1. LAY DESCRIPTION

Breast cancer is the most common cancer affecting women, and in 2014, approximately 15,000 Australian women were diagnosed with breast cancer. Research has demonstrated that breast cancer is not a single disease, but one that comprises many diseases and that the “one-size-fits-all” approach to treatment is not valid. Historically, treatment decisions have been based on clinical and pathological characteristics of the breast cancer, however, newer technologies based on molecular characteristics are now helping to further personalize treatment decisions for each individual patient. These technologies help us to understand the underlying biology of the cancer, which is remarkably different from patient to patient. Moreover this technology enables us to see details of each cancer beyond what can be seen under the microscope. These new molecular technologies have led to the development and commercial availability of several kits such as PAM50 (Prosigna®), EndoPredict® and Oncotype DX® as additional tools for refining and tailoring treatment plans for newly diagnosed breast cancer patients. This Study will examine the impact of EndoPredict® on the treatment recommendations of breast cancer patients seen at the Westmead Breast Cancer Institute (BCI), Victorian Comprehensive Cancer Centre and St Vincent's Hospital.

2. BACKGROUND and RATIONALE

Breast cancer is the most common cancer amongst women, with 1 in 8 women developing this disease over her lifetime. Worldwide, this incidence is increasing, and this may be related to a number of factors including early diagnosis through mammographic screening programs, an aging population and lifestyle factors such as obesity and alcohol use. In recent years, there have been remarkable improvements in survival rates from breast cancer through improvements in local and systemic therapies. Despite significant advances in adjuvant treatments, breast cancer remains the leading cause of female cancer-related deaths worldwide.

2.1 The heterogeneity of Breast Cancer

It is well recognised that breast cancer is not a homogeneous disease, and that a range of sub-types can be defined based on different biological features, which can separate patients into different treatment response and outcome groups. Traditional clinical-pathological variables including tumour stage, grade, hormone receptor status and human epidermal growth factor receptor 2 (HER2) status are currently used to help clinicians determine prognosis and guide treatment selection. In the last 10 years, the advent of high throughput gene expression profiling techniques has advanced the understanding of the molecular heterogeneity of BC, revealing that breast cancers can be classified into subgroups, with distinct clinical outcomes, on the basis of their expression of defined gene sets, often referred to as gene signatures. Four intrinsic subtypes that were initially identified through gene expression profiling, are linked to known disease features: the luminal A and B...
subtypes, commonly being hormone-receptor positive; the HER2-like subtype characterized by the increased expression of several genes of the HER2 amplicon; and, the basal-like subtype which is predominantly estrogen receptor (ER)-negative, progesterone receptor (PgR)-negative and HER2-negative\(^6\). Extensive genomic analysis of breast cancers has disclosed four coherent groups\(^6\), similar to the intrinsic subtypes defined by gene expression profiling. More recently, in the largest series reported so far, including deeper characterization of 1000 primary breast tumours combining DNA and RNA analyses, the METABRIC (Molecular Taxonomy of Breast Cancer) Consortium has identified 10 different molecular subgroups with distinct clinical outcomes\(^7\).

2.2 Limitations of Traditional Histo-pathologic Biomarkers

Historically, classification of breast cancers has been based on histological type, grade and expression of hormone receptors (ER, PgR and HER2). It is now widely accepted that these traditional prognostic factors based on clinical and pathological variables are unable to fully capture the heterogeneity of BC patients. Guidelines like the National Comprehensive Cancer Network (NCCN)\(^8\) used in the US, and the International St Gallen Expert Consensus\(^9\) used in Europe to guide treatment decisions take into account relapse risk based on “average” results. These guidelines cannot accommodate for the substantial variability that can exist between patients with similar stages and grades of disease.

The standard pathological features seem adequate to define clinically useful groups such as triple negative, hormone receptor-negative / HER2-positive and hormone receptor-positive / HER2-positive tumours for which treatment recommendations are seldom controversial. It is among the patients with “luminal” disease, defined by the presence of ER and/or PgR and negative HER2, that uncertainty about optimal treatment most commonly arises, as clinicians seek to avoid over-treatment and under-treatment. Luminal subtype tumours can be separated into two prognostic subgroups: luminal A, in which PR is higher and proliferation is lower, and luminal B, which have low PR and/or higher proliferation markers, and generally poorer outcome compared to luminal A.

