

A New Era of Clinical Diagnostics: How the Business Model is Changing.

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Remarks to BTIG Emerging Technologies in Healthcare Diagnostics
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Paradigm shifts in four major areas affecting healthcare - technology, clinical care, regulation and reimbursement – are having a major impact on the market for diagnostic testing.

Technology:

- The decreased cost and increased speed at which we are able to sequence a single human genome has made it possible to create **new kinds of diagnostic tests** based on a patient's unique genetic blueprint that can **diagnose a disease and predict which treatments are going to be most effective.**
- Under the **old regime of single analyte testing**, patients often underwent **multiple rounds of testing with inconclusive results causing delays** in identifying and administering the most effective treatments. This is especially important in **cancer care when time is short and the necessity of making an accurate diagnosis with the targeted treatments is critical.**
- Today, **multi-analyte panels** are being developed that can test patients for multiple chemical and genetic substances at one time. Determining the genetic variation that is causing a cancer is important to the **avoidance of ineffective and often toxic treatments like chemotherapy, assuring the highest quality of care.**
- Even more important is determining if a patient has **variants that are actionable...** meaning for which there is currently a therapeutic intervention that might work.
- In addition, the FDA has recently **given its approval to next generation sequencing technologies for use as clinical diagnostic platforms.**
- But sequencing for research is different than sequencing for clinical care.
 - In order to demonstrate the validity of a test using next gen sequencing, we need to be able to demonstrate that such a

diagnostic test is better than the current preferred method of diagnosing a particular disease.

- In order to **establish the value of a diagnostic test in clinical care**, it is important to know,
 - **How will the test be used in the clinical setting?**
 - Will the information received from the test result in a patient management decision and **change the course of treatment?**
 - If so, did the decision result in a **positive patient outcome?**
- Acquiring the data to answer these questions requires a sufficient volume of testing that can be difficult to achieve for a new product. Medical necessity and clinical utility difficult to establish.
- In addition, sequencing for clinical care needs to be much more accurate and precise than for research. **Sensitivity (true positives) and specificity (the absence of false positives) are important to determine positive predictive value (PPV)**, which must be as close as possible to 100% as possible in clinical situations where decisions about treatments that lead to life or death are being made.
- **Standardization** or the reproducibility of results from patient to patient is also an important element.

Clinical Care:

- There is a **seismic shift** occurring in clinical care right now, as medicine moves away from treatment based on **one size fits all to targeted interventions** based on a patient's genetic makeup.
- The current goal is to initiate **preventive, prospective interventions** before one gets sick rather than retrospective interventions.
- When a patient does get sick, the ability to predict whether and **how a patient will respond to available treatments** – means doctors and patients can make more informed decisions about choosing treatment over other approaches such as palliative care... especially at the end of life.
- The shift toward precision medicine faces huge challenges however. **Physicians are not prepared for this shift.** Only between 9% and 21% of physicians use genetic tests.

- Many **physicians say they don't understand genetic tests well enough to use them effectively.** In interviews Nancy J Kelley & Associates has conducted, the following **five factors were most important in influencing a physician's decision to use this approach:**
 - Actionable, sensitivity + specificity, ease of use, turn around time and reimbursement.
- It is imperative to educate clinicians and build a supportive environment around them for the use of these tests and the information they provide.

Regulation:

FDA:

- Tests that are sold as **diagnostic kits require FDA clearance** – a long and expensive process.
- Until now, the **FDA has not regulated laboratory developed tests (LDTs - CLIA)** but in the past has stated it has the right to do so.
- With the continued development of personalized medicine, advances in technology and business models, **LDTs are now more complex, have a nation-wide reach and present higher risks.**
- Recently, the FDA has come under **tremendous pressure** both within and without the agency **to regulate all LDTs.**
 - Those arguing for increased regulation point out the **importance of accuracy** in diagnostic testing so that patients and health care providers **avoid unnecessary treatments, do not delay needed treatments or be exposed to inappropriate therapies**, which could result in illness or death. They stress the need for accurate, consistent and reliable results.
- On July 31, 2014, the **FDA has released a draft framework for LDTs based on risk to patients** rather than whether they are made by a conventional manufacturer or a single laboratory. This **draft oversight framework includes pre-market review for higher risk LDTs**, like those used to guide treatment decisions, including the many companion diagnostics that have entered the market. The FDA would continue to exercise enforcement discretion for low-risk LDTs and LDTs for rare diseases.

- After statutory period for comment passes, FDA will issue draft guidance. Framework will be phased in over several years.
- **If FDA clearance becomes mandatory for a given test**, no payer will be able to develop or maintain a positive coverage policy until the test becomes compliant with clearance.

Reimbursement:

- **Objectives:**
 - Cover cost
 - Contribute to margin
 - Maximize reimbursement opportunities
- In order to establish reimbursement, **must establish analytical and clinical validity**, have a sufficient amount of data analysis that appears in peer-reviewed publications and demonstrate that the test has become the **accepted standard of care**.
 - Tests have to be actionable and improve the available information for physicians.
 - The results of the test require an **objective evaluation based on scientific evidence and clinical utility** which is very difficult to establish without the proper volume of utilization.
- Right now, there is **no established methodology for billing for Next Generation Sequencing**.
- Currently, molecular diagnostics and **NGS panels are billed with single analyte CPT codes for those genes embedded within a panel** which has led to a variety of pricing approaches.
 - **Stacked codes**, adding up the reimbursement rate for the CPT codes covered in the test being performed. The problem with this approach is that the resulting reimbursement rate may not be enough to cover the test.
 - **Cross-walking** the current molecular diagnostic codes to new NGS codes, when it is determined that the new service is comparable to something being coded and priced.
 - **Gap filling** when nothing is close to the methodology so a new price is created allowing consideration of the costs of performing a test as well as amounts allowed by third party payers.

- **Average reimbursement rate.**
- **Mixture of approaches above.**
- Finally, obtaining a **miscellaneous code** such as a Z code, that doesn't have pricing associated with it on the clinical fee schedule – allows the setting of a reimbursement rate based on the value of the test. Z codes can help to establish specific pricing for a unique panel.
- Medicare is currently evaluating codes for both next generation sequencing (NGS) and molecular diagnostics; new codes will be available for use effective 1/1/15. CMS recently accepted an NGS code that will cover genomic sequencing procedures and multi-analyte testing for 5-50 genes. No decision has been made as to whether they will use cross walk or gap filling to price NGS.
- The Protecting Access to Medicare Act of 2014 set the ground work for a market based payment model for Medicare rates beginning 1/1/2017. 2015 and 2016 will be critical in establishing market based values for NGS before this model is implemented.

Business Model

Due to all of the challenges described above, good science and technological innovation does not always translate into commercial success in the molecular diagnostics industry.

There are many challenges to building the right business model including establishing clinical utility, pricing, reimbursement, continued research and development, market penetration and acceptance.

Nevertheless, some great success stories are emerging that will change the future of diagnostics and healthcare. It will be interesting to see what develops.