GeneTalk

Breast Cancer Workshop

GENOME RESEARCH INNOVATION
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genetic knowledge integration

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WORKSHOP PROGRAM

OPTION A: 9 October 2008, 8h30-16h00
Medical Campus, Health Sciences, HW Snyman North, 3rd Floor, Lecture Room 3-65, University of Pretoria, Pretoria

TIME	TOPIC	SPEAKERS
8h30	**Registration**	
9h00	Introduction: Convergence of research and innovation	Prof Tony Bunn, MRC Innovation Centre
9h15	Hormonal prevention of breast cancer	Prof Greta Dreyer, University of Pretoria
10h00	Update on breast cancer tests available in South Africa	Dr Maritha Kotze, University of Stellenbosch
10h30	FDA approval of the Chromogenic *in situ* hybridization (CISH) test: HER2/neu pharmacogenomics	Linda de Waal, Celtic Molecular Diagnostics
10h45	**Refreshments**	
11h00	Modern breast health management	Prof Justus Apffelstaedt, Univ Stellenbosch
11h45	Clinical application of MammaPrint in South African patients	Dr Rika Pienaar, GVI Oncology, Panorama Hospital
12h30	FDA approval of the 70-gene MammaPrint service: Breast cancer prognostication and use of chemotherapy	Ronald van Klaveren, Agendia, The Netherlands
13h00	**Lunch**	
13h30	Obesity and cancer risk	Prof Nola Dippenaar, University of Pretoria
14h15	Application of nutritional genetics in clinical practice	Dr Hein Badenhorst, Molecular Diagnostic Services
15h00	Breast cancer genetic counselling, ethics and insurance	Julie Malan, Genetic Care Centre, Pretoria

OPTION B: 11 October 2008, 8h30-16h00
Faculty of Health Sciences, Teaching Block, 4th Floor, Lecture Room K4053B, University of Stellenbosch, Tygerberg

TIME	TOPIC	SPEAKERS
8h30	**Registration**	
9h00	Introduction: Bridging the gap between genetics and clinical practice	Prof Johann Schneider, Univ of Stellenbosch
9h15	Breast cancer pathology and prognostic indicators	Dr Karen Brundyn, Univ Stellenbosch
10h00	Update on breast cancer tests available in South Africa	Dr Maritha Kotze, University ofStellenbosch
10h30	FDA approval of the Chromogenic *in situ* hybridization (CISH) test: HER2/neu pharmacogenomics	Linda de Waal, Celtic Molecular Diagnostics
10h45	**Refreshments**	
11h00	Modern breast health management Clinical application of MammaPrint in SA patients	Prof J Apffelstaedt, Univ of Stellenbosch (on behalf of Dr Rika Pienaar)
12h00	FDA approval of the 70-gene MammaPrint service: Breast cancer prognostication and use of chemotherapy	Ronald van Klaveren, Agendia, The Netherlands
12h30	A global view of genomic applications in breast health management	Elaine Warburton, QuantuMDx, UK
13h00	**Lunch**	
13h30	Metabolic syndrome and cancer risk	Dr Dawie van Velden, Univ Stellenbosch
14h15	The folate-vitamin B12 metabolic pathway: a paradigm for nutrient- gene interaction in carcinogenesis	Dr Susan van Rensburg, Univ Stellenbosch
15h00	Breast cancer genetic counselling, ethics and insurance	Frieda Loubser, Genetic Care Centre and NHLS, Univ Cape Town

Accredited with 6 CEU's in level 1, including 2 ethics points

All speakers are acknowledged for their contributions to the information provided below.

Dear Healthcare Professional

Welcome to the 2nd Applied Genetics Workshop, which forms part of the Breast Cancer Awareness Campaign during October 2008.

This GeneTalk event was designed to provide a comprehensive and up-to-date overview of recent advances in the field of breast cancer management and research. A synopsis of the workshop content is provided in the pages to follow, with particular focus on breast cancer in relation to genetic testing performed within a clinical context. For background information on genetics, please download your free copy of the E-book entitled "Genetics in Family Practice" from Gknowmix.com.

With the completion of the Human Genome Project in 2003, a vast amount of information on genetic variability has become available. Despite the extensive data on the role of genetic variation in human disease, its translation into clinical practice has been slow due to the time required to accumulate population data on mutation frequencies, understand the significance of individual gene variants in disease expression, and develop suitable diagnostic tests.

Based on the knowledge that breast cancer is caused by genetic abnormalities (mutations) that are either inherited or acquired, a comprehensive *Breast Cancer GeneScreen* was developed, which is underpinned by the following components:

- Establishment of a network of registered genetic counsellors providing a support base to clinicians caring for cancer patients
- Implementation of a growing number of clinically-useful genetic tests to define cancer subtypes, predict disease recurrence and guide treatment decisions
- Ethically approved research projects including a service component, aimed at the integration of genetics into clinical practice

Gknowmix provides a platform for seamless integration of these components, each contributing to the establishment of a genetic database designed to link service delivery with evaluation of patient outcomes over time. The following steps are involved in pathology supported gene-based intervention, using a multi-disciplinary approach:

1) Document family history and evaluate the patient's current health status
2) Choose appropriate genetic test(s) based on family history and pathology
3) Combine information obtained in 1 and 2 into an informative test report
4) Apply test information for risk reduction intervention
5) Monitor response to treatment as part of compliance management

Your participation is deemed paramount to the success of the Genome Research Innovation initiative launched in collaboration with the Pathology Research Facility, University of Stellenbosch, in April 2008.

