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International Journal of Molecular & Immuno Oncology

Editorial

Why we should rely only on molecular tests based on Indian data

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Received : 28 April 2020
Accepted : 28 April 2020
Published : 13 May 2020

DOI
10.25259/IJMIO_13_2020

Quick Response Code:

Over the past 15 years, lung cancer has become the poster boy of personalized medicine, targeted therapy, and immuno-oncology.[1] Gefitinib initiated the transformation of how we treat lung cancer today, a great example of a drug that would have been lost in oblivion but for the effort to find out ethnic differences in molecular mutations.[2,3] Not only are there genetic differences between races (Caucasians vis-a-vis Asians), there is also heterogeneity within a single country like India.[4] Moreover, such variations have clinical implications in personalized treatment choices for optimizing patient management.[5] Figure 1 shows how such a systematic approach in sequencing therapy can lead to significant improvement in the survival of metastatic adenocarcinoma of the lung.

Such a situation is also applicable to other cancers, including breast cancer.[6,7] No wonder, the Indian Council for Medical Research guidelines on breast cancer clearly states that clinical utility of multigene signatures line MammaPrint and Oncotype Dx is uncertain because they are based on Caucasian population. Any test that has little data from the Indian patients is not ready for routine clinical use.[8] This is applicable irrespective from where the tissue or liquid biopsy is obtained from.[9]

To provide our patients with the benefit of such progress, we have to keep up to date with the evolving science and data. Moreover, medical oncologists seem to be ahead of the curve with more than half (63.5%) of all molecular testing being recommended by them, the rest coming from surgeons (15.3%), gynecologists (9.6%), patients themselves (6.2%), and general practitioners (2.6%).[10]

To disseminate this knowledge downstream, we have to understand the evolving terminology and the benefit of online resources.[11,12]

Let us take the example of hereditary breast cancer. We understand that risk is not straightforward Mendelian inheritance. While some germline variants disrupting gene function confer a high risk for cancer, many other variants (80–85%) have little or no clinical significance with respect to cancer risk. Earlier, we used to focus only on BrCa 1 and 2 genes. Now, we are wiser and have discovered several other high penetrance genes that confer risk of breast cancer (TP53, PTEN, PALB2, CHEK2, and ATM). Figure 2 shows the contribution of BrCa 1/2 genes versus others in three distinct ethnic groups. Table 1 shows the distribution of these mutations in a small cohort of these same ethnic groups studied in Singapore.[10]

When evaluating a risk of hereditary breast cancer, about 40% will have no mutation and the remaining will be equally divided amongst those having a known pathogenic mutation and those with a variation in the genetic sequence whose significance we are not sure of – the so-called variation of uncertain significance (VUS). Probands showing VUS might even have 2 (25%)

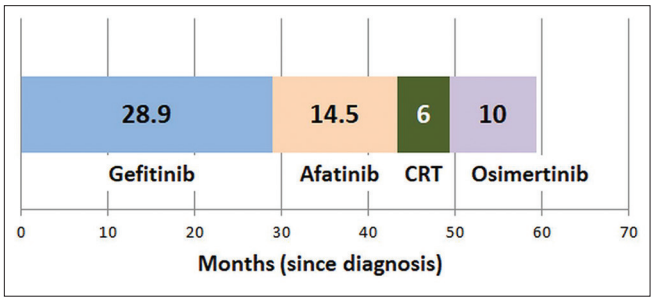

Figure 1: Representative overall survival in patients with adenocarcinoma lung with epidermal growth factor receptor mutation (del19).

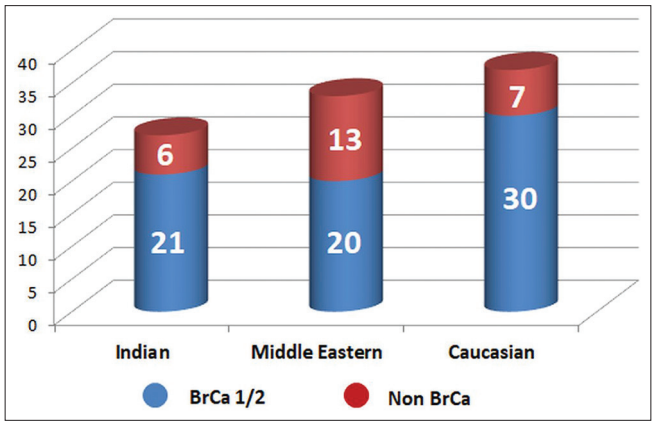

Figure 2: Ethnic comparison of pathogenic mutations (%) in patients with hereditary cancers.

Table 1: Ethnic comparison of genes involved in hereditary pathogenic mutations.

Mutation involving	Indian	Middle Eastern	Caucasian
BrCa1	5	3	9
BrCa2	1	1	3
TP53 and ATM	3	0	0
NEN and BR1P1	0	2	0
CDH1	0	1	0
Totalw	9	7	12

or more (10%) such mutations. Moreover, the incidence of such VUS identification increases as better NGS methods are used or multigene panels become more extensive. Assigning the right certainty (either way – pathogenic or non-pathogenic) requires a careful correlation with clinical outcome IN THE SAME ETHNIC GROUP. Figure 3 shows the location of specific BrCa1 mutations amongst three ethnic groups, highlighting the differences.

The same is the case when we use molecular testing, protein expression, immunohistochemistry, or other biomarkers for assigning risk, commonly called as predictors of outcome.[13,14] We, therefore, strongly urge all academically inclined oncology

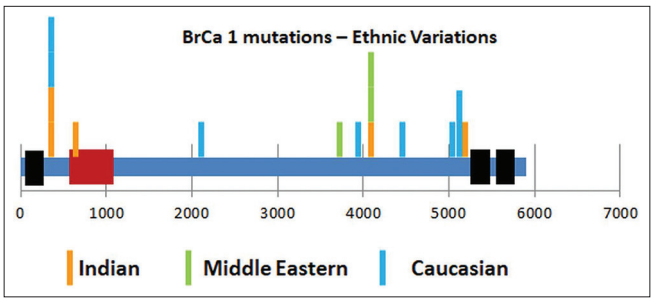

Figure 3: Ethnic comparison of location of pathogenic mutations in BrCa1 gene.

colleagues to join hands in pooling data from Indian patients and help make our own data more robust, reduce the redundance of VUS, and help patients be assigned to the right personalized cancer management pathway.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Parikh PM, Singh R. Why we should rely only on molecular tests based on Indian data. Int J Mol Immuno Oncol 2020;5(2):44-6.