Oxford Cancer Biomarkers

Pioneering precision medicine

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

UNIVERSITY OF OXFORD

2012
Founded

2018
First clinical application

2019
- Growing product use across the UK
- NHS Trusts and Private insurers

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OCB solutions: Precision Diagnostic Tests

Providing new standards of care

COLOPREDICT	COLOPROG®	TOXNAV®
A genetic risk assessment of developing CRC Law *et al*, *Nature Communications* 2019	Prognostic tool for Stage II CRC recurrence Danielsen *et al*, *Ann Oncol* 2017	Validated genetic assay for detecting 5FU/c toxicity in CRC Palles *et al*, *Ann Oncol* 2018
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
RISK	**PROGNOSIS**	**TREATMENT**

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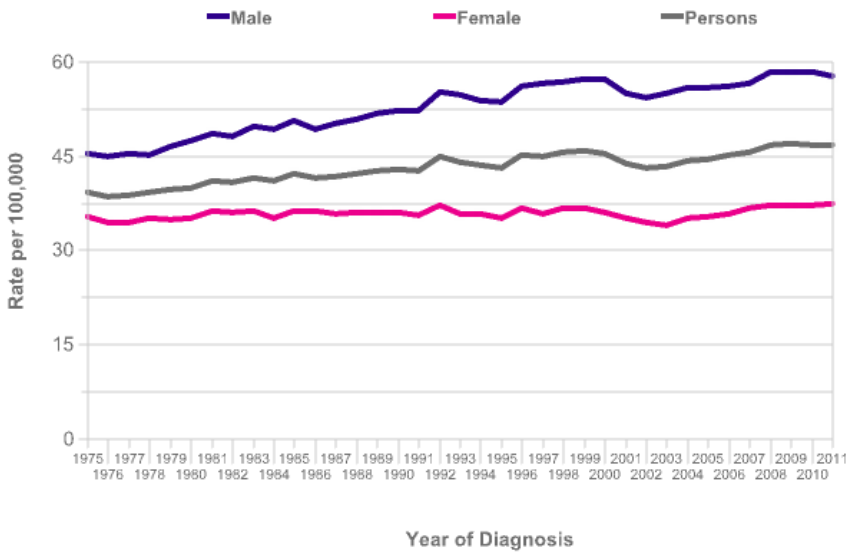
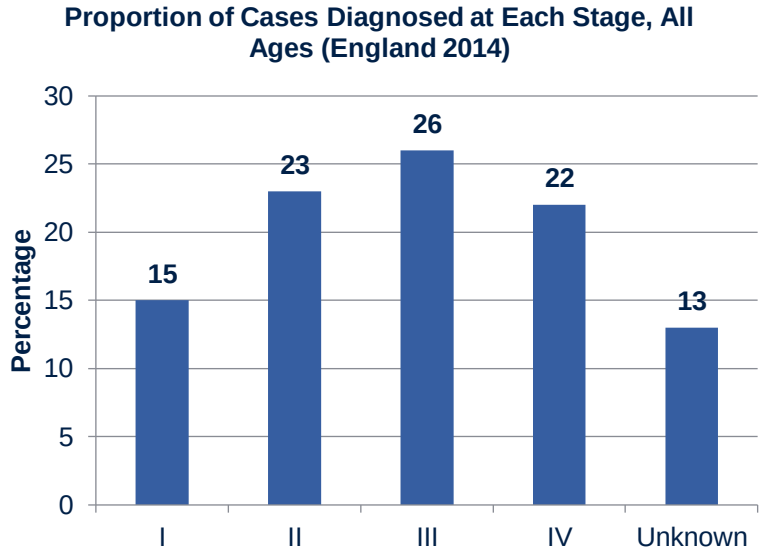
Colorectal cancer background

- 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
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

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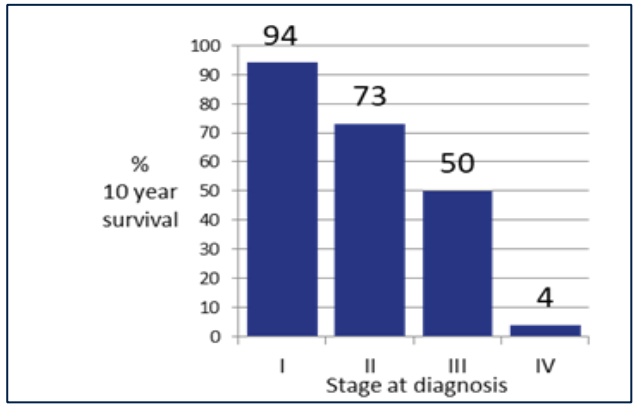
Urgent unmet needs in CRC