Yours sincerely

Dr Maritha J Kotze
Medical Biological Scientist (Genetics)

TABLE OF CONTENTS

BREAST CANCER GENETICS TOPICS COVERED:	Page
INTRODUCTION	5
Genetic Cause	5
High-penetrance BRCA1 & 2 genes	6
Low-penetrance genes	6
Addressing the lifestyle link at the gene-environment level	7
HER2/neu – pharmacogenomics	8
Transcriptional profiling	8
BREAST CANCER GENESCREEN	11
BRCA1 & 2 gene test	11
MammaPrint test	18
LATEST GENETIC TESTS FOR BREAST HEALTH MANAGEMENT	21
Intergenetics's OncoVue® breast risk test	21
DiaGenic's expression array for the early detection of breast cancer	21
The Roche AmpliChip Cytochrome P450 Genotyping test	21

INTRODUCTION

With the advent of the new millennium, breast cancer became – as it already is in most of the world – the most common female cancer in South Africa. Currently, about half of the women diagnosed with this dreaded disease, will die of it. Several new developments, some of which are available in South Africa, will personalize the treatment. On the diagnostic front, digital mammography improves the diagnosis of early breast cancers that are treatable by surgery alone. For established cancer, in the local therapy, the indications for breast conserving therapy are increasing so that about 60 – 70 % of women will retain their breast without compromising cancer control; oncoplastic tumour excisions improve the cosmetic outcome. For the remainder, skin-sparing mastectomy with immediate reconstruction is the treatment of choice, leaving the women with a sensate reconstruction of normal breast skin texture. Microvascular free tissue transfer has greatly improved radiotherapy tolerance of the reconstructed breast, obviating the need to delay reconstruction after cancer therapy. Regional therapy has radically changed: Where previously axillary dissection led to permanent discomfort in the arm, most women now have a sentinel node biopsy only.

Investigators now have the ability to identify the gene-expression fingerprint of an individual's tumour. Gene-expression profiling has shown to distinguish between patients at low and high risk for developing distant metastases and identify those who are likely to benefit from adjuvant therapy. The greatest challenge has now become the application of genomics to its use in clinical practice. Coordinated efforts among oncologists, surgeons, pathologists and geneticists are essential in the quest to incorporate new developments in breast cancer genetics into clinical practice.

Genetic Cause

Breast cancer kills approximately 400 000 women worldwide each year, and 800 000 more cases are diagnosed annually. In South Africa, more than 4000 women are diagnosed with breast cancer every year.

An understanding of disease aetiology represents the basis for cancer prevention and treatment. All breast cancers are caused by genetic abnormalities (mutations), which are either inherited or acquired:

- An inherited genetic abnormality can be passed on from a parent to a child (male or female), who has a 50% chance of inheriting the faulty gene (and a 50% chance of inheriting the normal copy of the gene).

- An acquired (or non-hereditary) genetic abnormality is caused by an error during gene reproduction or from interaction with environmental factors such as hormonal influences, toxic exposure or an inappropriate diet.

The process of tumourigenesis involves three distinct steps: initiation, promotion and progression. Initiation is an irreversible short-term event caused by DNA damage leading to mutagenesis. Cancer promotion is a reversible long-term process involving epigenetic mechanisms that result in the expansion of damaged cells to form an actively proliferating multi-cellular premalignant tumour cell population. Progression is considered an irreversible process caused by genetic instability that leads to mutagenic and epigenetic changes, which are related to the production of new clones of tumour cells with increased proliferation capacity, invasiveness, and metastatic potential.

Acquired genetic abnormalities account for more than 80% of breast cancers. Mutations in the BRCA1 and BRCA2 genes are the best-known cause of inherited breast cancer.

Prof Greta Dreyer provides an overview of breast health, with a special focus on hormonal prevention of breast cancer.

High-penetrance BRCA1 & 2 genes

Genetic testing for the major breast cancer genes, BRCA1 and BRCA2, has become standard practice in families with a strong family history of breast/ovarian cancer. In their normal form, the BRCA1 and-2 genes prevent breast cancer by producing a protein that control cell growth. When someone inherits a BRCA1 or -2 mutation from his or her mother or father the cell will still function normally if the normal gene copy inherited from the other parent is working properly. However, when the normal BRCA gene breaks down, for whatever reason, both copies of the gene are now abnormal and it can no longer control cell growth to prevent cancer. When breast cells multiply at a rate much higher than normal, some can invade healthy tissue and cause invasive breast cancer. This form of cancer differs from non-invasive cancer where cells also grow uncontrolled, but have not started to invade the normal surrounding healthy tissue.

The high-penetrance BRCA1 and BRCA2 genes explain less than 5% of the total breast cancer incidence and approximately 20% of the familial risk. A large proportion of familial breast cancer is caused by the cumulative effect of multiple inherited abnormalities that interact with each other and the environment to increase cancer risk. The influence of other cancer-related genes may also explain why some patients with a BRCA1 or BRCA2 mutation develop breast, ovarian or other forms of cancer at a relatively young age, while other family members with the same mutation remains healthy throughout life.

Approximately 5% of patients with familial breast cancer but without mutations in the BRCA1 and BRCA2 genes have a mutation in the CHEK2 gene (low-penetrance mutations), which has also been associated with male breast cancer. P53 mutations account for approximately 1% of familial breast cancer and radiotherapy is relatively contra-indicated in Li-Fraumeni syndrome due to increased risk of radiation induced malignancies. Genetic counselling is important to determine the appropriateness of genetic testing in patients and their at-risk family members.

Registered genetic counsellors, Julie Malan and Frieda Louser, discuss the limitations and benefits of BRCA mutation screening with relevance to counselling, ethics and insurance issues.

Low-penetrance breast cancer genes

The recent identification of six new breast cancer susceptibility genes found to be relatively common in the general population, has brought us a step closer to a polygenic approach to breast cancer prevention (Pharoah et al. 2008). Some of these risk alleles also increase cancer risk in BRCA1/2 mutation carriers (Antoniou et al. 2008). Differences in the modifying effects of minor risk alleles in BRCA1 and BRCA2 mutation carriers confirmed the distinct nature of these two types of breast carcinomas. Analysis of both high (BRCA1/2) and low-penetrance mutations in a single test therefore has great potential to identify high-risk individuals for intensified population-based preventive programs, such as screening mammography.

