Title: Germline Pathogenic Variants in Individuals with Renal Cell Carcinoma

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INTRODUCTION AND OBJECTIVES:

Germline genetic testing (GGT) is recommended for patients (pts) with renal cell carcinoma (RCC) and bilateral/multifocal disease, specific variant histology, a diagnosis < 46 years old, or a family history of renal neoplastic syndrome. Retrospective studies of selected cohorts with advanced disease or suggestive personal/family histories show a pathogenic/likely pathogenic germline variant (PGV) prevalence of 5-18%. However, the prevalence of PGVs and clinical utility of GGT in unselected cohorts of pts with RCC remains largely unknown.

METHODS:

All pts with an ICD-10 diagnosis code of RCC who underwent hereditary cancer multi-gene panel testing (MGPT) through Ambry Genetics from 2019-2021 were identified; clinician-reported clinical history was abstracted for those with PGVs. A cancer-unaffected cohort of pts who underwent MGPT during the same timeframe was also identified, excluding those younger than 60 years old. This analysis focused on PGVs in 67 genes, including 13 RCC predisposition genes, 20 DNA damage repair (DDR) genes, and 34 other genes. Multivariable logistic regression was used to assess the association between PGV status and RCC diagnosis, adjusting for age at testing, race, and sex at birth.

RESULTS:

A total of 3614 pts with RCC and 6985 cancer-unaffected pts were included. In the RCC cohort, 50% were female and mean age at testing was 55 years. In the cancer-free cohort, 84% were female and the mean age at testing was 66. The PGV prevalence was 8.7% in the RCC cohort and 8.9% in the cancer-unaffected cohort. Multivariable analysis of any PGVs were similar in the RCC vs cancer-unaffected cohorts (OR 0.93; 95% CI 0.79-1.10). However, PGVs in RCC predisposition genes were enriched in the RCC cohort vs cancer-unaffected cohort (OR 2.73; 95% CI 1.91-3.92) and PGVs in DDR genes were reduced in the RCC cohort vs cancer-unaffected cohort (OR 0.68; 95% CI 0.55-0.83).

CONCLUSIONS:

The overall prevalence of PGVs was approximately 9% in both RCC and cancer-unaffected cohorts. RCC predisposition genes were enriched in pts with RCC and DDR genes were enriched in cancer-unaffected pts. These findings support broader implementation of GGT for pts with RCC to guide screening for additional malignancies, management in advanced disease, and cascade genetic testing for family members.

	RCC cohort (N=3614)		Cancer-free cohort (N=6985)	
Gene	No. tested	No. with PGV (prevalence, %; 95% CI)	No. tested	No. with PGV (prevalence, %; 95% CI)
13 RCC Genes	3586	112 (3.12; 2.58-3.75)	6985	68 (0.97; 0.76-1.23)
20 DDR Genes	3595	171 (4.76; 4.08-5.50)	6985	479 (6.86; 6.28-7.48)
34 Other Genes	3596	38 (1.06; 0.75-1.45)	6985	94 (1.35; 1.09-1.64)
Any of the 67 genes (RCC, DDR, Other)	3614	314 (8.69; 7.79-9.65)	6985	624 (8.93; 8.27-9.63)