# PHARMA READINESS FOR DIAGNOSTIC INTEGRATION 2017

## WHICH PHARMA COMPANIES ARE DX READY FOR PRECISION MEDICINE IN 2017? BENCHMARKING, FINANCIAL RISKS AND PREDICTIONS

Diaceutics

This document was prepared using the Diaceutics Method ®

# DIACEUTICS: WHAT WE DO

Diaceutics is a global group of experts from the laboratory, diagnostic and pharmaceutical industries. Our goal is to help pharmaceutical companies to integrate diagnostic testing into their treatment pathways.

We are empowered through a real-time flow of testing data from our worldwide laboratory network which we use to help our pharma clients understand and leverage the diagnostic landscape.

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# WHAT'S NEW IN THIS YEAR'S REPORT?

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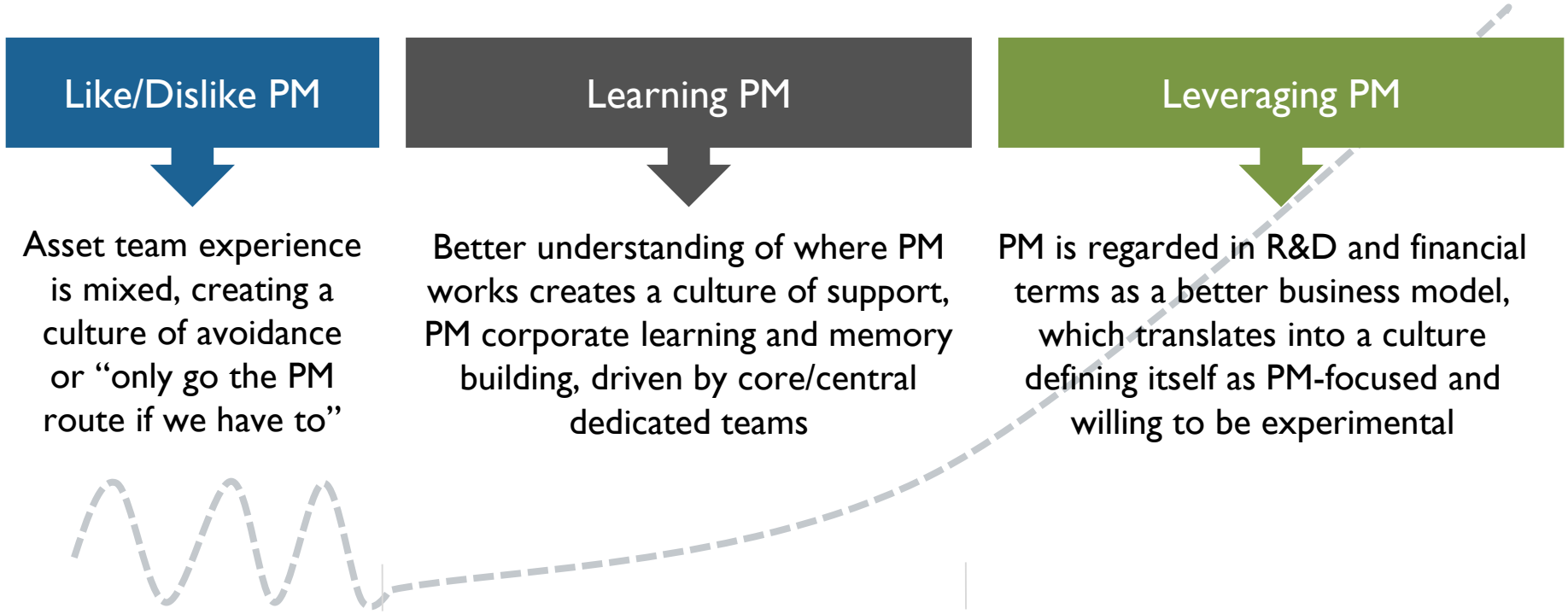
# EVOLUTION OF THE PHARMA READINESS FOR DX INDEX

- We have added one Big Pharma and eight mid-tier companies to the 2017 Pharma Readiness for Dx Index, applying analyses to 23 companies in total
- We have analysed the precision medicine (PM) credentials of over 1000 therapies on the market and in the pipeline to provide a 360° view of Dx-dependent therapy (Rx) assets.
- We continue to evolve and refine our Pharma Readiness benchmarking process. Specifically for 2017 we have:
  - Included analysis on therapy portfolios which are highly Dx-enabled, for example, hepatitis and diabetes.
  - Scored internal capability along our "Like it/Learn it/Leverage it" axis versus our previous year's PM-dedicated head count only. This reflects with more granularity our understanding of the impact of organizational structures on commercial performance.
  - Included Big Data and lab partnerships alongside Rx/Dx partnerships to reflect the evolution of PM beyond molecular testing and measurable impact of 'beyond the brand' strategies on 'propensity to prescribe' (P2P) rates (conversion of test positive results into prescriptions) regardless of the Dx technology used.
  - Ranked real-time experience with test launches versus previous years' channel control. This reflects the importance of 'commercial hands on the market' as a determinant of future success.
- In addition, this year's Full Report contains a series of specially commissioned opinion pieces looking at the key trends likely to shape the Pharma/Dx interface and PM marketplace in 2017 and beyond.

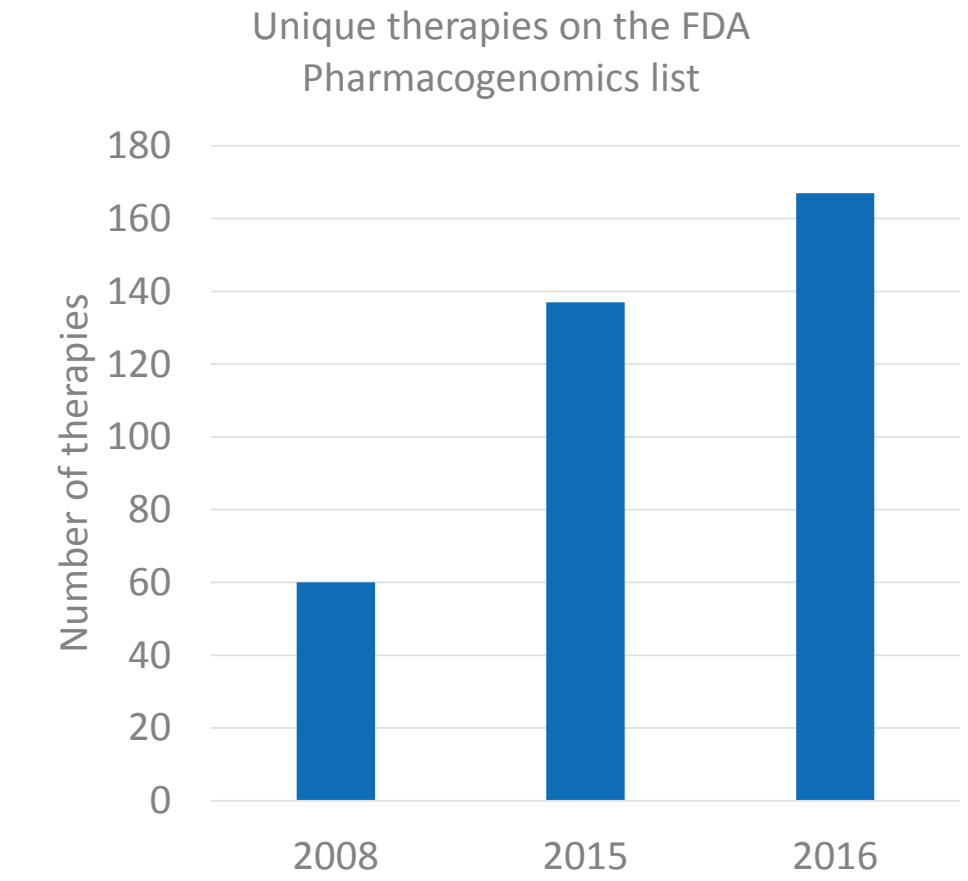
# FRAMEWORK FOR ORGANIZATIONAL EVALUATION: THE '3 Ls' OF PM INTEGRATION

- Based on our work over ten years and 200+ asset programs, we have determined that Pharma companies and their current organizational PM trajectories inside and outside oncology can be placed into one of three categories in our '3 Ls' scale: 'Like it/Learn it/Leverage it'.
- Companies are quantitatively ranked by an internal Diaceutics expert panel. The descriptions below provide an overall scoring guide.




Diaceutics Expert Insight: Our new PM catchphrase - like it, learn it, leverage it

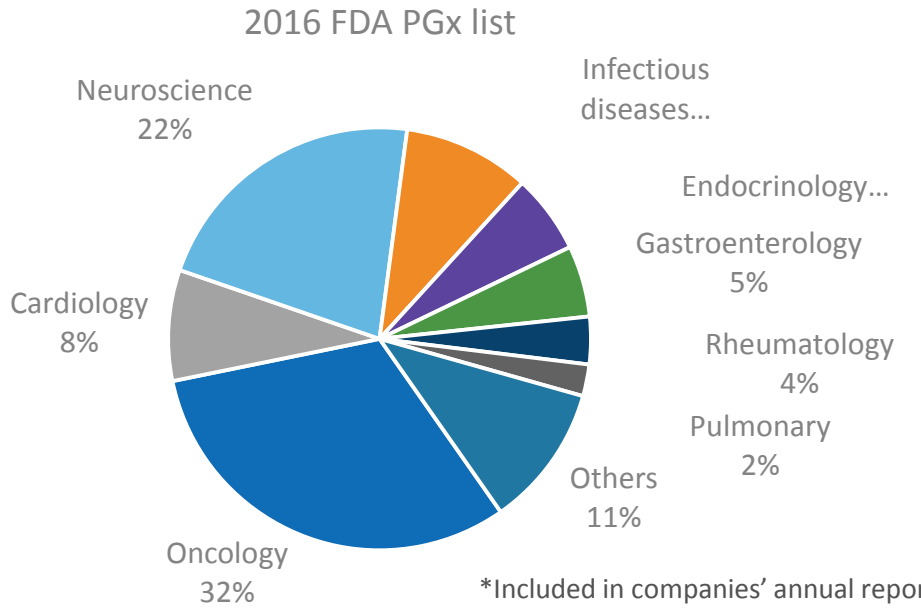
# THE FDA PHARMACOGENOMICS (PGx) LIST




FDA drug labelling may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

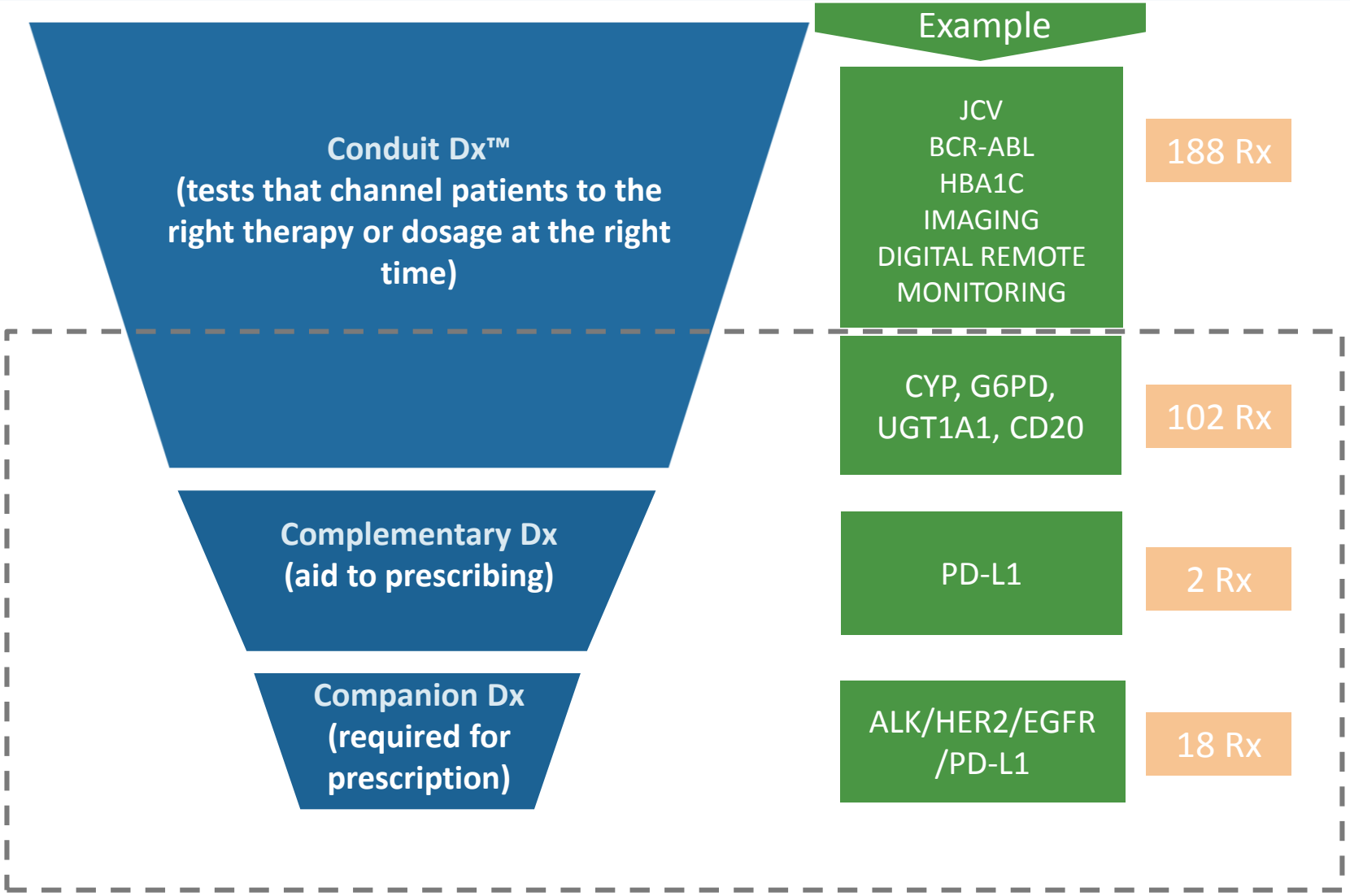
- The FDA continues to re-shape therapy labels alongside the evolving industry pipelines in all therapy areas.
- It has added 30 new therapies to its Pharmacogenomics therapy list in the 12 months since our last report in December 2015.
- Examples include recent launches such as Alecensa (ALK), Lynparza (BRCA) or Keytruda and Opdivo (PD-L1), as well as updates to the labels of established therapies such as escitalopram (CYP2D6), rosuvastatin (SLCO1B1) and sevoflurane (RYR).
- 87 leading brands* have now incorporated an FDA-mandated Dx citation across multiple therapy areas.
- Oncology remains the single most numerous indication on FDA PGx list.