Oestrogen exposure is one of the most important risk factors for breast cancer and its metabolites can attack DNA and cause double-strand breaks. Of particular relevance in this context are the catechol O-methyl transferase (COMT) gene involved in catechol oestrogen detoxification, the manganese superoxide dismutase (MnSOD) gene involved in protection against reactive oxidative species-mediated oxidation and the glutathione S-transferase (GST) M1 and T1 genes. Functional polymorphisms in these genes would not increase breast cancer risk on their own, but in patients with prolonged oestrogen exposure (e.g.

obesity, use of hormone replacement therapy), the risk for breast cancer may be significantly increased (Mitrunen et al. 2002; Cheng et al. 2005; Kocabas et al. 2005). Normal folate status furthermore appears to be of particular importance in this context, because an increasing number of COMT low-activity alleles are significantly associated with increased breast cancer risk in women with below median levels of folate (Goodman et al 2001).

Folate metabolism plays an important role in DNA methylation and cancer risk. Adequate intake of folate and other B-vitamins is of particular importance in patients with reduced activity of the enzyme methylenetetrahydrofolate reductase (MTHFR) due to genetic alterations. Two recent studies have shown that the relatively common MTHFR 677C>T mutation increase the risk of breast cancer in BRCA1 mutation carriers, and possibly also in patients with a genetic predisposition for ovarian cancer (Jakubowska et al. 2007; Pepe et al. 2007). The impaired alleles of the vitamin-dependent MTHFR enzyme can be restored to normal functionality by elevating intracellular folate levels (Marini et al. 2008).

The relation between folate and carcinogenesis is complex. Whereas a low folate status may enhance this process, and supplementation shown to be an effective chemopreventive agent in animal models if given prior to the establishment of early lesions, tumour growth may be enhanced by folate once a preneoplastic lesion is present. The role of folate in tumour growth is also exemplified by the use of folate antagonists (e.g. methotrexate, 5-fluorouracil) in cancer treatment, which target folate metabolism. Functional polymorphisms in genes encoding key enzymes involved in folate metabolism can predict treatment response to these chemotherapeutics. Przekop et al. (2007) describe a case of severe toxicity with a single dose of methotrexate (12.5 mg) in the presence of two copies of mutation 677C>T in the MTHFR gene. It was noted that routine pretreatment MTHFR gene testing could have prevented the adverse drug response in the patient, as either a reduced dose or alternative agent would have been indicated.

Dr Susan van Rensburg discusses the role of the folate-vitamin B12-metabolic pathway in cancer development and progression. Dr Maritha Kotze gives an overview of genetic testing in the context of service delivery and ongoing research activities.

Addressing the lifestyle link at the gene-environment level

It has been estimated that the combined effect of multiple low-penetrance cancer-related genes triggered by environmental risk factors may underlie approximately 10% of familial breast cancer. Upper body obesity and the related metabolic disorder have been identified as significant risk factors for breast cancer. The biochemical mechanisms include extraglandular oestrogen production, increased insulin biosynthesis and an increased production of leptin and decreased production of adiponectin by adipose tissue. Leptin stimulates, and adiponectin inhibits, tumour cell proliferation and the microvessel angionesis, which is essential for breast cancer development and progression (Vona-Davis et al 2006).

Based on the link between breast cancer and the metabolic syndrome, health strategies similar to those for prevention of heart disease are appropriate in some patients and/or their at-risk family members. For example, cancer patients with the Factor V Leiden mutation underlying inherited thrombophilia may have a significantly increased risk of venous thrombosis when overweight or during surgery, with administration of chemotherapy, tamoxifen or hormone replacement therapy. Genetic testing to promote well-being through incorporation of the emerging sciences of nutrigenetics (gene-diet interaction) and pharmacogenetics (gene-drug interaction) has been used by healthcare professionals with great success. This service is offered as part of wellness programs to reduce the risk of chronic disease, of which sporadic cancer forms a major component. This approach provides patients with a practical way to deal with risk factors on a daily basis. Emphasis is placed on the fact that the information provided is interpreted in the context of the family

history, personal medical history, biochemistry, anthropometry, dietary analysis, lifestyle risk factors, medication and supplementation usage. Pathology testing is done where appropriate to determine gene expression, if any, and to monitor response to treatment. Pre- and post-test counselling and follow-up by the referring healthcare provider forms the most important part of the process and largely determines health outcomes. The investigation of gene-environment interactions is not only useful, but also essential to gain a full understanding of the impact of genetic variation in health and disease.

Prof Nola Dippenaar provides an overview of the link between obesity and breast cancer. Dr Dawie van Velden takes this discussion a step further in relation to the metabolic syndrome and relevance of cardiovascular disease risk management. Dr Hein Badenhorst shares his clinical experience of using nutritional genetics to guide lifestyle changes in at-risk individuals.

HER2/neu - Pharmacogenomics

Over recent years, a number of commercialised prognostic and predictive tests have entered the area of breast cancer diagnostics. These new molecular tools apply methods that range from familiar immunohistochemistry (IHC), chromogenic (CISH) and fluorescence (FISH) in situ hybridization (CISH), to relatively unfamiliar quantitative real-time polymerase chain reaction (qRT-PCR) and genomic microarray technologies.

Response to therapy may be genetically determined and genetic testing may provide important information that would help physicians decide which strategy is most appropriate for each individual patient. An important example is the assessment of HER2/neu gene amplification. Patients with overexpression of this gene have a poor prognosis and will benefit from treatment with Herceptin (trastuzumab) that specifically targets the HER2 protein. Adjuvant treatment reduces the risk of recurrence and mortality by one half and one third, respectively, in patients with early-stage breast cancer. HER2 is amplified in approximately 18-20% of breast cancers and testing is routinely performed in patients with a new diagnosis of invasive breast cancer. Immunohistochemistry (IHC) is used as the primary test, with a score of 0 or 1+ interpreted as HER2-negative, a score of 3+ as positive and a score of 2+ interpreted as equivocal (or inconclusive) and automatically sent for genetic testing (Wolff et al. 2007).

