

Past, present, and future of molecular oncology in India

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ABSTRACT

Cancer has become an important public health issue in India as ICMR in its latest report on cancer status (summarized in Figure 1), has projected that the total number of new cases would be around 14.5 lakhs in 2016 and the figure is likely to reach 17.3 lakhs by the year 2020. Molecular oncology, a multidisciplinary specialty involving extensive use of genomics, computational biology, and tumor imaging, is the “backbone technology” for the management of the disease. In the modern day India, the growing significance of molecular genetics and cytogenetics in diagnosis as well as management of various cancers has also led to expansion of genetic diagnostic and counseling services. However, skewed geographical distribution, lack of awareness about the disease, symptoms, and diagnostic practices further augments the challenge of treating cancers in India. Lack of adequate infrastructure and absence of mass screening programs are key barriers to timely and accurate diagnosis in India. Key themes that may help in effective management of cancer include cost-effective, early diagnosis and screening; national planning based on robust and granular cancer registry; public-private partnerships to decentralize cancer care delivery and nurture centers of excellence.

Key words: Molecular oncology, cancer registry, molecular genetics

Cancer has become an important public health issue in India as ICMR in its latest report on cancer status (Figure 1), has projected that the total number of new cases would be around 14.5 lakhs in 2016, and the figure is likely to reach 17.3 lakhs by the year 2020. Over 7.36 lakhs people are expected to succumb to the disease in 2016, while the figure is estimated to shoot up to 8.8 lakhs by 2020 (icmr.nic.in/icmrsq1/archive/2016/7.pdf). Hence, it has become imperative that immediate concerted inputs from various agencies be put in, to tackle it.

Molecular oncology, a multidisciplinary specialty involving extensive use of genomics, computational biology and tumor imaging, is the “backbone technology” for the management of the disease. This field investigates the causative genetic alterations that lead to self-sufficiency in growth signals in cells, nonresponse to growth-control signals, evasion of apoptosis, limitless replication potential, sustained angiogenesis, invasion and metastasis.

Since the description of the Watson–Crick DNA model in 1953 to the eventual announcement of sequencing of the entire human genome (in late 1990s), the field of molecular biology has significantly evolved. Advances in this field over the past decade have led to the development of novel platforms such as polymerase chain reaction (PCR), real-time quantitative PCR, microRNA-based diagnostics, fluorescent *in situ* hybridization, gene chip and microfluidic microarrays, DNA methylation studies, single nucleotide polymorphism genotyping as well as high-throughput next generation sequencing. Making use

of such robust platforms, cancer genome projects, including The Cancer Genome Atlas (<https://tcga-data.nci.nih.gov/>) and the International Cancer Genome Consortium (<https://dcc.icgc.org/>) have so far mapped DNA alterations in more than 13,000 cancer samples. These massive sequencing efforts report huge variation in somatic mutations between and within the cancer subtypes. Most of the mutations are, however, “passenger” in nature (neutral or having no role in cancer). Hence, it is crucial to identify the “driver” mutations to identify the molecular elements of cancer. Network of cancer genes, a manually curated cancer gene database, has collected 1571 cancer genes, 518 of which are known cancer genes. The remaining 1053 genes are candidate cancer genes whose “driver” role has been predicted in at-least one original study using a variety of methods.^[2]

These and other such large scale studies have inculcated the development of targeted diagnostics and therapeutics that give an in-depth analysis of an individual’s genetic makeup to create a more personalized approach to health care. For instance, presence/absence of Philadelphia chromosome (Ph, fusion oncoprotein) can be easily checked by PCR which provides a sensitive method for diagnosis, confirmation, predicting response to targeted therapy, and monitor disease status. Imatinib was the first tyrosine kinase inhibitor approved by the Food and Drug Administration (FDA) for the treatment of chronic-, accelerated-, and blast-phase CML.^[3] Similarly, amplification of *N-myc* in neuroblastomas and *erbB-2* in breast and ovarian carcinomas predicts rapid disease progression. Hence, a more aggressive approach is warranted to treat

patients with these amplified oncogenes. Molecular analysis of *ALK* gene rearrangements and its over-expression are used to determine treatment and prognosis of Non-small cell lung cancer and anaplastic large cell lymphoma.^[4,5] Further, study of *BRCA1* and *BRCA2* gene mutations are used to determine the appropriate targeted therapy in ovarian cancer. Estrogen receptor/progesterone receptor status helps determining the hormone therapy in breast cancer.^[6] Molecular analysis reports suggest that cetuximab and panitumumab have a favorable survival impact in patients with *KRAS* wild-type colorectal carcinoma (CRC); as CRC patients with mutated *KRAS* do not benefit from antiepidermal growth factor receptor therapy. In addition, cetuximab plus fluorouracil + leucovorin + oxaliplatin is more effective in achieving a greater response rate and lower risk of disease progression in *KRAS* wild-type than mutated *KRAS* CRC. Cetuximab plus fluorouracil + leucovorin + irinotecan (FOLFIRI) improves survival and response rate in *KRAS* wild-type compared with FOLFIRI alone.^[7] Hence, molecular diagnosis has become increasingly important in dealing with cancer as such imperative information is being deciphered on the roles of specific genetic abnormalities in determining tumor behavior.

