10-year results of the International Breast cancer Intervention Study II (IBIS-II)

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Background: Two large clinical trials have shown the benefit of aromatase inhibitors in healthy women to reduce the risk of developing breast cancer (MAP.3 and IBIS-II). Here, we report blinded 10-year median follow-up efficacy data for the IBIS-II trial, which compared anastrozole to placebo in women at increased risk of developing breast cancer.

Material and Methods: 3864 postmenopausal women at increased risk of developing breast cancer were recruited into a double-blind trial of anastrozole (N=1920) versus matching placebo (N=1944) for 5 years. The primary objective of this study was to determine the efficacy of anastrozole in preventing breast cancer (both invasive and ductal carcinoma in situ (DCIS)), overall and particularly in the post 5-year time period. Secondary endpoints included prevention of oestrogen receptor positive breast cancer, breast cancer mortality, non-breast cancer deaths, other cancers, cardiovascular disease, fractures, and musculoskeletal events.

Results: After a median follow-up of 10.9 years (IQR 8.8-13.0), a total of 241 breast cancers have been reported (HR=0.50 (0.38-0.65), P<0.0001) (Table). The reduction was larger in the first 5 years (HR=0.39 (0.27-0.58), P<0.0001), but still significant after 5 years (117 new cases (49%); HR=0.63 (0.43-0.91), P=0.015) (Table). The effects in the two time periods were not significantly different (P=0.11). Invasive oestrogen receptor (ER) positive breast cancer was reduced by 54% with anastrozole (HR=0.46 (0.33-0.65), P<0.0001), with a continued significant effect observed in the post treatment follow-up period (Table). A non-significant effect was observed in invasive ER-negative breast cancer (HR=0.76 (0.39-1.45), P=0.4). A reduction in DCIS overall was observed (Table), with a very large reduction in those known to be ER-positive (HR=0.23 (0.08-0.69), P<0.0001). A total of 129 deaths have been reported, with no significant difference in all-cause mortality between the two treatment arms (63 vs. 66; HR=0.93 (0.66-1.32), P=0.7). Only 5 deaths from breast cancer (2 vs. 3) were reported, but number of events are very small and longer follow-up is needed. 321 cancers other than breast were reported, with a significant decrease observed with anastrozole (129 vs. 192, OR=0.66 (0.52-
Specifically, fewer endometrial cancers (4 vs. 8), ovarian cancers (5 vs. 9), lung cancers (5 vs. 12), and melanomas (9 vs. 18) were observed with anastrozole. A comprehensive adverse event profile will be reported.

**Conclusion:** This updated analysis of the IBIS-II trial confirms the significant reduction in breast cancer occurrence with anastrozole in the post-treatment follow-up period. These results indicate a long-term preventive benefit with anastrozole for ER-positive breast cancer in postmenopausal women.

**Table:** Number of events and Hazard Ratios (95% CI) according to treatment allocation and follow-up period.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of events</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>241 (81 vs. 160)</td>
<td>0.50 (0.38-0.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>0-5 years</td>
<td>124 (35 vs. 89)</td>
<td>0.39 (0.27-0.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5+ years</td>
<td>117 (46 vs. 71)</td>
<td>0.63 (0.43-0.91)</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>Invasive ER-positive</strong></td>
<td>151 (48 vs. 103)</td>
<td>0.46 (0.33-0.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>0-5 years</td>
<td>72 (20 vs. 52)</td>
<td>0.38 (0.23-0.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5+ years</td>
<td>79 (28 vs. 51)</td>
<td>0.53 (0.34-0.84)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>All DCIS</strong></td>
<td>42 (13 vs. 29)</td>
<td>0.44 (0.23-0.85)</td>
<td>0.015</td>
</tr>
<tr>
<td>0-5 years</td>
<td>22 (5 vs. 17)</td>
<td>0.29 (0.11-0.80)</td>
<td>0.011</td>
</tr>
<tr>
<td>5+ years</td>
<td>20 (8 vs. 12)</td>
<td>0.65 (0.26-1.59)</td>
<td>0.34</td>
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Ethnicity and the surgical management of early invasive breast cancer in over 137 000 women in England

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Introduction: There is limited information about the different patterns of surgical management by ethnicity of early invasive breast cancer in women in England and any potential inequalities in the treatment received for breast cancer.


