AutoGenomics

INFINITI® UGT1A1 Assay

Directional Package Insert (DPI)

For *In Vitro* Diagnostic Use

CE

FOR EXPORT ONLY

Manufactured by AutoGenomics, Inc., 1600 Faraday Avenue, Carlsbad, CA USA 92008

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AutoGenomics

INTENDED USE

The INFINITI UGT1A1 Assay is an *in vitro* diagnostic test for the detection and genotyping of the *1, *28, *36, and *37 of the TATA box region of the UDP- glucunorosyltransferase 1A1 (UGT1A1) gene in genomic deoxyribonucleic acid (DNA) obtained from EDTA-anticoagulated whole blood samples. The INFINITI UGT1A1 Assay is a qualitative assay for use in clinical laboratories upon prescription by the attending physician.

The INFINITI UGT1A1 Assay is indicated for use as an aid in the identification of patients with greater risk for decreased UDP-glucuronosyltransferase activity.

BACKGROUND INFORMATION

The response and sensitivity to a given drug could vary from patient to patient. This variation, particularly with drugs with a narrow therapeutic index, is due to a patient's ability to absorb, distribute, metabolize and excrete the drug.

One such drug is irinotecan (CAMPTOSAR®), approved worldwide for the treatment of metastatic colorectal cancer. The most clinically significant adverse events for patients receiving irinotecan-based therapy are diarrhea, neutropenia, nausea, vomiting and alopecia[1]. Irinotecan can induce both early and late forms of diarrhea and requires dose adjustment based on severity of diarrhea[1]. Severe diarrhea and neutropenia (Gilbert's Syndrome) in 20% to 35% of patients treated, and fatal events (up to 5.5% prevalence) during single agent irinotecan treatment have been reported, and concerns have been expressed regarding the rate of early deaths in colorectal cancer patients receiving the drug[4].

Irinotecan is activated by hydrolysis to its metabolite, SN-38, a potent topoisomerase I inhibitor responsible for the pharmacological and toxic effect of irinotecan[4]. Pharmacokinetic studies of irinotecan have shown large inter-individual variability of SN-38 exposure[1]. SN-38 is glucuronidated by Uridine diphosphate-glucuronyl tranferase enzymes (UGT), predominantly by UGT1A1 isoenzyme[1]. The TA repeats (5, 6, 7, or 8) in the TATA box of the UGT1A1 promoter region is inversely correlated with the gene transcription efficiency and overall enzyme activity[1]. The presence of seven repeats (TA7) compared to the normal genotype of six (TA6) repeats results in the variant allele UGT1A1*28. The insertion is most common in Caucasians and African populations[4]. This allele is associated with reduced gene expression and reduced glucuronidation in human liver microsomes resulting in decreased drug metabolism and increased toxicity[1].

Homozygosity for the TA7 allele has been associated with Gilbert's Syndrome, a common mild hyperbilirubinemia, estimated to be prevalent in 3% to 6% of the adult US population[4,8]. Severe neutropenia in Gilbert's Syndrome patients receiving irinotecan suggested the link between homozygosity of the TA7 allele and irinotecan toxicity[10].

Many studies report that patients who are homozygous for the UGT1A1*28 allele are at greater risk for irinotecan-induced toxicities, including severe diarrhea of neutropenia[4,5,6,7,9]. The CAMPTOSAR (irinotecan) package insert recommends a reduced initial dose be considered for patients homozygous for the UGT1A1*28 allele and are at an increased risk for neutropenia following initiation of CAMPTOSAR treatment.

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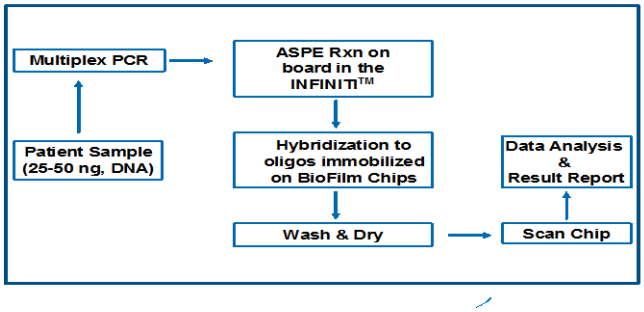
TEST PRINCIPLE/ASSAY OVERVIEW

