HEALTH CATALYSTS

# THE DIAGNOSTICS YEAR IN REVIEW 2017

# Introduction

2017 was an important year for Diagnostics' impact on healthcare - marked by multiple positive milestones. While many of these milestones were overdue, we should celebrate the increased traction of diagnostics in the home, in the clinic and in the research lab.

This year's *Health Catalysts Diagnostic Year in Review 2017* is organized around three major topics:

- Molecular Milestones
- FDA Firsts
- Investor Interests

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Recognition that molecular markers are a crucial and irreplaceable guide to treatment choice.

# Molecular Marker Milestones

**History:** The Diagnostic industry has been identifying molecular markers for over 25 years, since the early 1990's. The role of BRCA1 mutations in cancer prognosis was first published in Science in 1994, and Myriad launched their pioneering BRACAnalysis® test based on this research in 1996. Most well-known for breast cancer pharmacogenomics, BRCA testing was also used to choose therapy for other solid organ cancers. Since then, knowledge of the range of genes involved in cancer and the importance of specific pathological mutations in them has grown dramatically, along with the breadth of drugs that successfully treat specific defects.

**Today:** Panels of genes, and their mutations that drive a patient's disease are guiding treatment with available (though expensive) drugs as a routine practice. Effective outcomes and therapy results for patients have shown the efficacy of utilizing gene panels, such as Foundation Medicine's FoundationOne®.

# Molecular Marker Milestones *Continued*

**On May 23, 2017**, in an event more important than it might first seem, the FDA approved Keytruda® (pembrolizumab) based only on whether a tumor exhibits one of two biomarkers: high microsatellite instability (MSI-H) or mismatch DNA repair deficiency (dMMR). Keytruda® is one of the newest family of immune system targeting drugs that focus on the PD1/PDL1 pathway by which cancer cells evade a patient's immune system.

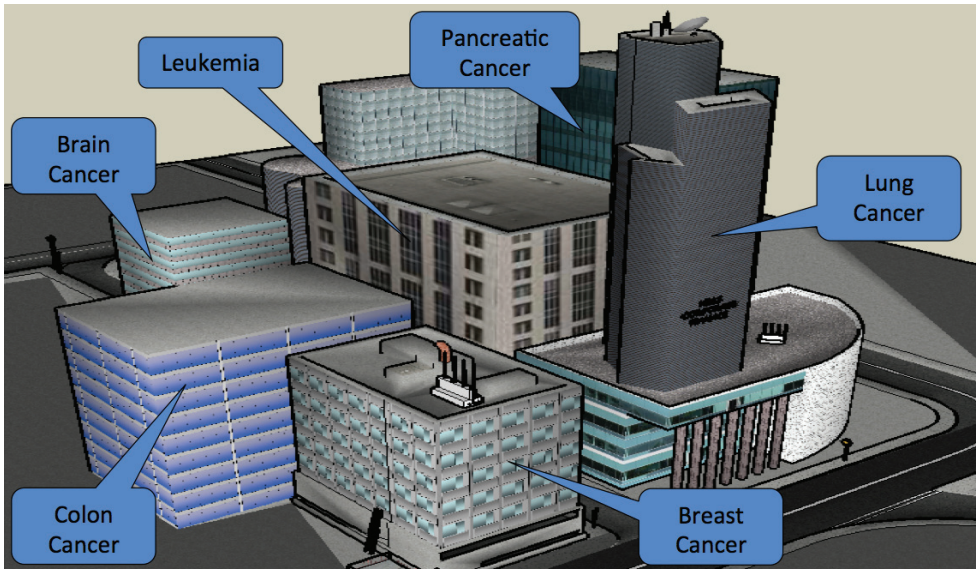
Historically, new cancer therapeutics have been approved for only a specific organ system, and thus used more frequently off-label versus on: up to 71% off-label versus 29% of the time, as documented in a recent study in the Journal of Clinical Pharmacy and Therapeutics, in June 2017. All this changed last May with the approval of Keytruda®, and it is highly likely that the number of tumors that respond positively to this treatment is even broader than the two defects currently approved by the FDA.

**Clinical Adoption:** First, physicians must be convinced that new molecular diagnostic assays have practical clinical utility. Adoption has been a slow process, but an increasingly compelling body of clinical research demonstrates that designing therapy based on molecular biomarker identification is more useful than the 2,000-year-old technique of categorizing their tumors by organ of origin. Early proof of this was convincingly demonstrated in the Journal of Clinical Oncology, November 2010, in which 86 advanced cancer patients were profiled molecularly. In all but one case molecular markers were found that changed treatment options, and with modified therapy (even at late stage) 27% of these patients experienced a greater than 30% lengthening of their progression-free survival time. Today, many more trials are being carried out to determine optimum treatment using a basket of molecularly guided treatment options. Early in 2017, the Precision in Pediatric Sequencing (PIPseq) program at Columbia University Medical Center released data on the first 100 children sequenced for mutations in 467 cancer associated genes; 38% of these patients had new therapies identified because of this testing. Toward the end of 2017, Genentech released the results of its "MyPathway" program that examined HER2 and BRAF mutations independent of the organ of origin. As a result, nearly one-quarter of patients (23 percent) had objectively measured treatment responses – 4 patients achieved complete remission and a further 48 showed partial response.

