Subtypes of breast cancer with varying response to treatment identified

It has been shown by researchers at Vall d'Hebron Institute of Oncology (VHIO) that HER2-positive breast cancer can be classified into four separate subtypes, and have demonstrated that one of these subtypes shows greater response to and greater benefit from chemotherapy and anti-HER2 treatment. Ultimately, this classification of tumor subtypes will lead to better treatment tailored to a specific tumor and improve targeted therapy against HER2-positive breast cancer.

The research is based on observations that HER2-positive tumors respond differently to targeted therapy with anti-HER2 agents – many tumors do disappear but some show no response or become resistant to anti-HER2 therapy combined with chemotherapy. Based on these observations, the aim of the current retrospective study of patients treated in the Phase III NOAH clinical trial was to establish the differences between treatment-resistant and treatment-sensitive tumors in terms of genomics.

It is fundamental to determine the molecular subtype of any breast cancer. Breast cancer was, until recently, classified into three groups dependent on the presence or absence of hormone receptors and the HER2 receptor: hormone-sensitive, HER2-positive and triple-negative (when not included in either of the first two groups). Largely as a result of advances in genomic technologies, over recent years, the classification has been further refined into at least four major breast cancer subtypes (luminal A, luminal B, HER2-enriched and basal-like). The group of researchers in the last year further fine-tuned the classification of hormone-sensitive tumors using genomics.

The group focused on HER2-positive disease in the current study. Approximately 20% of women with breast cancer have HER2-positive tumors, which are characterized by a large number of HER2 receptors and increased proliferative activity of the respective tumor cells – this results in a highly aggressive tumor and a consequent increased risk of relapse and cancer-related death. The prospects and treatment options for patients suffering from HER2-positive breast cancer have been greatly improved by the development of

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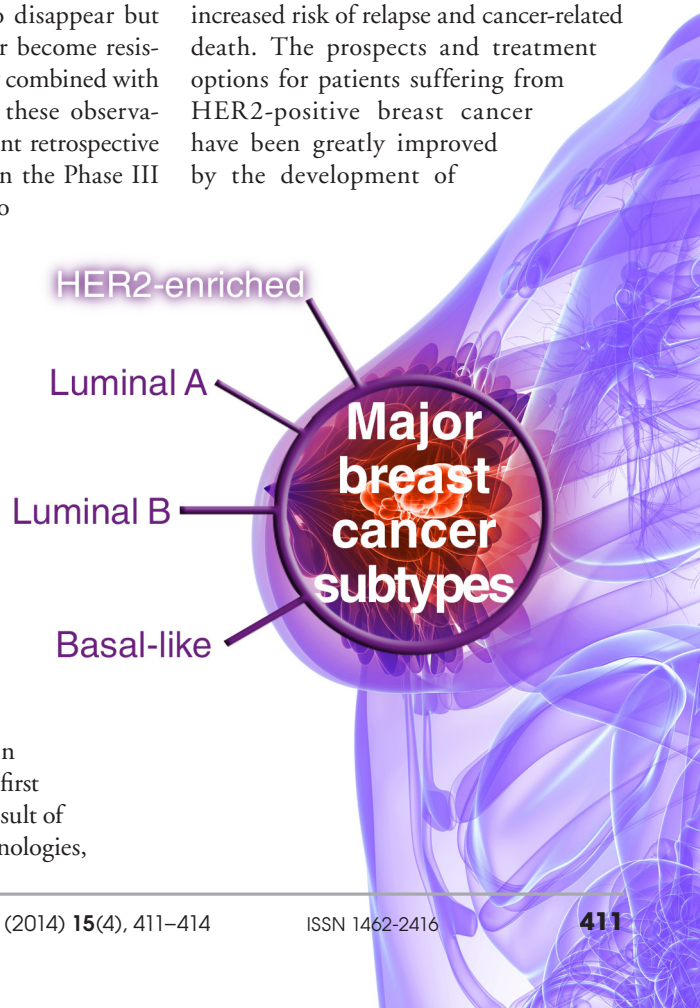

Future Medicine part of fsg

HER2-targeted therapies, such as trastuzumab and lapatinib. However, as HER2 breast cancer is still considered as a single subgroup, all patients receive a similar kind of treatment, even though not all HER2-positive breast cancer responds equally to such treatment.

The response of different molecular subtypes to treatment with anti-HER2 therapy was evaluated in this new study. The four genomic subtypes in breast cancer (luminal A, luminal B, HER2-enriched and basal-like) were revealed to be found in HER2-positive breast cancer and were also discovered to affect treatment response.

"Specifically, we have found that HER2$^+$ tumors in the HER2-enriched subtype have a highly activated HER2-signaling pathway, thereby making them especially sensitive to anti-HER2 targeted therapies such as trastuzumab. Therefore, among the four defined subtypes, HER2-enriched benefits most from specific anti-HER2 therapy," explains Aleix Prat, Principal Investigator of VHIO's Translational Genomics Group who led the study.