*Included in companies' annual reports

Source for 2008:: http://journals.plos.org/plosone/article/asset?unique&id=info:doi/10.1371/journal.pone.0007960.s001
Source for 2015/16: http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

# DX ENABLEMENT BEYOND PHARMACOGENOMICS: OUR '3 Cs'




- We suggest that in addition to Companion and Complementary Diagnostics, it is time for a third C – **Conduit Diagnostics™**. This means our legacy definitions of PM do not reflect the true Dx impact on therapy revenues and patient share. It also relates to the FDA's introduction of a second category of tests proximate and critical to therapy prescribing.
- Conduit Diagnostics™ is our suggested name for tests that channel patients to the right therapy or dosage at the right time, regardless of the technology platform used.
- Pharmaceutical companies pursuing partnerships in this area are thinking beyond the brand and molecular Dx.
- Our broader PM list analysed across our 23 target companies therefore includes analysis of ALL 3 Cs.

# Precision medicine: Looking for disruption in the wrong place?

*The pace of precision or personalized medicine (PM) right now is dizzying. The technology forecasters (Diaceutics included) warned everyone of the coming tsunami of pipeline precision therapy assets likely to be dependent upon an actionable biomarker. We also recognised that the affordability of genetic and molecular clinical disease profiling and the advance of health-tracking wearables such as phones and watches, will all eventually collide in cancers and diseases beyond oncology to deliver more precise intervention and better outcomes. Somehow this all seemed like light years away. Yet 2016 has been a landmark year for PM, with a big rise in PM market-related events being recorded in the first half of the year alone.*

*We will be the first to admit that we still need to join the dots between technologies to optimize the PM market. The regular misalignment of companion diagnostic adoption versus potential targeted therapy demand is a case in point and something we have spent ten years trying to change. To this we can add that sub-optimal education levels across stakeholders (laboratories/physicians/patients) seldom support the perfect supply and demand curves expected in mature healthcare markets and, of course, the uncertainties of the still unfolding science of PM in areas like immuno-oncology create gaps in our understanding of how to integrate PM into the patient pathway.*

*Clearly no single event will push PM over the edge towards its long promised transformation of healthcare delivery, but the sheer momentum of industrial, clinical and research activity being pointed away from imprecise towards precise medicine is without doubt accelerating the timeframe for us all.*

*Clayton Christenson in The Innovator's Dilemma called it right. The Harvard Business School professor points out that disruption will not come from the PM delivery chain - healthcare markets across the world are rapidly embracing and enjoying the benefits of PM - but from the inability of the suppliers (the innovators) to reinvent their business models fast enough to keep up, let alone lead the PM trajectory.*

*We should all (ourselves included), therefore, be aware that we risk being passed by as the pace of PM quickens.*

# WHAT'S HAPPENING IN THE MARKET TODAY?

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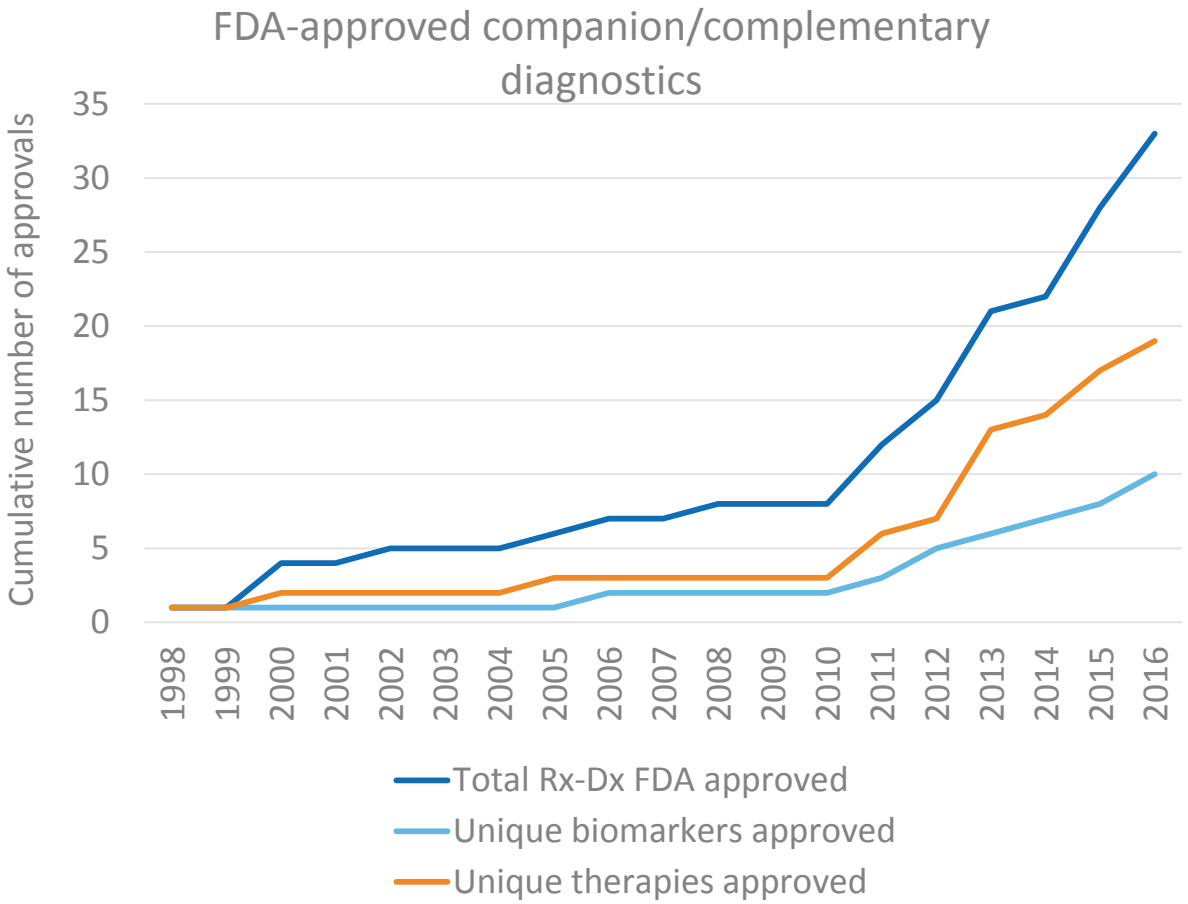
# THE UPWARD TREND IN PM CONTINUES

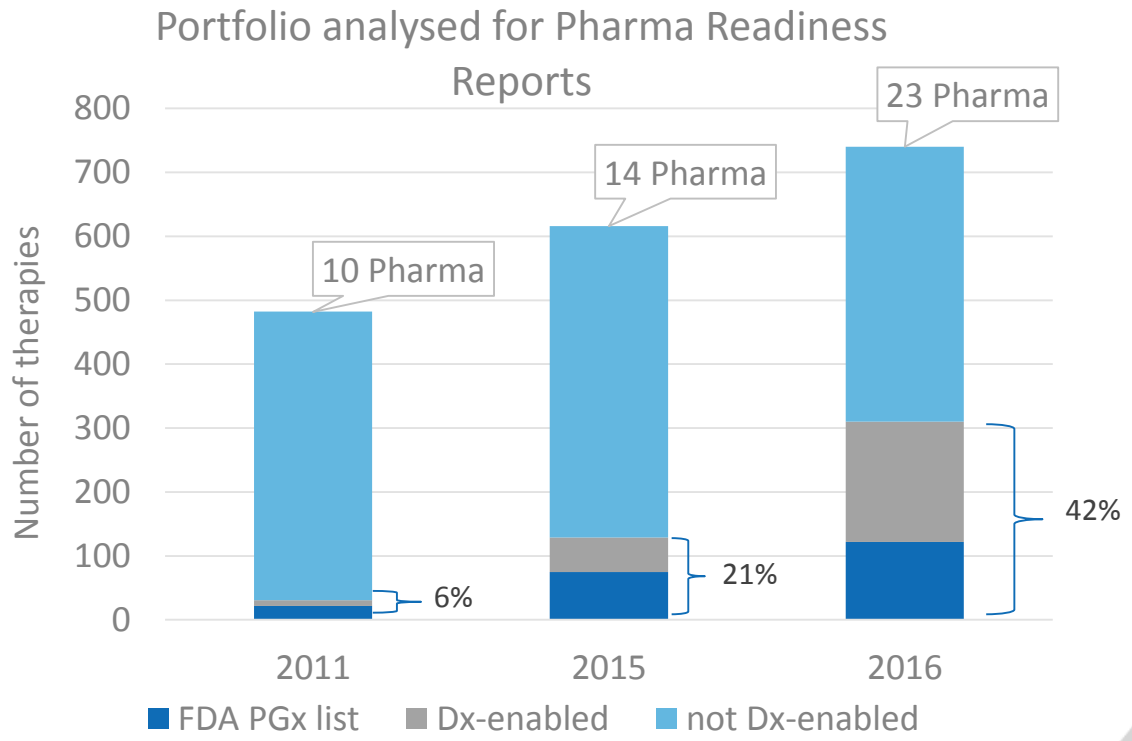
## FDA PHARMACOGENOMICS VIEW



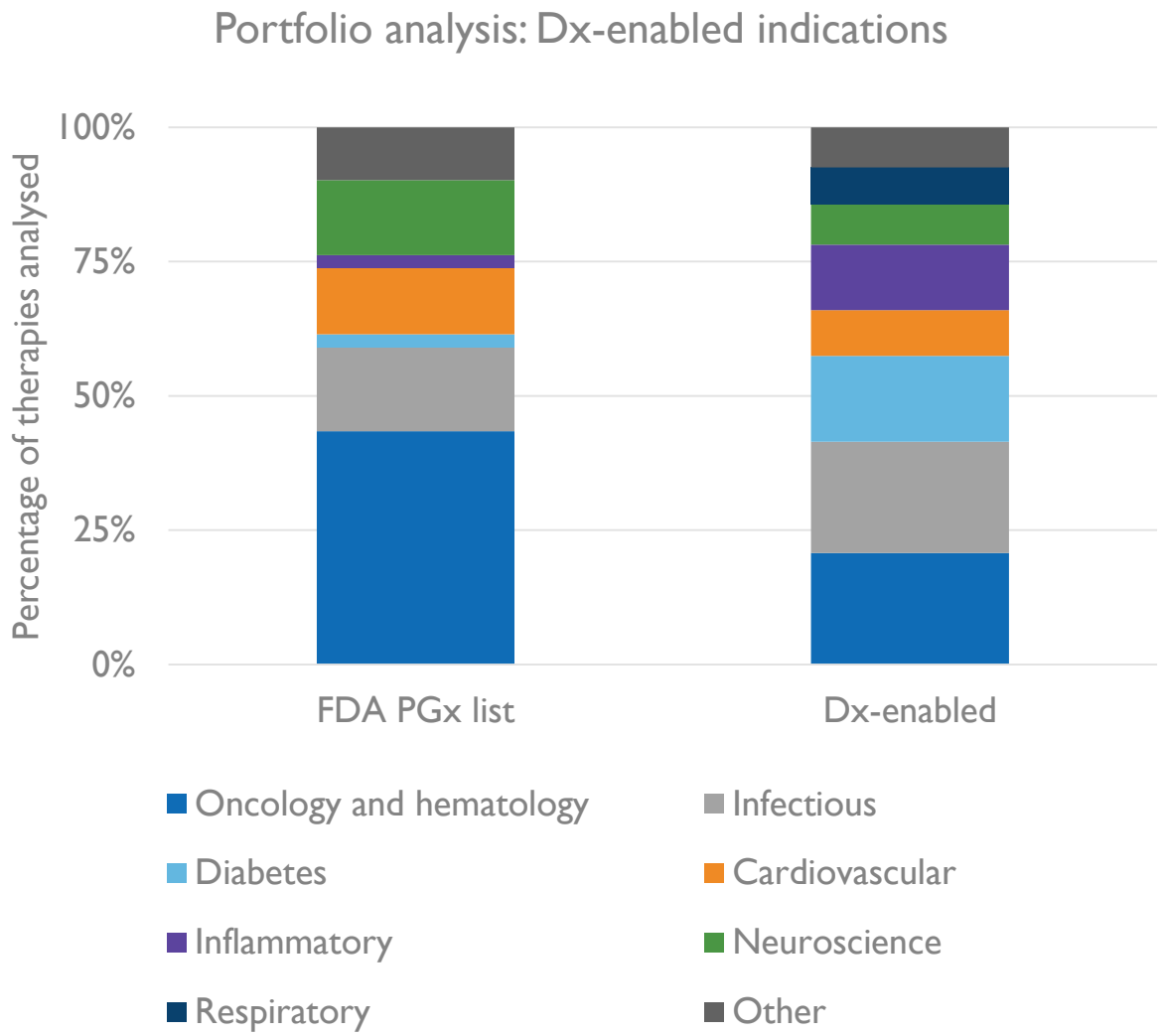

- We have witnessed another busy year for companion/complementary diagnostic launches with a total of six Rx-Dx combos approved, including two new therapies (Tecentriq and Venclexta) and two new biomarkers (PDGFRA and del17p).