The INFINITI UGT1A1 Assay is an *in vitro* diagnostic test for the detection and genotyping of the *1, *28, *36, *37 of the TATA box region of the UGT1A1 gene variant in genomic deoxyribonucleic acid (DNA) obtained from EDTA-anticoagulated whole blood samples. The INFINITI UGT1A1 Assay is a qualitative assay for use in clinical laboratories upon prescription by the attending physician. The assay protocol is based on five major processes:

(a) DNA extraction.
(b) PCR amplification of purified DNA from human genomic DNA.
(c) Labeling of the amplified product (detection primer extension).
(d) Hybridization of the labeled amplified product to a microarray by signature zip code / anti-zip code probe hybridization under isothermal conditions.
(e) Scanning of the microarray.
(f) Signal detection and analysis (determination of the UGT1A1 gene).

Steps (c) through (f) are automated by the INFINITI Analyzers.
A schematic overview of the assay is shown below.



DEVICE DESCRIPTION

The INFINITI UGT1A1 Assay is an *in vitro* diagnostic device which utilizes AutoGenomics' proprietary film-based microarray technology combined with process automation, reagent management and software technology for the detection and genotyping of the *1, *28, *36, and *37 of the TATA box region of the UDP- glucunorosyltransferase 1A1 (UGT1A1) gene in genomic deoxyribonucleic acid (DNA) obtained from EDTA-anticoagulated whole blood samples.

The INFINITI UGT1A1 Assay is comprised of the BioFilmChip® Microarray and the Intellipac® Reagent Module.

The **BioFilmChip Microarray** consists of a polyester film coated with proprietary multi-layer components designed for DNA analysis. The layers have been designed to provide a versatile surface to enhance test performance. The microarrays are designed to be assay specific. The INFINITI UGT1A1 Assay uses a microarray chip (L-Chip) which contains unused Capture Probes which could potentially be used for certain specific assays. Therefore, multiple assays can be developed using the same microarray.

The **Intellipac Reagent Module** which acts as a communication link contains up to four reservoirs that house the test reagents and has an integrated memory chip. Information on the reagent such as lot number, expiration date and volume usage is archived in the memory chip.

The INFINITI UGT1A1 Assay should be run using the AutoGenomics **INFINITI PLUS Analyzer**. The INFINITI PLUS Analyzer instrument is used for clinical multiplex systems intended to measure and sort multiple signals from

a clinical sample. The INFINITI Analyzers are designed to measure fluorescence signals of labeled DNA target hybridized to BioFilmChip microarrays. The INFINITI Analyzers automate the UGT1A1 assay and integrates all the discrete processes of sample (PCR amplicon) handling, reagent management, hybridization, detection, and results analysis. The assays are processed automatically and the spots are read by the built-in confocal microscope. Results are analyzed and presented as genotype calls.

Instructions on how to use the INFINITI PLUS Analyzer is provided in the INFINITI PLUS Analyzer Operator's Manual.

The INFINITI PLUS Analyzer is CE-marked.

WARNINGS AND PRECAUTIONS

Handling Requirements

- **For *in vitro* diagnostic use. To be used by qualified laboratory personnel.**
- This test is to be used only with whole blood collected in EDTA. Do not freeze/thaw blood samples. Specimens should be assayed as soon as possible.
- All patient specimens are potentially hazardous and care should be taken when handling materials of human origin. No test method can offer complete assurance that HCV, HIV or other infectious agents are absent.
  Follow the CLSI Guidelines (Molecular Diagnostics Methods for Infectious Diseases; Approved Guidelines; MM3-A).
- Upon receipt of samples, visually inspect sample condition. Specifically, look for abnormal signs that indicate that sample integrity has been compromised (e.g., evaporation, decrease in volume, precipitation, spills, discoloration, sedimentation, separation, turbidity, etc.). If you observe or suspect any sample abnormality, do not perform any test.
- Samples should be handled with extreme caution to prevent contamination, spillage, sample mix-up. Sample containers should be labeled clearly to prevent mix-up.
- Store samples at the specified conditions.
- To minimize the risk of cross contamination, sample preparation, PCR reaction set up and PCR product analysis should be performed according to approved guidelines such as CLSI (Molecular Diagnostic Methods for Genetic Diseases: Approved Guideline).
- Do not pool/mix reagents from different lots.
- Do not use a kit or reagent past its expiration date.
- Store kits and reagents according to the product label.