2.3 Ki67 as a prognostic marker

Immunohistochemical measurement of proliferative activity using the Ki-67 assay, over the last few years, has attracted much attention as an additional histo-pathological marker. There can be little doubt that Ki-67 scores carry robust prognostic information\(^10\), and that high values predict the benefit of addition of cytotoxic chemotherapy\(^11\). Nonetheless, its use remains controversial because a definition of a single useful cut-point and standardisation of practices across laboratories has proved elusive. Ki-67 displays a continuous distribution\(^12\) and there are several analytic and pre-analytic barriers that prevent standardized assessment\(^13\), and result in poor inter-observer reproducibility. In the 2015 St Gallen Expert Consensus\(^9\), the majority of the Panel was prepared to accept a threshold value of Ki-67 within the range of 20 – 29%, to distinguish ‘luminal B-like’ disease, although about one-fifth of the Panel felt that Ki-67 should not be used at all for this distinction.
2.4 Multi-parameter molecular marker assays

Molecular intrinsic subtypes can be defined by multi-parameter molecular tests such as the EndoPredict®, PAM-50 (Prosigna®)\textsuperscript{14} and OncotypeDx®\textsuperscript{15}, through their ability to interrogate a panel of genes simultaneously. In clinical practice, however, the key question is not in the separation of the molecularly-defined intrinsic subtypes, but the discrimination between patients who will or will not benefit from particular therapies. Several of the multi-parameter molecular tests have been developed for this purpose of providing information, to guide systemic treatment decisions, above and beyond histopathological markers. Moreover, studies such as Prat et al\textsuperscript{16} have demonstrated the additional utility of molecular tests such as PAM-50, to discriminate luminal A and B cases, when compared to the use of cut-offs for PgR and Ki-67, suggesting that such assays may be better prognostic tools for luminal tumours. Similarly in a validation study Filipits et al\textsuperscript{32} demonstrated that the multigene EP risk score (EndoPredict©) was a superior to traditional clinicopathological assessment in the prediction of distant disease relapse.

Several of these molecular platforms are now commercially available, and in many parts of the world including the United States, the use of these assays has been integrated into standard practice.

OncotypeDx® test is a commonly used 21-gene assay (Genomic Health, Redwood City, CA) developed on mRNA extracted from archived tumour samples of 447 patients from 3 studies\textsuperscript{15}. The expression patterns of 21 genes were used to develop an algorithm that yields a recurrence score (RS) classifying patients into three risk groups; high risk of recurrence was assigned if RS >31, intermediate risk if RS 18-30, and low risk if RS <18, and predicts the magnitude of benefit from the addition of chemotherapy to tamoxifen treatment\textsuperscript{17}. Retrospective validation studies have shown that RS was significantly correlated with distant recurrence, relapse-free interval and overall survival, independent of age and tumour size\textsuperscript{18} \textsuperscript{19}. Prospective validation results for OncotypeDx® are not available currently and the results of the TAILORx trial [Trial Assigning IndividuaLized Options for Treatment (Rx)], with over 10, 000 enrolled patients, are expected late 2017\textsuperscript{20}. Nonetheless, since 2004, OncotypeDX® has been widely used in the United States. In Australia, this test is only available to patients who are willing to pay $4000 per test.

For OncotypeDx®, tumour tissue from paraffin block samples must be submitted to a centralised testing facility in the United States for processing.

EndoPredict® (Myriad Genetics Australia Pty Ltd a distributor for Sividon Giagnostic GmbH) is quantitative real-time polymerase chain reaction (RT-qPCR) gene-based profiling test. This test...
was developed using 964 archived ER+/HER2 tumour tissue to identify common gene expression. EndoPredict measures comparing eight disease–relevant genes with three RNA normalization genes and to one DNA reference gene. Out of eight genes, three are associated with tumour cell proliferation and five with hormone receptor function. The result is expressed as an EP, which is a score, on a continuous scale from 0 to 15, that is positively correlated with risk of distant recurrence. The values are dichotomised such that a score of >5 is considered high risk and a score less than or equal to 5 is considered low risk. A further refinement of this score is provided through the incorporation of clinical variables into the algorithm. The inclusion of tumour size and nodal status provides the EPclin score, which provides the estimated risk of distant recurrence at 10 years (Dubsky Ann Oncology 2013).

