Microsatellite Instability - Defective DNA Mismatch Repair: ESMO Biomarker Factsheet

Authors: Aldo Scarpa\textsuperscript{1,2} Ivana Cataldo\textsuperscript{1,2} Lisa Salvatore\textsuperscript{3}

\textsuperscript{1}ARC-Net Research Centre and Departments of \textsuperscript{2}Pathology and \textsuperscript{3}Medical Oncology. University and Hospital Trust of Verona, Italy

Microsatellite instability (MSI) indicates a defective mismatch repair (dMMR) system

DNA Mismatch repair

DNA Mismatch repair is a highly conserved mechanism, involved in restoring DNA integrity after the occurrence of mismatching errors during DNA replication, recombination or iatrogenic damage\textsuperscript{1,2,3}. Four genes regulate the MMR mechanism: mutL homologue 1 (MLH1), mutS homologue 2 (MSH2), mutS homologue 6 (MSH6) and postmeiotic segregation increased 2 (PMS2). The four proteins codified by these genes from heterodimers, namely MLH1/PMS2 and MSH2/MSH6 (see image below). The biallelic inactivation of one of these genes, due to somatic or germline mutations or Epigenetic silencing, results in dMMR determining an increased rate of Mutations\textsuperscript{1,4,5}.

![Model of the proposed mechanism of Mismatch repair proteins, illustrating patterns of clinically relevant heterodimerization (reproduced with permission Vilar & Gruber (2010) Nat Rev Clin Oncol. doi:10.1038/nrclinonc.2009.237)\textsuperscript{9}](model.png)

Microsatellites

Microsatellites, or short tandem repeats, are repetitive DNA sequences with a unit length ranging from one (mononucleotides) to six bases (di-, tri-, tetra-, penta-, esa-nucleotides) distributed along coding and noncoding regions of the genome\textsuperscript{4}. They are highly polymorphic among subjects but stable in each individual\textsuperscript{6,7}. The repetitive nature of these regions makes them particularly sensitive to mismatch errors that in case of dMMR result in the accumulation of mutations of repeat length alterations, defined as Microsatellite instability (MSI), which is easily uncovered by the analysis of polyA Microsatellites. Therefore, MSI is a marker of dMMR\textsuperscript{6,7} and characterizes a hypermutable state of cells\textsuperscript{8}.
Definition of MSI/dMMR tumour

A tumour with MSI has thousands of mutations due to a defective DNA mismatch repair (dMMR) system, caused by biallelic inactivation of one of the four genes coding for the proteins involved in this mechanism. MSI is efficiently detected by a molecular test analysing few polyA DNA microsatellites that, due to their monomorphic composition, are highly prone to misalignments during DNA replication.

Clinical significance of MSI-dMMR

MSI testing assesses the functionality of the MMR system and has different clinical significance for sporadic and hereditary cancers. It has an established role in the identification of hereditary cancer syndromes and is of prognostic significance in surgically resected gastrointestinal cancers. It also has an emerging potential predictive value of response to immunotherapy \(^{10,11,12}\). These findings have recently increased the clinical request for MSI molecular testing as a predictive Biomarker for immunotherapy, increasing the need of a more targeted assessment of truly necessary exams to avoid excessive and fruitless costs for the health system.

MSI testing to detect dMMR

There are two clinically useful tests to detect a dMMR in cancer (see images below): i) identification of MSI by molecular testing of poly-A microsatellites, which represents direct proof of dMMR; ii) lack of immunohistochemical expression of MMR proteins that represents an indirect suggestion of a dMMR system, which should be confirmed with MSI molecular testing.

