**Clinical Utility of Diagnostic Exome Sequencing in Hereditary Cancer**

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**Background**: Since 2011, diagnostic exome sequencing (DES) has been instrumental in providing a diagnosis for patients with a broad spectrum of previously undiagnosed genetic disorders. Multigene cancer panels have successfully identified the molecular basis of heritable cancers in a wide variety of cases. When cancer panels fail to identify the mutation(s) in genes involved in heritable cancers, clinicians are beginning to utilize DES to identify causative germline mutations. This study aimed to assess the diagnostic yield of DES and characterize pathogenic findings in an unselected laboratory cohort of patients with a personal and family history of cancer.

**Methods**: We performed a retrospective analysis of 1500 consecutive patients undergoing DES. Overall results categories (positive/likely positive, novel, uncertain, negative) were determined according to predefined diagnostic variant assessment criteria and compared between patients with and without a personal history of cancer. Cases referred for “pure” cancer susceptibility were also compared to “cancer plus” cases referred for cancer histories with additional findings (such as autism, etc.).

**Results**: 52/1500 patients (3.5%) had a history of cancer, including 27 pure cancer susceptibility patients and 25 cancer plus patients. The majority (92.3%) of “pure” cancer patients reported previous uninformative molecular testing. Four (57%) of “pure” cancer patients without previous testing declined other genetic tests at the time DES was offered. Of the “pure” cancer cases, one clinician reported referring for DES due to suspicion of a cancer syndrome unavailable for germline testing, another for clinical history of familial non-medullary thyroid cancer. The remainder of ”pure” cases were referred for suspected hereditary cancer syndromes for which known associated genetic testing was negative or cancer histories not indicative of a specific hereditary cancer syndrome.

Positive or likely positive results were less frequent and uncertain results were similar among patients with and without a history of cancer (p= 1.038e-4, p= 0.812, respectively). The frequency of overall negative DES results was higher in patients with histories of cancer (p=0.002). Novel genetic etiologies were observed at similar frequencies in individuals with or without histories of cancer (p= 0.277).

There were no statistically significant differences in diagnostic yields among patients with “pure” cancer susceptibility and cancer “plus” cases. In the “pure” cancer cases, novel genetic etiologies included *RAD54L* (2 cases) and *STAT2*. Positive or uncertain findings were reported in 5 characterized oncology genes *(ATM, AXIN2, EGLN1, RAD51D, SMARCA4).* With the exception of one patient with a dual diagnosis (*ARHGAP11A, ETV6*), reported findings for cancer “plus” cases were in non-oncologic genes (*ADNP*, *COL7A1, KARS*).

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| Result Type | Cancer Susceptibility # of probands with result type/Total # of probands tested (%) | Cancer “Plus”# of probands with result type/Total # of probands tested (%) | Total Cancer Cases# of probands with result type/Total # of probands tested (%) | Non-Cancer Cases# of probands with result type/Total # of probands tested (%) |
| Characterized Genes Positive/Likely Positive | 1/27 (3.7%) | 2/25 (8.0%) | 3/52 (5.8%) | 407/1448 (28.7%) |
| Characterized Genes Uncertain | 3/27 (11.1%) | 1/25 (4.0%) | 4/52 (7.7%) | 139/1448 (9.6%) |
| Negative | 20/27 (74.1%) | 21/25 (84.0%) | 41/52 (78.8%) | 834/1448 (57.6%) |
| Novel\* | 3/24 (12.5%) | 1/19 (5/3%) | 4/43 (9.3%) | 69/1347 (5.1%) |

\*Among cases in which novel analysis was performed. Novel genetic etiologies were only analyzed in cases involving family trio testing, when ordered by a clinician, and if analysis of characterized genes was negative.

**Conclusions:** Overall diagnostic yield of DES for patients with histories of cancer is significantly lower than for non-cancer patients, with less positive and more negatives findings in patients referred with cancer histories. While this may be explained by the fact that well-established relevant genes had already been excluded in the vast majority of the cancer cohort, one would then expect a higher number of findings in novel genetic etiologies.

Surprisingly, the cases with a “pure” cancer susceptibility phenotype did not differ from those with a more complex phenotype, which may indicate the complexity of testing for cancer in individuals not diagnosed by more traditional cancer heritability tests. It is conceivable that future re-analysis in novel genes may impact the diagnostic yield, indicating the necessity for publishing novel cancer findings by DES and continued examination of the literature.