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

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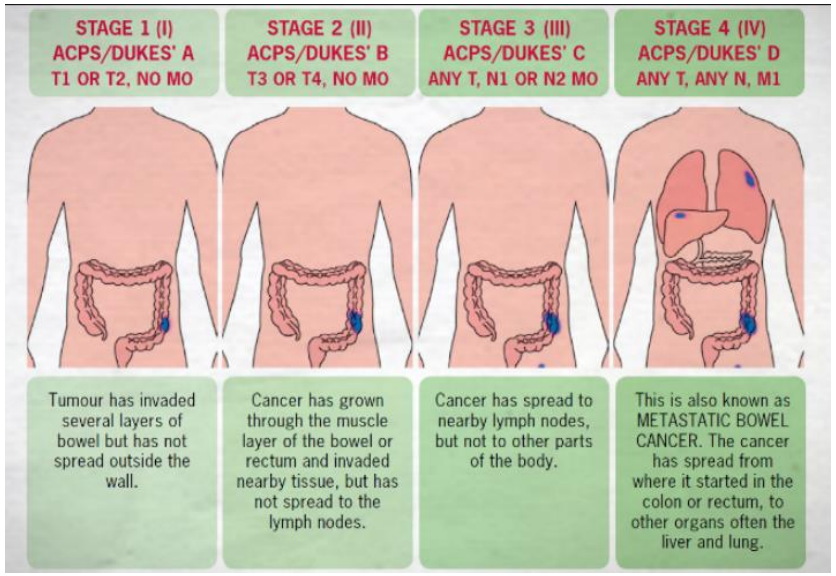
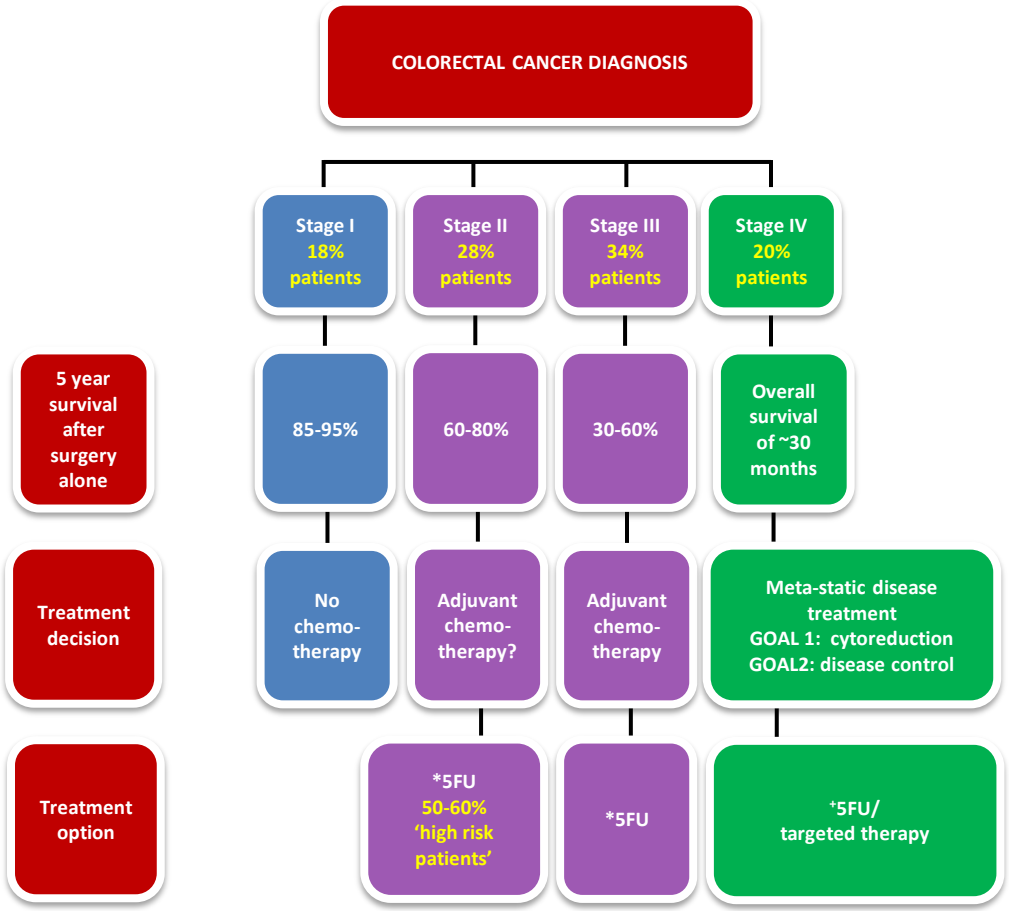
Challenges with treating CRC patients





- 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.

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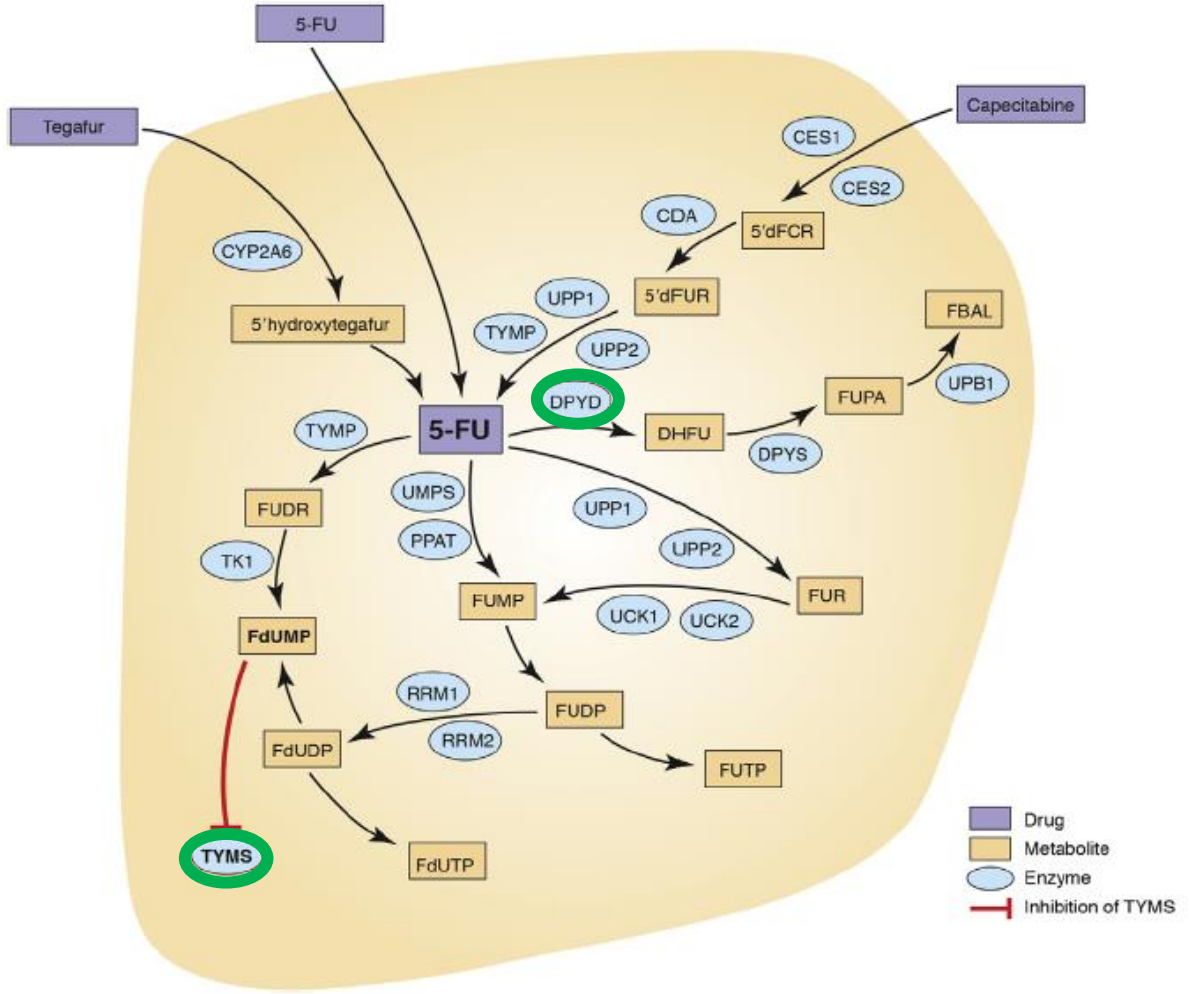
Fluoropyrimidines

