Challenges of Biomarker Development

(in Europe)

Disclaimer

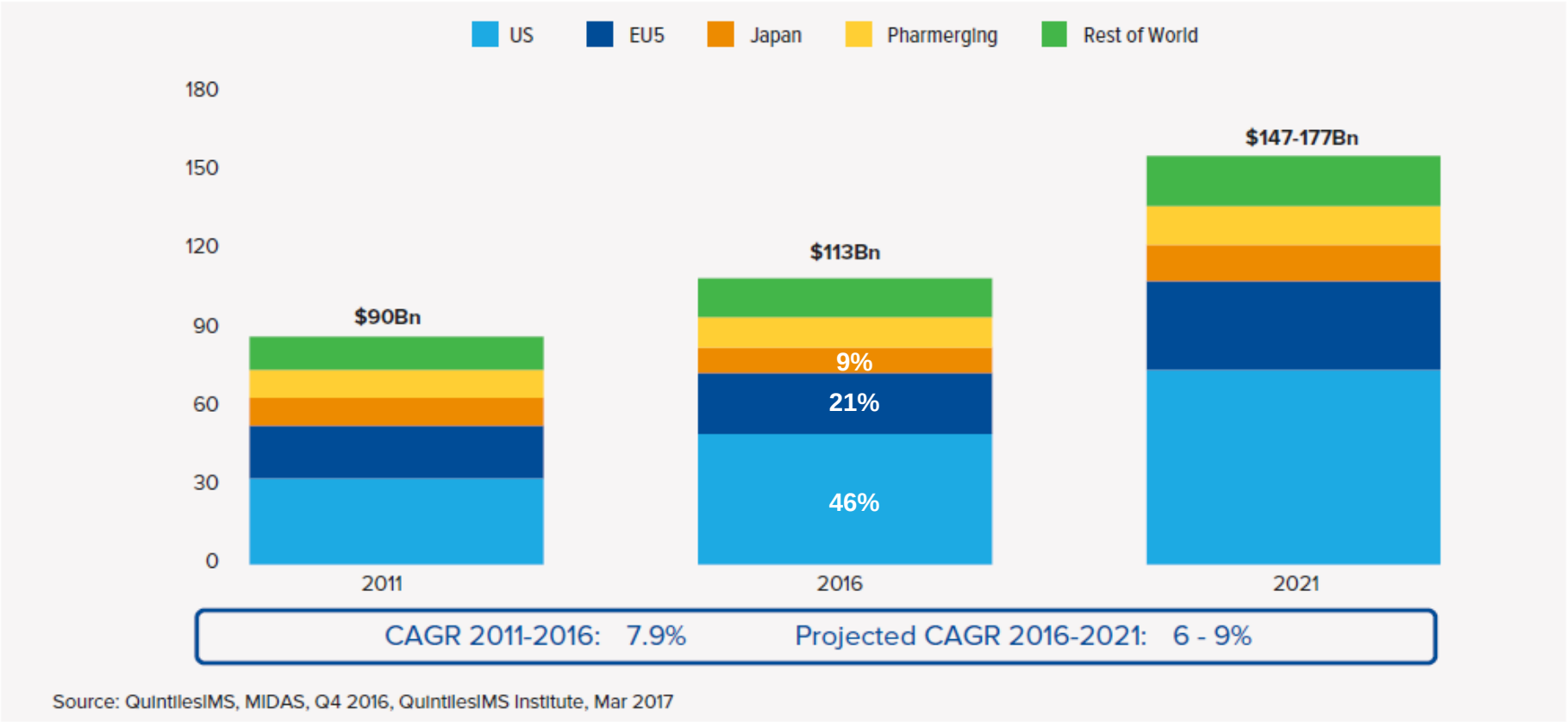
- I work for industry (diagnostics)
- We have worked with over 30 biopharma companies in the arena of biomarkers
- The presentation is my own and does not necessarily reflect the views of Biodesix nor those of our partners
- My biases come from working in oncology, particularly lung cancer

Biomarkers in general

- Lots of them
  - a naturally occurring molecule, gene, or characteristic by which a particular pathological or physiological process, disease, etc. can be identified
- But what we are interested in are those that can be used in clinical practice…which I will call 'tests'
- Why do we need clinically useful tests?
  - Giving the right therapy to the right patient
    - Maximizing outcomes, minimizing side effects and suffering

Global Oncology Costs- Financial Toxicity

Costs are increasing faster than the growth of our economies



Source: QuintilesIMS, MIDAS, Q4 2016, QuintilesIMS Institute, Mar 2017

Source: Global Oncology Trends Report 2017 (QuintilesIMS)

