

# Personalized Medicine: Evolving paradigm in Pathology

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## Abstract

The role of Pathologist is vital for diagnosis, treatment and prognosis of the disease. Today this role has assumed enormous proportions because the patient's diagnosis is based on molecular pathology tests and treatment on personalized medicine. It is the need of the hour that the pathologist embraces the new era of genomic medicine and institutes of pathology be adequately equipped to handle the challenges of molecular diagnosis. New curriculum in the post-graduate teaching should be introduced and training programs conducted for the pathologists to meet the requirements of personalized medicine. This article provides an insight to opportunities and challenges for pathologist of today, that call for urgent action.

**Keywords:** Pathologist, Personalized medicine, Molecular diagnostics, Challenges, Biomarkers, Companion diagnostics, Pharmacogenomics, PCR, microarray, Training programs

## Introduction

With the sequencing of the human genome and characterizing the 46 chromosomes, the health care has entered in a new world of medicine<sup>1</sup>. Since then, the terms personalized medicine, biomarkers, transitional medicine have been commonly used in pathology labs, in treating cancer patients, in drug research and drug development<sup>2</sup>

The definition and scope of the term "personalized medicine" varies widely. These examples have been selected to demonstrate the range of definitions that have been proposed: "The use of new methods of molecular analysis to better manage a patient's disease or predisposition to disease." – Personalized Medicine Coalition.<sup>3</sup> "Providing the right treatment to the right patient, in the right dose at the right time". – European Union.<sup>3</sup> "The tailoring of medical treatment to the individual characteristics of each patient" – President's council of Advisors on Science and technology<sup>4</sup>. "Health care that is informed by each person's unique clinical, genetic and environmental information." – American Medical Association.<sup>5</sup> "A form of medicine that uses information about a person's genes"<sup>3</sup>.

The developed countries are already engaged in advanced research, and clinical trials in this area are going on. They are organizing conferences and workshops. In India only few advanced centers have embraced it.

This review article highlights the challenges and opportunities faced by pathologists in adopting molecular pathology as part of their routine work and aims to sensitize them to seize the opportunity before it is too late.

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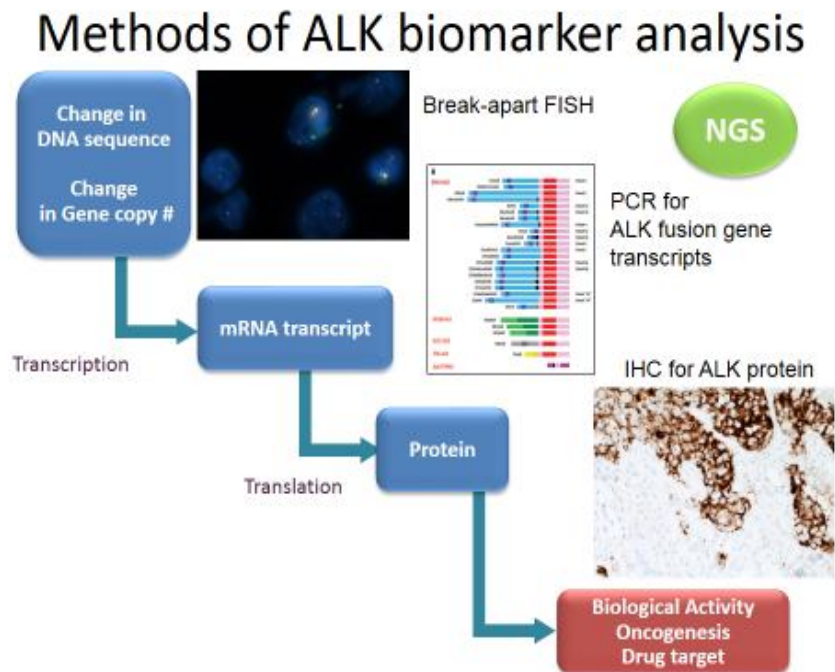
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### Interplay of Drugs and Lab Testing

The concept of personalized medicine is not new. The practice of medicine has always been about treating

each individual patient, and clinicians have observed that different patients respond differently to the treatment. (figure1).



