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Microsatellite instability high (MSI-H): A definitive predictive biomarker for immune checkpoint inhibitors (ICI) yet understudied in underrepresented minorities (URM) with gastrointestinal (GI) cancers

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Background:

- Mismatch repair deficiency (dMMR) results in MSI-H status and is the first tumor-agnostic biomarker predictive of response to immune checkpoint inhibitors (ICI).
- Among GI cancers, MSI-H is most frequent in colorectal cancer (CRC, 15%) gastroesophageal cancer (GEC, 5%) and small bowel and hepatopancreatobiliary (HPB, <5%).
- For CRC, MSI-H can be attributed to germline mutations (Lynch syndrome, 3%) or somatic inactivation (sporadic, 12%) of foundational MMR genes.
- Studies evaluating ICI efficacy in dMMR cancers focus primarily on non-Hispanic White (NHW) patients (pts).
- In this study, we explore 2 large databases and present data on prevalence, tumor genomic features, and outcomes in underrepresented minority (URM) patients with MSI-H GI cancers

Methods:

Retrospective analysis of MSI-H GI cancers

- Upper: Esophageal + Gastric + GEJ
- Mid: Hepatic + Biliary + Pancreatic + Small bowel
- Lower: Colon + Rectal + Anal

MSK-IMPACT and TEMPUS-LENS databases

- Primary analysis performed on MSK-IMPACT and further validation from TEMPUS-LENS

Patients were grouped by self-reported race and ethnicity into 4 arms:

- Non-Hispanic White (NHW)
- Asian
- Non-Hispanic Black (NHB)
- Hispanic
- URM = Asian + NHB + Hispanic

Age at diagnosis, tumor mutation burden (TMB), MMR gene alteration frequency, and molecular ancestry were analyzed using descriptive statistics. Overall survival (OS) was estimated with Kaplan-Meier Methods

Conclusions:

- Proportion of MSI-H GI cancers in URM patients is similar to that seen in NHW pts. However, the number diagnosed were **significantly lower by 8 - 15 fold**, which indicates **significant undertesting in URM patients**
- Younger patients were more commonly seen in MSI-H CRC URM compared to NHW.
  - **Asian and Hispanic patients were 10+ years younger than NHW.**
- Overall survival was similar between NHW and URM in patients with unresectable MSI-H colorectal cancer
- Concordance and similar proportion of MMR gene alteration pattern was seen among self reported races/ethnicities and molecular based ancestry determination

Results:

Figure 1. Distribution of TMB, sex, race/ethnicity, and MMR genes altered in cohort for MSI-H GI cancers

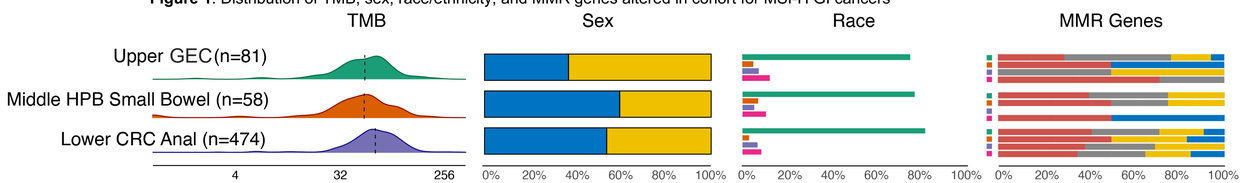

Figure 2a. Distribution of MSI-H within GI cancer types in NHW, Hispanic, Black, and Asian
HPB – hepatopancreatobiliary, CRC - colorectal

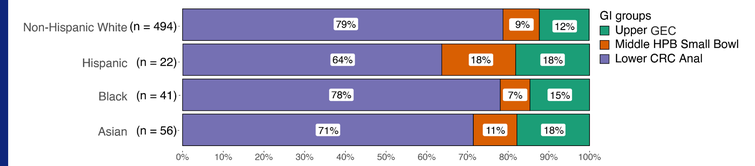

Figure 2b. Frequency of MSI-H in CRC and GEC by race/ethnicity

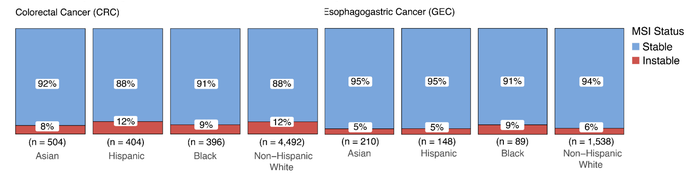

Figure 3. Median age at diagnosis for
A) NHW/URM. B) Asian/NHB/Hispanic/NHW

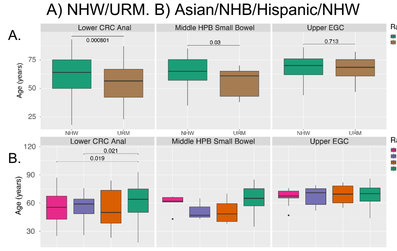

Figure 4. Median tumor mutational burden for
A) NHW/URM. B) Asian/NHB/Hispanic/NHW