Methods: Information on age at diagnosis, stage of disease, co-morbidities, region of residence, deprivation and year of diagnosis was included. A logistic regression model was used to estimate the odds ratio (OR) and 95% confidence interval for risk of mastectomy versus breast conserving surgery by ethnicity adjusting for the variables described.

Results: The overall mastectomy rate fell by ~5% during 2012 to 2016 in women of all ethnicities. In minimally adjusted analyses, all ethnic minority women had significantly higher risks of mastectomy compared to White women. However, following adjustment for age at diagnosis and stage of disease at presentation, there were no residual differences observed in the risk of mastectomy for women of most ethnic minority backgrounds examined. For example, compared to White women, the minimally adjusted and fully adjusted OR for mastectomy was 1.09 (1.01-1.18) and 1.01 (not significant) for Indian women, and 1.52 (1.36-1.71) and 1.08 (not significant) for Black African women.

Conclusions: This study provides nationally reliable data in England on the association between ethnicity and the surgical management of early breast cancer. Although the overall mastectomy rate is declining in all groups, the proportion of women undergoing mastectomy is higher in ethnic minority women compared to White women. However, allowing for the different patterns of age and stage at presentation, the surgical management of early breast cancer is similar in all women, regardless of ethnicity.
Surgical outcomes following neoadjuvant chemotherapy - a UK national prospective multi-centre cohort study

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Introduction: Potential advantages of neoadjuvant systemic therapy (NST) include downstaging disease to minimise surgery, and in vivo assessment of tumour sensitivity to therapeutic drugs. Considerable variation in NST use remains, however, and it is unclear whether pathological response rates reflect those reported in trials, or whether the downstaging achieved with neoadjuvant treatment impacts on surgical decision-making.

Aims/objectives: The NeST prospective multicentre study aimed to examine surgical decision making and outcomes following the use of neoadjuvant systemic therapy in early breast cancer across UK breast cancer units.

Methods: Women undergoing NST as their primary breast cancer treatment (chemotherapy (CT), endocrine (ET) and targeted therapies) in 37 UK centres from 1/12/17-30/11/18 were included.
Patient characteristics, tumour pathology, stage systemic treatments, surgical management data and pathological outcomes were collected.

**Results:** 926 patients received neoadjuvant chemotherapy (NAC) for 941 tumours (15 bilateral) during the study period. 46% had HER2+ disease, 32% triple negative disease and 21% ER+ HER2- disease. 51% (474 tumours) were node positive and 48% (456 tumours) node negative (1% unknown nodal status) at diagnosis. Cited indications for NAC were as follows (more than one option applicable to each patient):

- Downstaging (mastectomy to breast conservation) 37%
- Facilitate dual antiHER2 therapy 33%
- Inoperable disease 19%
- Improved cosmesis (reduced volume of excision) 17%
- Facilitate BRCA testing 9%
- Inflammatory breast cancer 6%

Centres were asked to indicate primary breast surgical treatment recommended prior to/without NST. At abstract submission, this data was available for 887 patients. 31 had inoperable disease. A total of 477 were considered to require mastectomy, with disease not amenable to breast conservation surgery (BCS). A further 379 patients were considered candidates for BCS. Data on final surgical procedure was available for 765 patients. Of those patients determined suitable only for mastectomy at diagnosis, 123 underwent BCS as their primary operation - a downstaging rate of 26%. The overall mastectomy rate in this cohort was 48%, with 33% having mastectomy and 15% mastectomy with immediate reconstruction.

In patients who were node negative at diagnosis, the axillary management plan was for sentinel lymph node biopsy (SLNB) after treatment in 372 cases (82%), with pre-treatment SLNB proposed in 45 cases (10%). In patients who were node positive pre-treatment, the planned axillary surgery was an axillary dissection in 308 patients (65%), with MDTs stating a plan to re-assess the axilla following treatment in only 153 cases (32%).

