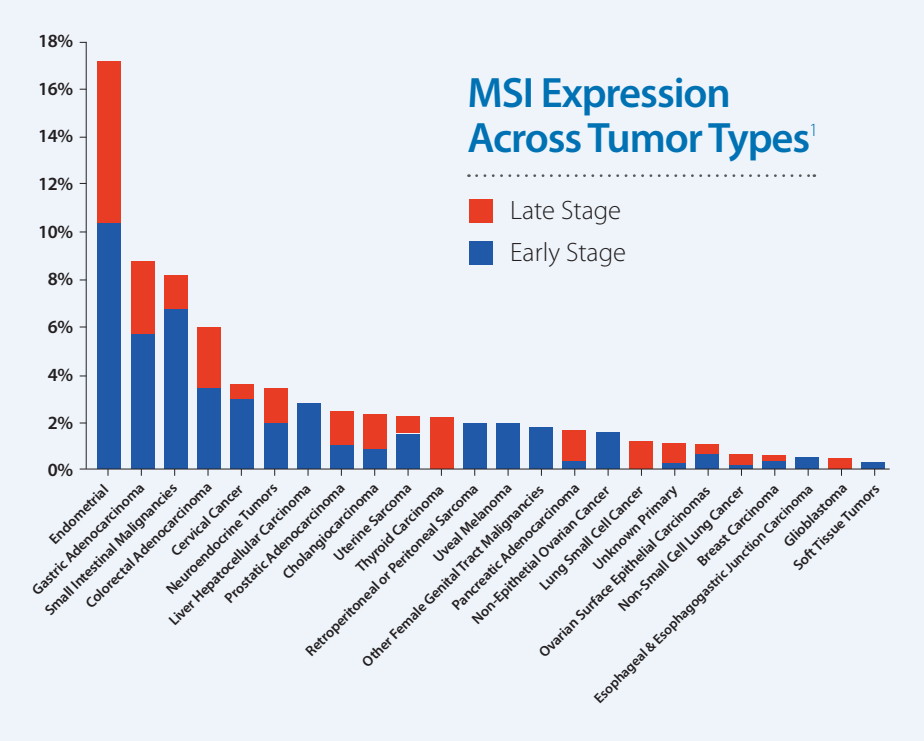
CARIS MOLECULAR INTELLIGENCE®
ENABLING PRECISION MEDICINE

Microsatellite Instability – Response to Immunotherapy

Caris Molecular Intelligence® tumor profiling includes Microsatellite Instability (MSI) testing via Next-Generation sequencing (NGS). MSI is caused by failure of the DNA mismatch repair (MMR) system. High levels of MSI correlate to an increased neoantigen burden, which may indicate the tumor is more sensitive to immunotherapy. MSI status is reported on pages one and two of the MI Profile Report, as well as in the NGS section in the Appendix.

MSI-High Status Across Caris Molecular Intelligence Cases

Earlier studies have associated MSI-High status with benefit to immunotherapy in metastatic colorectal cancer. Recent data, however, show that MSI is a useful indicator for predicting response to pembrolizumab in any solid tumor type.[1]