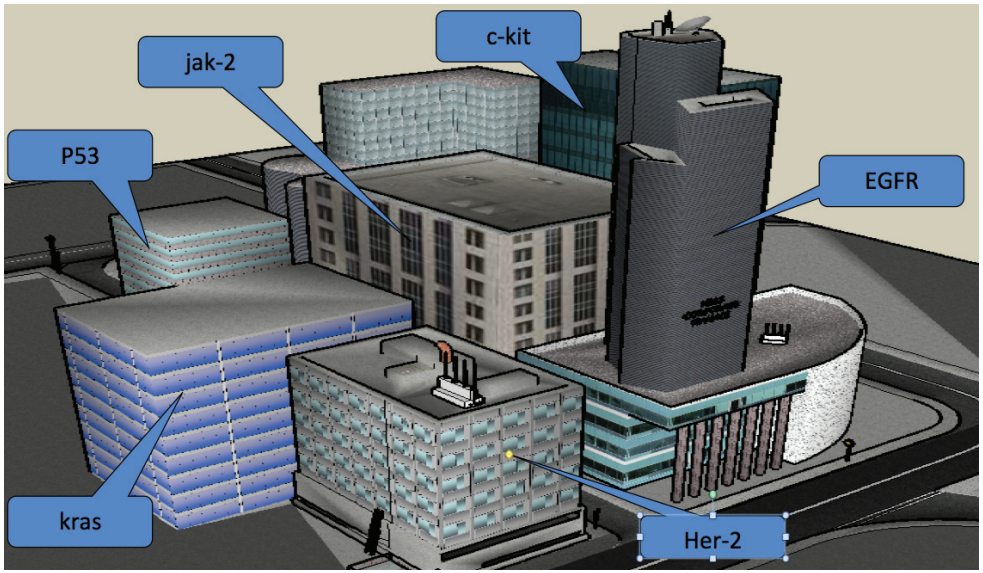
All this new study data, from top researchers at prominent companies and hospitals, gives us hope that rational clinical adoption of biomarkers as indicators of preferred treatment options will accelerate and move from academic centers for the sickest of patients to all centers and patients.

# Molecular Marker Milestones *Continued*

Hospitals Today
Organ-Based Treatment Paradigm




Hospitals in the Future
Mechanism-Based Treatment Paradigm



FDA is newly focused and taking actions underscoring the significant role of diagnostics.

# FDA Firsts

**NGS Gene Panels:** 2017 saw the first signs of broad gene panels taking over from the "One Test for One Drug" Companion Diagnostic paradigm. Approved companion Diagnostics for molecularly targeted drugs has been one of the hottest elements of the genomic testing market over the past 10 years. For drug companies, these single gene tests have proven very successful in identifying patients for whom a specific drug will likely be effective.

As the number of treatments available has grown, however, the one test for one drug paradigm is becoming onerous. Each test requires scarce and precious patient tissue that is easily exhausted, and only provides the answer for one possible therapeutic option among an increasingly broad armamentarium of choices. Broad or universal gene panels are the answer – discovery of all the mutations and treatments at the same time, from a single sample.

During 2017, the FDA approved three new "universal CDx" gene panels that are all next generation sequencing based, solid tumor tests. This action is setting a new precedent for how molecular profiling of tumors will be approved and carried out in the future. The first approval, in June 2017, was for ThermoFisher's next generation sequencing universal companion diagnostic, Oncomine, which is a relatively focused "universal" NSCLC panel but covers multiple genes and possible treatment options for the disease.

# FDA Firsts *Continued*

Then, later in 2017, two approvals were granted for more expansive multi-gene, organ of origin independent, clinically actionable tests. The first approval was for FoundationOne's CDx companion diagnostic test that screens for 324 genes, assessing the clinical utility of 15 approved therapies across 5 major tumor types. This approval was granted in a new parallel review process where FDA approves the test for marketing contemporaneously with CMS's approval of reimbursement. For Foundation Medicine, and the industry, this provides a seal of approval for the reliability and accuracy of their testing procedures and demonstrates that gene panels approved by FDA and CMS can be fast tracked to become the standard of care for every newly diagnosed cancer patient. The last of the approved gene panels was Memorial Sloan Kettering's MSK-IMPACT 468 gene panel, via a more traditional pre-market approval pathway.

**Companion Diagnostics and Therapeutics:** FDA approved over 50 new drugs in 2017, including a record number of personalized medicines. Of the 14 cancer drugs approved (12 by CDER, 2 by CBER), half were for genetically-determined indications. Only two had a Companion Diagnostic in the approval label:

- Idhifa for AML with CDx: Real Time IDH2 Assay
- Rydept for AML with CDx for FLT3 mutation

While Infinzi does not have a formal CDx in the label, it was approved with a 'complementary' PDL-1 assay for response rate. Alunbrig, for ALK+ non-small cell lung cancer, as well as Risquali and Verzenio for Her-2 negative breast cancer, all require a genetic test.