- 5-fluorouracil (5-FU) (Adrucil®)
- 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%



Rodrigues *et al*, Biomed Res International, 2016
Wigle *et al*, Pharmaceutics, 2019

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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.

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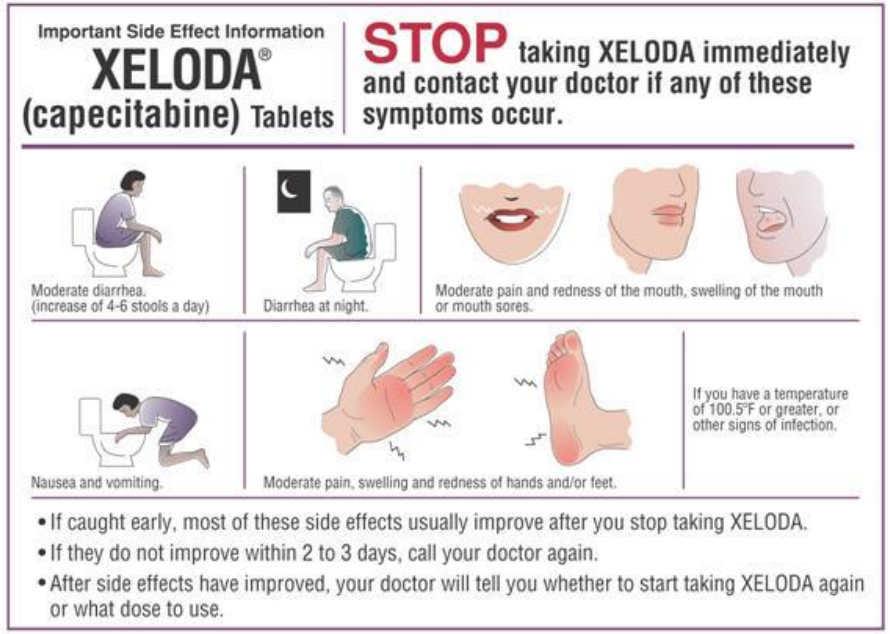
Fluoropyrimidine side effects



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.

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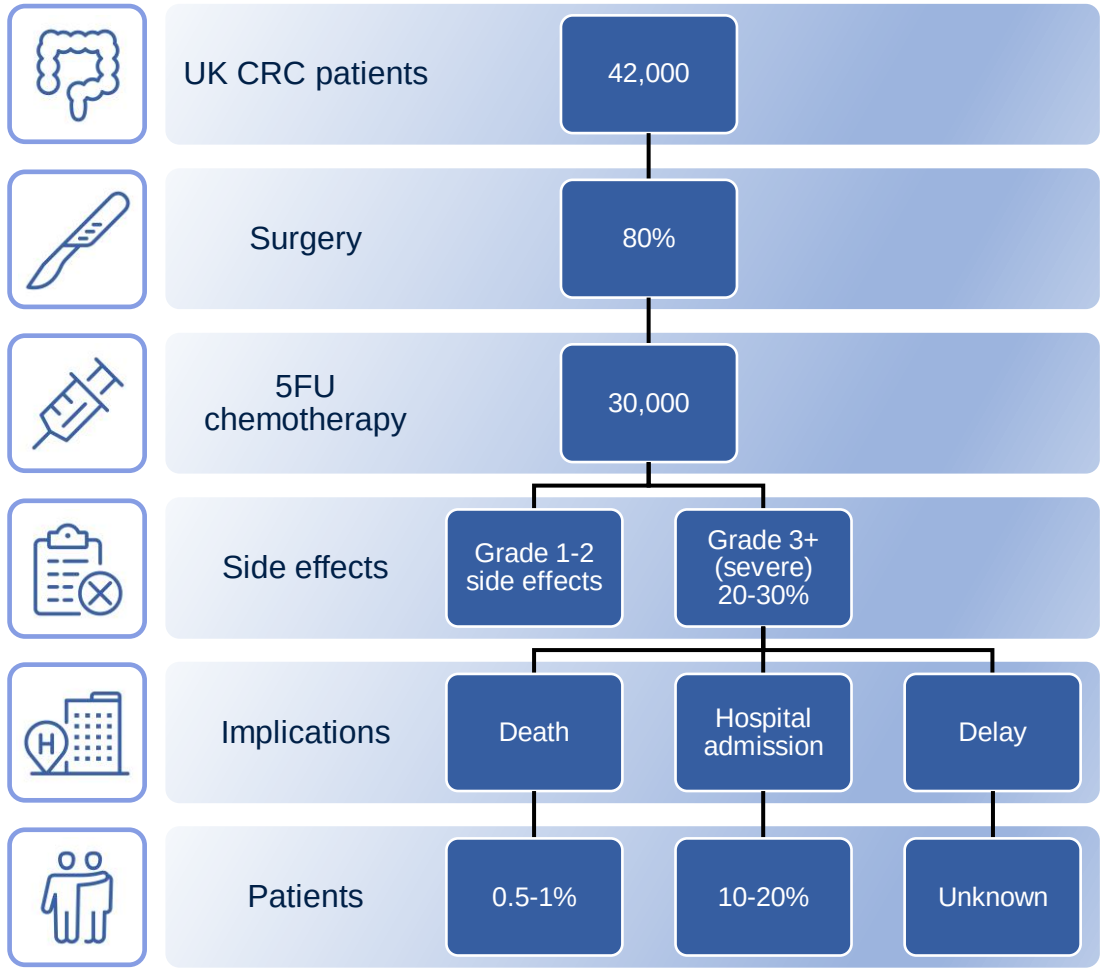
5FU-associated toxicity in CRC patients



