Risk assessment, disease prevention and personalised treatments in breast cancer: is clinically qualified integrative approach in the horizon?

Olga Golubnitschaja1,2*, Kristina Yeghiazaryan1,2, Vincenzo Costigliola3, Daniela Trog1,2, Michael Braun2,4,5, Manuel Debald2,4, Walther Kuhn2,4 and Hans H Schild1,2

Abstract

Breast cancer is a multifactorial disease. A spectrum of internal and external factors contributes to the disease promotion such as a genetic predisposition, chronic inflammatory processes, exposure to toxic compounds, abundant stress factors, a shift-worker job, etc. The cumulative effects lead to high incidence of breast cancer in populations worldwide. Breast cancer in the USA is currently registered with the highest incidence rates amongst all cancer related patient cohorts. Currently applied diagnostic approaches are frequently unable to recognise early stages in tumour development that impairs individual outcomes. Early diagnosis has been demonstrated to be highly beneficial for significantly enhanced therapy efficacy and possibly full recovery. Actual paper shows that the elaboration of an integrative diagnostic approach combining several levels of examinations creates a robust platform for the reliable risk assessment, targeted preventive measures and more effective treatments tailored to the person in the overall task of breast cancer management. The levels of examinations are proposed, and innovative technological approaches are described in the paper. The absolute necessity to create individual patient profiles and extended medical records is justified for the utilising by routine medical services. Expert recommendations are provided to promote further developments in the field.

Keywords: Inflammation, Cancer, Metastasis, Biomarker pattern, Predictive diagnosis, Preventive healthcare, Medical services, Medical record, Integrative personalised medicine, Innovative technologies, Genetic testing, Assay, Omics, Imaging, Immune system, Metalloproteinase, Adjuvant therapy, Computer assistance, Mathematical modelling, Tamoxifen, Ethics

Review

Cancer context

With the respect to the statistical data presented by the World Health Organisation [1], cancer is a leading cause of death worldwide, accounting for 7.6 million deaths (around 13% of all deaths) as registered in 2008 and permanently increasing over 13 million as projected for 2030. Economic factors play a role, since about 70% of all cancer deaths in 2008 occurred in low- and middle-income countries. The most fatal types of cancer are listed below in the decreasing order (deaths per year):

- lung (1.37 million deaths)
- stomach (736 000 deaths)
- liver (695 000 deaths)
- colorectal (608 000 deaths)
- breast (458 000 deaths)
- cervical cancer (275 000 deaths).

Breast cancer is the most common cause of cancer-related death among women

Hence in the USA, the highest cancer related incidence rates are currently registered for the breast cancer patient...
cohorts [2] – see Figure 1A. The combating and treating measures such as induced population screening by mammography and application of adjuvant therapies, keep breast cancer mortality mostly unchanged or even persistently declined over last ten years – see Figure 1B. However, the incidence of breast cancer continually increases worldwide during the past three decades. According to the statistical data published by the National Cancer Institute in the USA [3], the estimated new cases and deaths from breast cancer in the United States in 2012 are (in thousand cases)

- New cases: 226,870 (female); 2,190 (male)
- Deaths: 39,510 (female); 410 (male)

Breast Cancer Metastatic Disease (BCMD) is currently incurable: challenges of diagnostics and treatment

**Breast Cancer Metastatic Disease (BCMD)**

Diagnostic approaches routinely applied in medical practice are frequently unable to recognise early stages in breast cancer development that impair the outcome. At the time of diagnosis, a great portion of patients with breast cancer have locally advanced and/or distant metastatic disease. It is estimated that about 6% of breast cancer patients demonstrate a clinical picture of metastatic disease already at the time of diagnosis. Further 20% to 50% patients with primary breast cancer will develop metastatic disease despite the standardised treatments approached [4]. BCMD (stage IV) is the most advanced form of breast cancer. Once breast cancer has turned metastatic, the disease is recognised as the incurable one: the 5-year survival barrier will be reached by only 26% of patients treated for the BCMD.

**Distant metastases**

The lion’s share of about 90% of deaths in the overall breast cancer related mortality is caused by the distant metastases. Breast cancer spreads metastasis predominantly into lymph nodes, bone, lung, skin, brain, and liver [5], wherefrom only lymph nodes are considered as non-

---

**Figure 1**

A. Estimated cancer incidence in USA in 2009; B. Cancer related mortality as registered in USA in 2009; data adapted from [2].
distance metastases. With the poorest prognosis of approximately 80% mortality rate within first 12 months of diagnosis, brain metastases represent a devastating category of BCMD. Brain metastases are prevalent in hormone receptor negative but HER2-overexpressing subgroups and are typical for 30% of all HER2+ BCMD [4]. The particular challenge in treating brain metastases is created by the limited permeability of the blood–brain barrier for chemotherapeutics, the use of which, further, leads to brain inflammatory response with extensive gliosis surrounding the metastases. The treated brain metastases are further provoked for high proliferation but minimal apoptosis demonstrating unsatisfactory effects of current treatments. Therefore, innovative diagnostic approaches to trace the micrometastases and therapeutic approaches aimed at stabilising and eliminating distant metastases – both do not exist yet being emergent in the nearest future.

**Diagnosis of BCMD**

Advanced imaging technologies are currently considered as being the most appropriate tool to diagnose BCMD, to detect the primary lesions and to trace the distance metastases over the whole body (whole-body imaging). To currently well recognised technologies belong multidimensional and multimodal ones: CT, MRI, PET, SPECT, and ultrasound; PET and the combined PET/CT is the key tool for the whole-body scanning. However, there are some substantial clinical deficits which imaging technologies suffer from in pinpointing the disease type [4].

**RT-PCR** Small-size metastases in lymph nodes may be detected by amplification of the smallest amounts of transcripts produced by BCMD biomarkers such as CK19 and others. The greatest limitation of the methodology is false-positive results potentially received due to the mixed cell populations which cannot be completely excluded by the resection. A conclusion might be also doubtful, due to untargeted biomarkers, particularly for heterogeneous tumours that is, indeed, the frequent case [4].

**Disseminated and circulating tumour cells** Individual tumour cells in bone marrow and blood stream cannot be detected by conventional imaging. For poor prognosis, more relevant and better detectable are tumour cells disseminated in bone marrow (DTC), compared to circulating tumour cells (CTC) in peripheral blood [6]. However, the invasiveness of the DTC sampling hardly finds the acceptance by patients. Consequently, blood tests for the CTC detection is a promising approach, in particular for the diagnosing of BCMD which demonstrates the most abundant representation of tumour cells in blood followed by high rates of CTC in prostate cancer, in contrast to significantly lower levels of CTC spread by other tumour types [7]. However, this approach suffers from substantial technological limitations such as an extremely low frequency of CTC in a blood stream that makes the tool almost useless for the detection of BCMD at its early stages [8]. Consequently, the reliable results’ interpretation is currently possible only for the advanced stages of the tumour progression / BCMD and for patients with poor prognosis [9]. The promising diagnostic approach might be the molecular characterisation of CTC as the predictor of the tumour invasiveness and therapy response [6].

**Treatment of BCMD**

Currently applied strategies for the treatment of BCMD make use of systemic cytotoxic agents that lead to severe and irreversible organic side-effects significantly decreasing the life quality of the patients followed by a limited long-term success in metastasis suppression: only 1-3% of patients remain long-term disease-free after BCMD treatments [4]. Although new agents like paclitaxel, trastuzumab and aromatase inhibitors improve the short-term survival rates (up to 36 months), the therapeutic goals remain at the level of survival prolongation and symptoms palliation.

The experts are fully consent with the fact that novel drug targets should be elaborated for a successful BCMD treatment tailored to the patient. In this context, molecular defects driving clinical onset of BCMD, beginning with the initiation step to the micrometastasis progression till BCMD virulence, create the robust panel of the drug target candidates [10]. Recent reports from animal models of BCMD treatments keep a hope in potential improvements which, however, are not going to happen for the patients tomorrow.

**Breast cancer risk assessment**

“**Molecular portrait**” and more

Early detection of the tumour has been demonstrated to be highly beneficial for significantly enhanced therapy efficacy. An accurate navigation by predictive diagnosis may lead to full recovery after surgical resection [11]. Furthermore, a detection of individual predisposition to breast cancer represents the optimal way how the pathology may be diagnosed before its clinical onset and development of the fatal BCMD. Breast cancer risk assessment is currently extensively under consideration. The major problem, however, is linked to the multifactorial nature of the disease. Consequently, the list of parameters with impacts for the disease onset and progression at the individual level, i.e. personal risk factors differ significantly from patient to patient. This consideration leads to better understanding, why the “across-the-board” treatment of breast cancer is frequently ineffective, and the pathology specific “portrait” should be
created at the individual level. On this, any biological manifestation is operated and controlled at the molecular level. Therefore, the “portrait featuring” originates from the specific set-up of individual biomolecules and corresponding interaction among relevant pathways at molecular, subcellular and cellular levels. This “molecular portrait” creates an individual condition for the disease predisposition and promotion, which is recognisable and modifiable through individual pathology specific “molecular patterns”. For the clinically relevant and issue-sensitive interpretation, the informational input from the “molecular patterns” should be combined with complementary technologies such as medical imaging, which altogether contribute to the creation of the individual “patient profiles” as the robust platform for personalised healthcare services. The expected outcomes are conducive to more effective population screening, prevention early in childhood, identification of persons at-risk, stratification of patients for the optimal therapy planning, prediction and reduction of adverse drug-drug or drug-disease interactions.

Innate immune system as a putative origin of mammary gland

Resulting from the accumulated data from knowledge about morphological particularities, cell composition bioinformatics research, a new concept to the evolutionary origin of mammary gland has been presented suggesting that the gland’s initial function was the provision of innate immunity later evolving into its current nutritional role [12]. Indeed, immune cells are abundant in both physiologic and pathologic mammary tissue. The immune cells are implicated in the development of human mammary glands: leucocytic infiltrates have been detected in normal pubertal and adult gland tissue [12,13]. Furthermore, bone marrow depletion leads to blocked ductal elongation in murine experimental models of mammary gland development. Taking together the above listed facts, the decisive role of the immune cells in physiology of mammary glands is getting obvious. This fascinating discovery opens great perspectives for innovative diagnostic tools based on a minimally invasive blood test platform and might be highly beneficial for novel drug targets of increased efficacy in breast cancer treatments.

Immune cells and inflammation as tumour modifiers in breast: expression patterns of activated leucocytes collaborative with neoplastic cells under chronic inflammatory condition?

The paradoxical role of leucocytes as protectors, regulators, modifiers and causal players in the breast carcinogenesis becomes extensively discussed in current literatures. Both innate (myeloid) and adaptive (lymphoid) leucocyte types have been demonstrated as breast cancer modifiers [14]. Doubtless cytotoxic T-lymphocytes have a function in constraining tumour developments that is evident, in particular, for the tumours of viral origin [15]. On the other side, the chronic activation of leucocytes paradoxically play a role in initiating / potentiating carcinogenesis: infiltrating B-lymphocytes have been reported to represent the predominant lymphocytic population in premalignant breast tissue [14]. Further, B-cells represent the predominant lymphocytes during early breast cancer, whereas infiltrating T-lymphocytes are more extensive in higher graded ductal in situ and invasive breast carcinomas [16,17].

What is the mechanism of the tumour promotion by inflammatory leucocytes? The key-point is their unique plasticity in producing protein products and bioactive mediators essential for all stages in the tumour progression such as reactive oxygen species, tissue-remodelling (e.g. metalloproteinases) angiogenesis prompting (e.g. VEGF) protein-complexes [18,19]. Certainly, this enormous capacity is conditioned by the stage specific expression patterns in activated leucocytes. Under the chronic inflammatory condition the expression patterns of infiltrating leucocytes obviously become collaborative with those of neoplastic cells. An excellent example is provided by tissue-remodelling proteins secreted from activated leucocytes. An altered metalloproteinase activity impacts directly the mammary gland physiology during morphogenesis, hormonal cycle and lactation, as well as during inflammatory acute / chronic process, cancer pre-lesions, tumour progression, and metastatic disease. Besides other cell types in the population, inflammatory and immune cells are the major producers of metalloproteinases [20]. Although the impacts of the metalloproteinase activities are well acknowledged for mammary glands physiology and pathophysiology, the relevance of the metalloproteinase patterns as the breast cancer modifiers in the context of inflammation and immune cells represents won its recognition only recently in the scientific world [21].

