“What’s the difference between comprehensive BRCA1/BRCA2 testing and BART? “ This is just one example of questions we receive from clinicians that are trying to order the right genetic test. One test might be via DNA sequencing while another might be looking at gene rearrangements. When looking at a genetic test result, it is important to know what you are looking at, so we thought it would be nice to have a glossary of terms you might need to reference. This month, we will focus on the common breast cancer genetic tests and the types that exist.

First, the most important terms to understand are how the results are worded. Typically, a positive or deleterious test result is not a good thing; this is when a problem has been discovered in the gene that causes abnormal function and increased lifetime cancer risk. Negative in this case is good news – no recognized abnormalities in the gene were discovered. There are also polymorphisms – this means that there is a difference in the gene that is detected normally in at least 1% of a control population. This difference does not cause harm to the gene’s normal function and does not confer increased cancer risk for the patient. Some labs do not report polymorphisms on their test results while others still do.

The test result that can really confuse some clinicians and patients is a variant of uncertain significance (VUS). This means there is a difference in the genetic sequence, but we do not yet know if the difference causes abnormal gene/protein function or is just a normal genetic difference (polymorphism). There are many levels of evidence that a VUS has to achieve to be reclassified as positive or negative, so testing laboratories typically have very rigorous standards for how this works. Eventually, the lab will reclassify the result and send a revised report to the provider who ordered the test – it is up to the provider’s office to re-contact the patient to let them know where they stand. As genetic counselors, we also comb the literature to see what is the latest on the VUS, what type of biochemical change does the VUS cause in the protein, etc. In the case of a VUS, a patient’s screening recommendations are based on the family history only – for example, a patient with a striking family history of breast cancer and a VUS will still be managed as a high-breast cancer risk patient just based on the history.

Within the realm of BRCA1/BRCA2 testing (the most common form of hereditary breast cancer testing), there are generally 3 different types of tests that are done; 2 of these types tend to be run together so one might not realize two different tests are being performed. Comprehensive BRCA testing includes DNA sequencing (spelling out each nucleotide, or chemical, in the gene) of BRCA1 and BRCA2 via polymerase chain reaction (PCR), as well as targeted 5-site rearrangement panel of BRCA1 via recombination-specific PCR using primers specific for the normal gene as well as for the specific rearrangement. Rearrangements can be deletions or duplications of the gene sequence, as well as insertions (additions) of nucleotides.

As we have discussed in a previously published genetics article, there has been an additional BRCA test available since August 2006 named BART (BRCA Large Rearrangement Testing). BART examines coding regions of BRCA1 and BRCA2 for large rearrangements of the sequence as defined above but via different technology called multiplex quantitative PCR. The take-home message is that if a patient says they have had ‘rearrangement’ testing in the BRCA genes, it would be important to know to which one they are referring by obtaining a copy of the results. BART is concurrently
performed with sequencing if a patient meets certain clinical criteria based on personal and family
history, but otherwise it has to be requested separately. On a BRCA test result, BART is typically
called “comprehensive rearrangement” and will be listed under the headers of BRCA1 and BRCA2.
The 5-site rearrangement is only performed on BRCA1 and will read “5-site rearrangement panel”.

For our Ashkenazi (Eastern European) Jewish patients, there is another test of BRCA1 and
BRCA2 that is typically the first test with which a clinician should start; the laboratory calls this test
“Multisite 3 panel” which only looks for 3 founder mutations that are more common in this
population. A founder mutation is a genetic abnormality that is much more commonly seen in a
certain ethnic group; for example, every person of full Ashkenazi Jewish ancestry has a 1 in 40
chance (3%) to carry one of the 3 mutations without family history of breast or ovarian cancer. Two
of mutations are in BRCA1 (187delAG and 5385insC) and the other is in BRCA2 (6174delT). This
is performed by DNA sequence analysis of specific portions of these 2 genes to detect these
particular mutations. There are other populations (French-Canadian, Norwegian, Polish, Scottish,
etc) that also have BRCA founder mutations, which is another reason why it is important to note a
patient’s ancestry.

Finally, it is important to note that BRCA1 and BRCA2 testing, even in the comprehensive
analysis, is not entirely sequenced. There are certain pieces of these 2 genes that do not have a known
function so are not analyzed and only a certain portion of the introns (non-coding regions in genes)
between the exons (coding regions) are analyzed. This means that there are significant portions of
these genes that are not analyzed and account for part of the reason why this testing is not 100%
sensitive.

If you have a patient that you’d like to refer for genetic risk assessment, please contact your
friendly genetic counselor at 817-838-4871.