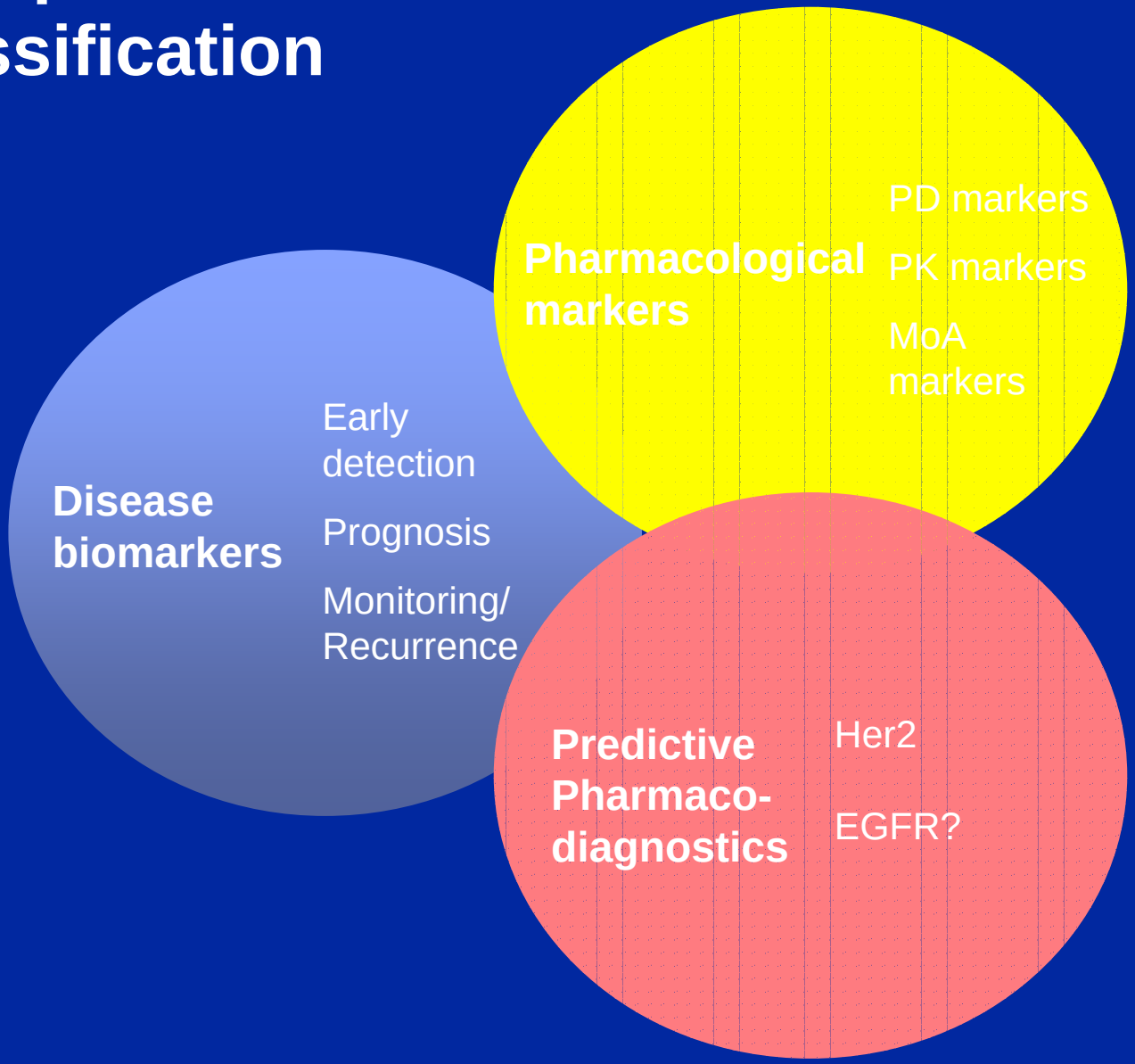
- **Pharmacodynamic** markers confirm biological activity of our drugs. They enable early go/no go decisions, and make optimization of dosing and schedule more efficient.

- **Prognostic** markers (e.g. CRP in rheumatoid arthritis) correlate with disease outcome. They improve our ability to design informative trials and to interpret them confidently.

- **Disease specific** markers (e.g. PSA in Prostate Cancer) correlate well with the presence or absence of the disease. In some cases, these can be used to identify disease subtypes that are more amenable to one therapaeutic intervention than another – or can be used to enrich trials for those most likely to respond.

- **Predictive** markers (e.g. HER2 over-expression in breast cancer) correlate with the activity of our drugs. They help match our drugs with appropriate patient populations.

One possible biomarker classification



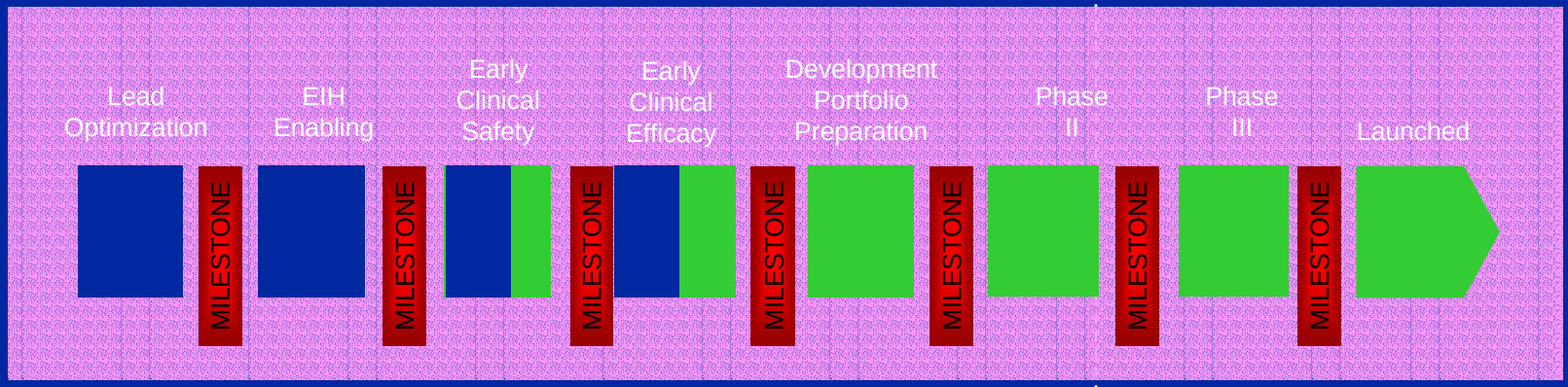
Biomarkers/Pharmacodiagnostics – Value Impacts

