Consensus Statement DOI: 10.18203/issn.2456-3994.IntJMolImmunoOncol20172642

Oncology Gold Standard™ consensus statement on counseling patients for molecular testing and personalized cancer care

Purvish M. Parikh[1], S. S. Hingmire[2], P. Bhavesh[3], K. Babu Govind[4], P. Mehta[5], A. Verma[6], S. Bondarde[7], R. Singh[8], N. Ghadyalpatil[9], B. Rangrajan[10], G. S. Bhattacharyya[11], H. Malhotra[12], D. C. Doval[13], A. A. Ranade[14], P. M. Shah[15]

[1]Director of Precision Oncology, Asian Cancer Institute, Mumbai, [2]Department of Medical Oncology, Deenanath Mangeshkar Hospital, Pune, Maharashtra, [3]Department of Medical Oncology, HCG Cancer Hospital, Ahmedabad, Gujarat, [4]Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, [5]Department of Medical Oncology, Asian Hospital, Faridabad, Haryana, [6]Department of Molecular Oncology, Max Hospital, New Delhi, [7]Department of Medical Oncology, Satabdi Hospital, Nashik, Maharashtra, [8]Department of Medical Oncology, Artemis Hospital, Gurgaon, New Delhi, [9]Department of Medical Oncology, Yashodha Hospital, Hyderabad, Telangana, [10]Department of Medical Oncology, Kovai Cancer Center, Coimbatore, Tamil Nadu, [11]Department of Medical Oncology, Fortis Hospital, Kolkata, West Bengal, [12]Department of Medicine, SMS Medical College, Jaipur, Rajasthan, [13]Department of Medical Oncology and Research, RGCI, New Delhi, [14]Department of Oncology, Avinash Cancer Clinic, Pune, Maharashtra, [15]Department of Medical Oncology, Shelby Hospital, Ahmedabad, Gujarat, India

Correspondence to: Dr. Purvish M. Parikh, E-mail: purvish@purvishparikh.com

ABSTRACT

Advances in molecular oncology technology and their application to personalized cancer care have evolved very rapidly over the past 5 years. At the same time, there are a lot of conflicting and often misleading statements available on the world wide web. This results in confusion and misunderstanding among cancer patients and their well-wishers. We realized that there was an urgent need for developing a consensus document to address this unmet need. Oncology Gold Standard and Molecular Oncology Society, therefore, took up the challenge and formed an expert group that together prepared this consensus statement on counseling patients for molecular testing and personalized cancer care. This is intended to benefit patients, family and friends by improving their broad understanding and equip them to make an informed decision and take active participation in decision-making for their own cancer management - with respect to prevention, diagnosis, treatment, and follow-up of cancer.

Key words: Genetic mutations, Hereditary cancer, Patient information, Precision oncology

Introduction

Advances in molecular oncology technology and their application to personalized cancer care have evolved very rapidly over the past 5 years.[1] At the same time, there are a lot of conflicting and often misleading statements available on the world wide web.[2] This results in confusion and misunderstanding among cancer patients and their well-wishers.[3] We realized that there was an urgent need for developing a consensus document to address this unmet need.[4] Oncology Gold Standard and Molecular Oncology Society, therefore, took up the challenge and formed an expert group that together prepared this consensus statement on counseling patients for molecular testing and personalized cancer care. This is intended to benefit patients, family and friends by improving their broad understanding and equip them to make an informed decision and take active participation in decision-making for their own cancer management - with respect to prevention, diagnosis, treatment, and follow-up of cancer.[5] Health-care professionals can make copies of this manuscript and make it available to cancer patients and their well-wishers as a patient information tool.

While every effort has been made to provide up-to-date information, medical knowledge is constantly changing. This is not meant to replace a consultation with a health-care professional. This patient information consensus statement contains forward-looking thoughts as well as interpretation of how technology will continue to assist in improving cancer care of individual patients. This consensus statement also includes personal thoughts and opinions of the expert group, which should not be interpreted as endorsement of these views by Molecular Oncology Society, Oncology Gold Standard, International Journal of Molecular and ImmunoOncology or the publishers.

Increasing incidence and risk of cancer – A lifestyle disease

The number of new cancer patients diagnosed every year is increasing – both in India as well as worldwide. The increase is higher in developing countries, where the resources to treat them are limited.[6,7]

Broad reasons for this increase are:

a. People are living longer. Life expectancy is increasing and

is expected to cross 100 years in many countries. In fact, recently a 101-year-old gentleman was operated for hernia in India! Cancer is a disease of advancing age, it is also bound to increase.

b. People take their health for granted and generally follow a lifestyle that leads to higher risk of noncommunicable diseases. As a result, incidence as well as problems of cancer, heart diseases, diabetes mellitus and stroke are rising rapidly, and have become the focus of the department of health for state and central governments.
c. People with suspected cancer are now seeking medical help, consultation and diagnosis.
d. Access to health infrastructure, trained personnel and equipment is increasing across the country.
e. Patients are willing to take treatment even for incurable conditions, have access to government schemes for cancer and are also more openly able to discuss about their cancer illness.

Today India sees more than 11 lakh new cancer patients every year. This has become a major healthcare problem, and the government has announced that cancer is one of the most important noncommunicable diseases on their priority list. General public must join hands with doctors, hospitals, NGOs and the government to ensure that cancer is prevented, diagnosed early and treated effectively across our country.[6,7]

Cancer outcomes are improving significantly

The outcome of patients with cancer has improved significantly and is improving further constantly.[8,9] This is based on our better understanding of the nature of cancer, its subtypes, its natural history, pattern of spread, basis of origin, effect of our lifestyle, mechanism of action of the treatment, and newer therapeutic modalities becoming available to us.

The most important advances made in the last few years in the field of cancer include molecular diagnostics and immune mechanisms of treatment.[1,10]

A. Molecular diagnostics refers to the use of modern techniques to detect changes at the molecular level that help us understand cancer better. It helps us identify if a person has:
   i. Increased hereditary risk of developing cancer
   ii. Increased acquired risk of developing cancer
   iii. Increased risk of spread of cancer
   iv. Aggressiveness or speed of growth of cancer
   v. What changes, if any, are responsible for making the cancer cells grow and spread
   vi. What biomarkers, if any, indicate the status of cancer within the body – is it responding, has it disappeared, has it come back, is it growing/spreading
   vii. What drugs/treatment agents are most likely to benefit the patient
   viii. What drugs/treatment agents are likely to work less/have more side effects
   ix. What drug should be selected from the options currently available as standard of care
   x. Which drug is most likely to benefit after standard of care is exhausted
   xi. What are the peculiar characteristics of his/her tumor that needs to be considered while deciding treatment, follow-up or subsequent management?

