

# **Pharmacogenomic Issues in Drug Development**

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Washington, DC  
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# **Technological hurdles**

- **Identification of the major variables that affect the safety and efficacy of a drug**
- **Effective utilization of all available information to individualize medical care**

# Technological hurdles

Identification of the major variables that affect the safety and efficacy of a drug

- **Genetic**
  - Germline variation
  - Somatic mutations
    - Only in oncology and ID
- **Non-genetic**
  - Dose
  - Schedule
  - Disease severity
  - Other drugs
  - Hepatic and renal function
  - Age
  - Food, supplements, and adherence

From Bedside to Bench to Bedside to Clinical Practice:  
An Odyssey with Irinotecan

Mark J. Ratain

*Clinical Cancer Research*

**March 15, 2006**

- **1993 – identification of relationship of SN-38 glucuronidation to severe toxicity (diarrhea)**
- **1995 – replication study to confirm relationship**
- **1996 – identification of responsible enzyme (UGT1A1) and candidate variant (*UGT1A1\*28*)**
- **1997 – demonstration of association of variant with SN-38 glucuronidation in hepatic microsomes**

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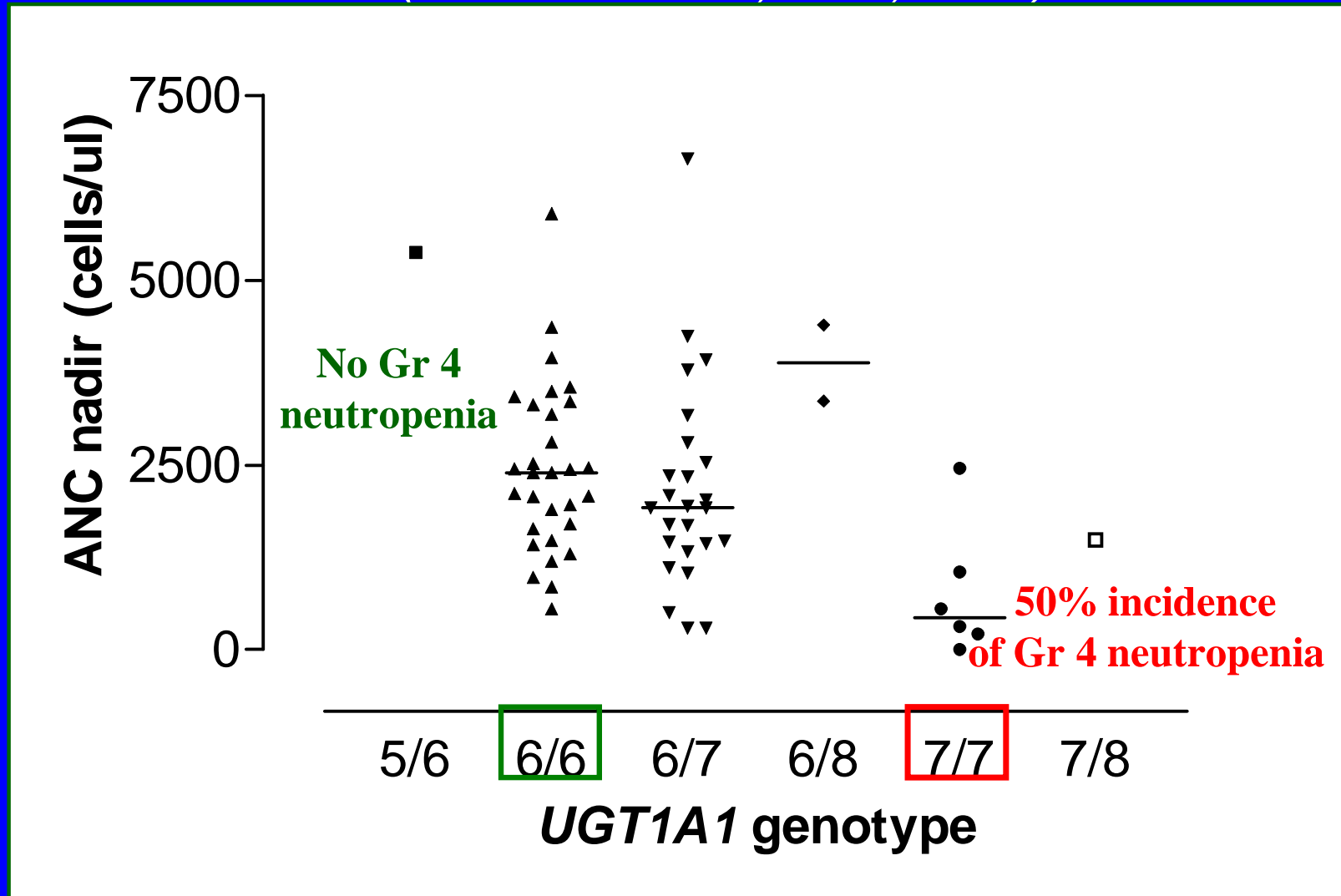
*Clinical Cancer Research*