Molecular patterns in activated leucocytes as the minimally invasive diagnostic tool for breast cancer risk assessment

Pursuing the above conclusions, it is getting obvious that the molecular/expressional patterns in orchestrated leucocytes are activated strictly in accordance to the precancerous / cancer stage. If detected in correlation with the corresponding disease initiation and progression stage, these patterns in activated leucocytes might be of high relevance for the diagnostic and treatment purposes. This consideration leads to the idea of creating a minimally invasive approach for breast cancer risk assessment based on ex vivo blood tests by examination of
the specific molecular/expressional patterns in circulating leucocytes.

The OVERALL TASK: Multimodal diagnostic approaches, disease specific biomarker-patterns, individual patient profiles, creation of medical records and treatments tailored to the person

Paradigm change from a delayed approach after clinical onset of the pathology to predictive diagnostics followed by targeted prevention and individualised treatment algorithms tailored to the patient, creates an innovative concept for advanced healthcare that is costs effective [22]. Particularly attractive are non-invasive diagnostic approaches considering disease-specific alterations in molecular patterns of blood cells and serum in predisposed individuals before clinically disease onset [11,23-29]. Identification of pathology-specific biomarker-patterns increases the specificity and predictive power of analytical approach. Combination of patterns at subcellular, intracellular and extracellular levels contributes to high sensitivity and specificity of the analysis. Mathemathic modelling of patient-specific profiles allows for an accurate prediction of individual predisposition before the pathology is manifested. Integrative medical approach by predictive diagnostics, targeted prevention and personalised treatments is considered as the medicine of the future. The expected outcomes are conducive to more effective population screening, prevention early in life, identification of persons at-risk, stratification of patients for the optimal therapy planning, prediction and reduction of adverse drug-drug or drug-disease interactions relying on emerging technologies, such as medical imaging, pharmacogenetics, *omics, disease modelling, individual patient profiles, integrative medical records, etc.

Technological design: integrative concept

The integrative concept of the technological design is summarised in Figure 2. An optimal set-up of stakeholders and a high quality of the performance of single operating steps (sub-projects) guarantee for a discovery and qualification of innovative diagnostic approaches and valid drug targets to be successfully implemented in clinical practice. The crucial step in the overall experimental scheme is a well-established patient model that reflects the clinical condition(s). Large-scaled studies to identify novel diagnostic biomarkers and therapeutic targets followed by validation, standardisation and application procedures are essential in breast cancer research.

Creation of medical records

Creation of medical records is the crucial step in the overall task of prediction, precise disease diagnosing and successful application of the treatment algorithms tailored to the person. Medical record should carry an integrative character presenting and evaluating disease relevant data at any applicable level of the examination / detection. The major points to be obligatory involved in the medical records related to the breast cancer are summarised below:

- Sur/name
- Date of birth / Age
- Ethnicity [30]
- Menopausal status [30]
- Menstrual cycle (duration, regularity etc.)
- History of pregnancies and childbirth
- Last date, type and result of past individual cancer screening (mammography, pap smear etc.)
- Breast / Cancer familial background (as described elsewhere)
- Histological statement for malignant tumours / benign indication
- Drug history: alcohol, nicotine etc.
- Medication history (i.e. steroids, blood pressure medication, anti-inflammatory medication etc.)
- For malignant tumours: evaluation of combined results by medical imaging, categorisation of the carcinoma (invasive lobular, ductal carcinoma in situ, etc.), TNM staging (size of cancer, nodal status,
type of metastases, receptor status, HER2, etc.

- For benign patients: acknowledged breast cancer risk factors (childless, lack of breast feeding, breast trauma / inflammations / biopsy, etc.) [30]
- Frequent co-morbidities (Diabetes type 2, cardiovascular disease, depression) [31,32]
- Environmental particularities (geographic factors, environmental toxicity, such as an excess of heavy metals and toxic compounds as described elsewhere)
- Inactive life-style and overweight (body mass index) that influence the pathology development and outcomes [31,32]
- Sleep disorders as the predisposition and the cause of cancer [33]
- Detectable stress factors with acknowledged impacts for BC development such as a shift-worker’s job [34]
- Breast / Cancer specific molecular patterns in blood (as discussed later in text)
- Metastasis specific biomarkers in blood (medical imaging and CTC detection as discussed above)

Construction of diagnostic windows for minimally invasive breast cancer risk assessment based on immune cells profiling

This multimodal approach utilises a combination of conventional analytical methodology for a creation of the pathology specific biomarker patterns at complementary levels of detection, namely

- Medical imaging (primary tumour, distanced metastasis)
- Subcellular / molecular imaging by “comet assay”
- DNA analysis (risk assessment for general tumour predisposition)
- Clinical differential proteomics as the “gene hunting” approach for pathology specific molecular patterns in blood cells
- Blood metabolomics for quantification of disease relevant metabolite patterns
- Quantitative analysis of enzymatic activities in blood plasma
- others

followed by mathematical modelling of pathology-specific profiles.

Here we demonstrate the analytical procedure for two levels of detection, namely molecular imaging by quantitative “comet assay” and clinical proteomics.

Subcellular / molecular imaging by “comet assay”-analysis

The “comet assay” provides a simple and effective method for evaluation of DNA damage and DNA-repair capacity in single cells such as leucocytes. The principle of the assay is based upon the ability of DNA fragments to migrate out of the cell under the influence of an electric field. An evaluation of the “comet” tail shape and DNA fragments migration pattern allows for assessment of DNA damage and repair capacity. DNA-damage is assigned to 4 classes based on the visual aspect of the comets, considering the extent of DNA migration as published earlier [35]. Comets with a bright head and almost no tail are classified as class I with minimal DNA damage. Comets with no visible head and a long diffuse tail are classified as class IV (severely damaged/apoptotic cells). Comets with intermediate characteristics are assigned to classes II and III dependent on the ratio R = T/r, where T is a length of comet’s tail and r is a radius of comet’s head. The characteristic value of R for class 1 is 1 (T ≈ r) and for class 4 is ∞ (r = 0). Comets with values 1<R<3 are classified as class 2 (see the original image). Comet classes are demonstrated with the image provided in the Figure 3.

Subcellular / molecular imaging by quantitative “comet assay” has characterised the breast cancer patients as follows:

- Increased damage to DNA
- Debilitated apoptotic reaction towards increased DNA damage
- Pathology specific comet patterns
- Impact of hormonal status on specificity of comet patterns among breast cancer patients
- Characteristic windows of comet patterns that may be utilised for breast cancer risk assessment – both positive (at high-risk) and negative (at low-risk) prediction.

![Figure 3 Image of the characteristic classes of comets (representing intact and damaged DNA) are shown ex vivo for circulating leucocytes [35].](image-url)
An example of the diagnostic windows for breast cancer risk assessment using comet classes I (intact DNA) and IV (apoptotic) is demonstrated in Figure 4 [36]. The constructed diagnostic windows clearly distinguish between tumour and benign patients and may be considered for the practical application in differential molecular diagnostics. For this diagnostic tool two parameters in medical records are of particular importance, namely the age and menopausal status.

Clinical differential proteomics as the promising tool for breast cancer risk assessment

Protein mapping in circulating leucocytes of breast cancer patients

The protein mapping performed in our recent project resulted in altogether 158 protein spots distinguished; the overall spots correspond to 74 proteins the amino acid sequences of which have been consequently identified utilising the analytical technology of MALDI-TOF – see Figure 5 [11]. The identified proteins are listed in the Table 1.

Concomitantly to the protein identification, the functional classification has been performed. The list of functional groups is provided with the separate Table 2.

Breast cancer specific expression patterns as potential candidates for the predictive-diagnostic biomarker panel

The expression profiles under the cancer condition have been quantified versus the control group with benign and no breast tumours detected [11]. The resulting information is provided in Table 1. In accordance to statistical analysis, altogether four categories have been built-up as follows: A. statistically significant alterations in the expression profiles under the cancer condition compared to the control group; B. statistically non-significant alterations in the expression profiles under the cancer condition compared to the control group; C. expression levels altered individually with highly heterogeneous expression profiles within the patient group versus stable expression levels within the control group; D similar expression-profiles within both patient and control groups of comparison. Here detected pathology specific patterns might be further considered for the creation of...
the biomarker panel of high predictive power in diagnosing of the breast cancer development.

**Group-specific versus individual therapy response: potential prognostic tool by proteomic blood tests?**

As it is summarised in Table 1, the reaction towards the standardised radiotherapy has been quantified at the level of the protein expression rates in circulating leucocytes. The resulting statistical analysis demonstrated following patterns: 14 proteins were significantly suppressed and 4 proteins were significantly induced in all patients tested. In contrast, further 4 proteins were individually (group-non-significantly) suppressed and 2 proteins individually (group-non-significantly) induced. However, for the absolute majority (50) of the proteins measured strictly individual post-therapeutic regulation (up- / down or unchanged) was monitored. These findings motivates a creation of the “follow-up” projects to learn more about “molecular signature” of the patient beneficial therapy response as the potential prognostic tool.

**What do we learn by the function of proteins involved in the breast cancer specific expression alterations in blood?**

Below listed groups (see Table 2) have been created according to the function(s) of individual proteins identified through the breast cancer specific profiles in circulating
Table 1 Protein profile alterations in breast cancer and under radiotherapy

| Spot number | Access number | Accession name | Protein name | Functional group number | Classification, references relevant for functional groups 19, 20 and 21 | Profile alterations versus controls | Alterations under radiotherapy |
|-------------|--------------|----------------|--------------|-------------------------|---------------------------------------------------------------------|----------------------------------|---------------------------------|
| 112-116     | P04040       | CATA_HUMAN     | Catalase     | 5, 9, 10, 11, 14, 18, 19, 20, 21 | anti-oxidant defence and detoxification protein [37-42]               | homogeneous suppression           | Individual reaction ↓            |
| 157         | P07737       | PROF1_HUMAN    | Profilin-1   | 1, 2, 11, 19, 20, 21     | Microfilamental network cell-migration related protein [11,43-48]     | homogeneous suppression           | homogeneous suppression ↓        |
| 23-27       | P63261       | ACTG_HUMAN     | Actin, cytoplasmic 2 (Gamma-actin) | 1, 2, 11, 14, 18, 19, 20, 21 | Microfilamental network protein [49-52]                                | homogeneous suppression           | homogeneous upregulation ↑ ↓ T=0,02 |
| 124         | P27797       | CRTC_HUMAN     | Calreticulin precursor CRP55 | 2, 11, 12, 17, 18, 19, 20, 21 | Endoplasmic reticulum calcium-storage protein regulating focal adhesion and cell motility [53-60] | homogeneous suppression           | Individual reaction ↓           |
| 155         | P30043       | BLVRB_HUMAN    | Flavin reductase, NADH-dependent reductase | 3, 6, 9, 11, 18, 19 | Riboflavin biosynthesis pathway [61]                                  | individual induction ↑ T=0,02     | homogeneous induction ↓ T=0,002  |
| 70-74       | P13645       | K1C10_HUMAN    | Keratin, type I cytoskeletal 10 | 1, 2, 11, 18, 19, 20, 21 | Microfilamental network protein [62-67]                                | homogeneous induction ↑ T=0,03     | homogeneous suppression ↓ T=0,1  |
| 136         | O00299       | CLIC1_HUMAN    | Chloride intracellular channel protein 1 | 8, 11, 14, 19, 20, 21 | Channel, osmosis, Ca2+-dependent apoptosis-related protein [66-71] | 2,5x T=0,04                      | Individual reaction ↓ |
| 156         | P08238       | HS90B_HUMAN    | Heat shock protein HSP 90-beta | 12, 13, 14, 11, 17, 18, 19, 20, 21 | Stress response protein [72-76]                                      | homogeneous suppression ↑ T=0,06    | homogeneous suppression ↓ T=0,02  |
| 141         | P13489       | RIN1_HUMAN     | Placental ribonuclease inhibitor | 3, 9, 12, 14, 17, 20, 21 | RNA/nucleotide turnover pathway [77-83]                                | homogeneous suppression ↑ T=0,06    | homogeneous suppression ↓ T=0,1  |
| 82          | P62937       | PP1A_HUMAN     | Peptidyl-prolyl cis-trans isomerase A | 4, 11, 12, 14, 17, 19, 20, 21 | Cyclophilin A is involved in protein folding, assembly, transportation [84-89] | highly upregulated in several MKs T=0,06 | Individual reaction ↓ |
| 28          |              |                | not identified protein |                          |                                                                      | highly upregulated in several MKs T=0,06 | Individual reaction ↓ |
| 53          |              |                | not identified protein |                          |                                                                      | highly upregulated in several MKs T=0,06 | Individual reaction ↓ |
| 142         | P08670       | VIME_HUMAN     | Vimentin      | 1, 2, 11, 14, 18, 19, 20, 21 | Microfilamental network cell-migration related protein [60,76,90-97] | 2x T=0,09                        | Individual reaction ↓ |
| 62, 85 93-95| P00915       | CAH1_HUMAN     | Carbonic anhydrase I | 5, 11, 18, 19, 20, 21 | Energy metabolism related protein [98-104]                             | 2x T=0,10                        | Individual reaction ↓ |
| 143         | P28838       | AMPH_L_HUMAN   | Cytosol aminopeptidase | 4, 11, 14, 19, 20, 21 | Regulatory protein-modification enzyme [101-102]                        | individual induction ↑ T=0,1       | homogeneous suppression ↓ T=0,1 |
| 135         | P49411       | EFTU_HUMAN     | Elongation factor Tu, mitochondrial precursor | 7, 20 | Mitochondrial protein synthesis machinery, critical role to maintain the translational fidelity [110,111] | homogeneous suppression ↓ 4x T=0,1 | Individual reaction ↓ |
| 45-46       | P52566       | GDIS_HUMAN     | Rho GDP-dissociation inhibitor 2 (Rho GDIf) | 1, 2, 11, 12, 14, 17, 19, 20, 21 | LyGDI plays a role in the onset of apoptosis and cell migration [11,112-116] | homogeneous upregulation ↑ T=0,1 | Individual reaction ↓ |

