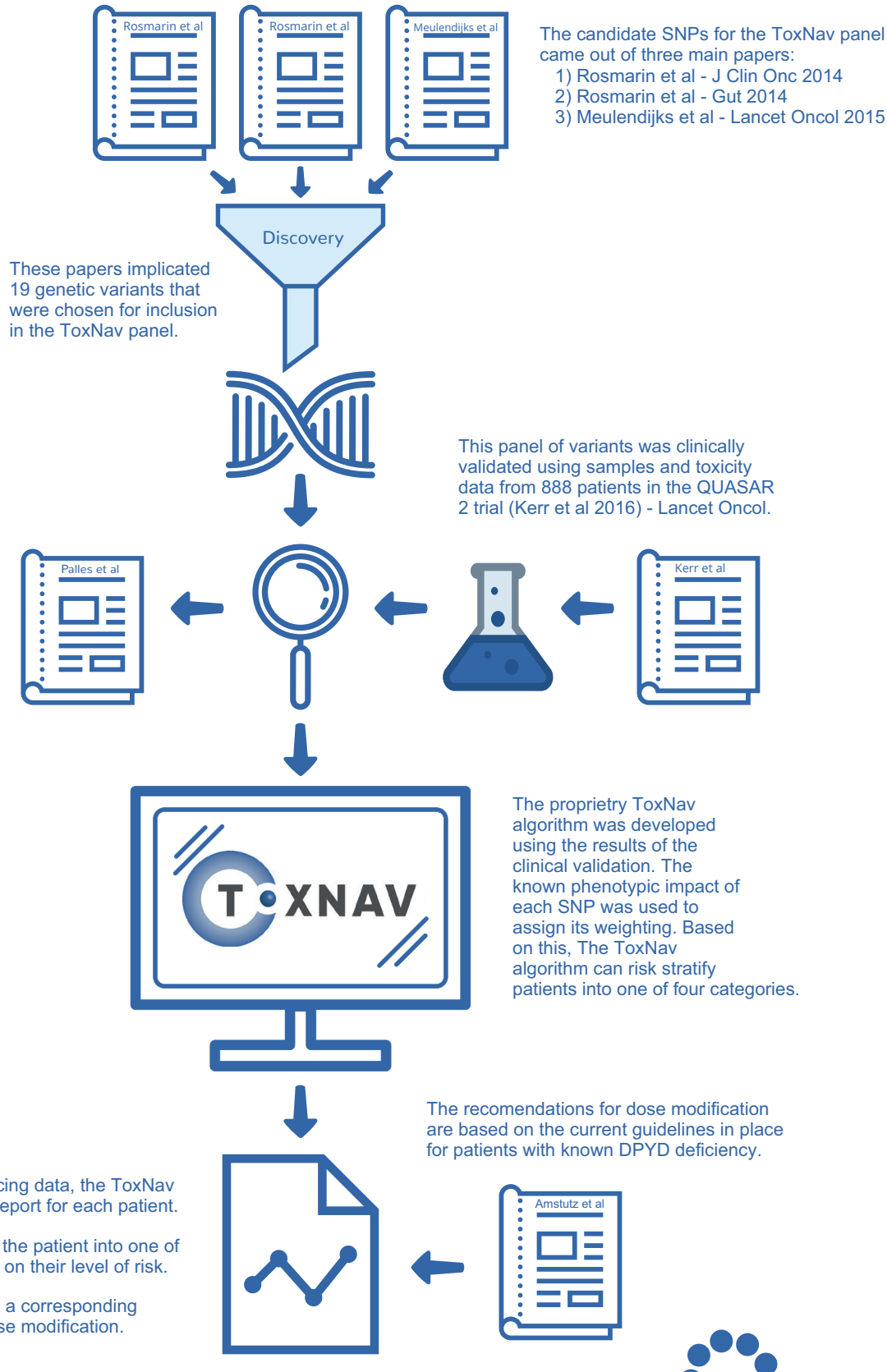
TOXNAV® Evidence Map

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



The candidate SNPs for the ToxNav panel came out of three main papers:

1) Rosmarin et al - J Clin Onc 2014
2) Rosmarin et al - Gut 2014
3) Meulendijks et al - Lancet Oncol 2015

These papers implicated 19 genetic variants that were chosen for inclusion in the ToxNav panel.

This panel of variants was clinically validated using samples and toxicity data from 888 patients in the QUASAR 2 trial (Kerr et al 2016) - Lancet Oncol.

Clinical validation of the 19 genetic variants included in the ToxNav panel can be found in the poster overleaf.

The proprietry ToxNav algorithm was developed using the results of the clinical validation. The known phenotypic impact of each SNP was used to assign its weighting. Based on this, The ToxNav algorithm can risk stratify patients into one of four categories.

The recomendations for dose modification are based on the current guidelines in place for patients with known DPYD deficiency.

Using patient sequencing data, the ToxNav software produces a report for each patient.

The report will stratify the patient into one of four categories based on their level of risk.

Each category carries a corresponding recomendation for dose modification.