Source: adapted from *Challenges to the Pathologist in Era of Personalized Medicine*. Professor Keith M Kerr, Aberdeen University Medical School, UK

Figure 1. Methods of Biomarker Analysis

The goal of personalized medicine model is to administer right drug, in right dose to the right patient and this is strongly dependent upon the complex interplay of the drugs and diagnostics. This

understanding of the molecular diversity and unpredictable nature of tumors independent upon a new generation of tests. (Table-1)

Table 1. Personalized Medicine Test Categories

Disease	Observation	Name of the Drug	Test
Colorectal cancer	Drug dosage	Camptosar	UGT1a1
Chronic myeloid leukemia	Drug efficacy	Gleevac	Quant BCR-Abl
Chronic myeloid leukemia	Disease status	Campath	Minimum residual disease
Breast cancer	Recurrence risk	Oncotype Dx	Multivariate analysis
Breast Cancer	Predisposition	BRAC Analysis	Gene sequencing and risk analysis
Breast cancer	Drug selection	Herceptin	HER2

Source: Adapted from *Personalized Medicine and Pathology Friend or Foe* by Mara G. Aspinall CAP Foundation

This new set of tests that has revolutionized the personalized medicine is called as COMPANION DIAGNOSTICS, that is the pharmaceutical compound for the treatment of the disease and the diagnostic assay for the molecular and genetic profiling of the tumor is linked together intimately<sup>2</sup>. According to Food and drug administration “a companion diagnostic is an in- vitro diagnostic or an imaging tool that provides information that is essential for the safe and effective use of corresponding therapeutic product<sup>3</sup>. The scientific discipline that deals with the ability to test for variations in genes and their expression through molecular

diagnostics and then to treat with the targeted drugs is called pharmacogenomics. This has immensely helped the physician and surgeons to know which patients will respond to the treatment and which will not decrease adverse drug reactions, decrease the total cost of treatment. This has been possible due to combination of two technical advances, one of them is development of sophisticated DNA and protein detecting techniques, advanced soft wares, including DNA sequencing, micro arrays, comparative genomic hybridization, and digital PCR mass spectrometry. The other is the gigantic leap in managing these data, by so called “cloud computing<sup>6</sup>”.

Patients with melanoma, colorectal cancer, leukemia or metastatic lung cancer, breast or brain cancers are now routinely offered a molecular diagnosis in some clinical centers. Melanoma can be further classified based on its genetic profile, (e.g. BRAF positive) and non- small cell

lung cancer can be EGFR positive or ALK positive. (Figure2) Treatments targeting BRAF, ALK and other gene mutations show a significant benefit over the older methods of trial and error medicine<sup>7</sup>.

### Personalised approach



- Personalised treatment consists of three essential components :
  - Oncogenic target that drives cancer growth
  - Predictive biomarker that detects presence of the target
  - Well conducted clinical studies that confirm treatment efficacy in the identified patient group