Laboratory Procedures

- Follow normal precautions for handling laboratory reagents.
- Follow safe laboratory procedures: do not pipette by mouth; wear protective clothing (e.g., disposable gloves laboratory coats) and eye protection; do not eat, drink or smoke in the laboratory work areas; wash hands thoroughly after handling samples and reagents.

Waste Handling

- Dispose of unused reagents, specimens and waste according to applicable country, federal, state and local regulations.
- Safety data Sheets (SDS) are available upon request from AutoGenomics Customer Service.

Sample Preparation

- Refer to the safety instructions in the package insert provided with the DNA extraction kit used.
- The PCR product cannot be stored prior to loading it onto the microarray. Use immediately.

INFINITI PLUS Analyzer

- **Read the INFINTI PLUS Analyzer Operator's Manual before operating the instrument.** Pay particular attention to "Notes".
- Follow the Caution and Safety Warning in the Operator's Manual.
- Refer to the Installation Requirements Section when installing the instrument.
- Refer to the Errors Section when errors are encountered while operating the instrument.
- Refer to the Help Section when problems are encountered.

STORAGE / STABILITY

BioFilmChip Microarray: 24 months Refrigerated (2 to 8°C)
Intellipac Reagent: 12 months Refrigerated (2 to 8°C)

Note: Remove the Intellipac and store refrigerated as soon as possible. Do not use after Intellipac has been opened for four weeks.

Amplification Mix: 18 months Frozen (-30 to -15°C)

Note: **Specific product expiration date is printed on the product label.**

MATERIALS PROVIDED (SUFFICIENT FOR 48 TESTS)

- Product Number 03-1050-02: INFINITI UGT1A1BioFilmChip® Microarray Magazine , 4 magazines per package
- Product Number 03-2050-02: INFINITI UGT1A1 Intellipac® Reagent Module,
  24 tests per module which contains:
  - 1.1 mL ASPE Master Mix:
    - PCR Buffer
    - dNTPs
    - ASPE Primers
  - 2.6 mL Hybridization Buffer
    - SSC
    - Hybridization Positive Control
    - Sodium Azide Preservative 0.08%
- Product Number 03-3050-02: INFINITI UGT1A1 Amplification Mix
  2 x 500 µL of PCR reaction master mix vials containing:
  - PCR Buffer
  - $MgCl_2$
  - dNTPs
  - PCR Primer Set for UGT1A1

  1 x 60 µL NA Mix
- Product Number 12-0330-02: Wash buffer

REAGENTS REQUIRED BUT NOT PROVIDED BY AUTOGENOMICS

- DNA Extraction Kits - The INFINITI UGT1A1 Assay can detect the *1, and *28, *36, and *37 of the TATA box region of the UGT1A1 gene using genomic DNA isolated from blood with sufficient purity, i.e., with the ratio of absorbance at 260nm to absorbance at 280nm of ≥ 1.60. Any DNA extraction method that meets this specification may be used. The INFINITI UGT1A1 Assay has been tested with several commercially available kits. The user can contact AutoGenomics for further information.
- Distilled Water (DNAse and RNAse free)
- Titanium Taq DNA Polymerase (Clontech (now Takara) Catalog # 639209)

EQUIPMENT

The following equipment is required but not provided with the assay reagents

- AutoGenomics Product Number 10-0020-99: INFINITI PLUS Analyzer.
- AutoGenomics Product Number 11-0020-00: INFINITI Waste Tray Liners
- Product Number 11-0100-00: 48-Well Plates and Product Number 11-0110-00: 48 Well Plate Lid
- AutoGenomics Product Number 11-0060-00: INFINITI Waste tray Stir Bars
- AutoGenomics Product Number 11-0080-00: INFINITI Pipette Tips
- 8-well Flat Strip Caps (Corning, Catalog No. PCR-2CP-RT-C)
- Pipettors
- Mini Centrifuge
- Pipette Tips
- Microfuge Tube Racks
- Thermocycler
- Vortex
- 0.2 mL Thin wall Tubes for PCR
- 1.5 mL Microcentrifuge Tubes

ASSAY PROCEDURE

DNA Extraction

Follow the instructions provided with the DNA extraction kit used.

Specimen Requirements

Purified DNA that is at a concentration of >20 ng/µL and has a ratio of A260/280 >1.6.

DNA Controls

It is required to run known controls in each test run. The recommended Coriell controls and their expected results are tabulated below.

