Oxford Cancer Biomarkers

Pioneering precision medicine

OCB COLOTEST PRODUCT PIPELINE

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Oxford Cancer Biomarkers (OCB) Background & Mission

- OCB spun out of Oxford University in 2012 from the laboratories of Nick La Thangue (Professor of Cancer Biology) and David Kerr (Professor of Cancer Medicine) to advance personalised medicine for oncology.
- The company is closely affiliated with the University of Oxford, where its founders lead research groups focused on translational cancer science.
- OCB develops and commercialises biomarker tests that enable more effective treatment for patients.
- Since 2014 focus on ColoTest platform of tests to determine risk of disease and of improve outcomes for patients with colorectal cancer (CRC)
- Mission to improve cancer treatment decisions:
    - Increased benefit, less toxicity and cost effective
- **Using our biomarker tests can provide more effective treatment for patients and economic savings for the healthcare systems.**

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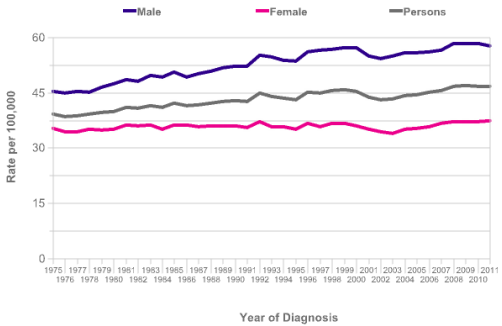
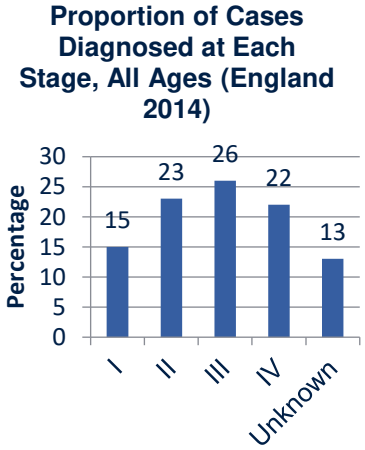
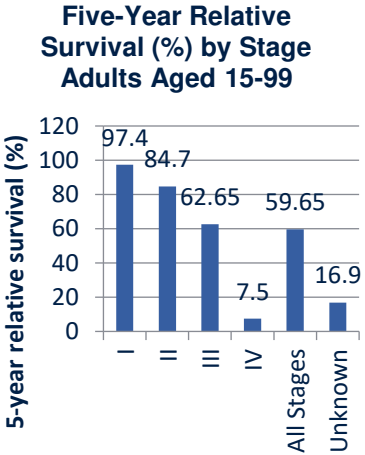
CRC tests - improving clinical practice

- Colorectal cancer:
  - 2nd most common in women and 3rd 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)
  - 41, 804 new cases in the UK in 2015 (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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CRC tests - improving clinical practice

- Incidence rates in the UK have remained stable since the early 1990s
- Survival is improving and has more than doubled in the last 40 years in the UK.
- Preventability estimates using the findings from the Continuous Update Project (WCRFI) show that about 45 per cent of cases of colorectal cancer in the UK can be prevented by lifestyle changes

- Clinical questions addressed by OCB's CRC biomarker tests:
  - who is most at risk from developing CRC?
  - will disease reoccur post surgery?
  - is the patient likely to have severe drug toxicity?

- Delivering a new standard-of-care:
  - right patient, right drug, right time, right cost

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What technology underpins OCB's tests?

- **ToxNav** and **ColoPredict**
  - genetic variation in important genes
  - DNA sequencing platform
- **OncoProg**
  - tumour morphology
  - DNA damage
- Read-out from tests
  - provides a measure of risk