## OUR '3 Cs' VIEW

- Using our '3 Cs' definition, in 2016 42% of 700+ therapies marketed by our 23 companies are biomarker-enabled in some way.
- This is up from 21% in 2015 – a result of our expanded Dx definition, new launches, new companies added and FDA label expansions.

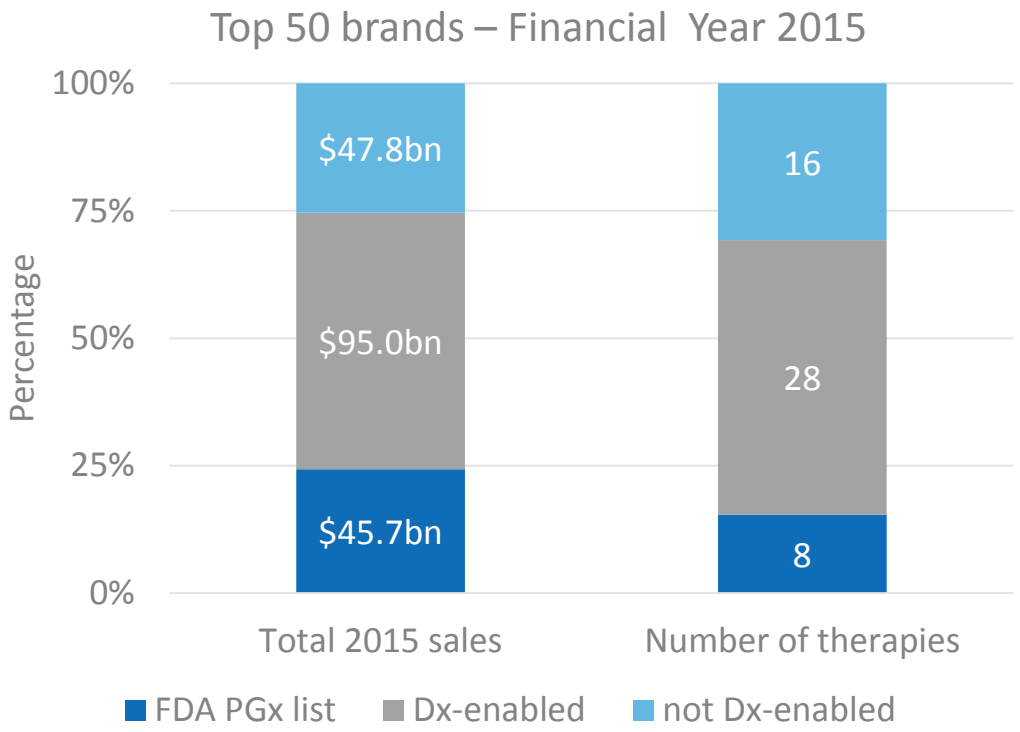


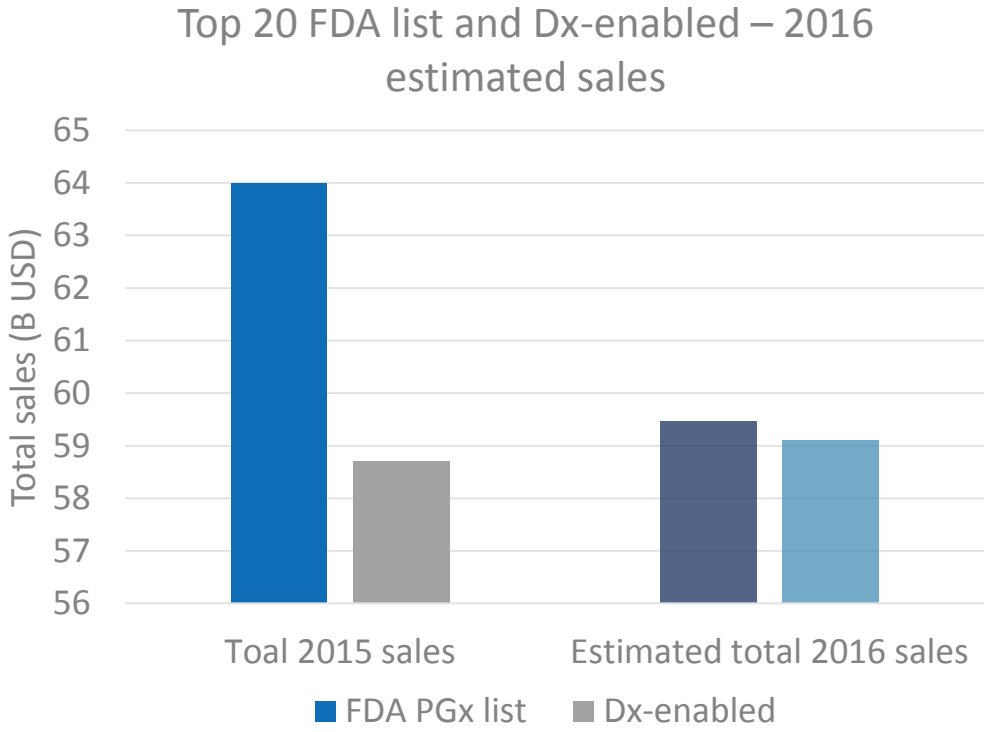
# NON-ONCOLOGY INDICATIONS INCREASINGLY DX-ENABLED ACROSS BOARD




- We increasingly see non-oncology indications exploring biomarker strategies and employing broad Dx strategies across the board.
- In diabetes, Hb1Ac monitoring is required for 30 therapies currently on the market, with many competitors actively researching response biomarkers for SGLT2 and DPP-4 inhibitors.
- In infectious diseases, genotyping of pathogens and dose adjustment due to CYP polymorphisms are the leading examples of Dx-enabled therapies.
- Across inflammatory diseases, we see monitoring for latent infectious disease (JCV, TB) and neutralizing antibodies, and use of imaging and digital biomarkers as key emerging strategies for personalized treatment.

# 70% OF THERAPY SALES ACROSS OUR 23 ARE DX-ENABLED



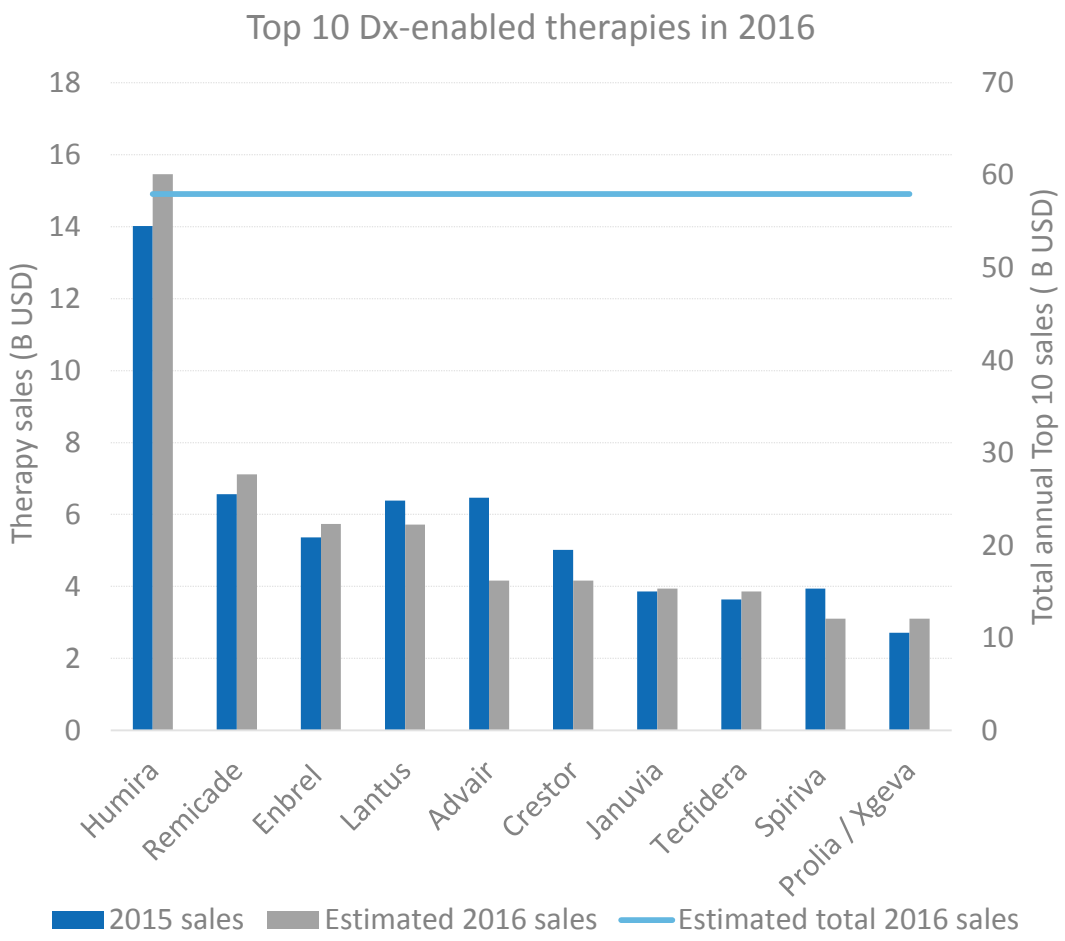




- 36 of the Top 50 selling pharmaceuticals in 2015 were on the FDA list or Dx-enabled, and brought in over $140bn in revenue.

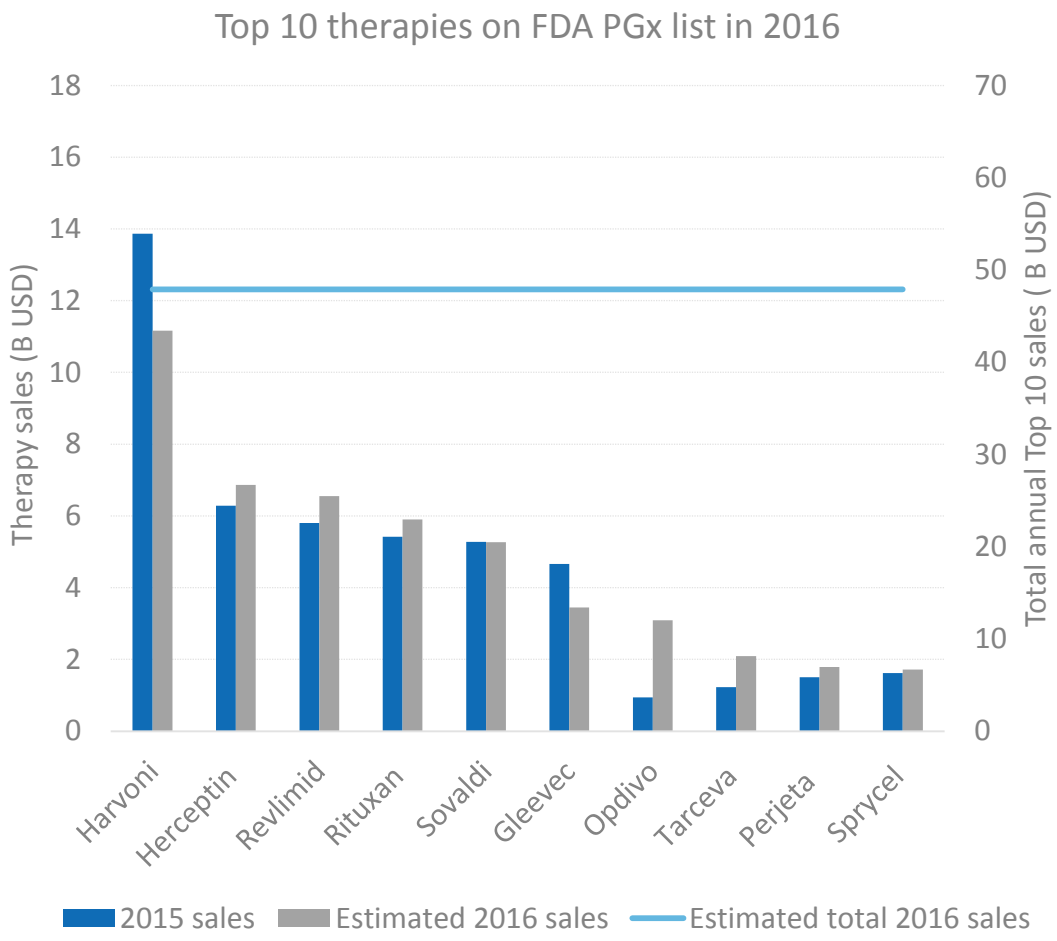
- Based on 2015 sales and H1 2016 sales, we have estimated income from the Top 20 therapies on the FDA PGx list and Top 20 Dx-enabled therapies.
- We expect a drop in revenues from FDA PGx therapies due to generic erosion in older therapies.
- Dx-enabled therapy sector is expected to grow steadily.

