Detection of microsatellite instability (MSI) with a novel set of 7 Idylla biomarkers on colorectal cancer samples in a multi-center study

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Background

Detection of microsatellite instability (MSI) is recommended for all patients with colorectal cancer (CRC). Current clinical reference methods are immunohistochemical (IHC) staining of mismatch repair (MMR) proteins and/or PCR analysis of frequently mutated repetitive regions of DNA. The prototype Idylla™ MSI Test has been developed using a new set of short homopolymers located in the ACVR2A, BTBD7, DIDO1, MRE11, RYR3, SEC31A & SULF2 genes. This marker set allows probe-based detection with great specificity in a simplified workflow compared to current methods.

Methods

Repeat length with this set of biomarkers was determined on 333 formalin-fixed and paraffin-embedded (FFPE) CRC samples using Idylla™ MSI Test prototype cartridges, which allow a fully automated workflow including sample preparation, DNA amplification and automated repeat length calling. A neural network based algorithm was built on a large cohort of reference/patients samples (n > 3000) obtained from different clinical sites (n>10) and different ethnic groups (n=5). Three-hundred fourteen samples were characterized by means of the Promega MSI analysis system and 272 samples by means of MMR protein IHC staining. Approximately 30% of the samples included in the study were previously characterized to be MSI-H by either one of these methods.

Results

Concordance analysis revealed an overall agreement of 98.7% (96.7%-99.5% 95% CI) with Promega and 97.6% (94.8%-98.9% 95% CI) with IHC analysis. Analysis of consecutive sections of 182 samples with the three methodologies revealed a higher number of invalid results for Promega (3.8%) and IHC (13.2%) compared to the prototype Idylla™ MSI Test (2.2%).

Conclusion

This study verified the robustness of the prototype Idylla™ MSI Test including novel MSI biomarkers to discriminate MSI-H from MSS status on a large and diverse set of CRC samples. The study was conducted in multiple centers demonstrating the possibility of a rapid and fully automated analysis for MSI testing close to the point of need. The prototype Idylla™ MSI Test provided accurate and reliable results within 150 minutes from just one FFPE tumor section (no normal reference sample required).