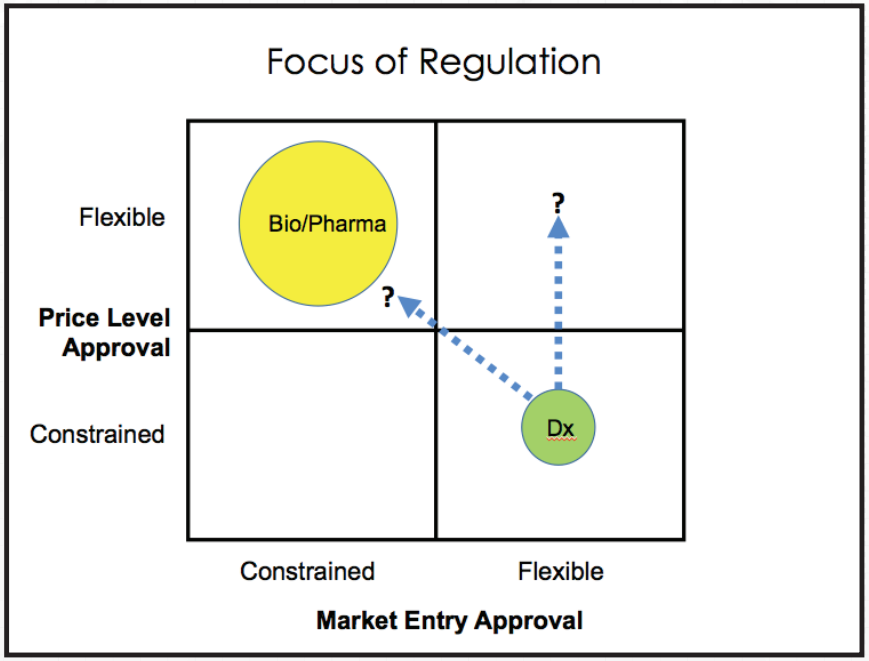
**Patient Direct Testing:** Support for at-home genetic testing was demonstrated by FDA's April 2017 approval of 23andMe's Personal Genome Service Genetic Health Risk tests for 10 conditions. Even more important was the recognized precedent set, establishing that 23andMe would not have to go through a long pre-market notification process for each new condition, each of which can be added after a "simple" one step review. The announcement describes the two-step process – an initial review followed by subsequent brief reviews for extensions – which is the identified future regulatory standard for these "non-diagnostic" tests. Companies which pass a one-time premarket review can offer new genetic risk tests, within certain areas, without further assessment.

**Mobile Apps:** FDA created initial guidance for iPhone and mobile apps in 2013 with an update in 2015. FDA has encouraged the development of mobile medical apps that improve health care and provide consumers and health care professionals with valuable health information. 2017 saw the first two major approvals under this umbrella. The first, in September 2017, was for a mobile app to help treat substance use disorders, developed by Pear Therapeutics. This application is designed to be prescribed by a clinician and used alongside patient counseling. The second approval, granted in November 2017 after a two-year process to satisfy the FDA's requirements, prompted AliveCor's announcement and launch of its Kardia Band, a mobile electrocardiogram (EKG) embedded in an Apple watch band.

# FDA Firsts *Continued*

**LDT Status:** The new FDA Commissioner, Scott Gottlieb, since his appointment in May 2017, has spoken many times on the need for the FDA to modernize but not raise hurdles for innovation. However, speaking at an AdvaMed Conference in September 2017, Gottlieb appeared to reverse course by throwing the regulation of LDTs back to Congress, stating: "The LDT industry is a mature industry. This is not an industry where FDA can just exercise enforcement discretion because it's a mom and pop industry. I think the right way is through legislation". Though he provided no details on what sort of legislative guidance was warranted, he recognized that the current CDER oversight process, which combines all diagnostics with devices, works against the interests of patients, stating that the FDA needs a "unique set of authorities to regulate diagnostics properly…." and "…my view is the old 510K and PMA pathways do not really fit well with modern diagnostics." Dr. Gottlieb was appointed as a "friendly to business" candidate, and all the signs indicate that the Commissioner will be carefully evaluating the correct balance between thoughtful regulation and speed to market.

**Regulation:** The Bio / Pharma industry has tightly regulated market entry approval with essentially un-regulated prices. In stark contrast, the Diagnostics industry has always had tightly regulated prices but lightly regulated market entry approval (especially for laboratory developed tests). This has created an inequality in which diagnostics companies make minimal profits and struggle with tight profit margins while pharmaceutical companies have profits among the highest of all public companies. This disparity is compounded by inconsistently applied regulatory oversight of the diagnostics industry. These factors have combined to discourage public and private diagnostic investment. However, there are indications of convergence as drug-diagnostic pairings and technology partnerships increase. A regulatory overhaul may be beginning: "We need to think differently about how we regulate diagnostics," said Gottlieb at the World Economic Forum in Davos in January 2018, speaking on a panel about the promise of precision medicine. That being said, we have heard this before, with few substantive changes occurring in recent years, and thus we remain skeptical but cautiously optimistic.