- **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)

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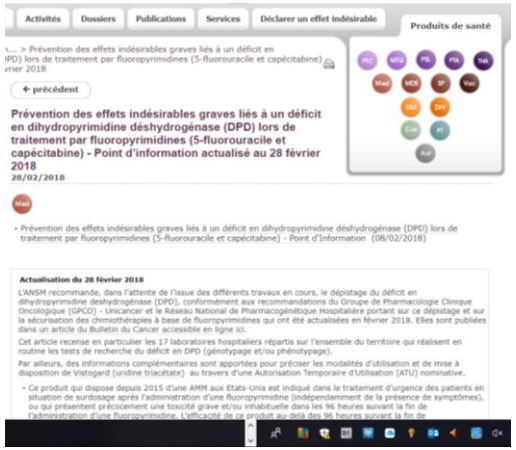
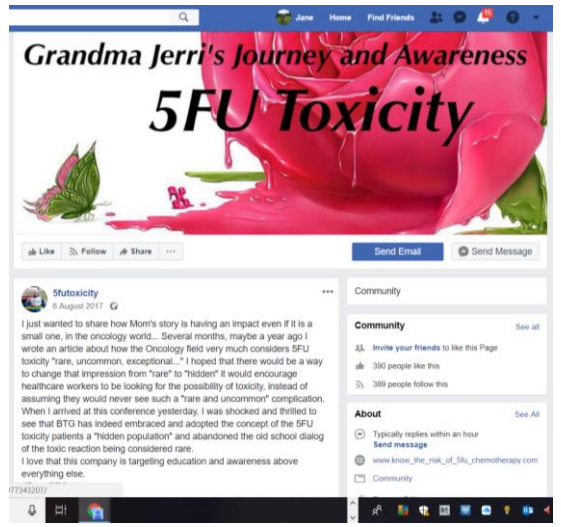
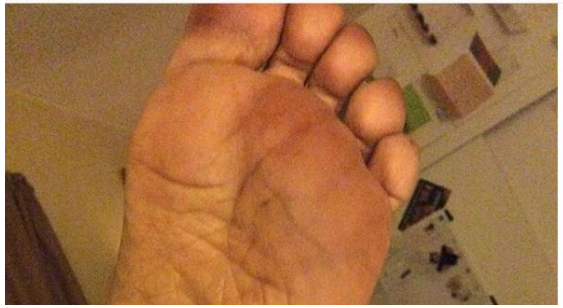
5FU Toxicity – recognised problem?

- 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







justsmilemymia • Follow

justsmilemymia 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

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)I 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.

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NHS costs of 5FU/capecitabine toxicity

Grade 1-2 toxicity

- 15,000 patients pa[1,2]
- ~£2m bed stay costs

Grades 3+ toxicity

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

Death

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

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

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Pioneering precision medicine

TOXNAV®

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[1]
- 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)[2,3]
- Validated using QUASAR 2 clinical trial and data set[4]
  - 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 ENOSF1 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 ENOSF1 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.

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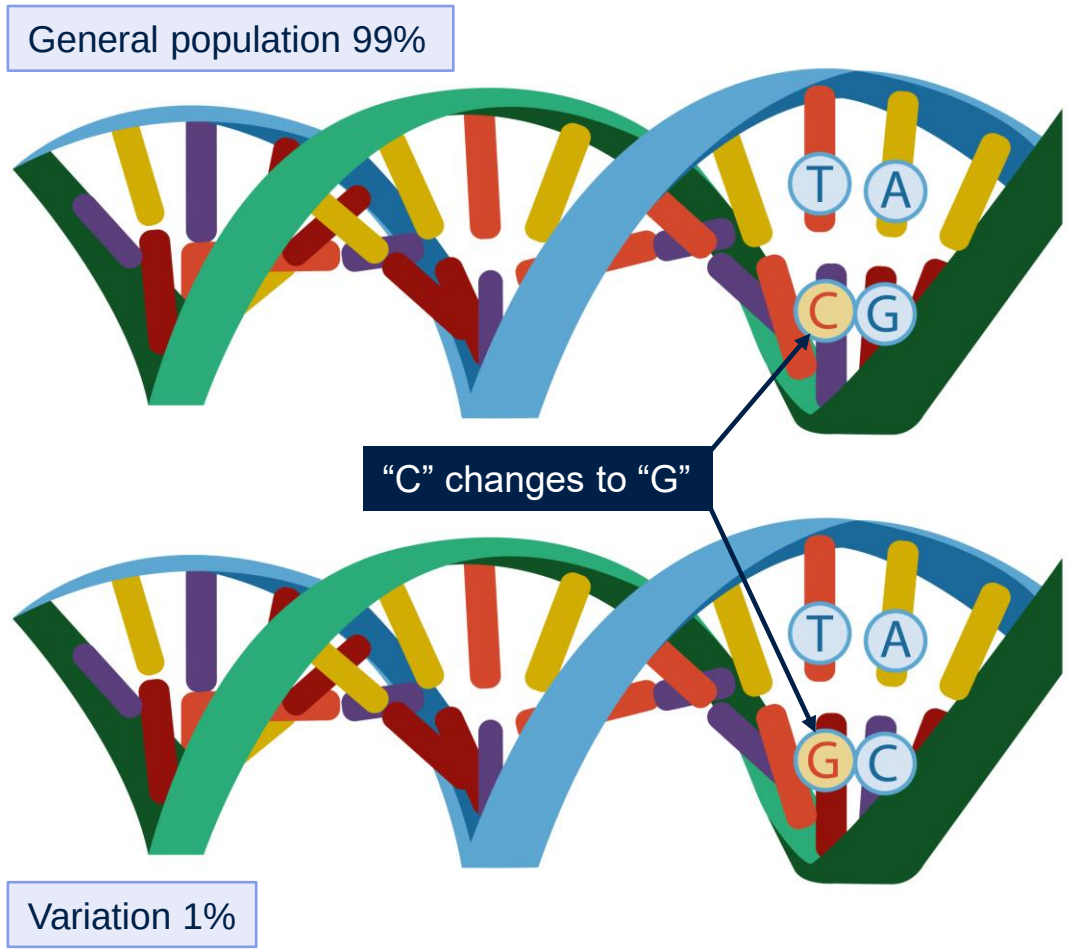
Single nucleotide polymorphisms (SNPs)