# DX-ENABLED THERAPIES INCLUDE MULTI $BN BLOCKBUSTERS

## OUR '3 Cs' VIEW




## FDA PHARMACOGENOMICS VIEW




We estimate that revenues from the Top 10 Dx-enabled therapies will exceed revenues from the Top 10 therapies on the FDA PGx list by $10bn (based on figures from H1 2016).

## Segmentation via testing is the new black

*Diaceutics is often asked by clients for the 'so what' impact of precision medicine (PM) on their targeted therapy launches. This has mainly been answered by communicating the importance of getting the basic diagnostic market infrastructure right in order to support seamless therapy prescribing. We also explain how reimbursement gaps, sample management delays and poor stakeholder education can repeatedly beleaguer companion diagnostic launches and indirectly hold back therapy prescribing. Each novel biomarker has its own rocky road to easy clinical access so we don't expect these issues to go away any time soon.*

*Simply put, the 'so what' impact for many target asset launches is that unless you focus early and diligently on building an efficient diagnostic market architecture, therapy access with the ensuing clinical and financial impact will be reduced. Our own estimate of the first PD-L1 launches in 2015/2016 suggests the impact of insufficient investment in PD-L1 testing infrastructure has cost pharma $770m in lost revenue on one indication alone in its first 18 months.*

*However, there is now an argument for moving our 'so what' impact horizons past the infrastructure 101s to the much more important understanding that PM is really about segmented patient management. This is not an issue when you have single or even dual targeted therapy launches into an indication. Herceptin, Epzicom and Tysabri were all launched under virtually monopolistic market conditions. Testing infrastructure issues were about increasing access to those therapies. Iressa/Tarceva, Zelboraf/Tafinlar were dual therapy launches that raised regulatory label issues over which test to choose and when, but even here the breakthrough therapies found their place. It is only when we have four to five therapies launching into an individual indication in a compressed timeframe, as with Anti-PD1 therapies targeting NSCLC, that the competitive rubber hits the road. Consider for a second the NSCLC physician's choices in 2012 - chemotherapy and first generation TKIs. Four years later the targeted therapy choices now include Xalkori, Opdivo, Keytruda, Tagrisso, Xalkori, Iressa, Gilotrif, Alecansa and Portrazza. In four more years we could see numerous therapy combination recommendations, as well as a revival of older chemotherapy drugs newly targeted with PD-L1. In fact, we count 18 therapy choices for the same patient population by this stage - brilliant news for patients.*

# OPINION PIECE (CONTINUED)

*The 'so what' impact for pharma competitors seeking to carve out and sustain market share by relying solely on outcomes, dosing convenience and price will not cut it. The winners here will be the marketers who recognise that understanding physician testing behaviour, and then shaping the biomarker educational and use landscape, will win the upcoming segmentation war. Only then will testing move from a rescue remedy for drugs to become a marketing tonic.*

# WHAT'S IN THE PIPELINE?

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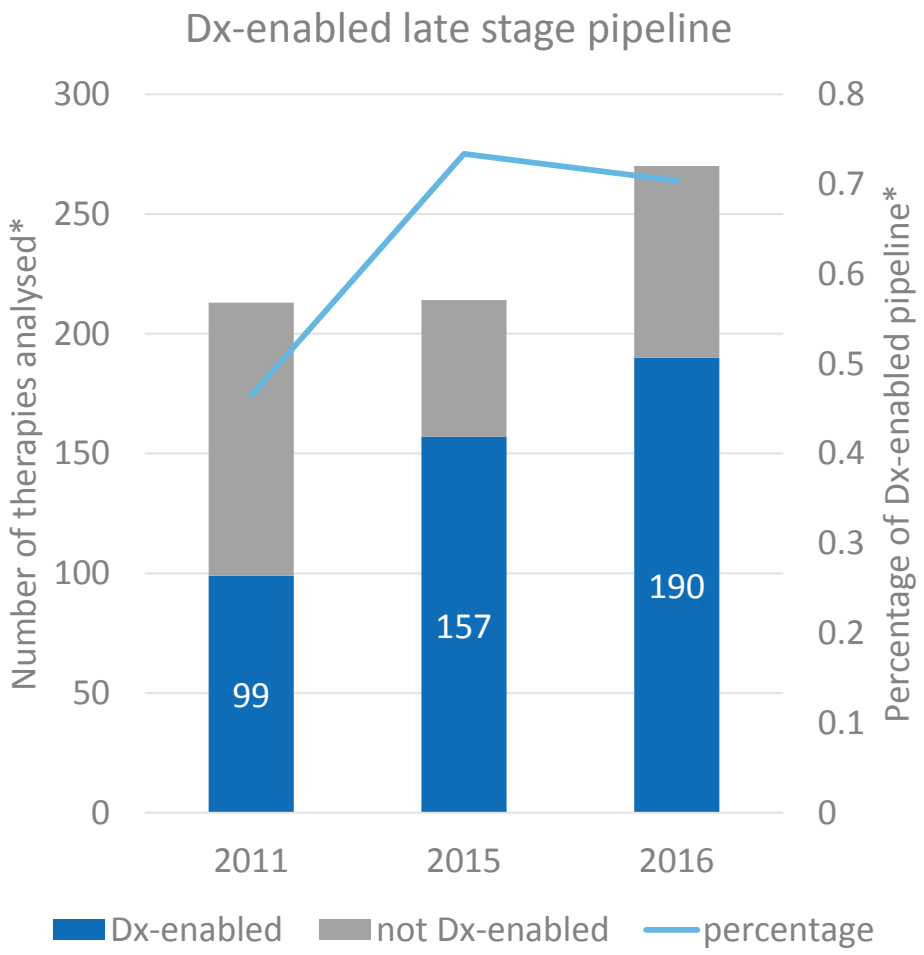
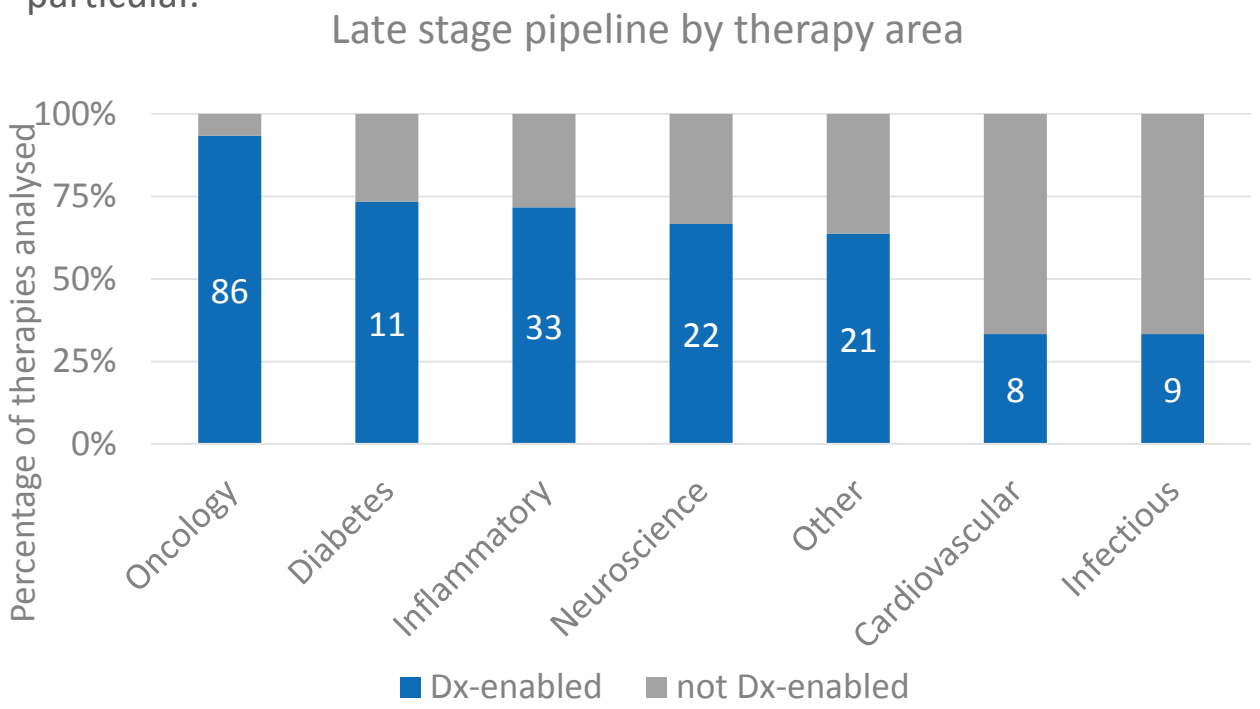
# DX-ENABLED THERAPIES DOMINATE LATE STAGE PIPELINE

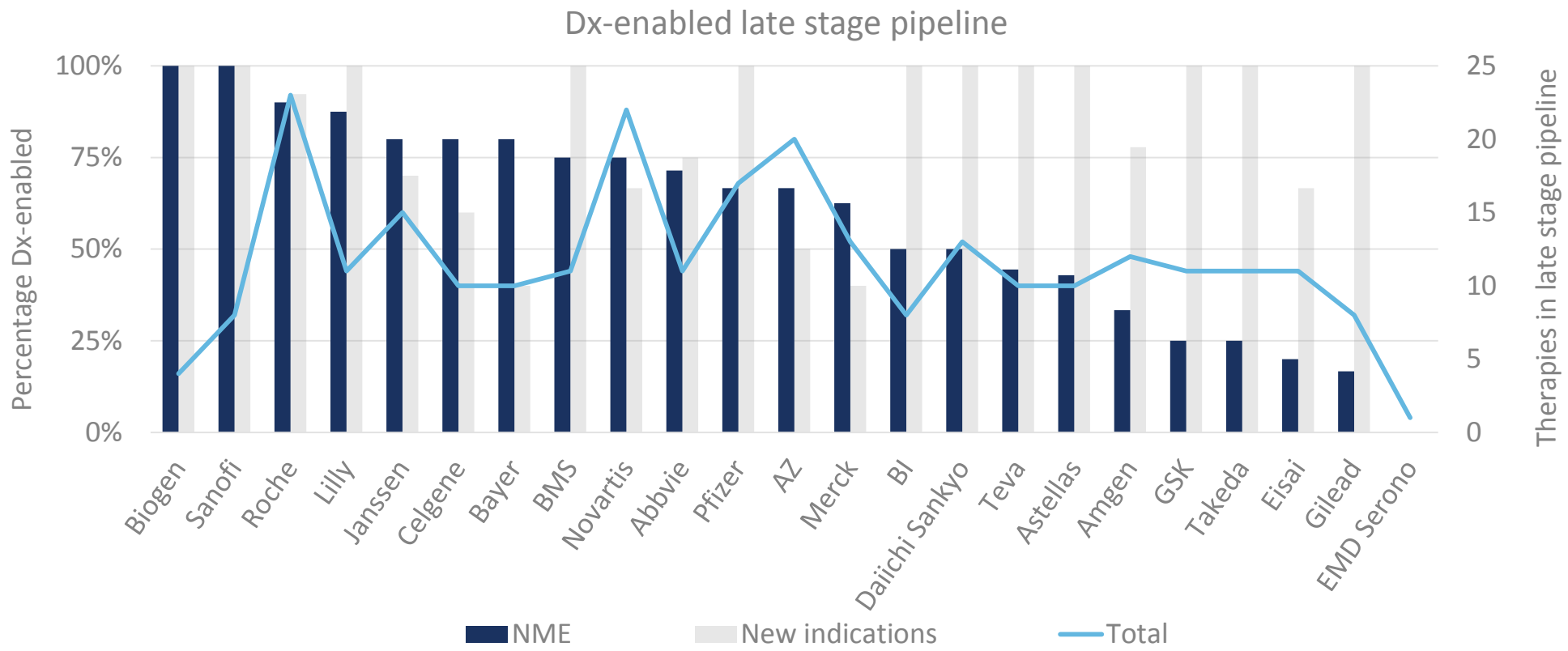



- We have analysed 270 late stage compounds within our 23 companies (Phase III and in registration), up from 214 different Phase III programmes in 2015.
- Today, 70% of new molecular entities (NME) are associated with a known biomarker, diagnostic strategy is pursued along with therapy development or, according to our research, could benefit from Dx strategy.
- Oncology pipeline has largely converted to Dx-enabled prescribing but other indications are also highly Dx-enabled, inflammatory diseases and diabetes in particular.



