



How to Think About Companion Diagnostics

Seven Questions to Consider

Introduction

Personalized medicine is one of the catch phrases of the 21st century, and with good reason. Advances in genetics and biochemistry promise to tease apart factors that explain why some patients benefit dramatically from a therapy while others receive no benefit at all, and lead some to experience side effects on medicines.

In order to accomplish such lofty goals, drugmakers are increasingly partnering with diagnostics companies to develop companion biomarker technologies. Diagnostics companies operate in a very different business and regulatory environment than bio-pharma companies, and partnerships can be complicated by contrary goals and misunderstandings. Before entering such a relationship, you should understand your potential partners' world view and economic incentives, as well as recognize potential pitfalls.

In considering a partnership with a diagnostics company, evaluate the following:

1. Do you understand the value proposition that a diagnostic brings to your drug?

Companion diagnostics may enable yet limit opportunities. A diagnostic can benefit patients by identifying those most likely to respond to a drug and least likely to suffer side effects. It can help investigators select patients most likely to produce cleaner data, thereby reducing sample sizes and development costs. Market size might be increased if a diagnostic identifies suitable

patients receiving a competing drug. A diagnostic may rescue a drug candidate that might otherwise fail. Companion diagnostics may limit opportunities by eliminating some who would otherwise be prospective patients, potentially reducing market share (e.g., overuse of antibiotics in patients with acute sinusitis, even though 90% of infections are caused by viruses, not bacteria; a rapid diagnostic would greatly reduce that market).

Bio-pharma companies must weigh advantages and disadvantages when making the decision to pursue a companion diagnostic. The balance of a companion diagnostic's advantages and drawbacks is typically favorable when a drug meets two criteria:

- An identifiable subset of a disease population exists that is a candidate for the drug
- Physicians are not likely to prescribe the drug without the diagnostic due to cost, side effects or other reasons

Identification of biomarkers allowed Roche and Novartis to reduce patient sample sizes and still gain approval for Herceptin® and Gleevec® respectively. Pfizer's Selzentry® would have failed clinical trials without identification of and focus on a responding sub-population.

If the decision to develop a companion diagnostic is not favorable for your drug, also evaluate whether your competitors' incentives are the same. Would your competitor reach the same conclusion?

Questions to Ask

1. Do you understand the value proposition that a diagnostic brings to your drug?
2. Have you considered all the adoption hurdles that diagnostics face?
3. Is there enough competition within the market for your diagnostic and why is this essential to your success?
4. Do you understand how the perspectives/motivations of the diagnostics company differ from yours?
5. Does your regulatory team appreciate that diagnostics play by different rules?
6. Will managed care or central payers pay for your diagnostic?
7. Is the diagnostics market a "one size fits all" market?

2. Have you considered all the adoption hurdles that diagnostics face?

Companion diagnostics are not saviors. They add to the up-front research and development costs before their utility is proven.

At the time of product launch, the diagnostics science and technology may not yet be at the same confidence level as a drug would be and the true relevance of chosen biomarkers to clinical outcomes may still be considered indirect and less than 100% predictive. Sensitivity of the diagnostics technology to specific biomarkers, reducing the occurrence of false positives or negatives, may be in its early stages.

Even if the test is ready, the market may be reluctant to immediately accept the diagnostic. Convenience, costs, and speed of the technology / testing platform may not yet be optimized.

The rapid strep test took twenty years to be implemented after the technology was developed. It first took ten years to develop the correct technology, then another ten years for the clinical guidelines to be changed and uptake to grow. *See chart below on rapid strep test adoption.*

Hurdles to diagnostics adoption can differ by country. Not every country has the same infrastructure or willingness to pay for diagnostics.

3. Is there enough competition within the market for your diagnostic and why is this essential to your success?

Bio-pharma companies should foster competition between diagnostics companies to spur on next generation tests, if

possible. Wedding a drug to a single diagnostic platform can be a poor fit for the target market. Once a diagnostic has been successfully developed and launched, its cost and reliability, not to mention clinical utility, is central to its success in the market.