Coriell Number	Description	Call
NA17113	*1/*1	*1 Homozygote
NA17114	*1/*28	*1/*28 Heterozygote
NA17115	*28/*28	*28 Homozygote
NA17127	*36/*37	*36/*37 Heterozygote

PCR Reaction

Note:

- Keep Titanium Taq DNA polymerase on ice.
- Completely thaw reagents on ice.
- Vortex the amplification mix tube for 2 to 5 seconds then centrifuge briefly to bring the contents to the bottom of the tube.
- To avoid contamination, a separate area is recommended for assembly of the PCR reaction. Decontaminate pipettes and all work surfaces with freshly prepared 10% bleach.
- Filter tips and gloves must be used when handling specimens and controls.
- The PCR product cannot be stored prior to testing. Use immediately.

1. Prepare the PCR master mix

Amplification mix	17. 75 µL
Titanium Taq DNA polymerase	0. 25 µL
NA Mix	1. 00 µL
Total volume of PCR Master mix	19.0 µL

Note: Calculate the amount of each reagent needed based on the number of reactions.

2. Gently vortex the PCR master mix then dispense 19 µl of master mix into wells of the 48-well plate.

3. Add 2 µl of sample DNA (>20 ng/µl) to each well.

PCR master mix	19.0 µL
Sample DNA	2.0 µL
Total volume of amplification reaction	21.0 µL

4. Place the 48-well plate, sealed with 8-well flat strip caps, in a thermocycler and immediately commence the amplification reaction using the following program.

Step No.	Temperature ºC	Time	No. of Cycles
1	94	2 min	N/A
2	94 54 72	20 sec 30 sec 30 sec	40x
3	4	Hold	1

Note: When an Eppendorf Mastercycler EP was used with the ramp rate set at 75%, the total cycling time was 1 hour and 32 minutes (± 15 min). If using other thermocycler models we recommend adjusting the ramp rate in order to obtain an equivalent total cycling time.

Sample Loading - INFINITI PLUS Analyzer

Carefully remove the 8-well flat strip caps to avoid splashing. Load the assembled 48WP with a clean lid (Catalog # 11-0110-00) (see instructions in the INFINITI PLUS Analyzer Operations Manual) in the appropriate orientation (with well A1 in the back left corner), assay specific magazines, Intellipac, INFINITI® Static Free Pipette tips, and buffer into the INFINITI® PLUS Analyzer.

Operation of the INFINITI PLUS Analyzer

Follow instructions in the **INFINITI PLUS Analyzer Operator's Manual (Part Number EM-34041).**

QUALITY CONTROL

- Maintain calibration of thermocycler according to manufacturer's specifications.
- Maintain calibration of INFINITI® PLUS Analyzer according to AutoGenomics' specifications.
- Maintain calibration of pipettes according to manufacturer's specifications.

LIMITATIONS

The results obtained from the INFINITI UGT1A1 Assay should be used and interpreted only in the context of the overall clinical diagnosis. AutoGenomics is not responsible for any clinical decisions that are taken.

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INTERPRETATION OF RESULTS

The INFINITI UGT1A1 Assay is designed to detect and genotype the *1, *28, *36 and *37 of the TATA box region of the UGT1A1 gene. The assay results are provided as a genotype "call", indicating which genotype was detected in the sample, i.e., *1/*1, *1/*28, *28/*28, "Other". "Other" indicates a genotype other than *1/*1, *1/*28 or *28/*28 (e.g., *1/*36. *1/*37, *36/*36, *37/*37, *28/*36, *28/*37, *36/*37) was detected in the sample.

When the assay is not completed, and no genotype call is made, the assay will need to be repeated. The report displays a message which indicates the reason why no genotype call was made. When an error occurs (e.g., "low DNA"), an Error Log is generated which identifies the problem. Please refer to the Trouble Shooting section of the INFINITI PLUS Analyzer Operator's Manual.

PERFORMANCE CHARACTERISTICS

Analytical Specificity

Studies related to specificity were conducted during assay development. PCR primer specificity was determined by amplicon size on a gel and sequencing the amplicon. DPE primer specificity was determined by the correct calls made by the assay using known genomic samples. Capture probe specificity was determined by hybridizing different oligos and demonstrating that correct oligo hybridizes to the known spot.