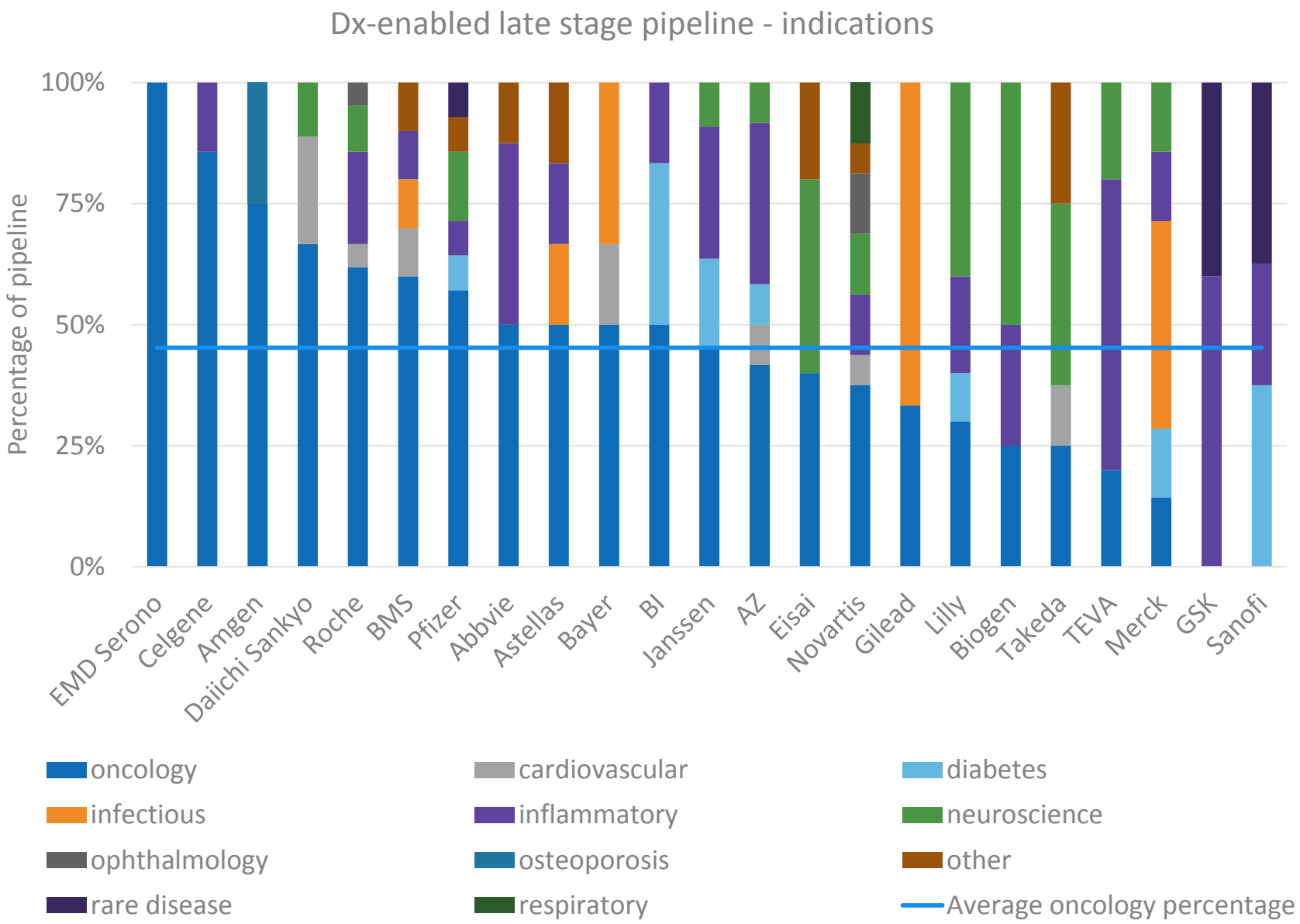

*In 2011-2015 analysis was made on the number of late stage programmes. In 2016 analysis was made on the number of individual therapies.

# INCREASING DX ENABLEMENT ACROSS LATE STAGE PIPELINE




- On average for our 23 competitors seven out of ten therapies close to market are now Dx-enabled.
- However, considerable pipeline variances across the competitive landscape suggest that, for many, a PM strategy is only part of their future competitive readiness.
- For those leading the field, programs in new indications for therapies already launched are more likely to be Dx-enabled.

# DX ENABLEMENT IS BECOMING MORE PORTFOLIO INTEGRATED




- Although oncology still dominates the diagnostic/therapy interface, our 23 companies in focus are deploying Dx enablement across their indication portfolios.
- Competitors that have not cut their teeth on oncology diagnostic launches are likely to lag in the experience stakes across other therapy areas.

# The diagnostic industry: Locked in yesterday's business model

*Make no mistake, the pharmaceutical industry right now could not manage to support the commercial roll-out of its targeted (precision) medicines (PM) without the scientific and technical support of the diagnostic industry. As the FDA migrates to a dual approval of medicines with their companion or complementary diagnostics, the interdependence between these different industries is solidified. Simply put, the diagnostic industry is now firmly part of the supply chain in the development of a PM future.*

*In 2016, 87 diagnostic companies were active in some way in the PM testing marketplace. Admittedly some of these are small technical houses sitting alongside veterans like Ventana, Qiagen and Thermo-Life Sciences, but it shows the diagnostic supply chain is thriving. However, there is a critical dilemma in the business partnering model between the pharma and diagnostic industries, namely which one is really responsible for developing the commercial testing marketplace? Diaceutics observes that pharma commercial teams continue to 'learn on the job' as they work out how to develop diagnostic markets which will enable their drugs. This happens because the diagnostic development partner has limited the team's responsibility to installing the test in a few primer labs across key markets. It is the equivalent of Pirelli delivering its tyres to Porsche and saying, "Thanks guys, now can you drag us into the marketplace alongside you?"*

*We all know the problems - partnering frameworks are couched in a way that make it tricky for a diagnostic company to take ownership of or be accountable for developing the marketplace for its test. In reality, there are no revenue-sharing milestone payments from pharma to diagnostic companies to guarantee a test will hit ALL the labs near their prescribers. And diagnostic companies have no incentive to promote a test that might generate less than $1m in profit. As far back as 2008 Diaceutics worked with pharma and diagnostic executives to research integrated commercial business terms for a win-win situation in PM. Sadly, (with one or two exceptions where we have shaped the commercial agreement) we still do not see any significant evolution in this critical dynamic. One positive consequence, however, is the increasing involvement of laboratories in owning what we call the laboratory-physician interface, or LPI. Since market development is as much about education and service delivery, it seems that laboratories and not diagnostic companies are emerging as the better partner for pharma when tackling the increasing complexities of the PM market.*

# WHICH COMPANIES ARE PUSHING FORWARD?

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# PHARMA IS STARTING TO LEVERAGE DX BEYOND THE BRAND…

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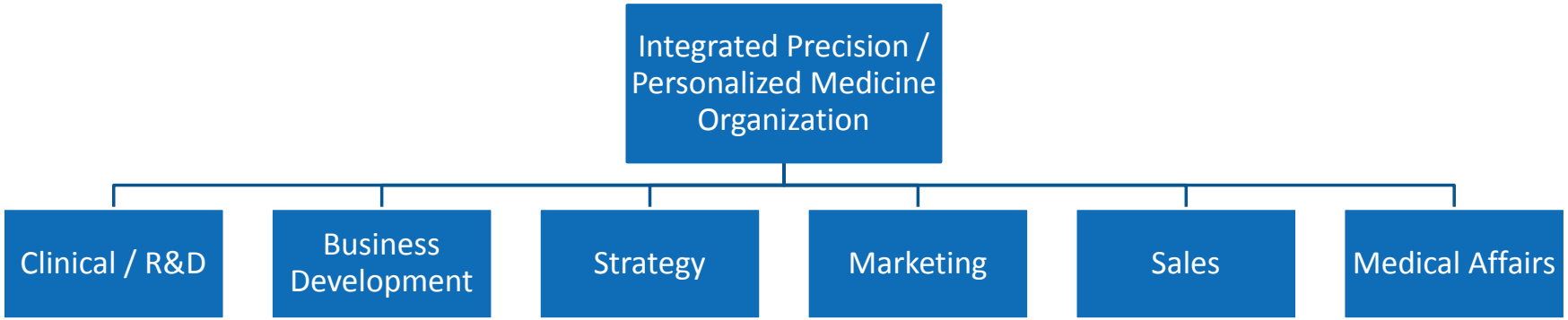


Moving the needle for MS outcomes

**Creating an innovative system to gather and apply real-world evidence to help improve patient care and research**

By Richard Rudick, M.D.
*Vice President*
*Development Sciences, Value-Based Medicine*

**Demonstrating a learning health system**

In addition, we are working to help how MS is diagnosed and monitored by making the technological and analytical tools not only more efficient, but also more quantitative and precise. We are also collecting blood samples from patients to create a large biorepository that we can harness to identify biomarkers of disease activity and progression, which will move us closer toward precision medicine for MS. Simply put, our goal is to work on multiple fronts to drive innovation and help set a new standard of care for MS.

CIO INSIGHTS

**Beyond the Pill, IT Leads the Technology Revolution at Teva Pharmaceuticals**

By Guy Hadari, VP & CIO, Teva Pharmaceuticals

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*NATURE REVIEWS CANCER* | PERSPECTIVES | OPINION

Defining actionable mutations for oncology therapeutic development

T. Hedley Carr, Robert McEwen, Brian Dougherty, Justin H. Johnson, Jonathan R. Dry, Zhongwu Lai, Zara Ghazoui, Naomi M. Laing, Darren R. Hodgson, Francisco Cruzalegui, Simon J. Hollingsworth & J. Carl Barrett

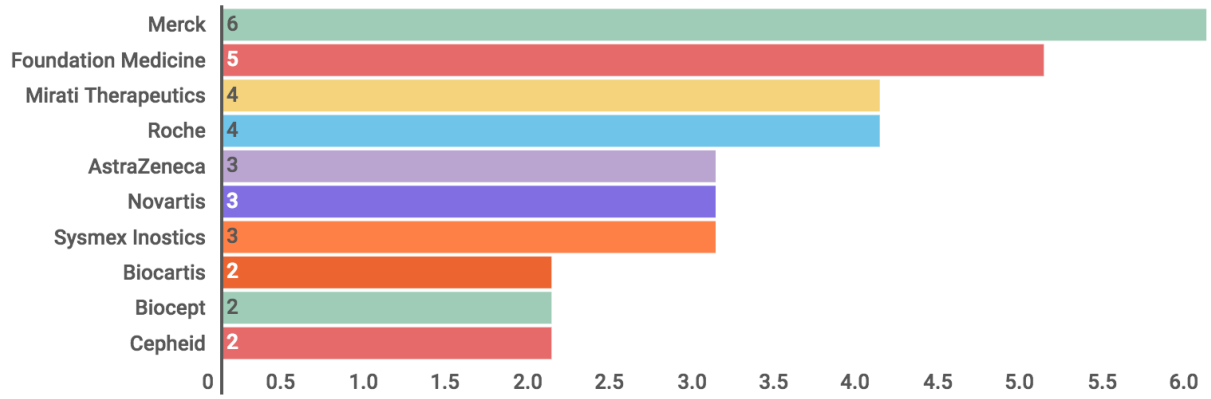
Affiliations | Corresponding authors

*Nature Reviews Cancer* **16**, 319–329 (2016) | doi:10.1038/nrc.2016.35
Published online 26 April 2016

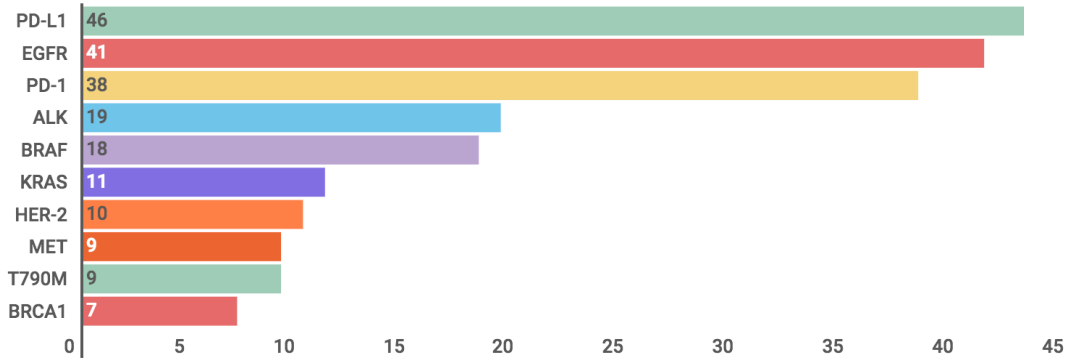
# …AND PROMOTE DX CREDENTIALS MORE WIDELY

We have analysed news flow (up to September 2016) to determine which of our companies in focus are shouting loudest about their Dx-related investments.