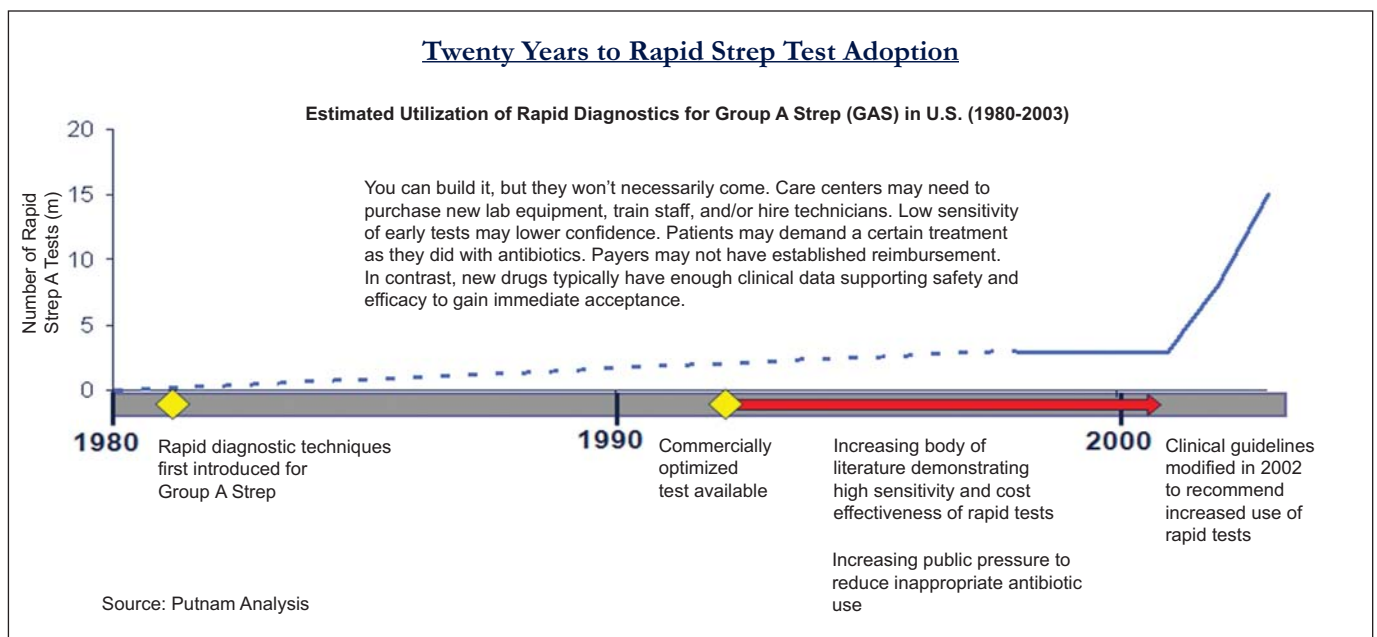
Monogram Biosciences created and focused on maximizing the value of Trofile™, the companion diagnostic for Selzentry®. While the diagnostic was crucial for FDA approval, Trofile™ is expensive with considerable lag time between testing and results. Analysts predicted it would limit Selzentry®'s uptake.

For Selzentry® and other drug products reliant on a companion diagnostic, it may not be possible to predict what the final diagnostic will look like or how expensive it will be at launch, but the diagnostics company will be focused on the value of its product, just as Monogram demonstrated when they announced the unexpectedly high price for Trofile™. Early development of competing diagnostics would have greatly limited the market power of Monogram's strategy.

