Biotech Perspective

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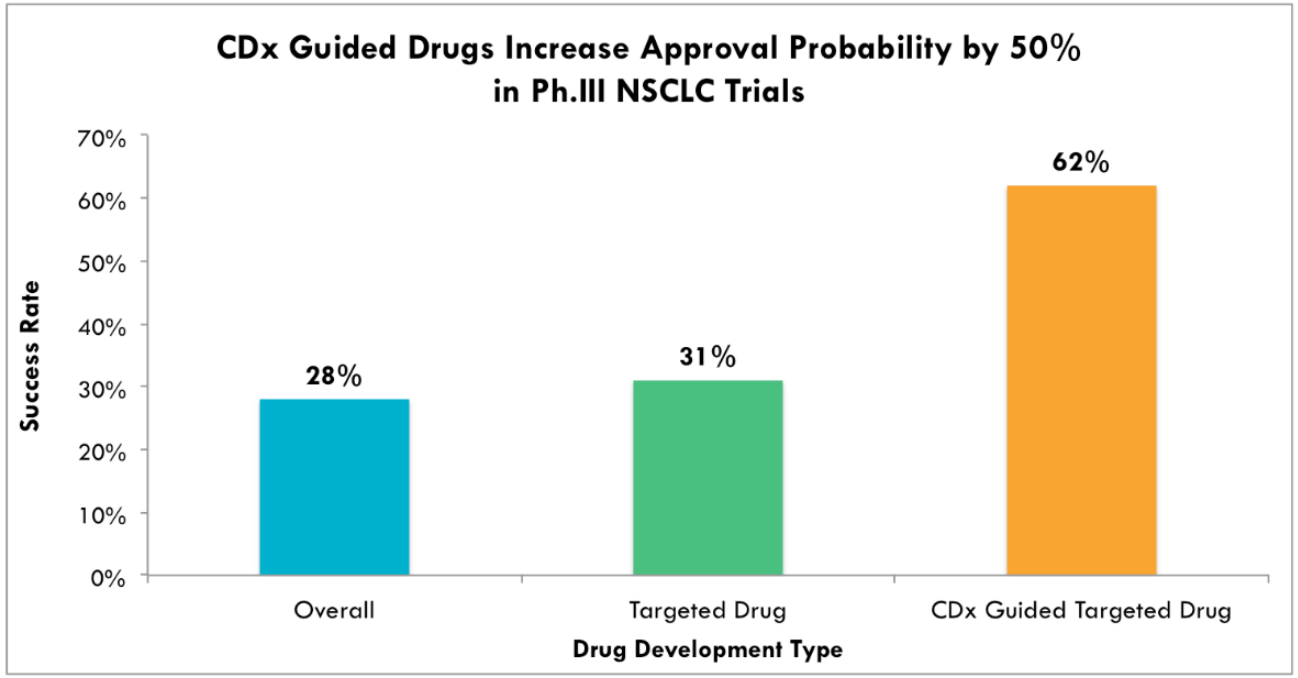
Benefits of Rx-CDx Co-development are Clear

- Improved cost-effectiveness
- Identify increasingly smaller sub-groups of patients benefitting from targeted therapy
- Increased Probability of Success in drug development
- Decreased clinical trial size requirements and time to approval
- Decrease overall cost of development



Source: ARK Investment Management LLC

Falconi et. al. JTO, Volume 9, Issue 2, February 2014, Pages 163-169

Growing Number of CDx Included in Approvals

- 27 FDA drug labels contain CDx requirement
- 26 are in Oncology/HaemOnc
- 12 are indicated in NSCLC
- Most approved CDx tests are single analyte assays
  - (1-Drug, 1-Target)
- NGS is emerging as a solution in malignancies with multiple CDx targets (e.g. Lung) but is challenged by market access & reimbursement limitations

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Rapid Expansion of IO Candidates Adding to Crowded Space