Dr Karen Brundyn provides a comprehensive overview of breast cancer pathology and the use of HER2/neu testing as part of routine clinical practice. Linda de Waal discusses the technical aspects of HER2 gene amplification.

Transcriptional profiling

This clinical heterogeneity of breast cancer is driven largely by abnormal gene expression within tumours. The current standard for prognostic stratification includes Adjuvant! Online, the Nottingham Prognostic Index, and the American Joint Committee on Cancer staging system, which form the basis of treatment guidelines issued by the National Institutes of Health (NIH) Consensus Statement on Adjuvant Therapy in Breast Cancer and the St. Gallen Consensus Statement. These tools integrate clinicopathologic factors into multivariate prediction models, that allow clinicians to estimate the relative risks for recurrence and mortality and estimate the potential benefits of chemotherapy for groups of patients with given disease characteristics. Nevertheless, they do not address the fundamental question oncologists and patients struggle with: Who as an individual (rather than as a group) will benefit from adjuvant therapy? Many different gene profiling tests for individualising breast cancer therapy have recently entered the market (Ross et al. 2008).

Agendia's 70-gene prognostic MammaPrint test, the first fully commercialised microarray-based assay for breast cancer, is now also available in South Africa. It improves discrimination between good and poor prognoses by several orders of magnitude compared with conventional prognostic factors such as lymph node involvement, size and grade of the tumour. Microarray analysis is used to predict whether a patient's breast cancer will spread to other parts of a patient's body. A low risk classification implies that the patient has a 95% chance of being metastasis-free within the following 5 years (90% within the following 10 years). Patients classified as "high risk" has a 78% chance of being metastasis-free within the following 5 years (71% within the following 10 years) (Van de Vijver et al. 2002; Van 't Veer et al. 2002; Buyse et al. 2006). Local experience indicates that about a third of all women will be saved chemotherapy.

Ronald van Klaveren gives an overview of the FDA-approved MammaPrint test and its use as a prognostic marker. The surgeon-oncologist team with most experience of using the MammaPrint test in South Africa, Prof Justus Apffelstaedt and Dr Rika Pienaar, discuss this new technology in the context of breast health management.

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BREAST CANCER GENECREEN: BRCA1 & 2 GENE TEST

What is it?
A DNA test that includes the analysis of mutations in the BRCA1 and BRCA2 genes using a multi-step process:

Mutation-specific: To screen at-risk family members for a known mutation previously identified in the index patient diagnosed with breast/ovarian cancer.

Population-specific: To screen for a limited number of mutations occurring at an increased frequency in certain ethnic groups (e.g. Ashkenazi Jews, Afrikaner Caucasians).

Full gene screen: To identify the cancer-causing mutation in high-risk patients who may have tested negative during the initial screen for family- or population-specific mutations.

First-degree relatives of affected patients have a 50% chance of inheriting the faulty gene. It is important to remember that despite the increased risk, not every person with an inherited BRCA1 or BRCA2 abnormality will develop cancer. Women without an inherited breast cancer gene abnormality (general population risk) have an approximately 10% risk of developing breast cancer over a 90-year life span, and a 1.8% risk of ovarian cancer.

The individual risk for developing breast and ovarian cancer depends on the gene implicated, the particular mutation and the family history but typically ranges between 45-86% lifetime risk for breast cancer and 10 – 48% risk for ovarian cancer. In men with a BRCA mutation the lifetime risk is approximately 6%, which is 80 times greater than in men without the familial risk.

The risks associated with BRCA1 and -2 mutations are affected by:

- The effect of the specific BRCA1/2 mutation on the protein's ability to suppress cancer
- How well other genes work in combination with BRCA1/2 to protect against cancer
- How certain genes react in the presence of environmental exposures such as lifestyle changes or medication

BRCA1/2 mutation screening is typically performed using a blood sample. However, when the person considered for genetic testing has had a bone marrow transplant using bone marrow donated from another person, the testing should be done on a blood sample stored before the transplant or from a biopsy or tissue scraping.

When do I recommend it?
A family history suggesting an inherited pattern and early onset breast cancer and/or ovarian cancer and ancestry are the most important criteria used when BRCA1 and BRCA2 mutation screening is considered. The following can be used as general guidelines for genetic testing, preferably following pre-test genetic counselling by a registered genetic counsellor to explain both the benefits and limitations of the test:

- **Familial risk**:
    - 4 close relatives diagnosed younger than 60 years;
    - 3 close relatives diagnosed younger than 50 years;

  - 2 close relatives diagnosed younger than 60 years and ovarian cancer in the family;
  - male breast cancer and any family history of breast cancer

- **Ethnic risk**: Founder populations such as patients of Ashkenazi Jewish or Afrikaner ancestry with a family history of breast cancer.
- **Personal risk**: Bilateral breast cancer at a relatively young age; ovarian cancer diagnosed younger than 30 years.

Women who are very anxious about their breast cancer risk or family history could benefit from a genetic counselling consultation, where these anxieties can be addressed and an individual risk assessment can be done. The importance of genetic counselling in the context of BRCA testing cannot be overemphasized. The implications of a potential positive/negative test result needs to be carefully considered in relation to treatment options and the impact on other family members. During the genetic counselling session the patient or his/her close relatives are given the opportunity to decide for or against testing, based on the particular situation and a process of risk assessment following the construction of a detailed family pedigree. Genetic counselling by a healthcare practitioner trained in this specialized field will therefore not always result in genetic testing. Post-test genetic counselling should also be encouraged by clinicians. Testing is discouraged in children under the age of 18 years, because no safe methods currently exist to help prevent breast cancer in young girls. Furthermore, everybody should be given the opportunity to decide for themselves whether they want information about their lifetime cancer risks.

