



# Regulatory Hurdles: Looking Forward

*Why the FDA Should Do More*

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# What are our goals?

- Drug developers want to utilize a companion diagnostic, *when appropriate*, to get the right drug to the right patient
  - A biomarker exists that would aid in the selection or stratification of patients
  - Such a biomarker should be (optimally) validated prospectively in a clinical trial, but retrospective validation may be good enough
    - § FISH selection for Herceptin
    - § *k-ras* mutations for Vectibix
    - § *EGFR* mutations for Iressa or Tarceva
    - § OncotypeDx for chemotherapy for ER+/node- breast cancer
  - The biomarker assay system must ensure accurate and reproducible performance by end-users
    - § As assessed by clinical utility/outcomes



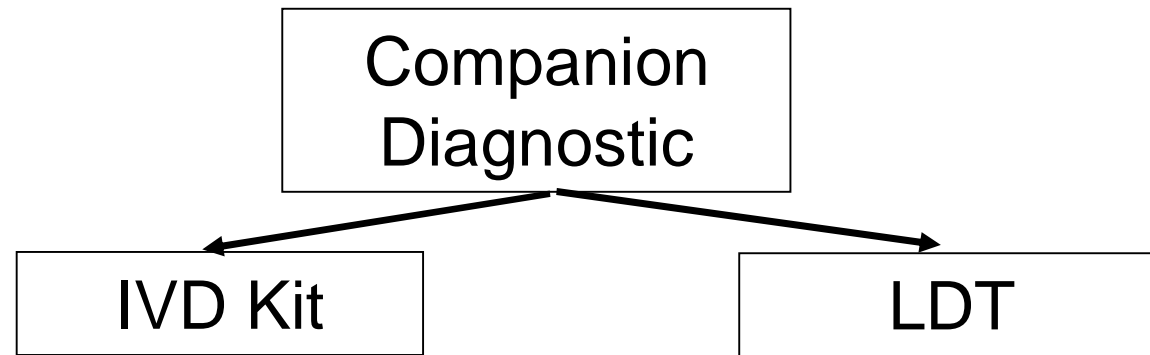
# So.....What is the Problem?

*“There appears to be an Inconsistent/Unclear path to clinical acceptance”*

- FDA criteria for clearance/approval may not consider specific clinical utility
  - § FDA clearance does not mean an assay should be used clinically
- “Home Brew rule” (=LDT’s)
  - § An assay can be marketed without FDA clearance
- Disagreement about what outcomes need to be improved, and how to measure them
  - § There is a disconnect among Guidelines Panels and between them and FDA

# Types of Companion Diagnostics

- *In vitro* diagnostic (IVD) kits v. lab developed test (LDT)
  - Both can follow a proper regulatory path





# Typical Diagnostic Regulatory Pathways

- Premarket Notification 510(k)
  - Applies to lower risk Class I and II devices
    - § E.g., prognostic/monitoring: CA-125, serum HER-2, RF, IgE, CTC, glucose, cholesterol
  - Demonstration of “substantial equivalence” to a predicate device
  - Reviews can vary from simple labeling assessment to multi-site prospective clinical studies
- Premarket Approval (PMA)
  - Required for Class III devices & new high risk devices without a predicate
    - § E.g. Screening/Predictive test: PSA, HIV, HER-2, EGFR, *k-ras*
  - Performance based: non-clinical and clinical data
  - The contents of a PMA are more substantial than 510(k)



# What Is A Citizen's Petition?

- A document submitted to the FDA to ask the agency to issue, change or cancel a regulation, or take other action
- Once submitted, the FDA will accept public comments, potentially hold public meetings, evaluate the petition and then provide a response



# Why did we file a Citizen's Petition in December 2008 related to companion diagnostics?

- There has been a proliferation of diagnostic tests
- Many make unsubstantiated, and therefore possibly inaccurate or misleading, claims *intending to guide treatment decisions*
- We believe FDA oversight is necessary to review test maker claims and help insure patient safety

# An example.....

Opening new treatment options to cancer patients.

## PGxTest: RITUXIMAB

Adding rituximab to combination chemotherapy increases overall response rates, response duration and progression-free survival in fewer than 60% of patients with the follicular type of non-Hodgkin's lymphoma (NHL). In addition, rituximab causes significant toxicity in 57% of patients.\* This toxicity and the drug's high cost have made rituximab a difficult choice for many practitioners and patients.

Now, PGxHealth is working to change that with the introduction of PGxTest: Rituximab in January of 2007.