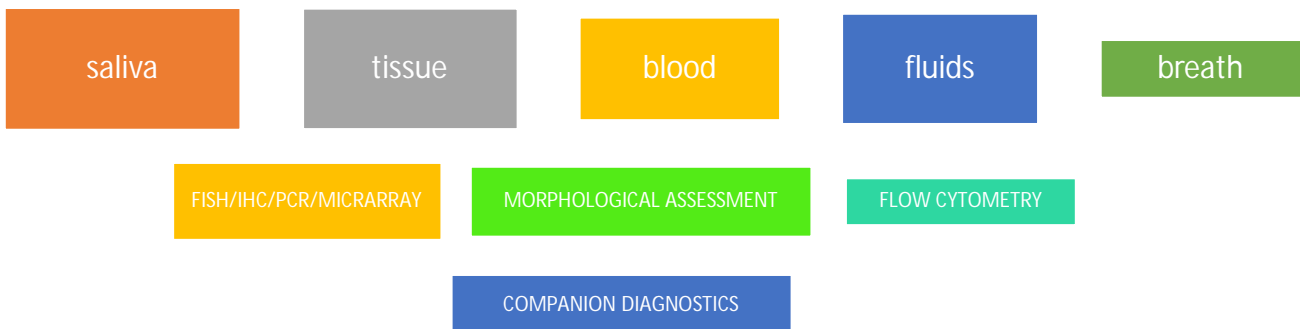


Figure 2.The Personalized Therapy Approach

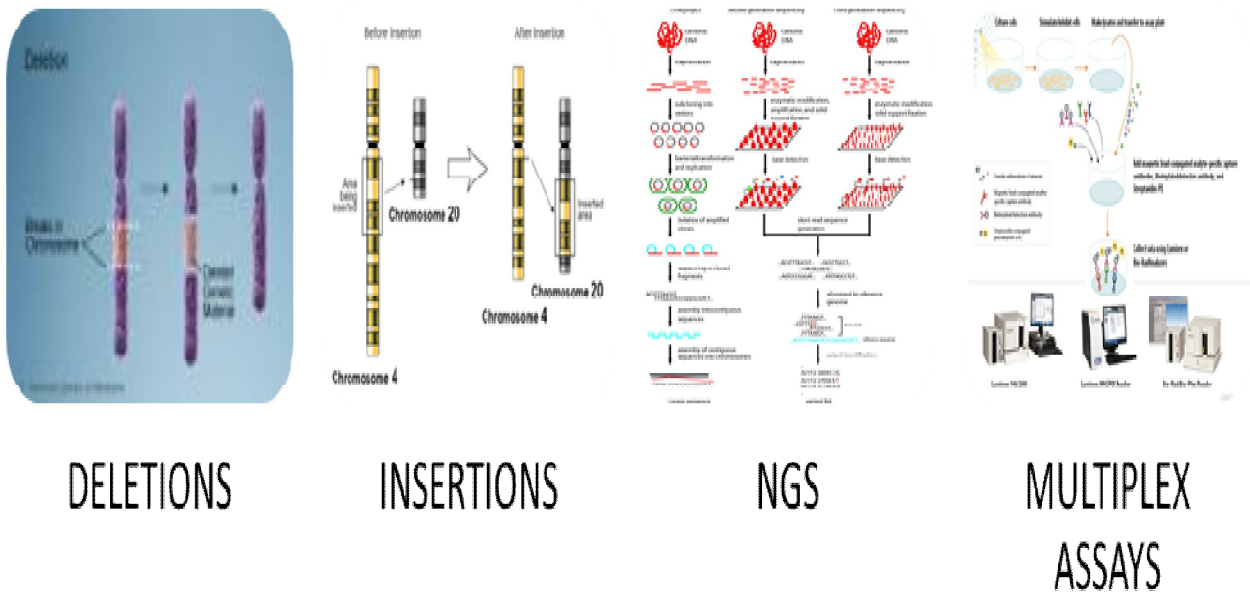
If we look into the personalized medicine timeline, we see that initially it was fear, followed by assessing its value in the patient’s health care and ultimately acceptance in promoting overall wellness and disease prevention. Similar emotions and internal struggles the pathologist seems to be undergoing in today’s era of genomic medicine. Definitely they are at a cross road today. They have the fear of the decline in their market value, they are apprehensive about the explosion of new molecular diagnostics tests. Another fear is handling of new types of specimens which are beyond

tissue. The pathologists show their trepidation about the new technology of “omics” winning over the morphology. Many questions loom large over them, as to which current technologies in pathology can be absorbed by other disciplines of medicine? Will they be able to absorb these technologies completely? How will it affect their growth prospects, jobs, academics and their place in growing industry of “omics” and post genomic era? How will other disciplines of medicine react to their switch from conventional pathologist to a clinical pathologist (table 2)

Table 2.Apprehensions of the Stake Holders

Payers	Additional Costs with No Returns
Physicians	Complex prescriptions
Patients	Access to new drugs shall be denied?
Regulators	Difficult task to handle the new complexities
Diagnosticians	More tests with less reimbursement
Pharmacology/Pharmacy companies	Decline in my market
Pathologists	Reduces my value in the market

Source: Adapted from *Personalized Medicine and Pathology Friend or Foe* by Mara G. Aspinall, CAP foundation



DELETIONS

INSERTIONS

NGS

MULTIPLEX  
ASSAYS

Source: Adapted from *Pathologist in the Era of Personalized Medicine* by Eric Walk

Figure 3. The All New Comprehensive Personalized Pathology Report

**Convert challenges into opportunities**

Indeed, the challenges to a pathologist are many. At the logistic level tissue and sample collection pose a challenge. Reliability of test, morphological assessment, DNA quantity and purity, single test or multiple tests, accuracy of the tests, false positive and false negative,

biomarker heterogeneity, timely delivery of report, communication with both physician and patient the relevance of the test and the cost factors. Despite all these problems, real hero would be who converts these challenges into opportunities and the pathologists are well capable of doing it.