Golubnitschaja et al. The EPMA Journal 2013, 4:6 Page 9 of 24
http://www.epmajournal.com/content/4/1/6
Table 1 Protein profile alterations in breast cancer and under radiotherapy (Continued)

| Gene ID | Protein Name | Function | Expression Profile | Interaction |
|---------|--------------|----------|--------------------|-------------|
| 148 P63104 | 1433Z_HUMAN | homogenous suppression | 2.5x T=0.1 |
| 67 P06702 | S10A9_HUMAN | high upregulated in several MKs | T=0.11 |
| 110 | not identified protein | homogeneous suppression | 2,5x T=0.1 |
| 123 P07237 | PDIA1_HUMAN | highly upregulated in several MKs | T=0.12 |
| 104 | not identified protein | individual reaction | T=0.1 |
| 131 P78371 | TCPB_HUMAN | individual reaction | T=0.05 |
| 19-21, 39 P60709 | ACTB_HUMAN | slightly increased | T=0.15 |
| 97 P60174 | TPIS_HUMAN | individual reaction | 2x T=0.2 |
| 44 ANXA1-HUMAN | Annexin A1 | homogeneous induction | T=0.1 |
| 80 P05109 | S10A8_HUMAN | homogeneous suppression | 2,0x T=0.24 |
| 37 P47756 | CAPZB_HUMAN | slightly increased | T=0.2 |
| 137 P30041 | PRDX6_HUMAN | slightly increased | T=0.2 |
| 9-11 P02679 | FIBG_HUMAN | homogeneous induction | 1.5x T=0.24 |
| 130 P10809 | CH60_HUMAN | slightly increased | T=0.15 |
| 36 Q5U077 | Q5U077_HUMAN | slightly increased | T=0.15 |
| 122 Q96C61 | Q96C61_HUMAN | homogeneous suppression | T=0.25 |
| 151 P07996 | TSP1_HUMAN | individual reaction | T=0.29 |

**CATEGORY B: non-significantly altered expression profiles in patients versus controls**

| Gene ID | Protein Name | Function | Expression Profile | Interaction |
|---------|--------------|----------|--------------------|-------------|
| 131 P78371 | TCPB_HUMAN | individual reaction | T=0.05 |
| 19-21, 39 P60709 | ACTB_HUMAN | slightly increased | T=0.15 |
| 97 P60174 | TPIS_HUMAN | individual reaction | 2x T=0.2 |
| 44 ANXA1-HUMAN | Annexin A1 | homogeneous induction | T=0.1 |
| 80 P05109 | S10A8_HUMAN | homogeneous suppression | 2,0x T=0.24 |
| 37 P47756 | CAPZB_HUMAN | slightly increased | T=0.2 |
| 137 P30041 | PRDX6_HUMAN | slightly increased | T=0.2 |
| 9-11 P02679 | FIBG_HUMAN | homogeneous induction | 1.5x T=0.24 |
| 130 P10809 | CH60_HUMAN | slightly increased | T=0.15 |
| 36 Q5U077 | Q5U077_HUMAN | slightly increased | T=0.15 |
| 122 Q96C61 | Q96C61_HUMAN | homogeneous suppression | T=0.25 |
| 151 P07996 | TSP1_HUMAN | individual reaction | T=0.29 |

Golubnitschaja et al. The EPMA Journal 2013, 4:6 Page 10 of 24 http://www.epmajournal.com/content/4/1/6
Table 1 Protein profile alterations in breast cancer and under radiotherapy (Continued)

**CATEGORY C: individual group-heterogeneous expression profiles in patients versus homogeneous one in controls**

| Protein ID | Gene Symbol | Description | Expression Profile | Reaction |
|------------|-------------|-------------|--------------------|----------|
| 86,87      | P00918      | CAH2_HUMAN  | Carbonic anhydrase II | 5, 11, 18, 19, 20, 21 | Energy metabolism related protein | Individual heterogeneous | Individual reaction |
| 103        | P02675      | FIBB_HUMAN  | Fibrinogen beta chain precursor | 11, 17, 19, 20, 21 | Microfilamental network cell-migration related protein | Individual heterogeneous | Individual reaction |
| 117-120    | O75083      | WDR1_HUMAN  | WD repeat-containing protein 1 | 4, 12, 11, 14, 20 | Cell-cycle and proteolytic machinery related protein | Individual heterogeneous | Individual reaction |
| 126        | P28331      | NUAM_HUMAN  | NADH-ubiquinone oxidoreductase 75 kDa | 5, 7, 9, 11, 14, 19, 20, 21 | Mitochondrial energy metabolism related protein | Highly heterogeneous | Individual reaction |
| 127        | P08133      | ANXA6_HUMAN | Annexin A6 (P70) | 2, 8, 11, 14, 16, 17, 19, 20, 21 | Membrane architecture and signalling protein | Individual induction | Individual induction |
| 128        | P11142      | HSP7C_HUMAN | Heat shock cognate 71 kDa protein | 4, 5, 11, 13, 14, 17, 18, 19, 20, 21 | Stress response protein, chaperone, ATPase | Individual heterogeneous | Individual reaction |
| 144        | Q53XX6      | ATPA_HUMAN  | ATP-synthase, H+ transporting mitochondrial protein | 5, 7, 8, 11, 18, 19, 20, 21 | Mitochondrial energy metabolism related protein | Individual heterogeneous | Individual reaction |
| 147        | P31946      | 1433B_HUMAN | 14-3-3 protein beta/alpha (protein-kinase-C inhibitor) | 4, 11, 12, 14, 17, 19, 20, 21 | Cell-cycle checkpoint, stress response protein | Highly heterogeneous | Homogeneous suppression |
| 152        | P14780      | MMP9_HUMAN  | Matrix metalloproteinase-9 | 11, 14, 15, 18, 19, 20, 21 | MMP9 Multifunctional tissue-remodeling protein | Highly heterogeneous | Individual reaction |

**CATEGORY D: similar expression-profiles among patients and controls**

| Protein ID | Gene Symbol | Description | Expression Profile | Reaction |
|------------|-------------|-------------|--------------------|----------|
| 1-5        | P18206      | VINC_HUMAN  | Vinculin |  | Cytoskeletal assembly associated protein | Similar | Individual reaction |
| 6-8        | P60709      | ACTB_HUMAN  | Actin, cytoplasmic 1 (Beta-actin) |  | Microfilamental network protein | Similar | Individual reaction |
| 12-13      | P68363      | TBA1B_HUMAN | Tubulin alpha-chain |  | Microtubule network protein | Similar | Individual reaction |
| 14-15      | P06576      | ATPB_HUMAN  | ATP synthase subunit beta, mitochondrial precursor |  | Mitochondrial energy metabolism related protein | Similar | Individual reaction |
| 16         | P07437      | TBB2_HUMAN  | Tubulin beta-2 chain |  | Microfilamental network protein | Similar | Individual reaction |
| 29-31      | P13645      | K1C10_HUMAN | Keratin, type I cytoskeletal 10 |  | Microfilamental network protein | Similar | Individual reaction |

Golubnitschaja et al. The EPMA Journal 2013, 4:6 Page 11 of 24

http://www.epmajournal.com/content/4/1/6
| No. | P | Homo sapiens | Gene Symbol | Gene Name | Protein Function | Protein Alteration | Reactivation States |
|-----|---|--------------|-------------|-----------|------------------|-------------------|-------------------|
| 40, 41 | P63261 | HUMAN | ACTG | Actin, cytoplasmic 2 (Gamma-actin) | Microfilamental network protein | similar | Individual reaction ↑ ↓ |
| 42 | Q6FHP5 | HUMAN | PHB | PHB protein | Prohibitin - negative regulator of cell proliferation and may be a tumor suppressor. Mutations in PHB have been linked to sporadic breast cancer. | similar | homogeneous suppression ↓ |
| 49-50 | P67936 | HUMAN | TPM4 | Tropomyosin alpha-4 chain | Microfilamental network protein | similar | Individual reaction ↑ ↓ |
| 88 | P02768 | HUMAN | ALBU | Serum albumin | Extracellular transport/carrier protein | similar | Individual reaction ↑ ↓ |
| 96 | P18669 | HUMAN | PGAM1 | Phosphoglycerate mutase 1 | Energy metabolism related protein | similar | homogeneous suppression ↓ T=0,1 |
| 99 | P00558 | HUMAN | PGK1 | Phosphoglycerate kinase 1 | Energy metabolism related protein | similar | Individual reaction ↑ ↓ |
| 100 | P68871 | HUMAN | HBB | Hemoglobin subunit beta | Oxygen carrier | similar | Individual reaction ↑ ↓ |
| 101, 102, 106 | P06733 | HUMAN | ENOA | Alpha-enolase | Multifunctional glycolytic enzyme | similar | Individual reaction ↑ ↓ |
| 107 | P14618 | HUMAN | KPYM | Pyruvate kinase, isozymes M1/M2 | Energy metabolism related protein | similar | Individual reaction ↑ ↓ |
| 125 | P14625 | HUMAN | ENPL | Endoplasmic precursor (94-kDa glucose-regulated protein) | Signal transduction pathways associated with endoplasmic reticulum stress | similar | homogeneous suppression ↓ T=0,1 |
| 129 | P13796 | HUMAN | PLSL | Plastin-2 | Microfilamental network protein | similar | homogeneous suppression ↓ T=0,02 |
| 132 | Q53QM2 | HUMAN | ACTR3 | Hypothetical protein ACTR3 | Currently uncharacterized protein | similar | homogeneous suppression ↓ T=0,1 |
| 133 | Q6IAT1 | HUMAN | GDI2 | GDI2 protein (GDP dissociation inhibitor 2) | Regulatory protein in the functional cycle and recycling of Rab GTPases | similar | Individual suppression ↓ |
| 134 | UQCR1 | HUMAN | Ubiquinol-cytochrome C reductase, mitochondrial processing peptidase Beta-family | Ubiquinol-cytochrome C reductase, mitochondrial processing peptidase Beta-family | similar | Individual reaction ↑ ↓ |
| 138 | P09211 | HUMAN | GSTP1 | Glutathione S-transferase P (GST class-p) | Stress response and anti-oxidant defence protein | similar | homogeneous induction ↑ T=0,07 |
| 139 | P07741 | HUMAN | APT | Adenine phosphoribosyltransferase | Nucleotide metabolism | similar | Individual reaction ↑ ↓ |
| 140 | P11021 | HUMAN | GRP78 | 78 kDa glucose-regulated protein precursor (GRP 78) | Energy metabolism related protein | similar | Individual reaction ↑ ↓ |
Table 1 Protein profile alterations in breast cancer and under radiotherapy (Continued)

| Spot | Accession | HUMAN | Description | Classification | Functional group number |
|------|-----------|-------|-------------|----------------|-------------------------|
| 145  | P13716    | HEM2  | Delta-aminolevulinic acid dehydratase | anti-oxidant defence and detoxification pathways | similar |
| 146  | Q5JQI4    | HSP71 | Heat shock 70 kDa protein 1A | Stress response protein | similar |
| 149  | Q06323    | PSME1 | Proteasome activator complex subunit 1 | The activator binds to proteasome 20S & enhances peptidase activity, e.g. under stress conditions | similar |
| 150  | P00491    | PNPH  | Purine nucleoside phosphorylase | Nucleotide- and nucleoside turnover, detoxification pathway | similar |
| 153  | P12429    | ANXA3 | Annexin A3 | Membrane architecture and signalling protein | similar |
| 154  | VDAC1     | HUMAN | Voltage-dependent anion-selective channel protein 1 | Membrane protein, regulation of cell growth / death via redox-control | similar |
| 158  | Q9Y3F5    | HUMAN | A6-related hypothetical protein | Twinfilin-2, Protein tyrosine kinase 9-like, actin-binding protein involved in motile and morphological processes | similar |