Immunohistochemical analysis (panels on the left) shows the expression of all four MMR proteins suggestive of a proficient mismatch repair system in this cancer. This is confirmed by the electropherograms of PCR amplified polyA Microsatellite markers indicated (panels on the right), where the profiles in tumour are identical to those seen in normal tissue of the same patient. This cancer is microsatellite stable (MSS) Credit for image: Aldo Scarpa.
Immunohistochemical analysis (panels on the left) shows lack of expression of MLH1 and PMS2 in cancer cells, suggestive of a defective mismatch repair system in this cancer. This is confirmed by the electropherograms of PCR amplified polyA Microsatellite markers indicated (panels on the right), where the profiles in tumour are shifted with respect to those seen in normal tissue of the same patient, due to alterations in size typical of unrepaired mismatch errors during DNA replication. This cancer is microsatellite instable (MSI).

Credit for image: Aldo Scarpa.

**MSI molecular test**

Molecular testing is performed on DNA from fresh, frozen, or paraffin-embedded tumour tissue using a PCR-based assay for detection of MSI. The highest specificity and sensitivity is reached using a panel of three or more polyA mononucleotide markers (BAT25, BAT26, NR-21, NR-22, NR-24, NR-27) \(^4,13,14\).

**Immunohistochemistry (IHC)**

Antibodies against the four MMR proteins are commercially available and IHC is used to detect the expression of the four MMR proteins (MLH1, MSH2, MSH6, and PMS2), whose loss is highly concordant (>90%) with DNA-based MSI positive testing with good specificity and sensitivity \(^4,15,16,17\). As said above, the 4 proteins involved form MLH1/PMS2 and MSH2/MSH6 heterodimers (Image Model of the Proposed Mechanism of Mismatch Repair Proteins). The loss of expression of a single protein or of a heterodimer couple suggests the presence of dMMR, which requires formal proof by MSI molecular testing, as IHC loss of expression may be a false result due to technical or biological reasons. Moreover, an inhomogeneous staining may occur for one or more of the four antibodies again to technical or biological reasons \(^18\).In cancers with dMMR proved by molecular testing, IHC loss of expression is used to indicate which Gene is defective due to germline or somatic mutation or inactivation by hypermethylation \(^19\). The major advantage of IHC is its wide and routine availability in pathology laboratories. Limitations of IHC include misleading information for rare cases with missense mutations in MLH1 or MSH6 genes with a normally translated but non-functional protein. In these cases positive IHC implies a false negative result for dMMR, and only molecular MSI testing can clarify the real functionality of MMR \(^19\). On the other hand, IHC detects MSH6 loss in a subset of MSH6 germline mutated tumours, implying a false positive result for dMMR where, however, the presence of a functional redundancy in the MMR system does not affect the proficiency of the MMR machinery, and this can only be clarified by a negative MSI molecular test \(^19\). Technical reasons may also cause false negative IHC results.

**Choice of test**

Molecular testing of polyA microsatellites is the choice to detect MSI as direct proof of dMMR in a given cancer. Immunohistochemistry can be used as an efficient indirect test for dMMR when a
molecular laboratory is not available; it is also useful in identifying which gene should be investigated for damaging alterations in the case of hereditary cancer syndromes.\textsuperscript{15}

**Confounding definitions of MSI in the literature of the last two decades**

There is much confusion in the literature of the last couple of decades due to the varying definitions of MSI used, linked to the plethora of different mononucleotide and polynucleotide Microsatellite markers used by the diverse authors and in different cancer types.