What are its benefits?
Genetic testing in a familial context is most beneficial when it starts with a family member diagnosed with early-onset breast or ovarian cancer. Once the cancer-causing mutation has been identified in the index case (mutation search), at-risk family members could then be screened reliably for the same mutation to exclude or confirm its presence (presymptomatic testing).

Even though a positive BRCA1/2 test result does not mean that the person will definitely get breast cancer, many women with an abnormal gene assume they will. Detection of a BRCA1/2 mutation may trigger anxiety, anger or depression. To prevent such responses and to benefit from genetic testing, pre- and post-test genetic counselling is strongly recommended.

An abnormal test result in a healthy individual justifies intensified screening intervals to detect any signs of cancer development at an early stage, when the cancer is most treatable and curable. Some women may consider risk-reduction surgery before cancer cells have an opportunity to form, but although the risk is significantly reduced it is not entirely eliminated. Testing may also be beneficial in patients already diagnosed with cancer, since detection of a BRCA mutation would improve the accuracy of risk assessment on which to base future treatment decisions and surveillance intervals.
Finally, knowledge about a genetic abnormality may influence treatment decisions (e.g. tamoxifen) and implementation of lifestyle changes. In a landmark study performed by King et al. (2003) in Ashkenazi Jewish women, it was shown that a healthy lifestyle could protect against development of cancer in BRCA1 and BRCA2 mutation carriers. Approximately 50% of breast cancer patients did not have any other family history of breast/ovarian cancer and the onset of breast cancer was significantly delayed in the absence of obesity and with high physical activity.

A normal test result without knowledge of the family-specific causative mutation could be difficult to interpret as it could either mean (1) that the person has a normal gene because she/he did not inherit the genetic abnormality or (2) that the result is uninformative because the family has a genetic abnormality that cannot yet be identified. Even if the causative mutation has been excluded in an at-risk family member, routine screening for breast cancer is still important.
Contrary to previous belief that exclusion of a causative BRCA1 or BRCA2 mutation reduces the risk to that of the general population (from ~85% to10%), recent studies have shown that close relatives without the cancer-causing BRCA mutation still have a greater chance (~3-fold increased risk by age 50 years) to develop cancer compared with the general population. These findings highlight the role of modifier genes (e.g. those involved in oestrogen or folate metabolism) and shared environmental risk factors (e.g. obesity, inactivity), in masking or exacerbating the effect of single genes. It may also provide a scientific basis for application of non-diagnostic DNA tests in the context of breast cancer, with the aim to exclude potential gene-environment mismatches relating to the emerging sciences of pharmacogenetics and nutrigenetics. The combined effect of genetic and lifestyle risk factors determine breast cancer pathology, which is interconnected with response to medical and nutrition intervention.

Scientific rationale
The potential for accurate risk assessment is the key motivator for undergoing BRCA1/2 mutation screening. Several studies have shown that uncertainty regarding breast cancer risk is a major cause of stress and reduced quality of life. Different risk implications have been reported for BRCA1 and BRCA2:

Cancer risk associated with BRCA1: Female mutation carriers have a 44-78% risk of breast cancer and an 18-54% risk of ovarian cancer by age 70.

Cancer risk associated with BRCA2: Female mutation carriers have a 31-56% risk of breast cancer and a 2.4-19% risk of ovarian cancer by age 70.

In families with multiple affected members the upper end of these risk estimates is likely to be appropriate due to co-inheritance of possible modifier genes and shared environmental exposure. BRCA1 and BRCA2 mutation carriers have a significantly increased risk of bilateral breast cancer and are also at increased risk of pancreatic, prostate, endometrial, and cervical cancer. BRCA2 mutation carriers also seem to have an increased risk of gall bladder/bile duct cancer and malignant melanoma. Male mutation carriers have a 6% risk of breast cancer by age 70, with a cumulative risk of nearly 20% for prostate cancer by age 80 years.

DNA sequencing of the entire coding regions of the BRCA1 and BRCA2 genes is the ultimate method for the detection of deleterious mutations in these complex genes. However, to improve cost-effectiveness, a diagnostic pre-screen focusing on detection of recurrent or founder mutations is routinely used in genetically homogeneous populations prior to more extensive analysis in mutation-negative patients. Founder mutations have been described in various populations, including Ashkenazi Jewish and Afrikaner Caucasian populations of South Africa.

Approximately 1 in 40 individuals with Ashkenazi Jewish ancestry – with our without breast cancer – has a defect in the BRCA1 or BRCA2 gene. In a study published in the New England Journal of Medicine in 1997, 2,3% of the more than 5300 men and women tested had one of the three genetic abnormalities known to be associated with a high risk of breast cancer in the Jewish Ashkenazi population. In a more recent study published in 2007 in the Journal of the American Medical Association on data obtained in 3000 women from different

ethnic groups, analysis of the BRCA1 gene revealed abnormalities in the following proportion of breast cancer patients:

- 8.3% of Ashkenazi Jewish women
- 3.5% of Hispatic women
- 16.7% of Africa American women younger than 35 years
- 2.2% of white women who were not Ashkenazi Jews

BRCA1 and BRCA2 mutations are the underlying cause of breast cancer in approximately 52% and 32%, respectively, in families with multiple affected individuals. In patients without a strong family history of cancer, mutations in these genes cause only 10% to 20% of breast cancer. The risk conferred by BRCA1/2 mutations is furthermore modified by other genetic and environmental factors, and a large proportion of patients with familial breast cancer do not have detectable mutations in any known gene.

What is it?
A DNA test that includes the analysis of one or multiple mutations in the BRCA1 and BRCA2 genes using a multi-step process:

Mutation-specific: To screen at-risk family members for a known mutation previously identified in the index patient diagnosed with breast/ovarian cancer.

Population-specific: To screen for a limited number of 3-7 mutations occurring at an increased frequency in certain ethnic groups (e.g. Ashkenazi Jews, white Afrikaners).

