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View From The Trenches:

Challenges & Opportunities In Personalized Medicine

Doing More to Personalize Testing℠

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VP, Business & Strategic Development
Genzyme Genetics

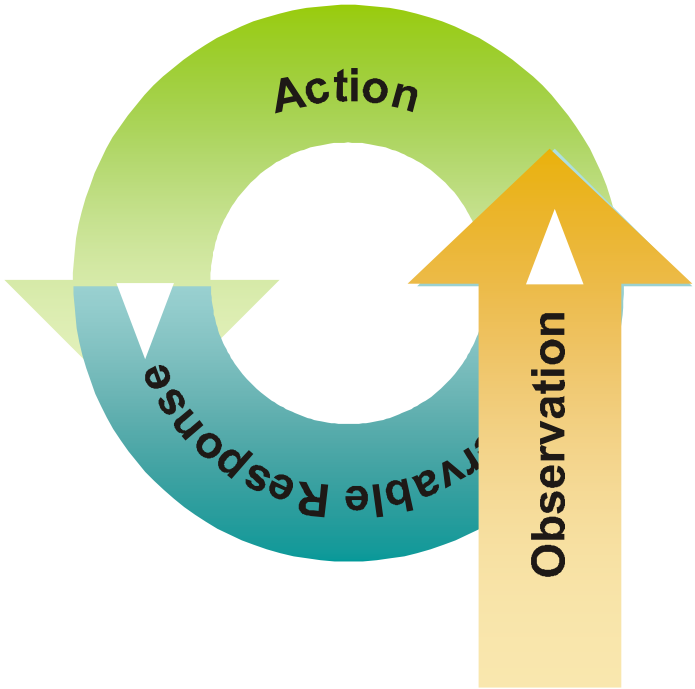
genzyme

Topics to cover

- Case for complex testing to personalize medicine
- Where we are on the adoption curve today
- Specific examples from the trenches
- Possible policy implications

Personalized Medicine

Old Paradigm: Trial and Error Medicine



Successful When it Leads to Innovation and Improves Standard of Care.

Fails When We Settle for "Trial and Error" Medicine *AS* the Standard of Care.

Personalized Medicine

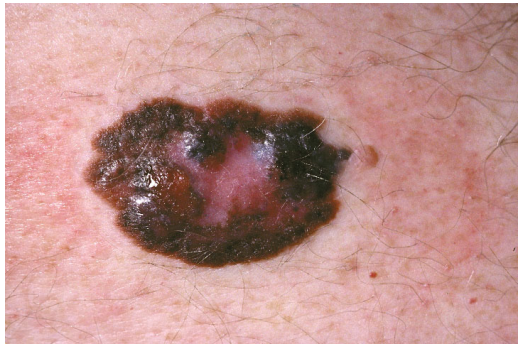
New Paradigm: Personalized Medicine

Linking Tests to Action and Therapy

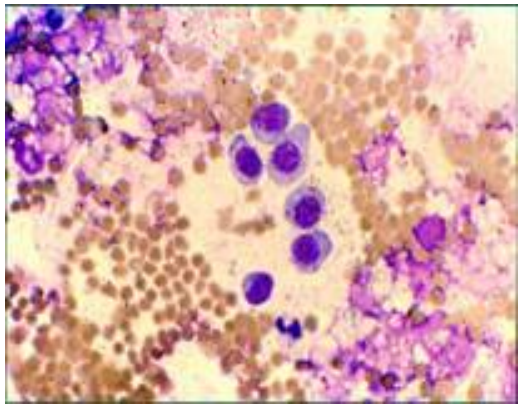
Breaking The Cycle of Trial and Error Medicine

