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

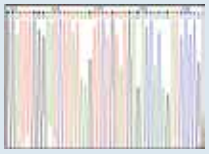
- Blood sample taken (EDTA)
- Sample requisition form and blood sample sent to laboratory

3

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

4

- Sanger sequencing carried out to detect genotype of 21 variants
- Data managed via secure server



5

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

6

Phenotype (genotype)	Implications for treatment	Dosing recommendations
Homozygous for wild-type allele, or normal, high DPYD activity	Normal DPYD activity "normal" risk for toxicity	Use label-recommended dosage and administration
Heterozygous, or intermediate activity	Decreased DPYD activity increased risk for severe or even fatal drug toxicity	Start with at least a 50% dose reduction, followed by titration of dose based on toxicity or pharmacokinetic test
Homozygous, or deficient activity	Complete DPYD deficiency increased risk for severe or even fatal drug toxicity	Select alternative drug

Recommended dosing of fluoropyrimidines based on genotype or DPYD activity (adapted from Caudle et al, 2013)[1].

7

- ToxNav Report received by clinician and risk category discussed with patient
- Personalised chemotherapy decision made

TOXNAV®

CE IVD

Oxford Cancer Biomarkers

ToxNav®

A novel assay to predict 5FU/capecitabine toxicity

What is ToxNav?

- A comprehensive panel of 21 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. Caudle KE *et al.* Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. Clin Pharmacol Ther. 2013 Dec; 94 (6): 640-5
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.