- Pharmacodynamic and Prognostic tests tend to increase value:
  - Size of the market is not affected
  - Revenues do not decrease and may increase e.g. better dosing and dose scheduling
  - Investments in markers generally offset by improved decision making/trial design, reduced attrition etc.
- Value impact of predictive markers less clear:
  - May reduce size of market
  - Offset by improved market penetration, increased average duration on therapy and pricing
  - May improve competitive position
  - Require case by case analysis

Biomarker strategy in Pharma R&D

Prototypic concept for the application of markers predicting response

Retrospective analysis of BMs on samples collected in Ph. 2 – correlation with response



Biomarker discovery

1

Biomarker test development / validation

2

Prospective recruitment of patients using BMs found to be useful at end of Ph. 2

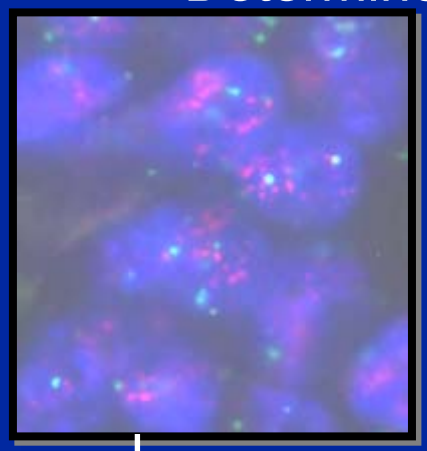
3

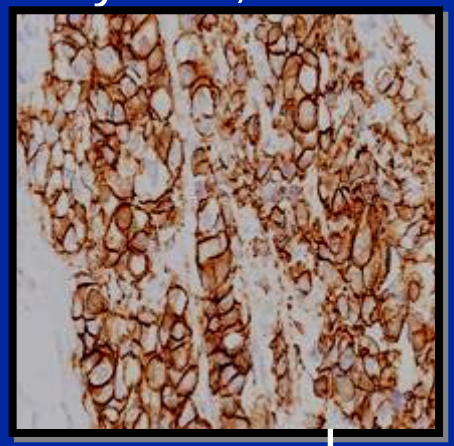
Sample collection and storage

Eligibility for Herceptin® therapy

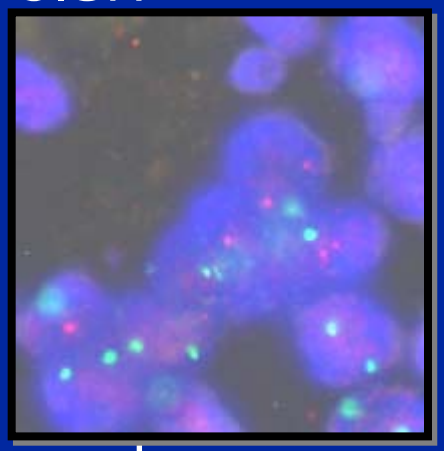
HER2 status

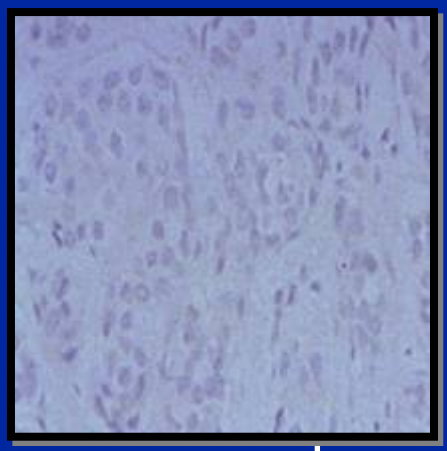
- Determined by IHC, FISH or CISH





FISH+ IHC+





FISH– IHC–

Eligible for Herceptin®

NO BENEFIT from Herceptin®

Response Prediction

- What is an acceptable response rate for a novel drug and when should one think about stratification with a response marker?
  - 90%
  - 80%
  - 70%
  - 60%
  - 50%
  - 40%
  - 30%
  - 20%
  - 10%

All candidates for response prediction marker approach?

Influence of indication, risk of ADRs etc.?

Defining the response phenotype
e.g. patients suffering from RA

Response measured by composite scores

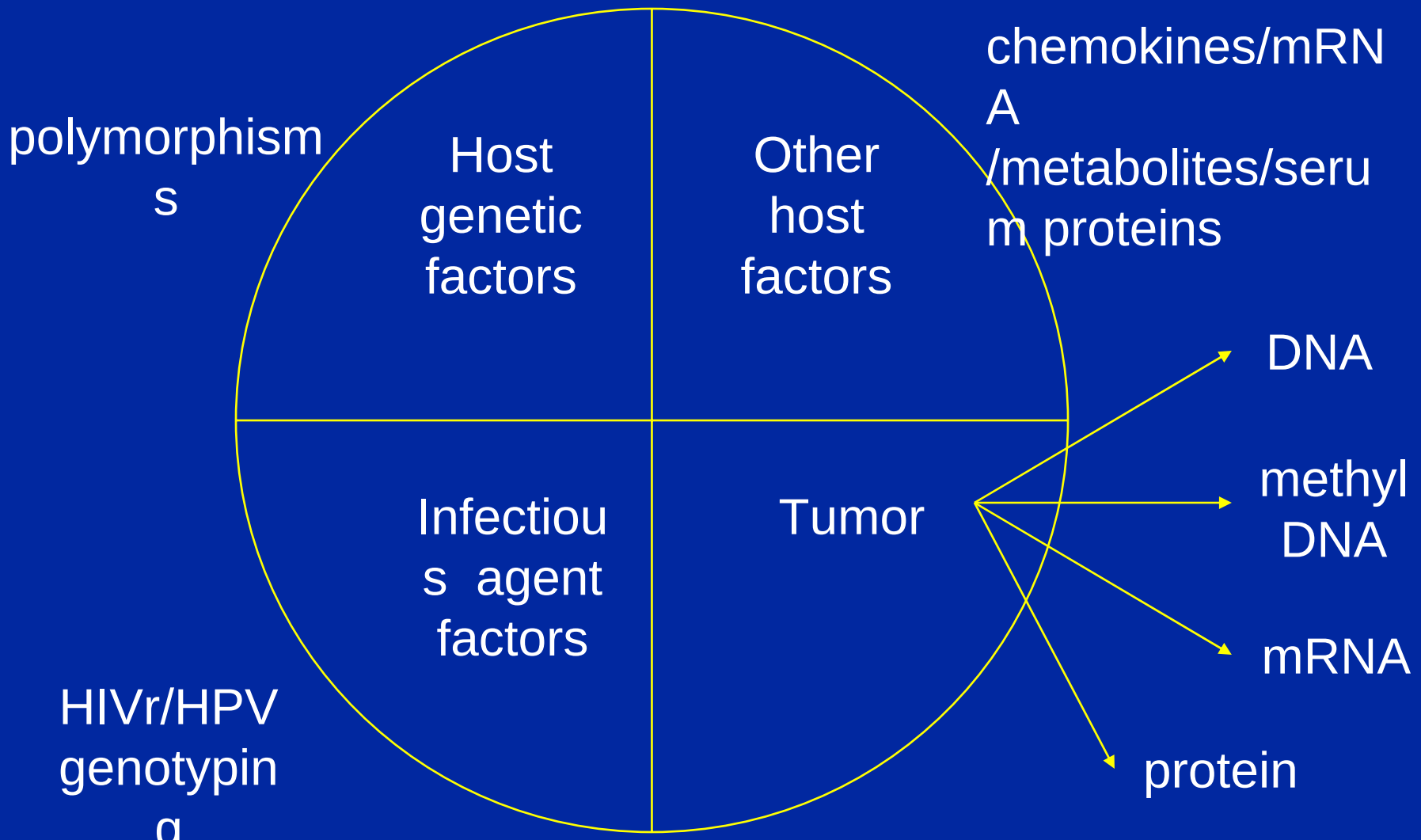
- **ACR (improvement not activity)**
  - ACR20 – a 20% improvement in TJC and SJC and in 3 of the following
    - Patient global assessment
    - Physicians global assessment
    - Patients assessment of pain
    - Degree of disability
    - Level of acute phase reactants
- **DAS (improvement and activity)**
  - Includes articular index, SJC, ESR, Patient global assessment
    - Good response DAS <2.4; △>1.2
    - Non-responder DAS >3.7; △<0.6
- **Different therapies may produce different effects on the components of a composite score – and therefore on the measurement of response**