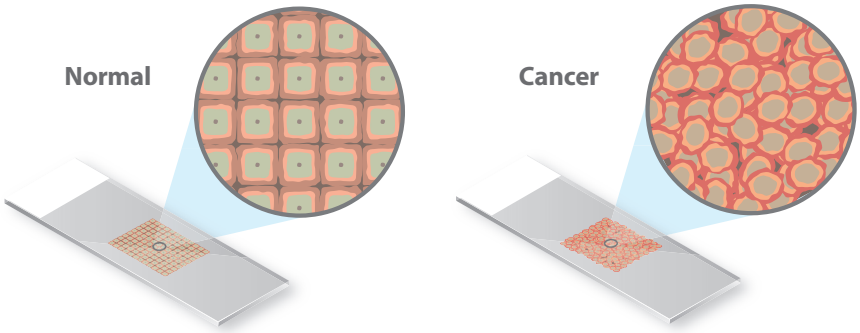


Traditionally, MSI is detected through polymerase chain reaction (PCR) by fragment analysis (FA) of five conserved satellite regions and comparing cancer tissue to normal tissue to identify differences in tandem repeats.[3-4] To validate MSI testing via NGS, Caris evaluated more than 7,000 target microsatellite loci and compared the results from PCR for 2,189 cases across 26 different tumor types. These data were published in Cancer Medicine and demonstrated that MSI testing with Caris' NGS platform is highly concordant with the traditional standard method of PCR-FA and is a more efficient and cost-effective approach to identifying patient candidates for immunotherapy.[2]

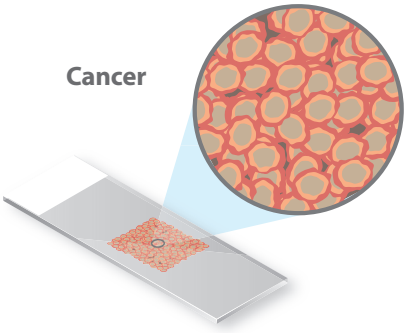
Concordance Data: PCR vs NGS[2]

Lineage	Sensitivity	Specificity	PPV	NPV
All	95.8%	99.4%	94.5%	99.2%
CRC	100.0%	99.9%	98.7%	98.7%

Traditional Approach: normal and cancer tissue required



Caris Approach: no normal tissue required; saving resources, costs and time



1. D. T. Le, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. Published Online 8 June 2017. DOI: 10.1126/science.aan6733. – **2.** Vanderwalde, A., Spetzler, D., Xiao, N., Gatalica, Z. and Marshall, J. (2018), Microsatellite instability status determined by next-generation sequencing and compared with PD-L1 and tumor mutational burden in 11,348 patients. Cancer Med. doi:10.1002/cam4.1372. – **3.** de la Chapelle, A., and H. Hampel. 2010. Clinical relevance of microsatellite instability in colorectal cancer. J. Clin. Oncol. 28:3380–3387. – **4.** Zhang, L. 2008. Immunohistochemistry versus microsatellite instability testing for screening colorectal cancer patients at risk for hereditary nonpolyposis colorectal cancer syndrome. Part II. The utility of microsatellite instability testing. J. Mol. Diagn. 10:301–307.

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CARIS LIFE SCIENCES

CARIS MOLECULAR INTELLIGENCE®
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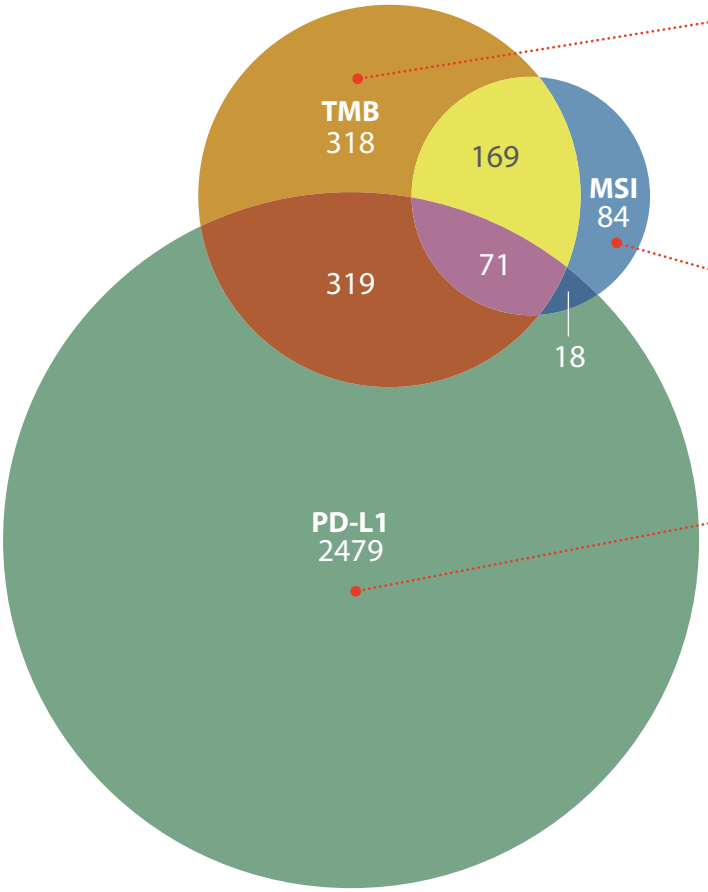
Unlock the Power of Immunotherapies