   Table 1 shows the common testing methods and their role in the diagnosis of cancer.

   Such potential information may be obtained by use of modern molecular testing tools/techniques. However, this is not applicable in all cases. Even when the testing is done, the result may not give any information which will influence the treatment decision or change in the treatment decision already taken. Patients and their families need to understand this very important limitation of such testing. Nevertheless, a small but significant number of patients with cancer benefit substantially from such testing. Furthermore, the current information explosion and ongoing development of several hundreds of targeted drugs have the potential of making this useful in more and more patients in the future.[11,12]
B. Molecular testing can involve:
   i. Deoxyribonucleic acid (DNA) testing
   ii. Ribonucleic acid (RNA) testing
   iii. Protein testing (proteomics).
C. For such testing the sample to be processed can include:
   i. Tumor biopsy fresh tissue
   ii. Tumor biopsy frozen tissue
   iii. Tumor biopsy paraffin block
   iv. Tumor tissue on microscopic slide
   v. Adjoining normal tissue (fresh or frozen or paraffin block)
   vi. Liquid biopsy - blood, urine, saliva, other body fluids for tumor cells or cell-free DNA.

   The advantages of liquid biopsy are that they can be repeated as frequently as necessary are not invasive and can track changes in the nature/behavior of cancer over time. It is important to note that liquid biopsy cannot replace normal fine needle aspiration cytology/core/

Table 1: Principles of diagnostic testing in cancer patients

Test	Relevance
Body imaging (X-ray/USG/CT scan/MRI/PET)	Stage of the cancer (localized/advanced/metastatic). Based on TNM staging
Light microscopy (conventional histopathology reporting	Type of the cancer (carcinoma/sarcoma/leukemia)
Special staining (immuno-histo-chemistry)	Subtypes of cancer (adenocarcinoma/squamous cell carcinoma/small cell carcinoma)
Molecular testing (DNA/RNA/proteins)	Driver mutations

MRI: Magnetic resonance imaging, CT: Computed tomography, USG: Ultrasonography, PET: Positron emission tomography, DAN: Deoxyribonucleic acid, RNA: Ribonucleic acid

incisional/excisional biopsy that is currently done for the diagnosis of cancer.[11]

D. Immuno-oncology has emerged as the most important advance of recent years, not only in the field of cancer but also in several other diseases.[13] Better understanding of the interaction between tumor cells and our body's normal immune cells is responsible for this. As the normal cell becomes cancerous, there is expression of new antigens on its surface. This can change how the body's immune system recognizes and reacts to the "foreign" cancer cells. The treatment can involve initiation, increase in or even the reduction of the immune response. New targeted agents that take advantage of the immune cell – cancer cell interaction can be divided into three groups:
   i. Acting through PD-1 pathway
   ii. Acting through PD-L1 pathway
   iii. Acting through CTLA-4 pathway.

A few of these are already licensed for use in India; some more are available in the other parts of the world and many more are under clinical development/research.

Over the past decade, there has been tremendous progress in the fight against cancer. More patients get cured, more patients have meaningful prolongation of good quality of life and fewer patients are dying from this disease. This is due to better techniques of diagnosis, availability of better health-care facilities, higher number of qualified oncologists as well as the use of modern drugs to treat patients.[1,10-13]

Molecular genetics and its application for ascertaining the risk of cancer, its early detection, its accurate diagnosis, in selecting the right treatment and dose as well as helping assess the status at follow-up or recurrence are very important additional tools in the fight against cancer.[10-14]

What Prevents Better Outcome in Cancer Patients?

While the health-care professionals use the best information, evidence and treatment techniques/strategies/molecules available to them, the result varies from patient to patient in a significant manner. Why is this?

The answer lies in factors unique to each tumor, each patient's genetic characteristics as well as external factors. While the unique characteristics of the patient's genetic makeup (normal cells as well as tumor cells) can be ascertained by the oncologist by specialized testing, the external factors are controlled solely by the patient and his/her family. Patients and their families need to take responsibility for own health in a proactive compliant manner if they want to optimize intended benefit for themselves.[15]

In the western world, early diagnosis is a reality in many cancers, and increasing number of lives are being saved. However, in India, the SAARC region as well as the majority of the low and middle-income countries worldwide - the procrastinating patient (and their families) are primarily responsible for high cost, increasing side effects and poor outcome of their cancer.[15-17]

Let us explain this radical statement by taking the example of a patient with breast cancer.[18,19]

Let us assume that a lady identifies a lumpish feeling in her breast for the first time today accidentally (or while performing monthly breast self-examination). The lump is likely to be about 1.5 cm in size, and there would be no spread to the axillary lymph nodes or elsewhere in the body (Stage I cancer). If she promptly seeks help from an oncology center, it would be diagnosed as early breast cancer. Her treatment would be simple one-step surgery (mastectomy), would involve a single short admission, she would recover in a matter of weeks, would not require further treatment and would have hardly any impact on quality of life. Her treatment would cost the equivalent of Rs 40,000/- and her chance of cure would be more than 90%.

Most women fail to do so. They wait for a few months for various reasons - hiding the possibility of cancer, "wishing" it disappears or having other priorities in life. The tumor grows in the meantime and becomes locally advanced (Stage II or III). Now, when she goes to the oncology center, her management changes. She requires chemotherapy followed by surgery; treatment lasts for 9-10 months, there is a significant impact on quality of life, and regular visits to the hospital are mandatory. The treatment cost is now equivalent to Rs 1,70,000/- and chance of cure reduces to about 50-60%.

Some women delay even further - till the disease spreads to distant organs and present to the oncology center with metastatic disease (Stage IV cancer) - typically up to 1 year after the lump was noticed first. Now her treatment would involve chemotherapy, radiation therapy and multiple lines of treatment which would continue intermittently for the rest of her life. Hospitals visits become frequent, there is a significant impact on quality of life and some side effects do not regress completely. The treatment cost is now in excess of Rs 7,00,000/-, and the chance of cure is practically zero.

While we have the potential to provide the best chance of care and cure to all our patients with cancer, delay in seeking proper medical help and failure to follow the advice of their doctors is responsible for increasing the cost of therapy, significant side effects and reduction in the chance of favorable response to therapy.[3,7,14,15,19]

Patients (and Families) Need to Take Responsibility for Their Own Health

No matter how hard the doctors try, no matter how many hospitals develop state-of-the-art cancer treatment facilities, no matter how much money is allotted by the government health authorities - the outcome cannot be improved unless

the patients start taking responsibility for their health and illness.[7,14-16,19]

Patients need to stop blaming others and start understanding their own responsibilities to themselves and their families.