Full gene screen: To identify the cancer-causing mutation in high-risk patients who tested negative during the initial screen for family- or population-specific mutations.
It is important to remember that despite the increased risk, not every person with an inherited BRCA1 or BRCA2 abnormality develops cancer. First-degree relatives of affected patients have a 50% chance of inheriting the faulty gene. Women without an inherited breast cancer gene abnormality have on average an approximately 10% risk of developing breast cancer over a 90-year life span, and 1.8% risk of ovarian cancer. In men with a BRCA mutation the lifetime risk is approximately 6%, which is 80 times greater than in men without the familial risk.

The risks associated with BRCA1 and -2 mutations are affected by:

- The effect of the specific BRCA1/2 mutation on the protein's ability to suppress cancer
- How well other genes work in combination with BRCA1/2 to protect against cancer
- How certain genes react in the presence of environmental exposures such as lifestyle changes or medication

BRCA1/2 mutation screening is typically performed using a blood sample. However, when the person considered for genetic testing has had a bone marrow transplant using bone marrow donated from another person, the testing should be done on a blood sample stored before the transplant or from a biopsy or tissue scraping.

When do I recommend it?
A family history suggesting an inherited pattern and early onset breast cancer are the most important criteria used when BRCA1 and BRCA2 mutation screening is considered. The following can be used as general guidelines for genetic testing, preferably following pre-test

counseling by a registered genetic counsellor to explain both the benefits and limitations of the test:

- **Familial risk**: 4 close relatives diagnosed younger than 60 years; 3 close relatives diagnosed younger than 50 years; 2 close relatives diagnosed younger than 60 years and ovarian cancer in the family; male breast cancer and any family history of breast cancer

- **Ethnic risk**: Founder populations such as patients of Ashkenazi Jewish or Afrikaner ancestry with a family history of breast cancer

- **Personal risk**: Bilateral breast cancer at a relatively young age; ovarian cancer diagnosed younger than 30 years

Women who are very anxious about their breast cancer risk or family history could benefit from a genetic counseling consultation, where these anxieties can be addressed and an individual risk assessment can be done.
The importance of genetic counseling in the context of BRCA testing cannot be overemphasized. The implications of a potential positive/negative test result needs to be carefully considered in relation to treatment options and the impact on other family members. During the counseling session the patient or his/her close relatives are given the opportunity to decide for or against testing, based on the particular situation and a process of risk assessment following the construction of a detailed family pedigree. Genetic counseling by a healthcare practitioner trained in this specialized field will therefore not always result in genetic testing. Post-test genetic counseling should also be encouraged by clinicians.
Testing is discouraged in children under the age of 18 years, because no safe methods currently exist to help prevent breast cancer in young girls. Furthermore, everybody should be given the opportunity to decide for themselves whether they want information about their lifetime cancer risks.

What are its benefits?
Genetic testing in a familial context is most beneficial when it starts with a family member diagnosed with early-onset breast or ovarian cancer. Once the cancer-causing mutation has been identified in the index case, at-risk family members could then be screened reliably for the same mutation to exclude or confirm its presence.
Even though a positive BRCA1/2 test result does not mean that the person will definitely get breast cancer, many women with an abnormal gene assume they will. Detection of a BRCA1/2 mutation may trigger anxiety, anger or depression. To prevent such responses and to benefit from genetic testing, pre- and post-test genetic counseling is strongly recommended.

An abnormal test result in a healthy individual justifies intensified screening intervals to detect any signs of cancer development at an early stage, when the cancer is most treatable and curable. Some women may consider prophylactic surgery before cancer cells have an opportunity to form, but although the risk is significantly reduced it is not entirely eliminated. Testing may also be beneficial in patients already diagnosed with cancer, since detection of a BRCA mutation would improve the accuracy of risk assessment on which to base future treatment decisions and surveillance intervals.
Finally, knowledge about a genetic abnormality may influence treatment decisions (e.g. tamoxifen) and implementation of lifestyle changes. In a landmark study performed by King et al. (2003) in Ashkenazi Jewish women, it was shown that a healthy lifestyle could protect against development of cancer in BRCA1 and BRCA2 mutation carriers. Approximately 50% of breast cancer patients did not have a family history of breast/ovarian cancer and the onset

of breast cancer was significantly delayed in the absence of obesity and with high physical activity.

A normal test result without knowledge of the family-specific causative mutation could be confusing as it could either mean (1) that the person has a normal gene because she/he did not inherit the genetic abnormality or (2) that the result is uninformative because the family has a genetic abnormality that cannot yet be identified. Even if the causative mutation has been excluded in an at-risk family member, routine screening for breast cancer is still important.
Contrary to previous belief that exclusion of a causative BRCA1 or BRCA2 mutation reduces the risk to that of the general population (from ~85-10%), recent studies have shown that close relatives without the cancer-causing BRCA mutation have a greater chance (3-fold increased risk by age 50 years) to develop cancer compared with the general population. These findings highlight the role of modifier genes (e.g. those involved in oestrogen or folate metabolism) and shared environmental risk factors (e.g. obesity, inactivity), in masking or exacerbating the effect of single genes. It may also provide a scientific basis for application of non-diagnostic DNA tests in the context of breast cancer, with the aim to exclude potential gene-environment mismatches relating to the emerging sciences of pharmacogenetics and nutrigenetics. The combined effect of genetic and lifestyle risk factors determine breast cancer pathology, which is interconnected with response to medical and nutrition intervention.

Scientific rationale
The potential for accurate risk assessment is the key motivator for undergoing BRCA1/2 mutation screening. Several studies have shown that uncertainty regarding breast cancer risk is a major cause of stress and reduced quality of life. Different risk implications have been reported for BRCA1 and BRCA2:

Cancer risk associated with BRCA1: Female mutation carriers have a 44-78% risk of breast cancer and an 18-54% risk of ovarian cancer by age 70.