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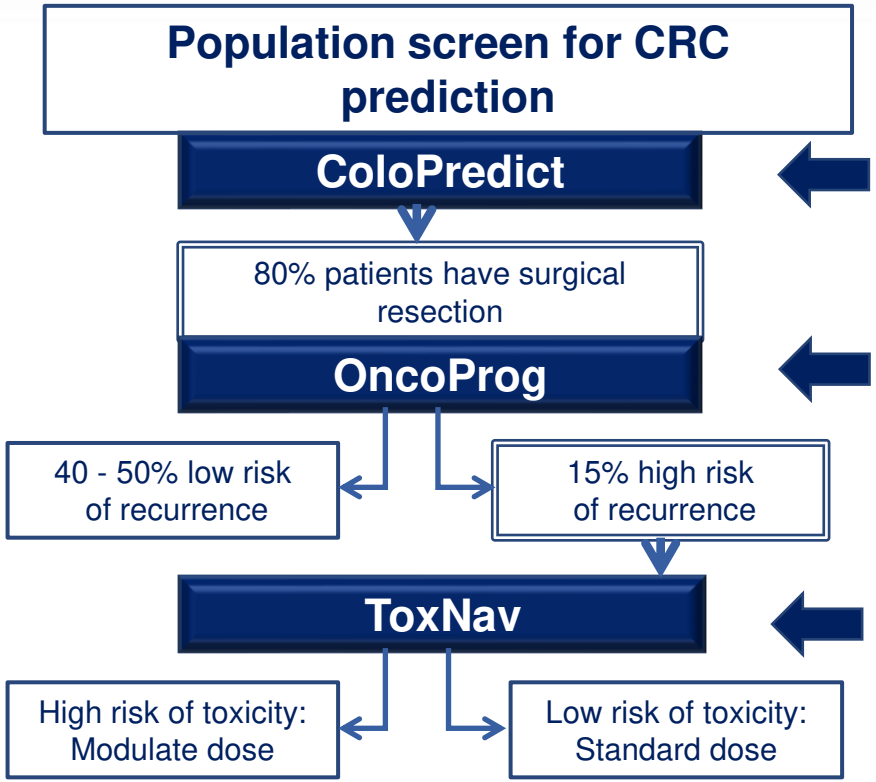
Precision diagnostic CRC tests – providing a new standard of care



Risk of developing disease

(n = 42,103 individuals)
WORK ONGOING

Risk of recurrence

(n = 2,624 patients)
DANIELSEN ET AL, ANNALS OF ONCOLOGY 2018

Toxic response to drug

(n = 888 patients)
MANUSCRIPT IN DRAFT

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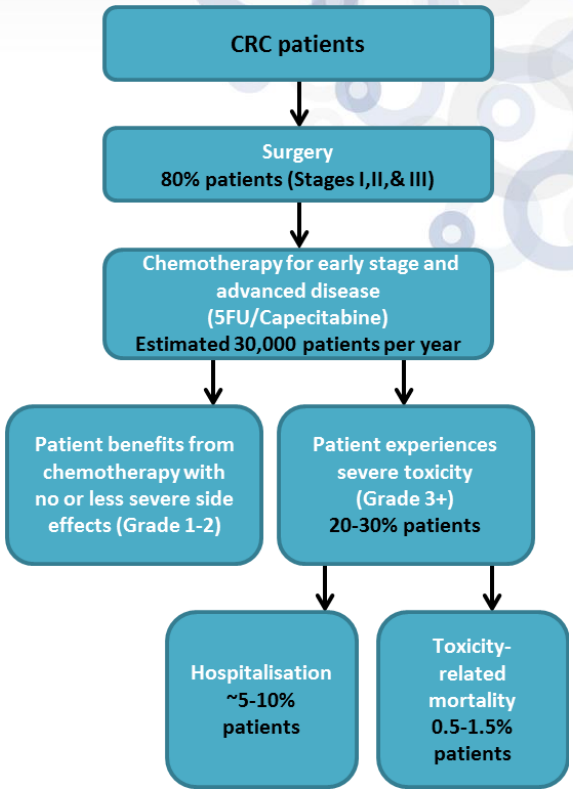
TOXNAV

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

5FU-associated toxicity in CRC patients

- 5FU/Capecitabine is currently used as first line treatment for tens of thousands of colorectal cancer cases each year in the UK.
- Toxicities are a burden to patients' quality of life and their carers and comes at a high financial burden to commissioners and health economies.
- Side effects include:
  - Neutropenic sepsis,
  - Diarrhoea,
  - Nausea/vomiting,
  - Stomatitis,
  - Hand-foot syndrome (HFS).



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ToxNav Background

- ToxNav measures the risk of high grade toxicity associated with treatment of colorectal cancer with fluoropyrimidine-based chemotherapy (5FU/capecitabine).

- Based on three key studies (GWAS and meta-analysis):
  - **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.
  - **Meulendjiks *et al*, Lancet Oncology, 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.

