

# Oxford Cancer Biomarkers



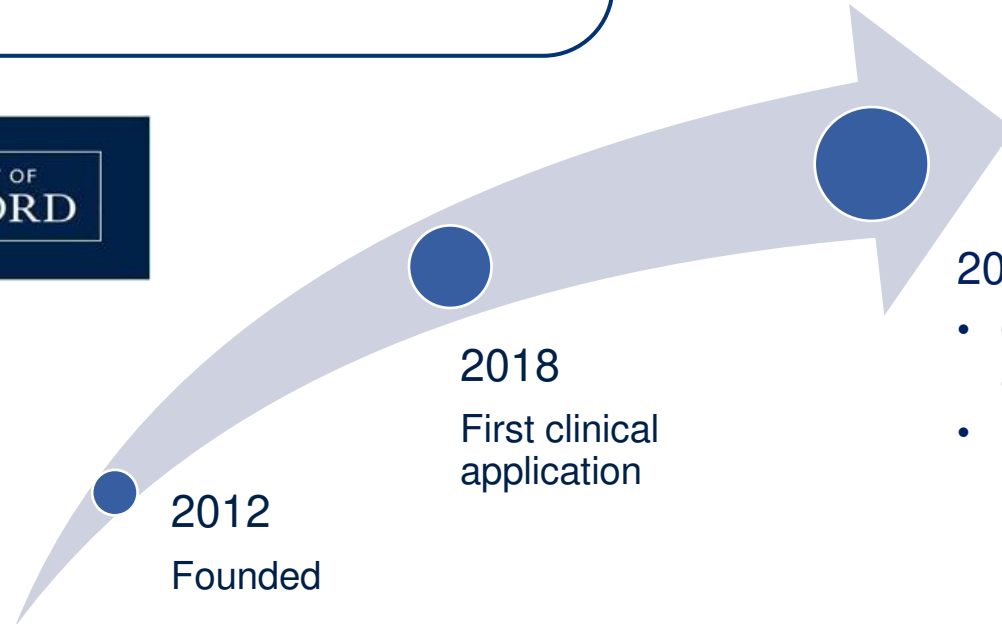
# Oxford Cancer Biomarkers

*Oxford University spin-out with proven capability to develop and validate clinically important tests from biomarker research*

- Expert knowledge, proprietary, validated on-market platforms
- Oxford Science Park, UK and Ningbo, China
- **Products:** Precision medicine biomarkers powered by artificial intelligence  
Screening and prognosis for colorectal cancer, extending to breast etc.  
Insight into the tumour micro-environment



THE OXFORD  
SCIENCE PARK



2012  
Founded

2018  
First clinical  
application




2019

- Growing product use across the UK
- NHS Trusts and Private insurers



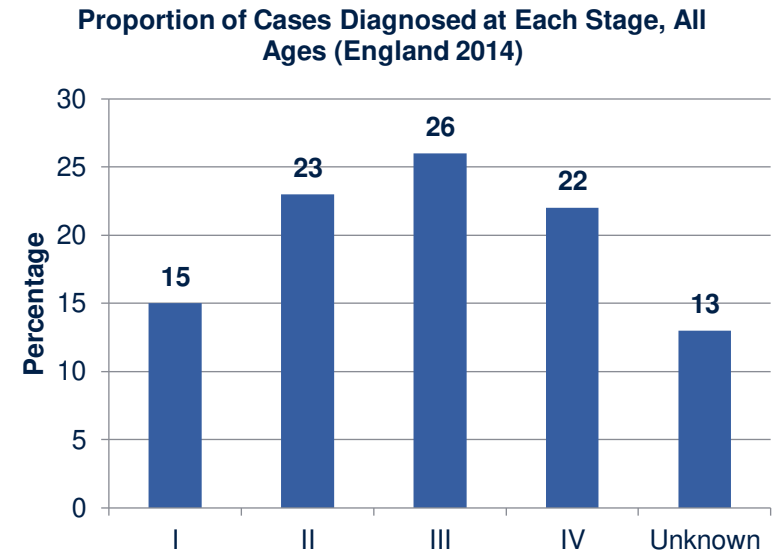
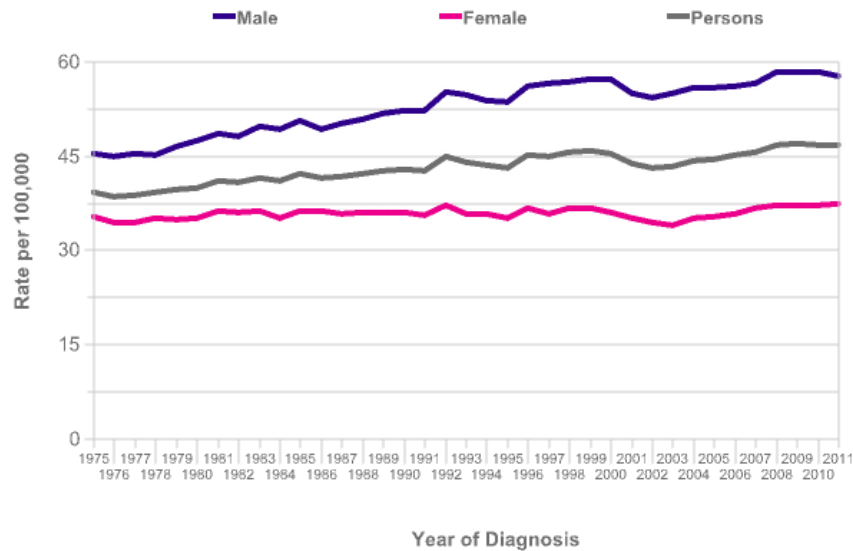
# OCB solutions: Precision Diagnostic Tests

*Providing new standards of care*

 CLOPREDICT	 CLOPROG®	 TOXNAV®
A genetic risk assessment of developing CRC <i>Law et al, Nature Communications 2019</i>	Prognostic tool for Stage II CRC recurrence <i>Danielsen et al, Ann Oncol 2017</i>	Validated genetic assay for detecting 5FU/c toxicity in CRC <i>Palles et al, Ann Oncol 2018</i>
Predict Plus+ To include risk prediction for other cancers	Stage III CRC prognosis Prostate and breast cancer validation	ToxNav® Real world use in other cancers
<b>RISK</b>	<b>PROGNOSIS</b>	<b>TREATMENT</b>

# Colorectal cancer background

- Second most common in women and third most common cancer in men
- 1.4 million newly diagnosed patients each year worldwide
- Annual costs in EU > €13bn (10% of total cancer related costs)
- 42,042 average new cases in the UK in 2014-16 (12% of total)

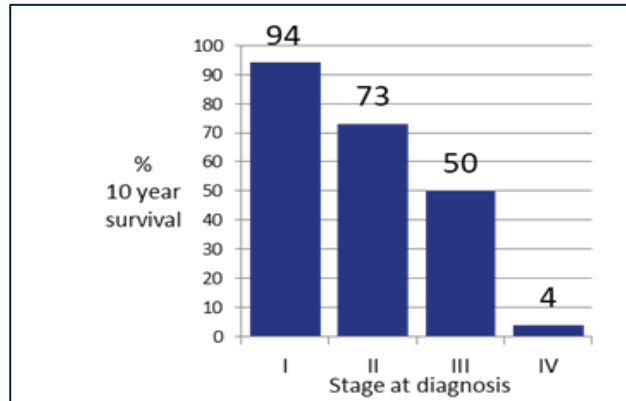


1. GLOBOCAN 2012 Colorectum Factsheet [http://globocan.iarc.fr/Pages/fact\\_sheets\\_cancer.aspx](http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx)
2. <https://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/colorectal-cancer-statistics>
3. <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer>
4. Luengo-fernandez R *et al*, Lancet Oncology 2013

