

Biomarkers and Clinical Care

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University of Chicago

AAAS/FDLI Colloquium
Personalized Medicine in an Era of Health Care Reform
Washington, DC
October 27, 2009

Conflict of interest disclosure (as of 10/17/09)

- I receive royalties related to UGT1A1 genotyping (based on licensing agreement between The University of Chicago and Mayo Medical Laboratories)
 - **Most recent quarterly royalty check was \$244.52**
- I consult to a number of pharmaceutical and biotech companies that could be impacted by any change in regulatory policy
- I am a director of AspenBio Pharma, which has submitted a 510(k) application to FDA to market a diagnostic test for appendicitis

Biomarker Definition

- A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

Janet Woodcock, 11/4/04

Categories of Biomarkers

- **Post-treatment biomarkers**
 - Measures of pharmacological activity
 - Surrogate endpoints
 - Nonvalidated
 - Validated

Categories of Biomarkers

- **Pre-treatment biomarkers**
 - **Prognostic**
 - Can be used to subdivide similar disease states
 - Predictive of natural history of disease
 - **Predictive**
 - Can be used to select therapies
 - Can be used optimize dosing

What are the opportunities?

- **Optimize the target population**
 - **Treat “good risk” population**
 - High likelihood of benefit
 - Low likelihood of toxicity
 - **Exclude “bad risk” population**
 - Low likelihood of benefit
 - High likelihood of toxicity

Oncotype DX® 21-Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION

Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN

ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

INVASION

Stromelysin 3
Cathepsin L2

HER2

GRB7
HER2

CD68

REFERENCE

Beta-actin
GAPDH
RPLPO
GUS
TFRC

$$\begin{aligned} \text{RS} = & + 0.47 \times \text{HER2 Group Score} \\ & - 0.34 \times \text{ER Group Score} \\ & + 1.04 \times \text{Proliferation Group Score} \\ & + 0.10 \times \text{Invasion Group Score} \\ & + 0.05 \times \text{CD68} \\ & - 0.08 \times \text{GSTM1} \\ & - 0.07 \times \text{BAG1} \end{aligned}$$

Category	RS (0 -100)
Low risk	RS <18
Int risk	RS 18 - 30
High risk	RS ≥ 31

Paik et al. *N Engl J Med.* 2004;351:2817-2826.

What are the opportunities?

- Optimize the selection of drugs
 - Select drug(s) with
 - High likelihood of benefit
 - Low likelihood of toxicity
 - Exclude drug(s) with
 - Low likelihood of benefit
 - High likelihood of toxicity



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Complete Summary



GUIDELINE TITLE

Diagnostic, monitoring, and **resistance** tests for **HIV**.

BIBLIOGRAPHIC SOURCE(S)

New York State Department of Health. Diagnostic, monitoring, and **resistance** tests for **HIV**. New York (NY): New York State Department of Health; 2005 May. 12 p.

- When resistance tests are obtained, expert advice in interpretation is strongly encouraged.
- Genotypic resistance testing should be performed before initiating treatment in anti-retroviral (ARV) therapy-naive patients to determine whether they were infected with drug-resistant virus.
- Resistance testing should be performed promptly in cases of virologic failure or incomplete viral suppression.
- Resistance testing should be performed while patients are still receiving therapy or have been off therapy for no more than 1 year.

EXIQON



ONCOTECH

EDR[®] ASSAY

Extreme Drug Resistance Assay

American Society of Clinical Oncology Technology Assessment: Chemotherapy Sensitivity and Resistance Assays

Deborah Schrag, Harinder S. Garewal, Harold J. Burstein, David J. Samson, Daniel D. Von Hoff, and Mark R. Somerfield for the ASCO Working Group on Chemotherapy Sensitivity and Resistance Assays

Recommendations

The use of chemotherapy sensitivity and resistance assays to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting. Oncologists should make chemotherapy treatment recommendations on the basis of published reports of clinical trials and a patient's health status and treatment preferences. Because the in vitro analytic strategy has potential importance, participation in clinical trials evaluating these technologies remains a priority.

