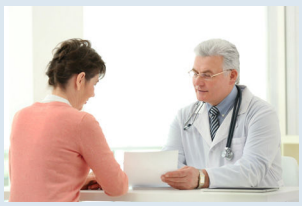
TOXNAV®

An innovative germline DNA test which predicts genetic susceptibility to severe 5FU/capecitabine toxicity

ToxNav workflow steps 1–7:

1



- Patients offered fluoropyrimidine chemotherapy
- ToxNav test requested by clinician

2

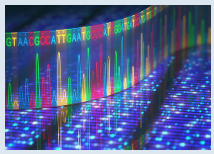
- Blood sample taken (EDTA)
- Sample requisition form and blood sample sent to laboratory

3

- Sample and requisition form received and logged by laboratory
- DNA extracted

4

- Sequencing carried out to detect genotype of 19 variants
- Data managed via secure server



5

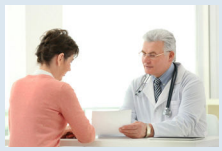
- Results transmitted from lab to OCB analysis suite
- Data imported to ToxNav software

6

Phenotype (genotype)	ToxNav Risk Category	Implications for Phenotypic Measures	Dosing Recommendations (for patients with no other contraindicating factors)
DPYD normal metabolizer	Standard Risk	Normal DPYD activity and normal risk of toxicity	No indication to change dose or therapy
	Standard Risk High Risk HFS	Normal DPYD activity and normal risk of toxicity. High risk of Hand-Foot Syndrome (HFS)	No indication to change dose or therapy Prevent HFS according to local guidelines
DPYD intermediate metabolizer	High Risk	Decreased DPYD activity and increased risk of severe or fatal toxicity	A capecitabine or 5FU monotherapy dose reduction of 50% is recommended
DPYD poor metabolizer	Critical Risk	Complete DPYD deficiency and increased risk for severe or fatal toxicity	Capecitabine or 5FU therapy is contraindicated and should not be administered

ToxNav risk stratification and dosing recommendation (based on guidelines from Amstutz et al, 2017[1])

7



- ToxNav report is received by the clinician within ten working days of sample receipt
- The toxicity risk is discussed with the patient and a personalised treatment decision is made

TOXNAV®

CE IVD

Oxford Cancer Biomarkers

TOXNAV®

A novel assay to predict 5FU/capecitabine toxicity

What is ToxNav?

- A comprehensive panel of 19 genetic variants associated with 5FU/capecitabine toxicity in the DPYD and TYMS/ENOSF1 genes[2]
  - Includes variants not found in other panels:
    - Variants found at a relatively low population frequency linked to severe (Grade 4) toxicities that may have fatal consequences
    - Hand Foot Syndrome
  - Uses the proprietary ToxNav algorithm to determine patient risk category
  - Panel derived from meta-analysis of all published genes associated with 5FU toxicity (n=4,855)[3,4]
- Developed using QUASAR 2 clinical trial samples and data set[2]
  - Well-documented toxic effects using CTCAE classifications

What does ToxNav do?

- Stratifies patients into risk groups based on their individual genotype
- 100% specificity for identification of people likely to die from 5FU/capecitabine toxicity[5]
- Identifies risk of Grade 4 haematological toxicities with a high degree of accuracy (98% specificity, 75% sensitivity, NPV 1, PPV 0.14)[5]

Why use ToxNav?

- Comprehensive panel of genetic variants providing optimum detection in general population
- Clinical validation[5] in 888 colorectal patient samples from a large scale clinical trial[2]
- Could save 10 lives in every 1,000 patients tested
- Potential savings of >£2,500 per patient who avoids Grade 3+ toxicities[6]
- Meets patient safety and enhanced patient experience standards (NHS Outcomes Framework)[7]

References:

1. Amstutz et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin Pharmacol Ther. 2017
2. Kerr *et al.*, Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial. Lancet Oncol 2016; 17(11): p. 1543-1557.
3. Rosmarin *et al.*, Genetic Markers of Toxicity from Capecitabine and Other Fluorouracil-Based Regimens: Investigation in the QUASAR2 Study, Systematic Review, and Meta-Analysis, J Clin Oncol 2014; 32 (10): 1031-39
4. Rosmarin *et al.*, A candidate gene study of capecitabine-related toxicity in colorectal cancer identifies new toxicity variants at DPYD and a putative role for ENOSF1 rather than TYMS. Gut. 2015; 64(1):111-20.
5. ESMO 2018 abstract: Palles *et al.*, An evaluation of the clinical utility of a panel of variants in DPYD and ENOSF1 for predicting common Capecitabine related toxicities.
6. Deenen MJ *et al.* Upfront Genotyping of DPYD*2A to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis. J Clin Oncology 2016; 34 (3):227-234
7. NHS Outcomes Framework: at-a-glance. Department of Health 2016.