Pharmacodiagnostic test requirements

- **Reliable tests**
  - low variability - robust and reproducible
  - highly predictive - genotyping accurate but generally limited predictive power
- **Easy to administer**
  - whole blood/serum - biopsy?
  - rapid test turnaround
  - value of test information outweighs acquisition costs (time/cost/invasiveness)
- **Widely available**
  - availability of test no hindrance to marketing of drug
  - testing platform with many placements or low acquisition costs
- **Concurrent**
  - approval of test concurrent with drug approval

Samples for pharmacodiagnostic tests

Invasiveness vs. predictive value



Clinical utility of response prediction

Key factors

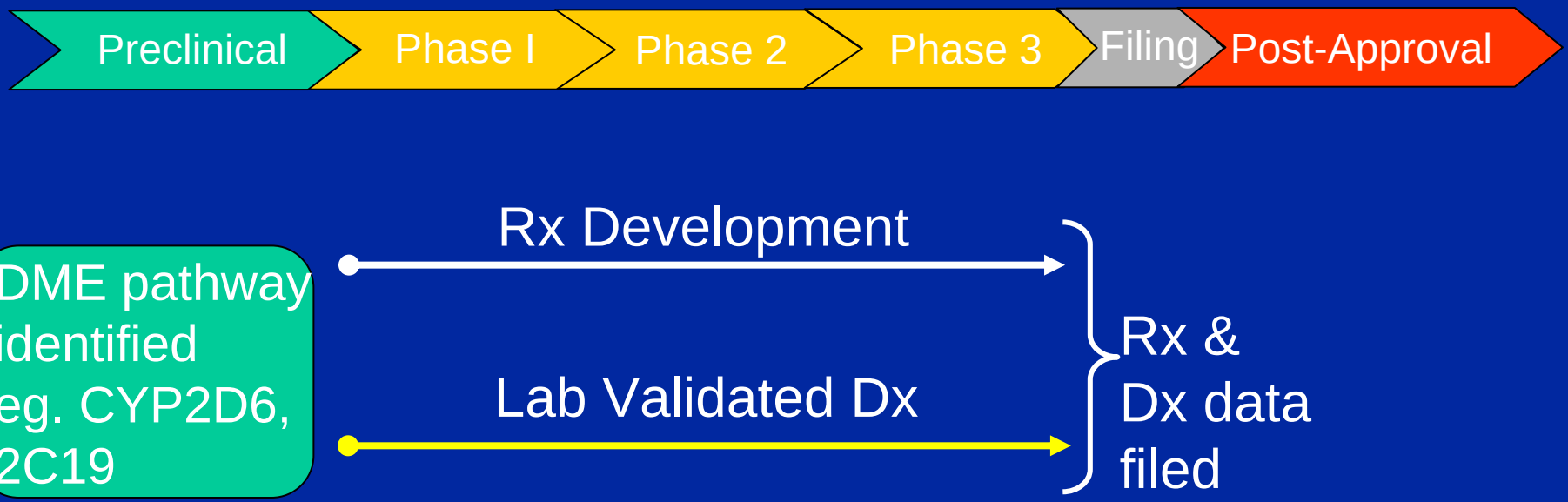
- Risks and benefits related to ‘Empiric Approach’
  - problems of trial and error
- Response rate to therapeutic
  - close 100% or close to 0%
- Relative costs
  - total cost of acquiring test information (time and money) versus savings from testing
  - perceived additional value due to reduction of patient uncertainty
- Relative predictive value
  - how well does the test work?
- Issues related to market acceptance/practicality
  - test platform availability, physician education and acceptance etc.

Coordinating Drug and Diagnostic Development

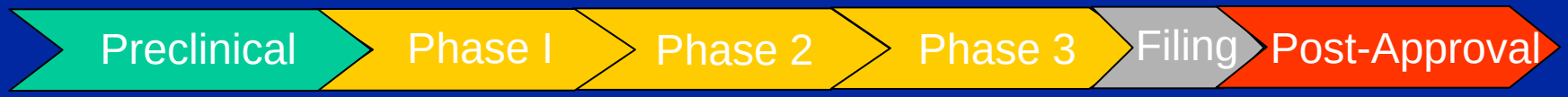
Challenges…

- Identifying the right biomarker early enough
- Developing Pharmacodiagnostic within Drug timelines
- Ensuring collection of enough of the right samples (definition of sampling conditions /storage/preparation etc.)

