Cancer had become the second leading cause of death in the United States in 1970 when National Cancer Act of 1971 was signed by President Nixon. Over the past few decades “War on Cancer” has urged the medical fraternity to try to decode this entity and strike the molecularly defined targets that are presumed to drive the cancer. Identification of breast cancer susceptibility genes BRCA1/2 therefore has been overwhelmingly hypothesized to be a keystone in this regard. It is worth reminding that together, BRCA1/BRCA2 mutations account for about 20 to 25 percent of hereditary breast cancers and only about 5 to 10 percent of all breast cancers.

Pathogenic (disease causing) mutations of BRCA1/2 have said to be hereditary and have high penetrance but the penetration is incomplete meaning that some carriers do “not” develop cancer in their lifetime. Also, incidentally discovered carriers often do not report family history.

National Comprehensive Cancer Network (NCCN) criteria for further genetic evaluation in hereditary Breast and Ovarian Cancer requires a detailed family history that even in specialized centers is dependent on patient’s reporting accuracy. Therefore, identification of high-risk patients is not easy and flawless.

Myriad Genetics Inc. was the sole provider of commercial full sequence BRCA1/2 test for some time but with new developing techniques and competitors trying to hold tight and not lose the game, new test panels as well as direct to customer testing are emerged. This has resulted in significant disparity in variant classification within and among databases. Variant classifications are the most important factor in interpreting genetic test results labeling a tested individual carrier or negative. Given the gravity of life-changing clinical suggestions from enhanced screening to prophylactic surgeries and chemoprevention that are offered to people with positive test results, this classification disagreement is a crucial issue which needs to be fully addressed before making the tests easily accessible for customers. A good test must be simple, accurate, precise or repeatable, sensitive, and specific. At present, BRCA1/2 mutation tests available do not have all the above-mentioned conditions and these issues should be clarified for the customers.

Breast cancer susceptibility genetic tests are performed in two settings: 1) Diagnostic genetic testing which is offered to the affected person (i.e. patient who already has pathological evidence of breast cancer) in a family with an unknown BRCA 1/2 mutation. 2) Predictive genetic testing which is offered to at risk but not affected biological kin once the disease-causing mutation has been identified within the family.

It means that in both settings the first person tested need to be the breast cancer patient. For any DNA testing the individual's autonomy should be respected. For that, person authorizing DNA testing should be under no pressure from family, society or third parties to agree. Till now, besides a few research trials that have reported PARP inhibitor therapeutic effect in some BRCA-mutated breast cancers, there is no clear evidence that the outcome of the disease will change for a patient diagnosed with BRCA-mutated breast cancer after finding out about BRCA status. That said, the most important incentive for a breast cancer patient “freely” authorizing genetic test would be providing information for not herself but other at risk relatives. This will have harmful effects on patient’s emotion and social relationships as well as financial burden. As mentioned above, more than 70% of hereditary
breast cancers have nothing to do with BRCA1/2 mutations and about 90% of all breast cancers are not BRCA1/2 mutation related meaning that counseling need to be an integral part of this procedure. This highlights how socially and scientifically irresponsible it is to promote direct to customer genetic tests.

Although precision medicine approach has worked in some hematological malignancies with clonal proliferation, breast cancer is among solid cancers in which carcinogenesis happens as a result of multistep complex biological mechanisms and epithelial stromal interactions are more relevant than clonal proliferation. That is why interpretation of estimates of the cumulative risk of cancer (to age 70 years) for BRCA1/2 mutations that vary substantially between studies should be carried out with much caution. Reported estimates for breast cancer risk varied based on retrospective studies that can not necessarily be implemented in real world practice. It is noted that BRCA1/2 mutation spectrum differs between the patients with breast cancer in the Cancer Genome Atlas (TCGA) and the carriers of the BRCA1/2 mutation in the general population. Several genetic and life-style cancer-risk modifying factors are identified that are not considered in the risk model predictors applied in those trials. A prospective cohort study was reported recently in which 3886 (out of 9856 recruited BRCA1/2 carrier women in 1997-2011) were eligible for breast cancer analysis. The results show that the breast cancer incidences per decade of age was between 23.5 to 28.3 per 1000 persons-years of age for age 31 to 70 years for BRCA1 carriers and between 21.9 to 30.6 per 100 person-years across 41-80 years for BRCA2 carriers. The cumulative risk estimate for breast cancer by age of 80 was in line with previous retrospective studies. Breast cancer risk varied based on mutation location. The results of this study suggest that a precise family history and mutation position should be well assessed in individualized counseling. These highlight the caution to be taken before suggesting direct to customer tests.

D’Andrea et al have recently published a review article where they conclude that there is no evidence of cost-effectiveness for BRCA screening of all newly diagnosed cases of breast/ovarian cancers followed by cascade testing of relatives. It seems that more surveys are necessary to be conducted before BRCA testing can be implemented in daily practice. As an Austrian study has shown, unfortunately younger and more educated females are seeking genetic counseling for hereditary breast and ovarian cancer due to Angelina Jolie Effect since 2013. Cultures differ widely in their traditions of gender roles, marriage and family life. In many communities, the genetic information will surely affect the decision about prospective marriage and deteriorate quality of life of young women and their families. Although in guidelines such as NCCN and European Society of Medical Oncology (ESMO) for clinical practice, referral for BRCA testing is recommended after genetic counseling, trained medical genetics specialists are not always accessible in some healthcare systems and in the case of direct to customer tests, genetic specialists are more or less employed by the provider which may pose a conflict of interest. That is why the burden of providing genetic testing and counseling to patients might fall on oncology medical practitioners. Medical professionals might not be able to police the unsupervised information on media and internet about the hype, but what they can and must be obliged to is 2500 years old Hippocratic oath and Primum non nocere. Medical practitioners should be very careful not to fall into defensive medicine practice for fear of liability. Using irrelevant terms such as “genetic screening test” for breast cancer and overstating benefits and downplaying harms of interventions available at present for possible BRCA1/2 mutation carriers are morally and ethically unacceptable. It is essential to remember that genetic risk is only a part of a person’s overall risk and theoretical benefits that have not been confirmed in clinical practice should not be mistaken for facts. Information transparency and high literacy are among the crucial elements to adhere to ethical principles in this era of emerging genetic testing for breast cancer.

References