# Modaplex

## MICROSATELLITE INSTABILITY TESTING


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# MSI IN CLINICAL RESEARCH

## FROM PROMISING CANDIDATE TO CLINICAL PRACTICE

### MSI EVALUATION AS A RESEARCH MARKER FOR IMMUNE-CHECKPOINT THERAPY RESPONSE

In recent years, immune-checkpoint inhibitors (ICIs) have revolutionized the treatment of patients with advanced cancer and ICIs have become a strong pillar in cancer treatment[1]. However, understanding the molecular biological background is still required when considering the best indication for ICI[2]. In this context several studies have demonstrated that MSI status, as a surrogate for a defective mismatch repair system (dMMR), is a positive predictor for the response to immune-checkpoint inhibitors[3,4,5]. Furthermore, since 2017 several IC-therapies have been approved by the US Food and Drug Administration (FDA) or EMA considering the tumor´s MSI status.

As the MSI status is a useful surrogate marker, clinical researchers are currently investigating MSI and its implications for predicting the response to immune checkpoint blockade in a variety of tumor entities[6].

### INVESTIGATION OF MSI IN ENDOMETRIAL CARCINOMA

The Cancer Genome Atlas Research Network (TCGA) performed an integrating genomic, transcriptomic, and proteomic characterization of endometrial carcinoma. Exome sequence analysis revealed four groups of tumors[7].

- **Group 1** carcinomas have somatic inactivating hotspot mutations in the POLE exonuclease domain and a very high mutational burden (ultramutated).
- **Group 2** includes endometrioid carcinomas which are microsatellite instable (MSI) (hypermutated), and present frequently with MLH-1 promoter hypermethylation and high mutation rates.
- **Group 3** tumors are typically endometrioid carcinomas with low copy number alterations, and a low mutational burden, while lacking POLE mutations and MSI-H.
- **Group 4** (Serous-like or copy-number high) show a low mutation rate, nearly universal TP53 mutations, and have a highly unfavorable prognosis.

Clinical researchers are now attempting to bring the TCGA molecular-based classification into clinical practice[8].

**REFERENCES**


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2 R.W. Jenkins et al, "Molecular and Genomic Determinants of Response to Immune Checkpoint Inhibition in Cancer", Annu. Re. Med., vol. 69, pp. 333-347, 2018.
3 D.T. Le et al, "PD-1 Blockade in tumors with Mismatch-Repair Defi ciency", N. Engl. J. Med., vol. 372, pp. 2509-2520, 2015. 5 D.T. Le et al, "Mismatch-repair defi ciency predicts response of solid tumors to PD-1 blockade", Science, vol. 357, no. 6349, pp. 409-413, 2017.
4 V. Lee et al. "Mismatch Repair Deficiency and Response to Immune Checkpoint Blockade." The oncologist vol. 21,10 (2016): 1200-1211.
5 Y. Eso et al. "Microsatellite instability and immune checkpoint inhibitors: toward precision medicine against gastrointestinal and hepatobiliary cancers." Journal of gastroenterology vol. 55,1 (2020): 15-26.
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7 Levine, D., The Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. Nature 497, 67–73 (2013).
8 Concin N, Matias-Guiu X, Vergote I, et al ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma International Journal of Gynecologic Cancer Published Online First: 18 December 2020.

# INTRODUCING THE MODAPLEX MSI SOLUTION

## DETERMINE MSI-H WITH MODAPLEX MSI ANALYSIS KIT


### ANALYSIS USING A STANDARDIZED INDIVIDUAL MSI-H ASSESSMENT

- Simultaneous analysis of proven dinucleotide and mononucleotide markers
- Obtain results through intuitive result analysis

### REPORT RESULTS WITH CONFIDENCE

- Verified with artificial material and tested on FFPE-derived CRC and EC sample material
- Include forensically accepted (human insertion/deletion polymorphism) marker as sample mix-up and contamination control
- Comprehensible MSI-H detection using optimal 10ng genomic DNA


### ENHANCE LABORATORY EFFICIENCY

- Setup as straightforward as setting up a PCR
- Modaplex Result Analyzer (Moda-RA) software enables the researcher to interpret markers intuitively

# MODAPLEX MSI ANALYSIS KIT

## PROVEN MARKER TO EMPOWER STANDARDIZED MSI-H ASSESSMENT

The combination of five mononucleotide markers (Bat-25, Bat-26, NR-21, NR-24, and Mono-27) and two dinucleotide markers (D5S346 and D17S250) allows the individual MSI status determination. This microsatellite panel has been proven to be highly sensitive and specific in providing results on MSI status across various tumor entities, such as endometrial carcinoma and colorectal cancer[1,2].