Cancer risk associated with BRCA2: Female mutation carriers have a 31-56% risk of breast cancer and a 2.4-19% risk of ovarian cancer by age 70.
In families with multiple affected members the upper end of these risk estimates is likely to be appropriate due to co-inheritance of possible modifier genes and shared environmental exposure.
BRCA1 and -2 mutation carriers have a significantly increased risk of bilateral breast cancer and are also at increased risk of pancreatic, prostate, endometrial, and cervical cancer. BRCA2 mutation carriers also seem to have an increased risk of gall bladder/bile duct cancer and malignant melanoma. Male mutation carriers have a 6% risk of breast cancer by age 70, with a cumulative risk of nearly 20% for prostate cancer by age 80 years.
DNA sequencing of the entire coding regions of the BRCA1 and BRCA2 genes is the ultimate method for the detection of deleterious mutations in these complex genes. However, to improve cost-effectiveness, a diagnostic pre-screen focusing on detection of recurrent or founder mutations is routinely used in genetically homogeneous populations prior to more extensive analysis in mutation-negative patients. Founder mutations have been described in various populations, including the Ashkenazi Jews and white Afrikaner population of South Africa.
Approximately 1 in 40 Ashkenazi Jews – with our without breast cancer – has a defect in the BRCA1 or BRCA2 gene. In a study published in the New England Journal of Medicine in 1997, 2,3% of the more than 5300 men and women tested had one of the three genetic abnormalities known to be associated with a high risk of breast cancer in the Jewish Ashkenazi population. In a more recent study published in 2007 in the Journal of the American Medical Association on data obtained in 3000 women from different ethnic groups,

analysis of the BRCA1 gene revealed abnormalities in the following proportion of breast cancer patients:

- 8.3% of Ashkenazi Jewish women
- 3.5% of Hispatic women
- 16.7% of Africa American women younger than 35 years
- 2.2% of white women who were not Ashkenazi Jews

BRCA1 and BRCA2 mutations are the underlying cause of breast cancer in approximately 52% and 32%, respectively, in families with multiple affected individuals. In patients without a strong family history of cancer, mutations in these genes cause only 10% to 20% of breast cancer. The risk conferred by BRCA1/2 mutations is furthermore modified by other genetic and environmental factors, and a large proportion of patients with familial breast cancer do not have detectable mutations in any known gene.

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BREAST CANCER GENECREEN: MAMMAPRINT TEST

What is it?

MammaPrint is a 70-gene microarray test, which is used to assess the risk of metastases at an early stage of breast cancer with greater accuracy than is possible using conventional methods. MammaPrint reveals the activity (expression) of 70 specific genes in the tumor sample and compares the resulting gene expression profile to reference expression profiles of 'Low Risk' or 'High Risk' profiles. The risk of tumor recurrence is determined according to the degree of similarity between the tumor's gene expression profile and reference profiles.

The test is typically performed on a tumor biopsy removed during surgery, which is placed in a special solution to preserve the RNA to be used in the laboratory analysis. To prevent destruction of tumor RNA by RNases from the hands, it is important to wear gloves when handling tumor tissue. Undamaged tumor RNA is essential for a successful analysis. To ensure sufficient RNA for the analysis, the sample should be taken from a region clear of necrotic and stromal tissue as this reduces the number of tumor cells in the sample. The best area to perform the biopsy is at the periphery of the tumor; the centre of a tumor is often necrotic, while the edges of the tumor often contain many stromal cells. The tumor biopsy must be taken within one hour of surgery.

Sample collection kits with clear instructions on the procedure used are provided to participating clinicians. It is then shipped overnight to Agendia's ISO 17025 certified laboratory in The Netherlands where the test is performed under an export permit obtained from the South African Department of Health. The sample must arrive at Agendia within 7 days of sampling. In general, results will be available for the physician and pathologist within 10 working days after receiving a tumor biopsy.

When do I recommend it?

To be eligible for a MammaPrint test, a breast cancer patient should fulfill the following criteria:

- Tumor size < 5.0 cm
- Up to 3 positive lymph nodes
- Stage 1 and Stage 2 invasive breast cancer
- ER+ or ER-
- Tamoxifen independent

Local experience of the MammaPrint service in routine clinical practice led to the following quotes from opinion leaders in breast cancer:

"Genomics is now an established and frequently used tool in medical research, and particularly in the oncology field. In breast cancer, genomics has led to a better understanding of the biology and to a molecular reclassification of the disease." – *Dr Rika Pienaar, GVI Oncology, Panorama Hospital, Cape Town, South Africa.*

"With the help of MammaPrint one-in-three patients can be saved from chemotherapy. This is a major relief to patients with good prognosis as chemotherapy is the most dreaded part of breast cancer therapy." – *Prof J Apffelstaedt, Faculty of Health Sciences, University of Stellenbosch, Tygerberg, South Africa.*

What are its benefits?

MammaPrint adds a new quality of data to existing prognostic tools as it gives better insight into the biology of the patient's breast cancer tumor. As the test allows a better distinction to be drawn between high and low-risk patients, it is possible to reduce the number of breast cancer patients who are treated with chemotherapy. This means an improvement in the

quality of life of breast cancer patients and substantial cost saving. It helps clinicians to make the best-informed decisions based on a clear risk assessment for the recurrence of distant metastases in breast cancer patients.
European research has revealed that approximately fifty percent of chemotherapy treatments among breast cancer patients are later discovered to have been unnecessary. MammaPrint is available for all lymph node-negative (and 1-3 node) breast cancer patients and there is no treatment restriction. If there is a low risk of the patient's cancer recurring, adjuvant therapy and the toxicity and other side-effects often associated with such treatment may be avoided. MammaPrint is used for prognostication and can not be used as a stand-alone predictive test in order to determine response to chemotherapy, patient treatment or to predict the outcome of disease.
FDA clearance in February 2007 has acted as a positive catalyst for reimbursement not only in the US, but also in Europe, Oceania, South Africa and Latin America.

