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

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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

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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-

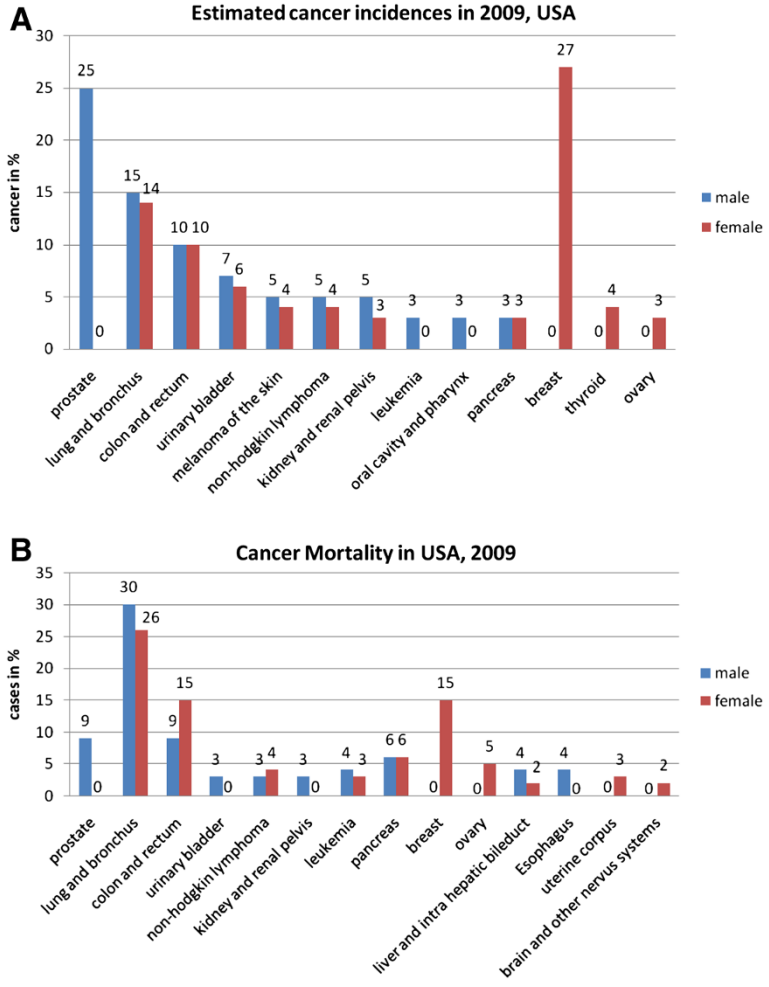

Figure 1 A. Estimated cancer incidence in USA in 2009; B. Cancer related mortality as registered in USA in 2009; data adapted from [2].

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 pre-cancerous / 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. Mathematic 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 sep-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,

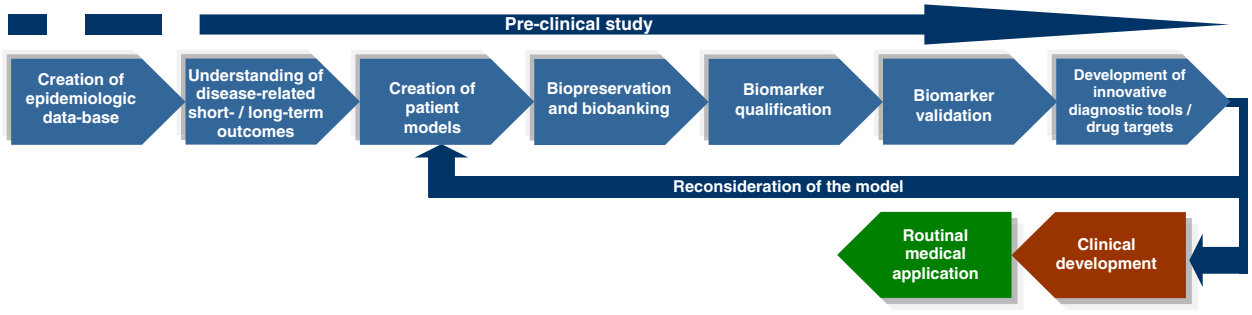

Figure 2 Moving from basic research to clinical implementation: basic steps in creating the robust diagnostic platform and treatments tailored to the person.

type of metastases, receptor status, HER2, etc.) molecular subtypes (luminal a & b, basal, 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 ($T \approx r$) 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.