- Patent filed March 2014, GB, EU, USA, China, India, Hong Kong

- IP licenced from Oxford University July 2015

- ToxNav UK partnership in place with Source Bioscience.

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ToxNav Description

- ToxNav determines genotypes of 20 genetic variants (SNPs) associated with toxicity.
- Platform agnostic, Sanger sequencing currently used for genotyping
- Patients are stratified into categories informing on risk of toxicity:
  - Critical risk
  - High risk
  - Standard risk
  - Standard risk * High Risk HFS
- ToxNav provides clinicians and patients with information that can help assist in the choice of chemotherapy treatment regimens after initial surgery.
- CE marked
- Proven health economic benefit for the NHS

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ToxNav Risk Reporting

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

*Updated in 2018

Critical RISK	• Variants present that would likely indicate DPD Deficiency. • **5FU/Capecitabine containing therapy is contraindicated and should not be administered as stated on the drug label.**
High RISK	• Variants detected are strongly associated with partial DPD Deficiency. • Patient has at least 2x the risk of grade 3/4 toxicity using a standard dose of 5FU/Capecitabine. • **5FU/Capecitabine dose modulation of 50% is recommended.**
Standard RISK	• No increased risk of grade 3/4 toxicity to patients when using a standard dose of 5FU/Capecitabine or 5FU monotherapy. • **5FU/Capecitabine dose of 100% is recommended unless the clinician feels that there are other factors which would mitigate dose.**
Standard RISK * High Risk HFS	• No increased risk of grade 3/4 toxicity to patients using a standard dose of 5FU/Capecitabine. • *There is a high risk of HFS, this risk is at least 2x the risk of the Standard Risk Population. • **5FU/Capecitabine dose of 100% is recommended. Advice on how to minimise/prevent HFS according to local guidelines is recommended.**

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test procedure steps 1-7

1

- Patients offered fluoropyrimidine chemotherapy
- ToxNav test requested by clinician

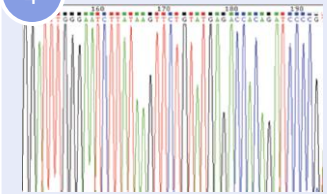
2

- 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

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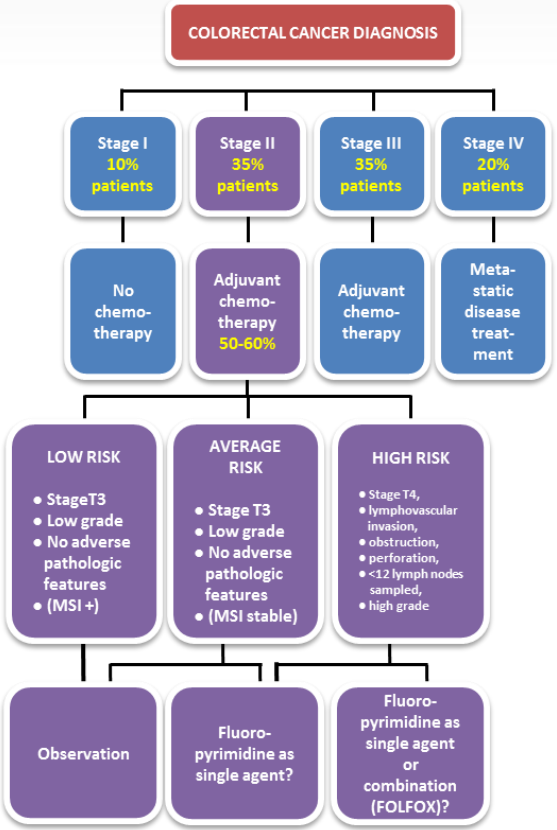
ONCOPRO G®

A prognostic marker for colorectal cancer: combining analyses of ploidy and stroma.

Treatment of Stage II CRC patients



- Adjuvant treatment can be an 'easy' decision in stage III CRC (although III A has a better prognosis than stage II !) but there is clinical controversy as to whether treatment should be offered to stage II CRC patients.
- Patients (and their doctors) would like to know the chance of cancer recurrence as this dictates follow-up and potential benefit from adjuvant chemotherapy.
- A number of tools are already available and used for selecting patients e. g.
  - T stage,
  - Grade,
  - Invasion,
  - Margin status,
  - No. lymph nodes,
  - Mismatch repair (MMR),
  - Microsatellite instability (MSI) status, etc.
- **BUT** no molecular markers have so far been routinely established in clinical practice to predict treatment benefit for Stage II patients.
- Currently, around 50-60 % of Stage II CRC patients receive adjuvant chemotherapy, a proportion of which is administered in combination, potentially over treating the general population of patients so that a small minority might benefit.

