Avoiding overtreatment
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Regarding a serious illness such as breast cancer, we as patients particularly welcome new research successes. Thus drugs such as Tamoxifen, Herceptin or aromatase inhibitors have become indispensable elements of breast cancer treatment.

In the field of chemotherapy, too, quite a lot has changed: Studies have shown new active ingredients to lead to better overall success. But does this really help each individual patient? Is it really necessary for almost all patients to be treated with chemotherapy and endure the side effects?

These questions can be answered with a definite “no”. But for a long time it was not possible to say precisely which patients do not require chemotherapy. On account of the fear of treating a patient without chemotherapy insufficiently, rather the majority was treated with cytostatics – following the principle “better safe than sorry”.

Fortunately for the patients, research has yielded successes in diagnostics as well. This was made possible mainly by new insights in the field of molecular diagnostics.

Today we know that in particular the biology of a tumour is crucial for the prognosis of the disease – and that patients with a very good prognosis can dispense with chemotherapy without jeopardizing the overall treatment success.

New methods permit precise molecular analysis of the genes that are important for prognosis. When in 2011 in the form of the EndoPredict the first test became available that can be performed directly on-site in the hospitals, it was important to us that the test should be available to the patients at our Municipal Hospital in Brunswick, too, as soon as possible.

We have campaigned for enabling the test to be carried out directly in our pathology, informing the patients very quickly which therapy is right for them. Many patients could thus already be spared chemotherapy – and patients with an increased risk of relapse find the knowledge of their tumour biology helpful in enduring the harsh treatment time in the fight against cancer.
With approximately 390,000 new cases each year in Europe, breast cancer is one of the most common cancers in women. But thanks to intensive research and to development of new therapies, most patients can now be treated successfully...
...but progress in diagnostics could not keep up with the advances in the treatment of disease. Thanks to new therapies on average many women live much longer. Still, the benefits for the individual patient have remained unclear for a long time.

In addition to surgery and radiotherapy, various so-called systemic therapies are available. These are effective throughout the body, for even in early breast cancer it cannot be excluded that some cells may have already detached from the tumour and spread through the organism via the blood and lymph vessels. These cells are to be eliminated by systemic therapies. The focus is on the use of chemotherapy, anti-hormones, and antibodies.

Crucial factors for the right choice of treatment strategy are molecular markers such as hormone receptors and the growth factor receptor HER2/neu. Thus, the tumours can be divided into three subgroups important for diagnosis (see figure above).

According to the current clinical guidelines, hormone receptor-negative (HR-) or HER2/neu-positive tumours are usually treated by chemotherapy, which is especially effective at controlling these two tumour subtypes.

In patients with hormone receptor-positive and HER2/neu-negative breast cancer, chemotherapy offers fewer benefits. This group includes about 65% of all breast cancer patients.

The majority of these patients could be sufficiently treated with antihormonal therapy, which has fewer side-effects, however some patients would still require chemotherapy. Since the classical diagnostic methods do not allow judging clearly which treatment is appropriate, as a precaution the majority of these patients are treated with chemotherapy “to be on the safe side”. Thus many patients are overtreated.

Detailed analyses of the growth behaviour of a tumour at the genomic level have been included into the accepted guidelines (e.g. AGO, St. Gallen, ESMO) only recently. The tests provide valuable additional information to select the therapy most appropriate for an individual patient. The first test of this kind that can be performed on-site in the tumour centres is EndoPredict.
EndoPredict is a multi-gene test for breast cancer patients. The test allows identification of a low-risk group that can expect a chance of more than 95% for metastasis-free survival for at least ten years under solely anti-hormonal treatment for five years.

The EndoPredict is the first mutagen test for breast cancer to provide significant additional information over all other commonly used methods.

The test is either carried out locally in the pathology lab close to the breast cancer centre. Tumour tissue from a standard punch biopsy or surgical specimen is sufficient for the test. Ideally, the result is available within eight hours.

For whom is EndoPredict suitable?

EndoPredict is suitable for the majority of patients with breast cancer, namely for those with a primary, hormone receptor-positive, HER2/neu-negative tumour. It is irrelevant whether lymph nodes have already been affected or not.

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**From tissue sample to therapy decision**

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<tr>
<th>PHYSICIAN</th>
<th>PATHOLOGY</th>
<th>TUMOUR CONFERENCE</th>
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<tbody>
<tr>
<td>Tumour sample from regular surgery or core needle biopsy</td>
<td>Analysis of the tumour sample using the EndoPredict test</td>
<td>Evidence-based therapy decision</td>
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- EITHER
  - Endocrine Therapy
- OR
  - Endocrine Therapy + Chemotherapy
After my breast cancer diagnosis and surgery, the tumour conference of the breast centre suggested chemotherapy to me. One of several markers present in my tumour indicated a need for chemotherapy. Friends called my attention to an article about promising new gene tests that were available. This raised my hopes that the test could assess my personal risk of relapse. This would be justification enough to either forgo chemotherapy to – in the worst case scenario – to know for certain that I would need to undergo chemotherapy to reduce my risk of disease progression. My practicing gynecologist arranged to have tumor material for EndoPredict diagnostics sent to a nearly pathology lab that was qualified to run this test. Incredible relief: The EndoPredict test yielded a low overall risk for me. I’m still glad that I refused to have chemotherapy on the basis of this result!
Then six individual institutes from all over Germany analysed a total of 964 tumour samples from patients with hormone receptor-positive and HER2/neu-negative breast cancer with the goal of developing a diagnostic test to spare many patients chemotherapy.

