A scoping review and meta-analysis on the prevalence of pan-tumour biomarkers (dMMR, MSI, high TMB) in different solid tumours

Appendix I. Detailed methods and results

RUNNING TITLE: Prevalence of dMMR, MSI and high TMB in different solid tumours

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Table of contents

List of supplementary tables

List of supplementary figures

1. Scoping review protocol and PRISMA-ScR Checklist

1) Scoping review protocol

Title of the review	A scoping review and meta-analysis on the prevalence of pan-tumour biomarkers (dMMR, MSI, high TMB) in different solid tumours
First reviewer	Dr Yoon-Jung Kang
Team of reviewers	Dr Julia Steinberg, Ms Sophie O'Haire, Dr Fanny Franchini
Supervisor/Project PI	Dr Julia Steinberg

1. Background to review

With increasing application of genomic medicine, many research efforts have been focusing on the identification of so-called "pan-tumour biomarkers", which can predict favourable response to a treatment for cancers originating from any tumour site.[1] A few drugs have recently received tumour-agnostic approval based on presence of a pan-tumour biomarker, including immune checkpoint inhibitors (e.g. pembrolizumab [Merck & Co., Inc.]), for the treatment of patients with solid tumours exhibiting mismatch repair deficiency (dMMR), microsatellite instability (MSI), or high tumour mutational burden (TMB).[2]

Given the relatively high cost of pembrolizumab and other potential targeted treatments,[3] a key question to inform health system planning and budget impact evaluations is how many patients might be eligible for these treatments based on the presence of these biomarkers. In particular, budget impact evaluations are an integral aspect of health technology assessments that summarise the information needed to inform policy and funding decisions (including e.g. drug efficacy, effectiveness, cost-effectiveness, and re-imbursement costs).[4] To facilitate such assessments, it is therefore crucial to map and consolidate the recent available evidence on the prevalence of the pan-tumour biomarkers, where possible, by cancer type as well as across all cancers. As approvals based on dMMR/MSI/high TMB currently focus on patients with advanced-stage disease, and biomarker prevalence may vary between cancer stages,[5] stage-specific prevalence estimates are also important where data are available.

2. Aims and specific objectives

Aim

To identify the available evidence on the prevalence of each of dMMR, MSI and high TMB in adult and paediatric solid tumours, by cancer type and cancer stage. Specific objectives are to:

1) provide a broader overview of studies reporting the prevalence of these three pan-tumour biomarkers; and
2) consolidate the evidence by cancer type and cancer stage. To the best of our knowledge, this is the first structured review on the prevalence of all three pan-tumour biomarkers (dMMR, MSI, high TMB) in a pan-cancer setting.

3. a) Criteria for including studies in the review

Population	Adult and paediatric cancer patients with solid tumours
Concept	The prevalence of the following biomarkers by cancer type and cancer stage (if available): • mismatch repair deficiency (dMMR) • microsatellite instability (MSI) • high tumour mutational burden (TMB)
Context	No limit to any setting
Type of evidence sources and publication status	• Primary research studies (including case series and analyses of large-scale genomic data) • review articles (including scoping reviews, systematic reviews and meta-analyses), letters, opinions and editorials that contain extractable data
Publication date	01/01/2018-31/01/2021
Language	English only

Note: See Supplementary Table S3 for the Detailed inclusion and exclusion criteria and information sources.

3. b) Criteria for excluding studies not covered in inclusion criteria

Population	Highly selected population (e.g. based on restriction to patients with family history or inherited predisposition to cancer, specific rare histological cancer subtypes only)
Concept	• Sample size ≤ 50 • TMB detected from circulating tumour DNA[6]
Context	None
Type of evidence sources and publication status	• Case reports • Conference abstracts • In vitro studies and in vivo studies • Non-academic literature (e.g., Health Technology Assessment reports)

Note: See Supplementary Table S3 for the Detailed inclusion and exclusion criteria and information sources.

4. Search methods

Electronic databases	MEDLINE, EMBASE
Other methods used for identifying relevant research	None
Journals hand searched	None

5. Methods of review

Details of methods	Title and abstract screening will be performed by one reviewer, with two reviewers double-screening 25% of articles to ensure reliability. Full-text review will be performed by one reviewer, with a second reviewer independently assessing 10% of studies to ensure reliability.
Quality assessment	Not applicable
Data extraction	Data extraction will be performed in duplicate for 10% of studies. If concordance is high, data extraction will be completed by one reviewer for the remaining studies.
Narrative synthesis	Not applicable

Meta-analysis	We will perform random-effect meta-analyses, using the inverse variance heterogeneity model to pool the Freeman-Tukey transformed proportions of cases with dMMR, MSI, or high TMB.[7] Heterogeneity across studies (for meta-analyses with ≥2 estimates) will be assessed based on the I^2 score estimate, with higher I^2 score indicating higher level of heterogeneity, and based on the heterogeneity test p-value (defining significance at $p<0.05$). All statistical analyses will be performed using R (Version 4.1.1) and the package "meta" (version 4.19-1).
Grading evidence	Not applicable

6. Presentation of results

We will present a narrative broader overview of studies reporting the prevalence of the three pan-tumour biomarkers, with figures displaying the proportion of studies with specific characteristics (e.g. cancer type or assay used) by publication year.