If they delay seeking appropriate medical attention in a timely manner, the cost increases 15 times, the duration of treatment increases 20 times, the side effects/impact of quality of life increases 25 times, and the chance of cure disappears.

When this happens, they need to realize that they have only themselves to blame.

The take home message, therefore, is that if patients want to improve their outcome; they must play a very proactive role themselves. This is the only way to get full benefit of doctors, hospitals, and government schemes available for their care. This is the only way to tackle the cancer menace without bankrupting themselves, their families, their communities, and their government.

Besides the example mentioned above, patients and families also contribute to their own inferior outcome by:

a. Failure to follow instructions about intake of medicines – compromising on dose delivery (especially true for oral medication – both cancer-directed systemic therapy as well as supportive care medication).
b. Use of alternative and complementary medicine without seeking the permission of or even informing their oncologists.
c. Continuing to follow unhealthy habits and lifestyle even after the diagnosis of their cancer (e.g., tobacco).
d. Procrastinating by not giving consent for medical management – either due to financial reasons or other conflicts within the family (everyone starts giving advice – often contradicting the recommendation by their oncologist).
e. Hiding facts from their health-care team – deciding for themselves which symptoms are trivial and not related to their cancer or its management.
f. Delaying reporting to the health-care facility – personal and social factors take precedence over seeking medical aid (e.g., fever starts at 1 am in the morning, patient does not inform anyone; starts shivering at 4 am and self-medicates with crocin, feels better; does not mention this to anyone after waking up in the morning; at 10 am fever and shivering return when no one else is at home; calls son who is at work, and takes another crocin; becomes drowsy by 1 pm and intake (food and fluids) suffers; grandchild comes home at 4 pm to find patient drenched in sweat and hardly able to speak; son reaches home from office by 530 pm; calls GP at 6 pm who says patient is serious; ambulance is called and patient reaches nearby hospital at 7 pm. Local doctor is not provided details of diagnosis of cancer or its ongoing treatment. Examination does not indicate any evidence of focus of infection. He starts treatment assuming routine infection (with standard antibiotics for community-acquired infection in otherwise healthy person); patient does not improve and now requires support for maintaining blood pressure and respiration; then family member divulge details of cancer diagnosis and treatment; found to have neutropenia following chemotherapy; broad spectrum IV antibiotics and granulocyte colony-stimulating factor commenced (required only for infection in cancer-related febrile neutropenia). Such a delay is responsible for as many as half of such patients dying within 48 h of the first sign of fever – solely due to the casual manner in which seeking urgent medical attention from their oncologist was delayed.
g. Not having faith in their healthcare team – selectively implementing the medical advice based on their own lay perception of what is necessary and what is not necessary (e.g., gargles with mouthwash is ignored as unnecessary).

If patients come on time, cancer will be detected in early stage, the treatment will be shorter, the side-effects shall be minimal, the cost will be significantly lower and the chance of positive outcome/cure will be highest. In spite of all efforts by doctors, hospitals, NGOs and government, the benefit to the patient can only be achieved if he/she proactively pays attention to his/her own health and follows all the instructions by health-care professionals.[7,14-16,19]

Cancer is Related to Mutations

Each individual unit of the human body is made of cells – the adult having about 3 trillion of such cells. Each cell has a cell wall, a nucleus, cytoplasm, and surface receptors. Inside the nucleus is the DNA and inside the cytoplasm is the RNA. Proteins are produced when the information stored in the DNA is transmitted to the cytoplasm via the RNA and interacts with Ribosomes that assemble the amino acids in the right sequence [Figure 1].

Genomics is the science that deals with analysis of a particular individual's genetic material, interpretation of how that

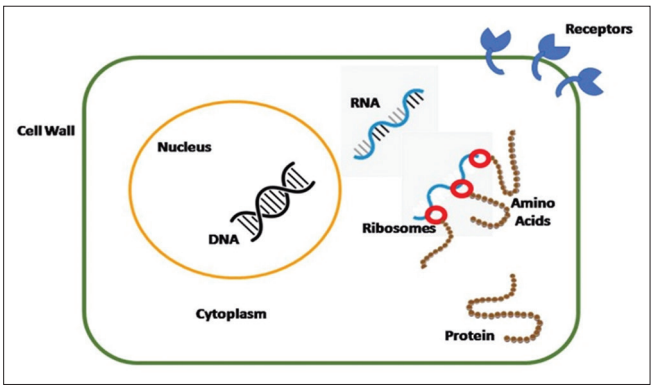

Figure 1: Basic structure of the human cell

interactions with itself, how it leads to all individuals on earth being different from each other (phenotypic variations) and how it relates to our external environment or external factors. At present, available molecular technology helps us understand this in a manner that has the capacity to help improve patient care.[1,10-12,20]

The knowledge existing in and about human body is stored in DNA. This is the human genome code.

The Human Genome Project has shown us that there are approximately 30,000 genes which are responsible for up to 1 million proteins in the human body. This was possible since this determined the genetic structure of the human genome - sequence of chemical base pairs (DNA) of all the genes in our cells (a staggering 3 billion of them in each human cell) – helping us understand its physical as well as a functional implication. The project was a task that started in 1990 and was completed by 2003 at the cost of billions of US dollars. Its outcome is archived at the Wellcome Foundation facility in the UK as an elegant example of human progress. It identified 1800 new disease genes – 1700 of them caused by corresponding single individual genes. In India, the first complete genome sequencing was done in 2012 for a woman from Kerala. In fact, all the human beings on planet earth share 99.5% of the genetic code. We are different from each other only in the 0.5% variations seen in the genetic code – also called as single nucleotide polymorphism (SNP).[21]

If damaged, these sequences of DNA (called genes) can be converted into cancer-causing genes (oncogenes). This can occur due to three factors – being born with defective genes, genes damaged due to toxins (e.g., smoking, alcohol, radiation exposure, and chemicals) or simple wear and tear of genes with ageing.[5,10,11,19,22]

Based on this insight and coupled with explosive availability of new technology as well as computational power, we are now able to make apply this knowledge for the benefit of individual patients in a real-time basis. Today, we can repeat the same testing in a matter of weeks and at the cost of few thousands of US dollars.

Each cell of the human body has 3 billion nucleotides that code for 30,000 genes and are responsible for the production of up to 1 million proteins. There is a very delicate balance between their interactions.

Cancer is a disease that is commonly associated and usually driven by changes in the genes (called proto-oncogenes) – at the molecular level. This change results in altered behavior of the cell and all the cellular elements mentioned above can be affected. Consequences include development and spread of cancer as well as chance of response to therapy. Today, such testing is available in most parts of India.[1,5,10-12,19-22]

Role of Molecular Genetics in Classification and Subtyping of Cancers

So far, cancer was classified based on organ of origin and appearance of cancer cells under the microscope (what the pathologist could visualize – often with special staining). This was dependent on the hypothesis that all cancers starting from a particular site/organ were biologically similar and will behave similarly. They were, therefore, classified on the basis of the cell type, presence/absence of regional lymph nodal involvement as well as distant metastasis (spread to other organs/sites in a non-contiguous manner).