In 1993 Manuel Perucho’s team\textsuperscript{20} reported the discovery of colorectal cancers harbouring ubiquitous somatic mutations (over 100,000) in simple repeated sequences, due to mutations in a DNA replication factor resulting in reduced fidelity for replication or repair. It was clearly reported that only tumours with affected polyA microsatellites carry mutations in other polynucleotide simple repeats\textsuperscript{20}. Five years later, a consensus workshop at Bethesda recommended a “NCI-reference panel” to assess MSI including two mononucleotides (BAT25 and BAT26) and three dinucleotides (D2S123, DSS346, D17S250), whose status in cancer DNA had to be compared with DNA from normal tissue of each patient\textsuperscript{21}. On the basis of the results of such a molecular test, tumours were classified into three different subtypes: MSI-high (MSI-H), if two or more microsatellite markers showed instability; MSI-low (MSI-L) if only one marker resulted unstable and MS-stable (MSS) if all the five markers resulted stable\textsuperscript{21}. The revision of these guidelines based on evidence that only MSI-H should be considered for the definition of true MSI tumours, and only if two positive markers were polyA microsatellites, suggested the use of a panel including three or more polyA markers\textsuperscript{22}. In fact, alterations in non-monotypic microsatellites (from di- to esa-nucleotides) may relate more to generalized chromosomal instability than to a deficient mismatch repair system\textsuperscript{23}. The contrasting evidence around clinicopathological differences between MSI-L and MSS is likely to be attributed to the use of variable MSI markers and definitions. Thus it is often impossible to distinguish between MSI-L and chromosomal instability, suggesting that these tumours be classified as a single molecular subset, i.e. MSS neoplasms\textsuperscript{2,22,24,25,26,27}.

**Hereditary cancer syndromes associated with MSI cancers**

**Lynch syndrome.** Hereditary Non-Polyposis Colorectal Cancer (HNPCC) or Lynch syndrome (LS) is the most frequent inherited cancer predisposition syndrome caused by a germline heterozygous mutation in one of the four MMR genes\textsuperscript{28}. These patients are characterized by early onset of tumours (average age <45 years), mainly colorectal and endometrial but also tumours in other organs, and usually present germline mutations in MLH1 or MSH2 (42% and 33%, respectively), followed by MSH6 and PMS2 (18% and 7%, respectively)\textsuperscript{29}. Several guidelines have been developed to identify HNPCC patients, from the Amsterdam guidelines\textsuperscript{30} through the Bethesda guidelines\textsuperscript{22}, to the Jerusalem Criteria\textsuperscript{31}, together with the suggestion to implement a universal testing of MSI in colorectal cancers\textsuperscript{19,32,33}.

**Lynch syndrome due to TACSTD1 germline mutations.** Another molecular alteration identified in HNPCC families is the heritable epigenetic silencing of MSH2 due to heterozygous germline deletion of Exon 3 of TACSTD1 gene encoding for epithelial cell adhesion molecule (EpCAM)\textsuperscript{34}.

**Biallelic mismatch repair deficiency syndrome.** Inherited homozygous mutations in any of the MMR genes identify this clinical syndrome characterized by gastrointestinal and brain tumours and haematologic malignancies along with café-au-lait macules in childhood and adults\textsuperscript{35}.

**Muir-Torre syndrome.** Germline mutations in MSH2 and MLH1 genes have also been identified in families with Muir-Torre syndrome characterised by Sebaceous gland tumours together with internal malignancies, commonly colorectal\textsuperscript{36}. 
Turcot's syndrome is clinically characterized by the early occurrence of primary brain and colorectal tumours and is caused by germline mutations in APC, MLH1 or PMS2 genes.36

MSI in different sporadic cancer types

Unfortunately, the variable definition of MSI and the plethora of markers and cut-off values used in the literature of the past 20 years have largely misguided the interpretation of published results, especially for non-colorectal tumours. In this factsheet, we revised the most pertinent literature on diverse cancers trying to discern the identification of true dMMR tumours, i.e. only those showing MSI-H and/or alterations in mononucleotide microsatellite markers.