- 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



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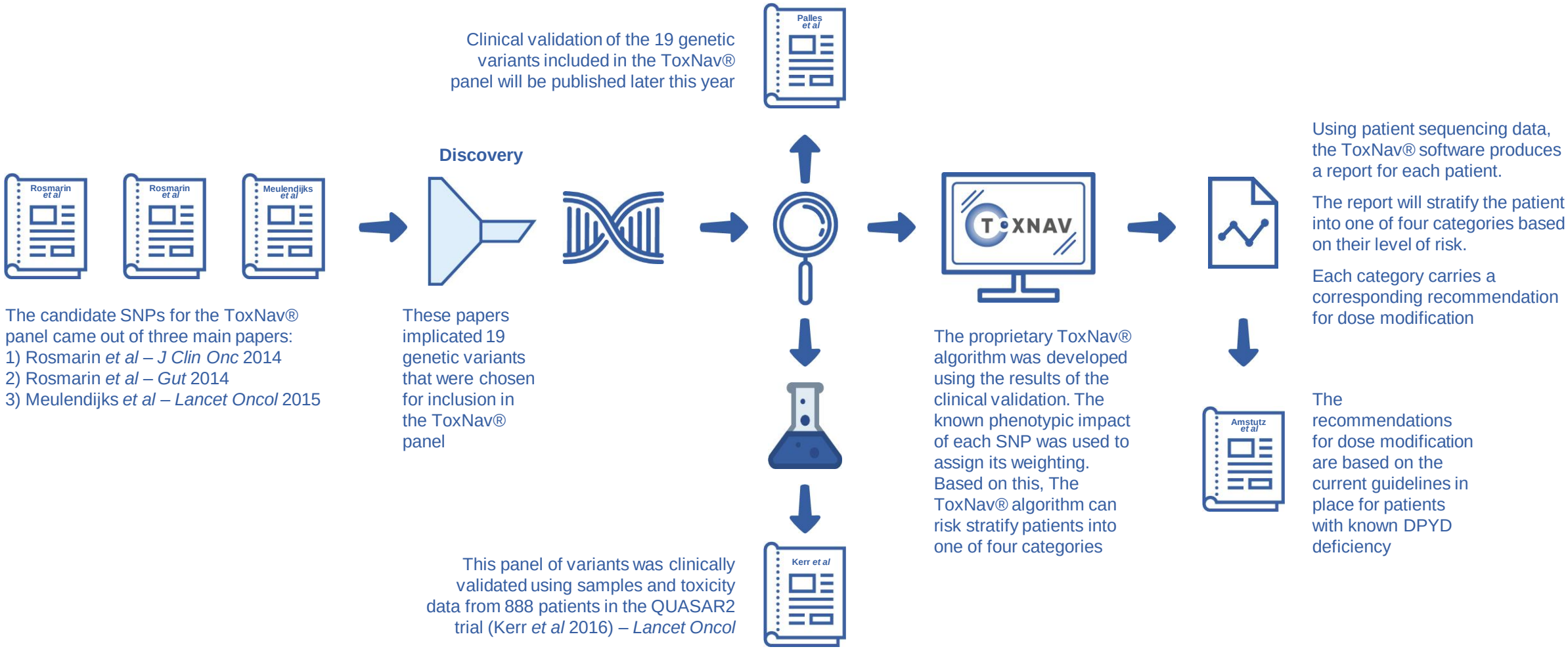
Discovery data



