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Genetic Testing in Cancer Care – The Need for an Increase Uptake in Southeast Asia

Ahmad Sufian Ab Rahman*[1]

ORCID Number https://orcid.org/0000-0003-1477-7390.

Corresponding Author: Ahmad Sufian Ab Rahman, Cancer CRI Centre, UCSI Hospital, Columbia Asia Bukit Rimau, Malaysia.

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Introduction

Cancer is a disease that has been associated with many causal theories. [1] It is not a newly discovered disease and the trace of cancer dated back even to the time of ancient Egypt as evident by the findings of it in the fossil of mummies and the writing of "this disease has no treatment" on their papyri. [2]

Today, while the causes that predispose human cells to cancer are many, interactional, and complex, it is well recognised that cancer is a genomic disease. [3] Similar to genetic changes that can lead to abnormalities and syndromes in children, genetic mutations over time lead to the development of various types of cancer. [4,5]

In Southeast Asia, common solid cancers include breast cancer, lung cancer, cervical cancer, prostate cancer, colorectal cancer, and liver cancer.[6] The WHO Globocan Data 2020 reported more than 1 million of new cases of cancer in Southeast Asia in 2020, and nearly 700 000 cancer deaths in the same year.[7] The challenges are real, and the need for preventive measures, early detection, and advanced treatments cannot be overstated.

While the approach needs to be multi-dimensional including strong policies, political will, fundings, environment, research, lifestyle and behavioural changes, the question on the roles of genes is fundamental. Unlocking the reads of genetic abnormalities in this region would be crucial to support the preventive measures, early detection, advance treatments, and prognostication, all of which would have significant impacts on the population at risk or already diagnosed with cancer in this region.

This article is intended to provide a broad and easy-to-follow discourse on genetic testing in cancer. The aim is to provide a better understanding on cancer genetic testing among general physicians and public in this region and advocate for a guided and evidence-based use of genetic testing in cancer care.

What is cancer genetic testing?

Cancer genetic testing is a testing performed on the DNA and RNA of cancer cells derived either through biopsy of tumour located in one of the organs in the body or through the blood testing. The test looks for chromosomal, DNA, and RNA abnormalities (mutations) that led to the development of cancer. [8]

There are two categories of mutations that we look at in cancer cells. The first one is called 'somatic mutation' which is a type of mutation specific to the cancer cells and is not present in the normal cells of the body.

The second type of mutation is called 'germline mutation' which is a type of mutation inherited from one generation to another. Germline mutation is found in both normal cells and cancer cells. **[**9**]**

Types of genetic testing

There are various types of genetic testing that can be performed depending upon the clinical situation. These include polymerase chain reaction (PCR), Fluorescent In-Situ Hybridisation (FISH), and Next Generation Sequencing (NGS). Next Generation Sequencing has been used much more frequently these days given its ability to sequence large segments of DNA and RNA swiftly to detect relevant mutations that could help with preventive measures, early detection, prognostication, and treatment decisions. **[**10,11**]**

What is cancer genomic profiling?

Cancer genomic profiling is a process of sequencing large segments of DNA / RNA from cancer cells to identify abnormal mutations called pathogenic mutations. The technology used to perform this sequencing is called Next Generation Sequencing (NGS) or its other name, Massively Parallel Sequencing. With this technology, we could sequence as little as several genes to the entire DNA sequence (whole genome) of cancer cells.

In cancer clinical practice (oncology), patients might be advised to have this genetic testing using one of available panels: genetic testing panel that can test for several relevant genes only (hotspot panel), a panel that tests for several hundred genes (comprehensive genomic profiling), a panel that tests the entire functional part of the genome (whole exome sequencing), or the testing of the entire genome (whole genome sequencing). The choice of panel would be dependent upon several factors including the type of cancer, family history, information about known genetic mutations if testing was performed previously, financial affordability, availability of treatment options, local clinical trials and patient's preference. **[**8,10,11,12**]**

Benefits of cancer genetic testing

There are several benefits to performing cancer genetic testing. These benefits are linked closely to the indications for doing the testing.