### About PGxTest: RITUXIMAB

**PGxTest:** Rituximab is a simple new genetic test that will:

- > Allow oncologists to confidently predict whether a patient with NHL is likely to respond to rituximab—before the drug is prescribed or in the face of toxicity.
- > Provide better treatment information for cases of diffuse large B-cell, follicular lymphoma, small lymphocyte lymphoma, marginal zone B-cell lymphoma, and other NHL subtypes.

One simple test can provide peace of mind and help you prescribe rituximab with confidence. That's the value of **PGxTest: Rituximab**.

PGxHealth, a division of Clinical Data, Inc., will release **PGxTest: Rituximab** in January of 2007. It is a pharmacogenetic test that uses DNA analysis to predict which

patients are good candidates for rituximab therapy.

**PGxTest:** Rituximab identifies a single nucleotide polymorphism in the FCGR3A gene. Strong statistical significance of this biomarker has been shown for efficacy in follicular NHL when measured at both 2-month and 12-month end points, with specificity well over 90!†

**PGxTest:** Rituximab provides clear-cut results, assigning patients to one of two categories: Less Likely to Respond Well or More Likely to Respond Well. When outcomes, safety, and cost are at stake, this is vital information. And with the high cost of rituximab (approximately \$10,000 per month) and the availability of other effective treatment options, **PGxTest: Rituximab** is a way for oncologists to help determine the probability of response to rituximab.

\* Carron G, et al. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcγRIIIa gene. *Blood* (2002); 99:754-758.

Weng WK and Levy R. Two Immunoglobulin G FcγR3A C Receptor Polymorphisms Independently Predict Response to Rituximab in Patients with Follicular Lymphoma. *Journal of Clinical Oncology* (2003); Vol. 21 (No 21): 3940-3947.

**PGxTest: Rituximab** was developed and its performance and characteristics determined by PGxHealth, a division of Clinical Data, Inc. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. **PGxTest: Rituximab** may be ordered only by physicians and is to be used solely for clinical purposes. Our testing laboratory is certified under the Clinical Laboratory Improvement Act of 1988 (CLIA-1988) as qualified to perform high complexity clinical laboratory testing.

## PGxHEALTH™

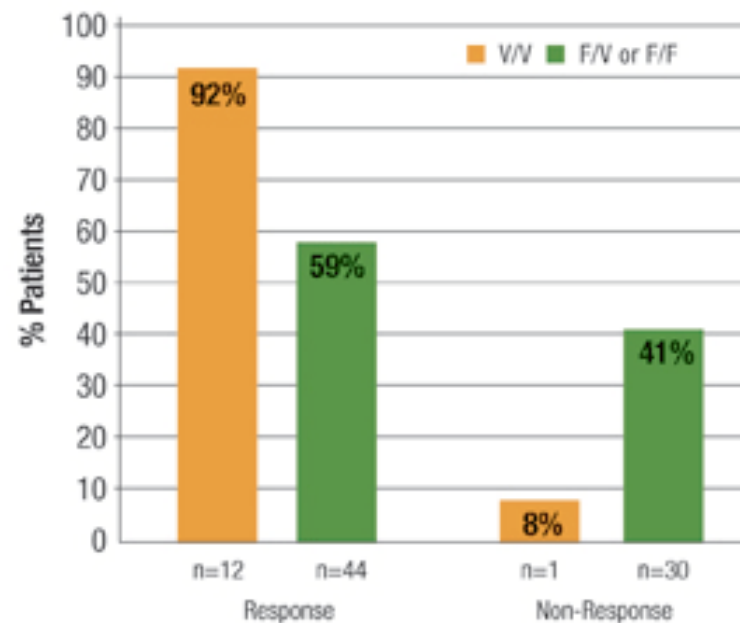
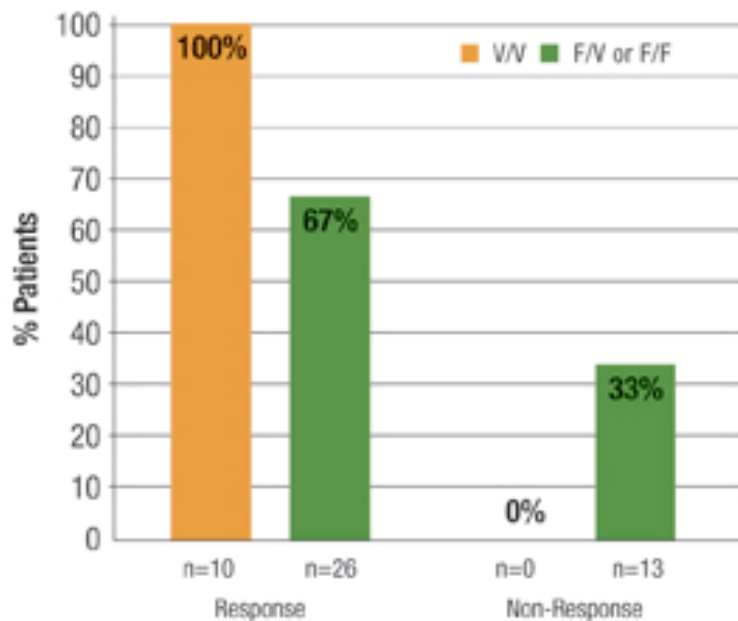
A DIVISION OF CLINICAL DATA  
FIVE SCIENCE PARK  
NEW HAVEN, CT 06511