It is now obvious that cancers arising within the same organ (e.g. breast) can differ in significant ways. They affect the way they grow, how they spread and how they would respond to specific types of therapy. It has also been discovered that certain mutations (vide infra) are responsible for the above changes – irrespective of which organ the cancer is originating in. For instance, if the same gene if affected by a driver mutation in a patient's cancer originating from the breast as also in another patient's cancer originating from the lung, both of them are likely to behave biologically in a similar manner and also respond to the same type of treatment. Discussion is already ongoing and, in the future, this will lead to an entirely novel way of classifying cancers in human beings – e.g., all tumors with "alk" mutation(s) being the main driver are likely to be called "alk-omas," irrespective of which organ the cancer is originating in.[23,24]

Interpreting the information made available from molecular changes (mutations) becomes part of the larger picture of biological markers (biomarkers). These are of two types – prognostic markers and predictive markers. Prognostic markers give an indication about the natural history of the disease, whereas predictive markers (actionable) allow the oncologist to decide what is the best treatment option. There are still other molecular alterations whose significance is yet to be identified. They are called variations of unknown significance.[4,10,11,25,26]

So if this testing is done in 100 patients with adenocarcinoma of lung, 55% will show a known mutation and <45% will remain with unknown genetic alterations [Figure 2]. The

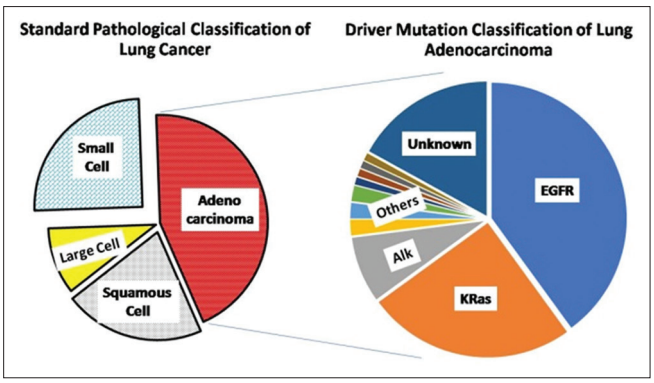

Figure 2: Standard pathological classification versus driver mutation classification in lung cancer

55% with known mutations will include 35% who will have actionable driver mutations. Such patients can be spared the standard doublet intravenous combnation chemotherapy and can be treated with single and simple oral medication (such as gefitinib, crizotinib, and afatinib).[23,24]

It is important to note that such mutations have wide variations in incidence and location within the genome with respect to geographical and ethnic spread. For instance, Figure 3 shows the relation of epidermal growth factor receptor (EGFR) mutation and lung cancer across several countries.[12] EGFR mutation positivity is seen in only about 5% of Caucasians, whereas it is as high as 51% in Korea and Japan. India is in between with an overall incidence of 40% - with the percentage being lower in the northern part of our country as compared to Southern states.

Today, we have several techniques that go beyond the standard pathological examination of the specimen under the light microscope. Such specialized tests enable us to get information beyond what can be seen by the naked eye. Molecular genetic changes give a better understanding of the disease. This insight has the potential to facilitate the selection of the best treatment option for patients with specific mutations.[4,10,11,25,26]

We now know that the chance (incidence) and type of mutations have geographical variations of importance. For instance, the EGFR mutations are seen in a tiny fraction of patients in the western world, whereas its incidence is higher in patients from India and surrounding countries. This is also true for anaplastic lymphoma kinase (ALK) mutations. This enables us to decide which testing is necessary and how to interpret its results specific for our patients.[4,11,12,23-26]

Sampling for Genetic Testing

Genetic testing will require one or more of the following samples – tumor tissue (fresh, frozen, paraffin block, microscopic slide, and cell block), adjacent normal tissue and or bodily fluid (saliva, sweat, blood, urine, cerebrospinal fluid, pleural fluid, and peritoneal fluid). These samples may be required at time of initial diagnosis, at frequent intervals while the treatment is ongoing, at follow-up after active cancer-directed treatment is completed and/or at the time of recurrence or progress of cancer. It may also be required to be done in blood relatives in special circumstances. The use of body fluids is also called liquid biopsy and is becoming of increasing importance. It is vital that the procurement of the sample, its storage conditions, its allocation to various testing, and its archival are properly planned. Biobanks and/or tissue repositories play a major role in ensuring this.[27,28]

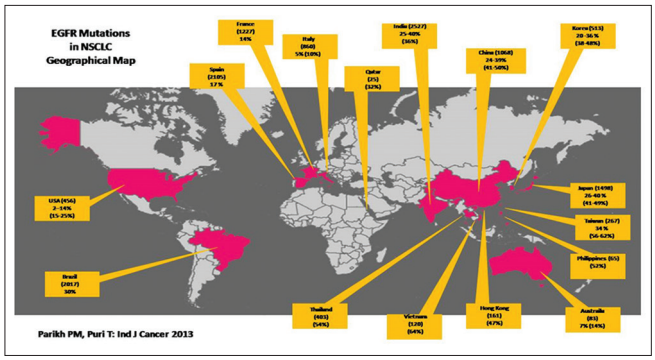

Figure 3: Geographical variation in epidermal growth factor receptor mutation incidence in Lung Cancer (reproduced from our publication in Indian Journal of Cancer, 2013, Publisher Wolter Kluwer Medknow)

After the procurement of the right patient sample, further testing can be divided into the wet lab and the *in silico* bioinformatics components. The wet lab is where the biological specimen undergoes physical testing – usually with sophisticated and automated machines (e.g., next generation sequencing). This takes from a few hours to a few days. The machine then gives out huge amounts of data (soft files in computer language) that can be about a 1TB of information per patient. This then gets analyzed using high calibre computers using artificial intelligence and involves dialogue with publicly available databases to understand the medical implications of any alteration. This usually takes about several weeks and requires super computational capabilities.[29]

Quality is critical to ensure that the sample is processed correctly in the wet lab as well as the big data is analyzed appropriately using the most recent databases. This will then provide a meaningful report. Hence, external quality assurance as well as internal quality controls is absolutely mandatory at all steps for such testing.