# FDA Firsts *Continued*

**Future:** All this activity is particularly impressive as the FDA today regulates diagnostics under the often understaffed Center for Device Evaluation and Regulation (CDER). CDER, which regulates all devices from wheelchairs to diagnostic devices (including molecular diagnostics), has historically shown little focus on the new generation of diagnostics. Looking forward, however, with companion diagnostics integrated into clinical standards, the rapid acceptance of genome sequencing and development of true convergence between diagnostics and data analysis, it is easy to imagine that the FDA will have much more work to do in the diagnostics world. So, might now finally be the time for the FDA to set up a Center for Advanced Diagnostics Evaluation and Regulation? We can call it CADER. We need "A Place of Our Own", acknowledging Diagnostics' crucial role in modern medicine and patient care.

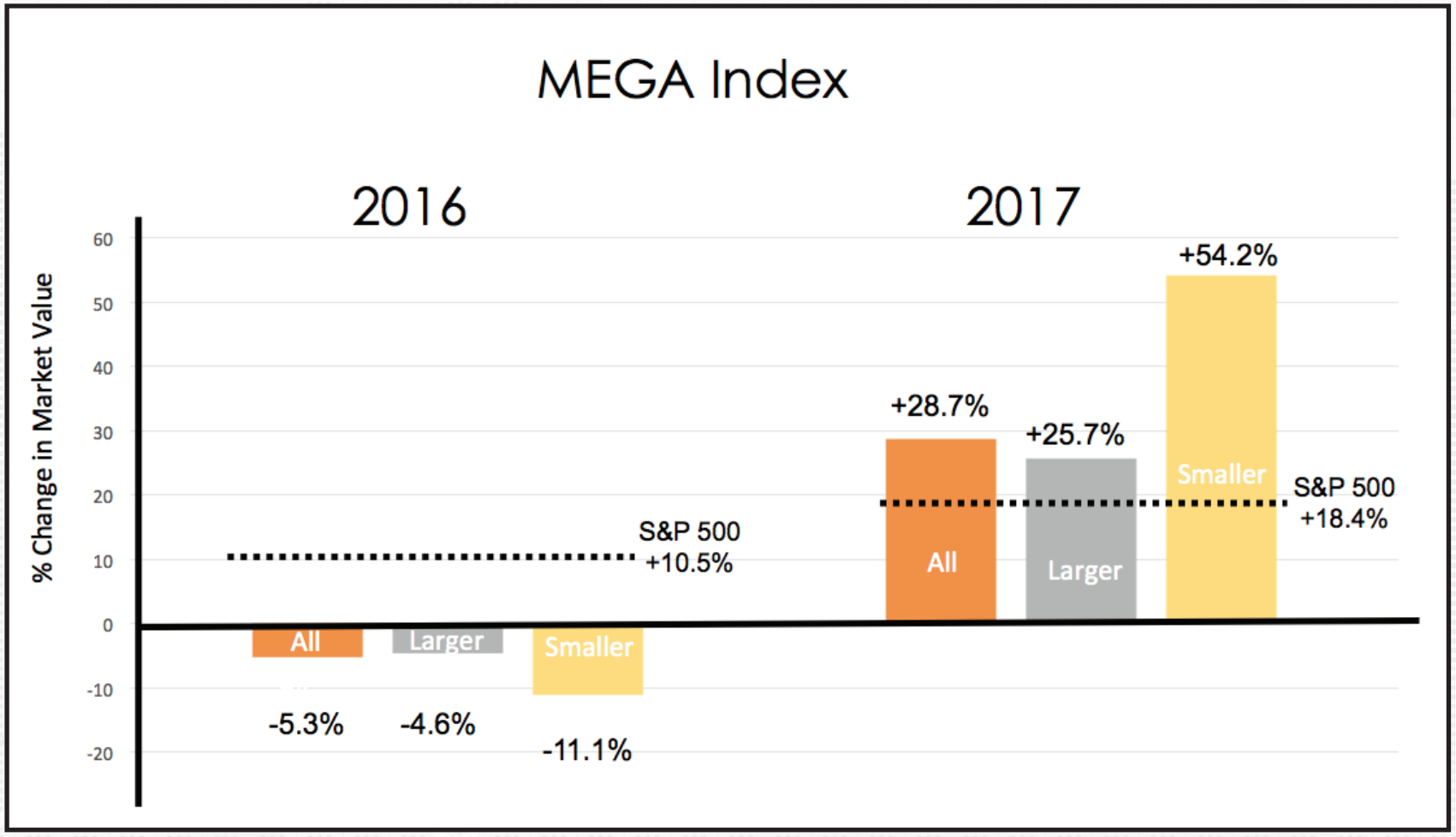
2017 saw Diagnostic companies and their investors rewarded in the stock market.