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OncoProg Introduction

- OncoProg determines the prognosis of Stage II colorectal cancer patients after treatment with fluoropyrimidine-based chemotherapy.
- Utilises digital pathology to examine specimens in order to determine DNA ploidy and tumour stroma content.
- Biomarkers are combined to stratify patients into categories informing on risk of recurrence:
  - High Risk (non-diploid and high stroma).
  - Intermediate risk (non-diploid and low stroma OR diploid and high stroma).
  - Low risk (diploid and low stroma).
- OncoProg provides clinicians and patients with information, that together with other relevant clinical parameters such as co-morbidities and performance status, can help assist in the choice of chemotherapy treatment regimens after initial surgery.

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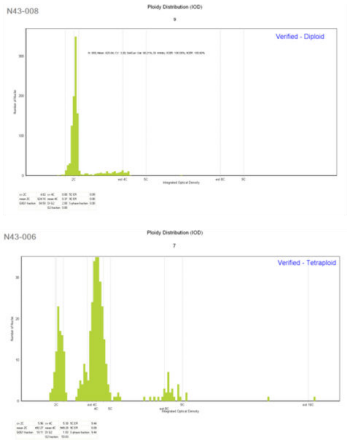
OncoProg - Sample analyses

Ploidy digital analysis

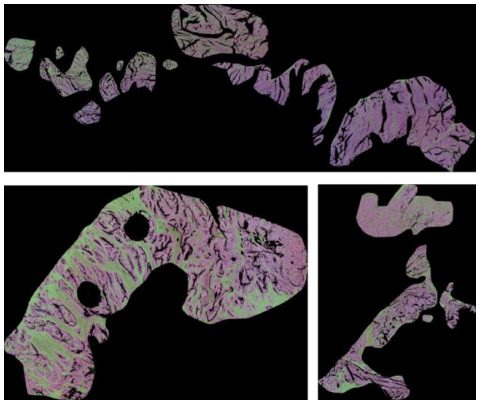
- Sample classified diploid when DNA content 2N.
- Sample classified tetraploid (non-diploid) when DNA content 4N or higher.
- 4N content significant even when at low levels.



Non-diploid = high risk
Diploid = low risk

Stroma digital analysis

- Pink: epithelial (tumour) tissue (H&E stain).
- Green: stroma tissue.
- Imaging software assigns false colour to stroma portion of tissue and uses this to calculate percentage stroma present in sample.



Stroma high ≥ 50% = high risk
Stroma low < 50% = low risk

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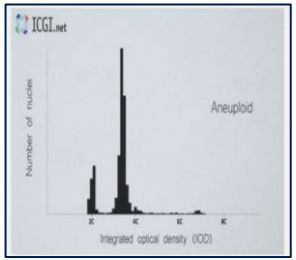
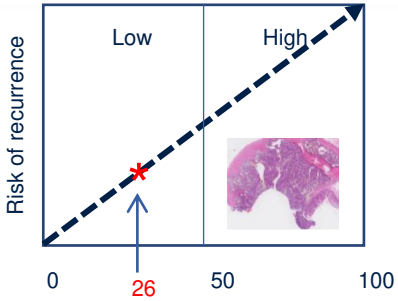
OncoProg Reporting (Example)

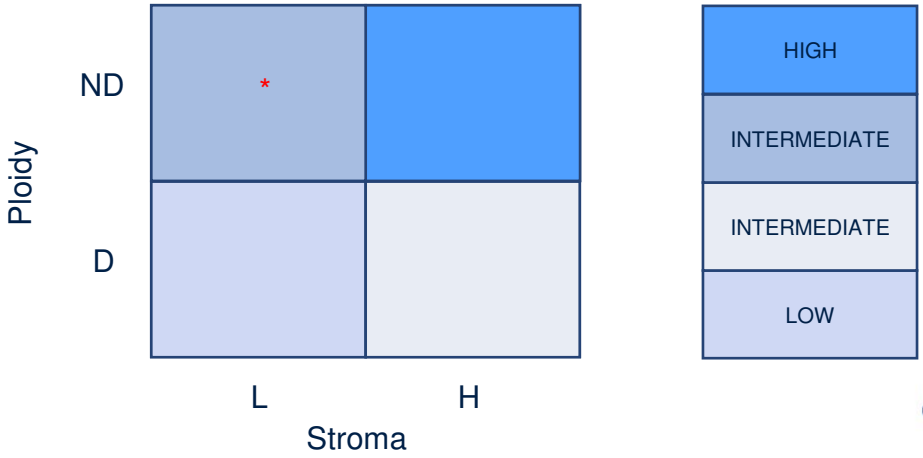
OncoProg Results:





OncoProg Designation: non-diploid (ND) low stroma (L)

Risk Categorization:



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OncoProg test procedure steps 1- 6

- Patient receives surgery
- Formalin fixed paraffin embedded (FFPE) tissue used for pathology

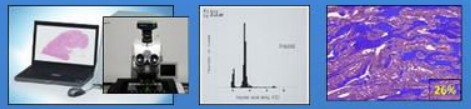
1

- Treatment discussed with patient
- ColoProg test requested by clinician via OCB website
- FFPE slide sent to OCB laboratory

2

- Sample and requisition form received and logged by laboratory
- Tumour sample processed for stroma and ploidy analysis

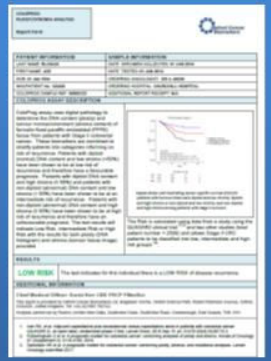
3

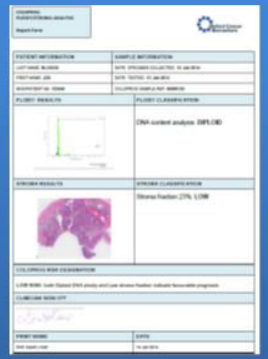


- Digital image analysis carried out for
  - Stroma (tumour image analysis)
  - Ploidy (DNA content determination)
- Stroma and ploidy data combined to produce risk category designation
- Final data set approved by pathologist

4

- Risk category designated
  - Low Risk
  - Intermediate Risk
  - High Risk
- Results verified by OCB clinician
- ColoProg clinical risk report generated





5

- ColoProg Report received by clinician and recommendation discussed with patient
- Chemotherapy decision made

6

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OncoProg Clinical Validation Study Design

- Combined colorectal cancer data set (2624 patients):
  - QUASAR2 trial (UK) 1092
  - Aker cohort (Oslo) 954
  - Gloucester cohort (UK) 578

  N.B. combined number of Stage II patients = 1029

DNA ploidy	Tumour stroma
1. Nuclei isolated from tumour region of FFPE sections	1. FFPE section H&E stain
2. Feulgen basic fuschin staining method	2. Tumour area confirmed by pathologist
3. Digital microscopy to determine DNA content	3. Digital pathology to determine stroma content
4. Tumours classified as diploid (D) or non-diploid (ND)	4. Tumours assigned: stroma low (≤50%) or stroma high (> 50%)

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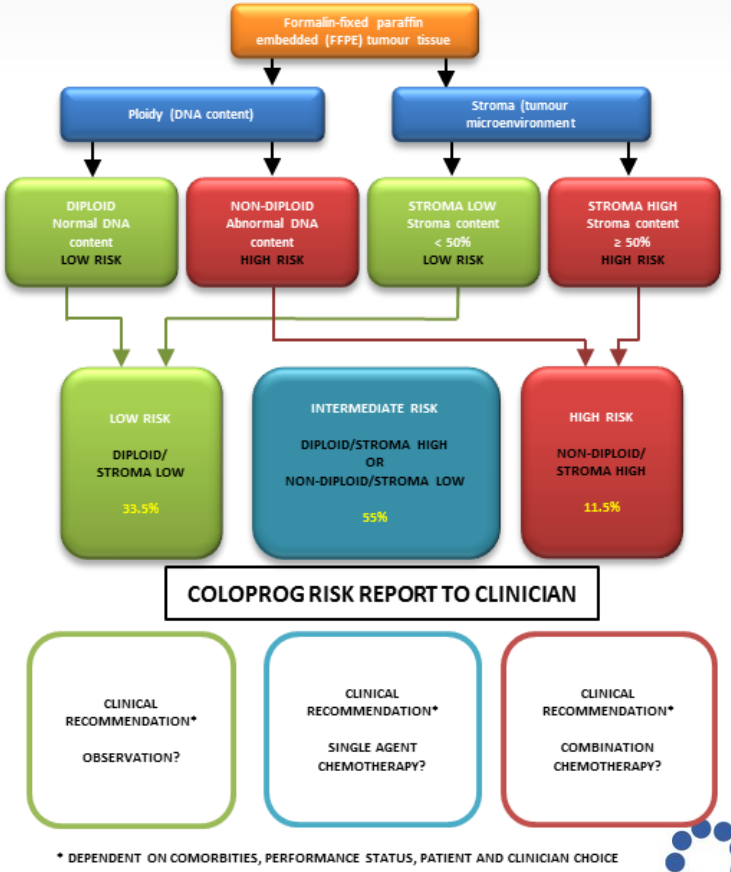
OncoProg Clinical Validation

