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Automating Tissue-Based Breast Cancer Diagnostics

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Its reliance on biomarker evaluation for diagnosis and treatment decisions makes breast cancer care a good example of personalised medicine. In addition to breast cancer biomarkers such as the oestrogen/progesterone receptor and the Ki-67 proliferation marker, HER2 (Human Epidermal growth factor Receptor 2) has received particular attention in recent years. 20 - 30 percent of women with breast cancer test positive for the HER2 protein, associated with an especially aggressive breast cancer variant. HER2 positive patients usually respond poorly to conventional chemotherapy, but benefit from therapy with Herceptin®, a humanised HER2 antibody that costs on average approximately 100,000 dollars per patient. Because this approach does not help HER2 negative patients, doctors need to reliably detect and quantify the expression of this biomarker in breast cancer patients or else risk prescribing expensive and ineffective therapy.

Biomarker detection and analysis is the responsibility of a hospital's pathology department, which follows standardised protocols to score each sample as objectively as possible based on visual criteria. While the ability of pathologists to interpret histomorphological characteristics, such as whether a tissue is cancerous, is extremely reliable, human interpretation of quantitative image features appears more difficult. Measuring the number of cells positive for a specific biomarker and, even more so, visually quantifying the intensity of biomarker stains, may suffer from significant inter-observer variability. However, objective and accurate assessment, especially in case of the predictive biomarker HER2, is highly relevant because therapeutic decisions rely on the quantitative scoring result.

Therefore, pathologists and clinicians now cite a growing need for accurate biomarker quantification tools that can support treatment decisions. Employing software to automate image analysis of histological sections can enhance doctors' understanding of breast and other types of cancer by providing insights into functional and molecular genetic characterisation of tumours. Charité Berlin is working on such a project, which is designed to provide pathologists with access to reliable, objective and standardised information that can inform treatment decisions around breast cancer. This project also has implications beyond pathology into radiology as both fields rely on visual analysis to understand patient disease states.

Seeking to arm its physicians with the best possible information about their patients' health, the Institute of Pathology at the Charité began working with Definiens, a provider of image and data analysis technology, to develop a software solution for automated scoring procedures for breast cancer patients. Based on previous healthcare projects, Definiens has shown the capability to provide robust quantitative image analysis solutions. Both organisations focus on developing a prototype that could be integrated into the pathology department and ensure oncology teams receive reliable information about patient disease states.

Overcoming the Challenges of Conventional Image Analysis

As pointed out above, the analysis of stained sections can vary between pathologists, affecting the reliability of such scores. Automated scoring algorithms are subject to no such inconsistencies, but image analysis technology is constrained in other ways. Pixel-based approaches often cannot determine the morphological features important in a tissue section, and are thus of limited value for most histopathological applications. Definiens' approach, however, unlike other technologies, is designed to analyse structures within the sample, and can understand the relationship of tissue structure, cellular components and subcellular features. These features are particularly important for histological biomarker analyses because they are the basis not only for accurate quantification but also for the reliable discrimination between tumour and healthy tissue.

The computer-assisted diagnostics systems the physicians and scientists from Charité pathology and Definiens conceived integrates different histopathological modalities (similar to different imaging sequences in MRI), analysing the tissue morphology with conventional H&E (Hematoxylin and Eosin) staining; quantifying the protein markers ER (estrogen receptor), PR (progesterone receptor), Ki-67 (cell proliferation), and HER2 with immunohistochemistry; and assessing the HER2 (Human Epidermal growth factor Receptor 2) gene amplification status with SISH (Silver In Situ Hybridisation).

Together, this allows the software to correlate the different tissue features within their spatial context and derive reliable, reproducible scores. While the current scope of the prototype is for research purposes only, the goal is to offer pathologists a comprehensive and objective basis for therapy recommendation, improving breast cancer treatment by selecting the appropriate therapy for the individual patient.

Scoring Mechanism

The software is designed to compute scores based on a wide range of clinically significant variables, particularly morphology and multiplex biomarker expression. In practice, scoring of the tissue section images according to the established algorithms - Elston-Ellis for H&E, Allred for nuclear IHC markers and HercepTest for membrane — allows the pathologist to communicate with clear and well-documented recommendations for targeted therapy. With respect to HER2, cases with a low expression (scores of 0 and 1+) are not suitable for further investigation for inhibitory treatment, while a high HER2 expression (score 3+) is predictive of the efficacy of Herceptin therapy. Cases that score 2+ are followed up with a measurement of the amplification of the HER2 gene using SISH, and, in case of amplification, Herceptin therapy is recommended.

To develop and validate a software prototype that can present a simple numerical score to physicians, Charité Berlin provides Definiens with 150 samples. For each sample, seven sections are stained: one for H&E, one each immunohistochemically stained for biomarkers HER2, ER, PR and Ki67, and SISH analysis for HER2 and Chromosome 17 (Chr17). All these data are fed into a three-level hierarchical classifier. First, relevant features are extracted from the image data for each slide. The programme then determines a score for each modality examined. Finally, the individual scores are combined into a total score to be reviewed by the pathologist and presented to the attending physician. Pathologists manually score half the samples as reference points.

Interface Development

The new prototype works with many different platforms because a pathologist's working environment is marked by a heterogeneous hardware and software environment. On the hardware side of the equation, slide scanners from Aperio, Leica, 3DHitech and Hamamatsu are common. A recently developed system from Philips promises even higher throughput and automation. The data management is often independent but connected to the hardware; companies such as Roche, Aperio and Nexus are the most common such data management providers in pathology labs.

To develop the software as an intuitive component of a pathologist's workflow, Charité Berlin and Definiens are paying special attention to the graphical user interface (GUI), implemented in a web browser with Web 2.0 technologies such as XHTML, Javascript and Ajax. This allows the pathologist to perform different jobs and access data and analysis with a variety of hardware (whether from a desktop, a laptop or a tablet) and operating systems (Microsoft Windows, Apple OS, Linux). The GUI is often similar, if not nearly identical, to radiology applications. The web-based GUI will also allow pathologists to perform remote work (e.g. telepathology) or to consult with other experts using the internet. The system may also be used for education purposes to train students for manual scoring and tissue examination.

Broader Implications

Collaboration between research and clinical disciplines enables physicians to draw upon new findings in predictive molecular pathology, where pathologists not only diagnose a certain disease but also provide molecular characterisation and recommend a particular therapy. In this regard, image analysis promises to provide insights into functional and molecular genetic mechanisms of tumours, and helps translate this knowledge into clinical practice. Furthermore, the software prototype provides a new, image analysis-based evaluation algorithm that considers a range of immunohistochemical factors in recommending treatment decisions. Given the need for more reliable, objective scoring regimens in pathology, it represents what Charité Berlin expects will be among the first in a new generation of image analysis programmes.

Such an image analysis approach can work similarly for radiology as for pathology. Given the convergence of the two fields, one can expect the development, implementation and benefits of new programmes to track Charité Berlin's experience with the breast cancer-oriented software thus far. In this case, software may well provide quality improvements that could augment physicians' clinical effectiveness and help patients receive the best treatment possible.

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