MEDICAL POLICY

SUBJECT: TUMOR CHEMORESISTANCE AND
CHEMOSENSITIVITY ASSAYS

POLICY NUMBER: 2.02.32

CATEGORY: Laboratory Test

EFFECTIVE DATE: 06/21/07

REVISED DATE: 06/19/08, 05/28/09

PAGE: 1 OF: 4

- *If the member's subscriber contract excludes coverage for a specific service it is not covered under that contract. In such cases, medical policy criteria are not applied.*
- *Medical policies apply to commercial and Medicaid products only when a contract benefit for the specific service exists.*
- *Medical policies only apply to Medicare products when a contract benefit exists and where there are no National or Local Medicare coverage decisions for the specific service.*

POLICY STATEMENT:

- I. Based upon our criteria and review of the peer-reviewed literature, tumor *chemoresistance* assays including but not limited to extreme drug resistance assays, as a guide to selection of chemotherapeutic drugs for individuals with cancer, have not been medically proven to be effective and are considered **investigational**.
- II. Based upon our criteria and review of the peer-reviewed literature, tumor *chemosensitivity* assays including but not limited to the histoculture drug response assay and the fluorescent cytoprint assay, as a guide to selection of chemotherapeutic drugs for individuals with cancer, have not been medically proven to be effective and are considered **investigational**.

SYNOPSIS OF CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

The information contained in this section provides a synopsis of Medicare coverage. For complete Southern California Medicare coverage please refer to the following: http://www.weisenthal.org/medicare_lcd_final.pdf

CMS has published a Local Coverage Decision for the geographic jurisdiction of Southern California, effective 2/19/07, regarding Oncologic in Vitro Chemoresponse Assays (L22555). This covers most of Medicare beneficiaries in all 50 states since the Oncotech, Inc. laboratory, which processes the Extreme Drug Resistance Assay (EDR®) is within the jurisdiction of this LCD.

Title: Oncologic in Vitro Chemoresponse Assays (L22555)

Contractor Determination Number: 06-02.5

Original Determination Effective Date: 2/19/07

Primary Geographic Jurisdiction: California - Southern

What are the opportunities?

- **Optimize dosing**
 - **Identify population at high risk of toxicity at standard dose that requires dose reduction**
 - **Identify population with low likelihood of benefit at standard dose that requires dose escalation**

Carl has metastatic colorectal cancer.
Now Genzyme can help you determine his
risk of serious adverse effects
before
he starts therapy.

Genzyme now offers the
Invader® UGT1A1 Molecular Assay,
an FDA-cleared innovative
screening test designed to
help you identify patients
who are at increased risk
for severe toxicity when
treated with irinotecan.
This simple blood test
will assist you in
making adjustments
in your patient's
therapy before
adverse effects
occur.



For more information about
Genzyme's cancer testing
services, including our
menu of innovative
tests that can help
physicians understand
a patient's response to
cancer therapy, visit
www.genzymegenetics.com
or call (800) 447-5816.