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

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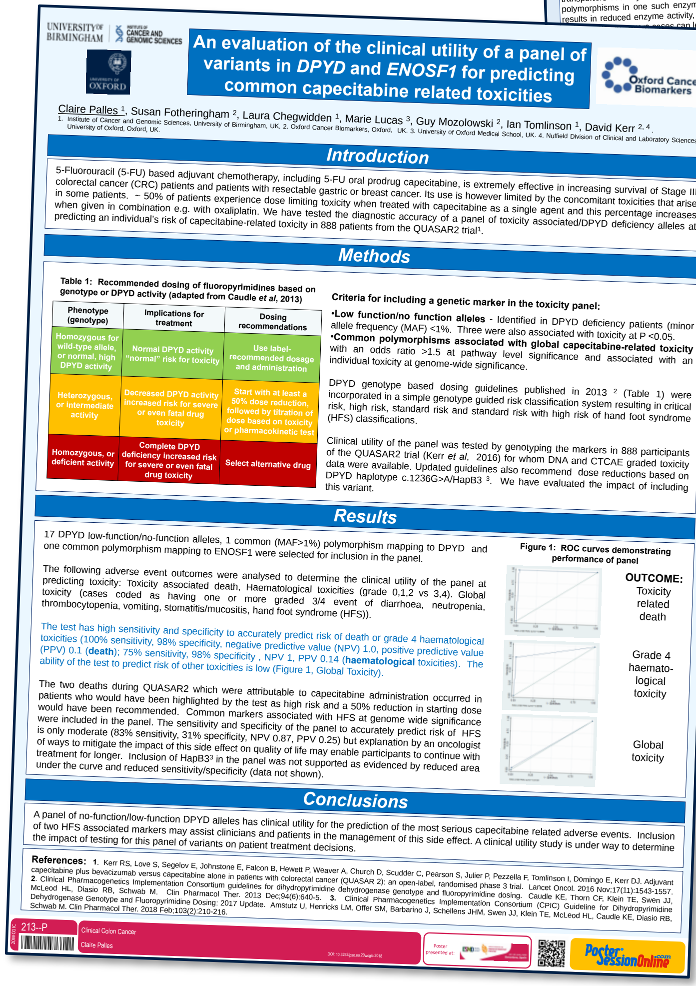
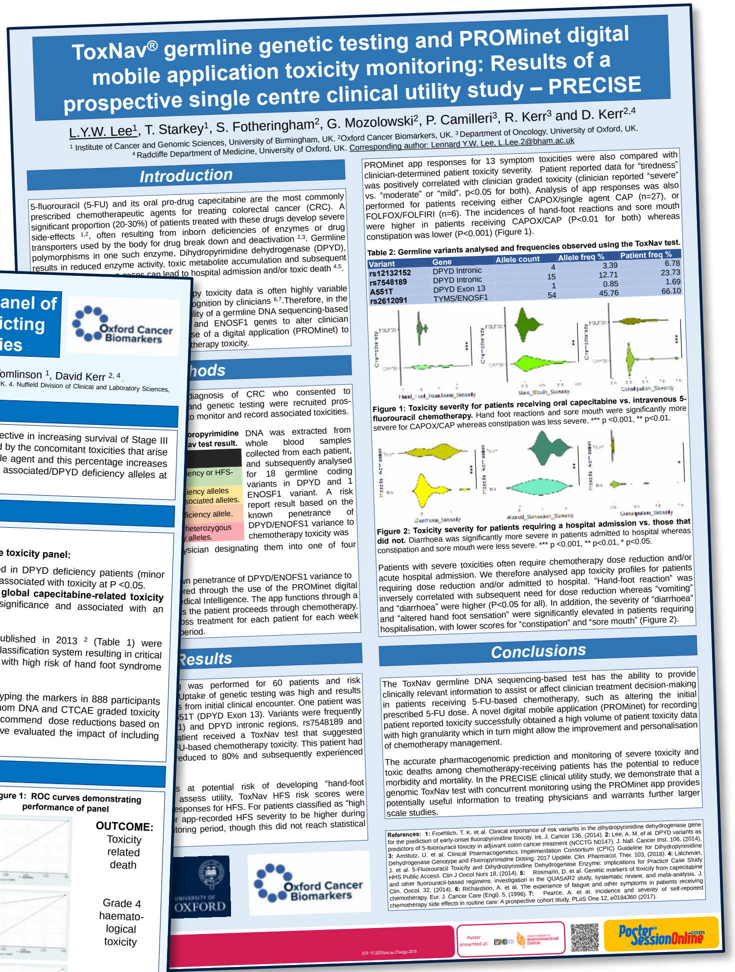
TOXNAV® Clinical validation

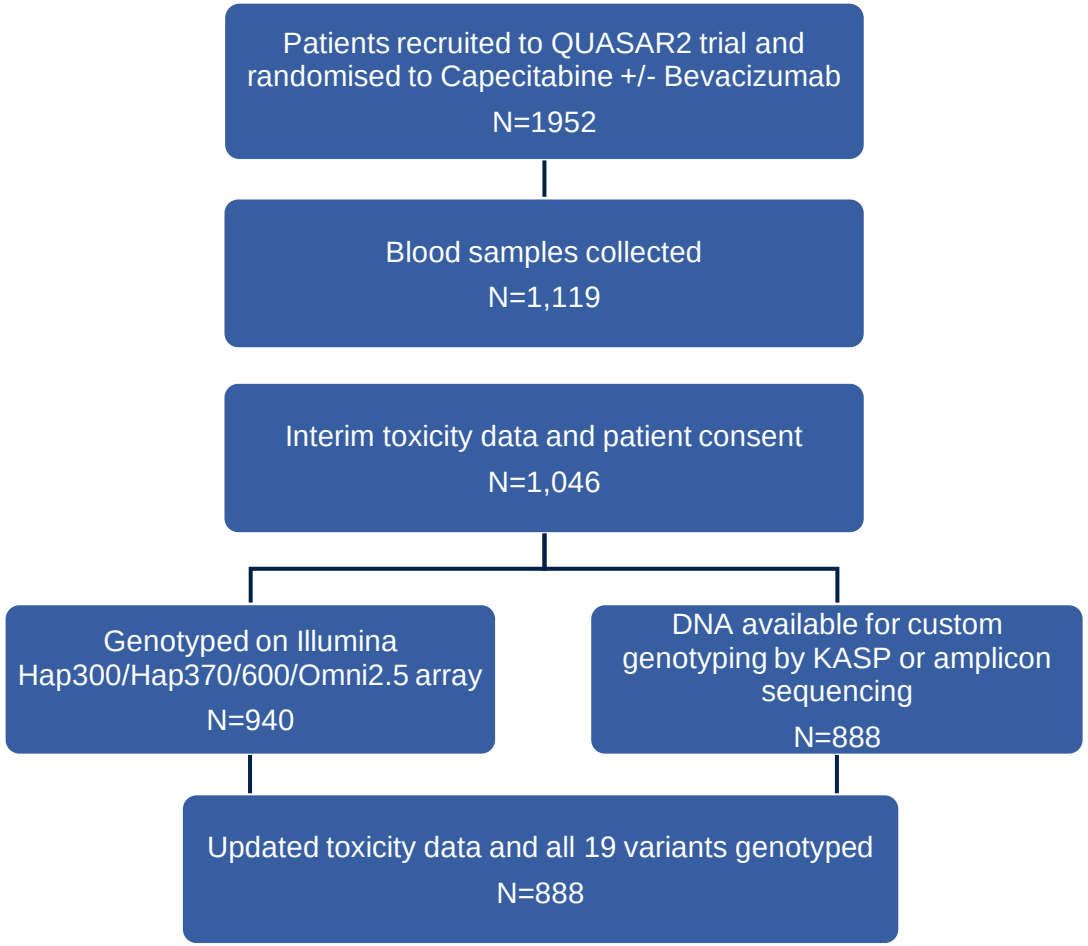
- **Clinical Validation Study**
  - QUASAR2 data set
  - ToxNav performance
  - Lead investigator: Dr Claire Palles, University of Birmingham
  - Presented at ESMO GI 2018
  - Manuscript in draft
- **Clinical Utility Study (PRECISE)**
  - 60 patients from OUH clinic
  - Assessment of ToxNav in clinical setting
  - Lead investigators: Prof. Rachel Kerr/ Dr. Lennard Lee
  - Presented at ESMO GI 2019
  - Published 2019