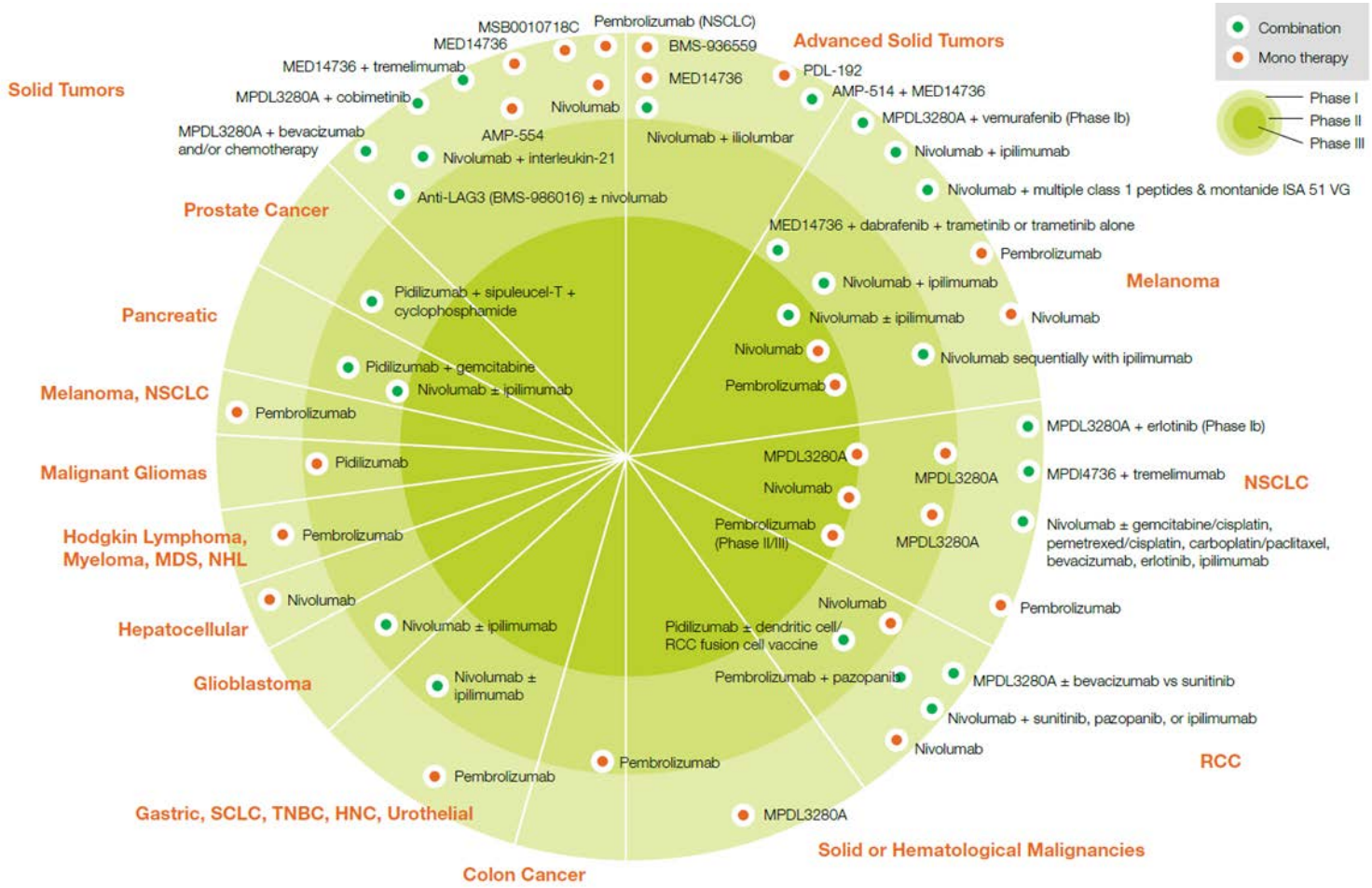
10 immune checkpoints targeting anti-PD-1/L1 are in development all following the same biomarker strategy