Pathological response data was available in 672 patients, with an overall pathological complete response (pCR) rate of 29% (defined as no residual invasive or in situ disease). pCR rate according to molecular subtype was 37% for HER2+ disease, 35% for TNBC and 7% for ER+, HER2-ve disease. The pCR rate in patients downstaged from mastectomy to BCS was 27%.

**Conclusions:** This UK national prospective study suggests that surgical downstaging remains a key indication for the use of NAC. Following NAC, 26% of patients in this series were downstaged from an original surgical plan for mastectomy, with NAC enabling BCS in these patients, confirming that this is a successful strategy for increasing breast conservation rates. However, based on this data it appears that surgical downstaging is no more likely in those with pCR compared to those without a pCR.
In the UK, the majority of patients who are node negative at diagnosis undergo post-treatment SLNB. However, most patients who are node positive pre-treatment are recommended to undergo axillary node clearance following chemotherapy, with only one third of cases having axillary re-assessment. Data collection is ongoing; updated data will be presented in January 2020.
Retesting of receptors status (ER, PR and HER2) and proliferation biomarkers (Ki67 and SPAG5) after receiving neoadjuvant chemotherapy (NACT) should be mandatory to guide the choice of the optimal adjuvant therapy in Breast Cancer (BC).

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Background: NACT is a standard option for BC (T2-4, N0-3, M0) and certain BC phenotypes. The choice of adjuvant therapy based on the pre-NACT biomarkers status may not be optimum for individual patient because dynamic phenotypic changes induced by NACT may alter the response to treatment.

Aim: The aim of this study is to determine the incidence of changes in the receptor status (ER, PR and HER2) and other proliferation biomarkers (Ki67 and SPAG5) before and after NACT and to assess the clinical significance of such changes.

Methods: Immunohistochemistry staining of ER, PR, HER2, Ki67 and SPAG5 in pre and post NACT tumours tissues from a consecutive series of 850 of LABC treated in the Nottingham University Hospital (NUH) from 2000 to 2018, have been centrally evaluated. All cases with conversion in HER2 status had also been tested by HER2-FISH. The results were validated in an external cohort of 250 cases. Treatment options are the same between the centres: (68%) received anthracycline plus Taxane (AC+T) NACT and 32% of patients have received NACT Anthracycline only (AC). Neoadjuvant HER2 targeting agents (Trastuzumab) or (Trastuzumab + Pertuzumab) had been prescribed to 16% of patients in addition to AC+T followed by adjuvant Trastuzumab (total=18 cycles). All pre-NACT ER+ patients were given at least 5 year of adjuvant endocrine therapy. In 2013 NUH started a prospective audit of retesting of receptor status in all post NACT surgical tumour samples. The results of the tests were presented to the weekly tumour board meeting and any change in the receptor status (ER and HER2) from negative (in the pre NACT core biopsies) to positive (in the post NACT surgical specimen) being considered for additional adjuvant treatment (Endocrine therapy for ER+ and Trastuzumab for HER2+ cases). The primary end points for this study are the % changes of biomarker changes and the disease free survival (DFS). The median follow up was 72 months.
Results: In pre NACT core biopsies 32% and 68% were HER2+ and HER2-; respectively. Twelve percent (12%) of the pre NACT HER2- tumours had a conversion to HER2+ in the post NACT surgical specimens. In this group of patients who subsequently received adjuvant Trastuzumab, 95% 3-year DFS was reported; which was similar to those patients who achieved pCR (3-year DFS; 90%) and was superior to cases which remained HER- in post NACT specimens (3-year DFS; 41%); (p<0.0001). Furthermore, similar patients with pre NACT HER- tumour before the 2013 audit, who did not receive Trastuzumab for the change of post NACT HER2+ receptors, has inferior 3-year DFS to those received adjuvant Trastuzumab based on the conversion (HR (95% CI)= 7.40 (1.04-52.86); p=0.046).