# Investor Interest Increasing

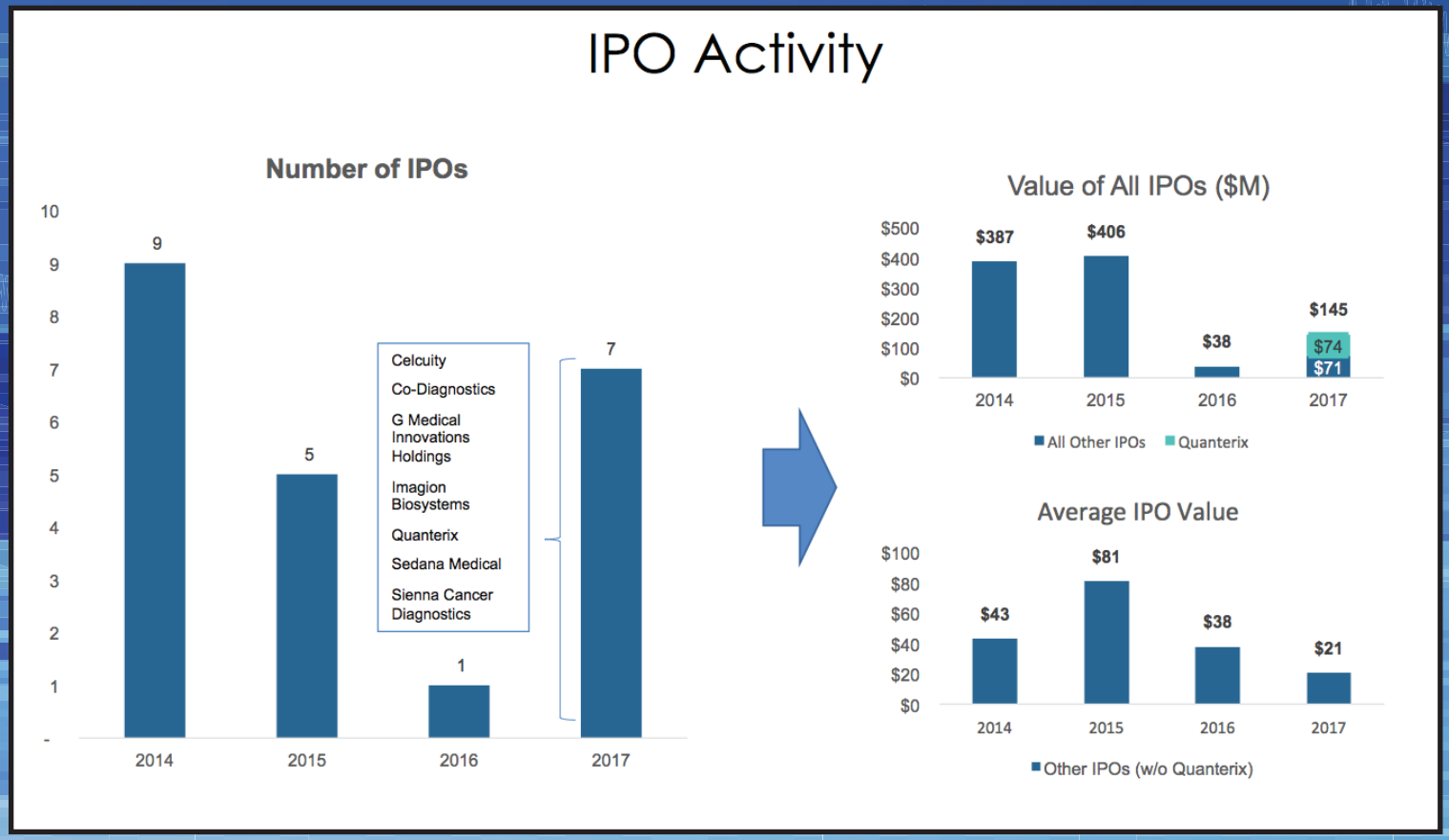
**MEGA Public Markets Index 2016:** 2016 saw was a year that the Diagnostic industry fared poorly in the public markets. In contrast, the S&P 500 appreciated 10.5% while investors in diagnostics (as measured by the MEGA Index) saw declines of 5.3%. The declines were even greater in the many smaller early stage public companies (smaller companies defined as those with less than $1 billion in revenue), whose aggregate value declined by 11.1%, more than 20% worse than the S&P 500.

**MEGA Public Markets Index 2017:** 2017 saw a substantial rebound where, on average, public diagnostics companies made up all of 2016's lost ground and surpassed the gains of the S&P 500. 2017 saw a major across the board recovery, but the biggest gains were among the smaller company group, which saw appreciation of 54.2% in the MEGA. Smaller companies are frequently more volatile than larger ones, but we believe this is a long-awaited re-awakening of interest in diagnostics investment, reaching a more appropriate balance with the traditionally stronger therapeutics arena. Real progress adding molecularly specific novel therapeutics has been made, but with treatment costs for cancer per course accelerating toward $1million or more, the value of getting the diagnosis correct the first time (and monitoring response) is also rising. The small public company market highlight of the year was Exact Sciences – the market value rose almost 350%, with revenue up almost 150% to $87 million.