**Annotation to Table 1:** 158 spots have been distinguished by protein mapping as stably expressed (i.e. by all members of the group) in circulating leucocytes of the group with breast cancer patients. Altogether 74 proteins have been identified within 158 spots. The protein mapping image is demonstrated in Figure 5. The spot number in the map (Spot number) and corresponding accession number (Access number) and name (Accession name) received from the SwissProt database is provided in the table together with the name of the identified protein (Protein name) in accordance with the current protein nomenclature. The column "Classification" provides information about the function(s) currently known for each protein. The corresponding number of the functional group(s) is/are provided in the column "Functional group number"; the designation of the functional group with the corresponding number can be found in the separate Table 2. The regulation manner (up / down regulation) and the severity of the expression profile alterations under the cancer condition have been qualified and quantified versus the values in the control group; the resulting information is provided in the column "Profile alterations versus controls". In accordance to the expression profile alterations, every mapped protein has been assigned to one of the altogether four CATEGORIES built-up as follows: A = 22 proteins with the statistically significant alterations in the expression profiles under the cancer condition compared to the control group (T ≤ 0.1); B = 12 with the statistically non-significant alterations in the expression profiles under the cancer condition compared to the control group; C = 9 proteins with the expression profiles altered individually with highly heterogeneous expression profiles within the patient group versus stable expression levels within the control group; D = 31 proteins with similar expression-profiles within both patient and control groups of comparison. Further, under the cancer condition, the expression alterations as the reaction towards the applied radiotherapy has been qualified (up / down regulation) and quantified as it is summarised for each protein in the column "Alterations under radiotherapy". The resulting statistics is provided here: 14 proteins homogeneously (group-significantly) suppressed (↓), 4 proteins homogeneously (group-significantly) induced (↑), 4 proteins individually (group-non-significantly) suppressed (↓), 2 proteins individually (group-non-significantly) induced (↑), 33 individually up- or down-regulated proteins (↑/↓), and 17 proteins with individual up-/or down-/or unchanged regulation (↑/↓) have been profiled under radiotherapy.
leucocytes (see Table 1). The literature sources relevant for the issue are listed in the Table 1 respectively to the functional groups. What do we learn from the exercise?

➢ According to the content summarised in the Table 2, it is evident that the breast cancer specific protein profiles affect a spectrum of the central biological activities in and of the cell.
➢ The multifactorial impacts of the disease are evident.
➢ Certainly there are effective interactions among individual functional groups: several proteins are involved and play a (key) role at least in two but frequently in a much higher number of the functional groups listed.
➢ All the proteins with expression rates altered under the breast cancer condition as described in this article, have been reported to stay in a kind of relation to cancer / breast cancer / metastatic activity. Moreover, some of the combinations of the proteins presented here have been already reported in relation to breast/cancer.

➢ However, the particular value of this article is in the systematic overview of the integrative panel of proteins/functional groups involved in the breast cancer specific molecular patterns in blood cells.
➢ Furthermore, the tool is obviously of high importance in favour of non-invasive prediction of breast cancer, since only very few literature sources could be found for breast cancer blood biomarker/patterns.

### Table 2 Systematic overview of the integrative panel of proteins/functional groups involved in the breast cancer specific molecular patterns in blood cells

| Nr. | Functional group                                                                 | Relevance for breast cancer in tissue [reference] | Relevance for breast cancer in blood [reference] |
|-----|----------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------|
| 1   | microfilamental network-associated and cytoskeletal-assembly proteins             | [48,223,224]                                     | [11]                                            |
| 2   | cell motility, migration & adhesion                                              | [225-227]                                       | [11]                                            |
| 3   | nucleoside / nucleotide turnover & metabolism                                     | [228,229]                                       |                                                 |
| 4   | protein metabolism (regulatory protein-synthesis & protein-modification enzymes, chaperons) | [230,231]                                       | [231]                                           |
| 5   | energy metabolism                                                                | [232-236]                                       | [232,236]                                       |
| 6   | vitamin metabolism                                                               | [237,238]                                       |                                                 |
| 7   | mitochondrial proteins                                                            | [239-241]                                       | [239,241]                                       |
| 8   | channels, membrane-architecture and intercellular-junction proteins               | [242]                                            |                                                 |
| 9   | anti-oxidant defence / red-ox control                                            | [243-246]                                       | [245]                                           |
| 10  | detoxification proteins                                                           | [247]                                            |                                                 |
| 11  | stress-response / -protection related protein                                     | [75,248-250]                                     |                                                 |
| 12  | cell-cycle machinery proteins                                                     | [251-253]                                       |                                                 |
| 13  | heat-shock proteins                                                              | [254-258]                                       |                                                 |
| 14  | apoptosis-related proteins / protection against apoptosis                          | [259-261]                                       | [262,263]                                       |
| 15  | tissue-remodelling enzymes                                                        | [21,264-268]                                     |                                                 |
| 16  | extra-cellular transport & carrier-proteins                                      | [258,269,270]                                   |                                                 |
| 17  | signal-transduction proteins / signalling pathways                                | [271-274]                                       |                                                 |
| 18  | longevity / ageing related proteins                                              | [275-278]                                       |                                                 |
| 19  | inflammation related / anti-inflammatory proteins                                 | [14,21,279]                                     |                                                 |
| 20  | (breast) cancer related inhibitor / promoter                                     | see references to individual proteins listed in the Table 1 |                                                 |
| 21  | cancer invasion and regulator of metastases formation                             | see references to individual proteins listed in Table 1 |                                                 |

Personalised treatments of the manifested breast cancer: where are we now?

During the last years several biomarkers as well as molecular factors have made their way into clinical routine. Extensive translational research, new mathematical models and computer-based analysis resulted in validated markers that allow personalised decision making for each individual patient already nowadays. Below we summarise the actualities and factors that have recently been shown to provide additional prognostic or predictive information and can finally spare ineffective or even harmful treatments (e.g. chemotherapy) and promote approaches tailored to the patient.
Clinicopathological factors, such as the histological subtype, tumour grade as well as the expression of the receptors for oestrogen, progesterone and HER2 belong to the most established evidence for making decisions over individualised therapeutic approaches. Therefrom, the expression levels of oestrogen receptor and HER2 are currently the best known predictive and prognostic biomarkers for individualised breast cancer therapy [280]. Increased expression rates of HER2 is the valid biomarker for an unfavourable prognosis in breast cancer management [281,282]. Furthermore, retrospective studies revealed a functional link between the level of HER2 expression and an individual patient response towards endocrine therapy and sensitivity to taxanes and anthracyclines [283-285]. However, the highest impact of HER2 in the clinical practice is its predictive and prognostic value indicating a response to trastuzumab and pertuzumab as well as to lapatinib (an inhibitor of the tyrosine kinase domain within HER1 and HER2 sequences) [286-288].

Further, a potential clinical utilisation of novel biomarkers dealing with the enzymatic complexes of cell proliferation, such as ki67 and uPA/PAI-1, is on the horizon. Hence, an elevated expression of ki67 is a potent marker for aggressive tumour types and a consequently poor prognosis [289,290]. Several studies demonstrated an association of ki67 expression level with the quality of patient response towards chemotherapy and endocrine therapy [291,292]. Consequently, ki67 has been included into the St. Gallen Consensus Recommendations to stratify breast tumours according to the level of proliferation [293]. In primary breast cancer, independent prognostic factors uPA/PAI-1 indicates a level of the tumour invasion and metastatic disease that is of particular value for treatments of the node-negative breast cancer [294,295]. Both factors have reached highest level of evidence (LOI-1) and have been recommended for the classification of the groups of risk in making decisions for treatments of the node-negative breast cancer [296,297].

The central role in creating an individual risk profile receives the computer assistance. For example, Adjuvant! Online is an internet-based algorithm aiming at prediction of the recurrence free survival and total survival over 10 years [298]. This programme takes into consideration the best established clinical and pathology-specific contributing risk factors such as tumour size, nodal involvement, histology, hormone receptor status and age in combination with co-morbidities registered. Adjuvant!Online may be potentially utilised to prognostic individual risks and benefits of endocrine therapy and / or variants of chemotherapy regimes proposed individually for the patients [299-301]. An alternative programme is PREDICT+ for the efficacy prediction based on individual HER2 parameters and hormone status [302-304].

Gene expression profiles receive more and more recognition in the overall breast cancer management including typification, prediction, prognosis and therapy regiments. Based on the common gene expression patterns, the molecular breast cancer subtypes have been grouped into five classes, namely Luminal-A, Luminal-B, Basal-like, ErbB2-like and normal-like ones [305,306]. Therefrom, each intrinsic breast cancer subtype is characterised by an individual prognostic relevance, patterns of the metastatic disease and typical response to single therapy approaches [307-309]. Consequently, these intrinsic subtypes have been included into the St. Gallen Consensus Therapy Recommendations [293]. For the first time in the history of breast cancer management, the Consensus Expert Panel decides on the individualisation of the adjuvant therapy considering the molecular patterns as follows:

- sole endocrine therapy in Luminal-A-cancers
- endocrine therapy in combination with chemotherapy in Luminal-B cancers
- sole chemotherapy in Basal-Like subtypes, and
- chemotherapy in combination with anti-HER2 -treatment in ErbB2-like breast cancer.

Further, there are commercially available multi-gene assays that may be used to prognostic individual recurrence scores and may assist in making decisions on single treatment regiments. The most common are MammaPrint and Oncotype DX assays [310,311]. Therewith, MammaPrint is able to distinguish breast cancer patients with a good prognosis to avoid unnecessary and even harmful treatments [312,313]. In contrast, the identified cohort of patients with a poor prognosis are more likely to achieve beneficial results by neo-adjuvant chemotherapy [314]. Oncotype DX is developed for patients with hormone receptor positive tumours undergoing endocrine treatment with tamoxifen. Therefore, this test identifies patients with a low risk of the tumour recurrence, who would not benefit from additionally applied adjuvant chemotherapy [315]. An add-value of the Oncotype DX application as evident for the node-positive disease, since patients with high tumour-recurrence scores may well benefit from anthracycline-based chemotherapy [316]. Both assays are currently under the prospective study in the MINDACT trial (MammaPrint) and TAILORx trial (Oncotype DX) to validate their overall clinical utility for the personalised application of adjuvant chemotherapeutic approaches [317,318].

**Recommendations and outlook**

Diagnosis and treatments of breast cancer metastasis disease (BCMD) are extremely challenging that prompts a development of emerging technologies for the effective prevention of breast cancer. Therefore, the overall task
is formulated as the integrative medical approach of the multimodal diagnostics, disease specific biomarker-patterns, individual patient profiles, creation of medical records and treatments tailored to the person. In this context, a minimally invasive breast cancer risk assessment appears to be a plausible approach for early / predictive diagnosis of cancer pre-stages and targeted treatments before the clinical onset of BCMD.

The multimodal diagnostics represents a model-based examination procedure with several levels of examination resulting in the extended patient profiles and medical records which should obligatory include an interview with the patient / a questionnaire form filled in for pathology relevant information, medical imaging, laboratory diagnostics and evaluation of pathology relevant risk factors. For the laboratory diagnostics it is highly recommended to use valid blood tests for the detection of the stage specific molecular patterns in activated leucocytes as explained above.

For the application of adjuvant therapeutic approaches, our ethical responsibility requests a carefully created balance between risks and benefits to justify the individually made decisions. A predictive genetic testing should be fixed by law to determine effective treatment options by evaluating efficacy, e.g. in the case of cytochrome P450 CYP2D6 genotyping to decide on tamoxifen application tailored to the patient.