By harnessing the body's immune system to detect and destroy tumor cells, **immune checkpoint inhibitors** are rapidly ushering in a new era of precision medicine.[1-4] Although immune checkpoint inhibitors have demonstrated durable clinical responses across several tumor types, these therapies are costly and may present toxic side effects.[1, 3-6]

Understanding the relationships between TMB, MSI and PD-L1 can help oncologists make more informed immunotherapy decisions.[12]



Tumor mutational burden (TMB) measures the total number of non-synonymous somatic mutations identified per megabase of the genome coding area. Tumors with high TMB likely harbor neoantigens and may respond more favorably to immunotherapies.[4-5,7]

Caris Experience data across all lineages: 33,000+

Microsatellite instability (MSI) is caused by failure of the DNA mismatch repair (MMR) system.[3] MSI-High correlates to an increased neoantigen burden, which may indicate the tumor is more likely to respond favorably to immunotherapies.

Caris Experience data across all lineages: 24,000+

Programmed death ligand-1 (PD-L1) is among the most important checkpoint proteins that mediate tumor-induced immune suppression through T-cell downregulation.[5,8] PD-L1 expression may indicate a more likely response to immunotherapies.[2,9-11]

Caris Experience data across all lineages: 64,000+

- = High TMB
- = MSI-H
- = High PD-L1
- = High TMB and MSI-H
- = MSI-H and High PDL-1
- = High TMB and High PD-L1
- = High TMB, MSI-H, and High PD-L1

N = 11,348

Identify Patients More Likely to Respond to Immunotherapies through Comprehensive Genomic Profiling PLUS (CGP+) with Caris Molecular Intelligence.

1. Topalian SL. N Engl J Med. 2012;366(26):2443-2454. doi:10.1056/NEJMoa1200690. – **2.** Patel SP and Kurzrock R. Mol Cancer Ther. 2015;14(4):847-856. doi:10.1158/1535-7163.MCT-14-0983. – **3.** Le DT. N Engl J Med. 2015;372:2509-2520. doi:10.1056/NEJMoa1500596. – **4.** Rizvi NA. Science. 2015; 384(6230):124-128. doi:10.1126/science.aaa1348. – **5.** Rosenberg JE. The Lancet. 2016; 387(10031):1909-1920. doi:10.1016/S0140-6736(16)00561-4. – **6.** Motzer RJ. N Engl J Med. 373:1803-1813. doi:10.1056/NEJMoa1510665. – **7.** Snyder A. N Engl J Med. 2014; 371:2189-2199. doi:10.1056/NEJMoa1406498. – **8.** Mellman I. Nature. 2011;480:480-489. doi:10.1038/nature10673. – **9.** Borghaei H. N Engl J Med. 2015;373:1627-39. doi:10.1056/NEJMoa1507643. – **10.** Garon EB. N Engl J Med. 2015;372(21):2018-2028. doi:10.1056/NEJMoa1501824. – **11.** Taube JM. Clin Cancer Res. 2014;20(19):5064-5074. doi:10.1158/1078-0432.CCR-13-3271.
12. Vanderwalde A. Cancer Med. 2018 Feb 13. doi: 10.1002/cam4.1372.

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