Personalized Medicine: Why Now?
Testing Technology of Yesterday

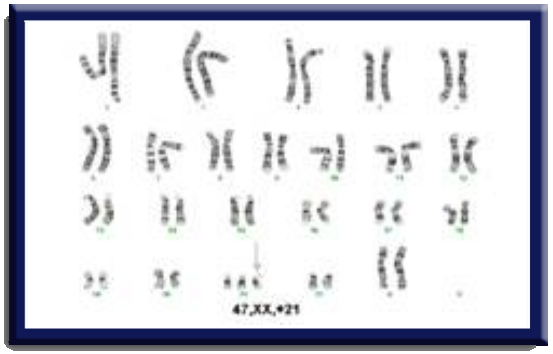
Tumor



Cell

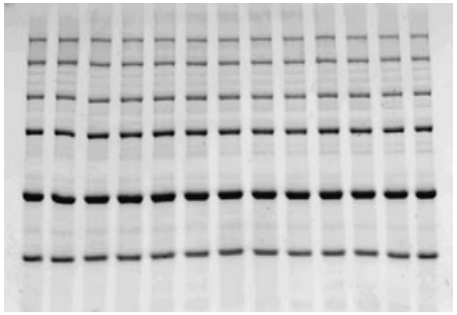


Chromosome

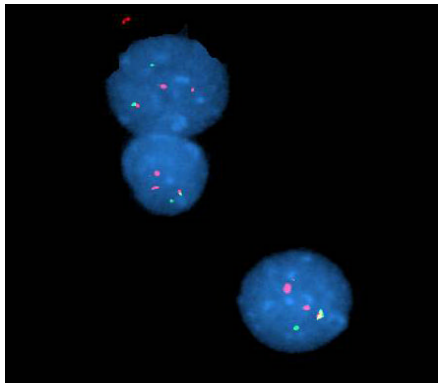


Personalized Medicine: Why Now ?
Testing Technology of Today

Protein

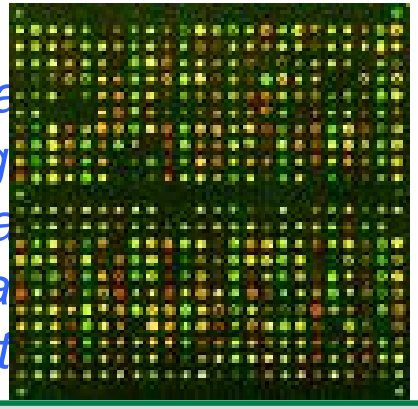


Genes

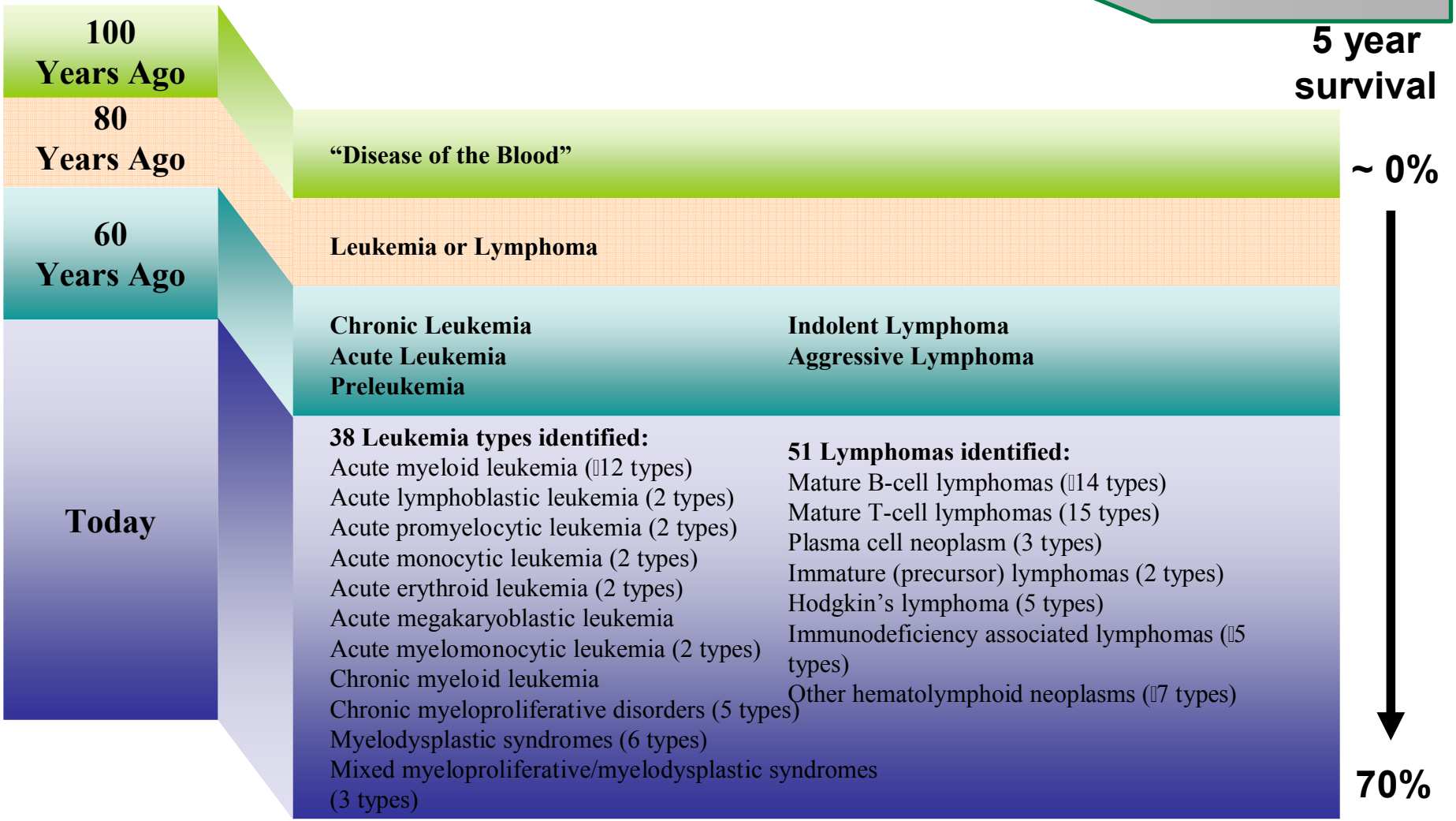


DNA

atcggctaattcgga
tttcgaaagctaatg
ctgagtcaattccga
gctatggatgatata
atattcgggatatatt



Saving Lives:
Positive Impact on Blood Cancers



Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Feuer EJ, Edwards BK (eds). *SEER Cancer Statistics Review*, 1975-2002, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2002/, based on Nov 2004 SEER data submission, posted to the SEER web site 2005.

Personalized Drugs Available Today

Which Drug Should I Use?		
Breast Cancer	Tamoxifen®	ER/PR
Breast Cancer	Herceptin®	HER2
Leukemia, Chronic Myelogenous	Gleevec®	BCR-ABL
Colorectal Cancer	Erbitux®	EGFR
Lung Cancer	Tarceva®	EGFR
Leukemia,MDS	Revlimid®	Deletion (5q)
How Much of the Drug Do I Need?		
Colorectal Cancer	Camptosar®	UGT1A1
Is The Drug Working?		
Leukemia, Chronic Myelogenous	Gleevec®	Quant BCR-ABL