[www.PGxHealth.com](http://www.PGxHealth.com)

To learn more about **PGxTest: Rituximab** or any of PGxHealth's other pharmacogenetic tests including **FAMILION™**, **PGxTest: Clozapine**, and **PGxTest: Warfarin**, visit [www.PGxHealth.com](http://www.PGxHealth.com) or call 1-877-4-RITUXIMAB (1-877-474-8894).

# But what about the data?

## Follicular Lymphoma





# But what about the data?

## Diffuse Lymphoma

### Effects of FCGR3A and FCGR2A polymorphisms on outcomes of patients with DLBCL treated with CHOP-like chemo vs. CHOP-R

J M Vose<sup>1</sup>, F Loberiza<sup>1</sup>, J Armitage<sup>1</sup>, P Bierman<sup>1</sup>, R Bociek<sup>1</sup>, L Rimza<sup>2</sup>, D Dorman<sup>3</sup>  
<sup>1</sup>University of Nebraska Medical Center, <sup>2</sup>University of Arizona Cancer Center, <sup>3</sup>Genentech

#### Multivariate Analysis For Progression or Death – FCGR2A

CHOP-R vs. CHOP-like		
H/H	0.40 (0.20-0.82)	0.01
H/R or R/R	0.57 (0.36-0.90)	0.02

#### Multivariate Analysis For Progression or Death – FCGR3A

CHOP-R vs. CHOP-like		
V/V	0.28 (0.10-0.77)	0.01
V/F or F/F	0.45 (0.31-0.67)	< 0.001



# What Is Genentech requesting in our Citizen's Petition?

- All *in vitro* diagnostic tests intended for use in therapeutic decision making be held to the same scientific and regulatory standards, regardless of whether the test is a “kit” (IVD) or a laboratory-developed test (LDT)



# Arguments Against FDA Oversight

- There are limited documented examples of safety issues arising from LDTs
- Insufficient FDA staffing and financial resources
- Tests are already reviewed through CMS' Clinical Laboratory Improvement Amendments (CLIA)
- FDA review would stifle innovation and provide an economic burden for test makers



# Genentech's Response

- Without FDA oversight, there is no reliable means for reporting safety issues
  - In the context of predictive diagnostics, “safety” can be defined as the right patient getting the right drug and the wrong patient not getting the wrong drug
- Claiming the FDA has insufficient resources assumes that test manufacturers have data needed to submit an application
- CLIA process reviews how the test is performed, not the substance of the claims made to aid in treatment decisions
  - We believe that proper clinical validation (outcomes) is essential for companion diagnostics being utilized to make treatment decisions

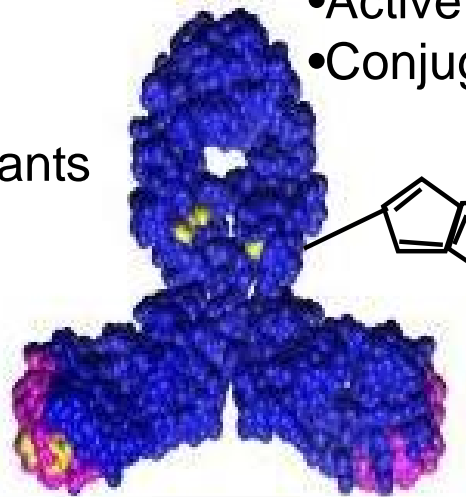


# When is a Marker Clinically Useful?

- The magnitude of effect is sufficiently large that clinical decisions based on the data result in outcomes that are acceptable
  - *Greater chance for benefit*
  - *Smaller toxicity risk*
- The estimate of magnitude of effect is reliable
  - *Analytical Reproducibility*
  - *Clinical trial/marker study design is appropriate*
  - *Results are validated in subsequent well-designed studies (Levels of Evidence I or II)*

