Case Summary 1/12

This case will help you understand:

Why Roche, in hindsight, did not optimally manage the operational implementation of Human Epidermal Growth Factor Receptor 2 (HER2) testing.

How Roche's lack of proactive Dx optimization impacted physicians' initial experience of Herceptin as a targeted therapy.

The negative financial impact that this suboptimal Dx implementation most likely had on Herceptin's brand performance.

The most important areas of 'leakage' in the Dx program that led to the loss of patients for Herceptin.

Key messages:

A pharma company with an Rx asset dependent on a test should take a proactive approach to managing the Dx environment from the outset, in order to drive adoption and avoid implementation flaws.

Physicians can be put off using a promising new targeted therapy if the Dx environment is not a straightforward exercise optimized to suit their needs.

A suboptimal Dx environment can cause substantial financial losses to an Rx asset.

There are several potential areas of considerable 'leakage' in any Dx environment. This leakage can result in the loss of patients demanding testing (for a drug that depends on such a Dx environment) and in the population indicated for testing by guidelines.

Key actions:

Understand the current Dx routine at the physician's office.

Understand propensity to prescribe (P2P) in terms of your plan. Prepare and revise your Dx strategy.

Prepare for a Dx technology evolution.

Herceptin is Indicated for Breast and Gastric Cancer 2/12

-----INDICATIONS AND USAGE-----

Herceptin is a HER2/neu receptor antagonist indicated for:

- The treatment of HER2-overexpressing breast cancer (1.1, 1.2).
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma (1.3).

Source: http://www.accessdata.fda.gov

So What?

Herceptin's enormous success as a targeted therapy is well known. But examining its story in detail provides valuable insights into the evolution of today's personalized medicine market.

Commentary

Herceptin is the poster child for personalized medicine, but a New York Times piece in June 2007, based on comments made at the American Society of Clinical Oncology annual meeting in 2007, suggested there had been diagnostic problems for more than a decade. But what's the real story?

Herceptin - an Example of Flawless Personalized Medicine Execution? 3/12

The New York Times

Cancer Drug May Elude Many Women Who Need It

CHICAGO — The breast cancer drug Herceptin is considered the model for the future of medicine tailored to each individual. The drug is given only to the 20 percent of breast cancer patients whose tumors have a particular genetic characteristic.

But now, nearly a decade after the drug's approval, evidence is emerging that the testing of the tumors can be highly inaccurate or that the wrong cutoff values are being used to determine who qualifies for treatment.

That could mean that as many as 40 percent of women with early breast cancer might benefit from the drug but are not getting it, some experts say. Yet other women may be paying for the drug and risking its side effects unnecessarily.

Dr. Pamela M. Klein, an executive at Genentech, the manufacturer of Herceptin, said the company was continuing to explore how to best identify patients for the drug.

"Here we are, 10 years into it," said Dr. Marc L. Citron, an oncologist in Lake Success, N.Y., "and we don't know how to test for it."

Source: The New York Times, June 12, 2007

So What?

Herceptin is financially and clinically successful, proving personalized medicines can generate blockbuster sales.

However, Genentech, the company that developed Herceptin, took a long time to take charge of and drive the companion diagnostic market.

Commentary

The chronology of the development of the HER2 testing market illustrates a typical diagnostic market development. The testing market has to date been developed by taking the following three routes:

1. Immunohistochemistry (IHC)
2. Fluorescence in situ hybridization (FISH)
3. Chromogenic in situ hybridization (CISH) which uses a DNA probe to look at the HER2 gene in a small sample of stained tumour tissue.

Herceptin and Dako's first generation IHC HER2 tests were approved by the FDA on the same day in 1998. But these tests did not work very well, identifying only half of the 25 per cent of breast cancer patients who might respond to Herceptin.

Around 2002, a second generation FISH technology launched by PathVysion was much more successful. The problem was that it proved difficult to export the technology from one testing laboratory to another. Dako's second generation diagnostic CISH test launched in 2005.

Since 1998, three different types of testing platforms have been used to detect HER2 overexpression, helping to build Herceptin's global sales to $4bn a year.

Herceptin Sales Grow Steadily Over Ten Years, Helped by an Evolving Dx Market 4/12

Dako

1999 - HercepTest (IHC): approved same day as Herceptin (1998)

PathVysion

2002 - Vysis Pathvision FISH test approved and added to Herceptin label

VENTANA

2005 - DakoCytomation Her2 FISH pharmaDx test approved

invitrogen

2008 - Genetic Test by Invitrogen called the SPOT-Light HER2 CISH Kit approved by FDA

VENTANA

2010 - Two molecular tests launched for breast and gastric cancer

Source: http://www.roche.com

So What?