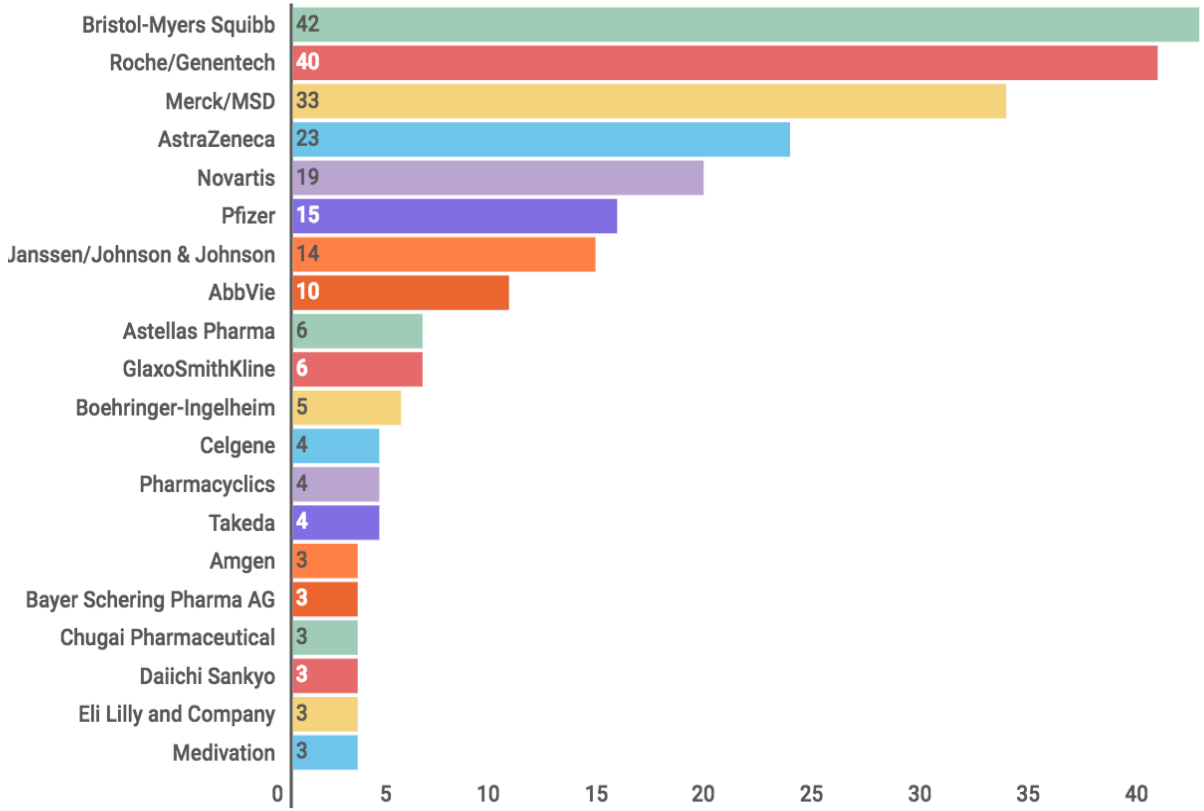
## 10 Rx/Dx collaborations most cited



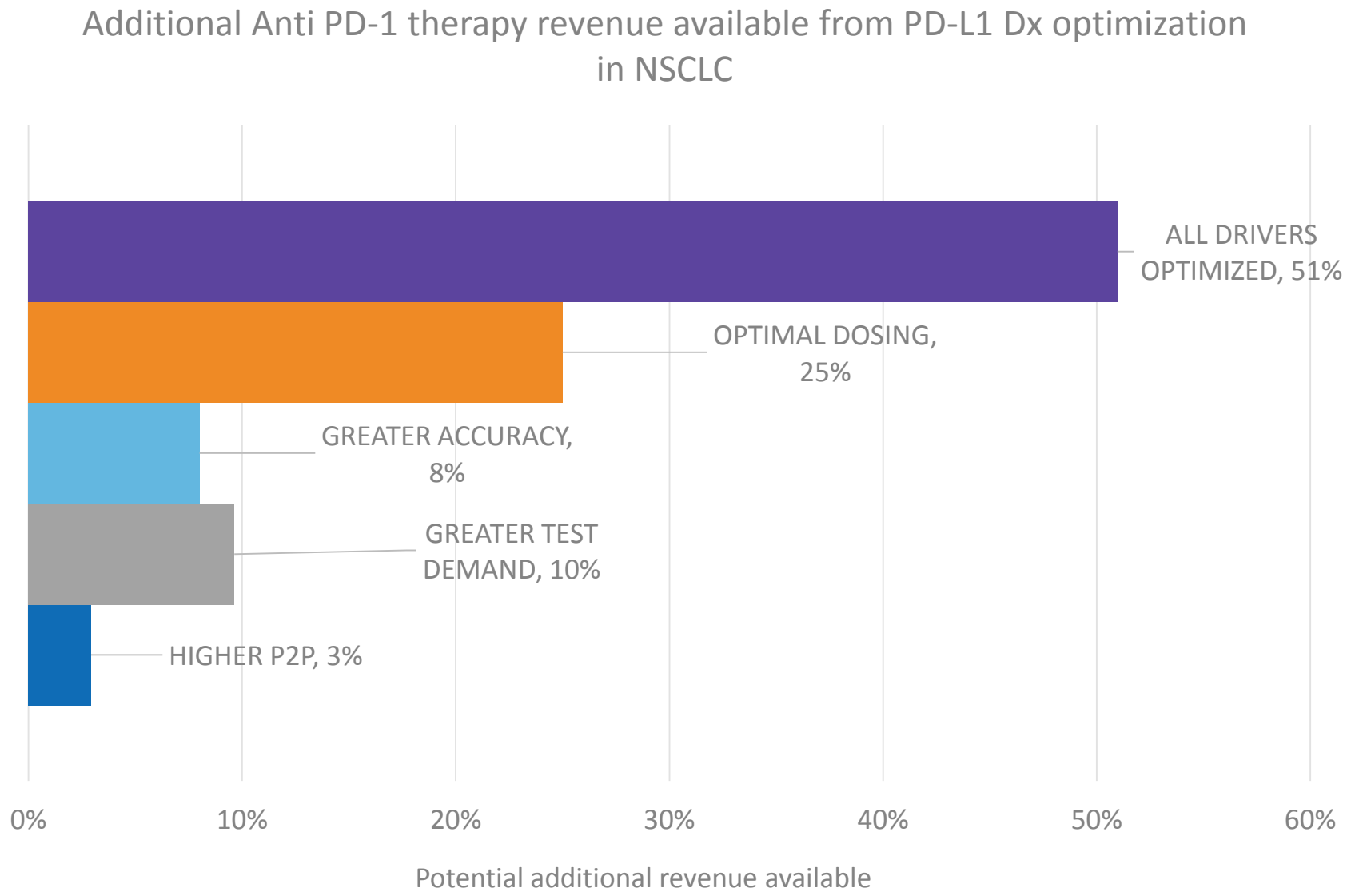

## 10 biomarkers most cited




## 20 Pharma companies most cited



# UNDERSTANDING THE FINANCIAL IMPACT OF BETTER DX IS KEY

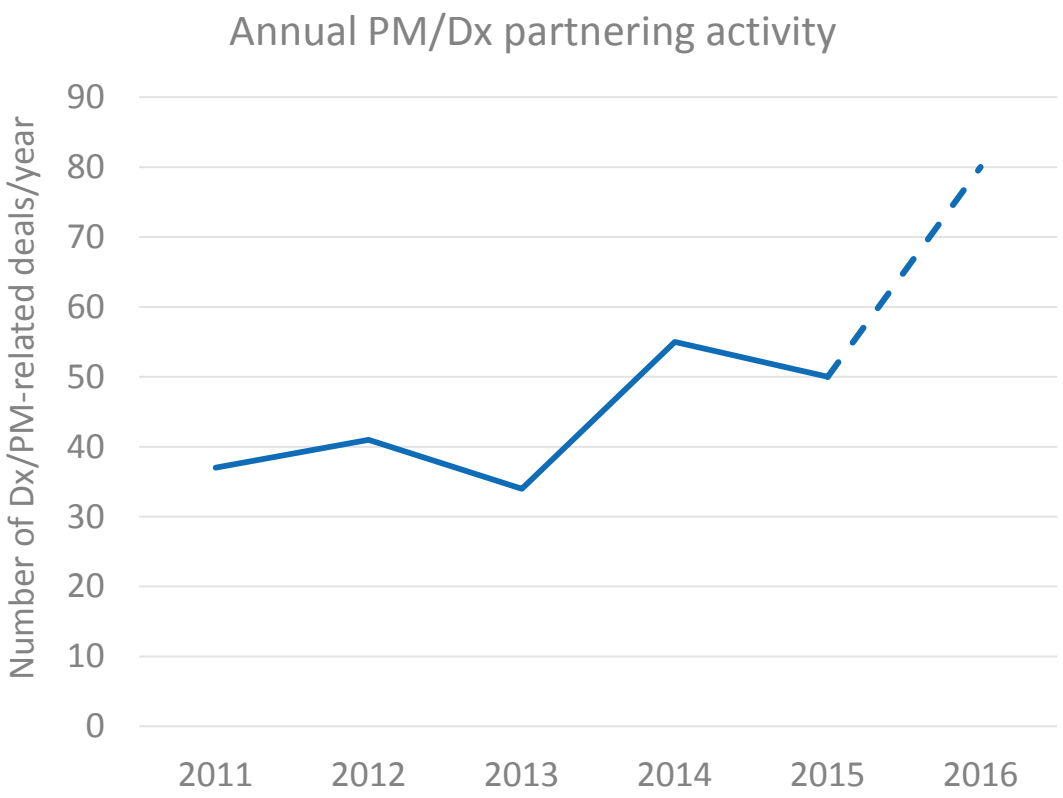



- Illustrative data shown represents the additional revenue available to immuno-oncology competitors from optimizing PD-L1 testing in support of therapy launches in NSCLC.
- The example shows that with smarter investment in Dx efficiency, an estimated $744m in additional anti-PD-1 therapy revenue could be delivered over a five year post-launch period.

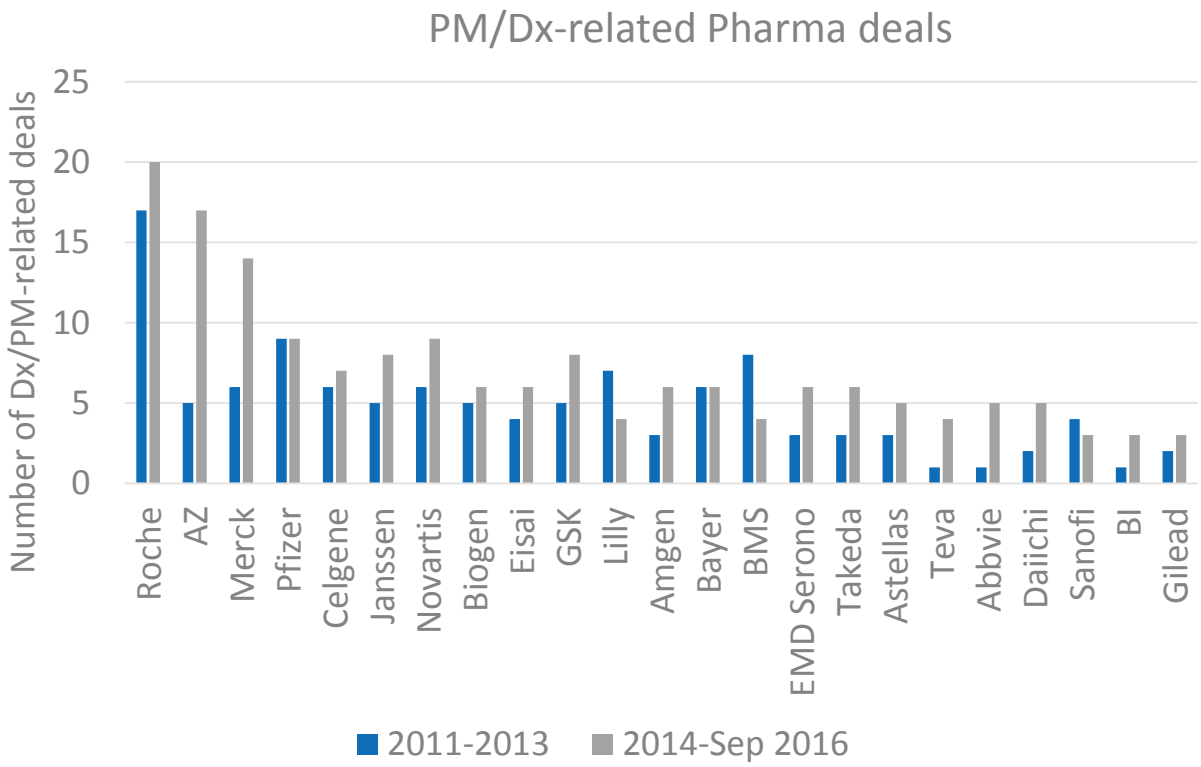
Source Diaceutics presentation, Tricon 2016

# RX/DX PARTNERING CONTINUES TO RISE…

- Our Dx partnering database now tracks competitors partnering across precision medicine and includes CDx, complementary Dx, conduit Dx, Big Data/bioinformatics and partnering for testing data.




2016 is set to be a record year for Pharma CDx and precision medicine partnerships with 59 Dx-related agreements already sealed in the first nine months. We estimate this could reach 80 for the whole year (based on discussions in play).