Detection of hereditary genes that cause the development of cancer

- Cancer genetic testing allows for the detection of hereditary genes (germline mutations) in affected patients and their families. This information is vital as it allows for other family members to be consulted, screened, and tested by clinical geneticists to assess their risks of harbouring the same mutations that could cause cancer.

For certain types of cancer, preventive and early detection measures including intensive cancer screening programs, preventative operations, or newer treatment approaches can be applied to prevent and improve the survival outcomes of patients. **[**8,13**]**

Expanding the options of cancer treatments using precision medicine approach

- Genetic testing allows clinicians to understand the abnormal mutations that drive the growth and different behaviours of these cancer cells. Some of these mutations called 'oncogene driver mutations' can be targeted using specific drugs. This approach is called precision oncology. The benefit of this approach over the use of chemotherapy alone is that precision oncology can provide a better treatment efficacy, less side effects, and a better quality of life for patients. There are various medicines available through the managed access programs that are provided by the pharmaceutical companies which can help to reduce the actual cost of these medications. This genetic information is also useful for cancer clinicians to identify available clinical trials that their patients can join. All of these broaden up the potential options of cancer treatments for patients. **[**14,15**]**

Guiding the use of immune-based therapy

- The treatment of cancer using medications that activate our immune system has become a crucial part in cancer therapy. The genetic information such as the presence of 'microsatellite instability

high (MSI-H)', or a 'high tumour mutational burden (TMB)' can guide the treatment using this therapy. Both predictive biomarkers have also led to the possibility of treating cancer based on these signatures alone regardless of the tumour histology. **[**16,17**]**

De-escalation in the intensity of use of chemotherapy

- Genetic testing can provide the information about sub-population that might not need to have chemotherapy following a cancer operation. For instance, the introduction of Oncotype DX assay has allowed for a refinement of cohort that would benefit versus the cohort that would not benefit from the administration of adjuvant chemotherapy in breast cancer. Similarly, the use of circulating-free tumor DNA (cfDNA) has been shown to help prognosticate and refine the cohort of colon cancer patients that would benefit from receiving adjuvant chemotherapy.**[**18, 19**]**

Detection of cancer resistance mechanisms

- Cancer is a cunning pathology that it develops resistance mechanisms over time following the exposure to cancer treatments. Cancer genetic testing allows for detection of these resistance mechanisms so that ineffective treatments can be stopped and replaced with the next therapy. Some clinical trials have also tested re-challenging patients with the same therapy once the resistance mutation clones are not detectable, providing a new perspective of dynamic treatment approach in cancer. **[**20,21**]**

Predicting the behaviour of cancer (prognostication)

- Cancer genetic testing can also help with identifying certain genes that predict the aggressive behaviour of cancer. This information is essential and taken together with other clinical data as well as patient's context, the clinician can advise patient on the intensity of therapy, the life expectancy, the initiation of advance care planning discussion, as well as the refinement of plan throughout the patient's cancer journey. **[**22,23,24**]**

Creating a cancer treatment roadmap that is more effective and financially affordable

- In the low and middle-income countries (LMIC), cancer treatments are expensive and unaffordable to many.**[**25**]** This is where having a good genetic testing upfront could help clinicians and patients to plan the route of treatment well by making use of the managed access programs, clinical trials, and deciding on the options of targeted therapy or immunotherapy based on the genetic information.

Cancer genetic counselling and discussing risks.

With any testings performed in medicine, there could be risks besides benefits. With genetic testing, there can be several implications for instance, implication on insurance coverage for self and family if germline mutation was found, getting non-definitive genomic results (variant of unknown significance), and negative study where no mutations can be targeted with precision therapy. **[**8,11**]**

Therefore, having a cancer genetic counselling session with a certified genetic counsellor, clinical geneticist, molecular pathologist, or treating oncologist would be valuable. It allows for an informed decision process to take place and would boost the confidence as well as quality of care for patients knowing that they have made an informed choice related to their care.

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