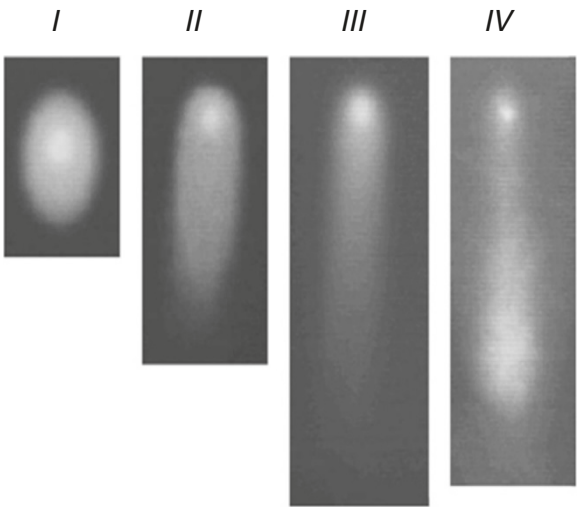

Figure 3 Image of the characteristic classes of comets (representing intact and damaged DNA) are shown *ex vivo* for circulating leucocytes [35].

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 promissing 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

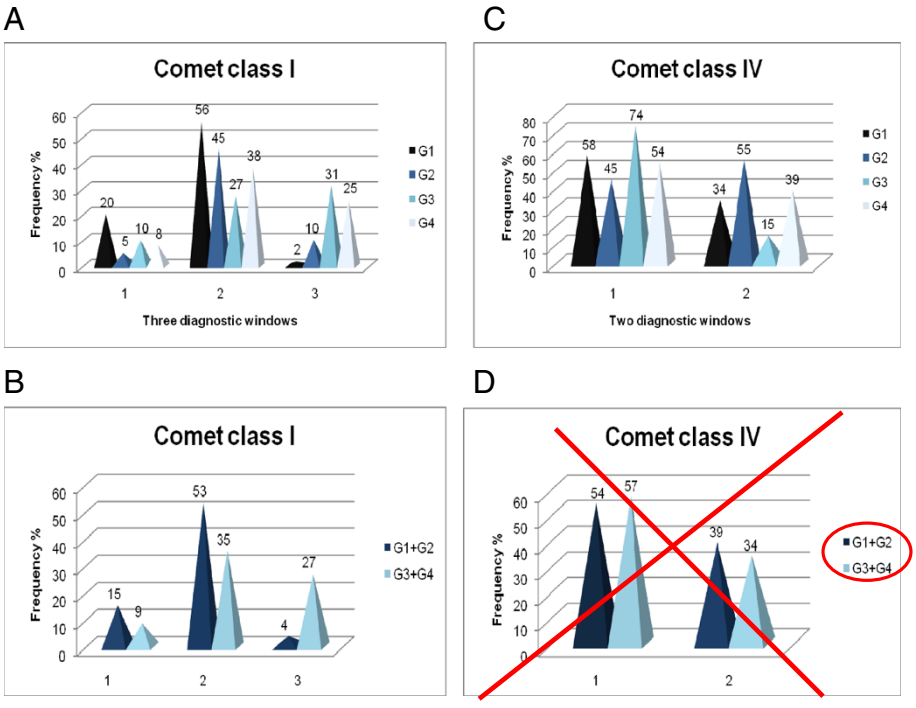

Figure 4 Diagrams estimating a predictive power of the comet-fractions (comet class I and IV), further utilised in the construction of diagnostic windows for breast cancer risk assessment (A, B and C); according to the diagnosis, the recruited patients are grouped as follows: pre-menopausal women with benign alterations in breast tissue (G1); post-menopausal women with benign alterations in breast tissue (G2); invasive lobular & ductal carcinomas in pre-menopausal women (G3); invasive lobular & ductal carcinomas in post-menopausal women (G4); data taken from [36]. Obviously, the diagnostic windows with the comet class IV patterns can be effective only when the hormonal status is considered as one of the selection parameters for subgrouping the patients and concomitant utilisation of the analytical approach proposed by this study.