# Urgent unmet needs in CRC

*Need to expedite earlier detection and improve care pathways*

Survival from early stage colon cancer is excellent

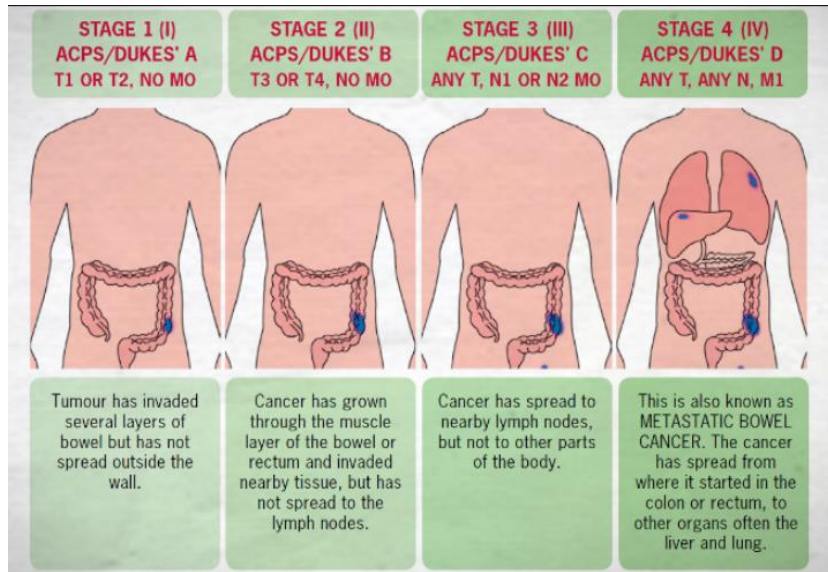


- 110,000 lives and £4bn could be saved in Europe through earlier identification of bowel cancer risk
- Cannot identify Stage II patients at risk of relapse leading to unnecessary overtreatment with chemotherapy

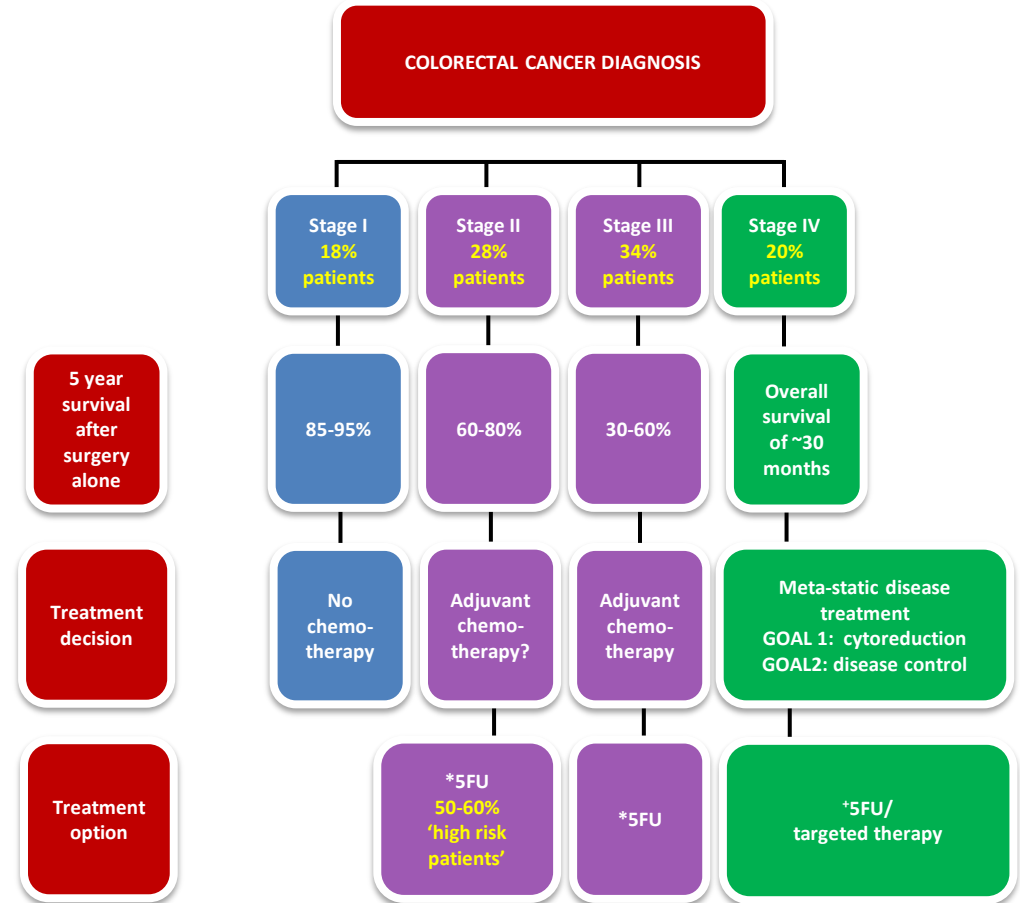
- 0.5-2% people will die from genetic susceptibility to 5FU
- 10-30% suffer severe side effects and hospitalisation