Invader® is a registered trademark of
Third Wave Technologies, Inc.
The Invader® UGT1A1 Molecular Assay
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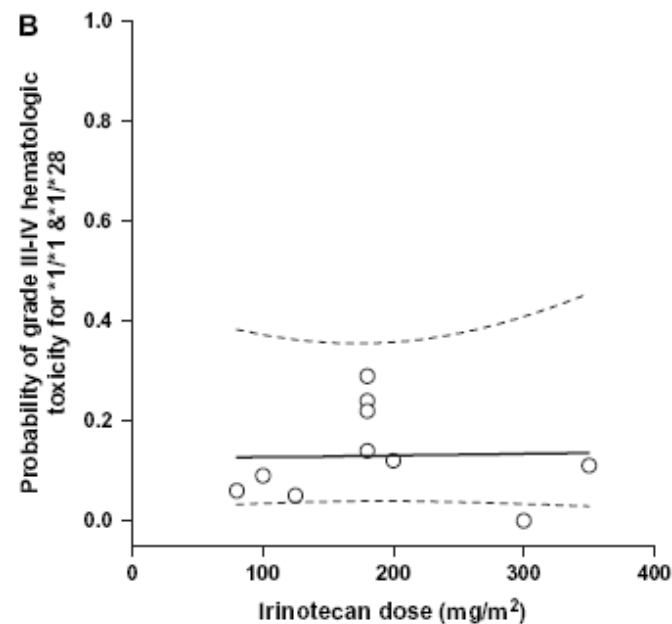
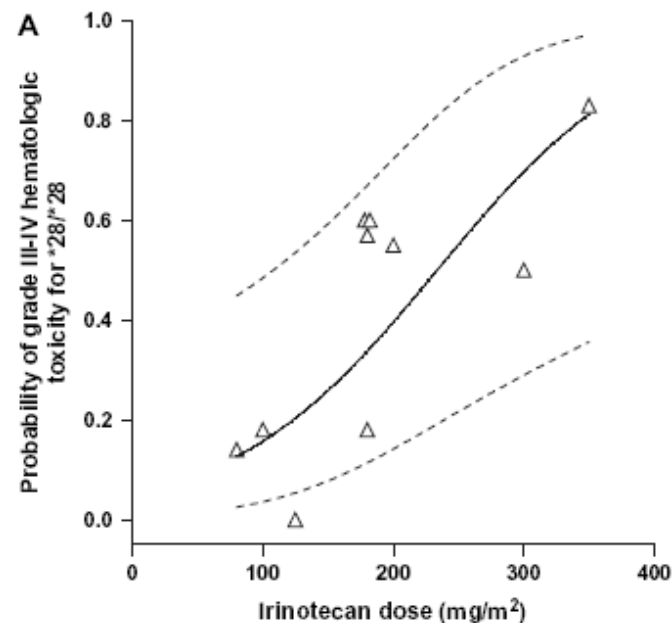
Experience Tomorrow's Cancer Testing Laboratory Today.