- Utilises digital pathology to examine specimens using proprietary algorithms to determine DNA ploidy and tumour stroma content.
- Biomarkers are combined to stratify patients into categories informing on risk of recurrence.
- Initially validated using the QUASAR2 clinical trial and two other studies (total patient number = 2624) and allows Stage II CRC patients to be classified into low, intermediate and high risk groups.



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OncoProg: Risk Stratification

Stage II patients can be stratified into low vs high risk groups using DNA ploidy and stroma classification (total n=2624, Stage II n=1029)

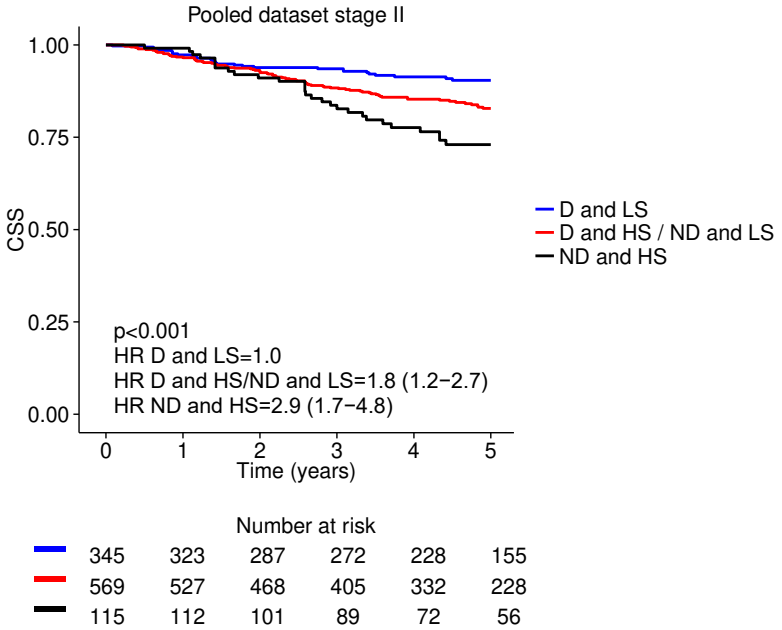

Figure 1: Kaplan-Meier plot illustrating cancer-specific survival (CSS) for patients with tumours that were diploid and low stroma (D and LS), diploid and high stroma or non-diploid and low stroma (D and HS/ND and LS), and non-diploid and high stroma (ND and HS) among patients with stage II tumours.

Danielsen HE *et al*. Prognostic markers for colorectal cancer; estimating ploidy and stroma. Annals of Oncology, mdx794, https://doi.org/10.1093/annonc/mdx794. Published: 27 December 2017

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OncoProg Clinical Validation: Conclusions

- High risk Stage II patients:
  - Can be divided into risk groups based on a combination of measurements of DNA ploidy and stroma.

- Automated digital pathology could facilitate adoption of biomarker analyses into patient treatment strategies.

- **END GOAL:** production of a prognostic test that can be offered to patients to inform the use of adjuvant treatment after surgery.

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COLOPREDICT™

A test performed on a DNA sample in normal people invited to participate in screening programme to determine lifetime risk of developing colorectal cancer.