Molecular analysis requires three steps – getting the right sample, doing the right test in the laboratory and processing the test result information to make a meaningful decision regarding patient management. Quality is crucial at all these stages. Moreover, this takes time. This process cannot be done in haste or without proper controls. It also requires the right equipment. For instance, the computational power required with whole genome sequencing is the equivalent of using a modern desktop computer continuously for 3 weeks.[11,12,27-29]

Hereditary Cancers

There is about 4000 inherited disease in humankind. Fortunately, the majority of cancers are not due to inherited genes. Hereditary cancers are only 5% or less of all cancers.[30] Preventive genetics deals with the application of molecular testing in an asymptomatic (seemingly normal) person to ascertain their risk of developing a specific disease (e.g., cancer) in the future. This science has rapidly evolved to increasingly become a standard component of modern health care. The use of BrCa1 (Breast Cancer gene) and BrCa2 testing by Anjelina Jolie to determine that she had a very high risk for breast cancer and her subsequent decision to undergo prophylactic bilateral breast as well as ovarian removal resulted

in wide publicity for this science. It has the potential to provide reasonably accurate risk assessment and for screening and prevention of specific cancers – with more than 1700 genetics tests being already available today.

The advantage of identifying a family with higher risk of hereditary cancers are: [30,31]

a. Identification of which members of cancer has that risk and more importantly which member of the family does not have this risk.
b. Use specific counselling protocols for those with higher risk.
c. Discuss the potential risks in future members of the family – to help them plan the family.
d. Initiate disease and risk specific surveillance procedures for those with higher risk.
e. Offer the prophylactic management options available – including advantages and disadvantages of each of them.
f. Allow the individual family members to decide which option they would like to follow.
g. Continue to answer their questions and support them through their life.

This approach also has some limitations that everyone should be aware of:

a. Confidentiality needs to be maintained at all stages by all stakeholders.
b. Sharing of information within the family should follow the wish of the index patient and each individual.
c. Not all persons will higher risk will develop cancer – there are other external, lifestyle, and environmental factors that can influence the outcome.
d. Individuals have different levels of coping ability and should be only given as much information as requested by them.
e. Concerned persons, patients and family members should take precautions against risk of misuse of information (by insurance agencies, employers).

Hereditary cancers form only about 5% of all cancers. If a family has more than one member affected by cancer, it need not be due to inherited defects. There are other factors shared by families that can be responsible for higher risk of cancer – such as smoking, obesity, lack of exercise, shared environmental exposure, and eating habits. Yet, it is important to screen and test for hereditary cancer risk in select groups of families – to tailor the screening, diagnosis, treatment, and follow-up recommendations for those with higher risk.[30-32]

Somatic Mutations

Any change in the DNA structure that changes the nucleotide base (A, T, G or C) will affect their sequence and thus the coding information stored in them. Our bodies are constantly subject to injury or damage that leads to several thousand such changes every year. The human body is so smart and efficient that almost all such changes get repaired by an automatic and active surveillance mechanism. If however, this change is not repaired and gets passed on to daughter cells, it becomes known as a mutation.[1,10,11,21,23]

When mutations occur at specific sites on the genome, they may lead to change in the behavior of cells (before and after they become cancerous). Such mutations are called driver mutations. They lead to alteration in the signaling within the tumor cells and can lead to a state of "addiction" – the cancer cell can thrive and reproduce only because of the product (or lack of product) as a result of the genetic change. In addition to conventional mutations, such changes can also be due to translocations and amplification.[33]

There is also possibility of heterogeneity within different parts of the same tumor, differences in the mutations between the primary and the metastatic sites as well as new mutations developing as the disease progresses. This is the reason why genetic/molecular testing may be required at frequent intervals as well as from more than one sites.[11,12,23,34]

There is also value in the genetic testing of normal cells in cancer patients. This is to identify the role of pharmacogenomic variations.[21,23,28,29] Each human being is different from others. While 99.5% of our genetic material is the same, it is the difference in the tiny 0.5% that makes one human being different from another one. Such a difference is due to a single nucleotide base in the sequence of the DNA structure that makes up our genes. This is called SNP. This also leads to a significant difference in how each of us handles (metabolizes) medicines given to us. There are more than 1000 drugs metabolized in the liver. The rate at which they get degraded will determine the time that the body is exposed to their active ingredients as well as their metabolites. This correlates with both efficacy as well as the toxicity of the drugs. For instance, patients who are ultra-rapid metabolizers of a drug will have fewer side effects but may also have a suboptimal therapeutic blood level and hence poorer response. On the other hand, poor metabolizers will be exposed to active drug for a longer time and might have better efficacy – at the same time having higher risk of toxicity.[35]

The indicative list of commonly used molecular tests for some cancers is shown in Table 2. This is divided into test which gives an idea about the natural history of the disease (prognostics), those that allow proper selection of treatment (predictive) and those that indicate degree of risk of hereditary cancers (preventive). This list is neither complete nor comprehensive. More tests are being added regularly.

Molecular changes (e.g., driver mutations) that convert normal cells into cancer can also undergo additional genetic changes with time. They can also be different in the primary tumor as compared to the subsequent recurrence or at the site of distant metastasis. This is part of the genetic instability seen with some cancers.[1,10,11,21,23,28,29]

The manner in which one person responds to a medication is different from another person. This is due to tiny variation in the genetic structure (called SNP). This difference in normal cells will determine how quickly or slowly a particular drug is degraded inside that person's body – information that can help determine what is the best drug and/or dose to be used in an individual.[21,23,28,29,33-35]

Targeted Therapy

Targeted therapy drugs work differently from conventional chemotherapy drugs. They are built to target specific points on or in the cell that influence cell survival, reproduction and/or spread. They affect normal cells less or differently as compared to conventional chemotherapy. They are "specific" – like homing missiles as compared to conventional bombing (when compared to military warfare). However, they are not free of side-effects. They have different side effects – some of which we are still to understand in detail.[1,10,12,13,23]

Future advances in the field of cancer management are likely to be available from such drugs – including novel molecules that come under the broad category of next generation of immunotherapy molecules.[12,13]

These new class of drugs can be divided into two broad categories – monoclonal antibodies (big molecules) and kinase inhibitors (small molecules).[10,12,17,23] As the name suggests, monoclonal antibodies are big molecules. They do not enter inside the cell (at least not in their intact form). They work by acting on the cell surface, at the cell membrane level. Here, they bind to specific receptor proteins. This leads to a conformational change in the receptors, and a new signal is transmitted into the cells. The classic example of such molecules are trastuzumab, cetuximab, and rituximab. The small molecules can enter inside the cell and can directly influence the metabolism and functioning of the cell from within its cytoplasm. They are usually kinase inhibitors (single or dual; reversibly or irreversibly). Classic examples of these are gefitinib, afatinib, and imatinib.[10,12,17,23]

The steps involved in using the molecular and genetic information to develop and select targeted therapy is shown in Table 3.