Validated biomarker



Biomarker identified…
In preclinical



-Identification of MOA
-Validation of PD marker in *in vitro* and animal models

Rx Development

Biomarker Assay Development

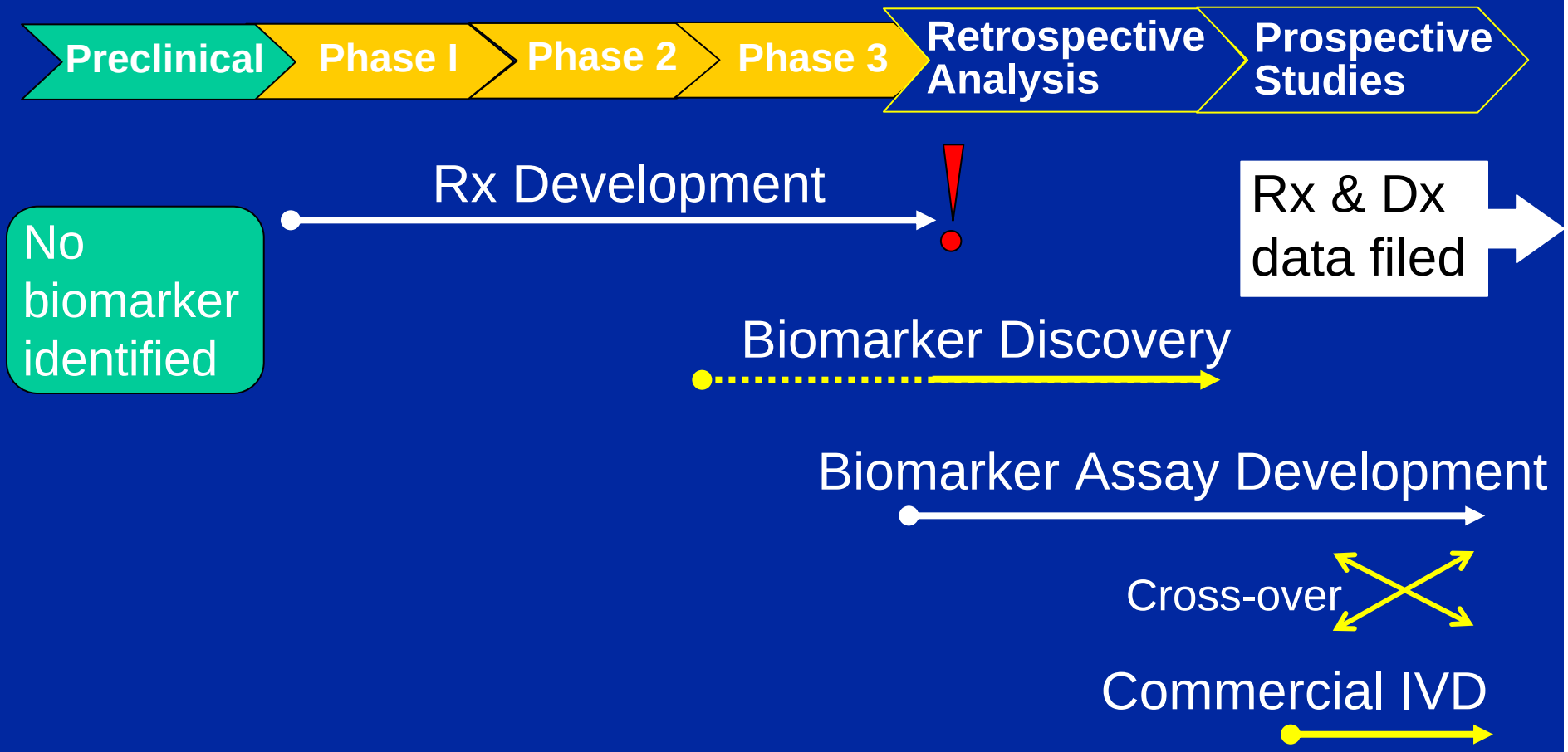
Cross-over

Commercial IVD

Rx & Dx data filed

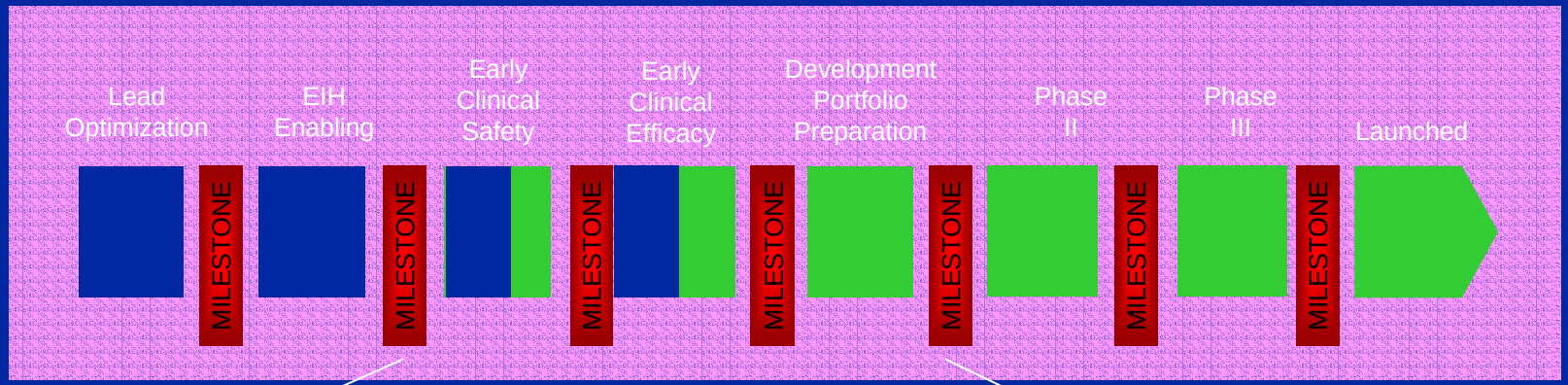
Eg. Herceptin

Biomarker identified post launch



Pharma development has to balance investments in biomarker work versus investments in new medicines