More individually tailored treatment strategies may become available to patients through establishing the genomic and clinical characteristics between each of the subtypes, which will lead to more robust treatment for those who will benefit from it. Second, those patients who may benefit from more effectively targeted treatment will receive a more personalized and precise therapy, which will lead to better and longer survival. It is hoped that the latter will be addressed by the PAMELA study, led by Prat through the support of a Susan G Komen foundation grant, involving various Spanish sites and coordinated by the SOLTI Cooperative Research Group. The primary objective of the PAMELA study is to identify those patients with HER2-positive tumors who can be cured with anti-HER2 biological therapies without the need for chemotherapy.

"There is no doubt that gene expression in breast cancer provides us with essential biological information to better determine the diagnosis, treatment, relapse risk and possibilities of survival," says Aleix Prat, "From this moment on, treatment strategies should be based on prior molecular characterization of the tumor, and we must therefore make every effort to ensure accuracy. Genomic tests provide such accuracy and are increasingly being used in daily practice. There really is no other option if we are to continue to combat cancer," he concludes.

Source: Prat A, Bianchini G, Thomas M et al. *Research-based PAM50 subtype predictor identifies higher responses and improved survival outcomes in HER2-positive breast cancer in the NOAH study.* Clin. Cancer Res. *20(2), 511–521 (2014).*

Breast cancer drug proposed as treatment for bladder cancer patients

Amplification of a known driver of some breast cancers, HER2, has been found in micropapillary urothelial carcinoma, a type of bladder cancer, by researchers at the Mayo Clinic (MN, USA). They have also shown that this amplification is associated with particularly aggressive tumors. As is the case for breast cancer, these findings suggest outcomes in micropapillary urothelial carcinoma (MPUC) patients with HER2 amplification could be improved by administering trastuzumab.

HER2 amplification in MPUC results in a form of cancer that is faster growing and spreads quickly with a higher chance of recurrence, which is also seen in breast cancer. Giving bladder cancer patients trastuzumab, which combats HER2 amplification and which is effective in HER2 breast cancers, will hopefully be an effective therapy.

"These findings show it is critical for pathologists to recognize this type of bladder cancer and that providers should be aware of and order the appropriate tests," says John Cheville, a Mayo Clinic pathologist and lead author of the study. "This will be essential for any clinical trial examining the effectiveness of trastuzumab in treating MPUC."

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Of patients with MPUC, 15% were found by the study to have HER2 amplification, compared with 9% of typical bladder cancers. The study also found that aggressive tumors were more likely in patients with HER2-amplified MPUC.

"Targeted treatments for HER2 positive breast cancer have led to markedly improved survival," says Cheville. "In one sense, what we are trying to do with HER2-positive bladder cancer is a relatively simple thing. We are trying to identify prognostic and therapeutic biomarkers, and ultimately match the most effective drug to the individual patient's tumor, rather than its location in the body."

HER2 amplification occurs in approximately 20–30% of cases of breast cancer and is a very important target in therapy, says Cheville. Similarly, using the latest molecular techniques it has been shown by researchers at the Mayo Clinic Center for Individualized Medicine's Biomarker Discovery Program that HER2 amplification is seen in some bladder cancers. These cancers result in more rapid tumor growth and expansion as they produce too much of the HER2 protein product.

Findings like this, which will allow individualized therapy for patients, represent the future of cancer care, and are the beginning of many more to come, said Cheville.

Identification and validation of 12 different molecular/genomic markers was completed by the Biomarker Discovery Program last year, mostly related to the

diagnosis, treatment and prognosis of a variety of cancers.

Source: Schneider SA, Sukov WA, Frank I et al. *Outcome of patients with micropapillary urothelial carcinoma following radical cystectomy: ERBB2 (HER2) amplification identifies patients with poor outcome.* Modern Pathology *doi:10.1038/modpathol.2013.201 (2013) (Epub ahead of print).*

Patient with rare type of leukemia cured by skin cancer drug

A novel treatment for hairy cell leukemia, a rare type of blood cancer, has been demonstrated by a team of scientists from the University of Leicester (UK), using a drug administered to treat skin cancer.

Vemurafenib, a BRAF inhibitor approved as a treatment for advanced melanomas, has been shown by the research to be effective in treating leukemia. The study demonstrated that malignant cells were cleared from the patient's blood and that they made a complete clinical recovery over a number of days following treatment with the oral therapy.

The patient was under care at the Leicester Royal Infirmary and the study was led by the University of Leicester.

Dr Salvador Macip, from the University of Leicester's Department of Biochemistry, explained: "A genetic study of the patient's blood cells allowed us to identify a mutation in the *BRAF* gene that is commonly found in skin cancers. This knowledge enabled us to combat the cancer cells with vemurafenib, which has had proven success as a BRAF inhibitor in melanomas, and showed similar success for this patient who had exhausted all other treatment options, which is fantastic."