In pre NACT HER2+ BC, 20% of cases had been converted into HER2- in the post NACT surgical specimens. These patients had better 3y-DFS (94%) compared to those who remained HER2+ in post NACT specimens (3y-DFS=70%; HR (95% CI) = 0.86 (0.77-0.97); p=0.01). Furthermore in those patients who received neoadjuvant HER2 targeting therapy has statistically higher incidence of post HER2- conversion (p=0.005) and lower level of post NACT proliferation markers (Ki67 and SPAG5); p=0.01. In pre NACT ER+/PR+ patients, those who has converted into ER+/PR- in post NACT specimens had shorter 5-year DFS (40%) in spite of receiving adjuvant endocrine therapy, compared to those who remained ER+/PR+ in post NACT specimen [5-DFS= 72%]; HR (95% CI)= 1.98 (1.18-3.31); p=0.009).

Conclusion: To our knowledge, this is the first report, which showed the significant clinical benefit of adjuvant therapy, based on the re-testing of the standard receptors status.
Metabolic reprogramming of ER+ breast cancer cells in response and resistance to the CDK4/6 inhibitor palbociclib

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Introduction. Endocrine therapy (ET) is the standard of care for oestrogen receptor-positive (ER+) breast tumours. However, a superior outcome is achieved in ER+/HER2- metastatic breast cancer patients receiving a combination of a cyclin-dependent kinases 4 and 6 inhibitor (CDK4/6i) (e.g. palbociclib, PD) together with ET. CDK4/6i have also been tested in ER+/HER2+ preclinical breast cancer models reporting encouraging results.

Aims. Despite the clinical advances of this combinatorial therapy, potential limitations, i.e. resistance, could emerge and investigating the metabolic adaptations underlying such resistance warrants further elucidation.

Methods. A panel of ER+ breast cancer cells sensitive to PD (PDS) and resistant derivatives (PDR) have been subjected to metabolic profiling using an array of complementary high-end techniques including ¹⁴C-radioactive glucose tracing, western blot and qRT-PCR analysis, together with Seahorse coupled to mass spectrometry analysis.

Results. This approach revealed a differential metabolic behaviour between sensitive and resistant cells. Moreover, the metabolic phenotype of PDR cells shows significant differences between HER2- and HER2+ subtypes. Specifically, ER+/HER2+ PDR cells show an enhanced glucose dependency in both basal and metabolic stressed conditions compared to PDS cells. Conversely, ER+/HER2- PDR cells exhibit a decreased glycolytic phenotype compared to their parental counterpart. We have therefore targeted these glucose dependencies using different approaches. Crucially, glycolysis inhibition resensitises ER+/HER2+ PDR cells to PD and potentiates the response of ER+/HER2- PDS cells to the therapy. The clinical relevance of our data was investigated in a cohort of ER+/HER2+ patients in which a subset of HK2 higher-expressing tumours show a worse prognosis and may be more susceptible to therapy resistance.

Conclusions. Our results suggest that the deregulated glucose metabolism could represent a strategic mechanism sustaining PDR. Identifying the underlying molecular mechanisms warrants further elucidation in order to identify potential targetable players or predictive biomarkers to be exploited to combat or delay PDR.
Pathological features and outcome of screen detected ductal carcinoma in situ (DCIS): Updated analysis from the UK Sloane Project

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Aims/Objectives: The Sloane prospective cohort study aims to examine the clinical, radiological and pathological features, patterns of care and outcomes for women with non-invasive neoplasia detected within the NHS Breast Screening Programme.

Methods: Contributing screening units completed radiology, pathology, surgery and radiotherapy pro formas prospectively for DCIS patients diagnosed between 2003-12. Outcome data (up to December 2016) for subsequent events developing 6 months or more following DCIS diagnosis for England patients were collected.