Biomarker impact on development

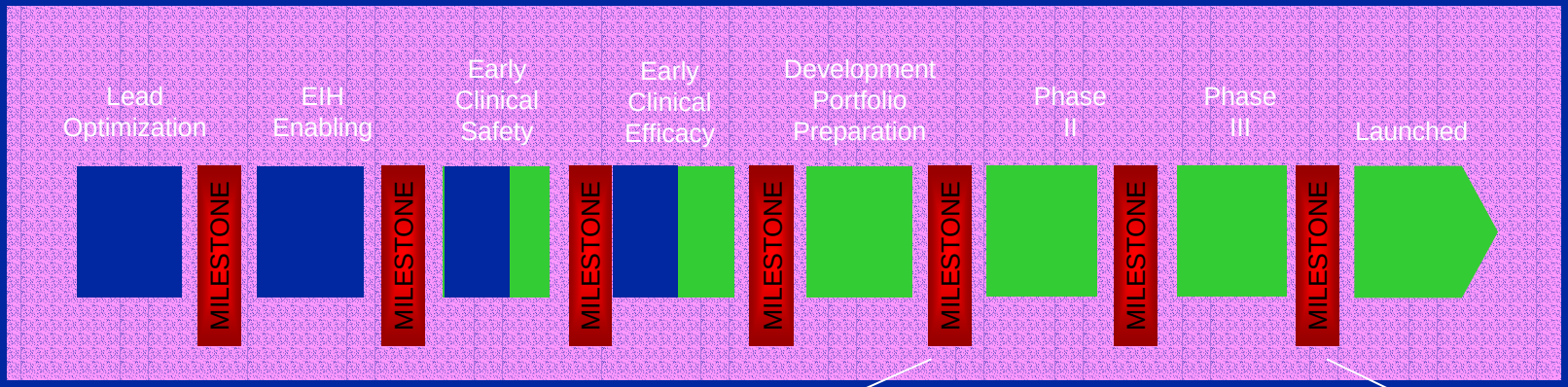


Early development

PD and Tox markers help with dose finding, dose regimen, and decisions on whether to progress a medicine or not or not

Prognostic and other disease markers correlate with disease outcome. They improve our ability to design informative trials and to interpret them confidently.

Biomarker impact on development



Late development

In a few cases, we expect to find therapy response markers which are predictive enough to allow us to recruit in phase III using these markers. This will simplify trials and allow medicines to get to the market which otherwise would not

In few cases we expect to be able to use surrogate markers in place of hard clinical endpoints that allow us to simplify and shorten trials. However, we expect that we will have to run post-registration trials to show an impact on the clinical endpoints.

We expect that an increased use of disease markers will allow use to run more effective/efficient trials and differentiate our compounds more effectively

We expect that these activities will lead to the development of innovative diagnostics, and improvements in the practice of medicine

Biomarker utility in Pharma Research and Development ❐

- **Biomarkers integral to effective Pharma R&D**
  - Key tool when faced with response heterogeneity
  - Allows dissection of diseases into underlying molecular etiologies
  - Increased information on Mechanism of Action, Proof of Concept and toxicology – aid in decision making on whether a compound should progress
  - Aid in dose-finding and compound differentiation
- **Highest utility in selected disease areas**
  - Oncology
  - Vascular and Metabolic Disease
  - Inflammation, Autoimmunity and Transplantation
- **Process changes necessary to realize benefits**
  - Biomarker plans ready in late discovery/early development
  - Increased investments in analytical tools and testing
  - Routine precautionary sampling and broader collection of plan specific samples

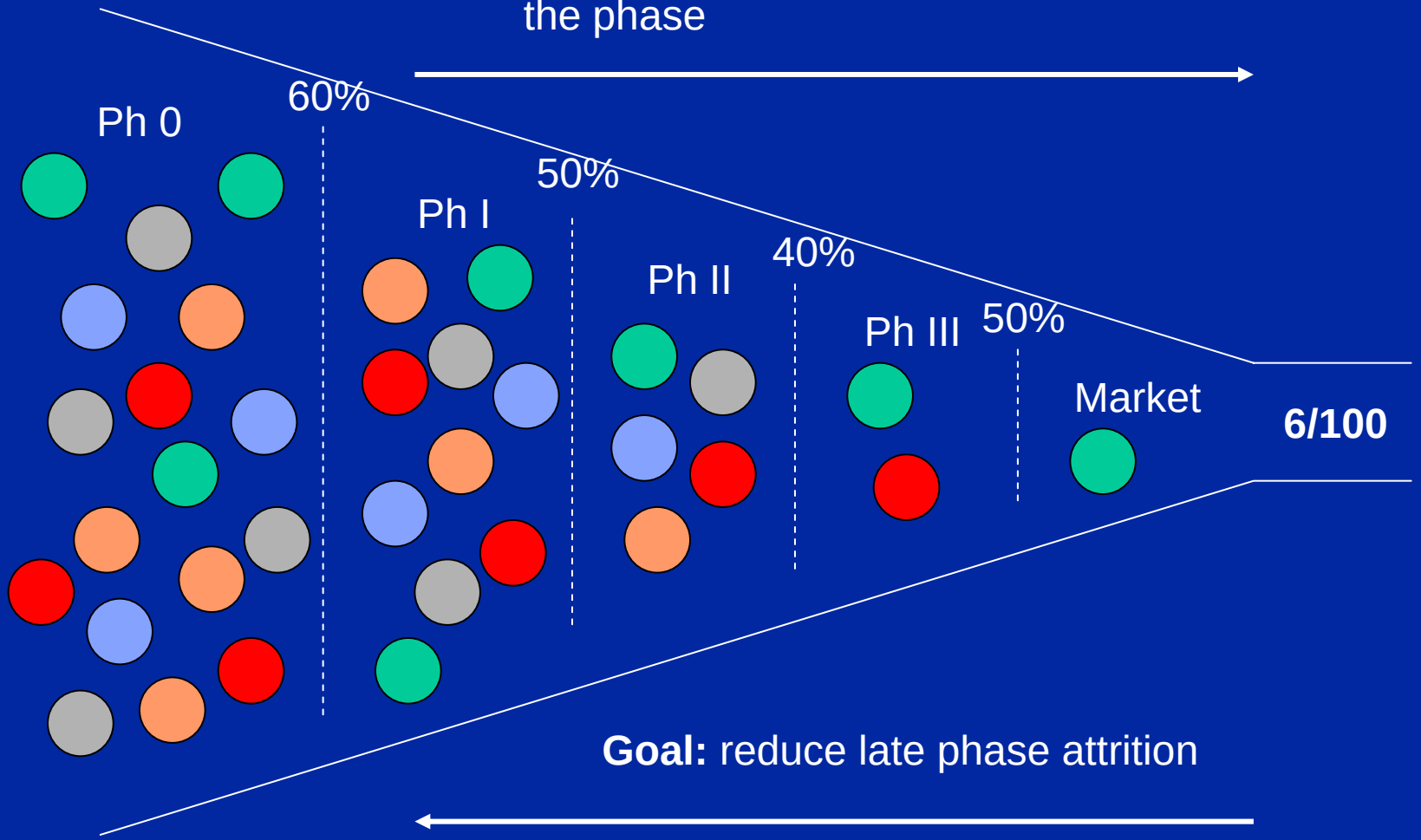
Impact of Pharmacodiagnostics on key Pharma Value drivers

- **Quantity:** Projects generated internally (Clinical Candidates, or CCS) or externally (any phase) neutral?
- **Quality:** Measured in success/attrition rates by clinical phases (0 – market) positive
- **Time:** Dwell time of project per phase negative
- **Cost:** Measured as cost per CCS for discovery; cost per clinical phase for compounds in the portfolio; upfront costs and milestones for external compounds negative
- **Project value:** Estimated sales per successful project positive

Adding predictive pharmacodiagnostics to drug development adds cost, uncertainty and complexity. Potential for value *creation* varies from project to project.