Targeting cancer while sparing the surrounding normal cells is the principle of targeted therapy. This should improve shrinkage of the tumor while reducing the side effects. It is important to understand that some new targeted therapy agents have different and novel side effects. Patients need to proactively assist their oncologists by strictly follow instruction regarding precautions to be taken as well as report any new symptom at the earliest. If such warning signs are ignored, the adverse effects can become life threatening and it might become too late to treat them appropriately.[1,10,12,13,17,23]

Personalized cancer care concept

Thus, personalized cancer care is the principle of best attempt to deliver the right treatment to the right patient at the right time based on better understanding of individual patient's tumor as well as normal tissue using genetic and molecular testing, targeted therapy molecules, and incorporating the insights into improving tumor kill efficiency while minimising toxicity.[1,12,24,36,37] It is not a new concept – having been standard of care since several decades. For instance, breast cancer patients whose tumors were estrogen receptor positive were given hormonal therapy (e.g., tamoxifen) and those with Her2/neu receptor positivity were treated with monoclonal antibodies (trastuzumab) or small molecule tyrosine kinase inhibitors (lapatinib).[11,18,19,31] Clearly, it has always been the basis of stratified approach to cancer management. Today, this approach has improved outcome in select group of more than 30 cancer types – including lung cancer, head-neck cancer, sarcoma, brain tumors, and ovarian cancer. Now, using modern tools of molecular genetics coupled with the computational predictive power of bioinformatics as an additional layer over and above the foundation of standard of care and evidence-based medicine, we now have many more options to deliver personalized cancer care [Figure 4].

Personalized medicine is moving away from the "one-size-fits-all" concept. Here, health care is based on the unique molecular characteristics of a specific tumor inside a unique human body and in the context of its surrounding environment, sociocultural background, and personal preferences.[1,12,14,37]

This process involves:

A. Patients providing complete medical history honesty

Table 2: Indicative list of commonly used molecular test (bio-markers) in some cancers

Cancer type	Prognostic/Predictive	Preventive
Breast	ER, PR, HER2, OncotypeDx, MammaPrint	BRCA1, BRCA2, TP53, PTEN, CDH1, PALB2, ATM, CHEK2 genes
Ovary	BRCA1, BRCA2	BRCA1, BRCA2, MMR genes
Lung	EGFR, ALK, ROS	-
Gastric	HER2	MMR, CDH1 genes
Colon	MMR IHC, MSI	MMR, PTEN, STK11, APC, MUTYH genes
Prostate	ARV7, TMPRSS2-ERG	BRCA1, BRCA2 genes
Brain	1p/19q codeletion, MGMT, IDH1/2, EGFR, TP53	TP53 gene
Pancreas	BRCA1, BRCA2 genes	BRCA1, BRCA2 genes
Sarcoma	SYT-SSX, EWS-FL1	TP53 gene
Thyroid (MTC)	-	RET

ALK: Anaplastic lymphoma kinase, EGFR: Epidermal growth factor receptor

Table 3: Steps in translating molecular information into targeted or personalized therapy

1	Deeper subtyping of cancer – including rare molecular changes
2	Identification of changes within and on surface of cell as a result of these molecular changes
3	Computerized (*in silico*) evaluation of what drugs can potentially block the detrimental changes in cell that leads to development and growth of cancer
4	Production of such drugs to target specific genetic alterations
5	Clinical trials to test these drugs and verify whether they really provide the intended benefit in human beings
6	Licensing of the manufacture and sale of such drugs by regulatory governmental authorities
7	Selecting the right patient for treatment with these targeted agents

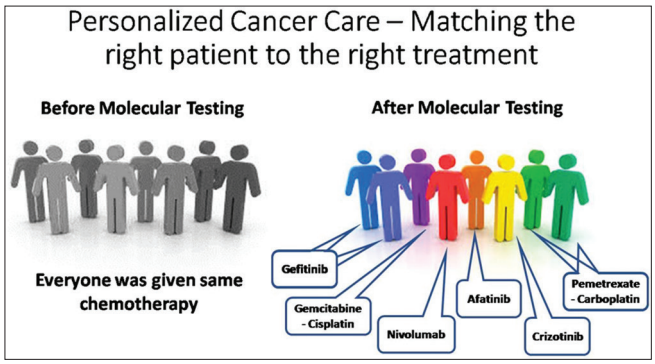

Figure 4: The difference in standard conventional therapy (before the molecular testing era) and personalized cancer care (using sophisticated molecular testing methodologies)

B. Physiological status and fitness of the patient
C. Stage of the cancer
D. Molecular characteristics of the tumor
E. Comorbidities and ongoing medication
F. Available licensed treatment options
G. Clearly defined preferences by the patient
H. Standard protocols being followed by the oncologist/ oncology center
I. Level of comfort and experience of the oncologist with the treatment options
J. Infrastructure and facilities available at the center providing treatment.

The role of the oncologists is only to be a guide. It is for the patient and their families to play an important role, take charge of their health and be an active part of all treatment decisions. Also, not all patients who undergo such testing will actually be found to have a molecular alteration that can be used as a target and will result in specific change in the treatment decision making.

At the same time, patients and families must clearly understand that failure of intended benefit is not in the hands of their doctors. Medicine is not like mathematics and outcome cannot be guaranteed under any circumstances. For instance, only a quarter of patients with adenocarcinoma of lung benefit from nivolumab, only one-third of patients with non-small cell lung cancer have their tumor shrinking with the standard of care treatment and only half the patients with Her2 positive breast cancer respond to trastuzumab.[1,12,14,18,19,38]

Progress in the fight against cancer will continue to be primarily supported by advances in this field. This will improve the chance of cure, reduce/delay the risk of cancer growth/ recurrence, increase the ability to kill cancer cells all over the body and/or improve quality of life by relieving symptoms.