Innovative medical records should be, further, developed to cover current deficits in the above listed clinical and laboratory expertise and to create individual patient profiles utilising mathematical modelling and integrative bioinformatics.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
OG created the concept of the project, made the data interpretation and drafted the article. KY carried out the molecular biological studies. VC participated in the creation of the concept of the article. DT supervised the patients recruitment and data collection at the Department of Obstetrics and Gynaecology. MD contributed to the drafting of the paper. WK supervised the project at the Department of Obstetrics and Gynaecology. HS supervised the patients recruitment and data collection at the Department of Obstetrics and Gynaecology. All authors read and approved the final manuscript.

Acknowledgements
Authors thank Dr. Michael Fountoulakis, Ms. Ageliki Papadopoulou and Mr. Kostas Vougas, Proteomics Research Unit and Biomedical Informatics Unit, Biomedical Research Foundation, Academy of Athens, Greece for their great laboratory expertise and to create individual patient to cover current deficits in the above listed clinical and laboratory diagnostics and evaluation of pathology relevant risk factors. For the laboratory diagnostics it is highly recommended to use valid blood tests for the detection of the stage specific molecular patterns in activated leucocytes as explained above.

For the application of adjuvant therapeutic approaches, our ethical responsibility requests a carefully created balance between risks and benefits to justify the individually made decisions. A predictive genetic testing should be fixed by law to determine effective treatment options by evaluating efficacy, e.g. in the case of cytochrome P450 CYP2D6 genotyping to decide on tamoxifen application tailored to the patient.

Innovative medical records should be, further, developed to cover current deficits in the above listed clinical and laboratory expertise and to create individual patient profiles utilising mathematical modelling and integrative bioinformatics.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
OG created the concept of the project, made the data interpretation and drafted the article. KY carried out the molecular biological studies. VC participated in the creation of the concept of the article. DT supervised the patients recruitment and data collection at the Department of Obstetrics and Gynaecology. MD contributed to the drafting of the paper. WK supervised the project at the Department of Obstetrics and Gynaecology. HS supervised the patients recruitment and data collection at the Department of Obstetrics and Gynaecology. All authors read and approved the final manuscript.

Acknowledgements
Authors thank Dr. Michael Fountoulakis, Ms. Ageliki Papadopoulou and Mr. Kostas Vougas, Proteomics Research Unit and Biomedical Informatics Unit, Biomedical Research Foundation, Academy of Athens, Greece for their great contribution to the proteomics related expertise.

Author details
1Department of Radiology, Rheinische Friedrich-Wilhelms-University of Bonn, Sigmund-Freud-Str. 25, Bonn 53105, Germany. 2Breast Cancer Research Centre, University of Bonn, Bonn, Germany. 3European Medical Association, Brussels, Belgium. 4Department of Obstetrics and Gynaecology, University of Bonn, Bonn, Germany. 5Department of Gynaecology, Red Cross Clinics Munich, Munich, Germany.

References
1. WHO: Cancer [http://www.who.int/mediacentre/factsheets/fs297/en/].
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ: Cancer Statistics, 2009. CA Cancer J Clin 2009, 59:225–249.
3. National Cancer Institute at the National Institutes of Health: Breast Cancer. [http://www.cancer.gov/cancertopics/types/breast].
4. Lu J, Steeg PS, Price JE, Krishnamurthy S,mani SA, Reuben J, Cristofanilli M, Donat G, Bidart L, Valero V, Hortobagyi GN, Yu D: Breast cancer metastasis: challenges and opportunities. Cancer Res 2009, 69:4951–4953.
5. Ross JS, Hortobagyi GN: Molecular Oncology of Breast Cancer. Ma: Jones & Bartlett Pub; 2004.
6. Hayashi N, Yamauchi H: Role of circulating tumor cells and disseminated tumor cells in primary breast cancer. Breast Cancer Res 2012, 19:110–117.
7. Allard WI, Matera J, Miller MC, Repollet M, Connelly MC, Rao C, Tibbe AGJ, Uhr JW, Terstappen LWWM: Tumor cells circulate in the peripheral blood of all major carcinomas but not in healthy subjects or patients with nonmalignant diseases. Clin Cancer Res 2004, 10:6897–6904.
8. Alix-Panabières C, Riethdorf S, Pantel K: Circulating tumor cells and bone marrow micrometastasis. Clin Cancer Res 2008, 14:5013–5021.
9. Ignatidis M, Xenidis N, Perastrak S, Apostolakis S, Polatkai E, Kalousi M, Sathopoulos EN, Sathopoulou A, Lianidou E, Chlouverakis G, Sotiriou C, Georgoulis V, Mavroudis D: Different prognostic value of cytokertatin-19 mRNA positive circulating tumor cells according to estrogen receptor and HER2 status in early-stage breast cancer. J Clin Oncol 2007, 25:5194–5202.
10. Nguyen DX, Masiagüé J: Genetic determinants of cancer metastasis. Nat Rev Genet 2007, 8:341–352.
11. Braun M, Fountoulakis M, Yeghiazaryan K, Schild HH, Kuhn W, Golubnitschaja O: How realistic are non-invasive approaches in breast cancer prediction? In Predictive Diagnostics and Personalized Treatment: Dream or Reality. Edited by Golubnitschaja O. New York: Nova Science Publishers Inc; 2009:433–446.
12. Vorbach C, Capechi MR, Penninger J: Evolution of the mammary gland from the innate immune system? Bioessays 2006, 28:606–617.
13. Howard BA, Gusterson BA: Human breast development. J Mammary Gland Biol Neoplasia 2000, 5:119–137.
14. Dehaidos DG, Coussens LM: Inflammation and breast cancer. Balancing immune response: crosstalk between adaptive and innate immune cells during breast cancer progression. Breast Cancer Res 2007, 9:R212.
15. Dunn GP, Old LJ, Schreider RD: The immunobiology of cancer immunosurveillance and immunodediting. Immunity 2004, 21:137–148.
16. Coronella-Wood JA, Hersh EM: Naturally occurring B-cell responses to breast cancer. Cancer Immunol Immunother 2003, 52:715–738.
17. Wong PY, Staren ED, Tereleshka N, Braun DP: Functional analysis of tumor-infiltrating leukocytes in breast cancer patients. J Surg Res 1999, 76:85–103.
18. Coussens LM, Werb Z: Inflammation and cancer. Nature 2002, 420:860–867.
19. Balkwill F, Charles KA, Mantovani A: Smoldering and polarized inflammation in the initiation and promotion of malignant disease. Cancer Cell 2005, 7:211–217.
20. Wiseman BS, Werb Z: Stomal effects on mammary gland development and breast cancer. Science 2002, 296:1046–1050.
21. Hjilla CV, Wood GA, Khokla R: Inflammation and breast cancer: metalloproteinases as common effectors of inflammation and extracellular matrix breakdown in breast cancer. Breast Cancer Res 2008, 10:205.
22. Golubnitschaja O, Costigliola V: Common origin but individual outcomes: time for new guidelines in personalized healthcare. Personalized Med 2010, 7:561–568.
23. Ross JS: Integrated diagnostics and personalized therapeutics in oncology. In Predictive Diagnostics and Personalized Treatment: Dream or Reality. Edited by Golubnitschaja O. New York: Nova Science Publishers Inc; 2009:399–431.
24. Yeghiazaryan K, Braun M, Mamlouk S, Chlouverakis G, Golubnitschaja O: Are side-effects of irradiation predictable for treatment of breast cancer patients? In Predictive Diagnostics and Personalized Treatment: Dream or Reality. New York: Nova Science Publishers Inc; 2009:447–456.
25. Gahan P: Circulating nucleic acids in plasma and serum: diagnosis and prognosis in cancer. EPMA J 2010, 1:503–512.
26. Mallmann M, Staratschek-Jox A, Rudowski C, Braun M, Gaarz A, Wolfgang M, Kuhn W, Schultze J: Prediction and prognosis: impact of gene
metastasis-associated proteins involved in gallbladder carcinoma metastasis by proteomic analysis and functional exploration of chloride intracellular channel 1. Cancer Lett 2009, 287:1–11.

70. Suginta W, Karoulias N, Atken A, Ashley RH: Chloride intracellular channel protein CLIC4 (p64H1) binds directly to brain dynamin I in a complex containing actin, tubulin and 14-3-3 isoforms. Biochem J 2001, 358:53–64.

71. Suh KS, Mutoh M, Nagashima K, Fernandez-Salas E, Edwards LE, Hayas DI, Crutchley JM, Marin KG, Dumont RA, Levy JM, Cheng C, Garfield S, Yuspa SH: The organellar chloride channel protein CLIC4/mtCLIC translocates to the nucleus in response to cellular stress and accelerates apoptosis. J Biol Chem 2004, 279:4632–4641.

72. Bellack J, Whitesell L: Hsp90: an emerging target for breast cancer therapy. Anticancer Drug Des 2004, 19:651–662.

73. Yaobin, Tong W, Zhu Y: Study on HSP70, 90 mRNA gene expression in non-invasive bladder cancer cell line. Modulated T-complex protein 1 and peptidyl-prolyl cis-trans isomerase ζ. Cancer Lett 2001, 172:7–15.

74. Knudsen JF, Carlsson U, Hammarström P, Sokol GH, Cantilena LR: Expression of Elongation Factor (EF)-Tu protein Survivin. Protein Survivin. Proteomics Clin Appl 2009, 3:1225–1235.

75. Thyparambil J, Bender L, Kline E, Ganesh T, Snyder J, Liotta D, Marcus A: Vimentin: A Novel Chemopreventive Target for Breast Cancer Metastasis. Cancer Res 2010, 69:5063–5063.

76. Kokkinos MI, Wafai R, Wong MK, Newgreen DF, Thompson EW, Waltham M: Vimentin and epithelial-mesenchymal transition in human breast cancer—observations in vitro and in vivo. Cells Tissues Organs (Print) 2007, 185:191–203.

77. Kusinska RU, Kordek R, Pluciniek E, Bednarek AK, Piekarski JH, Potemski P: Does vimentin help to delineate the so-called "basal type breast cancer"? J Exp Clin Cancer Res 2009, 28:118.

78. Vuoriluoto K, Haugen H, Kivivuo S, Mpindi J-P, Nevo J, Gjerdrum C, Tiron C, Lønss Jv, Isaka J: Vimentin regulates EMT induction by Slug and oncogenic H-Ras and migration by governing Axl expression in breast cancer. Oncogene 2011, 30:1436–1448.

79. Dourlen P, Ando K, Hamdane M, Begard S, Buée L, Galas MC: Modeling breast cancer in vivo: irreversible induction of invasive breast cancer epithelial-mesenchymal transition, myoepithelial histogenesis or histogenesis from progenitor cells with bilinear differentiation potential? J Pathol 2005, 206:451–457.

80. Moenner M, Vosoghi M, Ryazantsev S, Glitz DG: Hsp90: an emerging target for breast cancer. J Exp Clin Cancer Res 2009, 28:118.

81. Song F, Zhang X, Ren X-B, Zhu P, Xu J, Wang L, Li Y-F, Zhong N, Ru Q: Knockdown of ribonuclease inhibitor expression with siRNA in non-invasive bladder cancer cell line. Cell Stress Chaperones 2005, 10:86–103.

82. Zhong M-H, Lee J-S, Kim H-J, Jin D-I, Kim J-L, Lee K-J, Seo J-S: HS990 protects apoptotic cleavage of vimentin in geldanamycin-induced apoptosis. Mol Cell Biochem 2006, 281:11–121.

83. Liu J, Yu L, Tian Y, Cui X, Yan Q, Fu L: Inhibitory effect of ginsenoside-Rg3 on lung metastasis of mouse melanoma transplanted with ribonuclease inhibitor. Zhonghua Zhong Liu Za Zhi 2004, 26:722–725.

84. Chen J, Ou-Yang X, Gao J, Zhu J, He X, Song J: Knockdown of ribonuclease inhibitor expression with siRNA in non-invasive bladder cancer cell line BIU-87 promotes growth and metastasis potentials. Mol Cell Biochem 2010, 349:83–95.

85. Dickson KA: Effect of the Ribonuclease Inhibitor on the Biological Activity of Pancreatic-Type Ribonucleases. PhD thesis. Madison: University of Wisconsin; 2006.

86. Moenner M, Vosoghi M, Ryazantsev S, Glitz DG: Ribonuclease inhibitor protein of human erythrocytes: characterization, loss of activity to oxidative stress, and association with Heinz bodies. Blood Cells Mol Dis 2004, 32(2):162–169.