Effect of success rates on project assessment in Pharma R&D

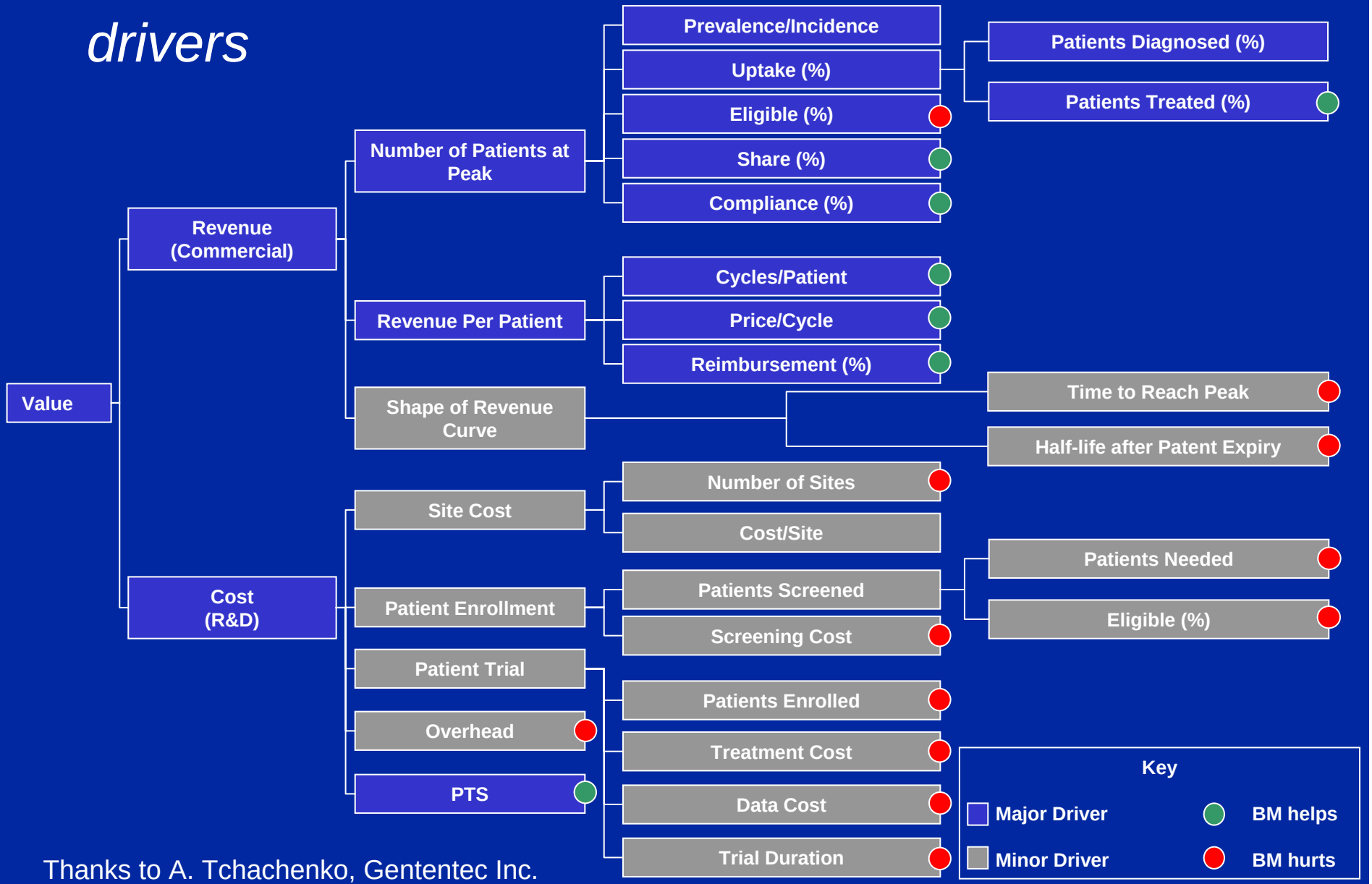
Costs per project: increase significantly the later the phase



Goal: reduce late phase attrition

Effects of PGx/PDx on Pharma Value flows

Business and R&D effects are main value drivers



Thanks to A. Tchachenko, Gententec Inc.

Personalized Medicine – economic rationale

Targeted therapies – (drug linked to a pharmacodiagnostic) can create additional societal value in at least four ways:

1. As the non-responders or poor responders are removed from the pool of users, their costs (monetary and negative utility) for adverse events are avoided.
2. Better targeting can lead to a greater volume of adoption by good responders (some of whom would not have used the drug previously).
3. Good responders may have improved compliance—and therefore additional net benefits— especially for long-term chronic therapies.
4. The improvement of predictability of outcome creates additional value for patients as they face less uncertainty.

What is the Value of an innovative medicine?

What fully informed patients would be willing to pay, based on:

- life years gained
- improvements in quality of life
- reduction of morbidity
- reduction in uncertainty

The Value of Innovation

How much are innovative medicines worth?

- WTP
- Societal value
- Innovator perspective

The Personalized Medicine Economic Value Proposal

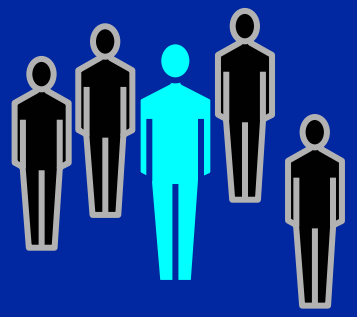
(To Patients, Company, Payer, Society)

- Decrease costs of adverse events
- Faster and more complete adoption
- Improved compliance
- Greater predictability of outcome

For Example:

NewDrug™ : 20% response rate

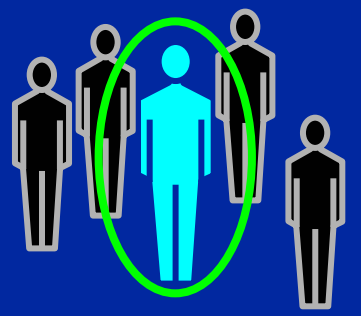
- Initial price estimate $1000 per year
- What are patients (payors) paying for?
- How much is it worth if you know you will respond (reduction in uncertainty)?
- What if there are side effects?