Results: Data for 11,337 patients is presented. The commonest DCIS size was <20mm (n=6067; 54%) and the largest proportion (n=7204, 64%) was of high cytonuclear grade. There was a small increase in the proportion of high grade DCIS (60% to 65%) coupled with a slight decrease in low grade DCIS (10% to 6%) from audit beginning to end. A steady increase in reported DCIS size, from a mean of 21.4mm in 2003 to 2004 to 24.1mm in 2011 to 2012 was documented. 61% of DCIS showed comedo necrosis representing 78% of the high grade lesions with marked variation in the percentage of cases showing comedo necrosis. The most common margin width for breast conserving surgery was 10mm or over (35%; 2814 patients) with only a minority (6%) of lesions having a margin of < 1mm. This is reassuring particularly in view of the changes in the national guidance regarding the adequacy of DCIS margin excision during the study period. Microinvasion was recorded in 7% of cases with a wide variation in the rate of reporting among screening units (0-30%) and a steady decrease over time. Out of the total 9,186 patients in England, 1098 (12%) developed DCIS or invasive malignancy in the ipsilateral or contralateral breast and 41 patients developed distant recurrences. The commonest event was ipsilateral invasive disease (n=413) followed by ipsilateral DCIS (n=225) with a median recurrence time of 62 and 37 months respectively. Further twenty patients had an unspecified ipsilateral recurrence. The proportion of high grade DCIS that experienced an ipsilateral recurrence
(6.6%) was lower than for intermediate (8.2%) or low grade DCIS (8.4%); for invasive ipsilateral recurrence this was 3.7% for high grade and 5.6% for intermediate and low grade.

Contralateral recurrences were more commonly invasive (n=325) than in situ (n=94) in nature with 3 recorded as recurrences of unknown disease. 77% and 54% of ipsilateral and contralateral DCIS recurrences occurred in the first 5 years following DCIS diagnosis. Invasive carcinoma developed over a longer period; 47% in the first 5 years and 44% in the subsequent 5 years for ipsilateral invasive recurrences and 46% and 43% in the first and next five years for contralateral invasive recurrences respectively. Most distant recurrences (59%) occurred in the first 5 years of follow up.

Conclusions: This study highlights the trends in pathology for screen detected DCIS over time. These include an increase in lesion size and in the proportion of high grade lesions and a decrease in the proportion of low grade DCIS and DCIS featuring microinvasion. Some pathological features (such as comedo necrosis) suffered from lack of consistency of pathological reporting. There is a low rate of subsequent events following a diagnosis of DCIS. Most DCIS recurrences developed in the first 5 years whereas ipsilateral and contralateral invasion continued to occur up to 10 years. This data sheds light on the natural history of screen detected DCIS and should inform management and follow up strategies.
Fulvestrant plus capivasertib versus placebo in metastatic ER positive breast cancer (FAKTION): A randomised, double-blind, placebo-controlled, phase II trial

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Background: The PI3K/AKT signalling pathway is frequently altered in patients with estrogen receptor positive breast cancer (ER+BC) and has been implicated in endocrine therapy resistance. Capivasertib is a highly-selective, oral, small molecule AKT inhibitor. The FAKTION trial investigated addition of capivasertib to fulvestrant for postmenopausal women with ER+, HER2 negative BC after relapse or disease progression on an aromatase inhibitor.

Aims/Objectives: The key objectives of the FAKTION study were to determine:

- the dose of capivasertib to be used in combination with fulvestrant 500mg;
- whether capivasertib enhances the efficacy of fulvestrant in patients with AI resistant ER+ve metastatic breast cancer;
- whether capivasertib is safe, tolerable, and feasible to deliver when combined with fulvestrant;
- the relative efficacy of capivasertib in women with PI3K/AKT/PTEN pathway activated vs non-activated tumours.

Methods: FAKTION is an investigator-led, double-blind, placebo-controlled, randomised phase II trial. Patients were randomised 1:1 to fulvestrant 500mg with either capivasertib 400mg bd or placebo (4 days on/3 days off starting C1D15). Minimisation factors were PIK3CA mutation and PTEN expression status, measurable/non-measurable disease, and primary/secondary endocrine resistance. The
primary endpoint was progression-free survival (PFS) with 90% power to detect a hazard ratio of 0.65 at a one-sided 20% significance level. Secondary endpoints included overall survival (OS), objective response and clinical benefit rates, safety and the effect of PI3K/AKT pathway activation on PFS.