Sporadic gastrointestinal cancers

Colorectal Cancer (CRC). About 15% of sporadic CRCs harbour MSI, the vast majority of which is related to MLH1 promoter hypermethylation, with subsequent silencing of gene transcription and loss of protein expression.5,15,38,39 The Association for Molecular Pathology recommends to subject all new colorectal cancers to MSI analysis to classify them into three subgroups: sporadic MMR-proficient, sporadic dMMR, or Lynch dMMR.15 MSI sporadic CRCs are characterized by specific clinicopathological features: mainly female gender, older age, right colon location, high grade, mucinous differentiation, signet ring or medullary histology, peritumoural lymphocytic infiltrate and Crohn-like inflammatory reaction, diploid status, lower stage and better prognosis.40 MSI is considered a favourable Prognostic factor in early stage CRCs, with longer disease free and overall survival (DFS and OS).41,42,43,44,45 Some authors hypothesize that their better prognosis may be partly explained by the increased immune response found in dMMR neoplasms.46 In the subset of metastatic CRC (mCRC) dMMR has a lower prevalence (5%) compared to early CRCs and is associated with a poor prognosis, possibly due to the higher incidence of BRAFV600E mutation in comparison to proficient MMR mCRC.46 Preclinical and clinical studies have demonstrated that dMMR negatively affects the response of CRCs to chemotherapeutics such as pyrimidine analogues, cisplatin, temozolomide and procarbazine. Moreover, fluorouracil-based adjuvant chemotherapy seems to improve patient outcome, in particular those with stage II colon cancer with MSS/MSI-L tumours but not those with tumours exhibiting MSI-H.41,42,47 A retrospective analysis has shown a statistically significant survival benefit for patients with dMMR tumours by the addition of bevacizumab to adjuvant FOLFOX therapy compared with patients with proficient MMR tumours.48 This data, deriving from a subgroup analysis, are preliminary and further investigation is needed particularly in metastatic setting. The utility of MSI status as a promising predictive marker for response to anti-PD-1 therapy in stage IV CRCs has been recently reported.10,11 Furthermore, a high frequency of Th1/CTL (cytotoxic T lymphocyte) infiltrate (TILs) has been detected in MSI CRCs associated with up-regulation of at least five immune checkpoint molecules, targets of inhibitors whose efficacy is under clinical testing.49 MSI can be acquired during chemotherapy by selective mutations in MMR genes.2,3

Gastric cancer (GC). GC shows MSI in about 15% of cases, which is usually associated with female sex, older age, antral location, intestinal histology, earlier stage and better prognosis.14,50,51,52 The incidence of gastric cancer in HNPCC is low.53 Although some conflicting results exist,4 MSI in gastric cancer may be considered a favourable prognostic indicator for both early14,52,55,56 and advanced stages.57,58 A study including 12 MSI and 64 MSS surgically resected GCs treated with adjuvant 5-fluorouracil (5-FU) therapy reported no difference between MSI and MSS with respect to OS.59 However, a more recent study including 796 (61 MSI and 735 MSS) resected GC patients reported at multivariate analysis that MSS patients had benefit from 5FU-based adjuvant chemotherapy in term of DFS and proposed MSI status as a predictive biomarker for 5-FU-based adjuvant chemotherapy in stage II and III gastric cancers after R0 resection.60 Recently significant correlations have been found between dMMR and immune system activity, suggesting that this group of patients might be optimal candidates for novel immunotherapies.61,62,63
Duodenal and Ampulla of Vater Cancer (AVC). Duodenal cancers and AVCs show MSI in up to 10% of cases.\textsuperscript{64,65,66,67,68,69} In AVC, MSI is associated with intestinal mucinous subtype, high-grade and markedly increased TILs\textsuperscript{65,66}, even if a noticeable subset of MSS AVCs with higher TIL counts occurs\textsuperscript{66}.

Esophageal carcinoma. MSI is restricted to Barrett’s-related esophageal adenocarcinomas, accounting for about 5% of this cancer type. It is associated with increased TILs and specific histotypes (medullary, signet ring cell, mucinous histology) similar to MSI colorectal cancers\textsuperscript{70,71}, and has been suggested as potential candidate to immunotherapy\textsuperscript{62}.