For Example:

NewDrug-test™ : response-prediction test

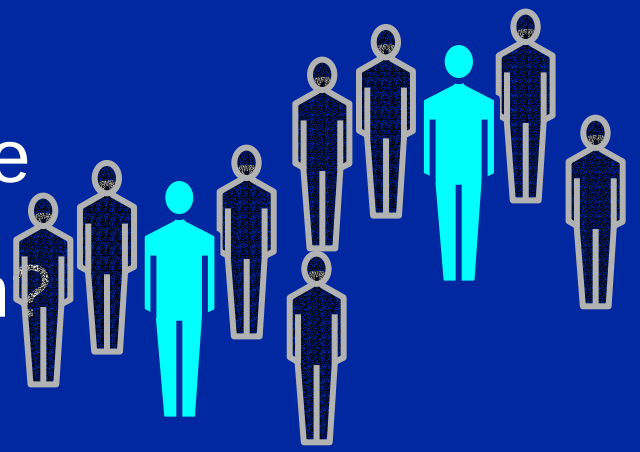
- Accurately predicts response to NewDrug™
- Based on readily-detectable biomarker
- Screen all patients, only treat those likely to respond

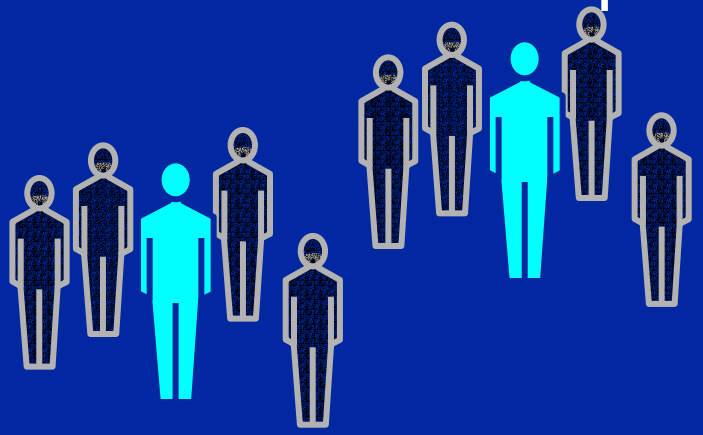


For Example:

NewDrug™ in combination with NewDrug-test™

- Targeted indication
- Differentiated, faster(?) uptake
- Improved competitive position
- What should the price be?





For Example:

NewDrug™ : 20% response; no side effects

No Test:	Perfect Test:
1000 Patients	200 Patients
WTP: $1000	WTP: $6000
Value Created: $1,000,000.	Value Created: $1,200,000.

Potential value of reduced uncertainty: $200,000

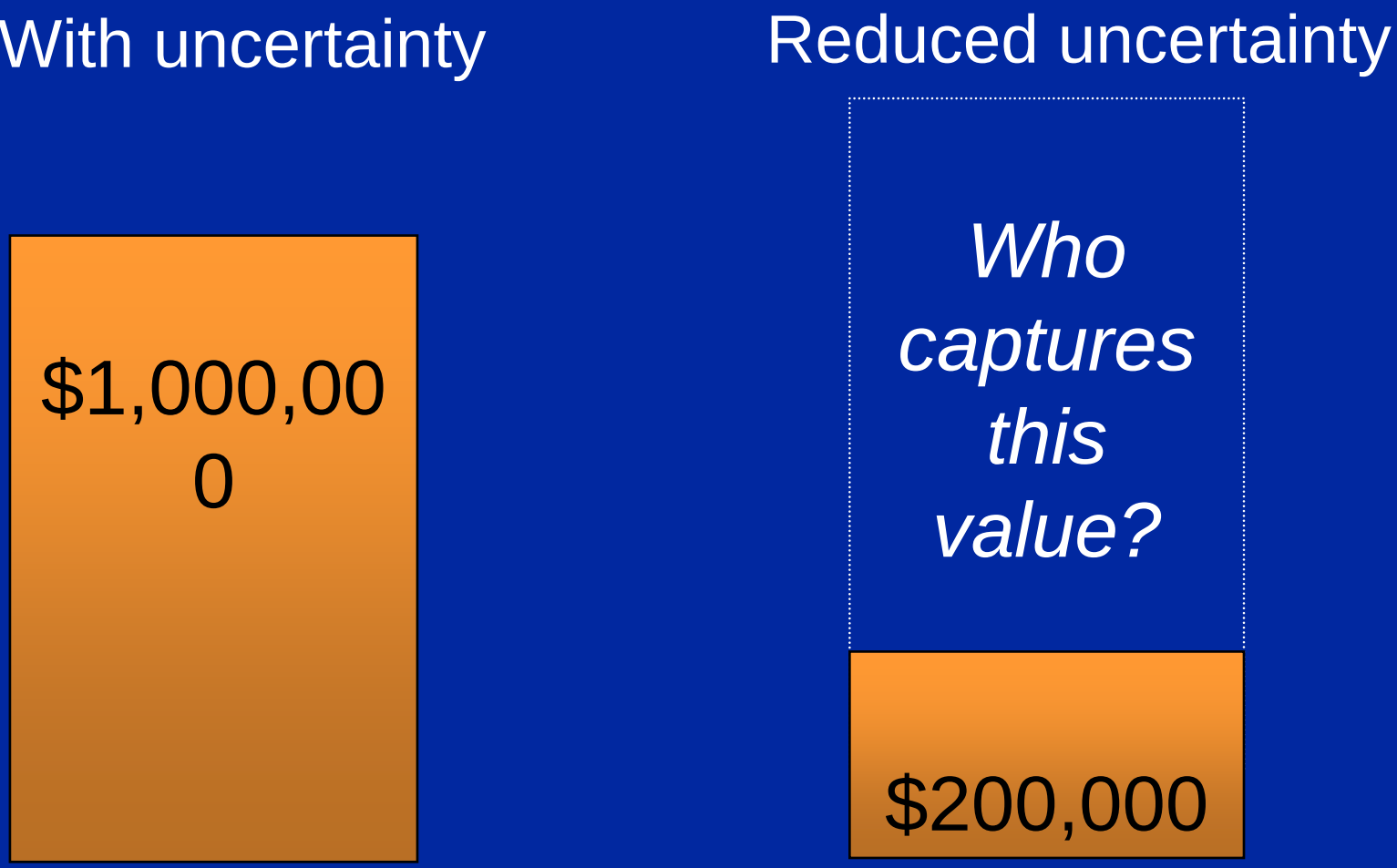
Value Creation: Reduced Uncertainty

Depends on manufacturer's ability to set price.