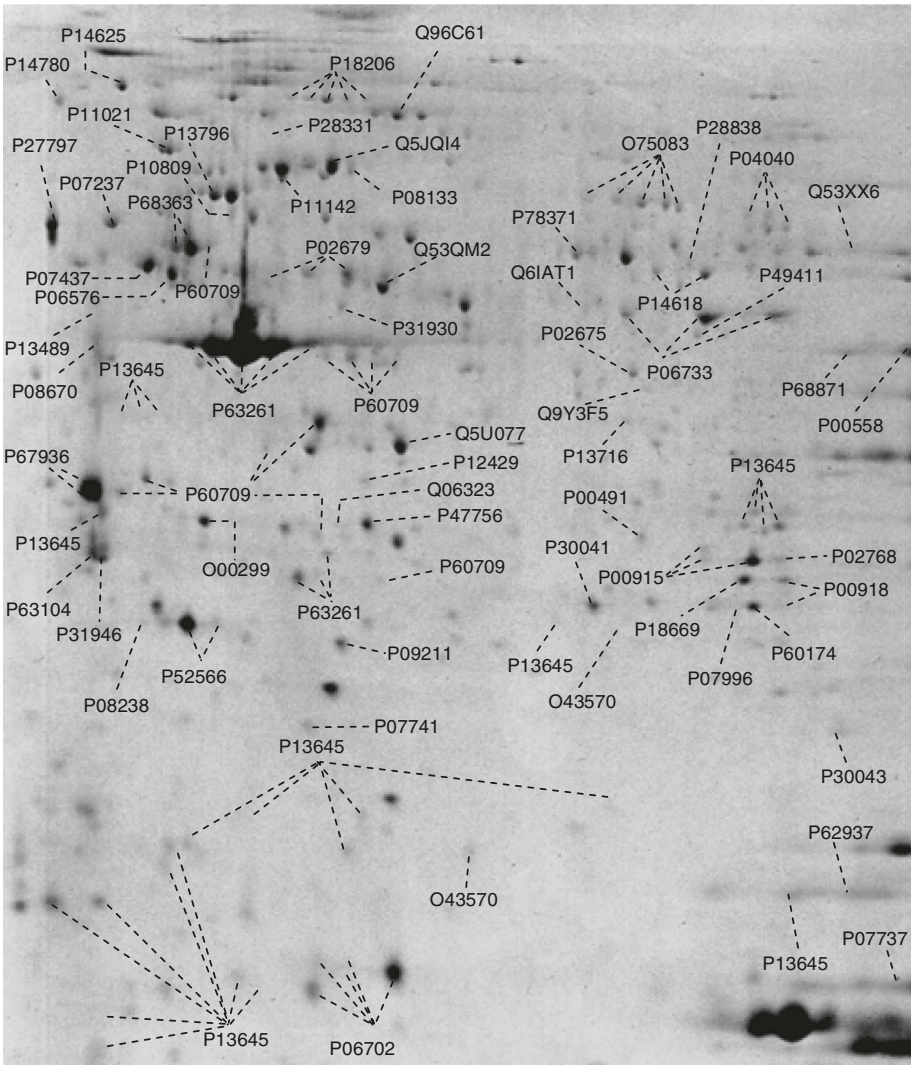

Figure 5 Protein mapping in circulating leucocytes of breast cancer patients; first-dimensional separation was performed in immobilised pH gradient (IPG) strips (Bio-Rad, USA) in the range of IP 4–7. Following first-dimensional separation, the extruded IPG-strips were equilibrated in gel equilibration buffer I (50 mM Tris–HCl, 6 M urea, 30% glycerol, 2% SDS, 1% DTT), followed by equilibration in buffer II (50 mM Tris–HCl, 6 M urea, 30% glycerol, 2% SDS and 260 mM iodacetamide) for 10 min before loading them onto polyacrylamide gels (12% SDS-PAGE) for the second-dimensional resolution in Mini-PROTEAN 3 (Bio-Rad). Altogether, 74 proteins were consequently identified by MALDI-TOF analysis; data taken from [11].