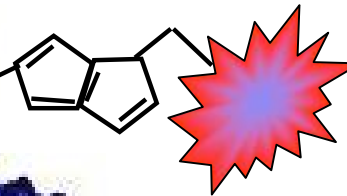
# Anatomy of an Antibody-Drug Conjugate

Antibody  
• Engineered variants



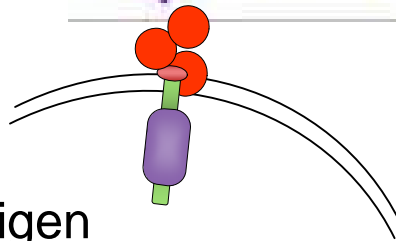
Linker

- Stable in circulation
- Cleavable or uncleavable
- Active drug released in tumor
- Conjugation chemistry



Drug

- Highly potent
- Non-immunogenic
- Maytansine (DM1)
- Auristatins (MMAE, MMAF)

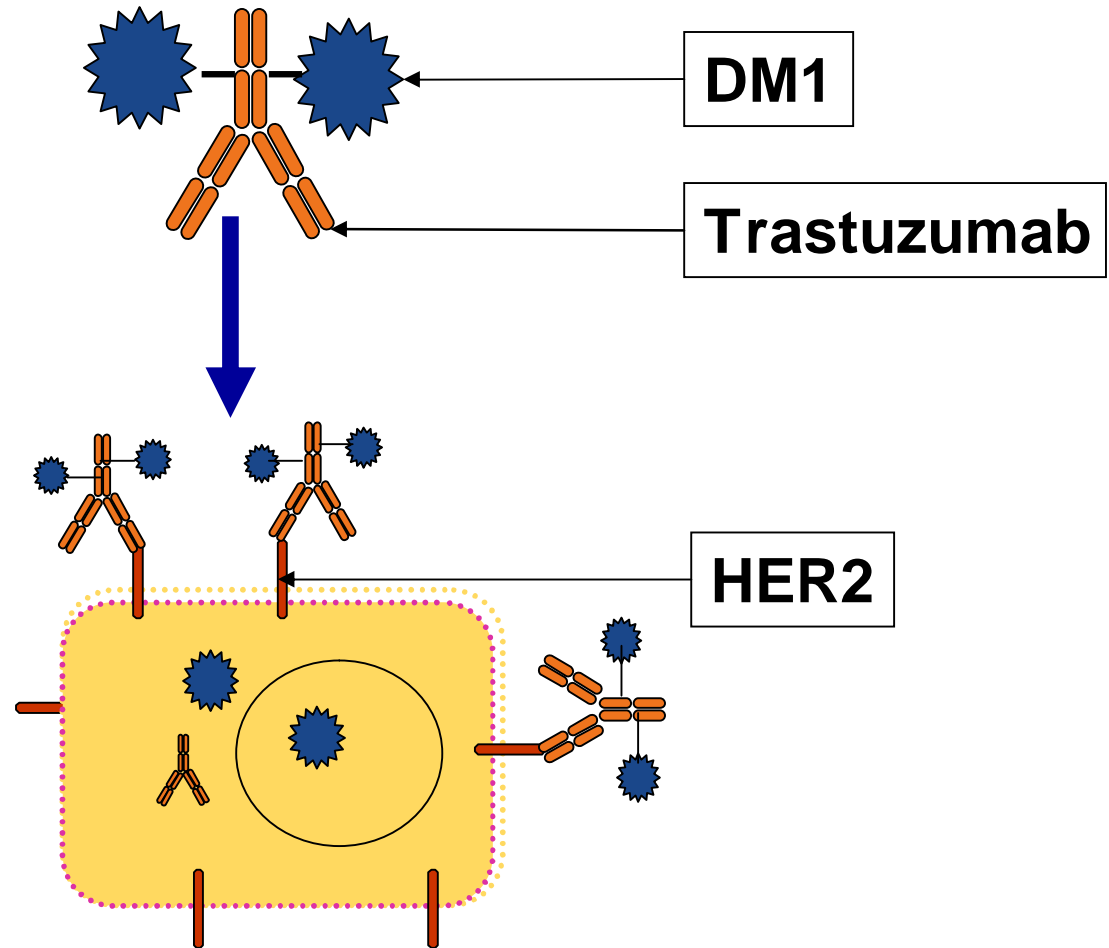


Antigen

- Present/over-expressed on tumor
- Absent/low-level expression on normal
- Internalization

# TDM-1 (Trastuzumab-DM1)

- Designed to:
  - preferentially deliver highly potent chemotherapy (DM1) to HER2+ tumor cells
  - maintain biological effect of trastuzumab
- Developed as:
  - potential therapy for Herceptin-naïve and Herceptin-pretreated HER2+ breast cancer