**March 15, 2006**

- **1996 – FDA approval on weekly schedule**
- **1997 – increasing preference among US clinicians for European (q3w) schedule**
- **1997 – initiated planning of prospective pharmacogenetic study on q3w schedule at 300 mg/m<sup>2</sup>**
- **1998 – FDA approved label revision to include q3w schedule at 350 mg/m<sup>2</sup>**
- **1998 – protocol amended**

# Neutropenia (q3 wk schedule) is Correlated with *UGT1A1* Genotype (\*28)

*(Innocenti et al, JCO, 2004)*



*Bar represents median values.*

*Nonparametric trend analysis among 6/6, 6/7, 7/7,  $p < 0.01$*

# Pharmacogenetics (PGx) of Irinotecan: Scientific and Clinical Impact of UGT Polymorphism: Background

Clinical Pharmacology Subcommittee of ACPS  
November 3, 2004

Lawrence J. Lesko, Ph.D., FCP  
Director, Office of Clinical Pharmacology and Biopharmaceutics  
Center for Drug Evaluation and Research  
Food and Drug Administration

# **CPSC Meeting, November 3-4, 2004**

## *PG Testing of Irinotecan*

### **Committee Votes (Yes-No-Abstain):**

**7/7 genotype is associated with a higher risk of neutropenia: 12-0-0**

**7/7 genotype is associated with a higher risk for acute/delayed diarrhea: 0-11-1**

**\*28 PG testing has adequate sensitivity and specificity: 9-0-3**

# Revised Camptosar<sup>®</sup> label (effective June 7<sup>th</sup>, 2005)

population is homozygous for the UGT1A1\*28 allele. In a prospective study, in which irinotecan was administered as a single-agent on a once-every-3-week schedule, patients

## Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1\*28 allele are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. A reduced initial dose should be considered for patients known to be homozygous for the UGT1A1\*28 allele (see DOSAGE AND ADMINISTRATION). Heterozygous patients (carriers of one variant allele and one wild-type allele which results in intermediate UGT1A1 activity) may be at increased risk for neutropenia; however, clinical results have been variable and such patients have been shown to tolerate normal starting doses.

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). The appropriate dose reduction in this patient population is not known.



# U.S. Food and Drug Administration

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## *FDA News*


**FOR IMMEDIATE RELEASE**  
P05-53  
August 22, 2005

**Media Inquiries:**  
Julie Zawisza, 301-827-6242  
**Consumer Inquiries:**  
888-INFO-FDA

**FDA Clears Genetic Test That Advances Personalized Medicine  
Test Helps Determine Safety of Drug Therapy**

- **Mayo Clinic obtained exclusive license to University of Chicago patent portfolio in November 2005**
  - **Third Wave Technologies (TWT) obtained nonexclusive sublicense from Mayo**
    - **Genzyme purchased exclusive right to use TWT test**
- **UC-Mayo deal received 2007 Deal of Distinction Award from Licensing and Executive Society**

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](http://www.genzymegenetics.com)  
or call (800) 447-5816.