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 radio-therapy
CATEGORY A: significantly (T≤0.1) altered expression profiles in patients *versus* controls							
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 ↓ 3x T=0,001**	Individual reaction **↑ ↓**
157	**P07737**	PROF1_HUMAN	Profilin-1	1, 2, 11, **19, 20, 21**	Microfilamental network cell-migration related protein [11,43-48]	**homogeneous upregulation ↑ 4,0x T=0,02**	**homogeneous suppression ↓ T=0,05**
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 ↓ 2x T=0,02**	Individual reaction **↑ ↓**
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 ↓ 2x T=0,02**	Individual reaction **↑ → ↓**
155	**P30043**	BLVRB_HUMAN	Flavin reductase, NADHP-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, Ca^{2+}-dependent apoptosis-related protein [68-71]	**↓ 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 ↓ 5x T=0,06**	**homogeneous induction ↑ T=0,02**
141	**P13489**	RINI_HUMAN	Placental ribonuclease inhibitor	3, 9, 12, 14, 17, **20, 21**	RNA/nucleotide turnover pathway [77-83]	**homogeneous suppression ↓ 3x T=0,06**	**homogeneous suppression ↓ T=0,1**
82	**P62937**	PPIA_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]	**homogeneous suppression ↓ 3x 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**	AMPL_HUMAN	Cytosol aminopeptidase	4, 11, 14 **19, 20, 21**	Regulatory protein-modification enzyme [105-109]	**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 GDIß)	1, 2, 11, 12, 14, 17, **19, 20, 21**	LyDGI plays a role in the onset of apoptosis and cell migration [11,112-116]	**homogeneous upregulation ↑ T=0,1**	Individual reaction **↑ ↓**

Table 1 Protein profile alterations in breast cancer and under radiotherapy *(Continued)*

148	**P63104**	1433Z_HUMAN	14-3-3 protein zeta/delta (protein kinase C inhibitor)	11, 12, 14, 17, 18, **19, 20, 21**	Cell-cycle checkpoint, stress response protein [117-119]	**homogeneous suppression ↓ 2,5x T=0,1**	**homogeneous suppression ↓ T=0,001**
67	**P06702**	S10A9_HUMAN	Protein S100-A9, Calgranulin	2, 11, 14, 18, **19, 20, 21**	Ca^{2+}-dependent cell-migration related protein [11,120-127]	**↑ 2,5x T=0,11**	Individual reaction **↑ → ↓**
110			not identified protein			**highly upregulated in several MKsT=0,11**	Individual reaction **↑ ↓**
123	**P07237**	PDIA1_HUMAN	Protein disulfide-isomerase precursor, PDI	4, 14, 9, 17, 18, **20, 21**	Stress-related protein modification enzyme [60,128-131]	**↓ 2,5x T=0,12**	Individual reaction **↑ ↓**
104			not identified protein			**highly upregulated in several MKsT=0,12**	Individual reaction **↑ ↓**
CATEGORY B: non-significantly altered expression profiles in patients *versus* controls							
131	**P78371**	TCPB_HUMAN	T-complex protein 1 subunit beta	4, **20, 21**	A member of chaperons family [132,133]	individual upregulation **↑** 2x T=0,15	**homogeneous suppression ↓ T=0,05**
19-21, 39	**P60709**	ACTB_HUMAN	Actin, cytoplasmic 1 (Beta-actin)	1, 2, 11, 14, 18, **19, 20, 21**	Microfilamental network protein [11]	slightly increased **↑** 1,5x T=0,16	Individual reaction **↑ → ↓**
97	**P60174**	TPIS_HUMAN	Triosephosphate isomerase	5, 7, **19, 20, 21**	Energy metabolism related protein [134-137]	individual upregulation **↑** 2x T=0,2	Individual reaction **↑ ↓**
44		ANXA1-HUMAN	Annexin A1 (Calpactin II)	9, 11, 14, 17, 18, **19, 20, 21**	Ca^{2+}-dependent phospholipid-binding proteins, potential anti-inflammatory activity [138-141]	individual upregulation **↑** 2x T=0,2	**homogeneous induction ↑ T=0,1**
80	**P05109**	S10A8_HUMAN	Protein S100-A8, Calgranulin	2, 11, 14, 18, **19, 20, 21**	Ca^{2+}-dependent cell-migration / tumour related protein [11,120-127]	homogeneous **↑** 2,0x T=0,24	Individual suppression **↓**
37	**P47756**	CAPZB_HUMAN	F-actin-capping protein subunit beta (CapZ beta)	1, 2, 11, 14, 18, **19, 20, 21**	Microfilamental network protein [142-145]	slightly increased **↑** T=0,2	Individual reaction **↑ ↓**
137	**P30041**	PRDX6_HUMAN	Peroxiredoxin-6	9, 10, 11, 14, 17, 18, **19, 20, 21**	Multifuctional anti-oxidant, defence, tumour-invasion and metastases related protein [146-150]	slightly increased T=0,2	Individual reaction **↑ ↓**
9-11	**P02679**	FIBG_HUMAN	Fibrinogen gamma chain	11, 17, **19, 20, 21**	Microfilamental network cell-migration related protein [151-157]	homogeneous **↑** 1,5x T=0,24	Individual reaction **↑ → ↓**
130	**P10809**	CH60_HUMAN	60 kDa heat shock protein	4, 5, 7, 11, 13, 17, **19, 20, 21**	Mitochondrial stress response protein, protein-folding [158-166]	slightly increased homogeneous level T=0,25	**homogeneous suppression ↓ T=0,1**
36	**Q5U077**	Q5U077_HUMAN	L-lactate dehydrogenase B	5, 7, 11, **19, 20, 21**	Energy metabolism related protein [134,167-172]	slightly increased **↑** 1,5x	Individual reaction **↑ ↓**
122	**Q96C61**	Q96C61_HUMAN	FLNA protein	1, 2, 11, 14, **19, 20, 21**	Filamin A - actin binding protein has essential role in intercellular junctions [173-178]	homogeneous **↑** 1,5x	Individual reaction **↑ ↓**
151	**P07996**	TSP1_HUMAN	Thrombospondin-1 precursor	2, 15, 11, 14, 17, **19, 20, 21**	The matricellular protein regulating cell adhesion and motility during tissue remodelling, in fibrogenesis & angiogenesis [179-189]	Individual induction **↑** T=0,29	Individual reaction **↑ ↓**