A lack of coordinated market development for Herceptin testing caused diagnostic issues.

Commentary

Our current understanding of the evolution of IHC and FISH testing methods reveals significant accuracy problems with the companion diagnostic test techniques that have helped to build the Herceptin market.

The issues raised at the American Society of Clinical Oncology in 2007 illustrate the frustration felt by doctors in using and interpreting routine HER2 tests. Key criticisms at the meeting included a lack of coordinated market development for HER2 testing, leading to implementation problems for doctors and laboratories for five to six years after launch.

Herceptin was still highly regarded, but the problems have led to negative perceptions of Genentech's market development. It was allowing the diagnostic market to operate on its own instead of driving it towards efficiency.

Roche's 2008 acquisition of Ventana, the companion diagnostics company, is likely to have been driven largely by a desire to own a large part of the HER2 diagnostics market and thereby improve the quality of testing.

Problems in Diagnostic Implementation 5/12

American Society of Clinical Oncology, Chicago 2007.

> *Dr. Michael Press, a pathologist at the University of Southern California stated 'as many as **one third** of positive antibody tests could be **false positives**'. One study found that when five pathologists looked at the same slides, they disagreed on the diagnosis in half the cases.*
>
> *Dr. Dennis Slamon of UCLA, who is largely credited with developing Herceptin, stated 'a high level task force is required to figure out how to reduce errors in testing for HER2'. As a first step, he said, '**any negative tumor samples** of women who got Herceptin in the clinical trials **should be retested** by independent blinded pathologists to make sure they're true negatives'.*

Source: American Society of Clinical Oncology, 2007

So What?

To avoid implementation problems with the test, it is necessary to take 'ownership' and optimize the development of the diagnostic market.

A late start on development of the diagnostic also contributed to Herceptin's implementation problems.

Commentary

Another study went beyond sensitivity problems to examine the key barriers to EU adoption of a companion diagnostic testing based on the history of HER2 and TPMT, a test identifying patients who might develop side effects.

Particularly notable is that even eight years after the launch of HercepTest alongside Herceptin, reimbursement barriers still existed and a fifth of physicians reported difficulty in interpreting the results.

Personalized medicine is more than just the launch of a companion diagnostic with a therapy; it requires 'ownership' of the development of the optimum diagnostic market. Genentech's late start is the main reason it encountered implementation problems with testing. After Herceptin's launch, Genentech collaborated with several diagnostic companies in parallel to develop the diagnostic HER2 market.

Many Physicians Struggle with HER2 Testing Six Years After Herceptin Launch 6/12

Aspect of Dx Implementation	% of Physicians Surveyed Experiencing Problems 2006
Storage and sending of samples	20% and 60% respectively
Reimbursement	50%
Communications with lab	53%
Limited testing capacity	47%
Interpretation of results	20%

Source: Woelderink et al '06

So What?

The adoption of the Herceptin platforms varies significantly.

Inferior technologies are often more widely used than superior ones introduced later.

Commentary

In the typical evolution of a diagnostic market, some testing technologies for the same biomarker will get used frequently while other platforms that may be more accurate, but harder to adopt, will be used less frequently. It will be important to manage the trade-off implicit between the objectives of high quality and high adoption levels.

Herceptin Testing Technologies are Adopted at Varying Rates 7/12

	CISH	FISH	IHC
Signal stability	Archivable	Fades over time	Archivable
Microscope	Bright-Field	Fluorescence	Bright-Field
Magnification	40x	60-100x	20-40x
CProtocol length	Overnight + 3hr, 55min	Overnight + 3hr, 12min	3hr, 2min
Morphology	Good	Limited	Good
Amount of training required	Medium	High	Low
Internal control	Yes	Yes	No
Interpretation	Objective / Quantitative	Objective / Quantitative	Subjective / Qualitative
Overall cost	Medium	High	Low
Market adoption by oncologists in 2008	1-2%	20-40%	100%

So What?