Leukemia, Chronic Myelogenous	Gleevec®	BCR-ABL mutations
Is My Disease Gone?		
Leukemia, Chronic Lymphocytic	Campath®	Minimal Residual Disease

The Personalized Medicine Timeline

Fear ⇨ **Value** ⇨ **Acceptance**

Will It Hurt Me?	***Will It Help Me?***	***I Want It!***

The Personalized Medicine Timeline

Fear

Pharma: Reduces My Market

Payers: Adds to My Cost Without Return

Doctors: Too Prescriptive for Me

Patients: Will I Be Denied Access to New Drugs?

Regulators: How Do We Handle New Complexities?

Diagnostics: More Tests With Poor Reimbursement

Genzyme Personalized Medicine Strategy Circa 2005

- Focus On Tests Connected Directly With Drugs
- License Aggressively Even On Relatively Little Data
- Get Tests To Market Quickly
- Win Community Physicians Over As Data Grow Stronger
- Drive Early Adoption Through Embrace Of Personalized Medicine

Bullish On Personalized Medicine!

UGT1A1 Testing
Key Events Leading to Test Launch

DOSAGE AND ADMINISTRATION

Dosage in Patients with Reduced UGT1A1 Activity

When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele (see CLINICAL PHARMACOLOGY and WARNINGS). However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment (see Tables 10-13).