# Investor Interest Increasing *Continued*



# Investor Interest Increasing *Continued*

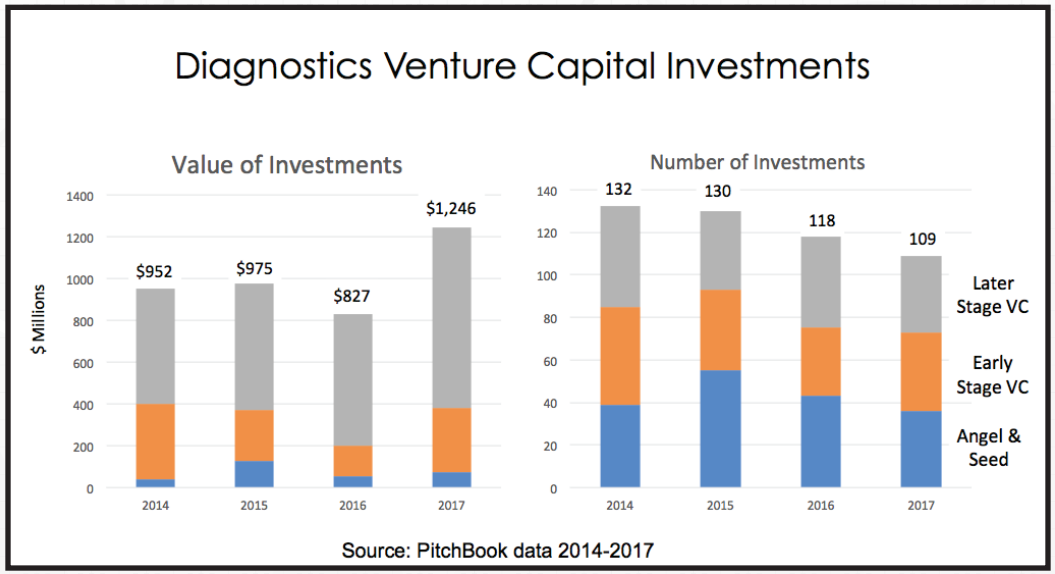



**IPO's:** Market optimism did not translate to meaningful diagnostic IPOs. There were only seven (7) IPOs throughout 2017, about the same number of companies that were delisted. Of the seven, the largest by far was, Quanterix which raised $74 million. The other IPO's were all under $25 million.

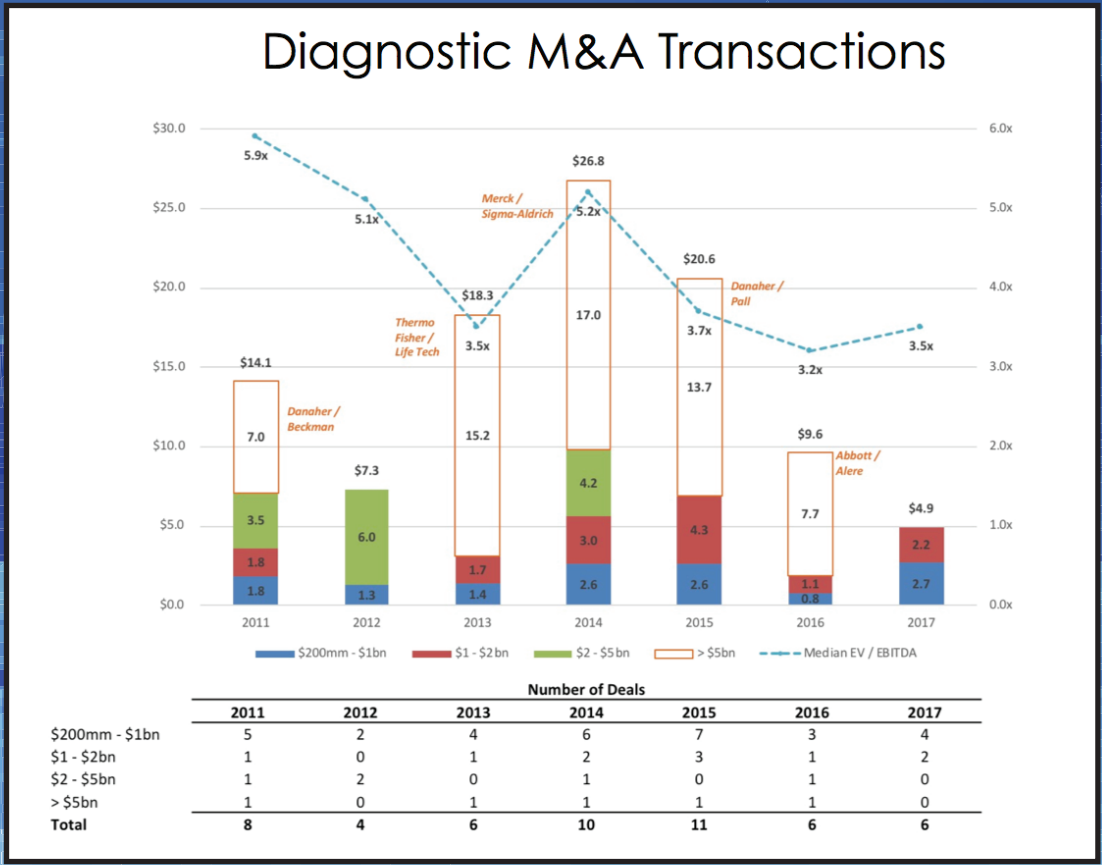
# Investor Interest Increasing *Continued*

**VC Investment:** Venture investors appear to be becoming more comfortable with Diagnostics opportunities, with a 51% increase in funds committed in 2017 to a total of $1.2 billion from the low levels of 2016, according to PitchBook data. 2017 is higher than either 2014 or 2015. This increase was primarily in the early and later stage venture capital rounds that finance the critical stage of moving seed and angel round science into the clinical laboratory.