# Challenges with treating CRC patients

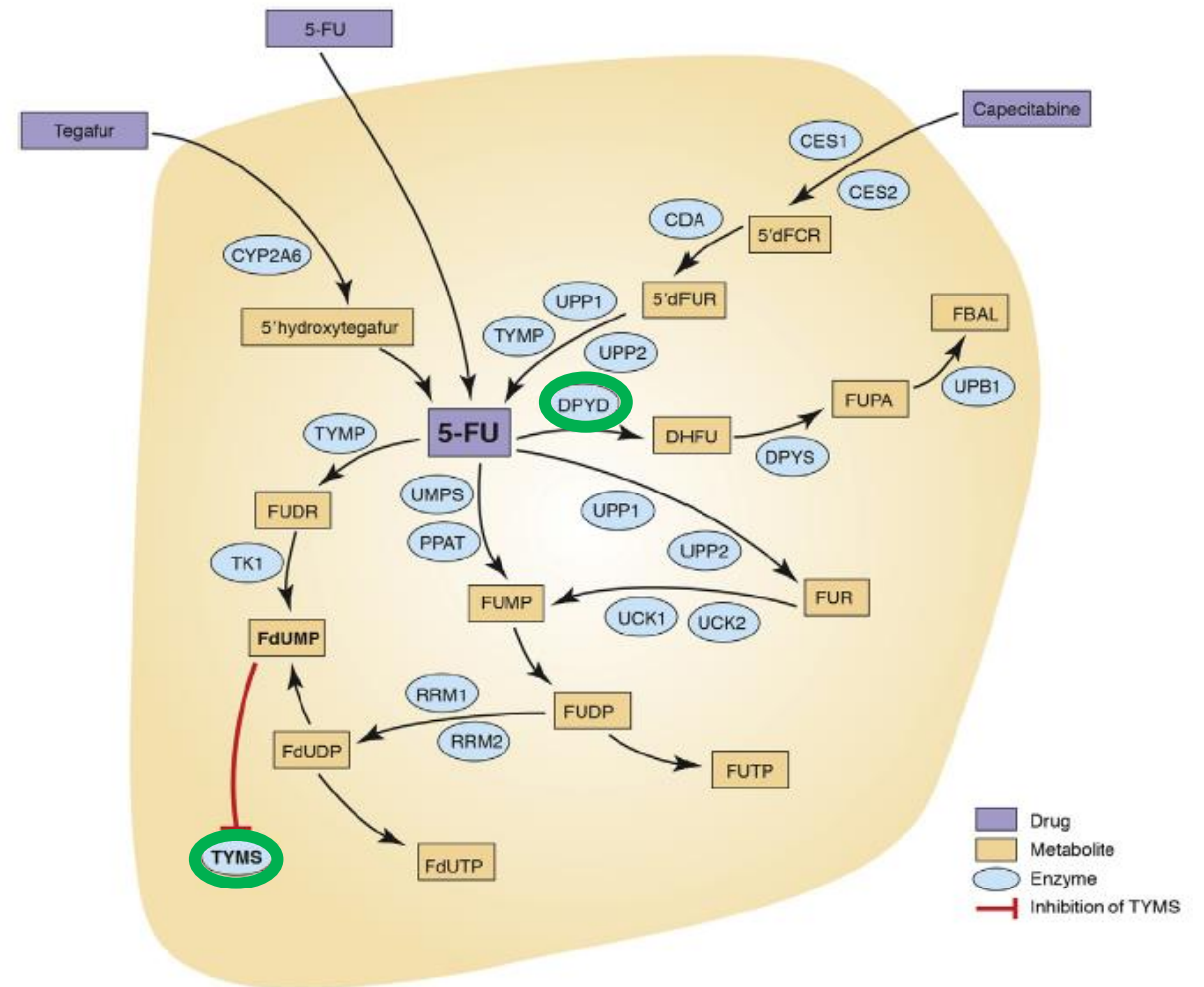


- Adjuvant chemotherapy is offered to patients with stage II and stage III cancer
- Patients (and their doctors) would like to know the chance of cancer recurrence as this dictates follow-up and potential risk/benefit from adjuvant chemotherapy.
- Decisions around treatment options are based on a variety of factors and must take risks to patients into considerations
- \*The standard treatment in the clinical guidelines for early colon cancer is a doublet schedule with oxaliplatin and a fluoropyrimidine (5FU/capecitabine). LaBianca *et al*, Annals of Oncology, 2013.



# Fluoropyrimidines

- 5-fluorouracil (5-FU) (Acrucil®)
- Antineoplastic drug – leads to build up of dUMP instead of dTMP
  - uridine instead of thymidine incorporated into DNA, overwhelming DNA repair mechanisms, leading to cell death
- First used in humans 1962
- Remains core component of treatment in number of cancers including colorectal cancer
- Oral pro-drugs capecitabine (Xeloda® Genetech) and tegafur
- Used in regimens - FOLFOX, CAPOX, FOLFIRI, FOLFIRINOX, FLOT
  - combined with Oxalplatin, IRINotecan, doceTaxel, leucovorin/FOLinic acid
- Severe adverse event rate of up to 30%



# Chemotherapy side effects

Adverse events (AE) are graded according to the CTCAE

(Common Terminological Criteria for Adverse Events) Current version V5.0 (2017) (NIH/NCI)

- **Neutropenia**
  - an abnormally low number of neutrophils (a type of white blood cell) in the blood
  - if severe, significantly increases the risk of life-threatening infection.
- **Nausea/vomiting**
  - Acute (within 24 hours of treatment) or delayed (persistent after 6-7 days)
- **Mucositis/stomatitis**
  - painful inflammation or ulceration of the mucous membranes anywhere along the gastrointestinal tract (mucositis) or mouth (stomatitis)
- **Hand-foot syndrome (HFS)**
  - Also known as Palmar-Plantar Erythrodysesthesia (PPE)
  - A skin reaction that occurs when a small amount of the medication leaks out of capillaries, usually on the palms of the hands and soles of the feet, which can damage the surrounding tissues.
- **Diarrhoea**
  - Can lead to complications including severe dehydration and malnutrition

## Grades


Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- |         |  |
|---------|--|
| Grade 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.   |
| Grade 2 | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.  |
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. |
| Grade 4 | Life-threatening consequences; urgent intervention indicated.  |
| Grade 5 | Death related to AE.   |



# Fluoropyrimidine side effects

**Important Side Effect Information**  
**XELODA<sup>®</sup>**  
**(capecitabine) Tablets** | **STOP** taking XELODA immediately and contact your doctor if any of these symptoms occur.



Moderate diarrhea. (increase of 4-6 stools a day)

Diarrhea at night.

Moderate pain and redness of the mouth, swelling of the mouth or mouth sores.

Nausea and vomiting.

Moderate pain, swelling and redness of hands and/or feet.

If you have a temperature of 100.5°F or greater, or other signs of infection.

- If caught early, most of these side effects usually improve after you stop taking XELODA.
- If they do not improve within 2 to 3 days, call your doctor again.
- After side effects have improved, your doctor will tell you whether to start taking XELODA again or what dose to use.

## What are the most common side effects of XELODA?

The most common side effects of XELODA are:

- diarrhea, nausea, vomiting, sores in the mouth and throat (stomatitis), stomach area pain (abdominal pain), upset stomach, constipation, loss of appetite, and too much water loss from the body (dehydration). These side effects are more common in patients age 80 and older.
- hand-and-foot syndrome (palms of the hands or soles of the feet tingle, become numb, painful, swollen or red), rash, dry, itchy or discolored skin, nail problems, and hair loss
- tiredness, weakness, dizziness, headache, fever, pain (including chest, back, joint, and muscle pain), trouble sleeping, and taste problems

These side effects may differ when taking XELODA with Taxotere. Please consult your doctor for possible side effects that may be caused by taking XELODA with Taxotere.

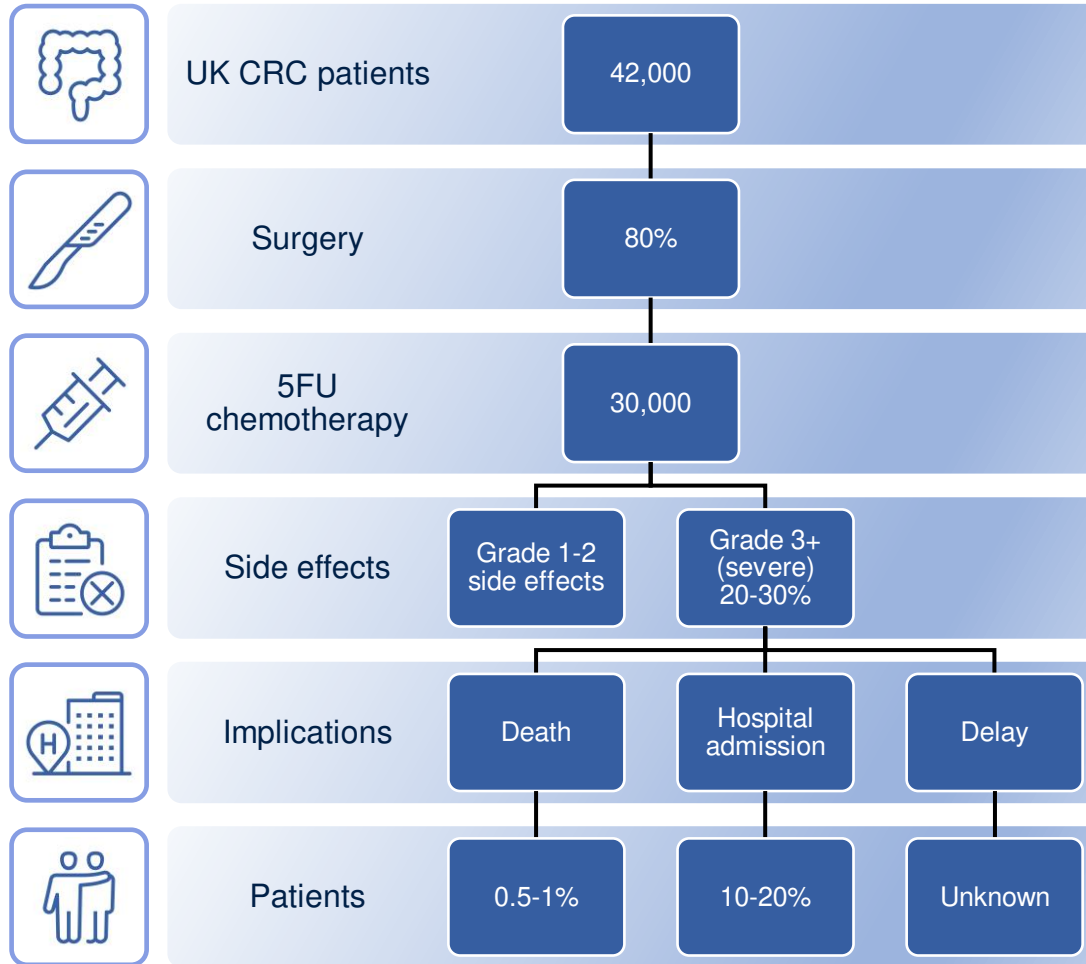
If you are concerned about these or any other side effects while taking XELODA, talk to your doctor.