Figure 1 Marker selection and development of the Idylla™ MSI Test

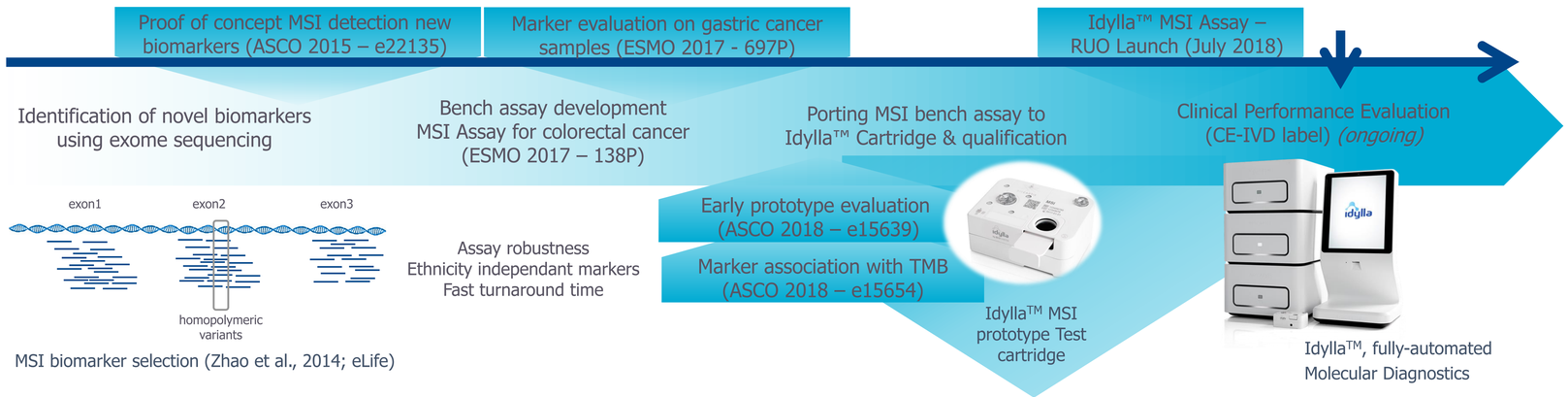


Figure 2 Detection methodology

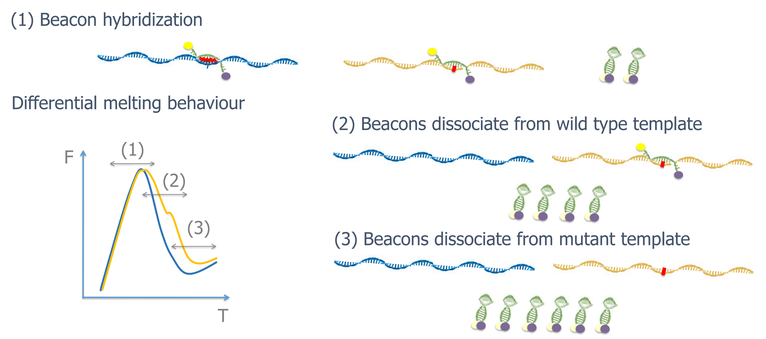


Figure 3 Automated detection and interpretation

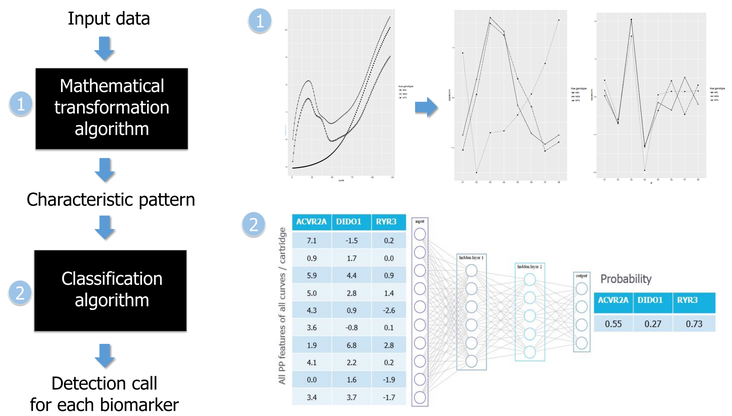
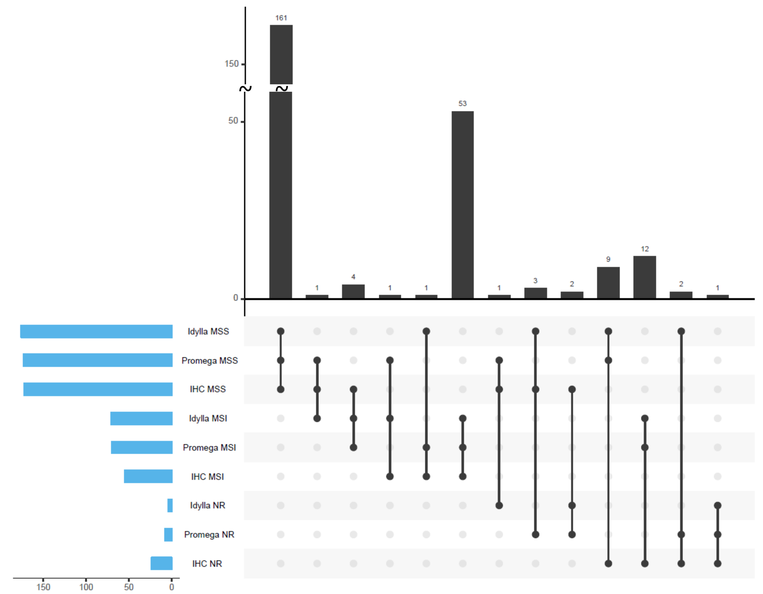


Figure 4 Concordance analysis

		(n=333) Promega MSI analysis			
		MSI-H	MSS	Failed	ND
Idylla™ MSI analysis	MSI-H	93	3	0	1
	MSS	1	206	5	20
	Failed	0	1	3	0
		OPA: 98.7% (96.7-99.5% 95% CI)			

		(n=333) IHC MMR analysis			
		MSI-H	MSS	Failed	ND
Idylla™ MSI analysis	MSI-H	55	5	12	24
	MSS	1	184	11	37
	Failed	0	3	1	0
		OPA: 97.6% (94.8-98.9% 95% CI)			

Figure 5 3-way concordance analysis



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