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							
86,87	**P00918**	CAH2_HUMAN	Carbonic anhydrase II	5, 11, 18, **19, 20, 21**	Energy metabolism related protein [98-100,103,104,190,191]	Individual heterogeneous	Individual reaction ↑ ↓
103	**P02675**	FIBB_HUMAN	Fibrinogen beta chain precursor	11, 17, **19, 20, 21**	Microfilamental network cell-migration related protein [151-157]	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 [189,192]	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 [193-197]	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 [127,198-201]	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 [202-206]	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 [207-212]	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 [118,213-216]	highly heterogeneous	**homogeneous suppression ↓ T=0,001**
152	**P14780**	MMP9_HUMAN	Matrix metalloproteinase-9	11, 14, 15, 18, **19, 20, 21**	MMP9 Multifunctional tissue-remodeling protein [217-222]	highly heterogeneous	Individual reaction ↑ ↓
CATEGORY D: similar expression-profiles among patients and controls							
1-5	**P18206**	VINC_HUMAN		Vinculin	Cytoskeletal assembly associated protein	similar	Individual reaction ↑ ↓
6-8, 17, 34, 38, 63, 105, 109, 111				not identified protein spots		similar	Individual reaction ↑ ↓
12,13, 32, 33, 43, 47, 48, 98	**P60709**	ACTB_HUMAN		Actin, cytoplasmic 1 (Beta-actin)	Microfilamental network protein	similar	Individual reaction ↑ ↓
14-15	**P68363**	TBA1B_HUMAN		Tubulin alpha-chain	Microtubule network protein	similar	Individual reaction ↑ ↓
16	**P06576**	ATPB_HUMAN		ATP synthase subunit beta, mitochondrial precursor	Mitochondrial energy metabolism related protein	similar	Individual reaction ↑ ↓
18	**P07437**	TBB2_HUMAN		Tubulin beta-2 chain	Microfilamental network protein	similar	Individual reaction ↑ → ↓
29-31, 51, 52, 1 54–61, 64, 79, 81, 83, 84, 89-92	**P13645**	K1C10_HUMAN		Keratin, type I cytoskeletal 10	Microfilamental network protein	similar	Individual reaction ↑ ↓

Table 1 Protein profile alterations in breast cancer and under radiotherapy *(Continued)*