Offsetting this positive trend was a reduction in the number of Angel or Seed investments made in 2017, down to 36 from 2016's 43, which itself was down from a recent high of 55 deals in 2015. This is the part of the venture financing equation that is hardest to track as many private deals go formally unrecorded and data is sketchy for the value invested in these very early rounds. Nevertheless, this start-up phase news if true is a disturbing trend. The number of investments in the substantially larger and better tracked early and late stage VC was essentially unchanged (73 vs 75 deals), but the value committed to each deal was substantially up - early stage average investment was up 80% over the $4.6 million in 2016 to $8.3 million in 2017; later stage average investment was up slightly less at 64% from $14.6 million in 2016 to $24.0 million in 2017. Early returns would say this positive trend is continuing in the first quarter of 2018, which is very good news for the degree of innovation that our industry is bringing to meet urgent and critical patient needs.



# Investor Interest Increasing *Continued*




Number of Deals

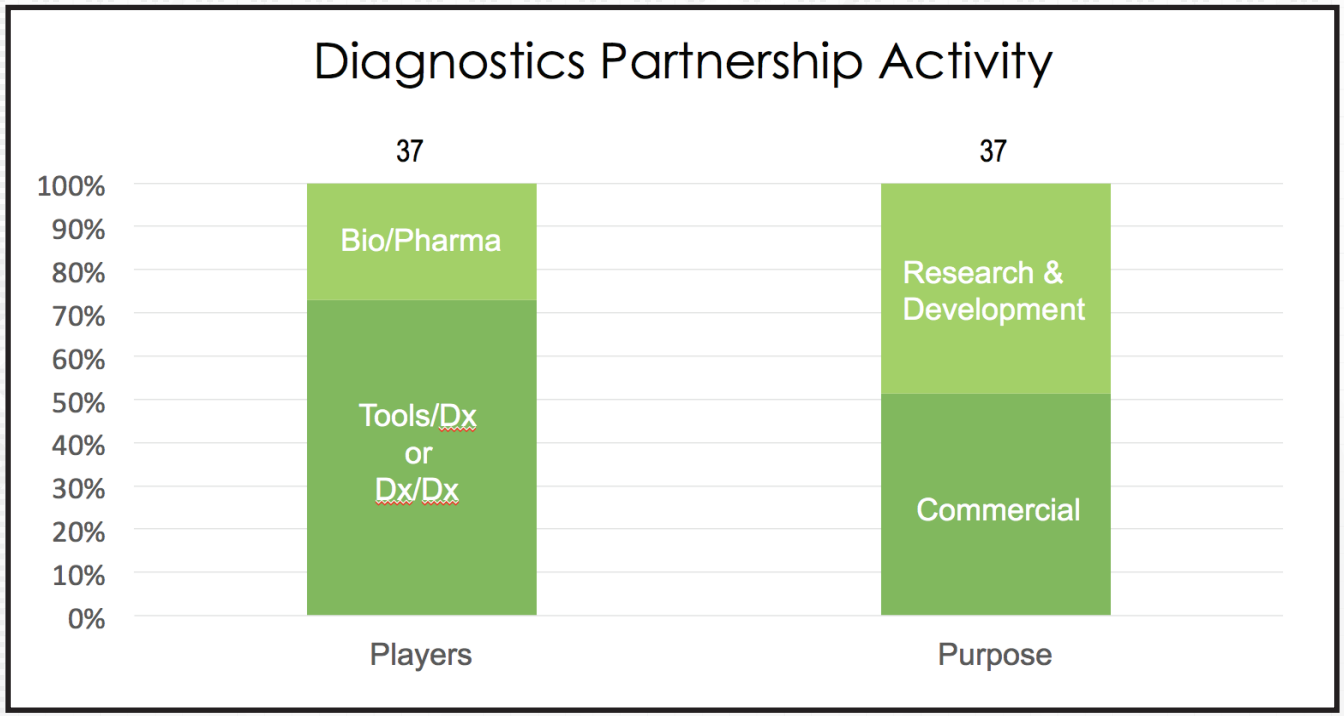
| | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|
| $200mm - $1bn | 5 | 2 | 4 | 6 | 7 | 3 | 4 |
| $1 - $2bn | 1 | 0 | 1 | 2 | 3 | 1 | 2 |
| $2 - $5bn | 1 | 2 | 0 | 1 | 0 | 1 | 0 |
| > $5bn | 1 | 0 | 1 | 1 | 1 | 1 | 0 |
| **Total** | **8** | **4** | **6** | **10** | **11** | **6** | **6** |

**M&A:** 2017 takeover activity ($200 million or more) showed an uptick from the very light 2016 market but still lower than it has been over most of the last few years. In 2017, six deals closed. The largest was Hologic's $1.9bn divestiture of their Gen-Probe division's share of a European blood supply molecular testing business to Grifols. (Hologic bought Gen-Probe for $3.7bn in 2012.) A similar post-acquisition rationalization deal of a smaller size was Siemens' purchase of two businesses from the former Alere portfolio for $680mm. The remaining five deals, were traditional exits (buyouts) of smaller but highly successful companies with a core diagnostic technology and market position developed to a scale and momentum to be of interest to a larger company. Examples were PerkinElmer's continued expansion with the $1.5bn to acquire Euroimmun and Tulip Diagnostics; Konica-Minolta acquired Ambry Genetics ($800mm upfront, plus $200mm in milestones) to build genetic panels into its imaging products.