Challenges	Opportunities
Integration of morphological diagnosis and molecular tests. .	To provide expert support, and education to every physician.
Interpreting the genomic data.	Curators of genomic information to patients, in context to disease, inter current health problems, and needs.
Intrusion of other medical disciplines, pharmaceuticals, biotechnology companies.	to acquire skills, demonstrate supreme control and expertise in this area
Regulators of molecular lab tests should be under the jurisdiction of pathologist. Reimbursement issues.	Prove that molecular based tests are cost effective and show the decline in "trial and error prescriptions and misuse of costly therapeutic drugs.
Affirmative stand for close cooperation and team work of all stake holders	To transcend barriers and evolve and maintain leading role.

(Adapted from A national agenda for the future of pathology in personalized medicine<sup>8</sup>.)

Pathologist have the unique skills to help other scientists and clinicians, make sense of complex tissue specimens comprising of many normal and aberrant cell population". William D. Trains, M.D attending thoracic pathologist, Department of Pathology, at Memorial Sloan Kettering Cancer Centre in New York City made his remarks at 16<sup>th</sup> World Conference on Lung Cancer".<sup>9</sup>

"Prediction of therapeutic response by molecular profiling is the logical and natural extension of the work of surgical pathologists".<sup>10</sup>

"Pathologists are the only professionals in the health care/scientific system that can interpret genomic, gene expression and proteomic data in the context of tumor morphology"<sup>2</sup>...Eric Walk

"Personalized Medicine success depends on pathologist ability to make accurate histologic and genetic classification of tumors".<sup>10</sup>

"Only pathologists can provide a comprehensive assessment of companion diagnostics and other

biomarkers on per patient, per clone and per cell basis"<sup>2</sup>...Eric Walk.

"Relying on these types of precision diagnostics makes the pathologist more visible to physician colleagues," says Gene Siegel, MD, Robert W. Mowry, Professor of pathology and director of the Division of Anatomic Pathology at the University of Alabama at Birmingham (UAB).

"It is typically pathologists and clinical laboratory professionals who educate doctors about the availability of new clinical lab tests and how to use them in their practice of medicine." Robert. L Michel<sup>11</sup>

"Companion diagnostic tests reside in the lab. Pathologists have total familiarity with the tests and they are best able to report test results to the clinician who is providing the therapy to the patient."<sup>3</sup>

"Because pathologists are the gateway to high quality, well characterized tissue specimens they are in a unique position to help push these studies forward"<sup>9</sup>.

Several recent studies led by modern molecular pathologists are a testament to their participation and leadership in genome based research of human diseases<sup>11</sup>.

As personalized medicine grows, pathologists need to play a more valuable and visible part in patient care. Now the pathologists and laboratory professionals should be engaged in the heavy task of developing guidelines and SOP's for both the laboratory tests and advanced laboratory diagnostics for giving out " a new personalized pathology report (figure2).The pathology report very soon shall be a completely new report with diagnosis in detail , prognosis of the disease and prediction of the drug efficacy for particular patient<sup>2</sup>. Pathologist will be able to discuss and answer all queries related to disease of the patient. Such pathologists whatever you may label them, "primary care pathologists", "clinical pathologists", "investigative pathologists", "molecular pathologists" or "diagnosticians" are and shall stay as the backbone of medicine.

### Pathology Training Programs

To meet with the challenges the pathologist need to undergo intensive training. Most pathology training programs in India are not adequately preparing their trainees in molecular profiling. This deficiency needs to be addressed. Possible solutions from extending training time through the development of the new or parallel lines. (e.g. anatomic pathology/translational molecular

pathology). Another approach might involve designing the new molecular pathology fellowship training programs that focus more on modern genomic. Some University programs of United States have emerged as role models for medical education in the future<sup>2</sup>. For example, Harvard, medical school has one of the longest standing student programs in which two to three-year course of training with 12-month clinical rotations are offered.

A number of other leading medical institutes like the Duke University School of medicine, Ohio State University Stanford University have actually combined classroom and clinical training in genomic approaches. Pathology trainees can update their knowledge by accessing journals on personalized medicine. Several online courses on genomic medicine are available, COURSERA is one of them, which help you to earn certificate after the end of the 6-8weeks program.

