Advances in the Diagnosis of Hereditary Kidney Cancer: Initial Results of a Multigene Panel Test

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Introduction

- Panel testing has been recently introduced to evaluate hereditary cancer, however, limited information is available regarding its use in kidney cancer.

Materials and Methods

- We retrospectively reviewed test results and clinical data of patients who underwent targeted multigene panel testing of up to 19 genes associated with hereditary kidney cancer from 2013 to 2016.
- The frequency of positive (mutation/ variant likely pathogenic), inconclusive (variant of unknown significance-VUS), and negative results were evaluated. A logistic regression analysis evaluated predictive factors for a positive test.

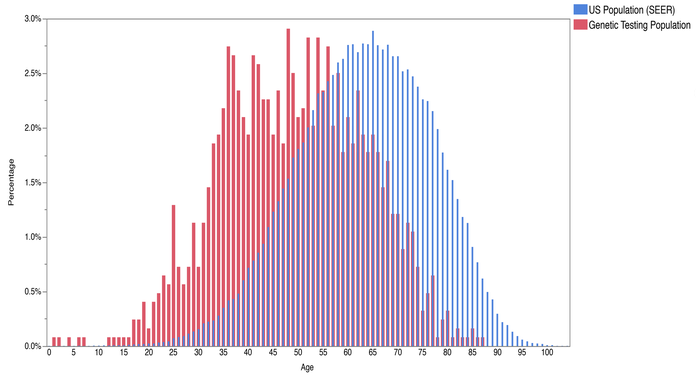
Table 1: Demographics and clinical characteristics of kidney cancer patients undergoing RenalNext

Ethnicity	African American	79 (6.4%)
	Ashkenazi Jewish	54 (4.4%)
	Asian	33 (2.7%)
	Caucasian	792 (64.1%)
	Hispanic	104 (8.4%)
	Other/Unknown	173 (14%)
Age at Onset	Mean (SD)	46.2 (13.7)
	Median	46
	Interquartile Range	36-57
Histology	Chromophobe	82 (6.6%)
	Clear Cell	459 (37.2%)
	Papillary (Type 1 and 2)	145 (11.7%)
	Other	256 (20.7%)
	Unspecified	293 (23.7%)
Sex	Male	668 (53.9%)
	Female	571 (46.1%)
Number of Patients with Second Cancer	None	859 (69.6%)

Table 2: Multivariate Predictive Model for Identification of a Positive Panel Test

Variable	OR (95% CI)	P Value
Age of Onset	0.975 (0.958-0.993)	0.0052*
Second Cancer Present		0.9041
No	Reference	
Yes	1.37 (0.82-2.40)	
Ethnicity		0.9245
White	Reference	
Non-White	0.977 (0.592-1.58)	
Gender		0.3267
Male	Reference	
Female	0.788 (0.485-1.267)	
Family History of Cancer		0.6983
No	Reference	
Yes	0.8835 (0.484-1.69)	
Family History of Kidney Cancer		0.9041
No	Reference	
Yes	1.034 (0.592-1.767)	

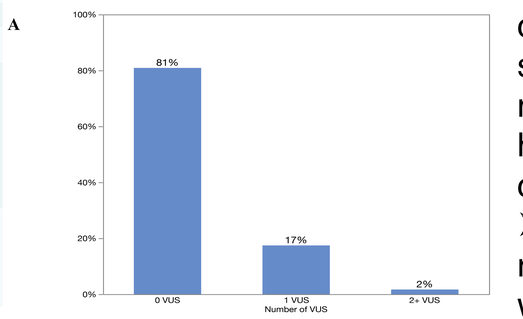
Figure 1: Comparison of kidney cancer patient age distributions by population

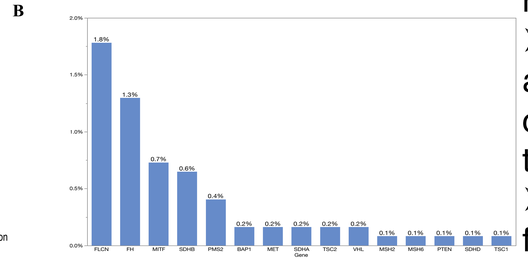


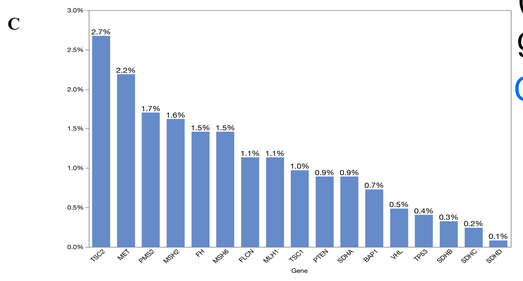
Results

- Patients evaluated with the RenalNext panel (n=1,235) were significantly younger (median age of 46) than the U.S. population of kidney cancer (p<0.0001).
- Overall, 6.1%, 75.5%, and 18.4% of individuals had positive, negative, and inconclusive results, respectively. The most commonly altered genes included *FLCN* and *FH*, which were 1.8% and 1.3% of cases respectively.

Figure 2a) Comparison of VUS from RenalNext, N = 1,235 patients. **b)** Comparison of mutations/VLP by gene from RenalNext, N = 1,235 patients. **c)** Comparison of VUS by Gene from RenalNext, N = 1,235 patients







Results

- Early age of onset was the only factor found to be predictive of a positive test on multivariate analysis (OR 0.975, 95% p =0.0052) and may be the only identifying characteristic of low penetrant syndromes, such as those associated with MITF mutations, which did not have singular histology nor a family history of kidney cancer.
- *TSC2, MET,* and *PMS2* had the highest rates of variants of unknown significance with 2.7%, 2.2%, and 1.7% of cases, respectively.
- Overall, 18 of 32 cases (56.3%) with available submitted histology were consistent with published literature based on the specific gene alteration.
- For cases with sufficient personal and family history provided, only 23 of 70 cases (32.9%) had strong suspicion for the noted gene alteration

Conclusion

- Multigene panel tests may be particularly useful for patients who lack distinguishing clinical characteristics of known hereditary kidney cancer syndromes.
- For low penetrant syndromes, family and personal history may not be reliable indicators of a hereditary syndrome.
- Our results support the use of early age of onset for genetic counseling and/or testing.
- Selecting multigene panel testing may be useful as discordant characteristics can be observed since not all patients have "classic" disease manifestations. The increase rate of VUS with testing argues for interpretation by an experienced team of genetic counselors.