**Stop taking XELODA immediately and contact your doctor right away** if you have the side effects listed below, or other side effects that concern you. Your doctor can then adjust XELODA to a dose that is right for you or stop your XELODA treatment for a while. This should help to reduce the side effects and stop them from getting worse.

- **Diarrhea:** if you have an additional 4 bowel movements each day beyond what is normal or any diarrhea at night
- **Vomiting:** if you vomit more than once in a 24-hour time period
- **Nausea:** if you lose your appetite, and the amount of food you eat each day is much less than usual
- **Stomatitis:** if you have pain, redness, swelling or sores in your mouth
- **Hand-and-Foot Syndrome:** if you have pain, swelling or redness of your hands or feet that prevents normal activity
- **Fever or Infection:** if you have a temperature of 100.5°F or greater, or other signs of infection

Your doctor may tell you to lower the dose or to stop XELODA treatment for a while. If caught early, most of these side effects usually improve after you stop taking XELODA. If they do not improve within 2 to 3 days, call your doctor again. After your side effects have improved, your doctor will tell you whether to start taking XELODA again and what dose to take. Adjusting the dose of XELODA to be right for each patient is an important part of treatment.

# 5FU-associated toxicity in CRC patients



- **5FU/capecitabine:**

- First line treatment for colorectal cancer
- Toxicities affect quality of life and impact care budgets

- **Toxic effects include:**

- Death
- Neutropenic sepsis
- Diarrhoea
- Nausea/vomiting
- Stomatitis
- Hand-foot syndrome (HFS)

# 5FU Toxicity – recognised problem?

- Recognised clinical need for DPYD screening
  - CPIC Guidelines advocate DYPD testing
  - France has national DPYD screening programme
  - UK NICE/NHSE recognise burden of 5FU toxicity
  - EMA review of fluoropyrimidine based chemotherapy toxicity underway
  - Genomics England includes DPYD in priorities for review
- Financial burden of not screening for 5FU toxicity
  - ~23,000 patients with CRC 5FU toxicity across Europe pa
  - ~€65m pa in treatment costs and 2,300 may die



justsmilemyia • Follow

justsmilemyia My feet and my hands are darkened and super sensitive due to the side effects of #Capecitabine 500 mg tabs. It hurts to walk and use my hands. There's a burning sensation that just doesn't go away or subside 🩹 The challenging part is absolutely nothing can be done to ease this side effect. 😞 #breastcancer #4thstagechronic #cancersucks #ouchthathurt #feet #pain #walkcarefully

[www.know\\_the\\_risk\\_of\\_5fu\\_chemotherapy.com](http://www.know_the_risk_of_5fu_chemotherapy.com)

## Blog

**13 March 2018**

A mother who lost her daughter due to the use of 5FU chemotherapy has been lobbying for change in the state of New York (USA). She has succeeded in get a bill introduced in the New York Assembly. The bill (#SS7710) proposes to pre-screen patients for DPD deficiency before the start of treatment with 5FU. May hat is off to her for her persistence and determination: 3 1/2 years of effort to get this far.

Prévention des effets indésirables graves liés à un déficit en dihydropyrimidine déshydrogénase (DPD) lors de traitement par fluoropyrimidines (5-fluorouracile et capecitabine) - Point d'information actualisé au 28 février 2018

Actualisation du 28 février 2018

L'ANSM recommande, dans l'attente de l'issue des différents travaux en cours, le dépistage du déficit en dihydropyrimidine déshydrogénase (DPD), conformément aux recommandations du Groupe de Pharmacologie Clinique Oncologique (GPCO) - Unicancer et le Réseau National de Pharmacogénomique Hospitalière portant sur ce dépistage et sur la sécurisation des chimiothérapies à base de fluoropyrimidines qui ont été actualisées en février 2018. Elles sont publiées dans un article du Bulletin du Cancer accessible en ligne ici.

Cet article recense en particulier les 17 laboratoires hospitaliers répartis sur l'ensemble du territoire qui réalisent en routine les tests de recherche du déficit en DPD (génotypage et/ou phénotypage).

Par ailleurs, des informations complémentaires sont apportées pour préciser les modalités d'utilisation et de mise à disposition de Vintgard (uridine triacétate) au travers d'une Autorisation Temporaire d'Utilisation (ATU) nominative.

Le produit qui dispose depuis 2015 d'une ADEL aux États-Unis est indiqué dans le traitement d'urgence des patients en situation de surdosage après l'administration d'une fluoropyrimidine (indépendamment de la présence de symptômes), ou qui présentent précocement une toxicité grave et/ou inhabituelle dans les 96 heures suivant la fin de l'administration d'une fluoropyrimidine. L'efficacité de ce produit au-delà des 96 heures suivant la fin de

Grandma Jerri's Journey and Awareness  
**5FU Toxicity**

I just wanted to share how Mom's story is having an impact even if it is a small one. In the oncology world... Several months, maybe a year ago I wrote an article about how the Oncology field very much considers 5FU toxicity "rare, uncommon, exceptional..." I hoped that there would be a way to change that impression from "rare" to "hidden" it would encourage healthcare workers to be looking for the possibility of toxicity. Instead of assuming they would never see such a "rare and uncommon" complication. When I arrived at this conference yesterday, I was shocked and thrilled to see that BTO has indeed embraced and adopted the concept of the 5FU toxicity patients a "hidden population" and abandoned the old school dialog of the toxic reaction being considered rare.

I love that this company is targeting education and awareness above everything else.

Community

390 people like this

389 people follow this

About

Typically replies within an hour

Send message

[www.know\\_the\\_risk\\_of\\_5fu\\_chemotherapy.com](http://www.know_the_risk_of_5fu_chemotherapy.com)

Community

# NHS costs of 5FU/capecitabine toxicity

## Grade 1-2 toxicity

- 15,000 patients pa<sup>1,2</sup>
- ~£2m bed stay costs

## Grades 3+ toxicity

- ~5,000+ patients pa<sup>1,2</sup>
- European studies found £2,500 average bed cost stay per patient admitted<sup>3,4</sup>
- Private hospital study found costs of £42k per patient with admissions due to toxicity<sup>5</sup>
- National impact >£6m bed stay costs alone

## Death

- 500 people pa<sup>3</sup>
- >£20k pp bed costs
- £250k economic benefit lost per death<sup>6</sup>
- Societal cost >£80m pa<sup>6</sup>

1. Extrapolated from: Loganayagam *et al. BJC* (2013) and 2. Kerr *et al. The Lancet* (2016). 3. Adapted from: Deenan *et al. J Clin Onc* (2016). 4. Adapted from Henricks *et al. European Journal of Cancer* (2019). 5. Adapted from Murphy *et al. Dose Response* 2018. 6. Hanly and Sharp, *BMC Cancer* (2014).