Jun 14, 1996	FDA approves irinotecan for 2nd-line treatment of colorectal cancer
1999 – 2005	Series of studies published connecting UGT1A1 polymorphisms to irinotecan-related toxicities (severe diarrhea and neutropenia)
Jun 7, 2005	FDA approves addition of information on UGT1A1 to irinotecan label
Aug 22, 2005	FDA approves Invader UGT1A1 Molecular Assay manufactured by Third Wave
Oct 27, 2005	Genzyme & Third Wave announce Preferred Marketing Relationship for U.S. launch of Invader UGT1A1 Molecular Assay testing service
Dec 6, 2005	Genzyme launches UGT1A1 polymorphism testing service

UGT1A1 Testing
Our Experience

What We Hear From Physicians

"I start patients on irinotecan, and when side effects occur, I lower the dose, stop a cycle, or stop treatment"

"I monitor bilirubin level, so do not need to test"

"If I determine my patient dose have a polymorphism, what dose do I use?"

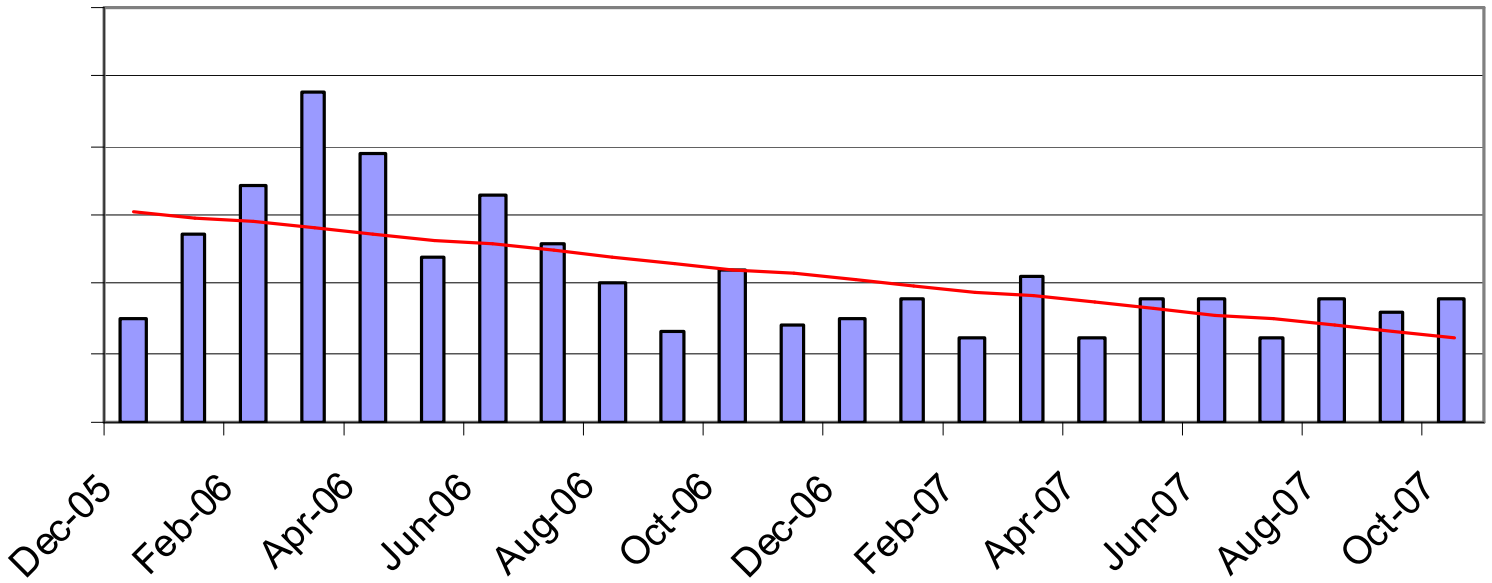
"Polymorphisms do not occur frequently enough for me to test all my patients"

Key Learnings

- Clinical utility data is necessary but not sufficient to drive physician adoption
- Physicians will use work-around solutions where modestly effective
- Inclusion in drug package insert does not necessarily lead to testing
- Package inserts must be clear on implication of test results for dosing

