Considerations for Cancer Family Studies

The primary goal of the cancer family studies program is to obtain segregation data that will ultimately aid in the classification of VUS as either pathogenic or benign.

As with other diseases, the primary goal of the cancer family studies program is to obtain segregation data that will ultimately aid in the classification of VUS as either pathogenic or benign. As such, the cases approved for family studies are those that will be most informative in the variant classification process. If your case is not selected for Ambry’s Cancer Family Study Program you may be notified of other studies for which your patient is eligible. Furthermore, cases that are not currently approved for variant study may be re-contacted by Ambry if an opportunity for VUS study becomes available at a later time. For more detailed information on the cancer family studies review process, please refer to the information below or contact one of our team members at FamilyStudies@ambrygen.com. Please note that the decision to approve or deny family studies occurs in the context of the particular variant and family; therefore, all cases are encouraged to apply (with the exception of the moderate penetrance genes listed directly below).

VUS in Moderate Penetrance Genes

At this point in time, patients whose results consist of a VUS in the following genes are not typically eligible for Ambry’s Family Study Program: ATM, BARD1, BRIP1, CHEK2, MRE11A, NBN, RAD50, RAD51C, and RAD51D. However, if a VUS in one of these genes is under active investigation and segregation data is deemed beneficial towards reclassification efforts we will reach out to our clients to request family studies.

Informative Family Members

The following family members are most likely to be informative for segregation analysis:

Affected individuals

- For common cancers such as breast cancer, the age at diagnosis is considered in the approval process with younger affecteds (i.e., <60) more likely to be selected over older affecteds (i.e., >60).
- For less common cancers such as ovarian cancer and pancreatic cancer, affecteds are likely to be approved regardless of their age at diagnosis.
- Generally speaking, approval of affected individuals is limited to cancers known to be associated with the gene in question. For example, in the case of a BRCA2 VUS, a relative with thyroid cancer would not be considered as an informative affected relative.

Older unaffected individuals

- Due to the varying age-specific penetrance observed amongst cancer susceptibility genes, age thresholds for unaffected individuals are gene specific; however, in most cases family members 75+ are more likely to be approved as older unaffecteds.
- For genes with significant de novo rates (e.g., APC, TP53, NFI), testing of parents and/or other close relatives may be approved regardless of age or affected status to assess for de novo mutation status.
Documentation of Clinical History

In some cases, additional clinical information will be requested prior to family studies approval to ensure accurate results interpretation. Some examples include:

Requesting documentation to confirm unaffected status

- Example: In the case of an MSH2 VUS, we would want to confirm that unaffected females still have their ovaries and uterus intact and would also request colonoscopy records for unaffected males and females to confirm that they are truly unaffected (i.e. confirming there is no history of adenomatous polyps removed at a younger age or having numerous adenomatous polyps removed).

Requesting documentation to confirm affected status

- Example: In the case of a CDH1 VUS, we would request pathology reports for affected family members to confirm their history of lobular breast cancer or diffuse gastric cancer.

In the case of a VUS in a gene with a well-characterized clinical phenotype such as NF1 or PTEN, documentation that the proband and/or family members have undergone comprehensive physical exam will be required to rule out other features of the disease.

Requesting prior genetic test results to avoid falsely attributing cancer history to a VUS, when relevant.

- Example: In the case of a PALB2 VUS, if the proband has a relative with early-onset breast cancer or ovarian cancer, we would require documentation that BRCA1/2 testing was performed to avoid falsely attributing cancer history to the PALB2 VUS.