Sporadic gynaecological cancers

Endometrial cancer (EC). EC is associated with defective MMR in up to 33% of cases\textsuperscript{4,10}, a proportion of which is related to HNPCC syndrome. Morphological heterogeneity, non-endometrioid histology and marked inflammatory response are distinctive characters of MSI-ECs\textsuperscript{72}. The universal screening of ECs for MSI has been suggested to identify Lynch syndrome patients\textsuperscript{73,74}. There is controversial evidence on the prognostic value of MSI in EC\textsuperscript{4,75,76,77}. A pooled analysis of 22 studies failed to identify a significant association between prognosis and MMR status, although the marked inter-study heterogeneity regarding patients’ characteristics, tests used for detecting MSI, and estimation of endpoints make it difficult to establish an exact role of dMMR in EC\textsuperscript{78}. MSI-ECs showed a high rate of PD-1/PD-L1 overexpression plus enhanced TILs, suggesting that MSI-ECs might represent the perfect candidates for PD-1 directed immunotherapies\textsuperscript{79}.

Ovarian cancer (OC). When considering only tumours tested for MSI using panels containing polyA mononucleotides the value of MSI in OCs is 10%\textsuperscript{4,80,81,82}. Germline mutations in MMR genes are detected in about 1% of cases\textsuperscript{4,82,83,84}. OC arising in women ≤ 50 years showed MSI in about 4% of cases, suggesting that these should be tested for MSI and, if unstable, for germline mutations in MMR genes\textsuperscript{80}. Inconsistent data have been reported regarding both the prognostic significance\textsuperscript{4,85,86,87} and predictive value\textsuperscript{4,88,89} of MSI.

Cervical Cancer. MSI occurs in about 5% of cervical cancers\textsuperscript{90,91} of any morphology, but possibly in higher proportions in squamous cell (SCC) histotype (11.8%)\textsuperscript{92}. No prognostic or predictive value seems to be associated with MSI status in this pathology\textsuperscript{90,92}.

Breast cancer. MSI is extremely rare in breast cancer ranging between 0-1% of cases\textsuperscript{10,93}, unless occurring in young women diagnosed with HNPCC\textsuperscript{94,95}.

Sporadic hepatic, pancreatic and biliary tract cancers

MSI is exceedingly rare if not absent at all in hepatic, biliary tract and pancreatic cancers.

Hepatocellular carcinoma. Only MSI-L has been reported in hepatocellular carcinoma\textsuperscript{96} and alterations in MMR genes are not implicated in its pathogenesis\textsuperscript{97}.

Pancreatic and periampullary cancers, including terminal bile duct cancers. MSI is almost non-existent in sporadic pancreatic ductal adenocarcinoma (PDAC) occurring in less than 1% of cases based on molecular MSI testing. A study on 338 sporadic pancreatic ductal adenocarcinomas using mononucleotide repeats showed MSI in only 1 case, which involved the pancreatic head, ampulla of Vater and duodenum\textsuperscript{98}. A recent study of 385 pancreatic cancers subjected to whole genome or exome sequencing reported 4 cases with MSI\textsuperscript{99}. MSI is also found in the peculiar and rare medullary subtype of pancreatic carcinoma, where it was found in 4 of 18 (22%) tumours\textsuperscript{100}. The rare pancreatic cancers occurring as part of HNPCC show MSI. A recent paper reported that 15% of pancreatic cancers showed loss of MMR proteins using immunohistochemistry but no proof of defective MMR machinery in these cases was furnished\textsuperscript{101}. A paper reporting MSI in 17% of cases used no polyA
microsatellites markers\textsuperscript{102}. While a paper reporting MSI in 13% of 100 cases using polyA markers which were also associated with a better prognosis, there was no distinction made regarding the site of origin of the cases and it is highly likely that the cases in this series were ampullary cancers\textsuperscript{103}, as also suggested by two recent studies of exome sequencing on periampullary cancers originating from ampulla of Vater, terminal bile duct or terminal pancreatic duct where up to 10% of cases had MSI\textsuperscript{68,69}.

