MICROSATELLITE INSTABILITY TESTING

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BIOTYPE INNOVATION

THE IMMUNE CHECKPOINT THERAPY CHALLENGE

SELECTING PATIENTS THAT ARE MORE RESPONSIVE TO IMMUNE CHECKPOINT BLOCKADE

Immune checkpoints are cell surface proteins that regulate the activity of the host's immune system. They are crucial for immune homeostasis as they prevent uncontrolled immune responses that may cause collateral tissue damage and autoimmune diseases. In the case of cancer, immune checkpoint pathways are often activated and promote suppression against nascent anti-tumor immune reactions. Blocking of immune checkpoint pathways by targeting the CTLA-4 or PD-1/PD-L1 axis have proven clinical response to a variety of tumor entities[1, 2]. Thus, immune checkpoint inhibition has the potential to become a pillar of cancer therapy.

Although some of the FDA- and EMA-approved agents depend on the protein-based expression detection of PD-1 and PD-L1, there is still great heterogeneity in responding to immune checkpoint inhibition. Therefore, the need for predictive biomarkers still exists[3]. Several studies have revealed that microsatellite instability (MSI), which is a surrogate marker for mismatch repair deficiency (dMMR), is a suitable indicator for predicting the clinical benefit for checkpoint blockade[4,5]. As dMMR is a common event in cancers of the gastrointestinal tract and endometrial tissue, MSI testing is a promising approach to determine the response to immune checkpoint inhibitors for those tumor entities[5, 6, 7].

REFERENCES

1 D.M. Pardoll, "The blockade of immune checkpoints in cancer immunotherapy", Nature Reviews Cancer, vol. 12, pp. 252-264, 2012.
2 M.A. Postow et al, "Immune Checkpoint Blockade in Cancer Therapy", Journal of Clinical Oncology, vol. 33, no. 17, pp. 1974-1983, 2015.
3 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.
4 D.T. Le et al, "PD-1 Blockade in tumors with Mismatch-Repair Deficiency", N. Engl. J. Med., vol. 372, pp. 2509-2520, 2015.
5 D.T. Le et al, "Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade", Science, vol. 357, no. 6349, pp. 409-413, 2017.
6 Z.R. Chalmers et al, "Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden", Genome Medicine, vol. 9, no. 34, 2017.
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MICROSATELLITE INSTABILITY (MSI)

CONTRIBUTE INFORMED DECISIONS FOR CHECKPOINT THERAPY WITH AN AUTOMATED MSI FRAGMENT ANALYSIS ASSAY

PROVIDE MEANINGFUL MSI RESULTS WITH A STRAIGHTFORWARD SET OF MICROSATELLITE MARKERS

- Simultaneous analysis of three dinucleotide and five mononucleotide markers
- Individually determine MSI-H status according to standardized NCI guidelines (known as Bethesda) and/or revised Bethesda guidelines
- Minimized peak stuttering facilitates instability assessment

REPORT RESULTS WITH CONFIDENCE

- Tested on archived FFPE-derived colorectal cancer material
- Include forensically accepted (human insertion/deletion polymorphism) marker as sample mix-up and contamination control
- Comprehensible MSI-H detection using optimal 2ng genomic DNA

ENHANCE LABORATORY EFFICIENCY

- Efficient workflow through automation
- Intuitive result interpretation with Biotype Innovation´s Modaplex Result Analyzer (Moda-RA) software
- Effective assessment of genomic instability caused by mismatch repair and/or polymerase deficiency

MODAPLEX
MSI ANALYSIS KIT

PROVIDE MEANINGFUL MSI-H RESULTS WITH A STRAIGHTFORWARD SET OF MICROSATELLITE MARKERS

The combination of five mononucleotide markers (Bat-25, Bat-26, NR-21, NR-24, and Mono-27) and three dinucleotide markers (D2S123, D5S346, and D17S250) allows the individual MSI analysis according to standardized guidelines known as the Bethesda and the revised Bethesda guidelines. These guidelines were originally established for the detection of Lynch Syndrome in 1998 and were revised in 2004. Over the past decade, however, these guidelines have proven to be highly sensitive and specific in providing results on MSI status across various tumor entities.