Scientific rationale
There has been an extensive effort over the past three decades to develop effective cancer therapies. However, according to recent statistics the overall incidence and mortality of cancer are not decreasing. The high incidence of breast cancer, which kills about 400 000 women worldwide each year, is of special concern in South Africa where more than 4000 women are diagnosed with breast cancer every year. About 40% of them are predicted to die from the disease. Breast cancer is currently curable in about 70% of patients, but only if it is diagnosed at an early stage and treated adequately.

MammaPrint uses advanced molecular technology (microarray analysis) to predict whether a patient's breast cancer will metastasize (spread to other parts of a patient's body). A low risk classification implies that the patient has a 95% chance of being metastasis-free within the following 5 years (90% within the following 10 years). Patients classified as "high risk" has a 78% chance of being metastasis-free within the following 5 years (71% within the following 10 years).

The use of MammaPrint as a prognostic indicator has been validated in three independent studies and is a much more accurate prognostic tool than traditional indicators such as NIH, St. Gallen and Adjuvant! Online, which show considerable discordance. Currently approximately 85% of breast cancer patients, identified with traditional prognostic algorithms as being high risk, receive chemotherapy. MammaPrint identifies only about 60% as high risk. Of the 15% patients with a good prognosis (and not needing chemotherapy) according to traditional prognostic algorithms, metastases developed in 24% of patients. In comparison, metastases only developed in 13% of the 40% good prognosis patients identified with MammaPrint with 96% overall survival rate (Van de Vijver et al. 2002). Prognostication with Mammaprint would therefore, by more accurately defining those who need adjuvant chemotherapy, save approximately 30% of patients with early breast cancer unnecessary chemotherapy.

Age when first detected, type of cancer (ER-positive tumors are the most common), nodal status, hormonal treatment with tamoxifen alone or in combination with polychemotherapy and whether or not the ovaries are removed, are all factors which may play a significant role in cancer recurrence and survival. A MammaPrint validation study performed by the TransBIG group showed that each classical feature such as estrogen receptor (ER) status and tumor size loose their significance when compared with the gene profile. There is 30% discordance in ER reading between laboratories worldwide, hence resulting in contradicting outcomes with similar protocols and wrong conclusions. Analytical laboratory test validation for MammaPrint demonstrated greater than 99.9% agreement.

In February 2007 the U.S. Food and Drug Administration approved MammaPrint for clinical use to determine the likelihood of breast cancer recurring within 10 years after a woman's initial diagnosis. "Clearance of the MammaPrint test marks a step forward in the initiative to bring molecular-based medicine into current practice," said Andrew C. von Eschenbach, M.D., Commissioner of Food and Drugs. "MammaPrint results will provide patients and physicians with more information about the prospects for the outcome of the disease. This information will support treatment decisions.

The costs of unnecessary therapy and dealing with frequent side effects are serious economic considerations. For example, it has been estimated that approximately 60-80% of patients with node-negative breast cancer will be alive 10 years after initial treatment without adjuvant therapy. Even so, up to 58% of patients with node-negative breast cancer may develop recurrent disease and reduction of cancer recurrence in patients has been documented as a result of adjuvant chemotherapy or tamoxifen. In this situation, it becomes crucial to identify patients with node-negative breast cancer at highest risk for recurrence so that they may receive appropriate adjuvant therapy, while patients at lower risk can be spared the toxic effects and unnecessary expenditure can be avoided.

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LATEST GENETIC TESTS FOR BREAST HEALTH MANAGEMENT

Not a day goes by without an announcement being made in the world's press that a scientist has discovered a new gene responsible for a particular disease or its progression. It is challenging for medical practitioners to identify whether the announcement relates to pure research and at a very early stage in development and whether there is a test entering the commercial arena. There are three genetic tests that will shortly be available to clinicians across the globe to support them in the field of breast health management.

Intergenetics's OncoVue® breast risk test

Oncovue® is the first genetic-based, breast cancer risk test that incorporates both individualized genetic-based SNPs and personal history measures to arrive at an estimate of a woman's breast cancer risk. The OncoVue Breast Cancer Risk Test is a result of research focused on understanding the role that multiple single nucleotide polymorphisms (SNPs) along with personal history measures contribute to a women's risk of developing breast cancer at various stages in her life.

DiaGenic's expression array for the early detection of breast cancer

The need to carry out breast cancer diagnosis is present in all stages of the disease, yet the diagnostic methods used vary widely and all have clear limitations. Mammography which is used in mass screening and diagnosis has difficulties in identifying small tumours and is poorly suited to several types of cancer and younger women. It has been shown in the Norwegian mass screening programme that only 16 out of 100 women who have been notified of a suspect mammogram actually had cancer. The gene expression signature method DiaGenic is developing using peripheral blood as sample material instead of tissue biopsies, has the potential to identify cancer earlier and in a far less invasive way. This makes the method particularly suitable for mass screening.

The Roche AmpliChip Cytochrome P450 Genotyping test

This is a new laboratory test system that will help doctors personalize treatment options for their patients. This system uses DNA extracted from a patient's blood to detect certain common genetic mutations that alter the body's ability to break down (metabolize) specific types of drugs. The enzyme produced from the gene that is tested, called cytochrome P4502D6 (CYP450D6), is active in metabolizing many types of drugs including antidepressants, antipsychotics, beta-blockers, and some chemotherapy drugs. Variations in this gene can cause a patient to metabolize these drugs abnormally fast, abnormally slow, or not at all. For example, the same dose that is safe for a patient with one variation might be too high (and therefore toxic) to a patient with a different variation who cannot metabolize the drug. Doctors can use a patient's genetic information to help them determine appropriate drugs and doses to prescribe. It is anticipated that this system can be used to ascertain how well a patient metabolizes Tamoxifen and some chemotherapeutic breast cancer drugs.

Elaine Warburton gives a global view of the latest genomic applications in breast health management, about to enter the commercial market.