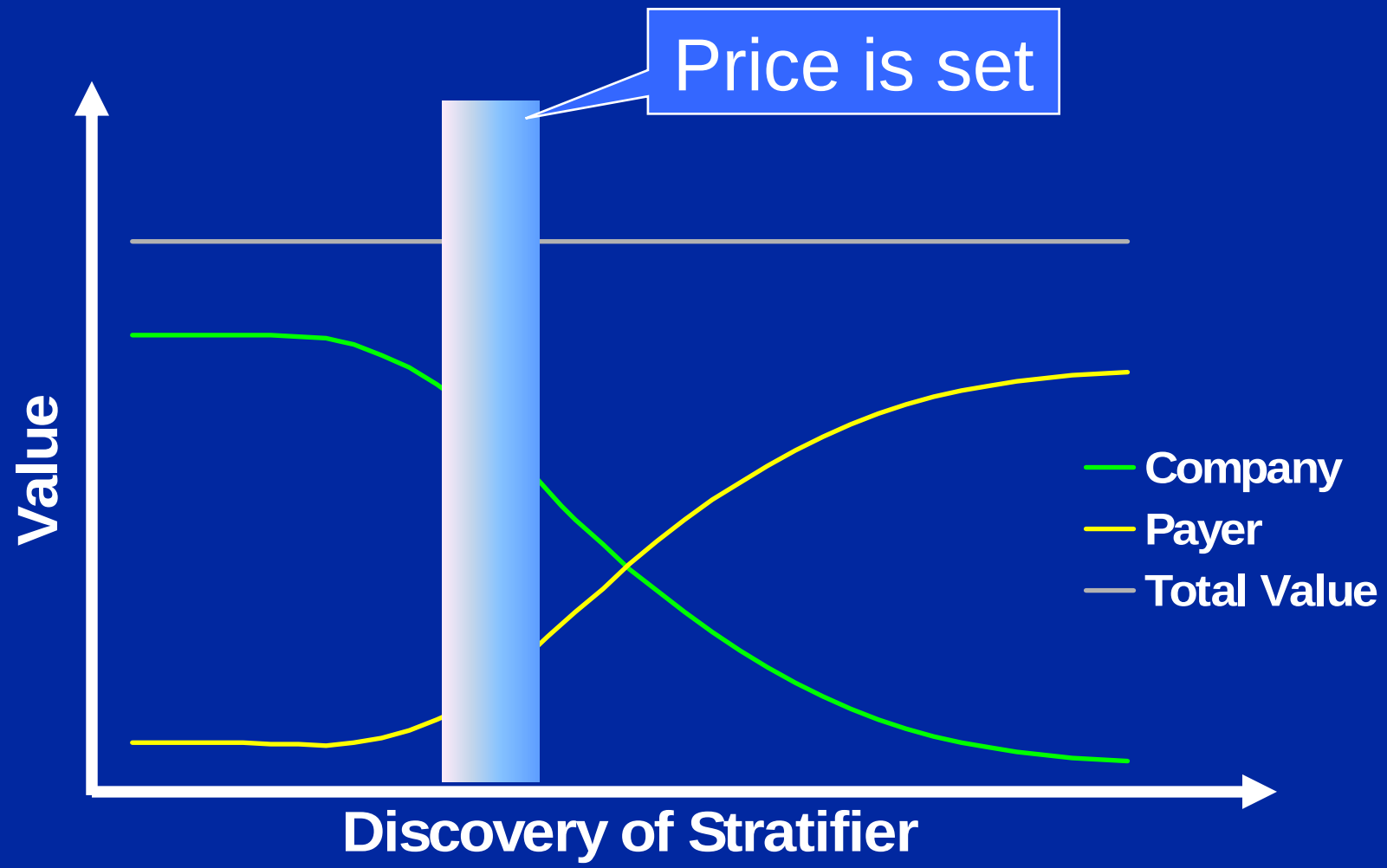
With uncertainty

Reduced uncertainty

What if the Pharmaceuticals manufacturer can't set the price?



Impact of timing



Diagnostics companies unable to capture this value

- Potential Diagnostics market:
  1000 patients per yr
- $1000/test = $1,000,000
- Current reimbursement schemes reward diagnostics insufficiently for value creation

Who Captures the Value?

Depends on:

- pricing and reimbursement conditions
- intellectual property protection
- competition
- timing

Key Messages

- Who will capture the value of a linked diagnostic-therapeutic depends on many factors, including pricing and reimbursement constraints, intellectual property protection, competitive market conditions, timing of entry, insurance market competitiveness, and the characteristics of the diagnostic and therapeutic products.
- Along with scientific and clinical considerations, whether, when, and how this value will be created is inextricably related to who captures it.
- Our view is that it would be wise to encourage value-based, flexible pricing and reimbursement systems to provide a level playing field that, together with IP protection, appropriately rewards diagnostic and therapeutic innovation

Summary

- Pharma companies recognize the societal value and scientific merits of Personalize Medicine concepts and are investing increasingly in biomarkers
- Finding and integrating predictive response markers into drug development is costly, complex and challenging – we do not expect to develop linked drugs/diagnostics on a regular basis in the near future – but there will be more examples
- The value impact of PM concepts on drug development varies from project to project. If a response marker is identified prior to drug launch, Pharma companies have incentives to work on the marker – this situation changes significantly post drug launch
- Incentives for diagnostic companies are limited by current reimbursement policies. Value based reimbursement would incentivize independent and co-operative (together with drug company) investments in this field.

Acknowledgements

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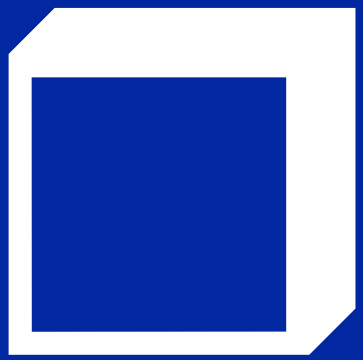

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