In the modern day India, the growing significance of molecular genetics and cytogenetics in diagnosis as well as management of various cancers has led to expansion of genetic diagnosis and counseling services. Medical genetics services are presently available in roughly 13 different premier cities of New Delhi, Lucknow, Vellore, Chandigarh, Hyderabad, Bangalore, Pune, Ahmedabad, Kochi, Trivandrum, Chennai, Manipal, and Mumbai. A large proportion of clinical as well as basic scientific research is conducted under the aegis of premier institutions such as Tata Memorial Center, Mumbai; Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Navi Mumbai; All India Institute of Medical Sciences, New Delhi; Post Graduate Institute of Medical Education and Research, Chandigarh; Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow; Centre for Cellular and Molecular Biology (CCMB), Hyderabad as they are recognized for clinical excellence as well as research contributions (<http://www.mohfw.nic.in>). ACTREC has the largest cancer genetics clinic and provides molecular diagnosis for many monogenic cancer syndromes. The molecular profiling investigations being carried out at the facility involve building signatures for risk assessment and prognosis in cancers of the oral cavity, cervix, breast and brain, and acute lymphocytic leukemia. Similarly, CCMB has ongoing research activities on drug discovery in colon cancer. Institute of Life Sciences, Bhubaneswar has developed nanoparticulate drug delivery systems for cancer therapy (breast and prostate) cells. They are also working on other areas for therapy development for leukemia, vaccine development for malarial disease and test of human immunology with the pathogens (like *Vibrio cholerae* and bacteria). There is no concrete data available for the exact number of diagnostic companies in India. One of the companies is Positive Bioscience, Mumbai,

which provides cancer genomics tests for cancer patients and personal genomics tests for determining disease risk in healthy individuals. Similarly, Mapmygenome, Hyderabad, provides diagnostics for genetic traits and inherited conditions and diseases.

According to a nationwide survey carried out in 2014, there are approximately 200-250 comprehensive cancer centers (which offer multi-modal treatment options). However, their major concentration is in metro cities (EY analysis). This poor geographic distribution of centers limits the access of patients to these advanced treatment options. On account of this skewed geographical distribution, lack of awareness about the disease, symptoms, and diagnostic practices further augments the challenge of mortality rates. Moreover, real cancer incidence in India is conservatively estimated to be at-least 2 times higher than the reported incidence as there are differences in cancer registry and randomized screening studies (Mitra *et al.*, 2010); there is under-diagnosis and low population coverage of the Indian cancer registries. In fact, no PAN-India registry exists that can provide a comprehensive cancer incidence or mortality data. The lone National Cancer Registry Programme (NCRP, established by the ICMR in 1981) provides population-based data from a selected network of 28 cancer registries located across the country (<http://www.ncrpindia.org/>). The data available from this registry has a few limitations such as it is more representative of urban population, there is under-recording of cancer cases and deaths, especially among older people.

In addition, lack of adequate infrastructure and absence of mass screening programs are key barriers to timely and accurate diagnosis in India. The country exhibits high mortality rates in head and neck cancer due to poor awareness levels resulting in ulcers being ignored by many patients, consequently delaying diagnosis; limited inclusion of advanced diagnostic tools in treatment protocols, such as positron emission tomography computed tomography, that can enable improved staging, assessment and treatment planning. Similarly, in case of stomach cancer, there is both lack of overt presentation of symptoms and standard screening tests resulting in poor detection rates. In addition, general physicians and gastroenterologists, who are the first point of contact for such patients, may not be adequately aware or trained to detect and refer, or treat these patients. As mentioned earlier, there is dearth of mass screening programs, for example, efforts for breast cancer screening using methods such as mammography is very low with <2% coverage of the female population.^[8,9] According to an assessment conducted by ICMR in association with the WHO in 2006, mass screening for human papillomavirus using Papanicolaou (PAP) smear method lacks feasibility due to high cost ([www.icmr.nic.in/Publications/plan/ICMR_XIIth_Plan_\(2012-2017\).pdf](http://www.icmr.nic.in/Publications/plan/ICMR_XIIth_Plan_(2012-2017).pdf)). Consequently, due to limited focus and allocation of public resources, less than 2% of female population can be covered with the current facilities available for PAP smear screening.^[10,11]

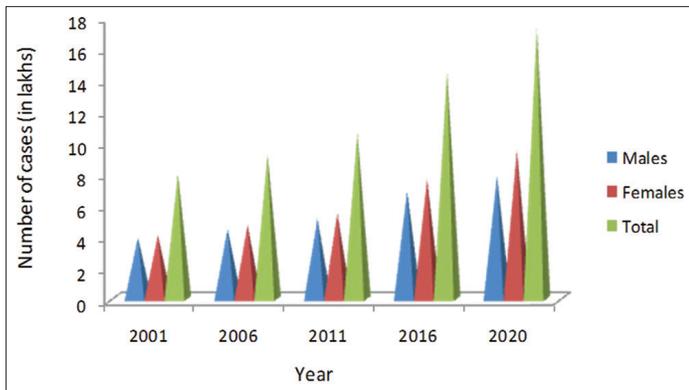


Figure 1: Projected Annual Numbers of New Cancer Cases by Gender during Quinquennial Years 2001-2016

To conclude, it is agonizing to realize that the cancer mortality rate in India is steep due to high incidence, late detection, and inadequate availability of quality, affordable care to majority of the population. Public awareness is needed to make people understand that both the cost and success of treatment is favorably skewed toward early detection of cancer. Further, deterioration in risk factors contributing to its high incidence has also been observed. These factors include increased alcohol consumption; increasing levels of obesity combined with lack of physical activity; changes in diet such as low fiber diet, increased consumption of processed foods, and increased meat consumption.

Key themes that may help in effective management of cancer include cost-effective, early diagnosis and screening; national planning based on robust and granular cancer registry; public-private partnerships to decentralize cancer care delivery and nurture centers of excellence.

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