40, 41	**P63261**	ACTG_HUMAN	Actin, cytoplasmic 2 (Gamma-actin)	Microfilamental network protein	similar	Individual reaction ↑ ↓
42		Q6FHP5_HUMAN	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**	TPM4_HUMAN	Tropomyosin alpha-4 chain	Microfilamental network protein	similar	Individual reaction ↑ ↓
88	**P02768**	ALBU_HUMAN	Serum albumin	Extracellular transport/carrier protein	similar	Individual reaction ↑ ↓
96	**P18669**	PGAM1_HUMAN	Phosphoglycerate mutase 1	Energy metabolism related protein	similar	**homogeneous suppression ↓ T=0,1**
99	**P00558**	PGK1_HUMAN	Phosphoglycerate kinase 1	Energy metabolism related protein	similar	Individual reaction ↑ → ↓
100	**P68871**	HBB_HUMAN	Hemoglobin subunit beta	Oxygen carrier	similar	Individual reaction ↑ ↓
101, 102, 106	**P06733**	ENOA_HUMAN	Alpha-enolase	multifunctional glycolytic enzyme	similar	Individual reaction ↑ → ↓
107	**P14618**	KPYM_HUMAN	Pyruvate kinase, isozymes M1/M2	Energy metabolism related protein	similar	Individual reaction ↑ → ↓
125	**P14625**	ENPL_HUMAN	Endoplasmin precursor (94-kDa glucose-regulated protein)	Signal transduction pathways associated with endoplasmic reticulum stress	similar	**homogeneous suppression ↓ T=0,1**
129	**P13796**	PLSL_HUMAN	Plastin-2	Microfilamental network protein	similar	**homogeneous suppression ↓ T=0,02**
132	**Q53QM2**	Q53QM2_HUMAN	Hypothetical protein ACTR3	Currently uncharacterized protein	similar	**homogeneous suppression ↓ T=0,1**
133	**Q6IAT1**	Q6IAT1_HUMAN	GDI2 protein (GDP dissociation inhibitor 2)	Regulatory protein in the functional cycle and recycling of Rab GTPases	similar	Individual suppression ↓
134		UQCR1_HUMAN	Reductase complex core protein I	Ubiquinol-cytochrome C- reductase, mitochondrial processing peptidase Beta-family	similar	Individual reaction ↑ ↓
138	**P09211**	GSTP1_HUMAN	Glutathione S-transferase P (GST class-pi)	Stress response and anti-oxidant defence protein	similar	**homogeneous induction ↑ T=0,07**
139	**P07741**	APT_HUMAN	Adenine phosphoribosyl-transferase	Nucleotide metabolism	similar	Individual reaction ↑ → ↓
140	**P11021**	GRP78_HUMAN	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)*

145	**P13716**	HEM2_HUMAN	Delta-aminolevulinic acid dehydratase	anti-oxidant defence and detoxification pathways	similar	**homogeneous suppression ⬇ T=0,07**
146	**Q5JQI4**	HSP71_HUMAN	Heat shock 70 kDa protein 1A	Stress response protein	similar	Individual reaction ⬆ ⬇
149	**Q06323**	PSME1_HUMAN	Proteasome activator complex subunit 1	The activator binds to proteasome 20S & enhances peptidase activity, e.g. under stress conditions	similar	Individual reaction ⬆ ⬇
150	**P00491**	PNPH_HUMAN	Purine nucleoside phosphorylase	Nucleotide- and nucleoside turnover, detoxification pathway	similar	Individual suppression ⬇
153	**P12429**	ANXA3_HUMAN	Annexin A3	Membrane architecture and signalling protein	similar	Individual reaction ⬆ ➔ ⬇
154		VDAC1_HUMAN	Voltage-dependent anion-selective channel protein 1	Membrane protein, regulation of cell growth / death via redox-control	similar	Individual induction ⬆
158		Q9Y3F5_HUMAN	A6-related hypothetical protein	Twinfilin-2, Protein tyrosine kinase 9-like, actin-binding protein involved in motile and morphological processes	similar	**Homogeneous suppression ⬇ T=0,1**

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.

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**	

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.

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 expressional 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 prognose 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 prognose 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 diagnostiscs 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 Radiology. MB 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 project at the Department of Radiology. All authors read and approved the final manuscript.

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