# The Role of Pathology in the Era of Personalized (Precision) Medicine: Shifting Sands of Time

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## Introduction

Diagnostic pathology in the early 19th century was restricted to postmortem assessment wherein the effects of disease and its sequelae were looked out for, described, and documented and thereby helping the medical personnel in identifying the disease in the clinic. However with the advent of light microscopy in the latter half of the 19th century, thanks to Rudolf Virchow (1821-1902) who was aptly named as "Father of modern pathology" there was a paradigm shift in the field of pathology where the pathologic diagnosis became an intrinsic component in patient management dictating what intervention would the patient need.

Detailed morphologic assessment and evaluation of a tumor under a light microscope led to the characterization of diverse types and morphology of a tumor setting in motion for the microscopic classification systems for several diseases. The classification especially of neoplastic tumors not only helped the pathologists to have a unified nomenclature but also created a better understanding of the diagnosis amongst the treating clinicians.

Just when the widespread knowledge of neoplastic pathology with well-defined classifications were doing round there was a major transpose in the field of pathology in the latter half of 20th century with the advent of immunohistochemistry which was of immense help especially in diagnosing the poorly differentiated neoplasms and more importantly immunohistochemistry served as a cornerstone in the sub classification of lymphoma which previously was solely dependent on morphology alone.

Twentieth century witnessed a major medical field awakening with many dramatic discoveries in cellular and molecular pathways. The knowledge accrued was extrapolated to improve disease diagnostics and prognostics. Many immunomarkers came into the fore which helped both in diagnosis and therapeutics. New genetic and molecular alterations were discovered which conferred differential prognosis for a single morphological disease entity highlighting the need and paving the way for the dawn of molecular classification of tumors.

The shifting sands of time in the field of pathology has propelled the pathologist out of a laboratory and commissioned the pathologist to the patient's bedside making pathology an integral part in the multidisciplinary/ tumor board meetings providing pertinent diagnostic, therapeutic and prognostic information where decisions are made for optimal management on a case-to-case basis paving the way for personalized (precision) medicine. (Figure 1)

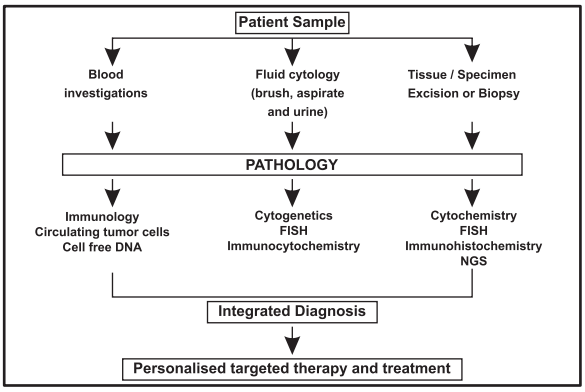


**Figure 1:** A proposed algorithm for the pathology role in personalized (precision) medicine.

## Precision Medicine and Pathology

Gone is the idea of one-size –fits-all approach because history and studies have proven that there are innumerable variables predicting the patient's response to therapy and it markedly differs from one person to person. Personalized (precision) medicine is currently the standard of care in all cancers. Precision medicine is an innovative approach of tailoring disease treatment considering an individual's genetic make-up, environment and lifestyle. Precision medicine takes help of massive parallel sequencing, high throughput technologies to enable detection of minute changes at different molecular levels (DNA, RNA, protein). DNA/RNA sequencing, tissue

microarray technology, mass spectrophotometry, comparative genomic hybridization and digital polymerase chain reaction are the platforms used in arriving at the best plan of treatment.

When a tissue or specimen arrives to pathology lab for tissue diagnosis it is triaged based on the preliminary diagnosis and is segregated into different forms of preservation for appropriate downstream applications. The pathologist examines the tissue and a histologic diagnosis made keeping in mind at the same to assess the tissue for tumor quantity and tumor adequacy for further molecular tests. The pathologist interprets the findings in concert with molecular biologist and reports the relevant details.

The clinician accordingly plans the management of the patient based on the integrated pathology report which now includes morphological, immunohistochemical and molecular report. Integrated pathology report is now routinely practiced in many subspecialties in pathology including neuropathology, thoracic pathology and soft tissue pathology to name a few.

**Role of Pathology in Patient Clinic**

Tumor board meets or multidisciplinary meeting is an integral component of oncologic patient management where the pathologist, radiologist, medical and surgical oncologist come in concert and discuss the diagnosis and plan the management of the patient which aids in optimal treatment decisions.

From an oncologic perspective, preliminary patient management is based on the small tissue biopsy. The surgical management and the neoadjuvant chemotherapy are based on the type and the grade of tumor coupled with informative immunohistochemical markers and molecular tests wherever pertinent. Hormonal receptor status and HER2 amplification status in breast cancer remains a major cornerstone of treatment decision and selection of therapy. Identification of alterations in EGFR, ALK, ROS gene mutations in lung cancer aids the clinician in selecting the targeted drugs for initial management. Few patients have progressive disease which might indicate underlying resistance to the targeted drugs where a repeat biopsy from the involved site can identify concomitantly the tumor and the resistant mutation it has accrued, for example identification of T790M mutation in patients with EGFR mutated lung cancer helps the clinician to escalate the therapy to Osimertinib which is effective in these patients.

