

# The Role of the Pathologist in the Era of Personalized Medicine

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## Increasing Workload of Cancer Diagnosis

According to reports from the American Society of Clinical Oncology (ASCO), within the next 14 years, cancer is predicted to become the leading cause of death in the United States, surpassing ischemic heart disease [1,2]. New diagnoses of cancer are expected to increase by up to 45% by the year 2030, from 1.6 million cases annually to 2.3 million cases [1,2]. These increasing numbers of cases of cancer will stretch clinical services even more, including the diagnostic services provided by the Pathologist (Table 1).

The development and applications of immunohistochemistry have brought phenotypic and functional identification of cells and tissues, with an impact on cancer classification. However, for malignant tumors, no single marker has proved to be a defining factor in distinguishing tumor type, grade or behavior and the predictive power of immunohistochemistry is not 100% accurate [3]. Clinical studies do not support that tumor sub-type guarantees the expected therapeutic response indicated from clinical trial data [3].

## Predictive Role of Histopathology

Prediction of the clinical outcome of cancer for individual patients is performed by the histopathological evaluation of tissue samples obtained during surgical biopsy or resection of the primary tumor [4]. Tumor staging, using the AJCC/UICC-TNM classification summarizes the primary tumor burden (T), the presence of tumor cells in draining and regional lymph nodes (N) and tumor metastases (M) [5]. However, it is now recognized that clinical outcome can vary among patients with the same tumor stage. The current classification systems for human cancer provide limited prognostic information and do not predict response to therapy.

The tissue-based techniques performed in the modern diagnostic clinical pathology laboratory now include 'predictive' immunohistochemistry (IHC), Fluorescence in-situ hybridization (FISH) analysis and the assessment of relevant tissue biomarkers [3,5,6]. Morphological biomarkers of angiogenesis, apoptosis, cell proliferation, macrophages, dendritic cells and lymphocyte subpopulations may all be detected and quantified using immunohistochemistry. From archived diagnostic tumor tissue samples, protein identification by immunohistochemistry (IHC) is routinely used and can be interpreted by light microscopy. Fluorescence in-situ hybridization (FISH) is a more expensive technique that requires laboratories with technical expertise for fluorescence microscopy. In the recent era of targeted therapy for cancer, including immunotherapy, the use of an immune score for tumor lymphocytic infiltration has also been proposed [7,8].

## New Initiative in Precision Medicine

Precision medicine is the approach to disease treatment and prevention, including cancer treatment and prevention that includes information on individual variability in genes, lifestyle, and environment for each person [9]. In January 2015, in the State of the Union address, President Obama announced the Precision Medicine Initiative (PMI) [9]. The PMI will include a Cohort Program that proposes to extend the role of precision medicine to all diseases, including cancer, by building a national research cohort of one million or more U.S. participants [9].

The US Food and Drug Administration (FDA) continue to approve companion diagnostics that provide biomarker information essential for the effective use of a corresponding therapeutic product [4,10]. In July 2015, the FDA announced that it would recognize a regulatory category called 'complementary diagnostics' for tests that provide additional information on how a targeted drug treatment may be used [11]. This new framework from the FDA will also regulate Laboratory Developed Tests (LDTs) manufactured and used within a single laboratory. The FDA's 2016 budget now includes scientific advancements and helps speed the development and evaluation of precision diagnostics and therapeutics [11].