UGT1A1 Testing
Our Experience

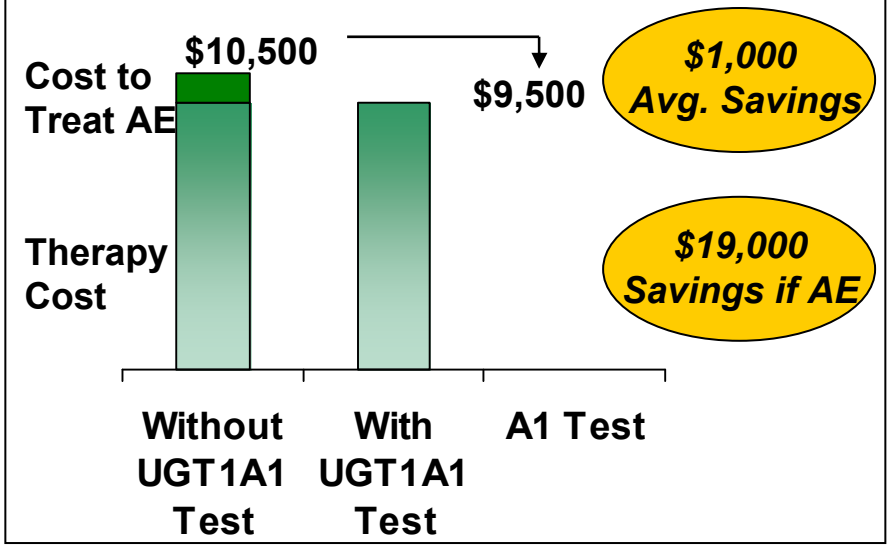
Genzyme UGT1A1 Volume Trend



Tests Save Money
UGT1A1 Testing For Colorectal Cancer

Value Based on Health Outcomes and Savings

Avg. Cost of Camptosar Therapy Per Patient



Reimbursement Based on CPT-Codes

Price of UGT1A1 Testing per Patient*

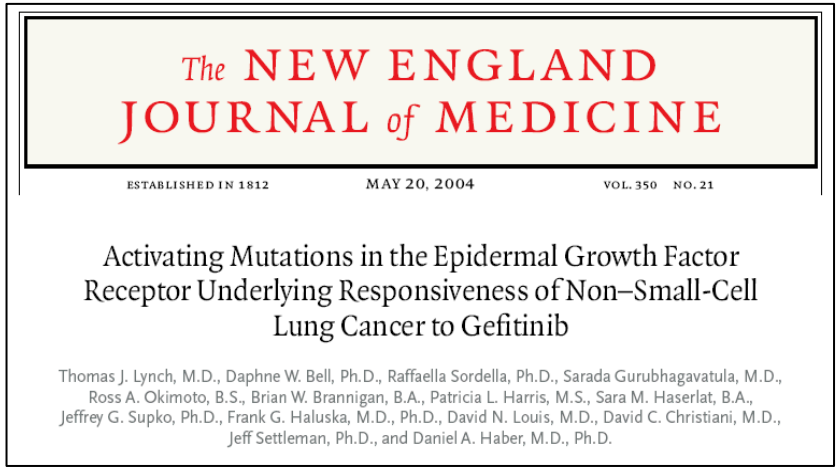
CPT Code	Description	Fee
83891	Extraction of highly purified nucleic acid	$ 5.60
83892	Enzymatic digestion	$44.80
83896	Nucleic acid probe(s)	$67.20
83903	Mutation scanning by physical properties	$93.70
83908	Signal amplification of patient nucleic acid	$93.70
83912	Interpretation and report	$ 5.60
Total		$310.60

UGT1A1 Test Delivers Healthcare Savings that are ~3x its Cost

*As measured by Invader UGT1A1 Molecular Assay and reimbursed by CMS

Sources: Kuderer et al. Mortality, Morbidity, and Cost Associated with Febrile Neutropenia in Adult Cancer Patients. Cancer (2006) 106:2258-66; Schrag. The Price Tag on Progress – Chemotherapy for Colorectal Cancer. NEJM (2004) 351(4):317-319.

EFGR Mutations
Key Events Leading to Test Launch



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

THE WALL STREET JOURNAL.