Recently predictive biomarkers which identify whether a patient will respond to a particular therapy have become a norm for certain tumors like HER2 receptor status in breast cancer which is a prototype. Some aggressive or poorly differentiated cancers where the patient is not responding to conventional treatment modalities, additional molecular markers or mutations are actively hunted for in a tumor sample which can aid in the addition of drugs which can prolong patient survival. Immune checkpoint inhibitors can be utilized in the therapy by performing immunohistochemistry and looking at the PD1 receptor status in the tumor infiltrating lymphocytes and the PDL1 receptor status in the tumor cells.

The time has come for most of the tumors which were previously classified based solely on morphology to transit into the era of molecular medicine where most of the tumor classification systems currently are on the road to adapting molecular classifications. A classic example would be the lymphoma and leukemia classification which initially was based on morphology alone (Rappaport classification, 1966) followed by addition of immunohistochemistry (Kiel classification, 1975), addition of molecular and clinical profile (Revised European America Lymphoma – REAL classification, 1994) to the current WHO classification which has undergone subsequent editions.

Molecular classification of breast cancer has been well established in the past decade with recent consolidation of molecular classification of endometrial cancer and urothelial cancer. Molecular classification of sinonasal cancers are still in the pipeline. It is now well known that the molecular subgroups have divergent disease biology which might dictate diverse treatment algorithms. The pathologist in the clinic is expected to give not only an integrated report but also provide a holistic report based on the current advances in oncological practice.

**Role of Pathology in Research**

The field of oncopathology witnesses new tumor entities by the day, thanks to the advent of molecular diagnostics. A new tumor/entity is birthed when a pathologist comes across a tumor which does not follow the book. When a cluster of similar cases are identified in the archives or subsequently, the tissue is subjected to molecular studies whichever platform is feasible. When those cases cluster in commonality with respect to genetic rearrangements which translates to clinically divergent prognosis, justifies the cause for those subsets to morph into a new entity. The trigger for identification of new entities is both from the pathologist and the treating physician. When a treating physician perceives the patient is not responding to the time-tested classic therapy of particular tumor or when a pathologist is not able to categorize a tumor into one basket, the communication of information and the transference of perspective amongst each other goes a long way in tailoring the therapy for the particular patient. This asynchrony of the morphology and the patient's

response to therapy gives an essential thrust for research.

An interesting and well-known example is CIC-DUX4 rearranged sarcoma which was previously clumped under Ewing sarcoma because they resembled in morphology and immunophenotype to an extent. Now CIC-DUX4 rearranged sarcoma is pathologically and clinically a distinct entity with divergent treatment and prognosis.

The ever-expanding study of molecular aberrations in different tumor subtypes have led to the discovery of many drugs. The so called 'druggable tumor specific molecular aberrations' are validated in clinical trial and then approved by FDA. These druggable molecular aberrations are initially validated across several available testing platforms and the most appropriate type is chosen as a routine diagnostic/prognostic test.

A classic example would be the discovery of NTRK (Neurotropic tyrosine receptor kinase) rearrangements in many tumors. Other than the classical infantile fibrosarcoma, NTRK rearrangements can be seen in a variety of tumors including secretory carcinoma, subset of pediatric gliomas, colorectal carcinoma, melanoma, and cholangiocarcinoma with NTRK rearranged sarcoma joining the list recently. US FDA approved Entrectinib and Larotrectinib, NTRK inhibitors got accelerated drug approval in 2019. Larotrectinib showed age agnostic and histology agnostic responses making it a breakthrough drug.

**The Next Generation Pathologist**

Pathology is not the same anymore limited to a histologic diagnosis. It is the integration of histologic, molecular, cytogenetic, genomic and epigenetic information into clinically relevant document which conveys the diagnostic, predictive and prognostic information. It is easier said than done. The pathologist must judiciously triage the tissue or specimen which comes to the laboratory for diagnosis anticipating the imminent tests which will be required across different platforms.

Many of the predictive markers can be assessed by immunohistochemistry whereas certain molecular classifications may require the use of cytogenetic and molecular tests ranging from regular PCR (Polymerase Chain Reaction) based assays to next generation sequencing. Appropriate tissue handling, preservation and storage is a critical part of this complex process because all downstream results are dependent on the tissue fidelity.

The future pathologist should be well versed not only with morphology but also molecular pathology which is a subspecialty in itself. A sound knowledge of morphology with an adequate connaissance of molecular pathology sets the apt platform for the genesis of a next generation pathologist which is the need of the hour.

There is a global trend towards sub specializing in pathology akin to surgical oncology where subspecializing is becoming the norm. This molecular era beckons for the realignment of pathology as a specialty where both the educational and the practical aspects of molecular pathology "has" to be intricately woven into the training residency programs with further organ or system based subspecialties. Because gone are the shackles that chained the pathologist to a laboratory, now the role of the pathologist has transcended beyond diagnostics into therapeutics and prognostication aiding the clinician in optimal patient management.

**Conclusion**

The so-called molecular revolution has ushered in a new era catapulting the pathologist to a different dimension where a banal morphologic diagnosis is not the norm. It calls for the judicious use and application of predictive biomarkers coupled with assessment of tumor mutations using next generation sequencing or other platforms with a tiny piece of tumor tissue at hand. It might not suffice to say that the pathologist transforms this tiny tissue which enters the laboratory into a giant leap of information aiding in optimal patient management and continuous medical knowledge.

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