In a retrospective validation study (GEICAM 9906 trial), 555 patients with node positive, ER+/HER2- breast cancer, who were treated with adjuvant chemotherapy followed by hormone therapy were analysed to evaluate the prognostic performance of EndoPredict. The EP score was significantly correlated with distant metastasis rate in this cohort. The estimated rates of MFS at 10 years were 100% for the EPclin-low risk group (0 events in 74 patients). EndoPredict requires a single section taken from the formalin-fixed-embedded tumour biopsy, and may be performed in a local laboratory. A result is usually available in a few days (including preparation time).

PAM50 (commercially available as PROSIGNA®) measures the gene expression profile of 58 genes (8 of which are housekeeping genes) by using a novel fluorescent barcoding technique on the NanoString nCounter® Analysis System. Prosigna provides the results on intrinsic subtype (luminal-A, luminal-B, HER2-enriched, and basal-like); risk of recurrence (ROR) score, and risk category. The ROR score is on a scale of 0-100, which is correlated with the probability of distant recurrence at 10 years for post-menopausal women with hormone receptor-positive, early stage breast cancer. The risk categories are reported as low, intermediate and high. Prosigna has been validated in 2 randomised trials (ATAC and ABCSG-8) as a predictor of disease recurrence at 10 years in both node positive and node negative women with early ER+ breast cancer treated for 5 years on endocrine therapy alone (tamoxifen or anastrozole).

One of the advantages of the EndoPredict test, over OncotypeDx, is that it is possible to perform the test in local laboratories that are suitably equipped. Performing the test locally enables careful tumour selection and correlation of the findings with other clinico-pathological features by the pathologists. To date, Australian experience with multi-gene platforms such as OncotypeDx®, EndoPredict® and Prosigna® is limited, partly because of
the associated cost of such technologies, limiting access to the hospital clinic, despite multiple studies in the literature demonstrating the advantages over traditional prognostic tools.

2.5 Benefits and Limitations of multi-parameter molecular marker assays

There is little doubt that there is significant potential advantage to these molecular assays, both in the assignment of intrinsic subtypes but also in the numerical scores that these algorithms assign recurrence risk. By defining clear cut-offs, these assays are able to overcome some of the individual variations in pathology assessments, as well as the subjectivity that comes with trying to interpret the clinical and histopathological factors together.

Clinically, these assays have been developed as prognostic markers, and not specifically as predictive markers even though they are often used to make decisions about the efficacy of cytotoxic therapy. This is done on the grounds that they may define a group of patients with a prognosis so good that even if chemotherapy were similarly proportionately effective as in higher risk patients, the absolute benefit may be thought insufficient to justify such treatment. Similarly, a test result indicating a worse prognosis may be used to justify the use of effective but more toxic endocrine therapy such as ovarian function suppression plus aromatase inhibitors or more intensive or prolonged chemotherapy.

Results from prospectively accrued, randomised controlled trials regarding long-term outcomes such as overall survival however, are lacking for all of these assays. Notwithstanding these awaited results, these commercially available products have already quickly penetrated into the clinics.

There have been a number of studies examining the effect of these molecular assays on clinical decision making. The results have been fairly consistent, showing a shift in the treatment decisions in about 30% of patients\textsuperscript{24 25 26} if the results of these molecular assays were made available to oncologists. The OncotypeDx\textsuperscript{©} test has been examined in Australia by de Boer at al. (2013)\textsuperscript{27} in 151 patients with early breast cancer. The OncotypeDX\textsuperscript{©} Recurrence Score information resulted in treatment recommendation change in 24% of node-negative and 26% of node-positive patients. The proportional change from chemo-hormonal therapy to hormonal therapy was significantly greater than from hormonal therapy to chemo-hormonal therapy for node-negative tumours (23% difference in proportions; \(p=0.02\)) and of similar magnitude for patients with node-positive tumours (25% difference in proportions \(p=0.14\)).

A retrospective evaluation of the impact of EndoPredict test on treatment decisions in 167 breast cancer patients has been examined in Germany by Berit Mania Muller at al. (2011)\textsuperscript{28}. In this study information was available for 130 of 167 patients. Of those patients, 62 (47.7\%) had an EPclin low score and the remaining 68 patients (52.3\%) had a high score. One third
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of the results of EndoPredict assay lead to change of planned therapy. This study suggests 25.4% planned chemotherapy recommendations could be revised based on EpClin score.