1 new drug

$2.5 billion

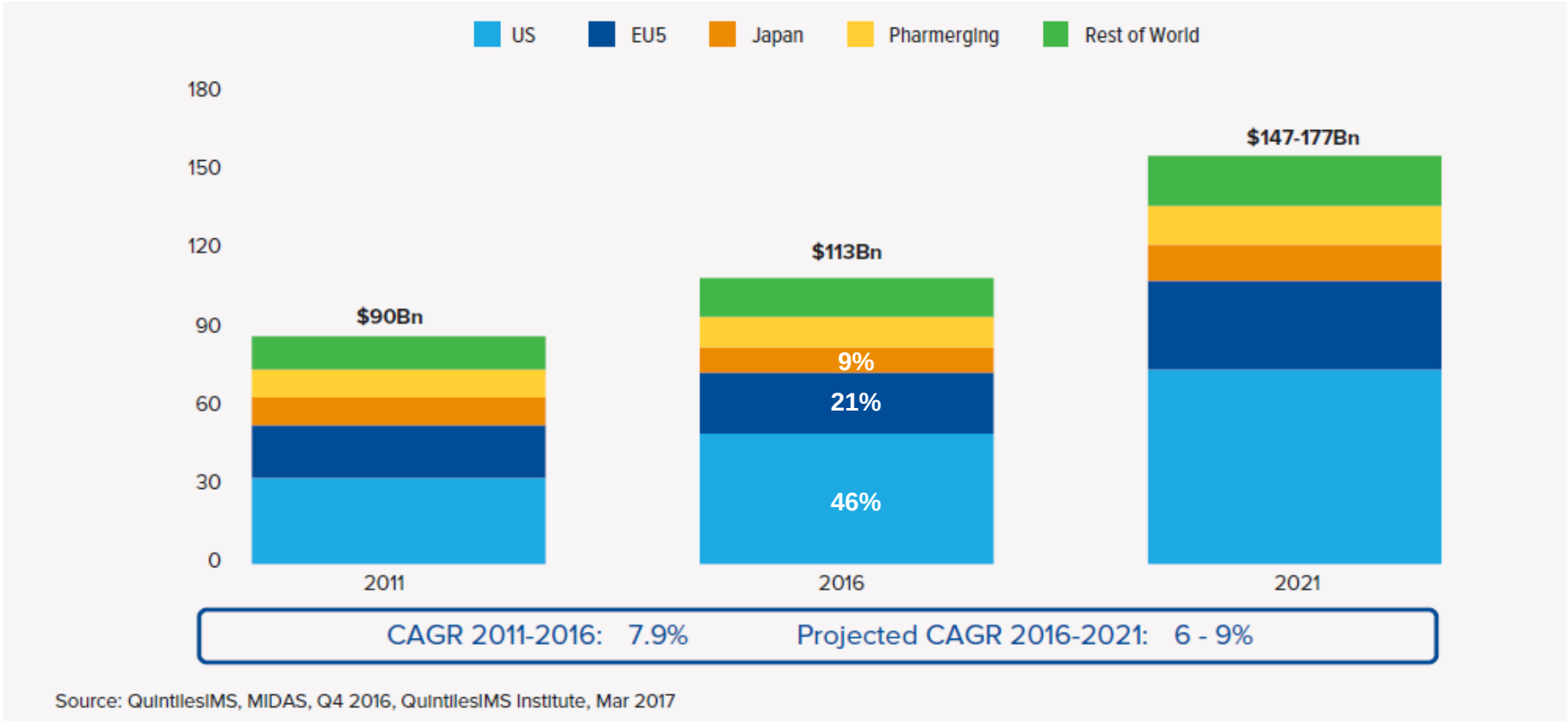
X 10 anti-PD-1 drugs

= $25 billion



Increasing Global Oncology Costs

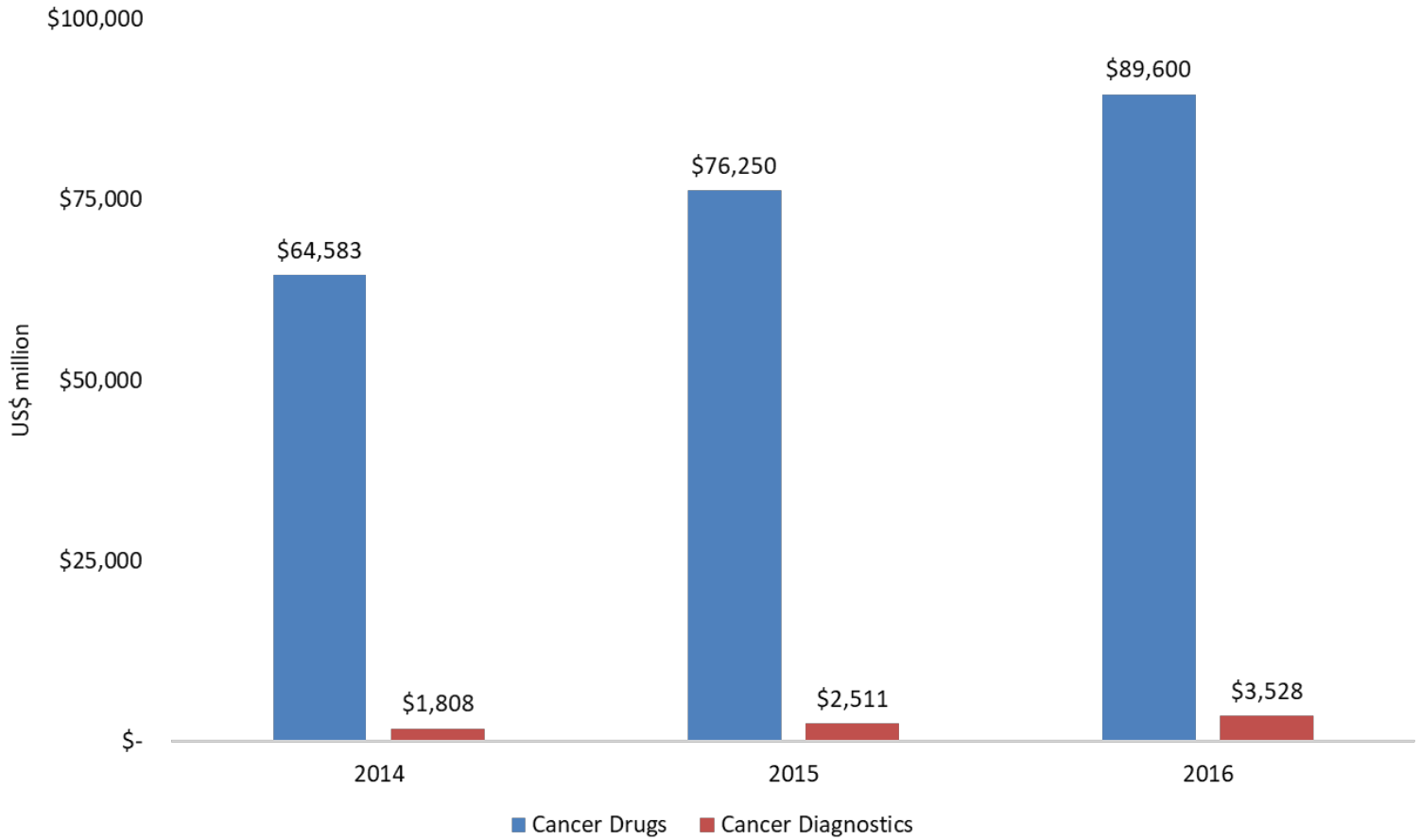
Costs are increasing faster than the growth of our economies



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

Source: Global Oncology Trends Report 2017 (QuintilesIMS)

Global Costs for Cancer Drugs vs. Molecular Diagnostics



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

Diagnostic Testing Continues to Evolve

Single Analyte

Make up the majority of CDx tests:

- IHC, ISH, PCR
- Lower Cost
- Largely decentralised
- High sample consumption for multiple test
- Commodity testing
- Highly vulnerable to LDT/Homebrew tests
- Minimal RoI for Dx Company

Multi-Analyte

Emerging solution where multiple targets exist:

- NGS, multiplexed PCR & IHC
- I.D. multiple targets with a single assay
- Requires more expensive capital investment
- Not readily accessible, drives semi-centralized approach
- Higher per sample cost, dependent on sample batching
- Slower TAT (NGS)
- More protection from commoditization & higher RoI
- Reimbursement challenges

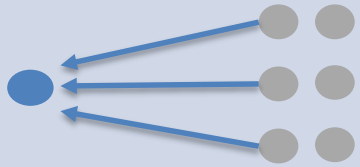
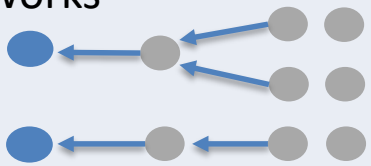
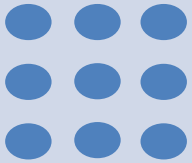
MAAA*

Novel solutions for interrogating complex biology:

- GEP (PCR, NGS, optical barcoding), Quantitative Proteomics (Mass Spec)
- Most commonly used in prognostic testing (Oncotype Dx), CDx tests are in development
- Complex workflow drives (semi-) centralized labs
- High development cost & per-sample cost
- Advanced logistics required to keep TAT low
- Good protection from commoditization and potential for RoI (if reimbursed!!)

