The Landscape of Cancer Diagnoses in *PMS2* Mutation Carriers, By Self-Reported Ancestry

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Background

- *PMS2* is a mismatch repair gene associated with Lynch syndrome and confers an elevated risk for colorectal, endometrial, and possibly other cancers.
- Estimates of associated cancer risks are nebulous given its low penetrance, especially among diverse populations.
- Understanding the landscape of cancer diagnoses in diverse populations is important to develop personalized management recommendations for *PMS2* mutation carriers.

Methods

- We performed a retrospective analysis within the Myriad Collaborative Research Registry (MCRR), a registry of de-identified clinical, genetic, and genomic data from 1,277,012 patients with cancer tested at Myriad Genetics.
- We queried the MCRR for patients with *PMS2* pathogenic and likely pathogenic variants in patients who received germline testing.
- We then compared the differences in cancer rates between *PMS2*-positive and *PMS2*-negative cohorts based on self-reported ancestries (Non-Hispanic White, Black, Asian).

Table 1. *PMS2* Rates in Germline Tested Cohort

Ancestry (total patients)	Total # Female* Patients with *PMS2* P/LP Variants	Positive Rate (%)
White (668,567)	1,141	0.17
Black (93,012)	64	0.07
Asian (36,196)	54	0.15

*Sex at birth female

Table 2. Total Cancer Cases by Self-Reported Ancestry

Ancestry (total patients)	Total Cancer Cases	Total Colon Cases	Total Endometrial Cases
***PMS2* Positive**			
White (668,567)	1,439	186	239
Black (93,012)	83	21	12
Asian (36,196)	66	8	16
***PMS2* Negative**			
White (668,567)	781,721	25,296	26,069
Black (93,012)	102,972	3,718	2,608
Asian (36,196)	39,727	1,150	1,267

Total cancer cases exceeds total number of patients. Individuals with multiple cancer diagnoses were not excluded from analysis.

Results

- *PMS2* mutation rates in the Non-Hispanic White, Black and Asian cohorts were 0.17% (1,141/668,567), 0.07% (64/93,012) and 0.15% (54/36,196), respectively (**Table 1**).
- Colon cancer frequencies were higher in the PMS2-positive ancestry-specific cohorts than in the PMS2-negative ancestry-specific cohorts (White: 3.99-fold; Black: 7.01-fold; Asian: 4.19-fold) (**Table 2, Table 3, Figure 1**).
- Endometrial cancer frequencies were higher in the *PMS2*-positive ancestry-specific cohorts than in the *PMS2*-negative ancestry-specific cohorts (White: 4.98-fold; Black: 5.71-fold; Asian: 7.60-fold) (**Table 2, Table 3, Figure 1**).

Figure 1. Ratio of Cancer Frequencies between *PMS2*-positive and *PMS2*-negative Cohorts

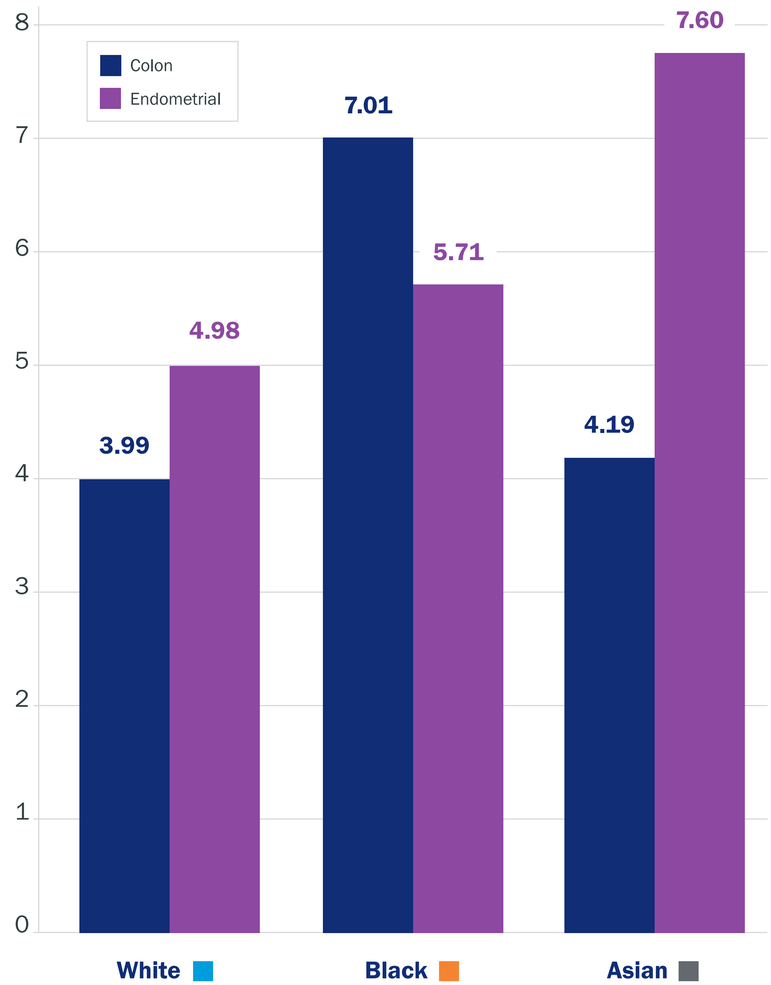

Table 3. Frequency of Cancer Diagnoses between *PMS2*-positive and *PMS2*-negative Cohorts, by Self-Reported Ancestry

Ancestry	Colorectal %	Endometrial %
***PMS2* Positive**		
White	12.93	16.61
Black	25.30	14.46
Asian	12.12	24.24
***PMS2* Negative**		
White	3.24	3.33
Black	3.61	2.53
Asian	2.89	3.19

Conclusions

- The frequencies of colon and endometrial cancers were higher in female *PMS2* mutation carriers across Non-Hispanic White, Asian, and Black populations.
- However, the magnitude of difference in cancer frequency ratios for *PMS2* mutation carriers varied between the three ancestries.
- This difference could be explained by multiple factors.
  - The Black and Asian cohorts had fewer patients versus the White cohort which could imply that these samples were underpowered to understand true difference in cancer frequencies
  - Social determinants of health may affect the ability of eligible patients to undergo hereditary cancer testing
- Multivariate logistic regression is required to determine statistical significance of these differences, but these data emphasize the importance of improved access to genetic testing services in diverse populations.