All companies increased the intensity of their PM/CDx partnering. From Jan 2014-Sep 2016 almost 1.5 times more deals were closed (164 in total) compared to 112 deals in the preceding 3 years (2011-2013). Roche is still the leader, completing a staggering 20 deals from Jan 2014-Sep 2016, but AZ and Merck have both have been partnering aggressively in the same period.

# …AND EXTEND BEYOND DX COMPANIES' LIMITED REACH

- Dx competitors are beginning to track real-time Dx adoption and performance to 'correct budget assumptions' and right-size investments. This drives faster Dx uptake than company norms in support of therapy, patient and financial goals.

## Thermo Fisher, Pfizer, Novartis Ready CDx Assay for FDA Submission

Oct 14, 2016 | Monica Heger

*Premium*

NEW YORK (GenomeWeb) – Thermo Fisher Scientific has completed the analytical validation of its universal companion diagnostic test that it is developing with Pfizer and Novartis, the company said this week.

At Arrowhead's Personalized and Precision Medicine conference in San Francisco this week, Mark Stevenson, executive vice president and president of life science solutions at Thermo Fisher, told GenomeWeb that with the analytical validation complete, the companies will now conduct the necessary clinical trials in order to submit the assay, which will run on Thermo Fisher's Ion Torrent PGM Dx platform, to the US Food and Drug Administration together with Pfizer's and Novartis' drugs.


Stevenson did not provide a timeline for when the first submission would occur, but said it would be "fairly soon."

The assay will analyze both DNA alterations and RNA gene fusions from around 50 genes using the AmpliSeq technology, Stevenson said.

The three companies collaborated on the design and analytical validation of the assay, Stevenson said, which was viewed as a pre-competitive space by the pharma companies. Pfizer and Novartis both plan to submit the assay to the FDA in conjunction with a lung cancer drug, but the companies each have their own target and will do their own submissions. Even though the test will analyze multiple markers, the FDA submissions will still be for one marker associated with one drug.

Once it is cleared, the test will be marketed as a kit to hospital laboratories, oncology centers, and other molecular diagnostic labs, Stevenson said.

## Cancer Genetics, Inc. Listed by Merck as a National Reference Laboratory for KEYTRUDA® (pembrolizumab) Companion Diagnostic Testing

PUBLISHED ON: Monday, December 5th, 2016 View all Media

## Roche launches imCORE, a global network of cancer immunotherapy centers of excellence

- **Research network of 21 academic centers from around the world to access and share technology, data and expertise to advance the science of cancer immunotherapy**
- **Roche will invest up to 100 million Swiss Francs to support basic and clinical research collaborations within the imCORE Network**

Diaceutics

## PD-L1: A chance to get things right?

*The extraordinarily dynamic PD-L1 testing and anti-PD-1 therapy space allows, for the first time, a real-time analysis of a truly competitive personalized medicine market, giving us the chance to analyse in detail the PD-L1 testing market's trajectory and ultimately improve our understanding of novel biomarker adoption in our increasingly dynamic and competitive landscape. Despite the uncertainties hanging over the first generation of PD-L1 tests, our data point to the fact that the space will require ever more PD-L1 testing and that by 2018 PD-L1 will become a hyperconnected oncology biomarker led by NSCLC.*

*In short, the data suggest a rapid integration of PD-L1 testing despite its uncertain molecular interpretation. One year after launch, PD-L1 already appears to be more integrated into oncology clinical trials than other biomarkers were 18 months post-launch. Use in over 70 US labs shows PD-L1 testing has a fast track pattern of uptake in parallel with treatment recommendations. This is all very encouraging, but there are issues including:*

- *Of the 70-plus US labs that have adopted PD-L1 testing, the majority have opted to make an LDT available. Kits are important in priming the market but, as with other biomarkers, labs decide on the best test going forward, so their impact in the space should be not be ignored. This appears at odds with FDA attempts to de-limit LDT use, although with a changing US administration this may be binned.*
- *Test availability can impact prescribing choices and the way labs offer a test could be a disruptive factor for pharma. Our research shows if only one PD-L1 test is offered by a lab it appears to limit prescriber choices.*
- *PD-L1 biology of expression determines that late disease is likely to reveal higher levels of PD-L1 expression whereas pre-treatment can also interfere with PD-L1 levels, so a patient's position in the diagnostic journey may be key to segmentation. This is not well articulated in clinical guidance.*
- *Clinical trials for immuno-oncology therapies in NSCLC reveal that PD-L1 will need to be integrated alongside more established biomarkers like ALK and EGFRm as part of future patient segmentation strategies. Testing guidelines are constantly lagging behind biomarker launches and this is likely to be increasingly so in the PD-L1 space. This inevitably limits direct-to-patient communication and prevents patients' easy understanding of the space. PD-L1 is unlikely, therefore, to be patient led, as HER2 is today.*

# OPINION PIECE (CONTINUED)

*Our real-time observation of PD-L1 reveals many issues of novel biomarker integration into treatment pathways and drug launch programs. Precision medicine continues to progress yet we still suffer from the lack of pre-launch market development of critical biomarkers, even though most of the PD-L1 issues have been seen before. Optimizing the potential of a still underdeveloped PD-L1 testing market could help to realise the $32bn per annum in expected drug revenues, but learning from it could shape hundreds of billions of dollars in future dependent therapy revenues.*

# HOW DO WE INTEGRATE THE ANALYSES?

PHARMA READINESS FOR DX INDEX

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# REFINING OUR DATA FOR THE PHARMA READINESS FOR DX INDEX

- To provide a snapshot of Pharma readiness for precision medicine and Dx-enabled therapy prescribing, Diaceutics has been integrating six key metrics along Commercial and Organizational Readiness axes for the past five years. The quantitative metrics captured, and how we continue to refine the data from year to year with greater insight, are defined below.
- Based on our 10+ years experience in the field we weight each of the six factors to determine those companies most likely atuned to the complexities of integrating diagnostics into the Pharma business model.
- The Index and our PM Bounce metrics (cumulative changes in share price) are to be used as an aid to discussion only and not for investment purposes.

## 2015

***Organizational Readiness Factors***

- *PM Ph3 Pipeline (%)*
- *Internal Division*
- *# Rx/Dx Partnerships*

***Commercial Readiness Factors***

- *PM Revenues (% of Total Revenues)*
- *Channel Control*
- *# PM Integrated Brands*

## 2016 - *What's new?*

***Organizational Readiness Factors***

- *PM Ph3 Pipeline (%)*
- *3L Score (Like it/Learn it/Leverage it)*
- *# Rx/ Dx/Big Data Partnerships*

***Commercial Readiness Factors***

- *PM Revenues (% of Total Revenues)*
- *(C)Dx launch experience*
- *# PM Integrated Brands*

## 2017

***Organizational Readiness Factors***

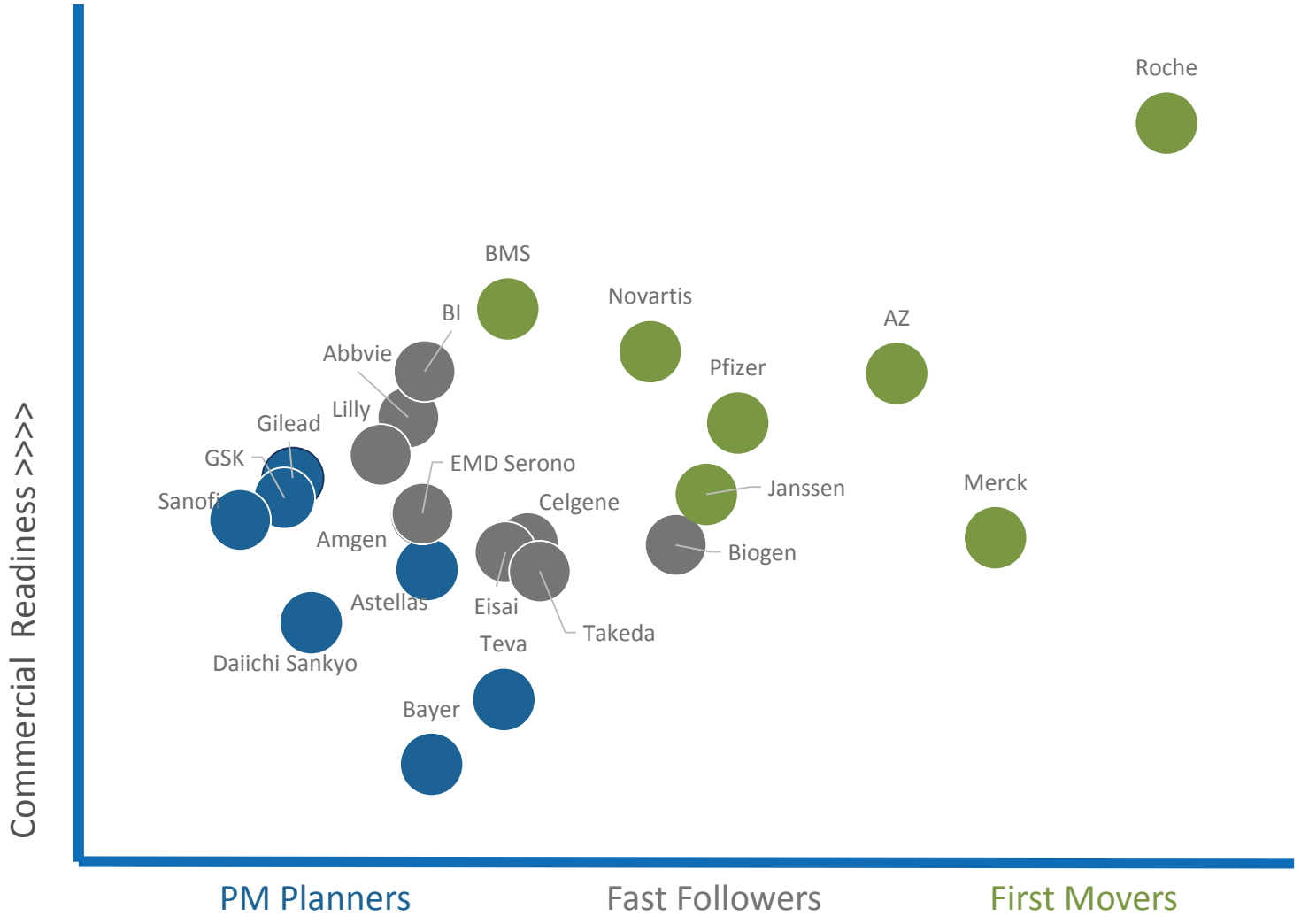
- *PM Ph3 Pipeline (%)*
- *3L Score*
- *# Rx/ Dx/Big Data Partnerships*
- *…?*

***Commercial Readiness Factors***

- *PM Revenues (% of Total Revenues)*
- *(C)Dx Launch Experience*
- *# PM Beyond the Brand*
- *…?*

# 2017 PHARMA READINESS FOR DX INDEX

- The Diaceutics Pharma Readiness for Dx Index integrates six key externally observed factors which are weighted. The Index illustrates a company's competitive position relative to its peers.




- Pfizer, AZ, Merck and BMS join Novartis and Roche as potential disruptors in the market.
- Several new entrants to our Index score highly - joining the Fast Followers segment.
- Relative to other companies with more recent diagnostic commercial experience, Janssen and Lilly drop back compared with 2015.
- We expect Teva, Astellas and Daiichi to join the Fast Followers in 2017/18.
- Strong early Dx-driven pipeline may result in GSK climbing up the Index from 2020 onwards.