\*Conservative lowest NHS bed stay costs at £250 pppd but £750 represents full costs



Pioneering precision medicine



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

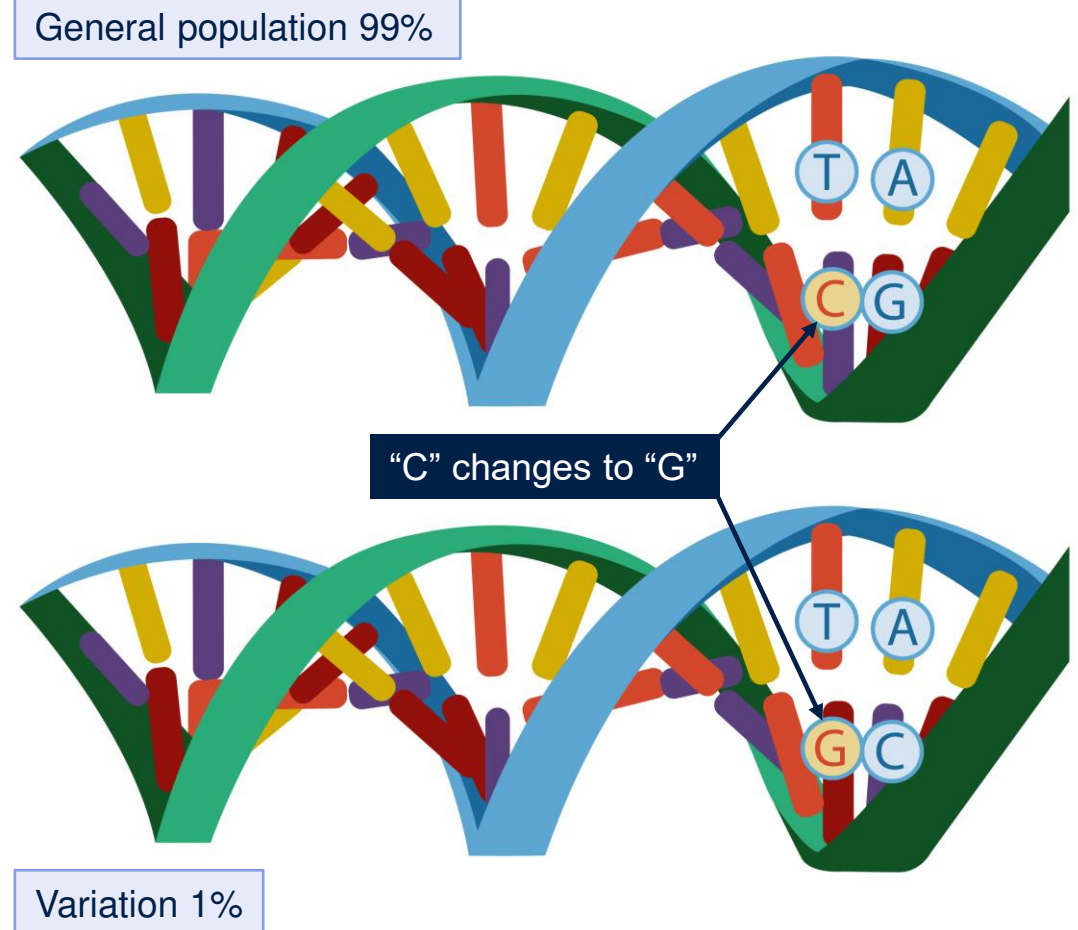
# What is TOXNAV® ?

- A comprehensive and clinically validated panel of 20 genetic variants of the DPYD and TYMS/ENSOF1 genes that are associated with 5FU/capecitabine toxicity<sup>1</sup>
- Includes variants not found in other panels:
  - Low population frequency variants linked to severe (Grade 4) toxicities - 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)<sup>2,3</sup>
- Validated using QUASAR 2 clinical trial and data set<sup>4</sup>
  - Well-documented toxic effects using CTCAE classifications
- CE marked technology

1. Palles C, *et al.* An evaluation of the clinical utility of a panel of variants in DPYD and ENSOF1 for predicting common capecitabine related toxicities. *Annals of Oncology* 29 (Supplement 5). 2. Rosmarin D *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. 3. Rosmarin D *et al.* A candidate gene study of capecitabine-related toxicity in colorectal cancer identifies new toxicity variants at DPYD and a putative role for ENSOF1 rather than TYMS. *Gut*. 2015; 64(1):111-20. 4. Kerr R *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.

# Single nucleotide polymorphisms (SNPs)

- Most common type of genetic variation among species
- Single base-pair change within a gene
- Within humans 99% of DNA sequence is the same and the remaining 1% makes a person unique
- Estimated 4-5m variations in DNA sequence (SNPs)
- Considered a SNP when it occurs in at least 1% of the population
- Found in protein coding and non-coding regions
- Variation can be harmless (eye colour) or harmful (cancer)
- Measured through Sanger or Next Generation Sequencing

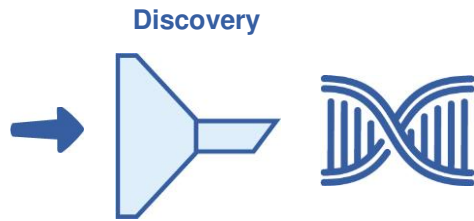


# Discovery data

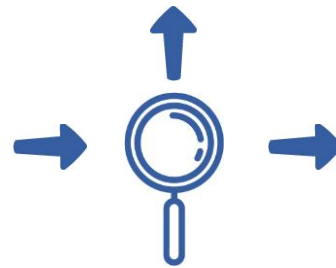
Clinical validation of the 19 genetic variants included in the ToxNav® panel will be published later this year



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 QUASAR2 trial (Kerr *et al* 2016) – *Lancet Oncol*



The proprietary 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



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 recommendation for dose modification



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

Rosmarin *et al*, *Gut* 2014: 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. Rosmarin *et al*, *JCO* 2014: Genetic Markers of Toxicity From Capecitabine and Other Fluorouracil-Based Regimens: Investigation in the QUASAR2 Study, Systematic Review, and Meta-Analysis. Meulendijks *et al*, *Lancet Oncol* 2015: Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. Kerr R, *et al*, *Lancet Oncol* 2016: Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial



# TOXNAV<sup>®</sup> Clinical validation

## Clinical Validation Study

- QUASAR2 data set
- ToxNav performance
- Lead investigator: Dr Claire Palles, University of Birmingham
- Presented at ESMO GI 2018
- Manuscript in draft

## Clinical Utility Study (PRECISE)

- 60 patients from OUH clinic
- Assessment of ToxNav in clinical setting
- Lead investigators: Prof. Rachel Kerr/ Dr. Lennard Lee
- Presented at ESMO GI 2019
- Published 2019

### ToxNav<sup>®</sup> germline genetic testing and PROMinet digital mobile application toxicity monitoring: Results of a prospective single centre clinical utility study – PRECISE

L.Y.W. Lee<sup>1</sup>, T. Starkey<sup>1</sup>, S. Fotheringham<sup>2</sup>, G. Mozolowski<sup>3</sup>, P. Camilleri<sup>4</sup>, R. Kerr<sup>5</sup> and D. Kerr<sup>2,4</sup>

<sup>1</sup>Institute of Cancer and Genomic Sciences, University of Birmingham, UK; <sup>2</sup>Oxford Cancer Biomarkers, UK; <sup>3</sup>Department of Oncology, University of Oxford, UK; <sup>4</sup>Radcliffe Department of Medicine, University of Oxford, UK; <sup>5</sup>Corresponding author: Lennard.Y.W.Lee.1@bham.ac.uk

#### Introduction

5-Fluorouracil (5-FU) and its oral pro-drug capecitabine are the most commonly prescribed chemotherapeutic agents for treating colorectal cancer (CRC). A significant proportion (20-30%) of patients treated with these drugs develop severe side-effects<sup>1,2</sup>, often resulting from inborn deficiencies of enzymes or drug side-effects<sup>1,2</sup>, often resulting from inborn deficiencies of enzymes or drug side-effects<sup>1,2</sup>, often resulting from inborn deficiencies of enzymes or drug side-effects<sup>1,2</sup>.

#### Methods

Diagnosis of CRC who consented to having their germline DNA sequenced for HFS-related variants were recruited prospectively to the study. Genomic DNA was extracted from whole blood samples and subsequently analysed for 18 germline coding variants in DPYD and 1 ENOSF1 variant. A risk report was generated based on the known penetrance of each 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.