Limits of Detection (analytical sensitivity)

The analytical sensitivity of the INFINITI UGT1A1 Assay was assessed by analysis of three blood genomic samples at concentrations of 10, 25, 50 and 100 ng DNA/µL. The genotypes in the samples were *1/*1, *1/*28 and *28/*28 as determined by bi-directional sequencing. The concentration was determined by spectrophotometry. The DNA was extracted using the Gentra Systems Puregene Extraction Kit. Forty replicates of each sample were assayed for a total of 480 tests. All 480 INFINITI UGT1A1 Assay results matched the genotypes as determined by bi-directional sequencing.

The Limit of Detection study demonstrated that the INFINITI UGT1A1 Assay can detect the target mutations at DNA concentrations of 10ng DNA/µL to 100ng DNA/µL. The recommended DNA concentration for the INFINITI UGT1A1 Assay is 25ng DNA/µL. The assay requires 2µL of the DNA sample.

Percent Agreement AGI vs. Invader UGT1A1 Molecular Assay

The INFINITI UGT1A1 Assay was compared to Invader or bi-directional sequencing as the comparator method. Three sites were used for the comparison studies. Each site tested its own patient samples with the INFINITI UGT1A1 Assay. Patient samples were de-identified to protect patient's identity. Bi-directional sequencing was performed to verify the sample result.

The results of the comparison studies comparing the INFINITI UGT1A1 Assay to bi-directional sequencing demonstrated.

94.0% agreement for *1 ($TA_{6/6}$) as compared with bi-directional sequencing on 1st run;
100% after repeat.
95.2% agreement for *28 Heterozygous ($TA_{6/7}$) as compared with bi-directional sequencing on 1st run;
100% after repeat.
92.0% agreement for *28 Homozygous ($TA_{7/7}$) as compared with bi-directional sequencing on 1st run;
98.0% after repeat.
86.7% agreement for "other" as compared with bi-directional sequencing on 1st run; 100% after repeat

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The results of the comparison studies are summarized in Table 1.

Table 1 Agreement between INFINITI UGT1A1 Assay and Bi-directional Sequencing

Genotype	Number Tested	Replicates per Sample	First Time Run				Final Result[a]			
			Number of Correct Genotype Calls	Number of Incorrect Calls	No Call	Agreement	Number of Correct Genotype Calls	Number of Incorrect Calls	No Call	Agreement
*1 ($TA_{6/6}$)	117	1	110	1c	6	94.0%	117	0	0	100%
*28 Heterozygous ($TA_{6/7}$)	104	1	99	1[c]	4	95.2%	104	0	0	100%
*28 Homozygous ($TA_{7/7}$)	50	1	46	1[d]	3	92.0%	49	1[d]	0	98.0%
Other[b]	15	1	13	0	2	86.7%	15	0	0	100%
Total	286	1	268	3	15[e]	93.7%	285	1[d]	0	99.7%

a Final result based on one repeat
b "Other" indicates genotype calls other than *1/*1, *1/*28 and *28/*28
c Incorrect Calls: AG41 and AG42 Sample switch. Repeat INFINITI results matched sequencing results.
d Incorrect Call: AG62 was possibly switched with AG 63 during purification for bi-directional sequencing. INFINITI results for AG62 matched INVADER (predicate) results. Repeat sequencing of AG63 confirmed sample switch, however, there was not enough sample available for repeat of sequencing of AG62.
e No Call: 13 assays due to instrument laser out of calibration. Repeat INFINITI assays after laser calibration gave correct calls.
2 assays due to suspect pipetting errors. Repeat INFINITI assay matched sequencing result

Assay Inter-Laboratory Reproducibility

A three-site study was conducted to demonstrate the reproducibility of the INFINITI UGT1A1 Assay. The study involved three lots of the INFINITI UGT1A1 Assay. The sites ran identical samples comprised of five genomic DNA samples and three whole blood samples. The sites were blinded to sample identity. At each site, each sample was run in triplicate per day/operator for six days. Three operators were required for each site. Results of the inter-laboratory reproducibility study are summarized in table 2.