In India it is in very nascent stages, though Tata Memorial Hospital Mumbai, Kolkata and AIIMS in Delhi and CMC hospital at Vellore, do organize few workshops and CME programs, but well-designed training programs which prepare the budding pathologists, post graduates to take up and meet the challenges of personalized medicine at a global level is the call of the day. This should be an important topic of discussion in seminars and conferences where blocks and barriers to its evolution should be addressed in detail amongst eminent pathologists, physicians and other stake holders.

### Discussion

Personalized medicine and its advantages are very appealing, but at the same time a reality check is required to assess how this model can be adopted in India. India with its growing population and high rate of both communicable and non-communicable diseases, will find it very difficult to import expensive drugs and technologies for better health care management. The focus therefore should be on innovations based on biotechnology and pharmacogenomics. One such initiative is IGV (Indian Genome Variation Consortium (Indian Genome Variation Consortium., a government funded program among six labs of the council of scientific and industrial research (CSIR) This program aims to provide data on validated SNP in over a thousand genes in 15000 individuals drawn from Indian subpopulations. This genetic information is expected to facilitate research in field of personalized medicine<sup>12</sup>. However, because of inadequate regulatory and reimbursement guidelines most of the health care systems are unable to truly assess the value of these



medical innovations and companion diagnostics. The stakeholders are still trying to make their way and the payers are reluctant as they face a lot of uncertainty with the price. The policy makers have the clout to make a difference, but they are concerned about the ethical

issues, like who can have access to the data base of personal information as well as health insurance benefits to the patients.<sup>13</sup> Despite all the problems, the time is now to embrace it and to walk on the road of the era of personalized medicine confidently.

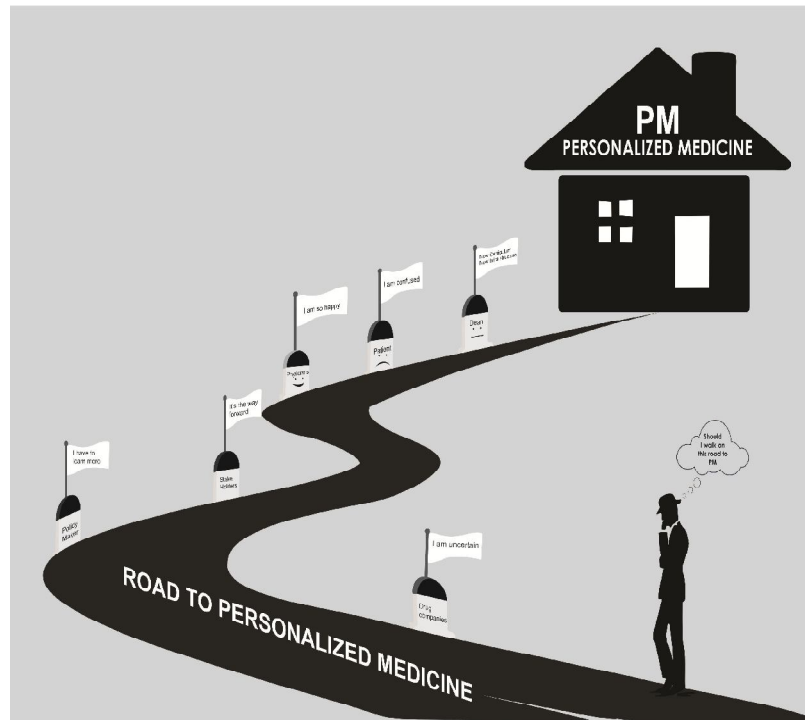


Figure 4. Road of the era of personalized medicine

To conclude the uses of human genomic data to optimize patient care is essence of personalized medicine. This provides a beautiful opportunity for pathologist of today to extend their role beyond the light microscope and bring about a major transformation from just being a reporting pathologist behind the curtain and microscope to a consultant diagnostic oncologist and molecular pathologist. Pathologists have been hesitant to depart from their comfort zone of morphological reporting to the unfathomable territory of genome and proteome. As the personalized medicine evolves, many phases will come, more targeted therapies will be developed, pathologist face a choice today, to take up the challenge and evolve simultaneously hand in hand, adapting in their new roles, as Charles Darwin said "survival of the fittest" or become increasingly less important and give way to other branches of medicine.

**Conflict of Interest:** None

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