#### 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

- Kerr RL, Lee S, Segalov E, Johnson E, Falcon B, Hewitt P, Weaver A, Chuzh D, Scudder C, Pearson S, Jullar P, Pizzella F, Tomlinson I, Domingo E, Kerr DJ, Aggarwal T. Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase phenotype and fluoropyrimidine dosing. *Clinical Pharmacology and Therapeutics*. 2019 Dec;106(6):1443-1454.
- McLeod HL, Diasio RB, Schmidt M. *Clin Pharmacol Ther*. 2013 Dec;95(6):643-649.
- Clinical Pharmacogenetics Implementation Consortium (CPIC). Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing; 2017 Update. *Annals of the New York Academy of Sciences*. 2018 Feb;1632(1):210-216.

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

Claire Palles<sup>1</sup>, Susan Fotheringham<sup>2</sup>, Laura Chegwidden<sup>1</sup>, Marie Lucas<sup>3</sup>, Guy Mozolowski<sup>3</sup>, Ian Tomlinson<sup>1</sup>, David Kerr<sup>2,4</sup>

<sup>1</sup>Institute of Cancer and Genomic Sciences, University of Birmingham, UK; <sup>2</sup>Oxford Cancer Biomarkers, Oxford, UK; <sup>3</sup>University of Oxford Medical School, UK; <sup>4</sup>Nuffield Division of Clinical and Laboratory Sciences, University of Oxford, UK

#### Introduction

5-Fluorouracil (5-FU) based adjuvant chemotherapy, including 5-FU oral pro-drug 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 toxicity that arise 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<sup>1</sup>.

#### Methods

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

Phenotype (genotype)	Implications for treatment	Dosing recommendations
Normal/typical activity for wild-type alleles, 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 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<sup>2</sup> (Table 1) were incorporated in a simple genotype-guided risk classification system resulting in critical (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 DPYD haplotype c.1236G>A/HapB3<sup>3</sup>. We have evaluated the impact of including this variant.

#### Results

**Figure 1: ROC curves demonstrating performance of panel**

**OUTCOME:** Toxicity related death, Grade 4 haematological toxicity, Global toxicity

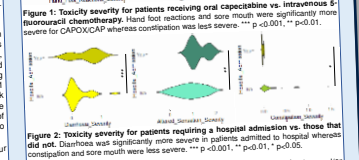
#### Conclusions

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.

PROMinet app responses for 13 symptom toxicities were also compared with clinician-determined patient toxicity severity. Patient reported data for 'moderate/severe' was positively correlated with clinician graded toxicity (clinician reported 'severe' vs. 'moderate' or 'mild', p<0.05 for both). Analysis of app responses was also performed for patients receiving either CAPOX (single agent CAP (n=7)), or FOLFOX (FOLFOX (n=4)). The incidence of hand-foot reactions and sore mouth (TOXNAV) were higher in patients receiving CAPOX (p<0.01 for both) whereas constipation was lower (p<0.001) (Figure 1).

**Table 2: Germline variants analysed and sequences observed using the ToxNav test.**

Variant	Allele count	Allele freq. %	Patient freq. %
rs12132162	4	3.59	6.73
rs7548189	15	12.71	23.73
rs2612091	1	0.85	1.89
rs2612091	54	45.76	66.10



Patients with severe toxicities often require chemotherapy dose reduction and/or clinicaly relevant information to assist or affect clinical treatment decision-making. We therefore analysed app toxicity profiles for patients requiring dose reduction and/or admitted to hospital. 'Hand-foot reaction' and 'diarrhoea' were higher (P<0.05 for all). In addition, the severity of 'diarrhoea' and 'altered hand foot sensation' were significantly elevated in patients requiring hospitalisation, with lower scores for 'constipation' and 'sore mouth' (Figure 2).

#### Conclusions

The ToxNav germline DNA sequencing-based test has the ability to provide clinically relevant information to assist or affect clinical treatment decision-making in patients receiving 5-FU based chemotherapy, such as altering the initial prescribed 5-FU dose. A novel digital mobile application (PROMinet) for recording patient reported toxicity successfully obtained a high volume of patient toxicity data with high granularity which in turn might allow the improvement and personalisation of chemotherapy management.

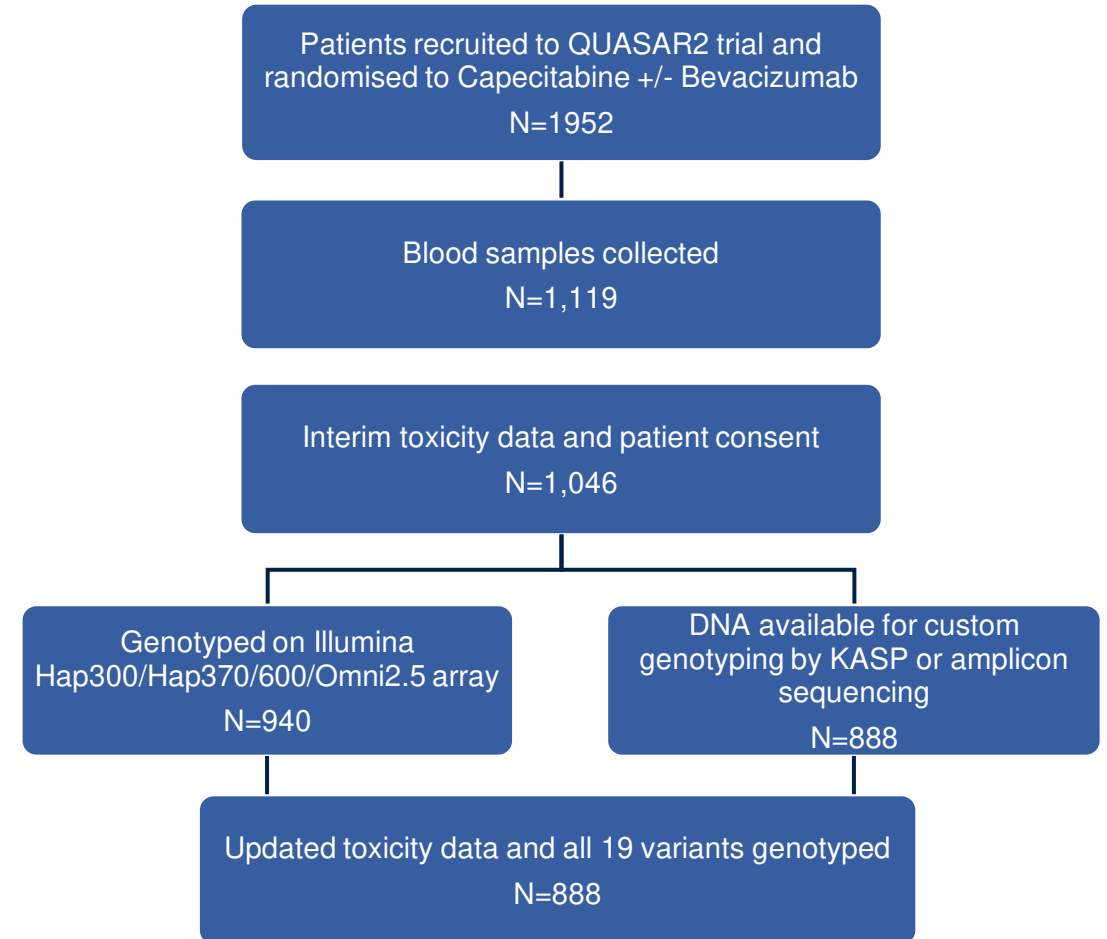
The accurate pharmacogenomic prediction and monitoring of severe toxicity and toxic deaths among chemotherapy-receiving patients has the potential to reduce morbidity and mortality. In the PRECISE clinical utility study, we demonstrate that potentially useful information to treating physicians and warrants further large scale studies.

**References:** 1. Fotheringham S, et al. Clinical importance of rare variants in the dihydropyrimidine dehydrogenase gene in patients with severe fluoropyrimidine toxicity. *PLoS One*. 2016; 11(4):e154100. 2. Kerr DJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing. *Pharmacotherapy*. 2017; 37(10):1143-1157. 3. Kerr DJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing. *Pharmacotherapy*. 2017; 37(10):1143-1157. 4. Kerr DJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing. *Pharmacotherapy*. 2017; 37(10):1143-1157. 5. Kerr DJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing. *Pharmacotherapy*. 2017; 37(10):1143-1157.