CDDF

Diagnostic/Biomarker Trends

- Targeted therapies are giving way to the next wave of treatments: immunotherapy
  - Where there are many biological factors to consider
- Liquid biopsy is gaining traction
- Available tools
  - Better & better; still dominated by sequencing
    - But the approaches are diversifying
- Significant investment in 'screening' and 'wellness'
  - Large markets attract large amounts of risk capital
  - Though not particularly in Europe
- Movement towards multivariate versus univariate
  - Which increases the complexity of the development process
- Machine learning / AI is finally coming to biomarker development
  - Though there is resistance to the 'black box'

General Challenges

- Discovery
  - Tools and reagents are expensive
  - Samples & data
    - As you tease out more complex biology you naturally need larger sample sets in order to effectively stratify
    - Sample curation is not uniform, particularly for post-hoc analysis
    - Well curated data is always a challenge
    - Having a biomarker strategy 'early' is not always an option
  - Managing variability / reproducibility
    - Batch effects; variable readouts; test variability; clinical annotation

General Challenges

- Development
  - Can be difficult to move from discovery to a logistically viable test
  - Regulatory requirements can be demanding
- Commercialization
  - Validation
    - Costs are high
  - Reimbursement
    - Very difficult
  - Market Penetration
    - Relatively slow, complex, and expensive
  - Competition, in many cases, can ride on the back of other's validation work

Challenges by Sector

- Many constituencies are involved in developing tests
  - each providing a unique benefit (or having a role to play)
  - each providing their own bias / challenge

Biomarker Constituencies

- Academics/researchers (purpose/biases)
  - Understanding biology in general to improve the understanding of disease etiology and progression
  - Biases / Challenges
    - Start from a biological hypothesis; known markers of relevance
    - Biased by the tool-set and approach they currently use
    - Herd effects
  - Counter trends:
    - Increasing amounts of biological data are leading to the use of machine (unsupervised/semi-supervised) learning

Biomarker Constituencies

- Biopharma/industry
  - Major force in driving the development of biomarkers
  - Facilitating the understanding of drug MOA & patient interactions
  - Bias towards the largest applicable population
  - Biased by the “in-place” infrastructure that enables testing
    - Novel / proprietary is the enemy of rapid adoption
  - Don’t like black box (machine learning) solutions
    - Introduces risk at the regulators and for adoption
  - Very careful control over clinical samples / data

Biomarker Constituencies

- Clinicians
  - Prognostic, predictive and monitoring tools
    - Informing prognosis, guiding treatment; monitoring resistance; dosing
  - Bias
    - Bias to treat
      - » “well tolerated”
    - Resistance to novel approaches
      - » Bias as to presumed causation (they are experts)
      - » Simply don’t believe black boxes; particularly ones developed independently of biopharma

Biomarker Constituencies

- Payers / Society
  - Containing costs (overall) and improving health
  - Inherent bias against paying
    - Use of institutional barriers hinders novel tests
  - Naturally risk averse
  - Historically diagnostics is a cost+ business
    - Very significant resistance from pretty much all constituencies to change this….