Tox_0002_2019_UKa June 2019

Oxford Cancer Biomarkers

An evaluation of the clinical utility of a panel of variants in *DPYD* and *ENOSF1* for predicting common capecitabine related toxicities

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Introduction

5-Fluorouracil (5-FU) based adjuvant chemotherapy, including 5-FU oral prodrug capecitabine, is extremely effective in increasing survival of Stage III colorectal cancer (CRC) patients and patients with resectable gastric or breast cancer. Its use is however limited by the concomitant toxicities that arise in some patients. ~ 50% of patients experience dose limiting toxicity when treated with capecitabine as a single agent and this percentage increases when given in combination e.g. with oxaliplatin. We have tested the diagnostic accuracy of a panel of toxicity associated/DPYD deficiency alleles at predicting an individual's risk of capecitabine-related toxicity in 888 patients from the QUASAR2 trial[1].

Methods

Table 1: Recommended dosing of fluoropyrimidines based on genotype or DPYD activity (adapted from Caudle *et al*, 2013)

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

Criteria for including a genetic marker in the toxicity panel:

•**Low function/no function alleles** - Identified in DPYD deficiency patients (minor allele frequency (MAF) <1%. Three were also associated with toxicity at P <0.05.
•**Common polymorphisms associated with global capecitabine-related toxicity** with an odds ratio >1.5 at pathway level significance and associated with an individual toxicity at genome-wide significance.

DPYD genotype based dosing guidelines published in 2013 [2] (Table 1) were incorporated in a simple genotype guided risk classification system resulting in critical risk, high risk, standard risk and standard risk with high risk of hand foot syndrome (HFS) classifications.

Clinical utility of the panel was tested by genotyping the markers in 888 participants of the QUASAR2 trial (Kerr *et al*, 2016) for whom DNA and CTCAE graded toxicity data were available. Updated guidelines also recommend dose reductions based on DPYD haplotype c.1236G>A/HapB3 [3]. We have evaluated the impact of including this variant.

Results

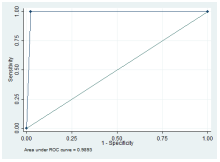
17 DPYD low-function/no-function alleles, 1 common (MAF>1%) polymorphism mapping to DPYD and one common polymorphism mapping to ENOSF1 were selected for inclusion in the panel.

The following adverse event outcomes were analysed to determine the clinical utility of the panel at predicting toxicity: Toxicity associated death, Haematological toxicities (grade 0,1,2 vs 3,4). Global toxicity (cases coded as having one or more graded 3/4 event of diarrhoea, neutropenia, thrombocytopenia, vomiting, stomatitis/mucositis, hand foot syndrome (HFS)).

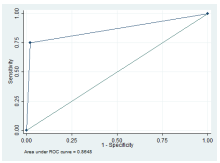
The test has high sensitivity and specificity to accurately predict risk of death or grade 4 haematological toxicities (100% sensitivity, 98% specificity, negative predictive value (NPV) 1.0, positive predictive value (PPV) 0.1 (**death**); 75% sensitivity, 98% specificity , NPV 1, PPV 0.14 (**haematological** toxicities). The ability of the test to predict risk of other toxicities is low (Figure 1, Global Toxicity).

The two deaths during QUASAR2 which were attributable to capecitabine administration occurred in patients who would have been highlighted by the test as high risk and a 50% reduction in starting dose would have been recommended. Common markers associated with HFS at genome wide significance were included in the panel. The sensitivity and specificity of the panel to accurately predict risk of HFS is only moderate (83% sensitivity, 31% specificity, NPV 0.87, PPV 0.25) but explanation by an oncologist of ways to mitigate the impact of this side effect on quality of life may enable participants to continue with treatment for longer. Inclusion of HapB3[3] in the panel was not supported as evidenced by reduced area under the curve and reduced sensitivity/specificity (data not shown).

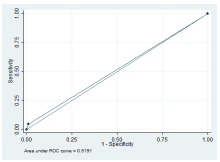
Figure 1: ROC curves demonstrating performance of panel



OUTCOME: Toxicity related death



Grade 4 haemato-logical toxicity



Global toxicity

Conclusions

A panel of no-function/low-function DPYD alleles has clinical utility for the prediction of the most serious capecitabine related adverse events. Inclusion of two HFS associated markers may assist clinicians and patients in the management of this side effect. A clinical utility study is under way to determine the impact of testing for this panel of variants on patient treatment decisions.

References: **1**. Kerr RS, Love S, Segelov E, Johnstone E, Falcon B, Hewett P, Weaver A, Church D, Scudder C, Pearson S, Julier P, Pezzella F, Tomlinson I, Domingo E, Kerr DJ. Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial. Lancet Oncol. 2016 Nov;17(11):1543-1557. **2**. Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. Caudle KE, Thorn CF, Klein TE, Swen JJ, McLeod HL, Diasio RB, Schwab M. Clin Pharmacol Ther. 2013 Dec;94(6):640-5. **3.** Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, Swen JJ, Klein TE, McLeod HL, Caudle KE, Diasio RB, Schwab M. Clin Pharmacol Ther. 2018 Feb;103(2):210-216.

20WCGIC 213--P
Clinical Colon Cancer
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DOI: 10.3252/pso.eu.20wcgic.2018
Poster presented at: ESMO 20–23 June, 2018 Barcelona, Spain
PosterSessionOnline.com