INDIVIDUAL MSI-H ASSESSMENT OPTIONS

Mononucleotide Markers	»	Bat-25
	»	Bat-26
	»	NR-21
	»	NR-24
	»	Mono-27
Dinucleotide Markers	»	D2S123
	»	D5S346
	»	D17S250

NCI Guidelines (Bethesda)

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

Mononucleotide Markers	»	Bat-25
	»	Bat-26
	»	NR-21
	»	NR-24
	»	Mono-27
Dinucleotide Markers	»	D2S123
	»	D5S346
	»	D17S250

NCI Guidelines (Bethesda)

	5 Bethesda Markers	Interpretation
No. of marker exhibiting instability	≥ 2	**MSI-H**
	1	**MSI-L**
	0	**MSS**

Mononucleotide Markers	»	Bat-25
	»	Bat-26
	»	NR-21
	»	NR-24
	»	Mono-27
Dinucleotide Markers	»	D2S123
	»	D5S346
	»	D17S250

Revised Bethesda

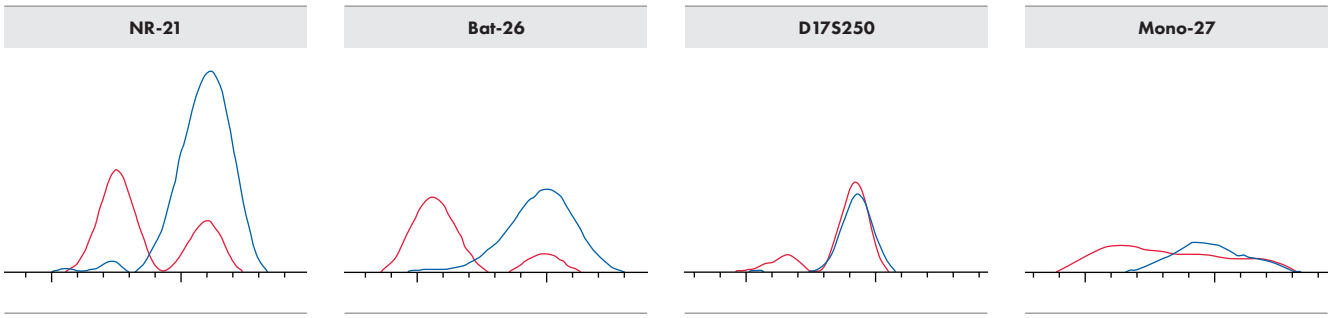
	5 Mononucleotide Markers	Interpretation
No. of marker exhibiting instability	≥ 3	**MSI-H**
	≤ 2	**MSI-L**
	0	**MSS**

The Modaplex MSI Analysis Kit enables laboratories to assess MSI-H results with a straightforward set of microsatellite markers. It has been demonstrated that a small number of markers is sufficient to provide meaningful results as the results are highly concordant with complex MSI sequencing panels[1]. Furthermore, they are sufficient to detect genomic instability in gastrointestinal tumors as MSI-H almost always co-occurs with a high tumor mutational burden (TMB)[2].