**Sporadic skin tumours and melanoma**

*Sebaceous skin tumour.* Sebaceous gland skin tumours (sebaceous hyperplasias, sebaceous adenomas, and sebaceous carcinomas) are ‘sentinel’ pathologies of Muir-Torre syndrome. About 25% of sporadic sebaceous skin tumours show MSI\textsuperscript{104,105}. Due to such high prevalence MSI testing is recommended in all sebaceous neoplasms regardless of patient’s age or other clinical characteristics\textsuperscript{106}.

*Melanoma.* The use of mononucleotide markers and properly defined MSI status in melanoma has been largely neglected, and explains the reported highly variable prevalence of MSI, ranging from 2% to 30% of primary cases and up to 77% in metastatic tumours\textsuperscript{4,107}. As such, also the information that MSI status increases from benign nevi (0%) through primary melanoma (11%) to metastatic melanoma (21%-77%) is largely unreliable and cast doubts on its utility to identify patients candidate to immunotherapy\textsuperscript{4,107,108,109,110}. The data for this neoplasms are too scant and the techniques used to define MSI are variable and questionable to draw definitive conclusions.

**Other sporadic cancers**

*Lung cancer.* Discrepancy in reported MSI prevalence in non-small cell lung cancer (NSCLC), ranging from 0% to 40%, is due to the different methodologies and cut-off values used to define MSI\textsuperscript{111,112,113}. When consented mononucleotide markers are used, MSI is absent in SCLC (0%) and exceedingly rare in NSCLC (0-1%), and thus no prognostic or predictive value of dMMR status exist in lung cancer\textsuperscript{114,115,116}.

*Glioma.* MSI is extremely rare (0.16%) in gliomas of adults\textsuperscript{117,118}. Controversial data exist on MSI in gliomas of paediatric age, adolescents and young adults, although all studies were performed using mononucleotide markers and a proper definition of MSI\textsuperscript{117,118,119,120,121}. MSI was reported in a significant proportion (between 18% and 33%) of high grade, paediatric and young adult gliomas, also in the setting of Turcot’s syndrome\textsuperscript{119,120} while other authors reported absence or a very low rate of MSI in paediatric and young adult gliomas (low or high grade)\textsuperscript{117,121}. In these papers, the syndromic or sporadic nature of the tumours analysed is not always clearly addressed.

*Prostate cancer.* In prostate cancer, MSI using mononucleotide markers and somatic mutations involving MMR genes has been reported in a subset of tumours ranging from 1% in primary to 12% in metastatic cancers\textsuperscript{10,122,123}. Males with HNPCC have a fivefold increased risk of developing prostate cancer\textsuperscript{124}.

*Thyroid cancer.* MSI due to dMMR does not have a role in thyroid cancer pathogenesis. The highly discordant data about MSI, ranging from complete absence\textsuperscript{125,126} to 63% of cases, again depends on varying markers and definitions used in the different papers\textsuperscript{127,128,129}.

*Head and neck squamous cell cancer.* In only around 1% of samples there is evidence of true MSI revealed when considering consented mononucleotide markers\textsuperscript{130}, while largely variable MSI definitions and markers used are responsible for the extreme range of frequencies (from 3% to 88%)\textsuperscript{130,131}.

*Renal cell carcinoma.* MSI is practically absent in renal cell carcinoma (0%-0.7%)\textsuperscript{132,133}.
Sarcoma. Reported MSI in soft tissue sarcoma and Ewing sarcoma appear to relate more to generalized genomic instability rather than to a dMMR system, and true MSI Phenotype is not detected in sarcomas\textsuperscript{23,134,135}.

**MSI and immunotherapy**

Use of immune checkpoint blockade molecules is a promising treatment even in advanced cancers resistant to all other chemotherapeutics\textsuperscript{10,136,137,138}. It has recently been demonstrated that tumours with high TILs usually harbour dMMR resulting in MSI with a significant upregulation of immune checkpoint proteins\textsuperscript{10,49}, suggesting that an increased mutational burden in MSI tumours leads to the creation of neoepitopes responsible for the immune response\textsuperscript{10,49}. Furthermore, the effectiveness of MSI status as a predictive marker for response to PD-1 blockade was recently reported in stage IV colorectal cancer patients\textsuperscript{10,11}.

