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Microsatellite instability testing

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N Engl J Med. 2017;377(25):2500–1.Article PubMed PubMed Central Google Scholar Page 2Cancer typeMSI-H (%)Cancer typeMSI-H (%)Cancer typeMSI-H (%)Cancer typeMSI-H (%)UCEC17.00–31.37BRCA0.00–1.53PRAD0.60–3.00KICH0.00COAD6.00–19.72KIRC1.47LUAD0.53–1.00KIRP0.00STAD9.00–19.09OV1.37–2.00BLCA0.49LAML0.00READ5.73CHOL1.35–3.00NBL0.45NPC0.00ACC4.35THYM0.81LGG0.39PAAD0–2.00UCS3.00–3.51LIHC0.80–3.00CLL0.30PCPG0.00CESC2.62–4.00HNSC0.78GBM0.25TGCT0.00WT2.44SARC0.78AML0.00THCA0.00–3.00MESO2.41SKCM0.00–0.64CTCL0.00UVM0.00–2.00ESCA1.63LUSC0.60DLBC0.00 Abbreviations: UCEC uterine corpus endometrial carcinoma, COAD colon adenocarcinoma, STAD stomach adenocarcinoma, READ rectal adenocarcinoma, ACC adrenocortical carcinoma, UCS uterine carcinosarcoma, CESC cervical squamous cell carcinoma and endocervical adenocarcinoma, WT Wilms tumor, MESO mesothelioma, ESCA esophageal carcinoma, BRCA breast carcinoma, KIRC kidney renal clear cell carcinoma, OV ovarian serous cystadenocarcinoma, CHOL cholangiocarcinoma, THYM thymoma, LIHC liver hepatocellular carcinoma, HNSC head and neck squamous cell carcinoma, SARC sarcoma, SKCM skin cutaneous melanoma, LUSC lung squamous cell carcinoma, PRAD prostate adenocarcinoma, LUAD lung adenocarcinoma, BLCA bladder carcinoma, NBL pediatric neuroblastoma, LGG lower-grade glioma, CLL chronic lymphocytic leukemia, GBM glioblastoma multiforme, AML pediatric acute myeloid leukemia, CTCL cutaneous T cell lymphoma, DLBC diffuse large B cell lymphoma, KICH kidney chromophobe, KIRP kidney renal papillary cell carcinoma, LAML acute myeloid leukemia, NPC nasopharyngeal carcinoma, PAAD pancreatic adenocarcinoma, PCPG pheochromocytoma and paraganglioma, TGCT testicular germ cell tumor, THCA thyroid carcinoma, UVM uveal melanoma Background: Cancers with a defective DNA mismatch repair (dMMR) system contain thousands of mutations most frequently located in monomorphic microsatellites and are thereby defined as having microsatellite instability (MSI). Therefore, MSI is a marker of dMMR. MSI/dMMR can be identified using immunohistochemistry to detect loss of MMR proteins and/or molecular tests to show microsatellite alterations. Together with tumour mutational burden (TMB) and PD-1/PD-L1 expression, it plays a role as a predictive biomarker for immunotherapy. Methods: To define best practices to implement the detection of dMMR tumours in clinical practice, the ESMO Translational Research and Precision Medicine Working Group launched a collaborative project, based on a systematic review-approach, to generate consensus recommendations on the: (i) definitions related to the concept of MSI/dMMR; (ii) methods of MSI/dMMR testing and (iii) relationships between MSI, TMB and PD-1/PD-L1 expression. Results: The MSI-related definitions, for which a consensus frame-work was used to establish definitions, included: 'microsatellites', 'MSI', 'DNA mismatch repair' and 'features of MSI tumour'. This consensus also provides recommendations on MSI testing; immunohistochemistry for the mismatch repair proteins MLH1, MSH2, MSH6 and PMS2 represents the first action to assess MSI/dMMR (consensus with strong agreement); the second method of MSI/dMMR testing is represented by polymerase chain reaction (PCR)-based assessment of microsatellite alterations using five microsatellite markers including at least BAT-25 and BAT-26 (strong agreement). Next-generation sequencing, coupling MSI and TMB analysis, may represent a decisive tool for selecting patients for immunotherapy, for common or rare cancers not belonging to the spectrum of Lynch syndrome (very strong agreement). The relationships between MSI, TMB and PD-1/PD-L1 expression are complex, and differ according to tumour types. Conclusions: This ESMO initiative is a response to the urgent questions raised by the growing success of immunotherapy and provides also important insights on the relationships between MSI, TMB and PD-1/PD-L1. Keywords: immunotherapy; microsatellite instability (MSI); next-generation sequencing (NGS); tumour mutational burden (TMB); tumour mutational load (TML).