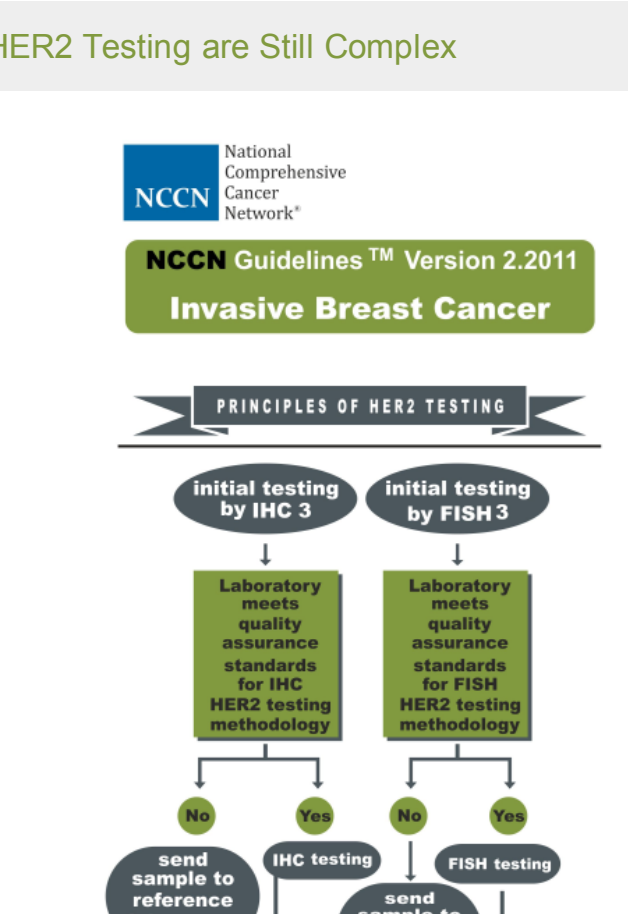
Even a decade after HercepTest, the National Comprehensive Cancer Network (NCCN) believes it is necessary to include special instructions around HER2 testing quality.

Multiple testing and retest steps are required to identify patients for Herceptin.

Commentary

Guidelines for accurate HER2 testing have developed over time. In particular, testing methods have been combined in a reflex algorithm, so if one test outcome is uncertain then a further test is required. It may take a significant amount of time and effort to develop and validate these reflex testing algorithms and ensure their inclusion in the guidelines. Until that point, and given the quality, interpretation and technology issues around HER2 overexpression testing, lack of physician confidence in the results manifests as suboptimal use of Herceptin.

Guidelines for HER2 Testing are Still Complex 8/12



Source: NCCN Guidelines Version 2.2011 Invasive Breast Cancer

So What?

Doctors' lack of confidence in the accuracy of companion diagnostic tests for Herceptin had a direct impact on their willingness to prescribe it.

Propensity to prescribe (or the ratio of therapy prescriptions written to test positive outcomes) is not automatic and needs to be earned.

Propensity to prescribe cannot be assumed to be the same for each indication of the therapy.

Commentary

Propensity to prescribe (P2P), shown here as the percentage of patients who tested positive and who received Herceptin, shows that:

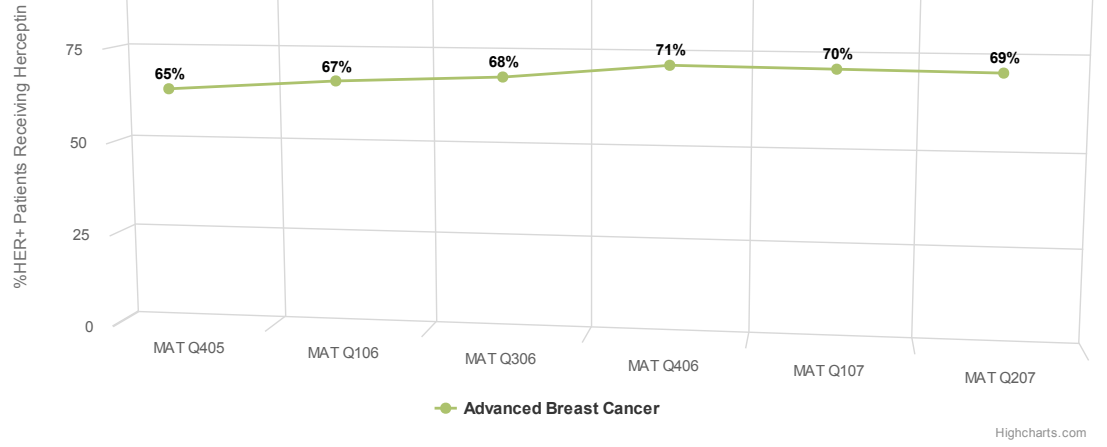
1. Not every companion diagnostic test positive patient receives Herceptin.
2. P2P starts low and increases with a growing confidence in the companion diagnostic test result, ease of access and the provider's view of the competitive niche.

In short, P2P is a reflection of the 'integrity' of the companion diagnostic testing program. Confidence in companion diagnostic testing had a direct impact on prescribing Herceptin.

It is wrong to think that almost all patients who test positive will go on to receive the drug of choice. The reality of personalized medicine is very different and P2P needs to be earned through investment in ongoing clinical research and publication. It is also critical to focus on the P2P ratio and design so that the maximum number of patients testing positive receive the targeted therapy.