## CHOOSE YOUR INDIVIDUAL STANDARDIZED MSI-H ASSESSMENT OPTION

| | |
|---|---|
| Mononucleotide Markers | » Bat-25<br>» Bat-26<br>» NR-21<br>» NR-24<br>» Mono-27 |
| Dinucleotide Markers | » D5S346<br>» D17S250 |

### MSI status assessment using mononucleotide- and dinucleotide-repeat marker[3]

| | > 5 Microsatellite Markers | Interpretation |
|---|---|---|
| No. of marker exhibiting instability | ≥ 30-40% | **MSI-H** |
| | < 30-40% | **MSI-L** |
| | 0 | **MSS** |

| | |
|---|---|
| Mononucleotide Markers | » Bat-25<br>» Bat-26<br>» NR-21<br>» NR-24<br>» Mono-27 |

### MSI status assessment using five quasi-monomorphic mononucleotide-repeat marker[4]

| | 5 Mononucleotide Markers | Interpretation |
|---|---|---|
| No. of marker exhibiting instability | ≥ 3 | **MSI-H** |
| | ≤ 2 | **MSI-L** |
| | 0 | **MSS** |


**REFERENCES**

1 Luchini, C et al. "ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach." Annals of oncology : official journal of the European Society for Medical Oncology vol. 30,8 (2019): 1232-1243

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3 C.R. Boland et al. "A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer." Cancer research vol. 58,22 (1998): 5248-57.

4 A. Umar, C.R. Boland et al. "Revised Bethesda Guidelines for Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) and Microsatellite Instability.", JNCI: Journal of the National Cancer Institute, Volume 96, Issue 4, 18 February 2004, Pages 261–268

# EVALUATION OF INSTABILITY

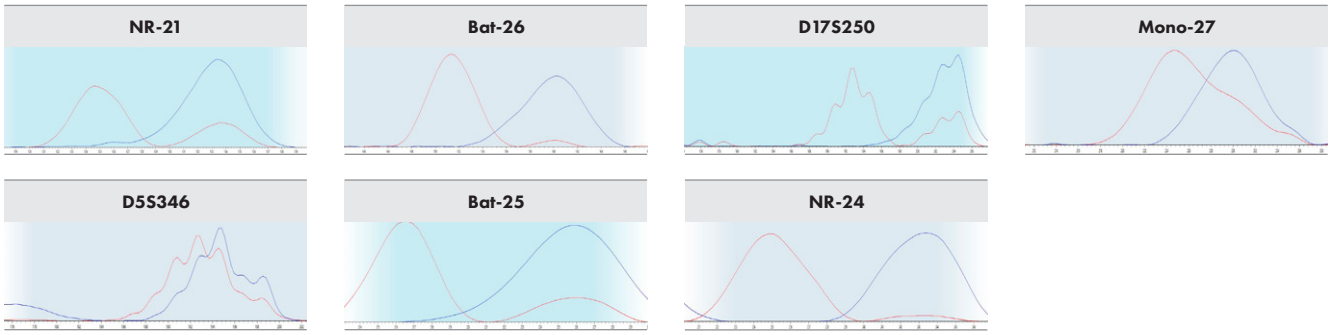
## EXPERIENCE INTUITIVE ASSESSMENT THROUGH AUTOMATIC PEAK-OVERLAY

Recently, certain testing procedures are available to determine the accurate MSI-H status such as PCR-based-, NGS-based- or fully automated approaches. Interestingly, several studies have demonstrated that different methods produce concordant results 95% - 100% when compared to each other[1,2,3].

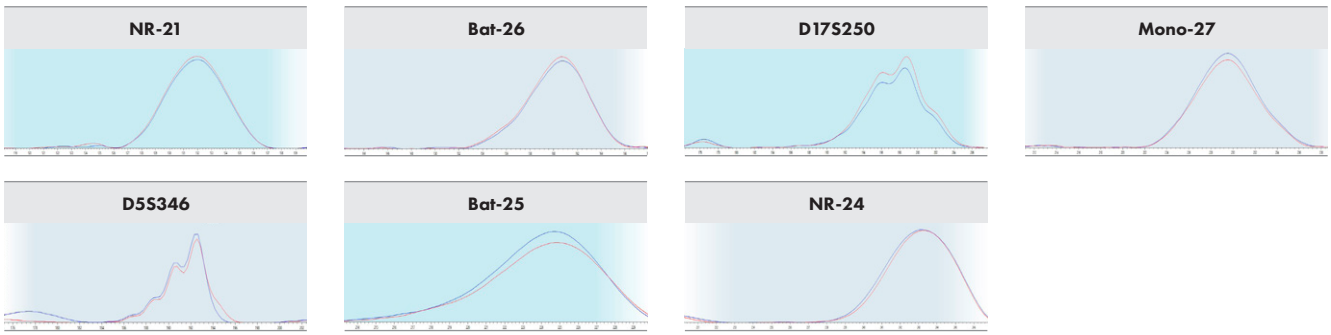
Regardless of the method, instability assessment requires careful estimation and knowledge of the technical limitations. For PCR-based systems, experience means to be knowledgeable on peak alterations and shift events. With Modaplex Result Analyzer Software, users can evaluate these peak alterations and shift events intuitively through an automated overlay of allele-peaks from tumoral and normal tissue.