# Investor Interest Increasing *Continued*

**Partnerships:** The Pharmaceutical and Biotech companies which have traditionally placed Diagnostics partners in the back seat are beginning to change their approach. The growing role of diagnostics in directing successful clinical development is evident from important pharma-diagnostic deal making in 2017: including Bristol Myers-Squibb's partnership with Qiagen, Janssen with Genome Health, Myriad with Clovis Oncology and Invitae with Alnylam. Bio Pharma seems to be acknowledging that they need diagnostics expertise as part of their team early in their development process.

The ten Biotech or Pharma / Diagnostic deals still represent only a minority of a total of 37 partnership deals, but they could account for a significant part of the future revenue to both parties. The remaining 27 deals were between Life Science Tools and Diagnostic companies or joint efforts between two diagnostic companies. These intra-industry deals represent a maturing of the Diagnostic industry, recognizing that best in class development is a team sport. In looking at all deals, they were split equally between diagnostics development and commercial arrangements.



# Thoughts on the Future *Continued*

**Reimbursement:** Rarely does a review of the Diagnostic market occur without mention of ongoing reimbursement challenges. 2017 is no exception but we don't yet have clarity on whether recent changes will turn out to be net better or worse for our future. So – for this year – just a brief mention of the biggest reimbursement concern - the effect of PAMA (Protecting Access to Medicare Act) implementation. PAMA was designed to reduce the cost of Medicare patients' diagnostic testing because of a 2013 OIG report that showed that the toughest commercial contracts were lower than Medicare. This issue goes beyond Medicare because its prices are a broadly accepted reference price for smaller commercial and public payors. The current consensus is that PAMA will reduce clinical laboratory revenues and income by 6-10%. The industry has tried many avenues to repeal, delay or modify this program, including the courts, yet to date without success. Hospital laboratory prices were not included in the data gathered to set prices; and the impact of this new pricing methodology will not be felt evenly. Hospital laboratory prices were excluded from Medicare's data gathering process, in part because inpatient diagnostics is bundled into the inpatient treatment code not via the CLFS (Clinical Laboratory Fee Schedule), ignoring that one half of hospital laboratory business is outreach that competes under the CLFS. Larger regional and national reference laboratories have already had to find ways to be profitable at the low contract prices and are diversifying into clinical trials and other less price regulated businesses.

For more complex and innovative tests there are positive aspects to PAMA that protect pricing and profitability in the interests of developing novel tests quickly. Most of these are only available from a single laboratory as an LDT that therefore controls its own prices. There is a transition/introduction provision for new tests to be priced separately until their market and utility becomes clear. These tests tend to be lower volume, and even at higher average prices account for very little of the total CMS budget, and are therefore not a primary focus for CMS. For the many new smaller companies PAMA is seen as providing pricing visibility and predictability once final PAMA decisions are made.

**Out of the Shadows:** Diagnostics may now be at an inflection point. We have been in the shadow of therapeutics, but recent events show us emerging into the light. Patients (all of us) are getting smarter, more sophisticated and less frightened of genomic data and the medical insight it offers. Patients are paying out of their own pockets for their DNA – at least snippets of it. Physicians are learning rapidly – often from their patients and their questions. Drug researchers are integrating diagnostic knowledge earlier in their process and paying diagnostics enough to make it a meaningful partnership from both sides.

# Thoughts on the Future *Continued*

**Diagnostics becomes a Data Business:** Most exciting yet still not fully developed is the use of big data in diagnostics. We have been saying that the Diagnostics Industry will soon be a "Data Business with a Wet Lab on the side". Laboratories and diagnostic developers are scrambling to hire data scientists and bioinformatics experts at a dizzying rate. The cost of wet lab operations continues to decline with higher volume and automation consolidated in an ever-smaller number of larger players. Electronic Medical Record companies are looking to add record capacity for increased diagnostic data demands. Companies are being bought and sold more for the value of their data than for their IP or operations.

We believe that all this activity will lead to a formalization of a new critical function – Integrated Data Interpretation. Neither physician nor researcher can integrate the volume of complex data arising from the many, increasingly sophisticated tests on their own. The use of gene panel tests will require understanding of the nuances of multiple positive signals, only a few of which inform diagnosis of the immediate pathology. Most importantly, in cancer where future prescribing will be based on the marker and not the organ of the cancer – physical examination and imaging studies will not be enough – data integration across all domains is necessary.

So, prepare for the emergence of the Integrated Data Interpreter. Combining multiple sources of diagnostic data – digital, in vitro, in vivo – will, ultimately, lead to the most accurate diagnoses. Not clear yet is the balance between person and machine, inevitably both will be essential. As this is being written, Roche and GE partnered in January 2018 to do just that: create a clinical decision support system, integrating imaging, genomic, biomarker, patient record, research data and more to enable earlier diagnoses and more targeted treatment plans. This may be the route that non-industry players take to enter diagnostics and healthcare more generally. Amazon, Google, Microsoft have far better capabilities to assemble data, interpret it and analyze it than any traditional healthcare players today. Watch this space closely as the future of our industry will be decided here.

# Acknowledgements

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