# Clinical validation study: methods

- Selection criteria for genetic variants\*:
  - Associated with global capecitabine-related toxicity with an effect size (odds ratio) > 1.5 at pathway level significance and with an individual toxicity at genome wide significance (n=2)
  - Identified in DPYD deficient patients with evidence of variant causing the phenotype (n=17)
- Clinical trial data set: QUASAR 2 (capecitabine +/- bevacizumab) 1952 total patients
- Adverse events grading
  - NCI Common Terminology Criteria for Adverse Events (CTCAE) system
  - Common Grade 3/4 side effects in QUASAR 2 (capecitabine only arm): diarrhoea 11% and HFS 21%
- Genotyping
  - 888 samples available for toxicity data and genotyping
  - Genotyping using SNP arrays (5), KASP genotyping (3), multiplex PCR (11)

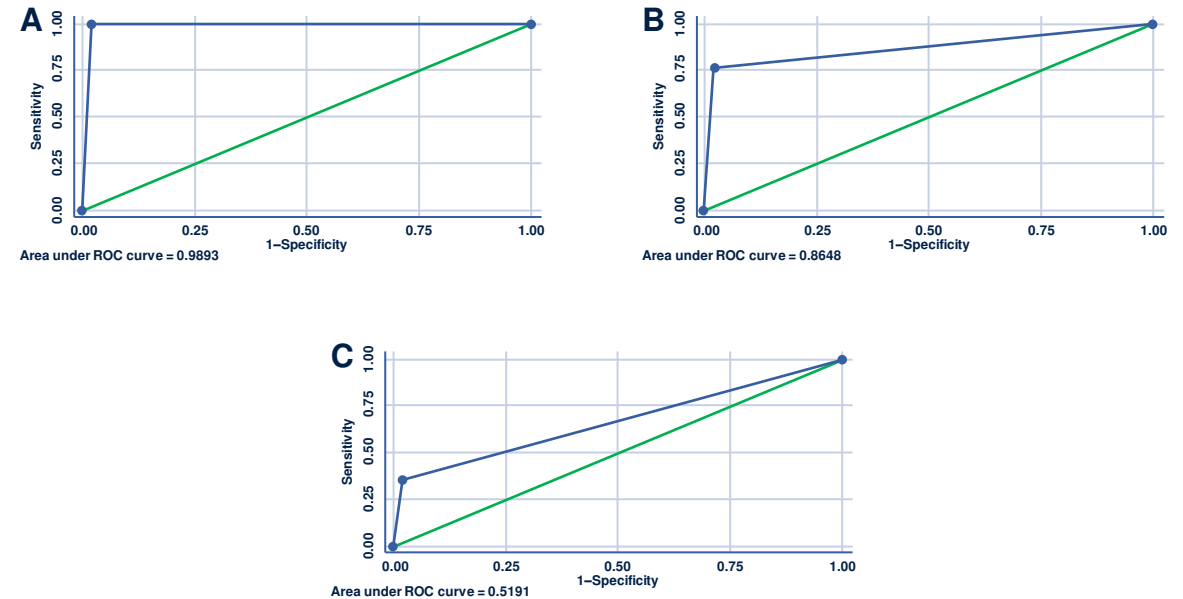


\*21 variants initially selected that met criteria above, but additional evidence gathered during study led to 2 variants being deselected for inclusion (Variant 4 & 18), leading to final panel of 19 variants

# TOXNAV<sup>®</sup> Clinical validation highlights

- QUASAR 2 clinical trial data: 888 patients
- Diagnostic accuracy of 19 SNP panel: ToxNav
- Risk of toxicity induced death:
  - Sensitivity 100%, Specificity 98%, NPV 1.0, PPV 0.1
- Risk of grade 4 haematological toxicities:
  - Sensitivity 75%, Specificity 98%, NPV 1.0, PPV 0.14
- Risk of HFS:
  - Sensitivity 83%, Specificity 31%, NPV 0.87, PPV 0.25

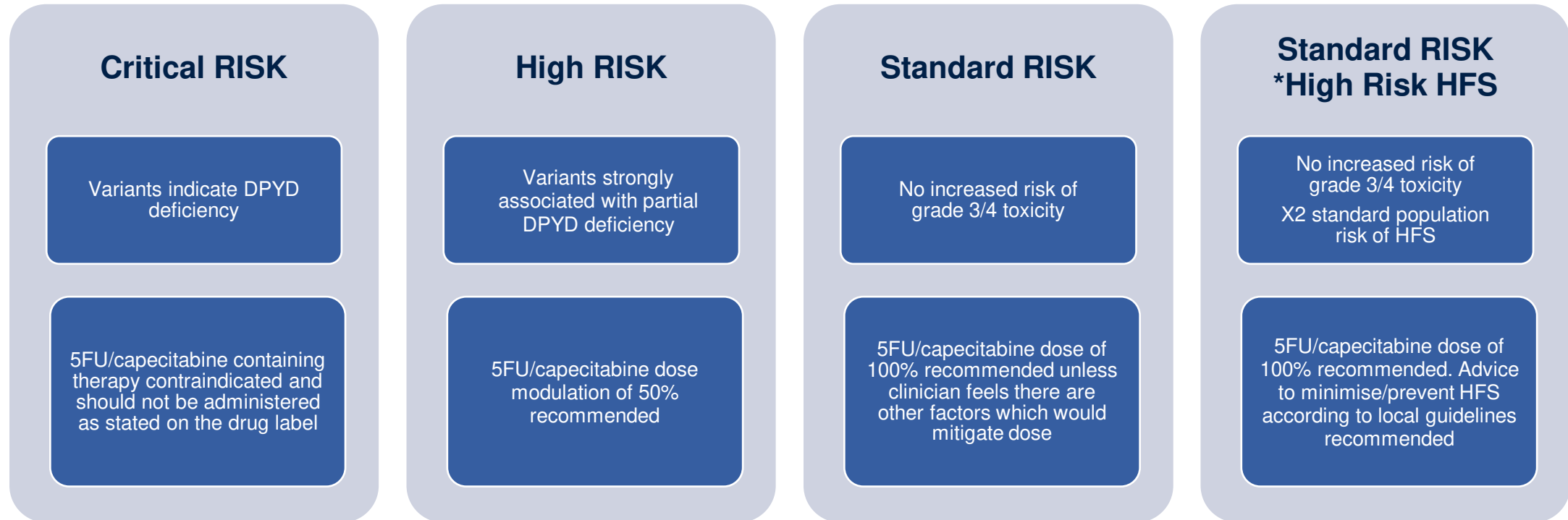
ROC curves showing performance of ToxNav for predicting toxicity induced death, neutropenia grade 4 events and global toxicity



**A.** Toxicity induced death, **B.** Neutropenia grade 4 events, **C.** Neutropenia grade 3 or 4 events

# **T•XNAV® Risk reporting**

- The likely DPYD phenotype is based on the genotype as determined by sequencing using information outlined in the original CPIC DPYD Guidelines (Caudle *et al*, *Clinical Pharmacology and Therapeutics*, 2013\*)