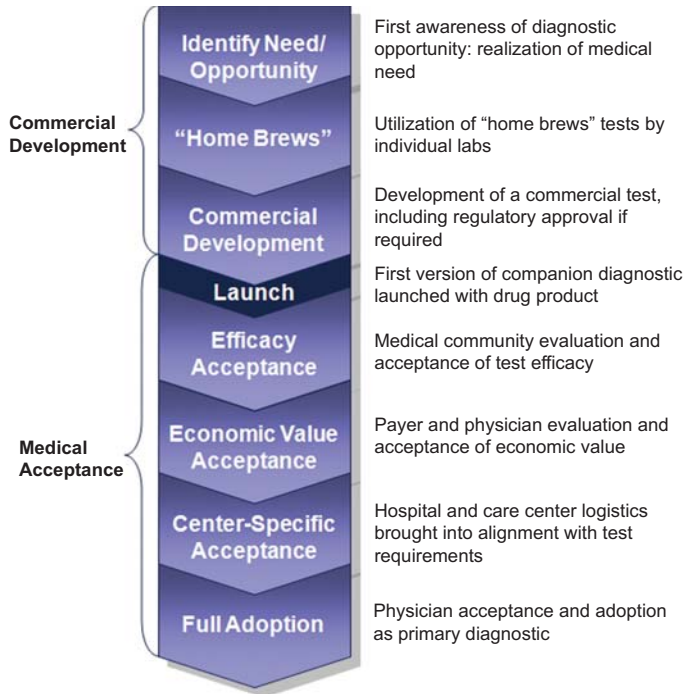
If a diagnostic winds up on a drug's label, it is important that it be reasonably priced and reliable. If physicians are resistant to employing a diagnostic for any reason, it can have a negative effect on the success of the drug. Pfizer's Selzentry® is one example, and Herceptin® is another, having been somewhat victimized by a diagnostic that relies on a technique with questionable accuracy (fluorescence *in situ* hybridization).

4. Do you understand how the perspectives / motivations of the diagnostics company differ from yours?

The diagnostics business model differs significantly from that of drugmakers. While some diagnostics companies have the



Diagnostic Adoption Hurdles



Source: Putnam Analysis

resources or are affiliated with a large corporation, most are usually not as well capitalized, making them more risk averse and less likely to embark on prospective clinical trials, or enter emerging markets without some degree of certainty. Diagnostics companies may therefore demand concessions from a potential partner, such as a financial investment or a fee-for-service agreement.

In addition to financial investments, diagnostics companies also are trending towards developing intellectual property around their tests or otherwise retaining rights to the test after

launch in hopes of creating a long-term revenue driver. With the increasing value of diagnostics, companies are pursuing both short- and long-term revenue goals.

Unlike bio-pharma companies that see a "drugable target" and pursue multiple pathways to unlock value, diagnostics companies typically use a single technology platform, which they attempt to leverage across multiple applications. Thus, in order to minimize technology and market risk of a diagnostic, bio-pharma companies should ally with several diagnostics companies or a larger technology diagnostics company to pursue multiple biomarkers and technologies.

5. Does your regulatory team appreciate that diagnostics play by different rules?

Diagnostics companies operate under very different regulatory pressures than bio-pharmaceutical companies. Diagnostics face a much lower regulatory burden than drugs and have a shorter life cycle. Some diagnostics do not require FDA approval, are launched with less supporting clinical data than physicians and payers are accustomed to seeing for pharmaceuticals, and are often not reimbursed. As a result, the medical community may be skeptical if costs are high, convenience is low, and false test results are frequent. It can take years, up to a decade or more, to achieve widespread use of a new diagnostic.

6. Will managed care or central payers pay for your diagnostic?

Diagnostics are not always accepted by insurance companies. Insurers typically insist that a diagnostic directly contribute to a better outcome in order to be reimbursable.

From the insurer's perspective, a diagnostic must create value, often by screening patients to avoid inappropriate treatment and

Types of Diagnostics and FDA Regulation

Molecular diagnostics fall into three general categories: Test Kits, Lab-Developed Tests (LDTs), and In Vitro Diagnostic Multivariate Index Assays (IVDMIAAs). The latter two are sometimes referred to as "homebrews."

Test Kits are made and marketed for any lab to use; the entire process of specimen collection through testing to results can be done in many settings. Examples include pregnancy tests, flu tests, allergy tests, and breathalyzers. Test Kits are regulated by the FDA.