### VISUAL ASSESSMENT TO EVALUATE THE "INSTABILITY" OF EACH MARKER

Typical results from a MSI-H FFPE colorectal cancer sample, 10ng; cancer tissue (red); normal adjacent tissue (blue)




Typical results from a MSS FFPE colorectal cancer sample, 10ng; cancer tissue (red); normal adjacent tissue (blue)





**REFERENCES**

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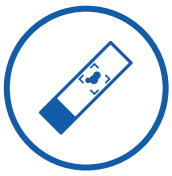
2 Y.F. Wong et al. "Detection of microsatellite instability in endometrial cancer: advantages of a panel of five mononucleotide repeats over the National Cancer Institute panel of markers." Carcinogenesis vol. 27,5 (2006): 951-5. doi:10.1093/carcin/bgi333

3 J. Siemanowski et al. "Managing Difficulties of Microsatellite Instability Testing in Endometrial Cancer-Limitations and Advantages of Four Different PCR-Based Approaches." Cancers vol. 13,6 1268. 12 Mar. 2021

# MODAPLEX MSI ANALYSIS KIT FEATURES

## GENERATE RESULTS WITH CONFIDENCE

The Modaplex MSI Analysis Kit enables the users to generate reliable MSI results. For this purpose, the kit is designed and developed according to customer requirements, ensuring a robust, safe, and flexible assay.



### TAILORED TO LABORATORY REQUIREMENTS

To address the limitations of poor quantity and quality of DNA in a formalin-fixed, paraffin-embedded environment, the Modaplex MSI assay has been verified on CRC and EC FFPE samples.

### RELIABLE RESULTS

The MSI assay is endowed with a comprehensive control concept. It comprises internal controls like a migration size standard as well as external positive and negative controls. In addition, the assay includes a forensically accepted marker serving as the sample-mix up and contamination control.

### APPLICABLE FOR LOW SAMPLE AMOUNTS

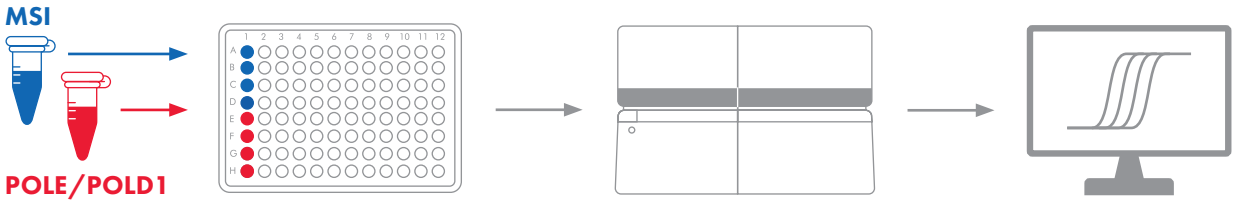
The Modaplex MSI assay is suitable for MSI-H detection using small sample inputs. Optimized to be used with a DNA input of 10ng, the assay is suitable for the widespread application on FFPE-derived sample material.

# MODAPLEX MSI WORKFLOW

## ENHANCE LABORATORY EFFICIENCY


The Modaplex MSI Analysis Kit is designed for use with the Modaplex instrument, a multiplex PCR bench-top system. It combines qPCR with capillary electrophoresis (CE) in an automated process. Therefore, users can individually combine tests for the purposes of mutational analysis, gene expression, copy number variation, gene fusion, and miRNA, among many others.

## STREAMLINE LABORATORY OPERATIONS WITH A COMMON PROTOCOL




**PCR set up**
15 min

**Automated Modaplex run**
~ 3 hrs

**Analysis with Moda-RA**
15 min

**3.5 hrs**

Because Modaplex assays will make use of a universal PCR program, you can perform these assays simultaneously through a workflow which is simple as setting up a PCR. Thus, microsatellite fragment analysis and POLE / POLD1 mutation detection can be individually combined and flexibly performed in a single Modaplex run in less than 3.5 hours.

## ORDER INFORMATION

| Product | Cat. no. | Application |
|---|---|---|
| Modaplex MSI Analysis Kit | 85-10701-0050* | RUO |
| Modaplex Instrument | 00-04901-0001 | |

For research use only. Not for use in diagnostic procedures.
*Not available in Italy and the USA

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