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

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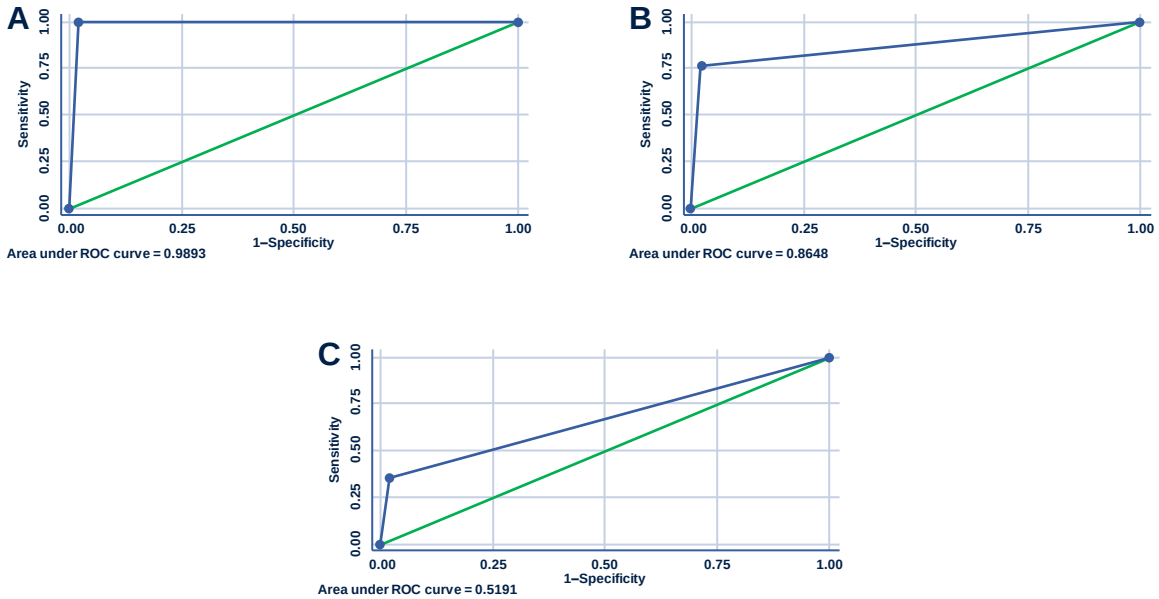
Clinical validation highlights

- 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

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*)

Critical RISK	High RISK	Standard RISK	Standard RISK *High Risk HFS
Variants indicate DPYD deficiency	Variants strongly associated with partial DPYD deficiency	No increased risk of grade 3/4 toxicity	No increased risk of grade 3/4 toxicity X2 standard population risk of HFS
5FU/capecitabine containing therapy contraindicated and should not be administered as stated on the drug label	5FU/capecitabine dose modulation of 50% recommended	5FU/capecitabine dose of 100% recommended unless clinician feels there are other factors which would mitigate dose	5FU/capecitabine dose of 100% recommended. Advice to minimise/prevent HFS according to local guidelines recommended

*Updated in 2017

Test procedure steps 1– 7

1

- Patients offered fluoropyrimidine chemotherapy
- ToxNav test requested by clinician

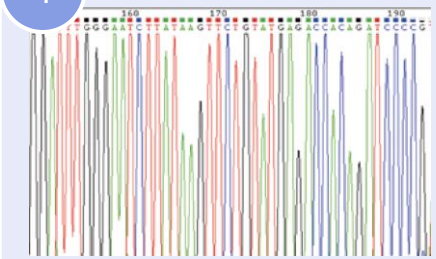
2

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

3

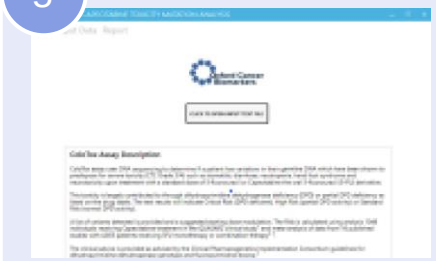
- Sample and requisition form received and logged by laboratory
- DNA extracted

4



- Sanger sequencing carried out to detect genotype of 20 variants
- Data managed via secure server

5



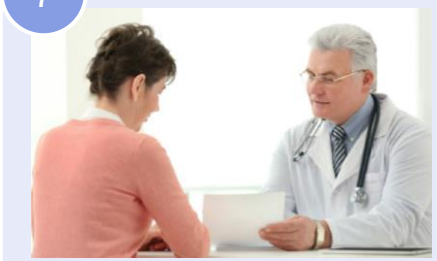
- Results transmitted from lab to OCB analysis suite
- Data imported to ToxNav software