Lab-Developed Tests (LDTs) are analyzed only by the proprietary laboratories that developed them, although specimen collection can be done anywhere. Genentech's HER2 diagnostic falls under this category. LDTs are generally not FDA-regulated (exception: IVDMIAAs), although the lab is usually inspected for safety by CLIA (Clinical Laboratory Improvement Amendments). LDTs are usually fast to market but may carry a credibility stigma due to the absence of regulation. Proliferation of competing LDTs can be rapid and uncontrolled by the pharmaceutical company that commissioned the original. Genentech has petitioned the FDA to encourage regulation of LDTs in an attempt to clear the market of poor-quality HER2 diagnostic tests.

In Vitro Diagnostic Multivariate Index Assays (IVDMIAAs) require proprietary, complex mathematical algorithms to analyze results; physicians cannot interpret the results directly. An example is the AlloMap® test used to manage potential for organ rejection in heart transplant patients. IVDMIAAs are frequently LDTs (developed and used only by proprietary labs), but are FDA-regulated.

reduce costs. The more expensive a diagnostic is, the greater its cost savings benefit must be to justify the expenditure.

For example, recent diagnostics offerings by some companies such as 23andMe and Navigenics provide patients with risk profiles for developing various conditions such as heart disease or cancer. Patients may find such tests interesting and useful for taking control of their own preventive measures, but insurers will not cover them because they do not dictate treatment decisions.

As one pharmacy director put it:
 “These tests are expensive, so it would depend on how definitive the answer of the test is. If a test were available for a definite go or no-go decision on treating a patient, I would be interested.”

Diagnostics face a further hurdle in that they frequently have little supporting published clinical evidence at the time they are introduced. Insurers are looking for published studies that demonstrate clinical utility. More often than not, published studies do not exist and insurers are left to make decisions with what imperfect information they have.

7. Is the diagnostics market a “one size fits all” market?

Not every physician has the same expectations of a diagnostic. Diagnostics generate Type 1 (false positive) or Type 2 (false negative) errors on a case-by-case basis, and these are important concerns for physicians. Some require accuracy at all costs and are willing to wait days or weeks to avoid false positives. Others need a result quickly and can accept a high false positive or negative rate. It is important to consider the consequences of false positives (increased expense, potential side effects of powerful therapeutics) and false negatives (untreated patients, inappropriately treated patients), and utilize or design a diagnostic with appropriate capabilities. Though dependent on the specifics of the medical situation, physician preferences play a role. Physicians weigh test results, costs, medical risks, and convenience.

When developing a diagnostic, companies should consider which trade-offs are more acceptable to the physician who will order the test. Those with patients who are at immediate risk of a condition will have no use for a test with a high rate of false negatives regardless of cost and convenience. On the other hand, the same physician might accept a high false positive rate as long as the safety risk and cost of the accompanying treatment are comparatively low.

Conclusion

Companion diagnostics must be viewed with a broader understanding of the diagnostics environment. They are useful, but like any new venture or research direction, there are roadblocks and pitfalls to navigate.

Consider carefully the value a companion diagnostic brings to your drug. Will it reduce market share by eliminating from consideration patients who would otherwise receive it? Or will it increase market share by identifying patients who would have otherwise been overlooked? Can you implement the design of the diagnostic to emphasize the latter?

Then think about the physicians who will use the diagnostic and prescribe the accompanying drug. Do they need a fast test? An accurate test? An inexpensive test? Chances are, you will have to make some trade-offs: fast and accurate, but expensive; cheap and fast, but inaccurate; or cheap and accurate, but slow. Make certain the test you develop is in line with physician and payer needs.

And finally, encourage competition. Wedding your drug to a single diagnostic platform can be a poor fit for the target market. Instead, in the early stages of clinical research, conduct exploratory studies with companies using a variety of platforms, and then select the most promising for further development.

Follow these steps, and the marriage between your drug and its companion diagnostic is likely to be a happy one.

About Putnam

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