87. Suginta W, Karoulias N, Aitken A, Ashley RH: The Influences of Human Placental Ribonuclease on the transcriptional activity of c-Jun towards cyclin D1. EMBO J 2001, 20:3459–3472.

88. Thaiparambil J, Bender L, Kline E, Ganesh T, Snyder J, Liotta D, Marcus A: Vimentin: A Novel Chemopreventive Target for Breast Cancer Metastasis. Cancer Res 2010, 69:5063–5063.

89. Kokkinos MI, Wafai R, Wong MK, Newgreen DF, Thompson EW, Waltham M: Vimentin and epithelial-mesenchymal transition in human breast cancer—observations in vitro and in vivo. Cells Tissues Organs (Print) 2007, 185:191–203.

90. Kusinska RU, Kordek R, Pluciniek E, Bednarek AK, Piekarski JH, Potemski P: Does vimentin help to delineate the so-called "basal type breast cancer"? J Exp Clin Cancer Res 2009, 28:118.
S-fluorouracil-induced breast cancer cell using proteomics analysis. J Cancer Res Clin Oncol 2010, 136:1477–1488.

112. Fritz G, Just I, Kaina B: Rho GTPases are over-expressed in human tumors. Int J Cancer 1999, 81:682–687.

113. Seraj MJ, Harding MA, Gildeme JJ, Welch DR, Theodorecs D: The relationship of BMR51 and RhoGDII gene expression to metastatic potential in lineage related human bladder cancer cell lines. Clin Exp Metastasis 2000, 18:519–525.

114. Fujita A, Shida A, Fujioka S, Kurihara H, Okamoto T, Yanaga K: Clinical significance of Rho GDP dissociation inhibitor 2 in colorectal carcinoma. Int J Clin Oncol 2012, 17:137–142.

115. Moissoglu K, McRoberts KS, Meier JA, Theodorecs D, Schwartz MA: Rho GDP dissociation inhibitor 2 suppresses metastasis via unconventional regulation of RhoGTPases. Cancer Res 2009, 69:2838–2844.

116. Zhang B, Zhang Y, Dagher M-C, Shacter E: Rho GTPase Inhibition Protects Cancer Cells against Drug-Induced Apoptosis. Cancer Res 2005, 65:6054–6062.

117. Vercoutter-Edouart AS, Lemoine J, Le Bourhis X, Louis H, Boily B, Nurcombe V, Revillon F, Peyrat JP, Hondermarck H: Proteomic analysis reveals that 14-3-3-Sigma is down-regulated in human breast cancer cells. Cancer Res 2001, 61:76–80.

118. Pan Y, Zhong L, Zhou H, Wang X, Chen K, Yang H, Xiaokai Y, Maimati A, Jiang L, Li X: Roles of vimentin and 14-3-3 zeta/delta in the inhibitory effects of heparin on PM-3C cell proliferation and B16-F10-luc-GS cells metastasis. Acta Pharmacol Sin 2012, 33:798–808.

119. Wong TT, Zhou L, Tong L, Zhao SZ, Li XR, Yu SL, Koh SK, Beuerman RW: Proteomic profiling of inflammatory signaling molecules in the tears of patients on chronic glaucoma medication. Invest Ophthalmol Vis Sci 2011, 52:7385–7391.

120. Croce K, Gao H, Wang Y, Mooroza T, Sakuma M, Shi C, Sukhova GK, Packard RRS, Hogg N, Libby P, Simon DI: Myeloid-related protein-8-14 is critical for the biological response to vascular injury. Circulation 2009, 120:4357–4363.

121. Leach ST, Mitchell HM, Geczy CL, Sherman PM, Day AS: S100 calgranulin proteins S100A8, S100A9 and S100A12 are expressed in the inflamed gastric mucosa of Helicobacter pylori-infected children. Can J Gastroenterol 2008, 22:461–464.

122. Carlson H, Peterson S, Enerbäck C: Cluster analysis of S100 gene expression and genes correlating to psoriasin (S100A7) expression at different stages of breast cancer development. Int J Oncol 2005, 27:1473–1481.

123. Kennedy RD, Gorski JJ, Quinn JE, Stewart GE, James CR, Moore S, Mulligan K, Carlsson H, Petersson S, Enerbäck C: Interaction of triosephosphate isomerase inhibits proliferation of chicken embryonal fibroblast cells. Asian Pac J Cancer Prev 2011, 12:2185–2188.

124. Fritz G, Just I, Kaina B: Rho GTPase Inhibition Protects Cancer Cells against Drug-Induced Apoptosis. Cancer Res 2005, 65:6054–6062.

125. Nair S, Hande MP, Lim LHK: Annexin-1 regulates Growth Arrest Induced by High Levels of Estrogen in MCF-7 Breast Cancer Cells. Mol Cancer Res 2009, 7:266–274.

126. Nair S, Hande MP, Lim LHK: Annexin-1 protects MCF7 breast cancer cells against heat-induced growth arrest and DNA damage. Cancer Lett 2010, 294:111–117.

127. Zhang Z, Huang L, Zhao W, Rigas B: Overexpression of triosephosphate isomerase inhibits proliferation of human myeloid leukemia cells. J Cancer 2012, 3:10265–10272.

128. Lee H-H, Lim C-A, Cheong Y-T, Singh M, Gam L-H: Calcium-binding proteins, S100A8, S100A9 and S100A12 are expressed in the inflamed large cell lymphoma. J Proteome Res 2010, 9:2396–2401.

129. Ang EZ-F, Nguyen HT, Sim H-L, Putti TC, Lim LH: Annexin-1 induced by anti-inflammatory drugs binds to NF-kB inhibiting its activation: Anticancer effects in vitro and in vivo. Cancer Res 2010, 70:2379–2388.

130. Zhan X, Xiao Z, Li C, Xiao X, Yang F, Li D, Li M, Li F, Chen Z: Triosephosphate isomerase and peroxiredoxin 6, two novel serum markers for human lung squamous cell carcinoma. Cancer Sci 2009, 100:2969–2975.

131. Hoffstrom BG, Kaplan A, Letso R, Schmid RS, Turmel GI, Lo DC, Stockwell BR: Inhibitors of protein disulfide isomerase suppress apoptosis induced by misfolded proteins. Nat Chem Biol 2010, 6:900–906.

132. Satish L, Johnson S, Wang J-HC, Post JC, Ehrlich GD, Kathju S: Chaperonin Containing T-Complex Polypeptide Subunit Eta ( CCT-eta) is a Specific Regulator of Fibroblast Motility and Contractility. PLoS One 2010, 1100536.

133. Wong STC, Zhao H: Molecular Diagnostic Methods for Predicting Brain Metastasis of Breast Cancer, International Patent US 2012/0184560 A1.

134. Poulsen N, Andersen V, Møller J, Møller H, Jessen F, Purup S, Larsen L: Comparative analysis of inflamed and non-inflamed colon biopsies reveals strong proteomic inflammation profile in patients with ulcerative colitis. BMC Gastroenterol 2012, 12:76.

135. Tamesa MS, Kuramitsu Y, Fujimoto M, Maeda N, Nagashima Y, Tanaka T, Yamamoto S, Oka M, Nakamura K: Detection of autoantibodies against cyclophilin A and triosephosphate isomerase in sera from breast cancer patients by proteomic analysis. Electrophoresis 2009, 30:2168–2181.

136. Dang Y, Wang Z, Guo Y, Yang J, Xing Z, Mu L, Zhang X, Ding Z: Overexpression of triosephosphate isomerase inhibits proliferation of chicken embryonal fibroblast cells. Invest Ophthalmol Vis Sci 2011, 52:7385–7391.
152. Lee J, Namkoong H, Kim H, Kim S, Hwang D, Na H, Ha S-A, Kim J-R, Kim J: Fibrinogen gamma-A chain precursor in CSF: a candidate biomarker for Alzheimer’s disease. BMC Neurol 2007, 7:14.

153. Akaruna N, Hoogland C, Takada YK, Saegusa J, Ye X, Liu F-T, Cheung AT-W, Takada Y: The COOH-terminal globular domain of fibrinogen gamma chain suppresses angiogenesis and tumor growth. Cancer Res 2006, 66:9601–9607.

154. Palumbo JS, Kombrinck KW, Drew AF, Grimes TS, Kiser JH, Degen JL, Bugge TH: Fibrinogen is an important determinant of the metastatic potential of circulating tumor cells. Blood 2000, 96:3302–3309.

155. Lu C, Mishra A, Zhu YJ, Metzler P, Cheng S-Y: Genomic profiling of genes contributing to metastasis in a mouse model of thyroid follicular carcinoma. Am J Cancer Res 2011, 1:1–13.

156. Zhu W-L, Fan B-L, Liu D-L, Zhu W-X: Abnormal Expression of Fibrinogen Gamma (FGG) and Plasma Level of Fibrinogen in Patients with Hepatocellular Carcinoma. Anticancer Res 2009, 29:2531–2534.

157. Du J, Zheng JH, Chen X-S, Yang Q, Zhang Y-H, Zhou L, Yao X: High preoperative plasma fibrinogen is an independent predictor of distant metastasis and poor prognosis in renal cell carcinoma. Int J Clin Oncol 2012 doi:10.1007/s10147-012-0412-x.

158. Domeika M, Domeika K, Paavonen J, Mårdh PA, Witkin SS: Expression of the 60 kDa heat shock protein in normal and inflamed liver. J Hepatol 1993, 19:159–166.

159. Chen W, Sylstad U, Bellmann K, Burkart V, Kolb H: Human 60-kDa heat-shock protein: a danger signal to the innate immune system. J Immunol 1999, 162:3212–3219.

160. Pockley AG: Heat Shock Proteins, Inflammation, and Cardiovascular Disease. Circulation 2002, 106:1012–1017.

161. Grundmann C, Kreutsmayer SB, Almanzar G, Wick MC, Wick G: Heat Shock Protein 60 and Immune Inflammatory Reactions in Atherosclerosis. Arterioscler Thromb Vasc Biol 2011, 31:960–968.

162. Kligman I, Grillo JA, Witkin SS: Expression of the 60 kDa heat shock protein in peritoneal fluids from women with endometriosis: implications for endometriosis-associated infertility. Hum Reprod 1996, 11:2736–2738.

163. Hwang YJ, Lee SP, Kim SY, Choi YH, Kim MJ, Lee CH, Lee JY, Kim DY: Expression of Heat Shock Protein 60 kDa is Upregulated in Cervical Cancer. Yonsei Med J 2009, 50:399–406.

164. Barazi HO, Zhou L, Templeton NS, Krutzsch HC, Roberts DD: Identification of Heat Shock Protein 60 as a Molecular Mediator of Protein dynamics in responder and non-responder solid tumor xenografts during oncolytic viral therapy. PhD thesis: Bayerische Julius-Maximilians-Universität zu Würzburg. 2008.

165. Golubnitschaja et al. The EPMA Journal 2013, 4:6

166. Hyder SM, Liang Y, Wu J: Expression of the 60 kDa heat shock protein in normal and inflamed human breast cancer cells. J Cancer Res 2009, 1:136–145.

167. Lopez-Dee Z, Pidcock K, Guitierrez LS: Thrombospondin-1: Multiple Paths to Inflammation. Mediators Inflamm 2011, 2011:1–10.

168. Rice AJ, Steward MA, Quinn CM: Thrombospondin 1 protein expression relates to good prognostic indices in ductal carcinoma in situ of the breast. J Pathol 2002, 195:921–925.

169. Alouai-Jamali MA, Song DJ, Benlimame N, Yen L, Deng X, Hernandez-Perez M, Wang T: Regulation of multiple tumor microenvironment markers by overexpression of single or paired combinations of ErbB receptors. Cancer Res 2003, 63:3764–3774.

170. Wang-Rodriguez J, Urtaud V, Rival A, Goodison S: Elevated osteopontin and thrombospondin expression identifies malignant human breast carcinoma but is not indicative of metastatic status. Breast Cancer Research 2003, 5:R136–R143.

171. Manni A, Washington S, Mauger D, Hackett DA, Verderame MF: Cellular mechanisms mediating the anti-invasive properties of the ornithine decarboxylase inhibitor alpha-difluoromethylornithine (DFMO) in human breast cancer cells. Clin Exp Metastasis 2004, 21:461–467.

172. Sargiannidou I, Zhou J, Tuszynski GP: The Role of Thrombospondin-1 in Tumor Progression. Exp Biol Med (Maywood) 2001, 226:726–733.