Similar results have been observed in studies with Prosigna©, although the impact on decision making has not been evaluated locally in Australia.

3. RATIONALE:

There is growing consensus that multigene prognostic tests provide useful complementary information to tumour size and grade in estrogen receptor-positive breast cancers. The tests primarily rely on quantification of ER and proliferation-related genes and combine these into multivariate prediction models. Ki-67 is currently used as an alternative marker of proliferation, due to its much lower cost, albeit with lesser analytical validity than the multigene tests.

EndoPredict® is one of several commercially available assays that measure the relative expression of proliferation genes, alongside other genes. EndoPredict has been recommended to be used to guide decisions on adjuvant systemic chemotherapy for ER+/HER2– and node negative breast cancer patients by American Society of Clinical Oncology Clinical Practice Guidelines (2016) 33. EndoPredict® has the advantage of being able to be tested locally in suitably equipped laboratories, and not having to have tumour tissue shipped overseas with associated delays in receipt of results. Unfortunately, in Australia, the experience with multigene assays has been limited due to significant costs.

The Westmead Breast Cancer Institute (BCI), located at Westmead Hospital, Sydney, offers a comprehensive range of diagnostic and treatment clinics for breast cancer patients, with a multidisciplinary and patient-focused approach. Over 400 new breast cancers are diagnosed and treated through BCI each year. All new and post-operative patients are seen by a team of surgeons, radiologists, pathologists, radiation oncologists, medical oncologists, breast care nurses and health support staff to develop and implement treatment plans for every patient. Similar arrangements exist at VCCC and St Vincent’s Hospital.

Treatment decisions are made in multidisciplinary meetings based on the histopathology results including tumour size, grade, nodal involvement, mitotic rate, lympho-vascular invasion, and biomarker status (ER, PR and HER2). More recently, Ki67 has been added to the pathology reporting as a marker of proliferation, despite the knowledge of its analytical and pre-analytical limitations. Results of molecular assays have not been used in these treatment decision algorithms to date.

This study will examine the impact of a prognostic gene profiling test EndoPredict® – on adjuvant treatment recommendations in early breast cancer patients, who are ER positive (which form the majority of breast cancers), seen at the Westmead BCI, VCCC or St Vincent’s Hospital. It will evaluate the effect of the EP Score and EPclin score using
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EndoPredict®, on treatment recommendations, by comparing treatment recommendations made prior to and following the availability of the EndoPredict® results. It will also examine the proportion of patients whose recommendations were changed from recommending chemotherapy to not recommending chemotherapy or recommending Endocrine therapy only to chemotherapy plus endocrine therapy after the results of the multigene test are made available.

This study will also assess the correlation of Ki-67 with EP score assignment of intrinsic breast cancer subtype and EPclin scores.

4. HYPOTHESIS

We hypothesise that:

The EndoPredict® test will result in a change in adjuvant treatment recommendations.

Very low and very high scores of Ki-67 will strongly correlate with EPclin scores of EndoPredict®

Intermediate values of ki-67 will not be strongly correlated with EPclin scores of EndoPredict®.

5. OBJECTIVES

Aims:
To determine whether EndoPredict® has an impact on adjuvant treatment recommendations for ER positive early breast cancer patients discussed / treated at BCI or other sites.

To determine the performance of Ki-67 values against EPclin scores of EndoPredict®.

Primary Objective:
1. To determine the proportion of patients whose adjuvant treatment recommendation is changed following receipt of EndoPredict® test results.

Secondary Objectives:
1. To determine change in treatment recommendations 1) from CHT to HT or 2) from HT to CHT
2. To determine change in treatment recommendations for 1) node negative patients 2) node positive patients
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3. To determine the factors which may influence the oncologist's decision to accept or refuse the EndoPredict® result (clinical factors such as age, co-morbidity)
4. To determine factors which may influence the patient's decision to accept or refuse the final MDT recommendation
5. To correlate Ki-67 values with Epiclin scores, and determine if suitable cut-offs can be established for the intermediate range where multigene testing may be of greatest benefit
6. To establish discordance rates risk categorisation between IHC and EndoPredict®

6.0 RESEARCH PLAN

This is a prospective study designed to evaluate the impact of the EndoPredict® test to change treatment decisions regarding adjuvant chemotherapy.