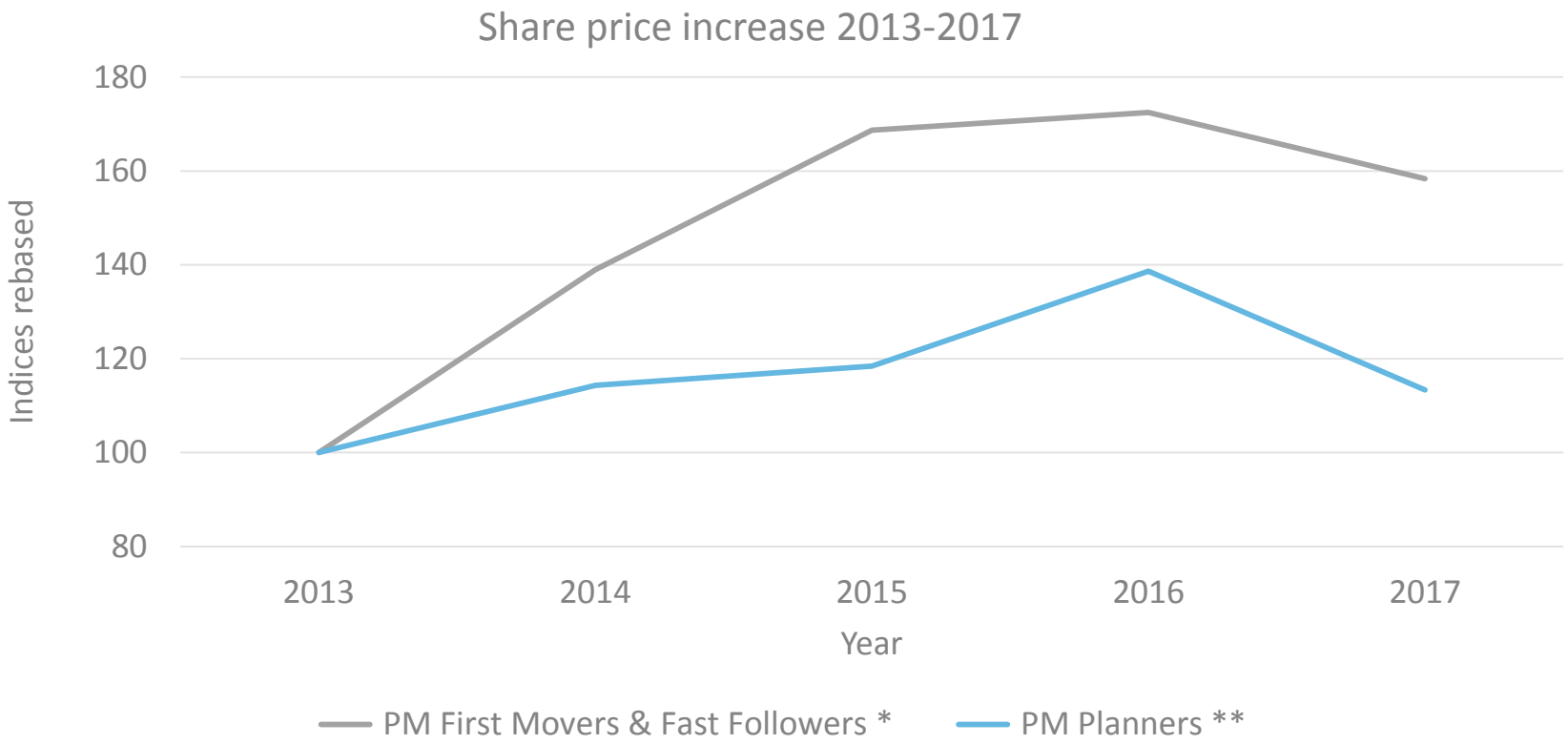
### Commercial Readiness

- Dx-driven revenues (%)
- (C)Dx launch experience
- PM integrated brands (#)

### Organizational Readiness

- Ph 3 of Dx-driven late pipeline (%)
- 3L Score (Like it/Learn it/Leverage it)
- Partnerships (#)

# DX READINESS INDEX THROUGH THE SHARE PRICE LENS




- Although oncology still dominates the diagnostic/therapy interface, our 23 companies in focus are deploying Dx-enablement across their portfolio of indications.
- Competitors who have not cut their teeth on oncology diagnostic launches are likely to lag in the experience stakes across other therapy areas.

*BMS, AZ, J&J, Novartis, Roche, Lilly, Celgene, Biogen, Takeda, AbbVie, Astellas, Amgen and Merck
**Sanofi, Eisai, GSK, Bayer, Daiichi and Teva

Diaceutics recognises that share price is driven by multiple strategic and impact factors. We make no claim to the role PM leadership plays in driving overall share price but offer this view for discussion only. This document has been prepared by the authors based upon information sources believed to be reliable and prepared in good faith. It is not investment advice and does not take into account the investment objectives and policies of any recipient.

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## The microeconomics of precision medicine are in poor shape

*The promise of precision medicine (PM) was always both clinical and financial. Unarguably, our delivery on the clinical promise is well underway - new approved targeted therapies prove that molecular targeting of patient subsets delivers significantly better outcomes and our pipeline analyses illustrate the best is yet to come. In contrast, our delivery on the financial promise has barely begun and, in almost every dimension, the microeconomics of PM are in poor shape.*

*Let's revisit the promised financial hypothesis of PM here. We expected the utilization of behavioural, genetic and molecular targeting to eliminate wasted healthcare cost, deliver greater incentives to all stakeholders and create transparency around value. Given that (in 2016) we are 18 years on from Herceptin's first use, the current reality is somewhat different. We see:*

1. *Sparse evidence of PM-enabled reduced healthcare cost emanating from real world health economists; it may exist…it's just not adequately reported (1);*
2. *Huge incentive imbalances across the supply chain stakeholders, with pharmaceutical companies migrating PM to a high-priced model while innovative front line laboratories are existentially squeezed by the indirect consequences of blunt reimbursement or national healthcare policies (2);*
3. *Little in the way of joined-up discussion at the disease level about where the value of PM actually lies and even less ownership of the debate (3).*

*Delivering on the financial promise starts with an illustration of what is broken, and in this regard at least there are some bright lights:*

- *The OHE/EPEMED-sponsored work to point out the undervaluation of diagnostics in PM (4);*
- *A growing understanding of how pricing models should reflect the value of diagnostics (5);*
- *The ripple effect across the industry C suites from Opdivo's failed 1st line NSCLC study and its profound impact on the BMS share price (6);*
- *The embryonic work of groups like the PM Connective (7) that explore financial opportunities at disease level as part of a PM architecture.*

# OPINION PIECE (CONTINUED)

*We are confident that, in the long term, a market economy will deliver a clear and obvious financial landscape for PM which makes great economic sense all round. In the short term, however, a step change is needed when it comes to dialogue, specifically between chief financial officers, economists, payers, policymakers and patient advocacy groups, all of whom need to re-arm with a better understanding of the financial drivers resident within the economic underbelly of PM. Without this, the short- to mid-term clinical promise of PM will be limited to the low hanging fruit and that would be a missed opportunity.*

***References***


*1, 2 http://www.paulkeckley.com/report/2016/6/20/the-conundrum-of-precision-medicine*

*3. See Undelivered Precision: Lack of Integration is the Remaining Obstacle, Slide 38*

*4. https://www.ohe.org/sites/default/files/WP_EpemedOHE_final.pdf*

*5. http://www.diaceutics.com/expert-insight-premium-content/?id=4746*

*6. http://www.fiercebiotech.com/biotech/merck-soars-bristol-myers-tumbles-opdivo-fail-first-line-nsclc*

*7. http://www.pmconnective.org/*

# KEY TAKEAWAYS AND PREDICTIONS

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# OUR KEY PREDICTIONS

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## 2017 — Dx Wake Up Call

- Considerable momentum for Dx-enabled therapies is building in the pipeline and on market experience.
- An increasing number of Pharma companies are chasing Roche hard in terms of their potential to launch market leading or competitively disruptive Dx initiatives.
- Our PM Bounce comparison suggests Dx strategies are beginning to be reflected in Pharma share price. This will be a space to watch as success and failure to integrate Dx into the therapy business model become more transparent to an informed investor base.
- LDT regulations will be binned.

## 2018 — Rx Segmentation by Dx is the New Black

- Growing realisation that CDx legacy definition no longer fits the breadth of Dx-enabled initiatives across the Pharma landscape.
- Key competitors leverage Dx technologies as they migrate beyond the brand to capture superior market share and justify high priced therapies.
- Dx technology will be used to segment highly competitive indications like NSCLC or breast cancer. Understanding the Dx role in segmentation marketing will be a new core commercial skill.
- The Dx company business model is unable to develop commercially-ready tests fast enough for Pharma. Partnering will be restricted to test development only.

## 2020+ — Investors Push for Clear Dx Enablement Strategies

- We forecast that Dx enablement of therapy will become the norm by 2020. Over 70% of new drug launches will be dependent upon an effective Dx prelaunch and launch strategy.
- Understanding a Dx's role as the ultimate segmentation and value creation tool will separate Pharma winners from losers by 2020.
- Partnering beyond the Dx company will become critical to accessing real-world commercial experience with test diffusion.
- Laboratories will rise as the better Pharma partner to support multi-technology rollout and direct physician education.

# Undelivered precision: Lack of integration is the remaining obstacle

*Precision medicine (PM) has offered this tantalizing promise for the last 20 years - earlier identification and intervention in the patient pathway using advanced diagnostic tools and precision therapies could have a transformative impact on disease. Oncology has been the logical starting point due to the adverse health outcomes and high costs, and many cancers, if caught early, can now be treated effectively, cured or managed as chronic conditions with targeted therapy.*

*Diagnostics and precision therapies have developed to a point where their pace of arrival on the market will continuously eclipse existing standards of care. Factor in the emergence of immunotherapies and innovative diagnostic tools like next generation sequencing and we already have the clinical options to succeed in PM. We can continue to fund and push for even better tests and treatment, but why not efficiently utilize the tools we already have available to deliver the promise of PM?*

*Currently, each player in the industry operates largely independently but only an integrated approach from all sides (clinical, scientific, technical, managerial, education, reimbursement and regulatory) can implement and ultimately deliver the financial as well as clinical potential of PM.*

*The numerous stakeholders (sitting separately in what we term 'silos') in the US healthcare system are rational players maximizing their own value. Unsurprisingly, integration is unappealing for these stakeholders and the true obstacle to PM. It's only the adoption of a value framework that can change behaviours and drive more collaboration which will unlock the financial promise of PM. In driving the development of a new valuation framework in one disease area - melanoma - via our support of the PM Connective, we hope to clearly demonstrate not only cumulative value for PM across silos but, more importantly, the quantitative and qualitative benefits (for each silo) of collaborating to reach PM solutions. The scientifically measured and replicable results will provide a 'GPS system' to guide integration and collaboration both across and within the healthcare silos.*

*The PM promise can be realised but it will require a new method of delivery to achieve its biggest impact.*

# ADDITIONAL INFORMATION

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# DEFINITIONS

- First Movers: Astra Zeneca, BMS, Merck and Pfizer now join Janssen, Novartis and Roche as first-movers in the market and are most likely to leverage diagnostics in the majority of their future marketed therapies.

- Fast Followers: A group of companies including Abbvie, Bayer, Boehringer Ingelheim, Celgene, Eisai, EMD Serono, Lilly and Takeda fall into the Fast Followers segment - rated as integrating diagnostics into a selection, but not the majority, of their commercial therapy programs.

- PM Planners: The remaining competitors are grouped as PM Planners, those actively planning the integration of testing into future launch programs, and include Amgen, Astellas, Bayer, Daiichi Sankyo, Gilead, GSK, Sanofi and Teva.

# '3 Ls' COMPARATIVE LANDSCAPE

| | Like it | Learn it | Leverage it |
|---|---|---|---|
| **Who drives PM internally?** | Asset teams<br>(needing a biomarker for regulatory purposes) | Asset teams<br>Translational Medicine | Asset teams<br>Translational Medicine<br>Senior Management |
| **Who supports PM internally?** | Likely PM apostles – individuals working from the bottom up.<br>Can be organized into a COE but unlikely to have influence; maybe an oncology-only focus | Likely a 'virtual' or small Centre of Excellence with the top down endorsement to help the organization learn | PM Responsibility devolved to individual executives through personal goals |
| **Senior management view** | Senior management is either sceptical or views PM only as a niche and unattractive commercially | Senior management has been educated on the commercial and financial opportunity and sees PM as a goal for majority of teams | Has learnt the PM rules and promotes PM as part of the corporate mission, delivering a higher investor ROI |
| **PM definition** | Responder CDx/Biomarkers | Responder CDx and Complementary Dx | Dx which differentiate and move Rx to first line |
| **R&D focus** | Pockets of PM excellence and 1-2 PM research collaborations | Translational Medicine and Strategic Research Alliances | Every project has a PM strategy |
| **Organizational integration** | Apostles and optional education | Investment in process and systems to enable mandatory education | Investment in process and systems to enable mandatory education |

# All therapies live in an unlit diagnostic ecosystem

*Our work over the past decade has convinced us in Diaceutics that whilst the term precision medicine (PM) is a useful scientific and clinical hypothesis promising to carry us into more targeted patient care, it is in fact also a label which obscures a larger interdependence between testing and therapy. Diaceutics has thus shifted its view away from perceiving PM as a construct only for targeted therapies and companion diagnostics (where the science allows us), to the realisation that EVERY therapy actually exists in its very own, often unlit, diagnostic ecosystem.*

*Illuminating this diagnostic ecosystem has just as much a role in guiding the right patient to the right drug at the right time as the handful of companion diagnostics we have used as our narrow flagbearer in PM. In fact, across the 23 companies analysed in our 2017 Pharma Readiness for Dx Report we believe that $200bn of therapy assets already have a direct or indirect dependency on their own diagnostic ecosystem.*

*But what if these diagnostic ecosystems could made more visible…would that profoundly impact patient access to therapies and, in turn, the return on investment for pharma brand teams competing for available patient share? Those of us who see the untapped diagnostic opportunities across the treatment pathway have, therefore, a key task in front of us - namely to quantify, analyse and communicate (with evidence) to pharma asset and financial leaders how $1 invested smartly in the diagnostic ecosystem will return $40-$60 back in new therapy revenue and, crucially, get more of the right patients on the right drug.*

*Within this report we have yet again returned to the dialogue that by incorporating non-companion (or complementary) tests in our analysis (as well as the brand new 'C' for Conduit Dx™) and framing the relationship between therapy ROI and the efficiency of the diagnostic and its ecosystem, we hope to awaken a whole new way of looking at PM. This is the view that precision is not narrowly confined to a few drugs, but rather lights up the opportunity for all drugs to achieve their full clinical potential faster.*

*We dare to imagine that every therapy commercial team has a bright, three dimensional map of the diagnostic ecosystem into which their therapy is launched, and this enables them to ask the question, "What if there were a test which could do…?"*

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