Test Predicts Response to Cancer Drugs: Genzyme Launches Method to Determine Who Will Benefit From 'Smart Drugs'

By SYLVIA PAGÁN WESTPHAL
Staff Reporter of THE WALL STREET JOURNAL
September 27, 2005

May 5, 2003	FDA approves gefitinib for 3rd-line treatment of advanced or metastatic NSCLC
May 20, 2004	Lynch et al. publish NEJM article on role of EGFR mutations in gefitinib response
Nov 11, 2004	FDA approves erlotinib for 2nd-line treatment of advanced or metastatic NSCLC
May 2, 2005	Genzyme announces exclusive license with MGH & DFCI to EFGR mutation IP
June 17, 2005	FDA amends gefitinib label to reflect failure to demonstrate survival benefit
Sept 22, 2005	Genzyme announces launch of EFGR mutation testing service
2005 – present	Multiple publications on tests to predict response to TKIs in NSCLC
July 1, 2006	C-Path announces effort to study tests to predict response to TKIs in NSCLC

EGFR Mutation Testing
Our Experience

What We Can Say About Adoption

- Only a small minority of CLC patients on TKIs receive testing
- Penetration is highest in leading academic centers

What We Hear From Physicians

"I am confused by the multiple testing options for NSCLC"

"I use clinical information (race, smoking habits) as a proxy for mutation status"

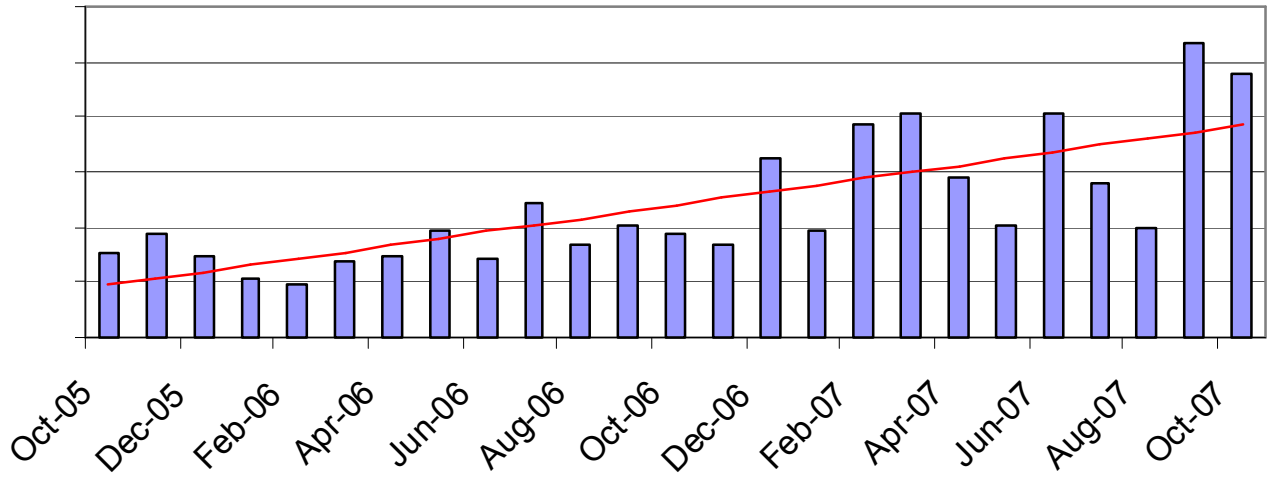
"TKIs are my last line of treatment. I am going to treat no matter what"

Key Learnings

- Connection between genetics and treatment not always crystal clear
- Community physicians cannot sort out conflicting data themselves
- Robust clinical utility data required to drive adoption by community physicians
- Physicians will substitute work-around solutions where modestly effective
- Physicians not inclined to de-select patients for treatment based on tests

EGFR Testing
Our Experience

Genzyme EGFR Mutation Volume Trend



New Criteria for Personalized Medicine Tests

- **Test Represents Only Reliable Way To Get Information**
- **Clear Path To Robust Clinical Utility Data**
  - Proof-If-Concept Data From Inventors
  - "Pivotal Experiment" Is Technically Feasible At Reasonable Cost
- **Economics Support Investment In Clinical And Market Development**
  - Reimbursement
  - IP & Exclusivity
- **Licensing / Partnership Terms Accommodate Investment Risk and Return**

Committed to Personalized Medicine!

Personalized Medicine
Dropping The Barriers

Education

- More information to physicians and health care providers
- More practice guidelines from physician organizations
- More focus in medical school on diagnostics and genetics

Data

- Industry wide cooperation to collect and analyze data on best use and outcomes with diagnostics

Reimbursement

- Based on value
- Appropriately account for regulatory burden