genzyme

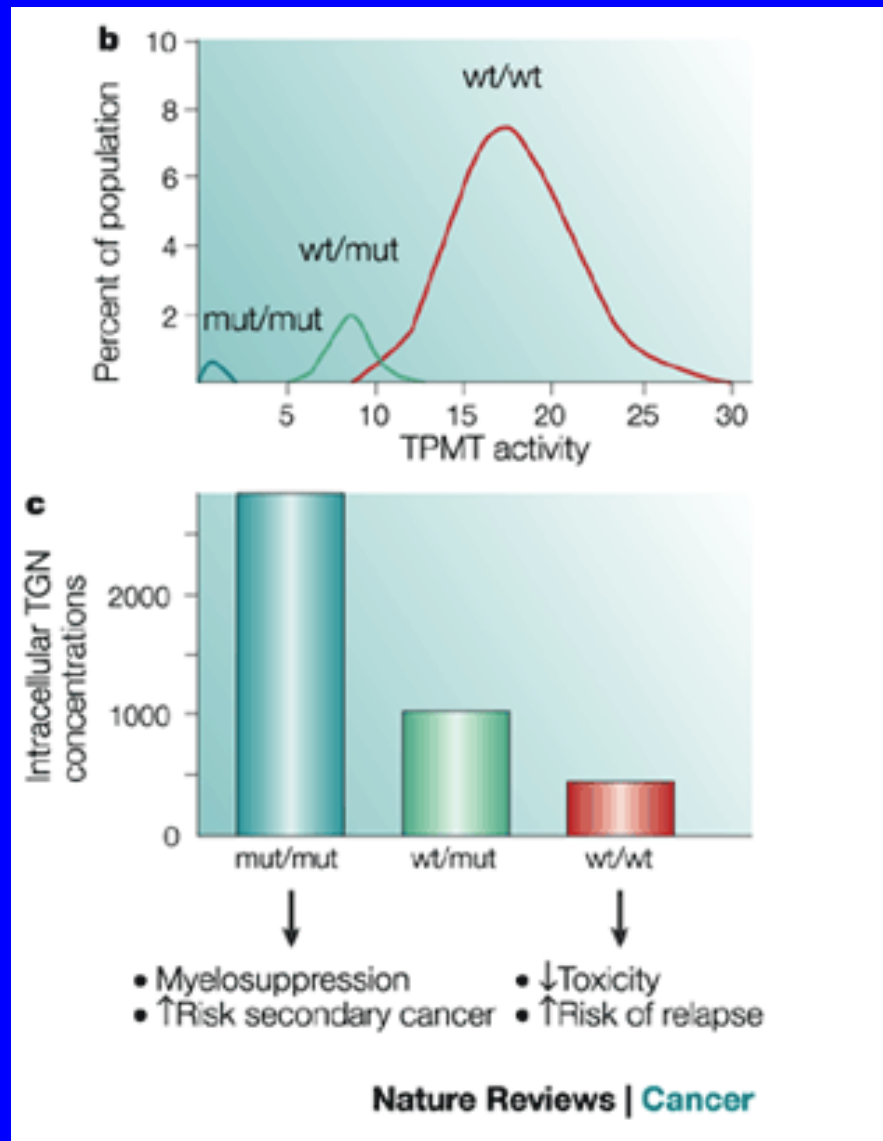
COMMENTARY

UGT1A1*28 Genotype and Irinotecan-Induced Neutropenia: Dose Matters

Janelle M. Hoskins, Richard M. Goldberg, Pingping Qu, Joseph G. Ibrahim, Howard L. McLeod



Relling & Dervieux, 2001



Getting the most from your thiopurine therapy

Why thiopurine testing is right for you



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PROMETHEUS[®] **Thiopurine Metabolites**

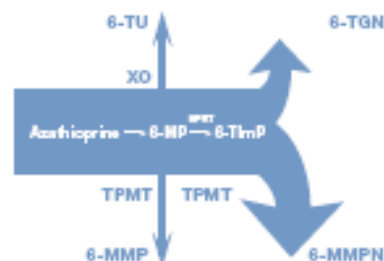
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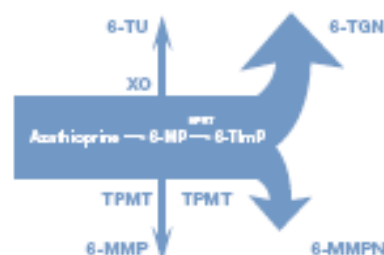
Added confidence to *therapeutic decisions*



Homozygous normal (89%)

↳ consider full dose¹

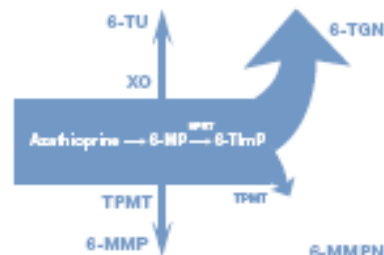
- Normal to high TPMT activity
- Results may be interpreted as lower relative risk for myelosuppression¹
 - Patients may tolerate a full dosing regimen of thiopurine therapy¹
 - Full dosing potentially reduces time to response²



Heterozygous (11%)

↳ reduced dose recommended²

- Intermediate TPMT activity
- Results may be interpreted as at risk for myelosuppression¹

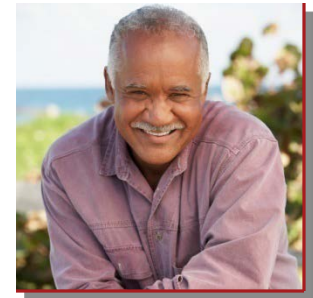


Homozygous deficient (0.3%)

↳ exclude from therapy¹

- Low to no TPMT activity
- Results may be interpreted as high risk for life-threatening myelosuppression

TheraGuide 5-FU™



CONFIDENTIAL



MMM447

**TheraGuide 5-FU™
Analysis Result**

PHYSICIAN

John Doe MD
Myriad Genetics, Inc.
320 Wakara Way
Salt Lake City, UT 84108

SPECIMEN

Specimen Type: Blood
Draw Date: Sep 1, 2007
Accession Date: Sep 5, 2007
Report Date: Sep 25, 2007