In today's era of personalized cancer care, each patient is managed as a unique individual. Oncologists try to identify what are the individual patient's features that should be taken into consideration while managing their cancer. Patients' preferences can also play an important role provided the patients and their families express this clearly.[1,12,14,18,24,36,37]

The use of this patient information consensus statement allows the cancer patients and their families to have a better understanding of their cancer as well as strengthen their ability to play a proactive role in their own disease, its management and outcome. It also empowers the patients and families to be responsible for their choices.[11,18,19,31,38]

Take Home Messages

1. Today India sees more than 11 lakh new cancer patients every year. This has become a major healthcare problem, and the government has announced that cancer is one of the most important noncommunicable diseases on their priority list. General public must join hands with doctors, hospitals, NGOs and the government to ensure that cancer is prevented, diagnosed early and treated effectively across our country.
2. Over the past decade, there has been tremendous progress in the fight against cancer. More patients get cured, more patients have meaningful prolongation of good quality of life and fewer patients are dying from this disease. This is due to better techniques of diagnosis, availability of better healthcare facilities, higher number of qualified oncologists as well as use of modern drugs to treat patients.
3. Molecular genetics and its application for ascertaining the risk of cancer, its early detection, its accurate diagnosis, in selecting the right treatment and dose as well as helping assess the status at follow-up or recurrence are very important additional tools in the fight against cancer.
4. While we have the potential to provide the best chance of care and cure to all our patients with cancer, delay in seeking proper medical help and failure to follow the advice of their doctors is responsible for increasing cost of therapy, significant side effects and reduction in the chance of favorable response to therapy.
5. If patients come on time, cancer will be detected in early stage, the treatment will be shorter, the side-effects shall be minimal, the cost will be significantly lower and the

chance of positive outcome/cure will be highest. In spite of all efforts by doctors, hospitals, NGOs and government, the benefit to the patient can only be achieved if he/she proactively pays attention to his/her own health and follows all the instructions by healthcare professionals.

6. Each cell of the human body has 3 billion nucleotides that code for 30,000 genes and are responsible for the production of up to 1 million proteins. There is a very delicate balance between their interactions.
7. Cancer is a disease that is commonly associated and usually driven by changes in the genes (called proto-oncogenes) – at the molecular level. This change results in altered behavior of the cell and all the cellular elements mentioned above can be affected. Consequences include development and spread of cancer as well as chance of response to therapy. Today, such testing is available in most parts of India.
8. Today, we have several techniques that go beyond the standard pathological examination of the specimen under the light microscope. Such specialized tests enable us to get information beyond what can be seen by the naked eye. Molecular genetic changes give a better understanding of the disease. This insight has the potential to facilitate the selection of the best treatment option for patients with specific mutations.
9. We now know that the chance (incidence) and type of mutations have geographical variations of importance. For instance, the EGFR mutations are seen in a tiny fraction of patients in the western world where as its incidence is higher in patients from India and surrounding countries. This is also true for ALK mutations. This enables us to decide which testing is necessary and how to interpret its results specific for our patients.
10. Molecular analysis requires three steps – getting the right sample, doing the right test in the laboratory and processing the test result information to make a meaningful decision regarding patient management. Quality is crucial at all these stages. Moreover, this takes time. This process cannot be done in haste or without proper controls. It also requires the right equipment. For instance, the computational power required with whole genome sequencing is the equivalent of using a modern desktop computer continuously for 3 weeks.
11. Hereditary cancers form only about 5% of all cancers. If a family has more than one member affected by cancer, it need not be due to inherited defects. There are other factors shared by families that can be responsible for higher risk of cancer – like smoking, obesity, lack of exercise, shared environmental exposure and eating habits. Yet, it is important to screen and test for hereditary cancer risk in select groups of families – to tailor the screening, diagnosis, treatment and follow-up recommendations for those with higher risk.
12. Molecular changes (e.g., driver mutations) that convert normal cells into cancer can also undergo additional genetic changes with time. They can also be different in the primary tumor as compared to the subsequent recurrence or at the site of distant metastasis. This is part of the genetic instability seen with some cancers.
13. The manner, in which one person responds to a medication, is different from another person. This is due to tiny variation in the genetic structure (called SNP). This difference in normal cells will determine how quickly or slowly a particular drug is degraded inside that person's body – information that can help determine what is the best drug and/or dose to be used in an individual.
14. Targeting the cancer while sparing the surrounding normal cells is the principle of targeted therapy. This should improve shrinkage of the tumor while reducing the side effects. It is important to understand that some new targeted therapy agents have different and novel side effects. Patients need to proactively assist their oncologists by strictly follow instruction regarding precautions to be taken as well as report any new symptom at the earliest. If such warning signs are ignored, the adverse effects can become life threatening and it might become too late to treat them appropriately.
15. In today's era of personalized cancer care, each patient is managed as a unique individual. Oncologists try to identify what are the individual patient's features that should be taken into consideration while managing their cancer. Patients' preferences can also play an important role provided the patients and their families express this clearly.
16. Use of this patient information consensus statement allows the cancer patients and their families to have a better understanding of their cancer as well as strengthen their ability to play a proactive role in their own disease, its management and outcome. It also empowers the patients and families to be responsible for their choices.

References

1. Jain M. Past, Present, and Future of Molecular Oncology in India. DOI: 10.18203/issn.2456-3994.IntJMolImmunoOncol20170051.
2. Gulia A. Social Media In Medical Practice: A Boon Or Bane!!! DOI: 10.18203/issn.0019-5359.IndianJMedSci20170480.
3. Lyerly HK, Fawzy MR, Aziz Z, Nair R, Pramesh CS, Parmar V, *et al*. Regional variation in identified cancer care needs of early-career oncologists in China, India, and Pakistan. Oncologist 2015;20:532-8.
4. Batra U, Parikh PM, Prabhash K, Tongaonkar HB; and Expert Group Members. Oncology gold standard™ practical consensus recommendations 2016 for treatment of advanced clear cell renal cell carcinoma. S Asian J Cancer 2016;5:167-75.
5. Parikh PM, Raja T, Mula-Hussain L, Baral RP, Ingle P, Narayanan P, *et al.* Afro Middle East Asian symposium on cancer cooperation. South Asian J Cancer 2014;3:128-31.
6. Shridhar K, Rajaraman P, Koyande S, Parikh PM, Chaturvedi P, Preet K, *et al*. Trends in mouth cancer incidence in Mumbai, India (1995-2009): An age-period-cohort analysis. Cancer Epidemiol 2016;42:66-71.
7. Goss PE, Strasser-Weippl K, Lee-Bychkovsky BL, Fan L, Li J, Chavarri-Guerra Y, *et al.* Challenges to effective cancer control in China, India, and Russia. Lancet Oncol 2014;15:489-538.
8. Ghadyalpatil NS, Supriya C, Prachi P, Ashwin D, Avanish S. Gastrointestinal cancers in India: Treatment perspective. South Asian J Cancer 2016;5:126-36.