\*Updated in 2017

# Test procedure 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 20 variants
- Data managed via secure server

5

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

6

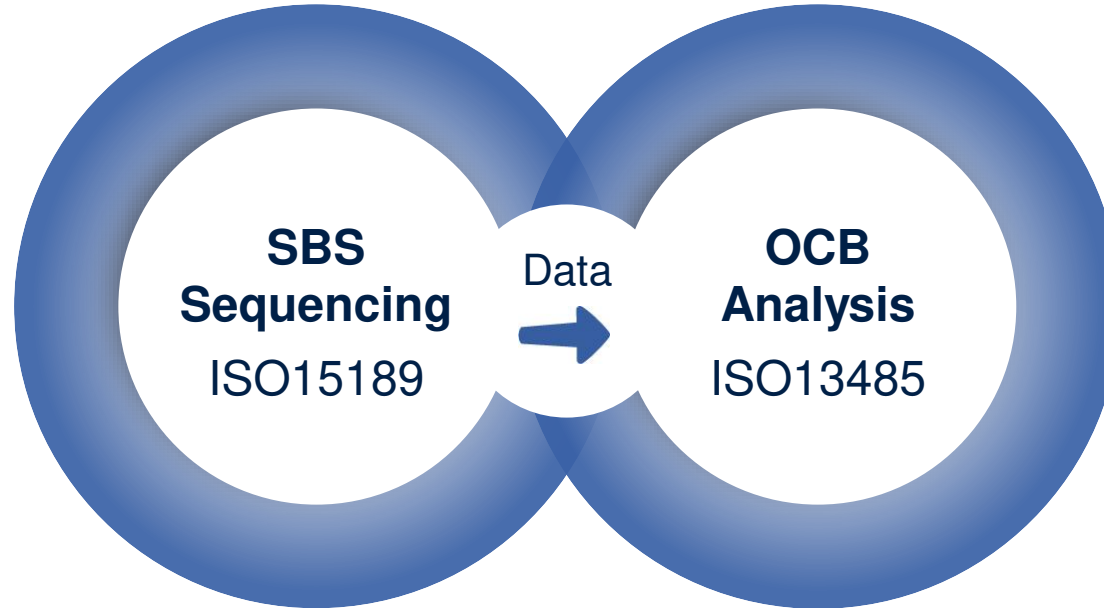
Phenotype (genotype)	Implications for treatment	Dosing recommendations
Homozygous for wild-type allele, or normal, high DPYD activity	Normal DPYD activity "normal" risk for toxicity	Use label-recommended dosage and administration
Heterozygous, or intermediate activity	Decreased DPYD activity increased 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)<sup>1</sup>

7

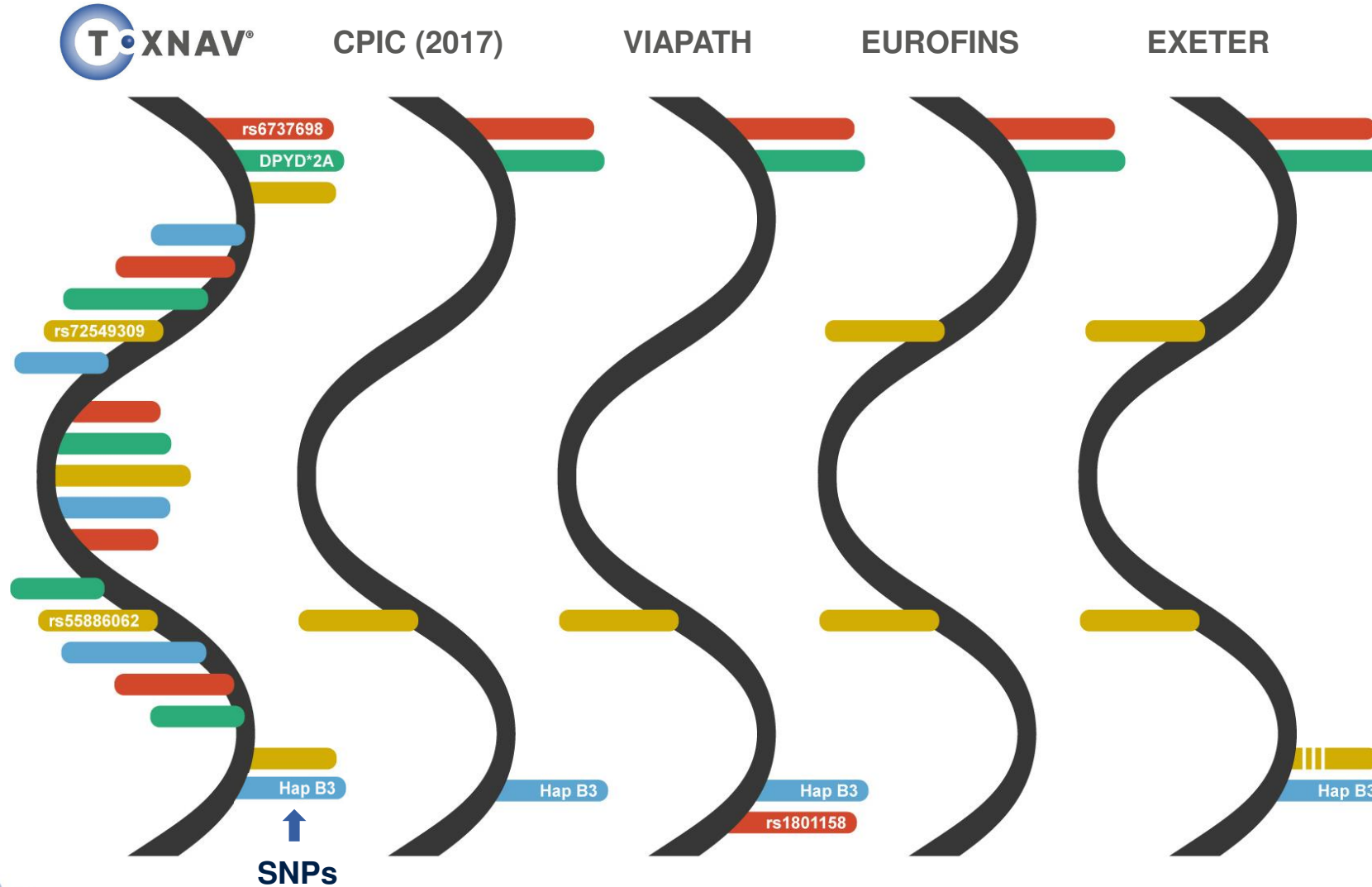
- ToxNav Report received by clinician and risk category discussed with patient
- Personalised chemotherapy decision made

# **TOXNAV® – meets all regulatory standards**



Software used for analysis and interpretation must be registered as a Medical Device and therefore we must comply with two different regulatory standards

# T•XNAV<sup>®</sup> Competitor comparison



# Compared to other tests

## Accurate

- 100% sensitivity/NPV 1.0 for risk of death
- 98% specificity/NPV 1.0 (Grade 4 haematological toxicities)

## Comprehensive

- 20 SNP panel
- Competitors have only 4-5 SNPs
- Includes Hand Foot Syndrome
- Includes SNP found in people with African heritage

## Validated

- Panel predicated on QUASAR 2 data set
- Validated in 888 CRC clinical samples
- Proven in hospital setting
- Competitor tests not validated
- CE marked and ISO accredited

## Convenient

- Simple blood test fits into pathology workflow
- No need to send samples in cold chain in limited time frame
- Maximum 10 working day turnaround



# Summary

- ToxNav provides a comprehensive genetic panel to test for variation associated with 5-FU toxicity<sup>1</sup>
- The panel is the only clinically validated test<sup>2</sup>
- Easy to administer as part of a routine blood test
- Reporting is easily interpreted to quickly guide clinical decision making
- Could save 10 lives in every 1,000 patients tested
- Potential savings of at least £2,500 p/p who avoids Grade 3-4 toxicities<sup>3</sup>
- Meets patient safety and enhanced patient experience standard in NHS Outcomes Framework and regulatory standards
  
- Growing use in the UK with both NHS Trusts and private insurers using ToxNav prior to 5-FU /capecitabine chemotherapy

1. Palles C, *et al.* An evaluation of the clinical utility of a panel of variants in DPYD and ENOSF1 for predicting common capecitabine related toxicities. *Annals of Oncology* 29 (Supplement 5). 2. Kerr R, *et al.* *Lancet Oncol* 2016 3. Adapted from: Deenan *et al.* *J Clin Onc* (2016).

# Questions





**Oxford Cancer  
Biomarkers**

Pioneering precision medicine