**BRCA1** and **BRCA2**: lack of certainty and its clinical implications

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**ABSTRACT**

In this time of ever-increasing incidence and mortality of cancer, genetic testing may be greatly valuable in determining appropriate clinical management. It is unfortunate that the result of these tests might be problematic. With positive result, patients should discuss with their clinicians what to do next. Patients with negative result might breathe out in relief from unnecessary intensive surveillance and prophylaxis, yet there is Variants of Uncertain Significance (VUS). Nowadays, VUS has become a challenging aspect in clinical management of cancer. Clinicians are expected to deliver the interpretation of test results with certainty, while they could not put aside the confounding factors of genetic testings.

**BRCA1** and **BRCA2** are two genes with high penetrance in breast cancer. The impact of their mutation would only manifest when there is loss of heterozygosity, as **BRCA1/2** are tumor suppressor genes and DNA repair regulators. Mutation of **BRCA1/2** gene is demonstrated within the tissue specimen and blood sample DNA, proving that it has occupied all tissues and thus inheritable.

In the case of **BRCA1/2** mutations, 10-20% of all genetic tests will result in VUS. One previous study of sixteen Indonesian patients, 13 (81.25%) patients had VUS. There were variants that had not been found in other population. The reclassification of VUS in **BRCA1/2** gene is not only a challenge to clarify its clinical impacts, but also an obligation to our community for further contribution in science.

There can be a set of factors suggesting that VUS might be a deleterious mutation:

1. **Co-segregation**: when the variant comes with multiple and multigenerational incidence of cancer, VUS is possible.
2. **Epidemiology**: when a case-control study demonstrates discrepancy in prevalence, VUS is possible.
3. **Co-occurrence with deleterious mutation**: when the variant is shared within the same gene in other individuals, VUS is possible.
4. **Evolutionary data**: when the sequence is carried across species, VUS is possible.
5. **Amino acid substitution**: when the substitute is structurally similar, VUS is impossible.

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