Patients will be recruited and consented either at pre or post-surgical visit.

At the pre-surgical assessment, patients (18-80 years, with ECOG status 0-1) will be identified as potential candidates for this trial if their core biopsy show an invasive breast cancer with clinical features of an early breast cancer over 10mm. These patients consent to RNA extraction and EndoPredict® testing of their surgical specimen should the histopathology of the surgical specimen satisfies all eligibility criteria of estrogen receptor-positivity (ER+), HER2-receptor negativity (HER2-) invasive breast cancer, with no more than 3 involved axillary lymph nodes. These patients will also consent for the use of any remaining RNA for future research and also long term follow-up. All standard histopathological factors will be recorded. For Ki-67 determination, low, intermediate and hot-spot assessments will be performed for all heterogeneous tumours using an individual cell counting method. Those tumours with homogenous Ki-67 expression will be assessed in a single area using the individual cell counting methodology previously established in the laboratory. All consenting and eligible patients will be enrolled into the Study. For the enrolled patients, the allocated pathologist will select the appropriate tumour material for testing with the EndoPredict®. Tissue sections will be cut from FFPE tissue blocks and mounted on glass slides for evaluation of ER, PR and Ki67. One section will be stained with hematoxylin and eosin for evaluation of tumour content and position. Guided by this, tumour material will be collected from 5μm sections (in general 1-2 will be sufficient) for extraction of total RNA for EndoPredict evaluation. All enrolled patients will be discussed at a multidisciplinary team (MDT) meeting, no later than 14 days from their surgical date. Adjuvant treatment decisions regarding chemotherapy and hormonal therapy will be documented, based firstly on the standard histopathology results only (including Ki-67) (the Initial MDT Recommendation) and secondly, on the basis of additional information from the EndoPredict® test result (the Final MDT Recommendation). Information regarding the
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specific chemotherapy and endocrine regimen, including name of drug, and intended treatment duration, will be recorded if the information is routinely available. If not, site needs to document if chemotherapy, chemotherapy plus endocrine therapy or radiotherapy is recommended.

Patients will be seen by the treating clinician (medical oncologist/breast surgeon) who will deliver and discuss the final MDT recommendation. Should the treating clinician not accept the final MDT recommendation, and another treatment (Clinical Treatment Decision) was recommended upon meeting the patient, the treatment change and the reason for this change will be documented.

Should the patient not accept the recommendation of the medical oncologist, then the reason for the refusal should be documented (Final Treatment Plan).

This Study will record the treatment that was actually received by the patient (Actual Treatment – type and duration). Patients enrolled in this study will be followed up annually for a total 10 years. Long-term follow-up (greater than 10 years) will record dates of breast cancer recurrence and death only, if feasible.

1. Recruitment Option 1: Pre-surgery

Pre-surgery Assessment

Patients (Age 18-80 with ECOG 0-1).
Clinically: T1-2, N0-1
Core Biopsy result – ER+ invasive breast

Patients consented for possible enrolment into Study

Surgery

Day 0

Day 1 – 5

Pathologist to confirm histopathology of consented patients. Patients to be enrolled if
If ER+ / HER2 - / T1-2 / N0-1/ invasive breast cancer

Mark the tissue at pathology

RNA extraction and EndoPredict® testing at Clinicallabs
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Recruitment Option 2: Post-Surgery

Surgery

Patients to be enrolled /consented
If ER+ / HER2 - / T1-2 / N0-1/ invasive breast cancer

Pathologist will be notified to mark the tissue and send the slides to Australian Clinicallabs

RNA extraction and EndoPredict® testing at Clinicallabs

MDT Discussions: Day 10-14 (One MDT)

1) Initial MDT Recommendation (based on histopathology results only)
2) Final MDT Recommendation (addition of EP and EPclinscores)

OR (Two separate MDT)

1) Initial MDT Recommendation (based on histopathology and IHC results only) – 1st MDT discussion
2) Final MDT Recommendation (addition of EP and EPclinscores) – 2nd MDT discussion

Medical Oncology Consultation:

1) Clinical Treatment Decision – based on Final MDT recommendation and patient factors (such as co-morbidities)
2) Final Treatment Plan: factoring in patient preference
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### Year 1-10

<table>
<thead>
<tr>
<th>Actual Treatment given – type and duration</th>
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<tbody>
<tr>
<td>Annual Clinic Review or “postcard” or “telephone” follow-up (each site will follow local procedures)</td>
</tr>
</tbody>
</table>

### Years 10+

Annual “postcard” or “telephone” follow-up for documentation of recurrence or death

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**7.0 Eligibility Criteria**

**Study Population**

**INCLUSION CRITERIA**

- Females (18 – 80 years)
- ECOG Performance Status 0-1
- Resected estrogen-receptor-positive, HER2-negative, early stage invasive breast cancer (T1-T2N0-1M0)
  - Estrogen receptor status will be evaluated by Immunohistochemistry (IHC) and more than 1% of stained tumor cells of any intensity will be considered positive.
  - HER2 status will be evaluated by in situ hybridisation using current ASCO-CAP guidelines for scoring (HER2:CEP17 ratio >2 will be considered positive).

**EXCLUSION CRITERIA:**

- Tumor size T3-T4
- Non-invasive breast cancer (e.g., Paget's disease, DCIS)
- Greater than 3 involved axillary nodes
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- Tumors that are estrogen-receptor negative or HER2 positive
- Distant metastatic disease
- Unable to give informed consent
- Significant co-morbidities or contraindications for adjuvant chemotherapy
- ECOG Performance Status 2-4

1. SAMPLE SIZE

Investigators will offer enrolment to consecutively seen women and 200 eligible patients will be recruited in the study.

2. STATISTICAL AND ANALYTICAL PLAN

Analysis will be performed using SPSS version 23 by the WSLHD statistician. The pre and post Endopredict recommendations are collated and compared at the conclusion of the study. Chi-square test or Fishers exact test will be used to compare the difference in the recommendations without and with Endopredict test results. Univariate comparisons will be performed using chi-square tests for equal proportion, student t-tests for normally distributed outcomes.

3. ETHICS

The study will be conducted according to the ethical principles of the Declaration of Helsinki in its current version (2004), the Good Clinical Practice guidelines (GCPs), NHMRC National Statement on Ethical Conduct in Research involving Humans (March 2007). In addition, all applicable local laws and regularity requirements relevant to the collection of Human Tissue Acts in the countries involved will be adhered to.

4. RESEARCH TIMELINE

<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
<td>December 2015</td>
<td>Ethics and Research Governance approval</td>
</tr>
<tr>
<td>Nov – Dec 2016</td>
<td>Commence recruitment at Westmead Hospital</td>
</tr>
<tr>
<td>December 017</td>
<td>150 Patients recruited</td>
</tr>
<tr>
<td>July 2018</td>
<td>Statistical analysis and preparation of manuscript</td>
</tr>
</tbody>
</table>
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| Yearly follow up – 10 years |

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3. [www.breastcancer.cochrane.org](http://www.breastcancer.cochrane.org)
4. [www.who.int/cancer](http://www.who.int/cancer)
8. [www.nccn.org](http://www.nccn.org)
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11 Criscitiello C, Disalvatore D, De Laurentiis M et al. High Ki-67 score is indicative of a greater benefit from adjuvant chemotherapy when added to endocrine therapy in Luminal B HER2 negative and node-positive breast cancer. Breast (Edinburgh, Scotland) 23[1], 69-75. 1-2-2014


20 www.genomichealth.com

21 www.nanostring.com

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23 Dubsky PC et al. Tamoxifen and Anastrazole as a Sequencing Strategy: A Randomized Controlled Trial in Postmenopausal Patients with Endocrine-Responsive Early Breast Cancer From the Austrian Breast and Colorectal Cancer Study Group. Journal of Clinical Oncology 2012; 30(7): 722-728


32 Miguel Martin Email author, Jan C Brase, Lourdes Calvo, Kristin Krappmann, Manuel Ruiz-Borrego, Karin Fisch, Alvaro Rodriguez-Lescure Clinical validation of the EndoPredict test in node-positive, chemotherapy-treated ER+/HER2– breast cancer patients: results from the GEICAM 9906 trial

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