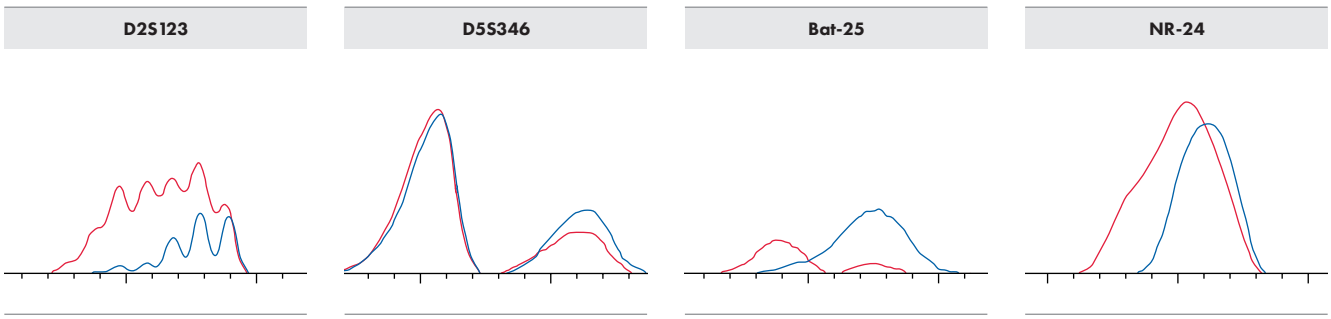
MINIMIZED PEAK STUTTERING FACILITATES INSTABILITY ASSESSMENT

Instability of microsatellites will be assessed visually by comparing allelic peaks from tumoral and normal adjacent tissue. Therefore, peak stuttering effects are minimized, allowing the customer to detect even minor changes in size.

FAM Channel (Typical results from a MSI-H FFPE colorectal cancer sample, 2ng; cancer tissue (red); normal adjacent tissue (blue)



TYE Channel (Typical results from a MSI-H FFPE colorectal cancer sample, 2ng; cancer tissue (red); normal adjacent tissue (blue)



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1 A. Vanderwalde et al, "Microsatellite instability status determined by next-generation sequencing and compared with PD-L1 and tumor burden in 11,348 patients", Cancer Medicine, vol. 7, no. 3, pp. 746-756, 2018.

2 Z.R. Chalmers et al, "Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden", Genome Medicine, vol. 9, no. 34, 2017.

MODAPLEX
MSI ANALYSIS KIT

REPORT RESULTS WITH CONFIDENCE

Modaplex MSI Analysis Kits support laboratories to provide trustworthy 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 low quantity and poor quality of DNA in a formalin-fixed, paraffin-embedded environment, the Modaplex MSI assay has been verified on colorectal 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 as sample-mix up and contamination control.

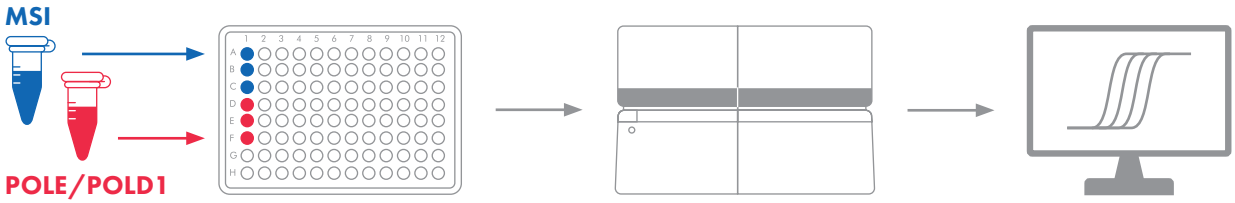
APPLICABLE FOR LOW SAMPLE AMOUNTS

The Modaplex MSI assay is suitable for MSI-H detection using small sample inputs. Optimized to be used with DNA inputs of ≤ 2ng, the assay is suitable for small biopsies.

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 and allows users to detect, differentiate, and quantify up to 50 DNA and RNA targets in a single well and run. 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



MSI and POLE/POLD1 PCR set up
< 0,5 h

Automated Modaplex run
~ 4 h

Analysis with Moda-RA
< 0,5 h

< 5h

A universal PCR amplification profile allows for the individual combination of tests such as the combination of MSI fragment analysis with polymerase epsilon and polymerase delta 1 mutation detection. The Modaplex workflow remains unchanged and comprises three steps which enable the completion of all tests in less than five hours.

ORDER INFORMATION

Product	Cat. no.
Modaplex MSI Analysis Kit	BTI-C002-E1-2-0050
Modaplex POLE/POLD1 Mutation Analysis Kit	BTI-C003-C1-2-0050

order@biotype-innovation.com

BIOTYPE INNOVATION

BIOTYPE INNOVATION GMBH
Moritzburger Weg 67, 01109 Dresden
Tel +49 351 8838 4500
Mail info@biotype-innovation.com
Web www.biotype-innovation.com

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