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

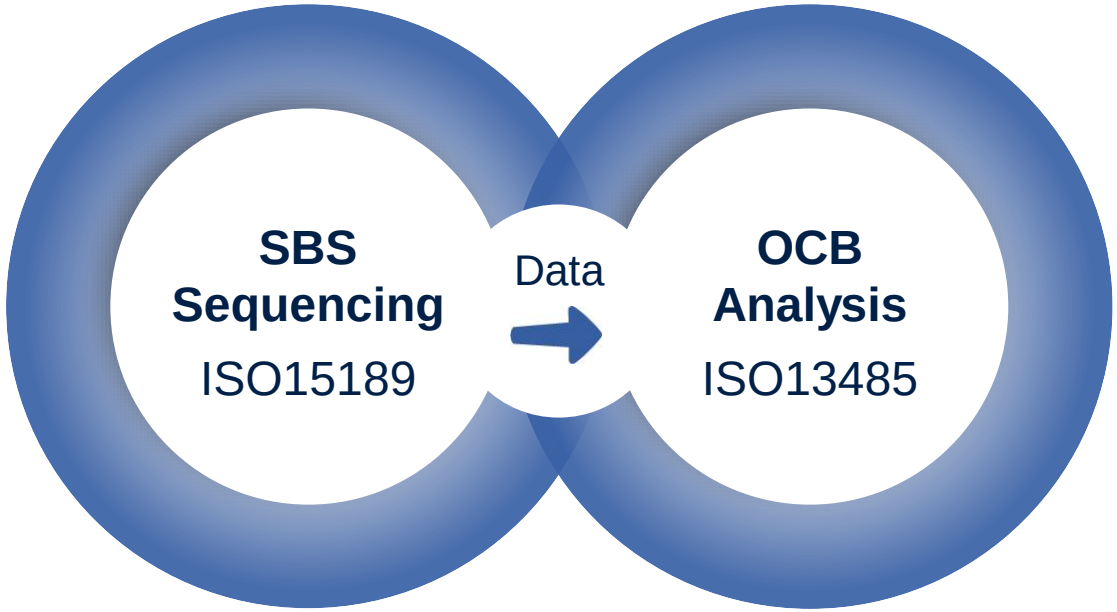
Recommended dosing of fluoropyrimidines based on genotype or DPYD activity (adapted from Caudle *et al*, 2013)[1]

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

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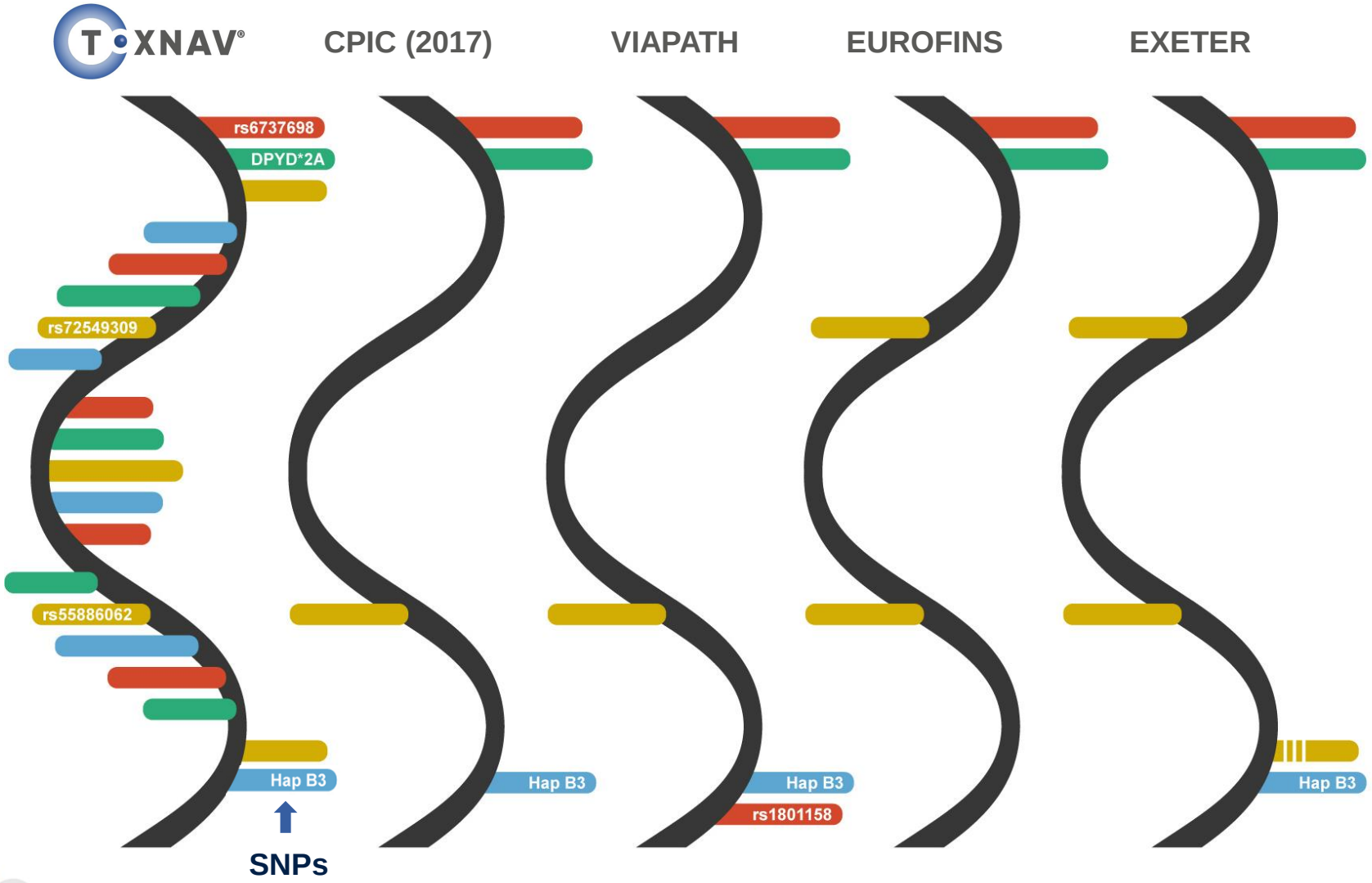
Competitor comparison



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[1]
- The panel is the only clinically validated test[2]
- 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[3]
- 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).

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Questions

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