

PATIENT INFORMATION

NAME:
DOB:
SEX AT BIRTH:

SPECIMEN DETAILS

BARCODE:
SAMPLE ID:
TYPE:
COLLECTED:
RECEIVED:

ORDERED BY

PROVIDER:

5-FU/CAPECITABINE RISK		
Severity	DPYD Activity Score	Recommendation
Hand-Foot Syndrome Risk		
Risk		Recommendation
Cardiotoxicity Risk		
Risk		Recommendation

IRINOTECAN RISK	
UGT1A1 Metabolizer Status	Recommendation

Clinical Interpretation:



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Results:

Genotype Result

Gene/Variant	Gene/Variant	Phenotype Result
DPYD		
ENSO1 (rs2612091)		
rs12132152		
DGLUCY (rs4904753)		
UGT1A1 (rs3054744)		



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Test Information:

DNA is isolated and regions of interest are amplified using polymerase chain reaction (PCR). Results are analyzed using MassArray Technology (Agena Biosciences). Germline variant results are interpreted using ToxNav to determine risk for severe toxicity (CTC grade ≥ 3) such as stomatitis, diarrhea, neutropenia, neurotoxicity, hand-foot syndrome, and cardiotoxicity upon treatment with a standard dose of 5-FU fluorouracil or capecitabine. Toxicity is largely due to dihydropyrimidine dehydrogenase (DPD) or partial DPD deficiency as listed on the drug labels. The risk is calculated using analysis 1046 individuals receiving Capecitabine treatment in the QUASAR2 clinical study and meta-analysis of data from 16 published studies with 4,855 patients receiving 5-FU monotherapy or combination therapy (Rosmarin et al. 2014. PubMed ID: 24590654). The clinical advice is provided as advised by the Clinical Pharmacogenetics Implementation Consortium guidelines for DPYD genotype and fluoropyrimidine dosing (Amstutz et al. 2018. PubMed ID: 29152729). Hand-Foot Syndrome risk is based on presence of either homozygous *ENOSF1/TYMS* c.742-227G>A and/or heterozygous g.97523004G>A variants (rs12132152) (Hamzic et al. 2020. PubMed ID: 31838077; Rosmarin et al. 2015. PubMed ID: 24647007). Cardiotoxicity risk is based on the presence of a homozygous *DGLUCY* c.-81-4023G>T variant with a sensitivity of 48% and a specificity of 90% (Claire Palles et al. A novel genetic marker of fluoropyrimidine-induced cardiovascular toxicity. J Clin Oncol 41, 3028-3028(2023); International Patent WO 2024/095015 A1).

UGT1A1 *28 is analyzed using melt curve analysis. *UGT1A1* results detect increased risk for severe toxicity (CTC grade ≥ 3) neutropenia following irinotecan treatment. Irinotecan related-severe grade 3/4 neutropenia is based on the presence of a *UGT1A1* *28/*28 genotype which is associated with a poor metabolizer status (Karas and Innocenti. 2022. PubMed ID: 34860573; Dean. 2015. PubMed ID: 28520360). In a meta-analysis of over 10,000 patients treated with irinotecan, patients with a *28/*28 genotype were at increased risk for grade 3 or higher neutropenia with a sensitivity of 11%, specificity of 94%, positive predictive value of 30% and negative predictive value of 82% (Hulshof et al. 2020. PubMed ID: 33125947).

Our assay detects all AMP tier 1 and 2 *DPYD* variants (Pratt et al.2024 PubMed ID: x 39032821) and the following additional *DPYD* variants for DPD deficiency: c.257C>T, c.601A>C, c.632A>G, c.731A>C, c.1399_1400del, c.1339+1G>T, c.1651G>A, c.1898del, c.2933A>G, and c.2983G>T; Hand-Foot syndrome variants g.97523004G>A and *ENOSFT1/TYMS* c.742-227G>A; cardiotoxicity variant *DGLUCY* c.-81-4023G>T; irinotecan-related neutropenia variant *UGT1A1* *28.

Limitations:

DPD deficiency, hand-foot syndrome risk, and cardiotoxicity due to fluoropyrimidine treatment are based on the variants included in this assay. Other *DPYD* variants or genetic markers may also contribute to fluoropyrimidine toxicity that are not within this assay. PCR amplification may be affected by rare sequence variants, interfering substances, poor DNA quality, or other factors resulting in allele dropout. Our assay does not determine the phasing of variants to determine if they are on the same or opposite alleles. Individuals with positive variant findings may benefit from genetic counseling to further discuss the result implications including health care management and family risk.

Liability Disclaimer:

This test was developed and validated by Mira Precision Health for clinical use. It has not been cleared or approved by the FDA. The report is not a diagnostic test, does not provide medical advice and is not a prescribing system. Recommendations are based on NCCN, CPIC, or other professional guidelines and results should be discussed with a physician or other health care provider to determine the best course of treatment for patients.

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Electronically Signed Date



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