Indeed, somatic hypermutation creating putative neoepitopes is generated not only by MSI/dMMR but also by a high mutational load of nonsynonymous mutations\textsuperscript{139,140,141} due to mutations in DNA polymerases POLE or POLD1, exposure to exogenous (cigarette smoke, UV radiation) and endogenous mutagens\textsuperscript{10,142,143}. Such hypermutation may reveal higher predictive power than MSI status as immunotherapy response biomarkers. However, they rely to date on whole-exome sequencing and mass spectrometry of tumour samples followed by extensive bioinformatic analysis, an approach not yet practical for routine diagnostics\textsuperscript{10}. By contrast, MSI molecular testing is already largely diffuse at the clinical level, which increases its potential as a ready-to-use approach to predict immunotherapeutic response in patients who have failed conventional therapy\textsuperscript{10}.

**Conclusions:**

Microsatellite instability is the effect of a defective mismatch repair machinery. Thus, the molecular test for MSI is the gold standard diagnostic tool to directly assess the proficiency of mismatch repair system.

1. Lack of immunohistochemical expression of one or more of the four proteins involved in MMR (MLH1, MSH2, MLH6, PMS2) is an indirect indication of a defective MMR which needs confirmation with a molecular test for MSI.
2. The MSI molecular test must be based on mononucleotide (polyA) markers. The use of polynucleotide markers should be discontinued as their alteration is often due to chromosomal instability rather than to mismatch repair alterations.
3. MSI testing suggestions based on available data are reported in the image below.

### MSI Testing Suggestions

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Testing suggestions</th>
<th>MSI prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>All cancers</td>
<td>15%</td>
</tr>
<tr>
<td>Gastric</td>
<td>All cancers</td>
<td>15%</td>
</tr>
<tr>
<td>Duodenal and ampulla of Vater</td>
<td>All cancers</td>
<td>Up to 15%</td>
</tr>
<tr>
<td>Esophageal</td>
<td>Barretts associated cancers</td>
<td>5%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>All cancers</td>
<td>Up to 33%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>All cancers</td>
<td>15%</td>
</tr>
<tr>
<td>Cervical</td>
<td>Advanced stage cancers</td>
<td>5%</td>
</tr>
<tr>
<td>Breast</td>
<td>None</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>None</td>
<td>No evidence</td>
</tr>
<tr>
<td>Pancreatic and perianillary</td>
<td>Medullary histiocyte, cancers of perianillary area</td>
<td>&lt;1% in pancreatic cancer, up to 15% in cancers of perianillary area</td>
</tr>
<tr>
<td>Sebaceous skin tumour</td>
<td>All tumours</td>
<td>25%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>None</td>
<td>Inconsistent data</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>None</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Glioma</td>
<td>Pediatric, young adults</td>
<td>Controversial data 0%-33%</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Advanced stage cancers</td>
<td>Up to 12%</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>None</td>
<td>No evidence</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>None</td>
<td>1%</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>None</td>
<td>No evidence</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>None</td>
<td>No evidence</td>
</tr>
</tbody>
</table>
References

44. Muller CI, Schulmann K, Reinacher-Schick A, et al. Predictive and prognostic value of microsatellite instability in patients with advanced colorectal cancer treated with a


83. Murphy MA, Wentzensen N. Frequency of mismatch repair deficiency in ovarian cancer: a systematic review This article is a US Government work and, as such, is in the public domain of the United States of America. Int J Cancer 2011; 129: 1914-1922.


Last update: 19 October 2016

Source: http://oncologypro.esmo.org/Science-Education/Factsheets-on-Biomarkers/Microsatellite-Instability-Defective-DNA-Mismatch-Repair