PATIENT

Name: Doe, Jane
Date of Birth:
Patient ID:
Gender: Female
Accession #: 00254463-BLD
Requisition #: 00254463

Test Results and Interpretation

HIGH RISK

Genes Analyzed

DPYD
TYMS

Results

No Variant Detected
2R/2R

Interpretation

No Variant Detected
High Risk

CONFIDENTIAL



MMM1295

**TheraGuide 5-FU™
Analysis Result**

PHYSICIAN

Jane Doe MD
Myriad Genetic, Inc.
320 Wakara Way
Salt Lake City, UT 84108

SPECIMEN

Specimen Type: Blood
Draw Date: Jun 26, 2008
Accession Date: Jun 27, 2008
Report Date: Jun 30, 2008

PATIENT

Name: Doe, John
Date of Birth:
Patient ID:
Gender: Male
Accession #: 00254902-BLD
Requisition #: 00000000

Test Results and Interpretation

MODERATE RISK

Genes Analyzed

DPYD
TYMS

Results

No Variant Detected
2R/2R

Interpretation

No Variant Detected
Moderate Risk

Major challenges regarding biomarkers in 2009

- **Reimbursement consistent with value**
- **Education of physicians and other health care professionals**
- **Informatics support for complex diagnostics**
- **Development of novel health care delivery systems for germline genotyping/sequencing**

Major challenges regarding biomarkers in 2009

- **Reimbursement consistent with value**
 - **Diagnostics can be marketed as CLIA-certified services without demonstration of safety and efficacy**
 - **Diagnostic reimbursement too low to support commercial randomized trials**
 - **If drug reimbursement was based on value, diagnostics would enable increased reimbursement for drugs**

Value-based reimbursement

- Assume “perfect” drug is worth \$10,000/month
 - All patients remain alive and asymptomatic while on drug
 - Copayment = price - \$10,000

Value-based reimbursement

- Assume that 10% of patients treated with WonderDrug for BlockbusterIndication benefit from the drug
- Assume that there is no way to know that a patient receiving WonderDrug is benefiting from the drug

Value-based reimbursement

- Hypothetical example
 - WonderDrug is indicated to prevent recurrence of breast cancer after primary therapy

Value-based reimbursement

- WonderDrug is worth \$1000 (10% of \$10,000) per month
 - Copayment = price - \$1000
- What would a diagnostic (WonderTest) be worth that identified (with 100% accuracy) the 10% of patients who benefit?

Value-based reimbursement

- **WonderDrug is worth \$10,000/month for WonderTest-positive patients**
- **WonderDrug is worth \$0/month (or less if toxic) for WonderTest-negative patients**

Value-based reimbursement

- The value of WonderTest depends on
 - WonderDrug price
 - Average duration on WonderDrug for those that do not benefit
 - Competition from “WonderDrug Wannabees”
 - WonderDrug toxicity
 - Synchronization of pricing of WonderDrug and WonderTest
 - Patient acceptance of copayments
 - Financial toxicity

Grade 5 Financial Toxicity

Daily Mail, Wednesday, June 25, 2008

S1

Suicide of cancer patient refused a lifeline

By Rebecca Camber

A CANCER patient killed himself after being told he had been refused a wonder drug by his local primary care trust.

Albert Baxter, 77, was terminally ill. But he was turned down for a drug which could have prolonged his life and shrunk his tumour.

In desperation, he offered to pay for the treatment. But he was told if he did so, he would also have to foot the bill for the rest of his treatment, which he could not afford.

The former bus driver had been diagnosed with renal cancer in January 2007.