**Results:** Between Mar 2015 and Mar 2018, 140 pts were randomised to fulvestrant + capivasertib (n = 69) or placebo (n = 71). After 112 events, median PFS was 10.3 months (m) for capivasertib compared to 4.8m for placebo (Hazard Ratio (HR): 0.57; 95% CI: 0.39 to 0.84; two-sided p=0.0035). With 37% data maturity, median OS was 26.0m for capivasertib and 20.0m for placebo (HR: 0.59; 95% CI: 0.34 to 1.05; two-sided p = 0.071). Capivasertib dose reduction was required in 37% of patients but only 12% discontinued due to toxicity. Full toxicity data and subgroup analyses including benefit by PI3K/AKT pathway alteration will be presented.

**Conclusions:** The trial met its primary endpoint. Addition of capivasertib to fulvestrant for patients with endocrine resistant advanced breast cancer resulted in significantly longer PFS and a strong trend to improvement in OS. Further development of capivasertib in this setting is indicated.

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Results from plasmaMATCH: A multiple parallel cohort, multi-centre clinical trial of circulating tumour DNA testing to direct targeted therapies in patients with advanced breast cancer

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Introduction: Circulating tumour DNA (ctDNA) testing may provide a more current assessment of the genetic profile of advanced breast cancer (ABC) than analysis of the primary tumour, with repeat advanced disease biopsy conducted infrequently in routine clinical practice.

Aims/objectives: plasmaMATCH was designed to assess the clinical utility of ctDNA testing to select patients for targeted therapies.

Methods: plasmaMATCH was an open-label, multi-centre, multi-cohort platform trial, consisting of ctDNA testing in ~1000 patients with ABC, with four parallel treatment cohorts with therapies matched to mutations identified in ctDNA (A:ESR1 mutation, extended-dose fulvestrant 500mg every 2weeks; B:HER2 mutation, neratinib+/fulvestrant (standard dosing); C:AKT1 in ER-positive
BC, capivasertib+fulvestrant (standard dosing); D:AKT1 in ER-negative BC or PTEN inactivating mutation, capivasertib). A fifth cohort (E) recruited patients with triple negative BC with no actionable mutation to receive olaparib+AZD6738, and will be reported separately. Each cohort had a phase II single-arm design.

ctDNA testing was conducted using digital droplet PCR (ddPCR) prospectively in all patients, and error-corrected sequencing with Guardant360 prospectively from part-way through recruitment and retrospectively for the remaining patients. Tumour sequencing from an advanced disease biopsy was conducted retrospectively, not influencing cohort entry. The primary endpoint for Cohorts A–D is confirmed objective response rate by RECISTv1.1. Secondary endpoints include clinical benefit rate, progression-free survival, safety and frequency of mutations identified in ctDNA screening.

**Results:** Entry into ctDNA testing for Cohorts A–D closed on 26/Apr/2019 and 1044 patients had been registered. ctDNA screening results were received for 1033 patients, with 142 patients entered into Cohorts A–D (A:84,B:21,C:18,D:19). ctDNA screening component and Cohorts A–D results will be shown, including primary and secondary endpoint results, agreement between ddPCR, error-corrected sequencing and agreement between ctDNA and most recently available metastatic tissue.

**Conclusions:** Results and conclusions, which will initially be presented at San Antonio Breast Cancer Symposium, Dec/2019, will be discussed.
Whole-genome-sequencing of triple negative breast cancers in a standard population-based clinical setting

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Background: Whole genome sequencing (WGS) brings additional insights to cancer genome interpretation. WGS has revealed mutational signatures, patterns of mutagenesis that arise as cells evolve towards malignancy. Mutational-signature-based algorithms such as HRDetect have been developed, revealing many homologous-recombination-repair deficient (HRD) cancers that would otherwise go undetected.