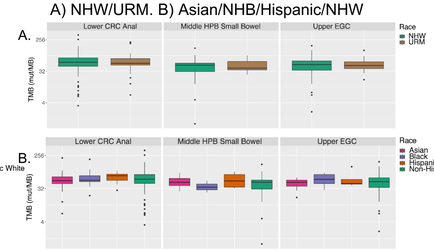

Figure 5. Overall survival for NHW and URM Patients with unresectable MSI-H CRC

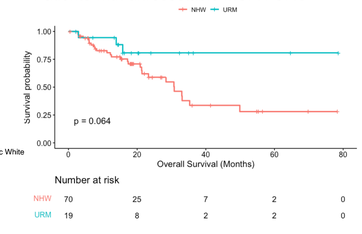

Figure 6. Concordance between molecular ancestry and self-reported race

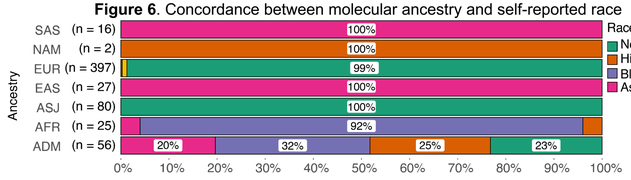

Figure 7. MMR gene alteration frequency. A) Self-reported race. B) Molecular ancestry

Table 1. MSI-H frequency, age, TMB, and MMR gene FA by race/ethnicity in MSK-IMPACT and TEMPUS cohorts. *MMR gene FA: Most frequently altered MMR gene*

MSKCC – IMPACT					
		NHW	**NHB**	**Asian**	**Hispanic**
CRC *N = 5,796*	MSI-H %	11.7%	8.8%	8.1%	11.9%
	Median Age	67	61	57	55
	Median TMB	58	54	50	61
	MMR gene FA (%)	MSH6 (22%)	MSH6 (17%)	MLH1 (15%)	MSH6 (28%)
GEC *N = 1,985*	MSI-H %	5.7%	9.0%	5.2%	5.4%
	Median Age	71	70	68	68
	Median TMB	50	75	49	44
	MMR gene FA (%)	MLH1 (16%)	MLH1 (50%)	MSH6 (36%)	MSH2/6 (12%)
Other GI *N = 5,318*	MSI-H %	1.4%	1.4%	1.4%	1.8%
	Median Age	65	50	64	66
	Median TMB	51	30	48	55
	MMR Gene FA (%)	MSH6/PMS2 (17%)	(0%)	MSH6/PMS2 (17%)	MLH1/MSH2/6 (17%)
TEMPUS					
		NHW	**NHB**	**Asian**	**Hispanic**
CRC *N = 3,838*	MSI-H %	7.9%	3.4%	4%	5.1%
	Median Age	72	58	76	51
	Median TMB	35	29	39	37
	MMR Gene FA (%)	MSH6 (61 %)	MSH6 (66.7%)	MSH6 (66.7%)	MLH1 (69%)
GEC *N = 1,502*	MSI-H %	3.3%	9.4%	6.9%	6.3%
	Median Age	72	75	79	68
	Median TMB	28	36	28	31
	MMR Gene FA (%)	MSH6 (43%)	MSH6 (50%)	MSH6 (40%)	MSH6 (53%)
Other GI *N = 3,305*	MSI-H %	1.1%	1.4%	0.8%	1.0%
	Median Age	66	56	74	64
	Median TMB	21	9	41	26
	MMR Gene FA (%)	MLH1 (41%)	MSH2/6 (25%)	MSH2 (100%)	MSH6 (75%)

Future Directions:

- Comprehensive genomic analysis at MSKCC and TEMPUS database are underway looking at TME and ancestry data.
- Validation of clinicogenomics of MSI-H GI cancers in other large cohorts.
- Determine effect of immunotherapy on survival of NHW and URM patients with MSI-H gastrointestinal cancers.
- Investigate younger age for URM patients with MSI-H GI cancers.

Acknowledgments

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