As you move from adjunctive to first-line therapy this ratio changes and P2P cannot be assumed to be the same for each indication of the therapy.

Physicians' Propensity to Prescribe is a Key Metric to be Understood 9/12



Even in 2005, the majority of HER2 testing is still relying on the IHC method and up to 20 to 60 per cent variability in sensitivity is reported in HER2 studies. This serves to undermine physicians' confidence in the test answer.

Overall P2P rates remain high, despite testing confidence, as Herceptin is regarded as the only therapy in the HER2 class. Tykerb is eventually launched by GSK in 2008 but does not make a significant impact on Herceptin P2P levels.

So What?

Herceptin is a very successful personalized medicine product, but its sales could have been significantly higher with better diagnostic market preparation.

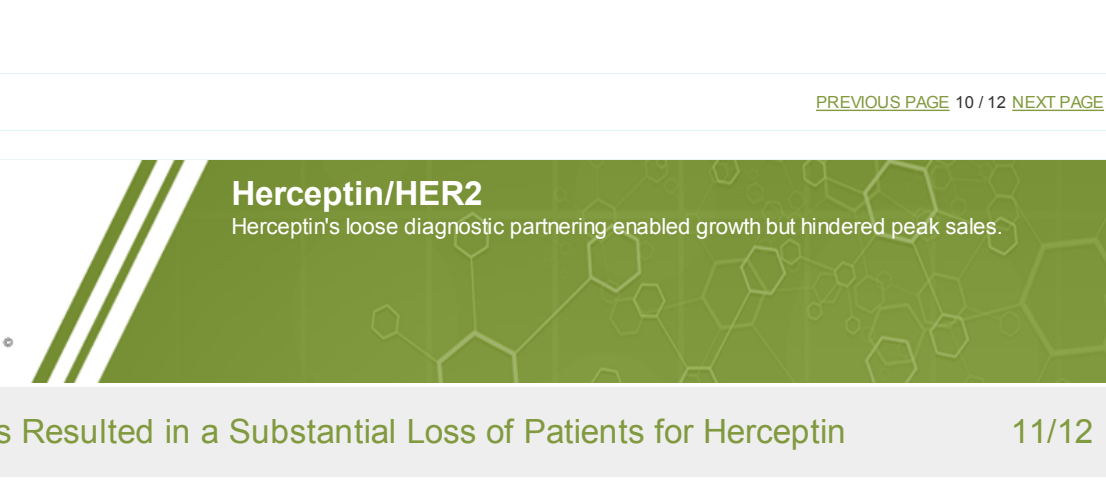
Diaceutics estimates that Genentech's lack of an upfront investment of $10-20m, needed to drive test adoption and standardize the companion diagnostic, has potentially cost between $2-3bn in lost revenue in the US alone.

Commentary

Diaceutics' financial model of the HER2/Herceptin revenue flows from launch shows the key role played by test adoption and P2P, or the ratio of Herceptin prescriptions to HER2 overexpressers.

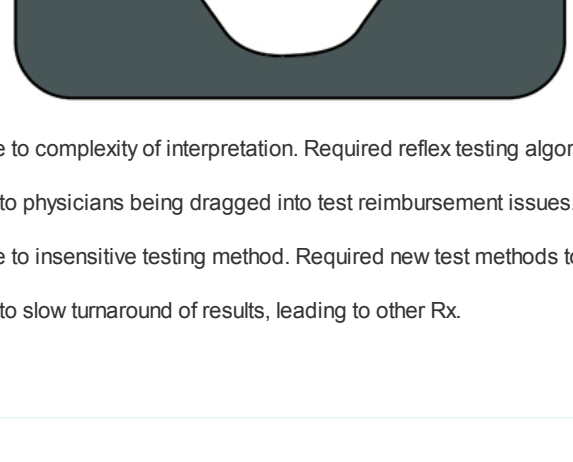
Genentech did not 'own' the HER2 test, or the laboratory service levels and counsellors required to deliver a seamless service to physicians. While this would not matter in a monopoly, it may help to differentiate the company in a competitive targeted-therapy market.

Herceptin Sales Could Have Been Higher 10/12



Source: Roth et al '10

Diagnostic Inefficiencies Resulted in a Substantial Loss of Patients for Herceptin 11/12



- 20% loss of potential Herceptin Rx due to complexity of interpretation. Required reflex testing algorithm to be developed.
- 8% loss of potential Herceptin Rx due to physicians being dragged into test reimbursement issues.
- 40% loss of potential Herceptin Rx due to insensitive testing method. Required new test methods to be developed.
- 7% loss of potential Herceptin Rx due to slow turnaround of results, leading to other Rx.

Source: Roth et al '10

Key Messages 12/12

Key messages:

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