Methods: To gauge general potential clinical prognostic value of WGS and specifically HRDetect, we sequenced 254 triple negative breast cancers (TNBC) that had associated treatment and outcome data collected between 2010-2015 via the population-based SCAN-B study (ClinicalTrials.gov ID NCT02306096).

Results: 59% of tumours are predicted to have HRD (HRDetect-high). 67% of HRDetect-high cases are explained by germline/somatic mutations of BRCA1/BRCA2, promoter hypermethylation of BRCA1, RAD51C hypermethylation or biallelic loss of PALB2. HRDetect provides independent prognostic information, with HRDetect-high classification associated with better outcome on adjuvant chemotherapy for invasive disease-free survival (Hazard Ratio, HR=0.42, 95% confidence interval, CI=0.2-0.87), and distant relapse-free interval (HR=0.31, CI=0.13-0.76), regardless of how BRCA1/BRCA2 are abrogated or whether a genetic/epigenetic cause was identified. HRDetect also highlights an intermediate-score category with poorest outcome, with potentially targetable...
biological abnormalities (e.g. replication stress). WGS uncovers ~2% of TNBCs with mismatch-repair deficiency – another targetable DNA repair defect, not typically looked for in breast cancer.

**Conclusions:** To our knowledge, this is the first, large-scale application of WGS and mutational signatures to a prospective, well-characterized population-derived cohort of TNBC collected through routine clinical diagnostic settings. Added-value is clear: potential prognostic capabilities, improved discrimination of HRD tumours from those with alternative pathophysiological abnormalities, incidental detection of targetable abnormalities that would otherwise escape detection and improved discernment of TNBC tumours that are poor responders to standard-of-care. This study advocates for WGS in TNBCs, in the first instance to better inform stratification into clinical trials and ultimately, to improve clinical decision-making in this area of unmet clinical need.
A 3D-printed electrochemical sensor for measuring reactive oxygen/nitrogen species production from breast cancer cells and ex vivo-cultured tumour tissue

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Introduction: Reactive oxygen/nitrogen species (ROS/RNS), frequently elevated in cancer, have pro- and anti-tumourigenic effects. It is unclear how ROS/RNS levels change over time in primary and metastatic tumours and how this impacts treatment efficacy. Limitations in current ROS/RNS detection methods prevent evaluation of multiple species simultaneously over prolonged time frames and elucidation of their pathological roles.

Aims/Objectives: To design an electrochemical sensor for the detection of ROS/RNS, from ex vivo-cultured breast cancer tissue.

Methods: In vitro electrochemical sensing of multiple ROS/RNS (e.g. $\text{H}_2\text{O}_2$ and Nitric Oxide) was performed to characterise the sensitivity and selectivity of the sensor. 4T1 and 66cl4 murine breast cancer cell lines and ex vivo-cultured primary tumours generated following their injection into BALB/c mice were used for biological measurements. Baseline ROS/RNS was measured by sensing and compared to fluorescent imaging using ROS-sensitive dye, dichlorofluorescein (DCF). Chemotherapeutics (paclitaxel, doxorubicin and vinblastine) were used to modulate ROS/RNS levels, with sensing monitoring changes. Ex vivo tissue viability was assessed up to 96h using Ki67 immunohistochemical staining.

Results: In vitro measurements showed strong sensitivity and selectivity of the sensor for ROS/RNS detection compared to common non-reactive molecules (e.g. lactate). ROS/RNS signals were detected in both cell lines and the sensor produced stable measurements continuously over 24h. Ki67 staining showed tumour tissue remained viable for 72h with a significant decrease only observed at 96h (two-way ANOVA). DCF imaging confirmed that chemotherapy treatment increased ROS levels (n=3) and changes in the ROS/RNS signal were concurrently detected using the sensor.

Conclusions: A 3D-printed electrochemical sensor has been developed to measure multiple ROS/RNS from biological material over extended time frames. Translating this technology for use with human tissue biopsies will allow investigation of how changing ROS/RNS levels impact treatment response, facilitating greater efficacy.