9. Shah SB, Sharma S, D'Cruz AK. Head and neck oncology: The Indian scenario. South Asian J Cancer 2016;5:104-5.
10. Rosell R, Neninger E, Nicolson M, Huber RM, Thongprasert S, Parikh PM, *et al*. Pathway targeted immunotherapy: Rationale and evidence of durable clinical responses with a novel, EGF-directed agent for advanced NSCLC. J Thorac Oncol 2016;11:1954-61.
11. Jain A, Suryavanshi M, Batra U, Goyal P, Doval D, *et al*. Circulating Tumor Cells In Breast Cancer. DOI: 10.18203/issn.2456-3994. IntJMolImmunoOncol20170052.
12. Parikh P, Puri T. Personalized medicine: Lung Cancer leads the way. Indian J Cancer 2013;50:77-9.
13. Romano G, Gawlinski A. New frontiers in oncology: Immune checkpoint inhibitors in combination therapy. Drugs Today (Barc) 2017;53:103-15.
14. Prasad N, Bakshi A, Deshmukh C, Hingmire S, Ranade A, Parikh P. Importance of dose intensity in treatment of advanced non-small cell lung cancer in the elderly. South Asian J Cancer 2012;1:9-15.
15. Begum M, Islam MJ, Akhtar MW, Karim S. Evaluation of delays in diagnosis and treatment of childhood malignancies in Bangladesh. South Asian J Cancer 2016;5:192-3.
16. Kumar P, Aggarwal H. Oncology status in five SAARC countries: A critical appraisal of 2012 versus 2014 statistics. S Asian J Cancer 2016;5:175.
17. Parikh P, Bansal S. Chronic myeloid leukemia in the Imatinib era-compilation of Indian data from 22 centers involving 8115 patients. Indian J Med Paediatr Oncol 2013;34:145-6.
18. Rangarajan B, Shet T, Wadasadawala T, Nair NS, Sairam RM, Hingmire SS, *et al.* Breast cancer: An overview of published Indian data. South Asian J Cancer 2016;5:86-92.
19. Parikh PM. Converge Breast Cancer Update 2014 - Editor in Chief ISBN No 978-81-923972-2-1, publisher Medintel Servics Pvt Ltd.
20. Parikh PM, Ranade AA, Govind B, Ghadyalpatil N, Singh R, Bharath R, *et al.* Lung cancer in India: Current status and promising strategies. South Asian J Cancer 2016;5:93-5.
21. Singh A, Singh N, Behera D, Sharma S. Polymorphism in XRCC1 gene modulates survival and clinical outcomes of advanced North Indian lung cancer patients treated with platinum-based doublet chemotherapy. Med Oncol 2017;34:64.
22. Bajpai J, Chaturvedi P, Parikh P, Gupta S. Common Cancers - Indian Data 2015 - Editors, publisher Indian Society of Medical & Pediatric Oncology.
23. Mehta P, Bhajoni PS, Mehta SW. Response To Afatinib, After Gefitinib And Erlotinib, In A Patient With Advanced Adenocarcinoma Of Lung With Brain Metastasis: A Case Report. DOI: 10.18203/issn.2456-3994. IntJMolImmunoOncol20170056.
24. Mano H. ALKoma: a cancer subtype with a shared target. Cancer Discov 2012;2:495-502.
25. Parikh PM, Ranga RR, Prabhash K, Devan AK. Lung Cancer Update 2009 – Editors, publisher Medintel Services Pvt Ltd.
26. Abbasi M, Mirmomeni MH, Khazaei S, Ranjbaran R. Detection Of P53 Exon 9 Gene Mutation In Bladder Cancer By Polymerase Chain Reaction-Single-Strand Conformation Polymorphism Method. DOI: 10.18203/issn.0019-5359.IndianJMedSci20170492.
27. Shankar SK. Let us promote bio-banking in India for translational research. Neurol India 2015;63:644-6.
28. Mirza S, Jain N, Rawal R. Evidence for circulating cancer stem-like cells and epithelial-mesenchymal transition phenotype in the pleurospheres derived from lung adenocarcinoma using liquid biopsy. Tumour Biol 2017;39:1010428317695915.
29. Shilpi A, Bi Y, Jung S, Patra SK, Davuluri RV. Identification of Genetic and epigenetic variants associated with breast cancer prognosis by integrative bioinformatics analysis. Cancer Inform 2017;16:1-13.
30. Mannan AU, Singh J, Lakshmikeshava R, Thota N, Singh S, Sowmya TS, *et al.* Detection of high frequency of mutations in a breast and/or ovarian cancer cohort: implications of embracing a multi-gene panel in molecular diagnosis in India. J Hum Genet 2016;61:515-22.
31. Darooei M, Poornima S, Salma BU, Iyer GR, Pujar AN, Annapurna S, *et al.* Pedigree and BRCA gene analysis in breast cancer patients to identify hereditary breast and ovarian cancer syndrome to prevent morbidity and mortality of disease in Indian population. Tumour Biol 2017;39:1010428317694303.
32. Suryavanshi M, Kumar D, Panigrahi MK, Chowdhary M, Mehta A. Detection of false positive mutations in BRCA gene by next generation sequencing. Fam Cancer 2016.
33. Pandilla R, Kotapalli V, Gowrishankar S, Chigurupati M, Patnaik S, Uppin S, *et al.* Distinct genetic aberrations in oesophageal adeno and squamous carcinoma. Eur J Clin Invest 2013;43:1233-9.
34. Ma SS, Srivastava S, Llamosas E, Hawkins NJ, Hesson LB, Ward RL, *et al.* ROR2 is epigenetically inactivated in the early stages of colorectal neoplasia and is associated with proliferation and migration. BMC Cancer 2016;16:508.
35. Lévesque E, Bélanger AS, Harvey M, Couture F, Jonker D, Innocenti F, *et al.* Refining the UGT1A haplotype associated with irinotecan-induced hematological toxicity in metastatic colorectal cancer patients treated with 5-fluorouracil/irinotecan-based regimens. J Pharmacol Exp Ther 2013;345:95-101.
36. Parikh P, Prabhash K, Naik R, Vaid AK, Goswami C, Rajappa S, *et al*. Practical recommendation for rash and diarrhea management in Indian patients treated with tyrosine kinase inhibitors for the treatment of non-small cell lung cancer. Indian J Cancer 2016;53:87-91.
37. Parikh PM, Thakur BB. Lung Cancer in the Elderly, in Lung Cancer Monograph. ICP, API; 2012.
38. Kobayashi H, Omori S, Nakashima K, Wakuda K, Ono A, Kenmotsu H, *et al*. Response to the treatment immediately before nivolumab monotherapy may predict clinical response to nivolumab in patients with non-small cell lung cancer. Int J Clin Oncol 2017.

How to cite this article: Parikh PM, Hingmire SS, Bhavesh P, Govind KB, Mehta P, Verma A, Bondarde S, Singh R, Ghadyalpatil N, Rangrajan B, Bhattacharyya GS, Malhotra H, Doval DC, Ranade AA, Shah PM. Oncology Gold Standard™ consensus statement on counseling patients for molecular testing and personalized cancer care. Int J Mol ImmunoOncol 2017;2:47-57.

Source of Support: Nil. **Conflict of Interest:** None declared.