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The Invader® UGT1A1 Molecular Assay®  
is manufactured and distributed by Third  
Wave Technologies, Inc.

Experience Tomorrow's Cancer Testing Laboratory Today. **genzyme**

# Can *UGT1A1* genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? An evidence-based review

*Glenn E. Palomaki, BS<sup>1</sup>, Linda A. Bradley, PhD<sup>2</sup>, Michael P. Douglas, MS<sup>2,3</sup>, Katherine Kolor, PhD<sup>2</sup>, and W. David Dotson, PhD<sup>2,3</sup>*

## Recommendations from the EGAPP Working Group: can *UGT1A1* genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan?

*Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group\**

**Genetics in Medicine,  
January, 2009**

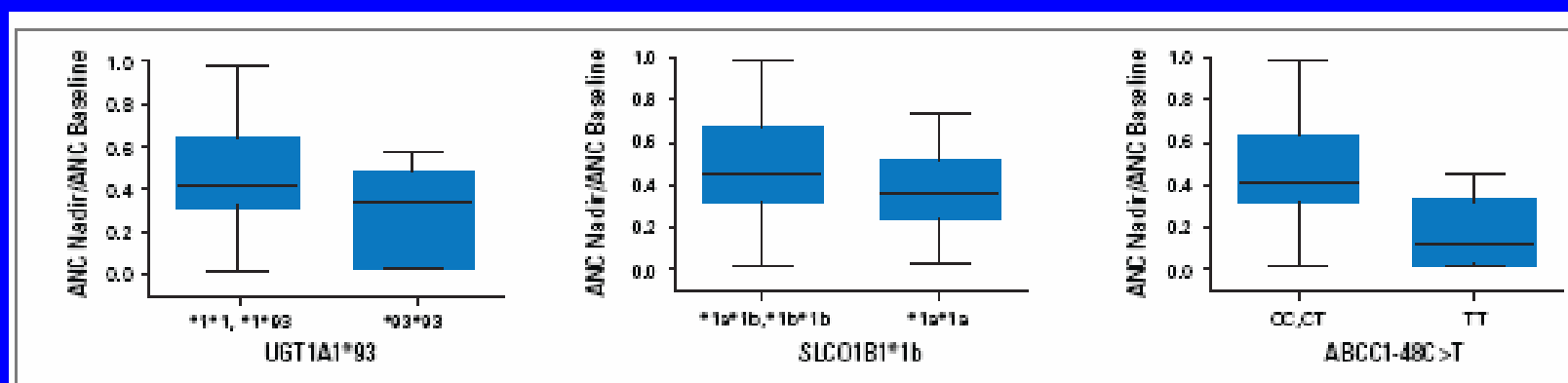
# EGAPP Working Group

Outcome	Risk ratio (95% CI) versus <i>*1/*1</i> genotype	
	<i>*1/*28</i>	<i>*28/*28</i>
Severe neutropenia <sup>15,31-35</sup>	1.82 (1.16-2.85)	3.51 (2.03-6.07)
Severe diarrhea <sup>31-36</sup>	1.40 (0.94-2.08)	1.63 (0.64-4.14)
Tumor response <sup>31,37</sup>	1.09 (0.83-1.43)	1.70 (1.24-2.33)

- **Did not consider relationship of irinotecan dose to risk ratio**
- **Did not include a large unpublished study**
- **Raised concern that genotyping of no benefit if response and toxicity correlated**

## Comprehensive Pharmacogenetic Analysis of Irinotecan Neutropenia and Pharmacokinetics

Federico Innocenti, Deanna L. Kroetz, Erin Schuetz, M. Eileen Dolan, Jacqueline Ramirez, Mary Relling, Peixian Chen, Soma Das, Gary L. Rosner, and Mark J. Ratain



