Background Recent advancements in immunotherapy are revo-
lutionizing the landscape of clinical immuno-oncology and have 
significantly increased patient survival in a range of can-
cers. Notably, immune checkpoint blockade therapies have 
induced durable responses and provided tremendous clinical 
benefits to previously untreated patients. However, unleashing 
immune system against cancer also disrupts the immuno-
logic homeostasis and induce inflammatory responses, resulting 
immune-related adverse events. The precise mechanisms under-
lying immune-related adverse events (irAEs) remain unknown. 
Furthermore, it is unclear why immune checkpoint blockade 
threats only induce irAEs in some patients but not the 
others. In this study, we systematically characterize the func-
tional impacts of immune checkpoint blockade on the patient 
immune system at single-cell resolution.

Methods The peripheral blood mononuclear cells (PBMCs) 
from seven cancer patients with melanoma, non-small cell 
 lung cancer, or colon cancer (MSI-H) receiving immune 
 checkpoint inhibitors (CPIs), i.e. anti-PD-1+anti-CTLA4 
 combo or anti-PD-1 single agent, were collected at three 
serial time points (T1, T2, and T3). During the immunothe-
rapy, four patients developed irAEs, including colitis (2X), 
immunopneumonitis (1), hyper/hypothyroidism (1), while three 
patients showed no signs of irAEs. In total, we generated 
and characterized single cell gene expression profiles for 
more than 65,000 cells from 21 PBMC libraries. Further-
more, we simultaneously measured TCR and BCR from nine 
selected samples, thus generating a comprehensive profile of 
Immune repertoire upon CPIs.

Results We systematically characterized T cells, B cells, mono-
cytes, NK cells, and platelets from PBMCs. Both checkpoint 
blockade and patient comorbidity affect PBMC populations. 
We found that irAEs are often associated with an acute 
increase in monocytes and decrease in T cells. After repeated 
CPI treatment, PBMC populations remained relatively stable. 
We characterized specific subsets within each cell type that are 
associated with CPI treatment as well as patient clinical condi-
tions, and identified signature genes for each subset. For 
example, Mucosal-Associated Invariant CD8 T cells were 
strongly enriched in the PBMC population of the colon cancer 
patient. In the melanoma patient who received 
anti-PD-1+anti-CTLA4 combo but didn’t develop colitis, we found 
enriched NK cell subsets expressing chemokine such as 
XCL1 and CCL4. Furthermore, we found prominent T cell clonal 
expansion in this patient compared to the two melanoma 
patients who developed colitis. The administration of steroids 
after irAEs led to massive anti-inflammatory responses in 
PMBCs, often characterized by the prominent expression of 
AREG.

Conclusions Our study characterized the functional impact of 
CPIs on patient PBMCs. Our data demonstrated that single 
cell RNA sequencing provides a powerful tool to dissect and 
identify clinically actionable biomarkers for response prediction 
and side effects alleviation in patients receiving immunother-
apy in the era of precision medicine.

Ethics Approval This study was approved by the Institutional 
Review Board (#1050678) at Intermountain Healthcare (Salt 
Lake City, UT USA)

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Microsatellite Instability/Mismatch Repair 
Biomarker Testing Disparities in Patients with 
Advanced Colorectal Cancer: Implications for 
Immune Checkpoint Inhibitors

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Background Immune checkpoint inhibitors have revolutionized 
outcomes for patients with a spectrum of cancer types, including 
the first tissue/site-agnostic FDA approvals (in 2017 for 
2nd-line and 2020 for 1st-line) for advanced cancers with 
DNA microsatellite instability-high/mismatch repair deficiency 
(MSI-H/MMRd). However, the factors associated with patients’ access to MSI/MMR testing are unknown.

Methods Patients ≥20-years-old who newly presented with his-
topathologically-confirmed stage 4 colorectal adenocarcinoma 
from 2010–2016 were identified from the National Cancer 
Database, which comprises >70% of all newly-diagnosed 
cancer patients in the U.S. Patients were excluded if they lacked 
data about MSI/MMR testing or were initially diagnosed at 
another institution. The primary outcome was receiving MSI/ 
MMR testing, either via immunohistochemistry or molecular 
diagnostic. Patient demographic, socioeconomic, and care set-
ting characteristics were evaluated for association with MSI/ 
MMR testing, as well as between MSI/MMR testing and 
immunotherapy receipt, using multivariable logistic regression.

Results Of 45,326 newly-diagnosed stage 4 colorectal adeno-
carcinoma patients, only 26.5% (n=11,998) received MSI/ 
MMR testing – rising from 14.4% in 2010 to 41.1% in 2016 
(adjusted odds ratio [aOR] 1.26/year, 95% confidence interval 
[95%CI] 1.25–1.29, p<0.001). Overall, patients who were 
older (referent 60–69-years-old; 70–79-years-old aOR 0.83, 
95%CI: 0.77–0.89, p<0.001; 50–59-years-old aOR 1.25, 95% 
CI: 1.16–1.33, p<0.001), male (aOR 0.94, 95%CI: 0.90–0.99, 
p=0.01), or of Black non-Hispanic race/ethnicity (aOR 0.87 vs. 
White non-Hispanic, 95%CI: 0.82–0.94, p<0.001) were 
indeed less likely to receive testing.Additionally, patients who were either uninsured (referent private insurance, 
aOR 0.78, 95%CI: 0.70–0.86, p<0.001), Medicaid-insured 
(aOR 0.87, 95%CI: 0.80–0.94, p=0.001), or Medicare-insured 
(aOR 0.87, 95%CI: 0.81–0.93, p<0.001); or diagnosed at 
community (referent academic/NCI-comprehensive cancer 
program, aOR 0.60, 95%CI: 0.56–0.66, p<0.001) or 
comprehensive community (aOR 0.76, 95%CI: 0.72–0.80, p<0.001) 
cancer programs, were also significantly less likely to be 
tested. Even for patients diagnosed in 2016, untreated patients 
received independently less immunotherapy than tested patients (aOR 0.61, 95%CI: 0.53–0.68, p<0.001).

Conclusions MSI/MMR testing rates for stage 4 colorectal can-
cer patients have dramatically improved in recent years, but 
appeared underutilized in patients that were older, of Black 
non-Hispanic race/ethnicity, uninsured or Medicaid-insured, or 
diagnosed at community programs. Our findings suggest that 
socioeconomic and care setting opportunities exist for improv-
ing access to testing of this important predictive biomarker for 
immune checkpoint blockade.