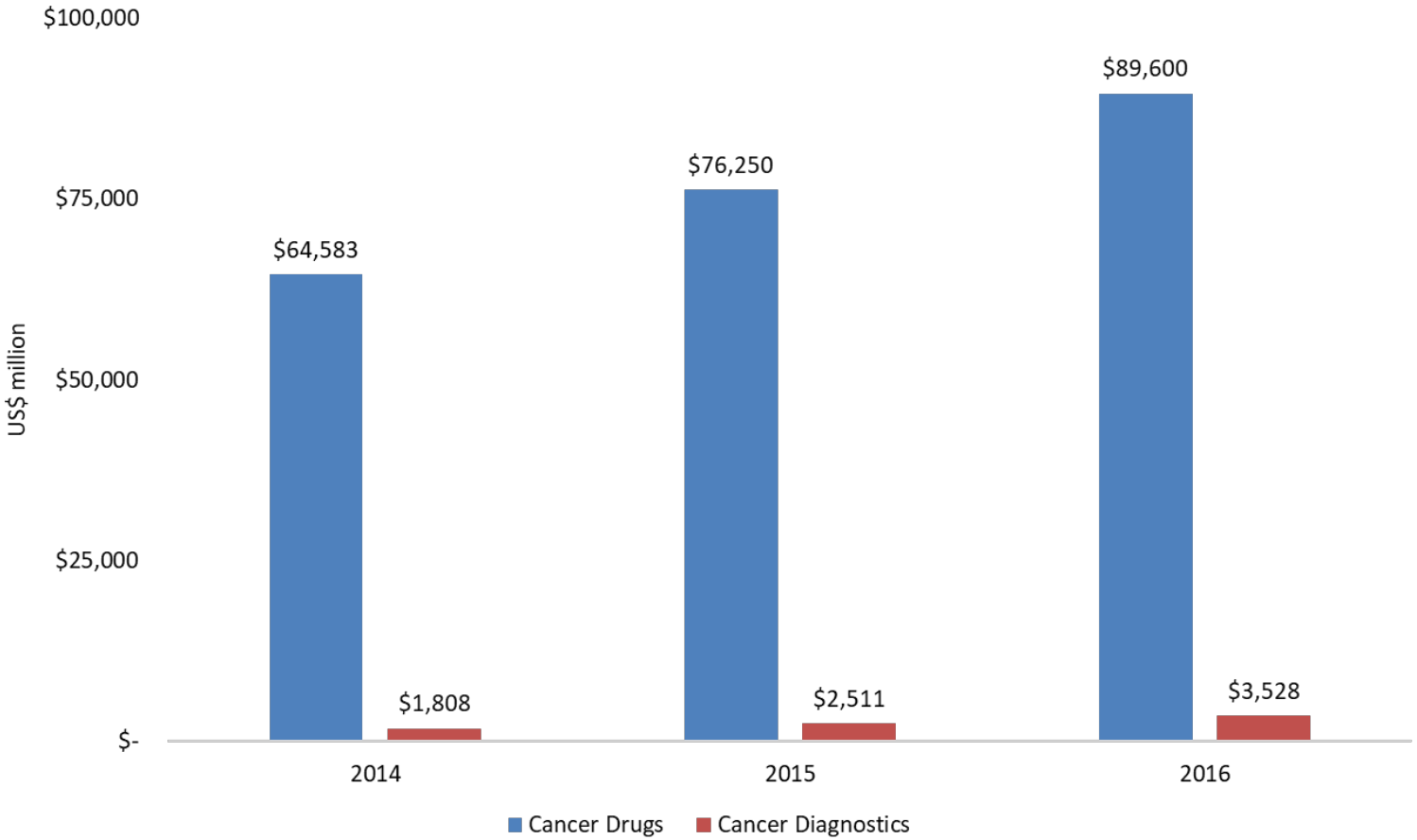
Biomarker Constituencies

- Patients
  - Ultimately the main beneficiaries of precision medicine
    - But often lack a voice
    - Patient advocacy is not well developed in Europe
  - Patient pay is rising
    - Genetic profiling (risk assessment, prenatal screening)
    - Wellness & monitoring
    - In certain geographies

Biomarker Constituencies

- Diagnostic Industry
  - Dominated by 'logistics' companies
    - Commodity business driven by margin considerations…not research (akin to generics)
  - Discovery industry is small
    - Miniscule funding compared to drugs
    - VC's stay away because the path to commercialization is so difficult
      - Even when you can demonstrate proof of principle
    - But this is where innovation can happen

Global Costs for Cancer Drugs vs. Molecular Diagnostics



Source: Combined (and calculated) data from Seo 2018 and Quintiles Global Oncology Trends (2017)

Discovery/Development is more important then ever

- It takes substantial focus and resources to create truly useful tests, particularly multivariate tests
  - So the focus is often on the largest markets given the constraints on pricing and reimbursement
    - But that may not be where the most value is
  - We need champions focused on specific unmet needs

Finally: Benefits of Europe

- Access to samples
  - Better rules and willingness to work with companies
    - Often keep control of samples from pharma studies
    - Can more easily share their own samples
  - Current regulatory hurdles are lower
    - But this may be changing

Drawbacks of Europe

- From Bench top to bedside?
  - Getting reimbursed is very hard…
    - Fragmented markets
    - Major resistance to value-based pricing
  - Locals dominate access and testing
    - And typically only want to add commodity products to their menus
    - Pharma wants companion diagnostics that are widely available

Opportunities

- Lower the costs
  - For discovery, validation
  - Broader support for funded clinical studies
    - Competition from pharma; reduce reliance on pharma $$s
    - More pressure on pharma to share samples/data
  - Unified approvals with broad support for reimbursement across geographies
- Improve the pricing for clinically useful and cost-effective products
  - Reward risk and innovation *when successful*

Summary

- The tools we have for probing biology are rapidly improving and provide fantastic promise
  - Improve patient outcomes; manage costs & toxicities
- *Useful* biomarkers are getting more complex (and better) and are more needed than ever
- But the hurdles from discovery through to delivery to the clinic are very high
- You need dedicated champions to make it happen
  - and they need mechanisms of support to overcome the hurdles