# TDM-1: Final Results from a large phase II study

## Heavily Pre-Treated HER2+ MBC

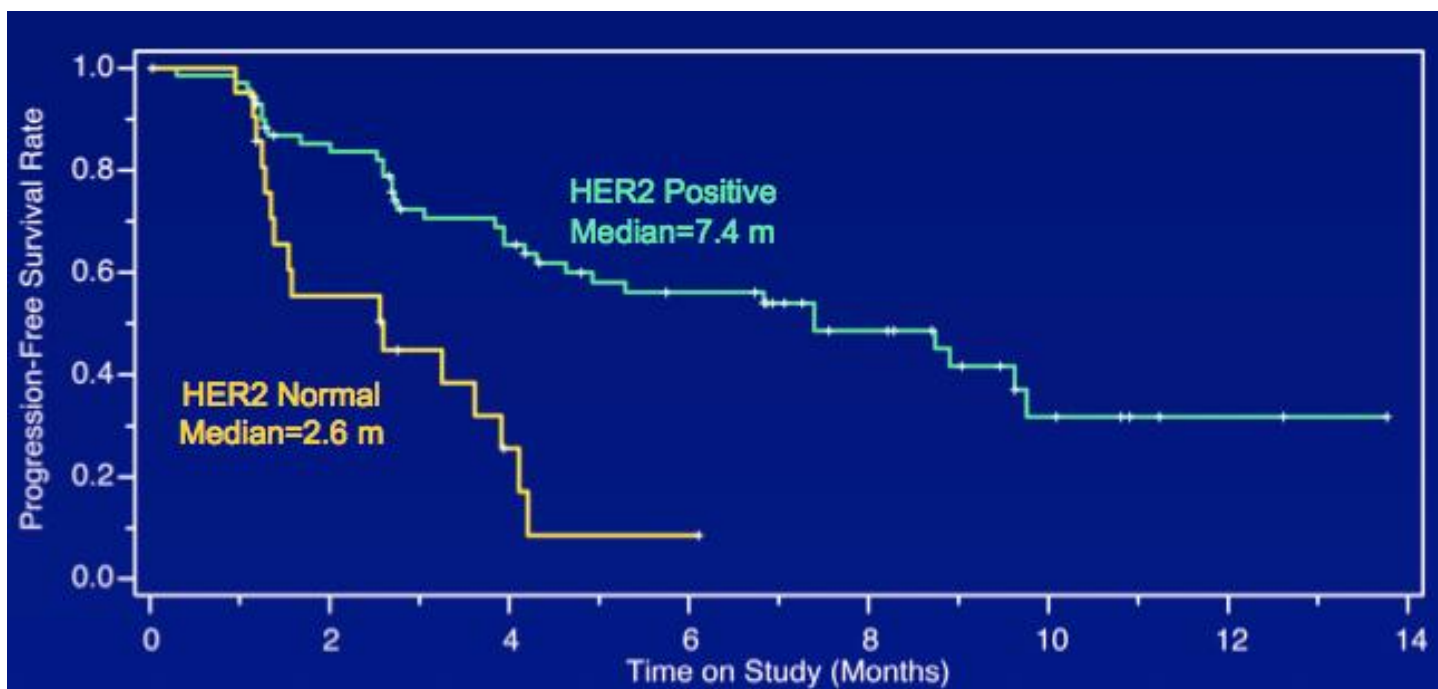
<b>Tumor Response</b>	<b>Independent Review (n=112)</b>	<b>Investigator (n=112)</b>
Objective Response Rate % (95% CI)	25.0 (17.5–33.6)	38.4 (29.8–47.5)
Clinical Benefit Rate % (95% CI)	34.8 (26.1–43.9)	44.6 (35.5–54.3)

# How good (or bad) is current HER2 testing?

## Our results with TDM-1

22%  
false  
Positive  
rate (!!)

Objective Response Rate	IRF (%) (95% CI)	Investigator (%) (95% CI)
Centrally HER2-positive (n=75)	32.0 (22.1–43.0)	48.0 (36.3–59.9)
Central HER2-normal (n=21)	4.8 (<1–21.8)	9.5 (1.7–29.8)





# Summary

- Genentech supports the development of diagnostic tests that advance personalized medicine
- It is important that diagnostic tests are accurate, reliable and clinically valid
- Any test making a claim that could influence a treatment choice should be reviewed by the FDA

*IF WE DON'T IMPROVE THE REGULATION OF  
COMPANION DIAGNOSTICS WE WILL NEVER FULLY  
REALIZE THE PROMISE OF PERSONALIZED MEDICINE*