or previously published work. The algorithm has been subsequently further tested on a second cohort[2] to assess the reproducibility of the approach.

References:

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O-23 IMPRINTED GENE METHYLATION IN BLOOD AND RISK OF BREAST CANCER

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Loss of imprinting is a common observation in tumours but it is not known whether this results from other pathologies or whether imprinting changes may predispose to disease. We set out to determine whether women newly diagnosed with breast cancer had altered imprinted gene methylation in non-tumour tissue (blood cells) compared to women without the disease.

Over 1000 women – newly diagnosed with breast cancer and disease free controls – were recruited at Aberdeen Breast Clinic. A sample of 92 controls and 92 cases were matched for age, weight, height, BMI and menopausal status. Multiple methylation sites were measured in two imprinted genes (IGF2 and PEG3) in blood DNA. Methylation was determined by pyrosequencing using a Qiagen PyroMark MD system after bisulphite conversion of DNA using Epitect Bisulfite kits (Qiagen, Crawley, UK). Analysis of variance was carried out using STATA 11MP (Stata Corp, College Station, USA).

The mean population methylation level was 47.6 (SD 2.5)% for PEG3 and 50.0 (SD 5.5)% for IGF2. Compared to controls, women diagnosed with breast cancer had significantly different levels of methylation in PEG3 ($p < 0.001$). IGF2 methylation was also different between groups but this was only approaching statistical significance ($p = 0.058$). Methylation was not related to menopausal status. These differences in normal tissue suggest that altered imprinted gene methylation may precede the development of the disease. They also point to early life programming as a possible cause of breast cancer.

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O-24 INVESTIGATION OF BRCA1 AND BRCA2 UNCLASSIFIED VARIANTS USING RNA STUDIES: EXPERIENCES AND INTERESTING CASES FROM THE WEST MIDLANDS REGIONAL GENETICS LABORATORY

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A very successful high throughput screening strategy for the BRCA1 and BRCA2 genes has now been established at the West Midlands Regional Genetics laboratory (WMRGL) since 2006. However having resolved the problems of large backlogs and long reporting times the challenge has now shifted to the prediction of the functional consequence of variants of unknown clinical significance which account for a significant proportion of reported sequence alterations in BRCA1 and BRCA2.

Laboratory methods to identify which of these sequence variants are pathogenic mutations would have utility for counseling and clinical decision making when identified in patients with a family history of breast cancer.

The WMRGL currently undertakes RNA investigations on unclassified sequence variants for several familial cancer disorders for both local and external referrals. To date we have undertaken analysis on 92 cases covering 13 different disorders including non-cancers. RNA investigations specifically for BRCA1 or BRCA2 variants have been performed on 25 samples. An overview of the service will be presented together with results from interesting cases highlighting the challenges faced in interpretation of this data.

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O-25 ER POSITIVE SCREEN DETECTED BREAST CANCERS (SDBC) DO NOT REQUIRE CHEMOTHERAPY

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Meta-analysis of symptomatic breast cancer trials advises chemotherapy to women <70 years of age at high risk of death (i.e. benefit of >1% survival benefit from treatment) but UK screen detected breast cancers (SDBC) (aged 50–65 years) have an overall 97.2% 5 year relative survival compared to 77.6% for symptomatic cancers. Guidelines recommend chemotherapy for all cancers >10 mm in size (i.e. 35% SDBC) whereas in 2001/2 only 23% SDBC in the UK received chemotherapy.

To determine which women benefit from chemotherapy, we analysed 1681 symptomatic and SDBC in Manchester. SDBC had a lower risk of relapse with 5 year cancer mortality for oestrogen receptor (ER) positive cancers being low in the Excellent (0%), Good (GPG) (1%) and Moderate Prognostic Group 1 (MPG1) (4%) but higher in the symptomatic GPG (4.1%) and MPG1 (15.5%) ($p \leqslant 0.001$). The ABS at BASO Audit 2001/2 indicates 5 year survival improvements in the Moderate Prognostic Group 2 (MPG2) and the Poor Prognostic Group (PPG) for SDBC since 1990.

ER positive SDBC had a <0.6% mortality annually whereas the symptomatic cancers had a 5% annual mortality in the first 5 years. ER positive SDBCs represent a group with a low risk of relapse, not requiring chemotherapy. Improvements in survival of SDBC relate to better treatment of ER negative and HER2