*Multianalyte Assay with Algorithmic Analysis

Other factors are enabling new models…eliminating barriers

Test Network Strategy	Examples	Considerations
Sole-source 	• Myriad BRCA 1&2 for Lynparza • Tropism testing for Selzentry (HIV) • JCV testing for Tysabri (MS)	• Increased sample journey challenges, such as sample transport • Increased likelihood of test accuracy within a single performing lab • Possible cross-border commercialization challenges
Referral Networks 	• FISH testing for ALK	• May be a way to gain benefits from consolidation, but still leverage regional expertise • Increased sample journey challenges, such as sample transport
De-centralized 	• IHC for HER-2 • IHC for PD-L1	• Will likely improve sample to result speed and convenience for physicians • Increased risk of inaccuracy related to variable lab proficiency and test-specific experience

The decentralized business model minimizes logistical hurdles but adds quality/accuracy and timing risk

Adapted from Boston Healthcare Associates, Inc. Global Commercialization of Companion Diagnostics: Biomarker Strategies to Improve Market Access, 11/3/2018

The 1-Drug, 1-Test Paradigm Cannot Continue

- Multiple targets in each tumor type requires multiplexed testing
- Continuing advances in the Immuno-Oncology landscape will require more complex testing methods
  - PD-L1 IHC alone is insufficient, already demonstrated by varying cutoffs for different indications and antibodies
  - MSI & TMB add to the complexity, others on the horizon (IFN-γ signature)
  - Rule-out tests in development (Primary Immune Resistance, Hyperprogression)
  - Multiple combinations of IO therapies and chemotherapies inevitable
- MAAA CDx tests are on the horizon but need a clear path to reimbursement in Europe

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Highly Fragmented Approach to CDx Reimbursement

Country	P&R Process for CDx	Assessment coordination with Rx	Timeframe of assessment/ Reimbursement from Rx approval	Payer mix	Importance of innovative nature of Rx/CDx for access
UK	National centralized process (England, Scotland, Wales& NI separate)	Single integrated Rx + CDx process through NICE	Well-defined but Rx-centric and may take 1 year or longer	Mostly public; approximately 10% have supplementary private cover	Focus on Rx & overall cost
Germany	Ad-hoc process	Currently not coordinated but proposed legislation aims to provide synchronous Rx/CDx access	No delay if existing EBM code matches the CDx but may take 2 years or longer for a new EBM code	Mostly public; approximately 10% private	Focus on Rx
France	National and centralized but more than one process possible	Not coordinated except INCa, which tries to secure simultaneous access; unlike the non-synchronous CNEDiMTS assessment pathway	Variable, it can take several years before reimbursement	Mostly public but 90% have some complementary private cover	High

Highly Fragmented Approach to CDx Reimbursement

Country	P&R Process for CDx	Assessment coordination with Rx	Timeframe of assessment/ Reimbursement from Rx approval	Payer mix	Importance of innovative nature of Rx/CDx for access
Italy	Regional, decentralized	No formal process, some regions perform HTA	Variable across regions	Mostly public; approximately 15% have supplementary private cover	Moderate
Spain	Mostly regional and local level after national review	Not coordinated	Variable; Hospital reviews after national and regional decisions add to delays	Mostly public; approximately 13% have supplementary private cover	High

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Barriers to Innovation

- Multi-variate tests may address complex clinical dilemmas but are mechanistically more complex
  - Harder to explain to regulatory authorities & payors who are already challenged with existing CDx tests
  - Not likely to be ubiquitous on drug launch, requires centralized approach with advanced logistics
  - Usually come from innovative but smaller companies with limited international footprints
- Machine learning approaches add to difficulty with regulatory and payors submissions

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Drawbacks of Europe

- Getting reimbursed for more advanced testing is very challenging…
  - Highly fragmented markets with lack of consistent approach to HTA for CDx
  - Major resistance to value-based pricing for diagnostics
- Local reference/pathology labs dominate testing markets
  - And typically only want to add commodity products to their menus
- Pharma wants companion diagnostics that are widely available and have minimal risks
  - Drives reluctance to move towards novel testing

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Finally: Benefits of Europe

- Progress is being made
  - For 5EU countries, there's a lack of consistency but defined paths to reimbursement in the UK, with Germany and France making progress
  - Challenges are lower in some regions outside of the 5EU
- Access to samples
  - Academia willing to collaborate with Dx companies
    - Often retain control of samples from pharma studies
    - Can more easily share their own samples
    - Benefits development of prototype assays and stand-alone diagnostic tests independent of pharma
- Current regulatory hurdles are lower
  - But this is changing (IVDD to IVDR)

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Thank You!

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