The influence of more than 20,000 genes was examined in this study. Eventually eight genes were identified as relevant for this therapeutic decision. These genes allow more detailed understanding of the aggressiveness of a tumour.

Based on the activity level of the genes, the EndoPredict (EP score) is calculated using a mathematical formula that evaluates the results on a scale from 0 to 15, values above 5 correspond to the high-risk group.

EndoPredict is the only test of its kind which by default also takes into account the important long-established prognostic factors of tumour size and lymph node status. Combination with the EP score yields the EPclin score. For this it could be demonstrated that as a standalone value it has more significance for patient prognosis than all commonly used examination methods combined.
After the relevant genes had been identified in the identification study and the formulas for calculation developed, the performance of the test was reviewed in two independent clinical trials of the Austrian Breast and Colorectal Cancer Study Group (ABCSG). All the patients in the studies had been treated exclusively with anti-hormonal therapy and without chemotherapy.

The EndoPredict test was performed in laboratories in Germany without knowledge of the patients’ actual clinical outcome. The results were sent to ABCSG in Vienna and compared to the actual courses of disease only there. In these studies it was shown that the test provides additional information complementing the major prognostic factors. Among the patients with a low risk of relapse according to EndoPredict, only four percent have suffered metastasis within ten years. The reliability of the test has thus been successfully demonstrated.

Further analysis of the study data showed that the test result allows a more precise prognosis than the guidelines alone. Thus, according to the S3 guidelines (2008) 1,371 patients belonged to an intermediate, clinically unclear risk group. Of these, EndoPredict unambiguously identified a further 840 as having an excellent prognosis.

<table>
<thead>
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<th>Risk groups by guideline and EndoPredict</th>
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<tr>
<td>1,702 patients</td>
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<tr>
<td>248 patients</td>
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<tr>
<td>low risk</td>
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<tr>
<td>ENDOCRINE THERAPY</td>
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<tr>
<td>5,3% metastases</td>
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<tr>
<td>1,371 patients</td>
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<tr>
<td>intermediate risk</td>
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<tr>
<td>EndoPredict®</td>
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<tr>
<td>840 patients</td>
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<tr>
<td>low risk</td>
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<tr>
<td>EPclin low risk</td>
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<tr>
<td>4,5% metastases</td>
</tr>
<tr>
<td>531 patients</td>
</tr>
<tr>
<td>high risk</td>
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<tr>
<td>EPclin high risk</td>
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<tr>
<td>OR</td>
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<tr>
<td>EITHER ENDOCRINE THERAPY</td>
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<tr>
<td>19,7% metastases</td>
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<tr>
<td>ENDOCRINE THERAPY + CHEMOTHERAPY</td>
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<td>44,5% metastases</td>
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...but tumours positive for hormone receptors and negative for Her2/neu in particular often still metastasise at a later date. Even after 10 years, this type of cancer may form metastases. So far, no gene expression test has been able to calculate the probability for such late metastases.

At the San Antonio Breast Cancer Meeting 2012, the world’s largest breast cancer congress, new data concerning EndoPredict and late metastases were presented: The test identifies a patient sub-population with a low risk for occurrence of metastases both in the first five years (approximately 3%) and in the sixth to tenth year after diagnosis (about 2%).

This suggests not only that the EndoPredict test is able to spare patients unnecessary chemotherapy, but also that this group is sufficiently treated with a five-year anti-hormonal therapy and does not need extended therapy.

If metastases are diagnosed in the course of breast cancer, this often occurs in the first five years after diagnosis...
Anti-hormone therapy has been a part of breast cancer therapy for more than 30 years. Many tumour cells contain so-called hormone receptors – docking sites for the hormones oestrogen and progesterone. When the hormones match the corresponding receptor, the cell receives a growth signal. The objective of anti-hormonal therapy is to prevent hormones from reaching the receptors, thus “starving” the cells.

In anti-hormone therapy with tamoxifen, the receptors are blocked and the oestrogens cannot “dock” any more. Another variant of anti-hormone therapy is an option for women after menopause. In these patients, no oestrogen is produced in the ovaries any more. By taking aromatase inhibitors, the residual production of oestrogen in muscle and adipose tissue is additionally suppressed. Thus, oestrogen can no longer act on the tumour cells.

For a long time, the standard was an anti-hormonal therapy of five years. Current guidelines recommend, however, an extended treatment period of up to ten years.
“Having to undergo chemotherapy - that is a horrible experience that I would never wish on a woman. Your hair falls out, your blood count is unstable, and for months and months you feel miserable all the time. In addition, I do not know what long-term damage the chemotherapy may do to me. Of course, you want to take any therapy if it really helps! That's why, in my opinion, it's good that there is now a test that might spare us breast cancer patients from having to undergo unnecessary chemotherapy.”
• Unambiguous prognostic assessment
• Personalized treatment decision
• Unnecessary chemotherapy can be avoided
• Risk assessment even for late metastases
• Can be carried out locally in the pathology lab
• Results are quickly available
• Results are assessed by the attending specialists taking into account all medical examination results
• Additional information to complement established prognostic factors