**Table 1:** Practical Considerations for Pathologists in the Era of Personalized Medicine.

Adequate samples of diagnostic tissue are needed to support the increasing portfolio of diagnostic tests required to provide information for physicians and surgeons to treat patients with cancer.
Tissue yields from every sampling procedure should be maximized, using the safest possible procedures.
Pathological data derived from tissue samples are now key determinants of treatment choices for patients with cancer.
The fullest possible clinical information should accompany tissue samples to prevent the waste of resources on unnecessary tests.
Simple predictive Immunohistochemistry (IHC) can reduce the 'cancer-NOS' rate in small diagnostic samples.
Biomarker testing on tissues includes: a) Morphological tumor characteristics; b) Immunohistochemistry (IHC) for protein expression; c) In-situ hybridization which informs about gene copy number or gene rearrangement; d) Mutation testing that reflects changes in DNA gene sequences.
The consistency of pre-analytical steps involved in handling, fixing and processing tissue samples are critical to obtaining accurate biomarker tests.
Histological assessment of material submitted for non-morphological testing (DNA-based or RNA-based) is vital to confirm the presence of tumor.
Biomarker test results should be reviewed in the context of the histopathology, to consider sample adequacy, tissue heterogeneity and risk of false-positive / false-negative results.
Laboratory-based tests should be supported by high-quality internal and external Quality-Assurance (QA) schemes.
A Multidisciplinary Team (MDT) approach to diagnosis and treatment of cancer is a required standard of care.
Pathologists will continue to be important members of the MDT and regular participants in the 'tumor board.'
Multiplex approaches to tissue biomarker analysis may allow simultaneous assessment of several biomarkers within one tumor sample.
It is likely that several different types of test will be required on the same tumor samples, which will always be a problem when tissue is limited, as in biopsy material.

## Molecular Pathology

Molecular pathology now involves pan-genomic analysis, expression array analysis of many thousands of genes, proteomics, RNA analysis and next-generation sequencing of entire cancer genomes continue to provide data [4,12,13]. In support of these techniques, it is important that the Pathologist evaluates the material used for nucleic acid extraction. With these increasing diagnostic demands, there is an increasing requirement for consistent tissue handling, fixation and storage and performance of proteomic and genomic techniques to avoid false-negative or false-positive results [4,12,13].

Some major technical improvements include the introduction of next-generation sequencing and its application to formalin-fixed paraffin-embedded (FFPE) tissue in as part of the routine diagnostic process. The analyses of many genetic alterations can be done in parallel without increasing turn-around time. With this development come the potential new strategies to apply 'off-label' targeted therapies, for treatment-resistant tumors or rare tumors [13].

## Tissue Biobanking

A major bottleneck in biomarker identification and drug development is the availability of high-quality biospecimens with the necessary patient information [14]. A biobank is a repository that collects and stores biological samples, including human tissues, together with genetic and clinical data [14]. Biobanks are a key driver for next-generation biomarkers and drug discovery. They allow validation of the clinical significance of genomic mutations using research to analyze large and diverse collections of patient data. Biobanks are recognized to be increasingly important following the discoveries made by the Human Genome Project which led to rapid developments in genomic research [14]. For tissue-based biobanks, the Pathologist is key in ensuring the required quality control of tissue, including its use, preservation and also analysis of tissue adequacy.

In 2005, the National Institute of Health (NIH) Office of Biorepositories and Biospecimen Research Branch (BBRB) established a system to address what it referred to as, 'the most pressing problem facing 21st-century molecular medical research: limited availability of carefully collected and controlled, high-quality human biospecimens' [15]. The BBRB has developed both evidence-based and standardized processes for the use of human tissue for research and drug development with emphasis on the Ethical, Legal, and Social Issues (ELSI) that are now required to support translational research [15]. This approach will facilitate future regulatory approval of tissue-based molecular therapeutics and their associated companion molecular assays [14].

## Clinical Trials

The role of the Pathologist in clinical trials is to assess tissue samples, perform quality assurance (QA) of tissue adequacy and characterization, to provide an assessment of tissue morphology and other biomarker data [4]. As an example, in 2005/6, the ISEL Phase 3 study of non small-cell lung cancer (NSCLC) reported the largest analysis to date of the relationship between tumor tissue biomarkers and clinical response [16]. In this placebo-controlled study of gefitinib (Iressa), six biomarkers were analyzed in tumor samples. High epidermal growth-factor receptor (EGFR) gene copy number measured by IHC and FISH was a predictor of a gefitinib-related effect versus placebo, on overall survival [16]. This study also highlighted the difficulties in tissue availability for multiple biomarker studies and the importance of histopathology of the tissue samples, which led to further studies using multiplex analysis [17].

Pathologists have an increasing and more complex role than ever. Not only are they responsible for making a tissue diagnosis, but they also have an increasing role in the care of tissue samples and

the biomarker analysis required to place patients into therapeutic categories in this new era of personalized medicine.

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