173. Parkkila S, Rajaniemi H, Parkkila AK, Kivela J, Waheed A, Pastorekova S, Pastorek J, Sly WS, Parkkila S, Karumanchi SA, Stillman IE, Arany Z, Parikh SM: Angiotensin AT1 receptor antagonism ameliorates murine renal protease changes induced by diabetes. J Proteome Res 2009, 8:5541–5549.

174. Lohse AW, Dienes HP, Herkel J, Hermann E, van Eden W, Büschenfelde KHM: Expression of the 60 kDa heat shock protein in normal and inflamed human 60-kDa heat shock protein in women with pelvic inflammatory disease. Hum Reprod 1996, 9:719–726.

175. Xu Y, Binar MA, Su J, Xu B, Kristiansen G, Varga Z, Teng L, Ingber DE, Mammoto A, Kumar R, Alouai-Jamali MA: Fibrin A regulates focal adhesion disassembly and suppresses breast cancer cell migration and invasion. J Exp Med 2010, 207:2421–2437.

176. Stevenson RP, Veltmann D, Machesy LM: Actin-bundling proteins in cancer progression at a glance. J Cell Sci 2012, 125:1073–1079.

177. Yu N: The role of the P2Y2 nucleotide receptors in vascular inflammation. PhD thesis: University of Missouri, 2007.

178. Zhong Z, Yeow W-S, Zou C, Wessell R, Wang C, Pettell RG, Quong JN, Quong AA: Cyclin D1/Cyclin-Dependent Kinase 4 Interacts with Filamin A and Affects the Migration and Invasion Potential of Breast Cancer Cells. Cancer Res 2010, 70:2105–2114.

179. Manni A, Washington S, Mauger D, Hackett DA, Verderame MF: Cellular mechanisms mediating the anti-invasive properties of the ornithine decarboxylase inhibitor alpha-difluoromethylornithine (DFMO) in human breast cancer cells. Clin Exp Metastasis 2004, 21:461–467.

180. Sargiannidou I, Zhou J, Tuszynski GP: The Role of Thrombospondin-1 in Tumor Progression. Exp Biol Med (Maywood) 2001, 226:726–733.

181. Lohse AW, Dienes HP, Herkel J, Hermann E, van Eden W, Büschenfelde KHM: Expression of the 60 kDa heat shock protein in normal and inflamed human breast cancer cells. J Cancer Res 2000, 63:1047–1050.

182. Manni A, Washington S, Mauger D, Hackett DA, Verderame MF: Cellular mechanisms mediating the anti-invasive properties of the ornithine decarboxylase inhibitor alpha-difluoromethylornithine (DFMO) in human breast cancer cells. Clin Exp Metastasis 2004, 21:461–467.

183. Lopez-Dee Z, Pidcock K, Guitierrez LS: Thrombospondin-1: Multiple Paths to Inflammation. Mediators Inflamm 2011, 2011:1–10.

184. Rice AJ, Steward MA, Quinn CM: Thrombospondin 1 protein expression relates to good prognostic indices in ductal carcinoma in situ of the breast. J Pathol 2002, 195:921–925.

185. Alouai-Jamali MA, Song DJ, Benlimame N, Yen L, Deng X, Hernandez-Perez M, Wang T: Regulation of multiple tumor microenvironment markers by overexpression of single or paired combinations of ErbB receptors. Cancer Res 2003, 63:3764–3774.

186. Wang-Rodriguez J, Urtaud V, Rival A, Goodison S: Elevated osteopontin and thrombospondin expression identifies malignant human breast carcinoma but is not indicative of metastatic status. Breast Cancer Research 2003, 5:R136–R143.

187. Fontana A, Filleur S, Guglielmi J, Frappart L, Bruno-Bossio G, Boissier S, Cabon F, Clezardin P: Human breast tumors override the antiangiogenic effect of estramustine-1 in vivo. Int J Cancer 2005, 116:686–691.

188. Manni A, Washington S, Mauger D, Hackett DA, Verderame MF: Cellular mechanisms mediating the anti-invasive properties of the ornithine decarboxylase inhibitor alpha-difluoromethylornithine (DFMO) in human breast cancer cells. Clin Exp Metastasis 2004, 21:461–467.

189. Sargiannidou I, Zhou J, Tuszynski GP: The Role of Thrombospondin-1 in Tumor Progression. Exp Biol Med (Maywood) 2001, 226:726–733.

190. Le Th: Protein dynamics in responder and non-responder solid tumor xenografts during oncolytic viral therapy. PhD thesis: Bayerische Julius-Maximilians-Universität zu Würzburg. 2008.

191. Yu N: The role of the P2Y2 nucleotide receptors in vascular inflammation. PhD thesis: University of Missouri, 2007.
evidences on mitochondrial injury and impaired oxidative metabolism in breast cancer. Mitochondrion 2012, 12:363–369.

196. Suhane S, Bere D, Ramanujam VN: Biomarker signatures of mitochondrial NDUF53 in invasive breast carcinoma. Biochim Biophys Acta 2011, 41:590–595.

197. Kulawiec M, Ovens KM, Singh KP: mtDNA G10398A variant in African-American women with breast cancer provides resistance to apoptosis and promotes metastasis in mice. J Hum Genet 2009, 54:647–654.

198. Gerke V, Moss SE: Annexins: From Structure to Function. Physiol Rev 2002, 82:331–371.

199. Stogbauer F, Weigert J, Neumeier M, Wanninger J, Sporrer D, Weber M, Schaffer A, Enrich C, Wood T, Grewal T, Aslanidis C, Buechler C: Annexin A6 is highly abundant in monocytes of obese and type 2 diabetic individuals and is downregulated by adiponectin in vitro. Exp Mol Med 2009, 41:501–507.

200. Villà De Muga S, Timpson P, Cubillos I, Evans R, Hayes TE, Rentero C, Hegemann A, Reverter M, Leschner J, Pol A, Tebar F, Daly R, Enrich C, Grewal T: Annexin A6 inhibits Ras signalling in breast cancer cells. Oncogene 2009, 28:363–377.

201. Salwe AM, Koumangoye R, Guillory B, Ochieng J, Wu S-Y, Zhang Y-L, Hu S-Y, Zhao W-L, Zhu X-M, Lou G-L, Ni J: The 14-3-3 cancer connection. J Hum Genet 2011, 56:1191–1195.

202. Fujita T, Satoh T, Maeda T, Baba S: Inhibition of PKC-σ-dependent MMP-9 expression in MCF-7 human breast cancer cells. PLoS One 2011, 6:e29363.

203. Fatummbi M, Shetlon J, Atovin SA: MMP-9 increases HER2/neu expression and alters apoptosis levels in human mammary epithelial cells (HMEC). Breast Cancer Res Treat 2012, 135:519–530.

204. Huttenlocher A, Horwitz AR: Integrins in cell migration. Cold Spring Harb Perspect Biol 2013, 5:a009504.

205. Squatrito S, Kaur S, Guha S, Bato SK: The multifaceted roles of neutrophil gelatinase associated lipocalin (NGAL) in inflammation and cancer. Biochim Biophys Acta 2012, 1826:129–169.

206. Yokoda S, Chiba S, Furuyama H, Fujii N: Cerebrospinal fluids containing anti-HSP70 autoantibodies from multiple sclerosis patients augment HSP70-induced proinflammatory cytokine production in monocytes. J Neuroimmunol 2010, 218:129–133.

207. Debelec-Butuner B, Alapinar C, Varisli L, Erbaykent-Tepedelen B, Hamid SM, Gonen-Korkmaz C, Korkmaz KS: Inflammation-mediated abrogation of androgen signaling: An in vitro model of prostate cell inflammation. Mol Carcinog 2012, doi:10.1002/mc.21948.

208. Buxton ILO, Yokdang N, Matz RM: Protein modifications as potential biomarkers in breast cancer. J Proteome Res 2012, 11:3782–387.

209. Conney SS, Latchman DS: Do heat shock proteins have a role in breast cancer? Br J Cancer 1996, 74:717–721.

210. Niedé P, Denniss R, Maynard M, Chambon M, Basile I, Gary-BoBO M, Garcia M: Heat shock cognate 70 protein secretion as a new arrest growth signal for cancer cells. Oncogene 2010, 29:117–127.

211. Yokota S, Chiba S, Furuyama H, Fujii N: Cerebrospinal fluids containing anti-HSP70 autoantibodies from multiple sclerosis patients augment HSP70-induced proinflammatory cytokine production in monocytes. J Neuroimmunol 2010, 218:129–133.

212. Debelec-Butuner B, Alapinar C, Varisli L, Erbaykent-Tepedelen B, HAMID SM, Gonen-Korkmaz C, Korkmaz KS: Inflammation-mediated abrogation of androgen signaling: An in vitro model of prostate cell inflammation. Mol Carcinog 2012, doi:10.1002/mc.21948.

213. Zhao Y, Kong X, Li X, Yan S, Yuan C, Hu W, Yang Q: Metadherin mediates lipopolysaccharide-induced migration and invasion of breast cancer cells. PLoS One 2011, 6:e29363.

214. Fatummbi M, Shetlon J, Atovin SA: MMP-9 increases HER2/neu expression and alters apoptosis levels in human mammary epithelial cells (HMEC). Breast Cancer Res Treat 2012, 135:519–530.

215. Squatrito S, Kaur S, Guha S, Bato SK: The multifaceted roles of neutrophil gelatinase associated lipocalin (NGAL) in inflammation and cancer. Biochim Biophys Acta 2012, 1826:129–169.

216. Yokoda S, Chiba S, Furuyama H, Fujii N: Cerebrospinal fluids containing anti-HSP70 autoantibodies from multiple sclerosis patients augment HSP70-induced proinflammatory cytokine production in monocytes. J Neuroimmunol 2010, 218:129–133.

217. Debelec-Butuner B, Alapinar C, Varisli L, Erbaykent-Tepedelen B, Hamid SM, Gonen-Korkmaz C, Korkmaz KS: Inflammation-mediated abrogation of androgen signaling: An in vitro model of prostate cell inflammation. Mol Carcinog 2012, doi:10.1002/mc.21948.

218. Buxton ILO, Yokdang N, Matz RM: Protein modifications as potential biomarkers in breast cancer. J Proteome Res 2012, 11:3782–387.

219. Conney SS, Latchman DS: Do heat shock proteins have a role in breast cancer? Br J Cancer 1996, 74:717–721.

220. Niedé P, Denniss R, Maynard M, Chambon M, Basile I, Gary-BoBO M, Garcia M: Heat shock cognate 70 protein secretion as a new arrest growth signal for cancer cells. Oncogene 2010, 29:117–127.
238. Welsh J. Vitamin D metabolism in mammary gland and breast cancer. Mol Cell Endocrinol 2011, 347:55–60.

239. Verma M, Kagan J, Sidransky D, Srivastava S. Proteomic analysis of cancer-cell mitochondria. Nat Rev Cancer 2003, 3:789–795.

240. Solazzo M, Fantappiè O, D’Amico M, Sassoli C, Tani A, Cipriani G, Bogani C, Formigli L, Mazzanti F. Mitochondrial expression and functional activity of breast cancer resistance protein in different multiple drug-resistant cell lines. Cancer Res 2000, 60:7235–7240.

241. Chen Y-W, Chou H-C, Lyu P-C, Yin H-S, Huang F-L, Chang W-S, Fan C-Y, Tu H-F, Lai T-C, Lin S-T, Lu Y-C, Wu C-L, Huang S-H, Chan H-L. Mitochondrial proteomics analysis of tumorigenic and metastatic breast cancer markers. Funct Integr Genomics 2011, 11:225–239.

242. Talhouk R. On cell-matrix interactions in mammary gland development and breast cancer. Cold Spring Harbor Perspect Biol 2012, 4:20133040.

243. Manda G, Nechifor MT, Neagu T-M. Reactive Oxygen Species, Cancer and Anti-Cancer Therapies. Curr Chem Biol 2009, 3:342–366.

244. Acharya A, Das I, Chandhok D, Saha T. Heat shock proteins in breast cancer progression. Cancer 2009, 116:1686–1696.

245. Zhang D, Tai LK, Wong LL, Chiu L-L, Sethi SK, Koay ESC. Proteomic study reveals that proteins involved in metabolic and detoxification pathways are highly expressed in HER-2/neu-positive breast cancer. Mol Cell Proteomics 2005, 4:1686–1698.