Table 2 Inter-Laboratory Reproducibility of the INFINITI® UGT1A1 Assay by Genotype calls

Genotype	Samples Tested	Tests per Site	Site	Genotype Calls	First Time Run				Final Result[b]			
					Correct Calls	Incorrect Calls	No Calls	% Correct Calls	Correct Calls	Incorrect Calls	No Calls	% Correct Calls
***1/*1**	1	18	1	18	17	0	1	94.4%	18	0	0	100
			2	18	17	0	1	94.4%	18	0	0	100
			3	18	18	0	0	100%	18	0	0	100
			Total	54	52	0	2	96.3%	54	0	0	100
***1/*28**	1	18	1	18	17	0	1	94.4%	18	0	0	100
			2	18	16	0	2	88.9%	18	0	0	100
			3	18	18	0	0	100%	18	0	0	100
			Total	54	51	0	3	94.4%	54	0	0	100
***28/*28**	1	18	1	18	18	0	0	100%	18	0	0	100
			2	18	18	0	0	100%	18	0	0	100
			3	18	16	2	0	88.9%	18	0	0	100
			Total	54	52	2	0	96.3%	54	0	0	100
Other[a]	5	90	1	90	81	7	2	90.0%	90	0	0	100
			2	90	81	3	6	90.0%	90	0	0	100
			3	90	88	1	1	97.8%	90	0	0	100

Genotype	Samples Tested	Tests per Site	Site	Genotype Calls	First Time Run				Final Result[b]			
					Correct Calls	Incorrect Calls	No Calls	% Correct Calls	Correct Calls	Incorrect Calls	No Calls	% Correct Calls
			Total	270	250	11	9	92.6%	270	0	0	100
All	8	144	1	144	133	7	4	92.4%	144	0	0	100
			2	144	132	3	9	91.7%	144	0	0	100
			3	144	140	3	1	97.2%	144	0	0	100
Total for Assay				432	405	13[c]	14[d]	93.8%	432	0	0	100

a "Other" indicates genotype calls other than *1/*1, *1/*28 and *28/*28
b Final result based on one repeat
c 13 Incorrect calls
genotype call on 1 assay was *1/*1 vs. expected "other"; correct call on repeat
genotype call on 10 assays was *28/*28 vs. expected "other"; correct call on repeat
genotype call on 2 assays was "other" vs. expected *28/*28; correct call on repeat
d 14 No calls
8 due to instrument PMT problems
4 due to instrument not detecting a pipette tip
2 due to low DNA

Drug Interference
Evaluation of potential interference from bilirubin, cholesterol, and heparin demonstrated that presence of these compounds in concentrations of 8mg/dl bilirubin, 70 mg/dl cholesterol and 133 v/dl heparin do not interfere with the INFINITI UGT1A1 Assay.

Sample Carry-Over
No sample carry-over was detected when 300ng of a positive sample was followed by 10 ng of a second positive sample, and when 300 ng of a positive sample was followed by a "No Template Control" or water. All genotype calls were 100% correct.

BIBLIOGRAPHY

1. Proceedings from FDA Clinical Pharmacology Subcommittee, November 3-4, 2004 (http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079B1 03 Topic1-TabA).

2. Ando Y et al "Polymorphisms of UDP-glucuronosyltransferasegene snd irinotecan toxicity" Cancer Research 2000; 60:6921-6926.

3. Beutler E et al "Racial variability in the UDP-glucuronosyltransferase 1 (*UGT1A1*) promoter: A balanced polymorphism for regulation of bilirubin metabolism?" National Academy Science 1998; 95:8170-8174.

4. Innocenti F et al "Genetic Variants in the *UDP-glucuronosyltransferase* 1A1 Gene predict the risk of Severe Neutropenia of Irinotecan" Journal of Clinical Oncology 2004; 22(8):1362-1388.

5. Lyer L et al "Genetic predisposition to the metabolism of irinotecan (CPT-11). Role of uridine diphosphateglucuronosyltransferace isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes" Journal Clinical Investigation 1998; 101:847-854.

6. Lyer L et al "*UGT1A1*28* polymorphism as a determinant of irinotecan disposition and toxicity" Pharmacogenetics Journal 2002; 2:43-47.

7. Marcuelo E et al "UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer" British Journal Cancer 2004; 91(4):678-682.

8. Owens D et al "Population Studies on Gilbert's Syndrome" Journal of Medical Genetics 1975; 12:152-156.

9. Rouits E et al "Relevance of Different UGT1A1 Polymorphisms in Irinotecan-Induced Toxicity: A Molecular and Clinical Study of 75 Patients" Clinical Cancer Research 2004; 10:5151-5159.

10. Wasserman E et al "Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports" Ann Oncology 1997; 8:1049-51.