ColoPredict™ Introduction

- **ColoPredict™ :** A population-based test that measures a person's risk of developing CRC.
- **Validation:** currently validated in a cohort of 51,000 people and results published in world leading journals.
- **Aim:** to identify populations of normal individuals at high risk (5-10x risk greater than average) of developing CRC:
  - Allowing patients to adapt their lifestyle appropriately and undergo more intensive surveillance.
- **Improved screening strategies:** good evidence that screening shifts detection of CRC to early stage (Stages 1 and 2 as opposed to Stages 3 and 4), and dramatically improves patient survival and decreases the cost of treatment.
- **Enhancing current screening programs:** ColoPredict™ is seen as complementary to and not a replacement for any of the current faecal tests which are used for CRC screening.
- There are no genetic tests of this type currently available which have undergone the same standard of clinical validation as ColoPredict™.

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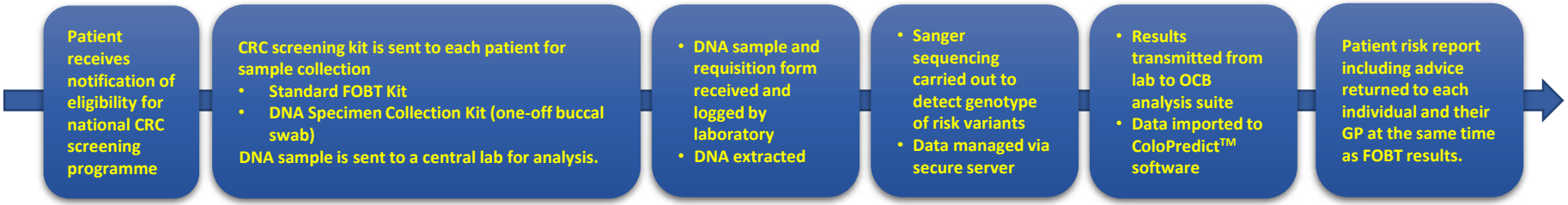
ColoPredict™ Validation and Delivery

- ColoPredict™ consists of an algorithm of highly validated SNPs associated with lifetime risk of CRC.
- SNPs identified from an extensive Genome Wide Association Study of 48,576 European subjects (26,660 CRC cases and 21,916 cancer free controls).
- The risk scores can also be combined with additional risk factors such as family history of CRC, the incorporation of family history and SNP algorithms has been previously published as an effective way to identify those at the greatest risk.
- **ColoPredict™ test procedure:**



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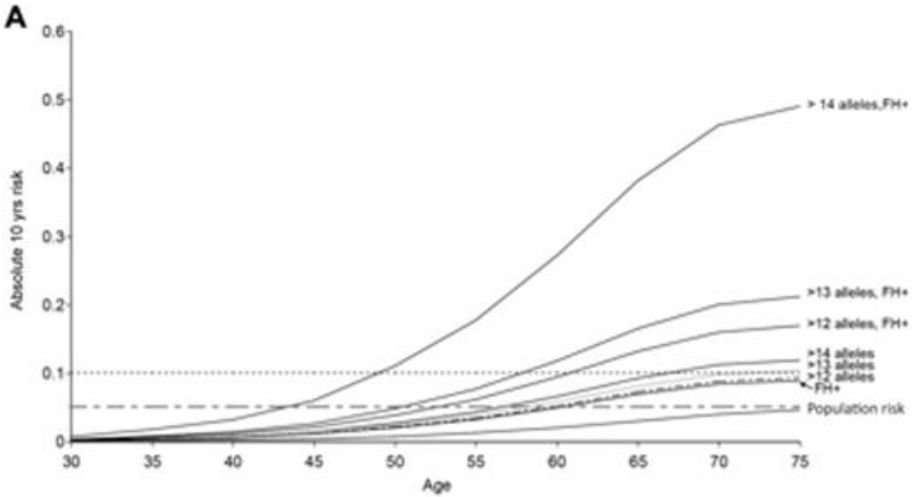
ColoPredict™ clinical validation

A germline DNA test to assess genetic susceptibility to lifetime risk of colorectal cancer

- Genome Wide Association Study (GWAS): 44,389 Europeans (24,395 CRC cases, 19,994 cancer-free controls).
- Estimates suggest 100 variants account for majority of genetic risk.
- Currently 20 variants described by test, 10 of which are in the public domain.
- The test checks for 40 alleles generating a score for increased lifetime CRC risk.



FH+ = Family history known and is used to stratify high risk individuals

Data from Dunlop *et al* (2012), Gut.

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