246. Stresing V, Baltizskueta E, Rubino N, Blanco J, Arríbalt M, Valls J, Janier M, Clézard P, Sanz-Pampolona R, Nieva C, Marro M, Dmitri P, Sierra A. Peroxiredoxin 2 specifically regulates the oxidative and metabolic stress response of human metastatic breast cancer cells in lungs. Oncogene 2013, 32:2394–2404.

247. Feldman DE, Chauhan V, Koay ESC. The unfolded protein response: a novel component of the hypoxic stress response in tumors. Mol Cell Res 2005, 3:597–605.

248. Curtis CD, Thorngren DL, Nardulli AM. Shared signaling pathways in normal and breast cancer stem cells. Breast Cancer in the Post-Genomic Era. Edited by Golubnitschaja I-F, Lai T-C, Lin S-T, Lu Y-C, Wu C-L, Huang S-H, Chan H-L. Cold Spring Harb Perspect Biol 2011, 3:7235.

249. Feldman DE, Chauhan V, Koay ESC. The unfolded protein response: a novel component of the hypoxic stress response in tumors. Mol Cell Res 2005, 3:597–605.

250. Curtis CD, Thorngren DL, Nardulli AM. Shared signaling pathways in normal and breast cancer stem cells. Breast Cancer in the Post-Genomic Era. Edited by Golubnitschaja I-F, Lai T-C, Lin S-T, Lu Y-C, Wu C-L, Huang S-H, Chan H-L. Cold Spring Harb Perspect Biol 2011, 3:7235.

251. Dressing GE, Lange CA. Apoptosis and melanin oncostatic actions. Cancer Detect Prev 2006, 30:118–128.

252. Perik PJ, Van der Graaf WTA, De Vries EGE, Boomsma F, Messerschmidt J, Van Veldhuisen DJ, Sleijfer DT, Gietema JA. Circulating apoptotic proteins are increased in long-term disease-free breast cancer survivors. Acta Oncol 2005, 44:175–183.

253. Vegda S, Posovsky C, Zelter S, Peter B, Bayer E, Geißmann D, Schulte-Hermann R, Geimer C. Plasma from cancer patients featuring a characteristic protein composition mediates protection against apoptosis. Mol Cell Proteomics 2002, 1:387–393.

254. Mangia A, Malfeittone A, Rossi I, Paradiso A, Ranieri G, Simone G, Resta L. Tissue remodelling in breast cancer: human mast cell tryptase as an initiator of myofibroblast differentiation. Histopathology 2011, 58:1096–1106.

255. Parasharuma N, Lobo NA, Ito K, Mosley AR, Habte FG, Zabala M, Smith BR, Lam J, Weissman IL, Clarke MF, Gambhir SS. Remodeling of endogenous mammary epithelium by breast cancer stem cells. Stem Cells 2012, 30:2114–2127.

256. Kim BG, Gao M-Q, Choi YP, Kang S, Park HR, Kang KS, Cho NH. Invasive breast cancer induces laminin-332 upregulation and integrin β4 neoexpression in myofibroblasts to confer an anoikis-resistant phenotype during tissue remodelling. Breast Cancer Res Treat 2012, 14:888–899.

257. Timmermans AM, Montaize H, Trapman-Jansen AM, Martens JW, Foekens JA, Umar A. Abstract 806: Extracellular matrix metalloproteinase inhibitor (EMMPRIN) and CD44 protein complexes are exclusively formed in basal- and normal-like breast cancer cell lines. Cancer Res 2012, 72:806–806.

258. Glunde K, Gugino S, Solaymani P, Pathak AP, Ichikawa Y, Bhuwalma ZM. Extracellular acidification alters lysosomal trafficking in human breast cancer cells. Neoplasia 2003, 5:533–545.

259. Imai Y, Ohmori K, Yasuda S, Wada M, Suzuki T, Fukuda K, Ueda Y. Breast cancer resistance protein/ABCG2 is differentially regulated downstream of extracellular signal-regulated kinase. Cancer Sci 2009, 100:1118–1127.

260. Colis JE, Moreira JMA, Cavadas B, Gromov P, Friis E, Rank F, Gromova I. Identification of extracellular and intracellular signaling components of the mammary adipose tissue and its interstitial fluid in high risk breast cancer patients: toward dissecting the molecular circuitry of epithelial- adipocyte stromal cell interactions. Mol Cell Proteomics 2005, 4:502–522.

261. Cos S, González A, Martínez-Corrpa C, Medavilla MD, Alonso-González C, Sánchez-Barceló EJ. Estrogen-signaling pathway: a link between breast cancer and melatonin oncostatic actions. Cancer Detect Prev 2006, 30:118–128.

262. Perik PJ, Van der Graaf WTA, De Vries EGE, Boomsma F, Messerschmidt J, Van Veldhuisen DJ, Sleijfer DT, Gietema JA. Circulating apoptotic proteins are increased in long-term disease-free breast cancer survivors. Acta Oncol 2005, 44:175–183.

263. Perik PJ, Van der Graaf WTA, De Vries EGE, Boomsma F, Messerschmidt J, Van Veldhuisen DJ, Sleijfer DT, Gietema JA. Circulating apoptotic proteins are increased in long-term disease-free breast cancer survivors. Acta Oncol 2005, 44:175–183.

264. Perik PJ, Van der Graaf WTA, De Vries EGE, Boomsma F, Messerschmidt J, Van Veldhuisen DJ, Sleijfer DT, Gietema JA. Circulating apoptotic proteins are increased in long-term disease-free breast cancer survivors. Acta Oncol 2005, 44:175–183.

265. Perik PJ, Van der Graaf WTA, De Vries EGE, Boomsma F, Messerschmidt J, Van Veldhuisen DJ, Sleijfer DT, Gietema JA. Circulating apoptotic proteins are increased in long-term disease-free breast cancer survivors. Acta Oncol 2005, 44:175–183.

266. Perik PJ, Van der Graaf WTA, De Vries EGE, Boomsma F, Messerschmidt J, Van Veldhuisen DJ, Sleijfer DT, Gietema JA. Circulating apoptotic proteins are increased in long-term disease-free breast cancer survivors. Acta Oncol 2005, 44:175–183.

267. Perik PJ, Van der Graaf WTA, De Vries EGE, Boomsma F, Messerschmidt J, Van Veldhuisen DJ, Sleijfer DT, Gietema JA. Circulating apoptotic proteins are increased in long-term disease-free breast cancer survivors. Acta Oncol 2005, 44:175–183.

268. Perik PJ, Van der Graaf WTA, De Vries EGE, Boomsma F, Messerschmidt J, Van Veldhuisen DJ, Sleijfer DT, Gietema JA. Circulating apoptotic proteins are increased in long-term disease-free breast cancer survivors. Acta Oncol 2005, 44:175–183.

269. Perik PJ, Van der Graaf WTA, De Vries EGE, Boomsma F, Messerschmidt J, Van Veldhuisen DJ, Sleijfer DT, Gietema JA. Circulating apoptotic proteins are increased in long-term disease-free breast cancer survivors. Acta Oncol 2005, 44:175–183.

270. Perik PJ, Van der Graaf WTA, De Vries EGE, Boomsma F, Messerschmidt J, Van Veldhuisen DJ, Sleijfer DT, Gietema JA. Circulating apoptotic proteins are increased in long-term disease-free breast cancer survivors. Acta Oncol 2005, 44:175–183.

271. Perik PJ, Van der Graaf WTA, De Vries EGE, Boomsma F, Messerschmidt J, Van Veldhuisen DJ, Sleijfer DT, Gietema JA. Circulating apoptotic proteins are increased in long-term disease-free breast cancer survivors. Acta Oncol 2005, 44:175–183.

272. Perik PJ, Van der Graaf WTA, De Vries EGE, Boomsma F, Messerschmidt J, Van Veldhuisen DJ, Sleijfer DT, Gietema JA. Circulating apoptotic proteins are increased in long-term disease-free breast cancer survivors. Acta Oncol 2005, 44:175–183.

273. Perik PJ, Van der Graaf WTA, De Vries EGE, Boomsma F, Messerschmidt J, Van Veldhuisen DJ, Sleijfer DT, Gietema JA. Circulating apoptotic proteins are increased in long-term disease-free breast cancer survivors. Acta Oncol 2005, 44:175–183.
Maloni L, Zinno L, Lauria R, Bianco AR, De Piccadici S: A meta-analysis on the interaction between HER-2 expression and response to endocrine treatment in advanced breast cancer. Clin Cancer Res 2005, 11:4741–4748.

Hayes DF, Thor AD, Dressler LG, Weaver D, Edgerton S, Cowan D, Broadwater G, Goldstein LJ, Martinis S, Ingle JN, Henderson IC, Norton L, Winer EP, Hudis CA, Ellis MJ, Berry DA: HER2 and response to paclitaxel in node-positive breast cancer. N Engl J Med 2007, 357:1496–1506.

Pritchard KI, Shepherd LE, O' vaginal EP, Andreadis IL, Tu D, Bramwell VH, Levine MN: HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med 2006, 354:2103–2111.

Gianni L, Pienkowski T, Im Y-H, Roman L, Tseng L-M, Liu M-C, Lluch A, Staraloskwa E, de la Haba-Rodriguez J, Im S-A, Pedrini JL, Poirier B, Morandi P, Semiglavoz V, Srimuninnimit V, Bianchi G, Szado T, Ratnayake J, Ross G, Valagusa P: Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012, 13:25–32.

Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J. Characteristics of primary breast cancer that overexpresses HER2. N Engl J Med 2001, 344:783–792.

Geyer CE, Forster J, Lindquist D, Chan S, Romieu C, Pienkowski T, Jagiello-Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J. Efficacy and safety of paclitaxel and trastuzumab in combination with adjuvant cisplatin for node-positive breast cancer: results of the phase III國際多中心試驗 (TH285). J Clin Oncol 2005, 23:716–725.

Ozanne EM, Brathwaite D, Sepucha K, Moore D, Esserman L, Belkora J: Sensitivity to input variability of the Adjuvant! Online breast cancer prognostic model. J Clin Oncol 2009, 27:214–219.

Eastern Cancer Registry and Information Centre: PREDICT. [http://www.predictmhr.nhs.uk/]

Wishart GC, Badjik CD, Azzato EM, Rashbass J, Caldás C, Pharoah PDP: A population-based validation of the prognostic model PREDICT for early breast cancer. Eur J Surg Oncol 2011, 37:411–417.

Wishart GC, Badjik CD, Dicks E, Provenzano E, Schmidt MK, Sherman M, Greenberg DC, Green AR, Golubnitschaja et al. The EPMA Journal [http://www.epmajournal.com/content/4/1/6]

Armstrong N, Van De Vijver MJ, He YD, van de Vijver M, Van't Veer LJ, Ravdin PM: The 70-gene signature as a signature for survival in breast cancer. N Engl J Med 2004, 350:2187–2197.

Smid M, Wang Y, Zhang Y, Siewerts AM, Yu J, Klijn JGM, Foekens JA, Martens JVM: Subtypes of breast cancer show preferential site of relapse. Cancer Res 2008, 68:3108–3114.

Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M,贝尔格 J, Botstein D, Brown PO: Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001, 98:10869–10874.

Bayes M, Zhou Y, Fritsche LG, Hildebrandt J, Carter S, Aas T, Geisler S, Johnsen H, Høivik E, Heldal M, Røiseland MO, Ross GB. Clinical implications of the 70-gene expression signature. J Clin Oncol 2010, 28:2687–2694.

Wishart GC, Badjik CD, Dicks E, Provenzano E, Schmidt MK, Sherman M, Greenberg DC, Green AR, Golubnitschaja et al. The EPMA Journal [http://www.epmajournal.com/content/4/1/6]
317. Rutgers E, Piccart-Gebhart MJ, Bogaerts J, Delaloge S, Veer LVT, Rubio IT, Viale G, Thompson AM, Passalacqua R, Nitz U, Vindevoghel A, Pierga J-Y, Ravdin PM, Werutsky G, Cardoso F: The EORTC 10041/BIG 03–04 MINDACT trial is feasible: results of the pilot phase. Eur J Cancer 2011, 47:2742–2749.

318. Sparano JA, Paik S: Development of the 21-gene assay and its application in clinical practice and clinical trials. J Clin Oncol 2008, 26:721–728.

doi:10.1186/1878-5085-4-6
Cite this article as: Golubnitschaja et al.: Risk assessment, disease prevention and personalised treatments in breast cancer: is clinically qualified integrative approach in the horizon? The EPMA Journal 2013 4:6.