His oncologist, Dr Fiona McKinna told him that the drug

'He built
up his
hopes':
Albert
Baxter,
left, with
partner
Barrie
Curryer



Major challenges regarding biomarkers in 2009

- **Education of physicians and other health care professionals**
 - Minimal awareness of most physicians of advances in diagnostics
 - Most physicians have little expertise in genomics
 - Randomized trials are few and far between

Major challenges regarding biomarkers in 2009

- **Informatics support for complex diagnostics**
 - Data generation is straightforward, but interpretation is difficult to impossible for average physician
 - Will be necessary for optimal utilization of full genome information

Major challenges regarding biomarkers in 2009

- **Development of novel health care delivery systems for germline genotyping/sequencing**
 - **Transition from laboratory diagnostic to service model**

Vision for implementation of personalized therapeutics - 1

- **All patients will be offered collection and storage of DNA samples for medical purposes**
- **Genotyping will be prospectively performed for all variants of potential clinical importance**
 - **Except those that predict disease risk (based on current law)**
 - **Will be periodically (e.g., annually) updated**

Vision for implementation of personalized therapeutics - 2

- **A “genetic exam” will be part of most physician encounters**
 - Including all that include drug prescribing
- **The genetic exam will be enabled by informatics support**
 - Ideally linked to electronic medical record

Vision for implementation of personalized therapeutics - 3

- **Business model for genotyping**
 - High volume
 - Low cost (universal benefit) per patient
- **Business model for “genetic exam”**
 - Subscription basis or “per click”
 - Charged to physician or patient
- **Supported by subspecialists who provide consultative services in personalized therapeutics**

MACROSCOPY

Personalized Medicine: Building the GPS to Take Us There

MJ Ratain¹

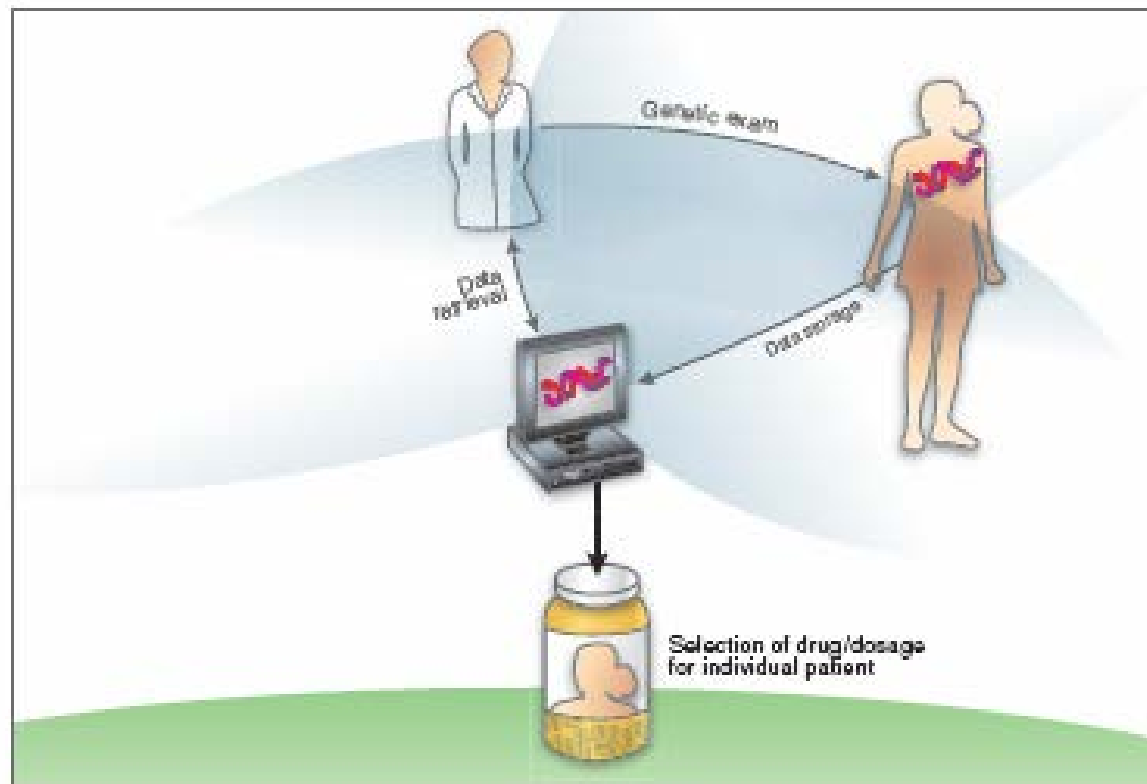


Figure 1 GPS (Genomic Prescribing System).