Log ANC nadir, log cells/ $\mu$ L

*ABCC1* IVS11 -48C>T

*UGT1A1*\*93

*SLCO1B1*\*1b

TT, CC, CT

\*93\*93, \*93\*1, \*1\*1

\*1a\*1a, \*1a\*1b, \*1b\*1b

-0.401 0.148 .009

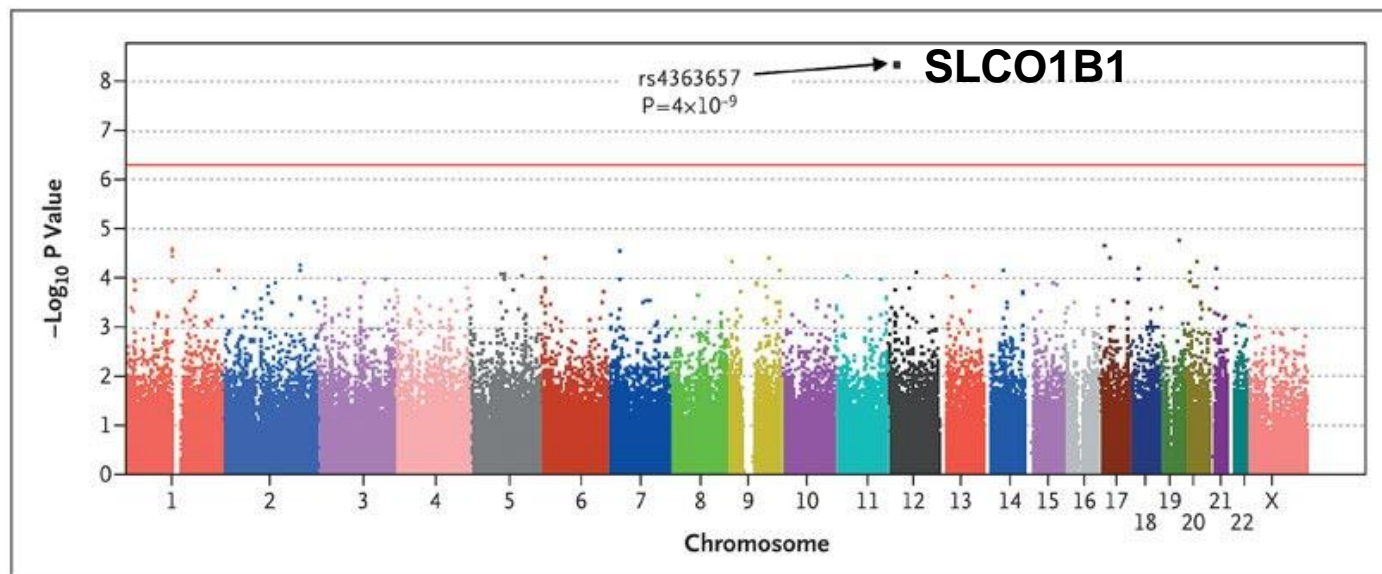
-0.373 0.111 .001

-0.211 0.071 .004

*The* NEW ENGLAND  
JOURNAL *of* MEDICINE

*SLCO1B1* Variants and Statin-Induced Myopathy —  
A Genomewide Study

The SEARCH Collaborative Group\*



**85 cases, 90 controls**

# **Current strategy for pharmacogenomics**

- **Collect DNA samples in conjunction with large clinical trials**
- **Perform genome-wide typing to identify candidates associated with both toxicity and efficacy**
- **Conduct replication studies using samples from other similar studies**
- **Perform mechanistic studies to confirm function**

# Launching a Global Alliance for Pharmacogenomics

*U.S. and Japanese Scientists Partner to Study Genetic Factors that Influence the Safety and Effectiveness of Medicines*

FOR IMMEDIATE RELEASE:  
April 14, 2008

Contact:  
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301-496-7301  
[alisa.machalek@nih.gov](mailto:alisa.machalek@nih.gov)



# Technological hurdles

Effective utilization of all available information to individualize medical care

- **MD education**
  - Pharmacology
  - Genetics
- **MD implementation**
  - Data overload
  - Reliability of data
    - Commercial software
    - Literature
  - Availability of tests



**PGRN**