"What was most surprising was that the drug did not work in the way we expected it to. Whilst it successfully blocked BRAF and killed the cancerous cells, there was no ability to block the downstream cascade of signals. Therefore more research is required to better understand how this drug works to ensure we are able to use it in the best possible way."

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"This is one of the first clinical examples of this treatment for hairy cell leukemia and we are the first researchers to do a biochemical study of the samples and discover that the drug does not do what it's supposed to be doing."

This example of precision medicine was achieved by targeting the cancer through the tailoring of treatment to the individual patient, with clinicians and research scientists working side-by-side to provide the best possible care.

Professor of Haemato-Oncology at the University of Leicester, Professor Martin Dyer, who is Honorary Consultant Physician, Department of Haematology at Leicester's Hospitals, said: "Precision medicine in which clinicians and basic scientists collaborate to deliver novel and rapid personalized therapies to cancer patients like this is essential."

"We drew blood from the patient on a daily basis, which was analyzed back in the lab to monitor the effects of the drug. The more understanding we have of how treatments such as vemurafenib kill cancer cells, the more effective and targeted treatments can be."

University of Leicester Pro-Vice Chancellor and Head of the College of Medicine, Biological Sciences and Psychology, Professor David Wynford-Thomas, said: "The importance of the close working partnership between the University of Leicester and Leicester's Hospitals is highlighted in advances such as this. World-class research at the University brings direct benefits to patients in Leicester's hospitals in diverse areas including cardiovascular health, kidney research, lung health, diabetes, cancer research and many other areas.

"I am delighted that our research has had such a direct benefit locally – it is another first for the University of Leicester and Leicester Royal Infirmary."

Source: Samuel J, Macip S, Dyer MJ. Efficacy of vemurafenib in hairy-cell leukemia. N. Engl. J. Med. *370(3), 286–288 (2014).*

About the News & Views

The News & Views highlights some of the most important events and research in the field of pharmacogenomics. If you have newsworthy information, please contact:

Sarah Jones, Commissioning Editor, *Pharmacogenomics*,
Future Medicine Ltd, Unitec House, 2 Albert Place, London, N3 1QB, UK;
Tel.: +44 (0)20 8371 6090;
s.jones@futuremedicine.com

Genomic tumor testing becomes more accessible to patients

New gene sequencing equipment and panels developed by clinical laboratory experts and physicians at Dartmouth-Hitchcock Norris Cotton Cancer Center (NCCC; NH, USA) have shown 100% accuracy when testing for abnormal DNA in cancerous tumor cells. The precision of the test for routine patient care was confirmed by the results published in *Clinical Chemistry and Laboratory Medicine* meaning physicians can tailor treatments through knowledge of an individual's DNA, so improving the chances of a successful outcome.

"We evaluated next-generation tools for gene sequencing in our clinical laboratory," said Gregory Tsongalis, director, molecular pathology. "The equipment and approach we are using is faster, more sensitive, and more reliable than previous approaches. It paves the way for routine genetic testing in personalizing cancer care here at the Norris Cotton Cancer Center."

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The test is performed at the NCCC Department of Pathology Clinical Laboratory, which is in compliance with the Clinical Laboratory Improvement Amendment (CLIA) – this body certifies laboratories to standards of quality, proficiency and safety. The laboratory is also accredited by the College of American Pathologists, which perform the gold standard in laboratory accreditation.

"This takes genetic sequencing information or molecular profiling of tumors and puts it into the hands of physicians treating patients today," said Tsongalis

Over 400 patient samples have been run by the laboratory and approximately 80% of these were found to have genetic mutations. Genetic mutations that change the course of treatment are identified in approximately 50–60% of the tests. The test turnaround time is 1 week to 10 days. Tumor samples from metastatic colon cancer, melanoma, gliomas and non-small-cell lung cancers are tested by physicians and scientists. Tests for breast cancer, leukemia and lymphoma will be added in the next few months. Testing on known mutations as a single-gene test is reimbursed by patients' insurance companies. However, each sample is run against a wide panel of genetic mutations by the NCCC laboratory. As part of a molecular profiling strategy to personalize therapy for an individual patient, the Cancer Hotspot Panel tests for mutations in 50 common cancer genes. DNA, which is supposed to well ordered, is considered damaged or mutated when there is an extra or missing section. Mutations in genes can be either inherited or caused by environmental exposure to carcinogens such as sunlight and cigarette smoke. DNA that is damaged can send the wrong messages to cells, which can result in them multiplying and growing in ways that can lead to tumors. Through identification of a tumor's specific mutations physicians can chose medications that precisely target that location for treatment.

Source: Tsongalis GJ, Peterson JD, de Abreu FB et al. *Routine use of the Ion Torrent AmpliSeq™ Cancer Hotspot Panel for identification of clinically actionable somatic mutations.* Clin. Chem. Lab. Med. *doi:10.1515/cclm-2013-0883 (2013) (Epub ahead of print).*

– All stories written by Sarah Jones
Illustrated by Clare Dolan