Meta-analysis results will be presented using tables and forest plots as appropriate.

2) Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

Supplementary Table S1. PRISMA-ScR Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON SECTION
TITLE			
Title	1	Identify the report as a scoping review.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Introduction paragraph 3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Introduction paragraph 3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Methods paragraph 2
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Methods ("Search strategy" sub-section)
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Methods ("Search strategy" sub-section)
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Methods ("Search strategy" sub-section); Appendix I.2
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Methods ("Selection criteria" sub-section); Figure 1; Appendix I.2
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Methods ("Data extraction" sub-section)
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Methods ("Data extraction" sub-section)
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Methods ("Quality assessment and risk of bias" sub-section)

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON SECTION
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Methods ("Synthesis of results" sub-section)
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Results ("Search results" sub-section)
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Results ("Search results" sub-section)
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Not performed as per Item 12 above
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Results ("Overview of literature reporting the prevalence of dMMR/MSI/high TMB" sub-section); Results ("Meta-analyses of the prevalence of dMMR/MSI/high TMB" sub-section)
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Results; Tables 1-4; Appendix I.4; Appendix. I.5
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Discussion paragraphs 1-5
Limitations	20	Discuss the limitations of the scoping review process.	Discussion paragraphs 9-10
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Conclusions
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Funding

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where sources of evidence (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with information sources (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.[8]

2. Background, search strategy and section criteria

dMMR indicates a reduced ability to repair DNA damage, typically due to loss of function in the MMR genes *MLH1*, *MSH2*, *MSH6*, and/or *PMS2*.[9] A contributing factor (especially for some cancer types) can be germline pathogenic variants in the MMR genes ('Lynch syndrome', with these variants increasing cancer predisposition).[10] dMMR tumours are very often hypermutated and thus exhibit MSI and/or high TMB. Similarly, MSI can lead to high TMB and vice versa, but both MSI and high TMB can also arise through non-dMMR mechanisms.[9] The hypermutation can lead to the generation of a higher number of neoantigens, which is related to better immune checkpoint inhibitor response, thus linking these biomarkers to the targeted treatments.[11]

Supplementary Table S2. Final search terms and the number of titles and abstracts identified in EMBASE and Medline searches on 01/02/2021

No	Search terms	Results
1	(microsatellite instability or msi).tw.	28,944
2	(microsatellite adj2 unstable).tw.	1,232
3	(mismatch repair or mmr or dmmr or mmrd).tw.	39,125
4	(tmb or tumo?r mutation burden* or tumo?r mutation load* or tml).tw.	11,006
5	1 or 2 or 3 or 4 ***Articles with explicit keywords related to MMR, MSI or TMB***	69,871
6	(cancer* or carcinoma* or tumo?r* or neoplas* or malignan*).tw.	8,189,812
7	5 and 6	40,630
8	limit 7 to (English language and humans)	33,059
9	**Remove case reports, conference abstracts, duplicates (EMBASE and Medline) and limit to studies published between 01/01/2018 and 31/01/2021**	**3,890**

Supplementary Table S3. Detailed inclusion and exclusion criteria and information sources

Category	Details
Population	Inclusion criteria: adult and paediatric cancer patients with solid tumours (see Supplementary Table S4) • Data for children were considered separately where available • Data from populations of any ancestry were included, as early evidence suggests no substantial differences in the prevalence of dMMR and MSI among colorectal cancers from different ancestries[12, 13] Exclusion criteria: highly selected population, e.g. based on restriction to • patients with family history or inherited predisposition to cancer (e.g., Lynch syndrome probands or their families) • patients with specific medical conditions such as immunocompromise (e.g., transplant patients, HIV patients) • patients exposed to a specific risk factor (e.g., individuals with gastric cancers with a prior Helicobacter Pylori infection) • specific rare histological cancer subtypes only (e.g., sebaceous skin neoplasm, neuroendocrine carcinoma of the cervix)

Category	Details
	• specific molecular cancer subtype only (e.g., colorectal cancer with *BRAF* mutation, triple-negative breast cancer), except for ovarian cancer where guidelines generally recommend dMMR/MSI testing in specific histologic subtypes only [e.g., endometrioid, clear cell carcinoma])[14]

Concept	<u>Main review question</u>
	The prevalence of the following biomarkers by cancer type and cancer stage (if available):
	• mismatch repair deficiency (dMMR; determined by immunohistochemistry as loss of MLH1/MSH2/MSH6/PMS2 staining, or based on genetic loss of function of *MLH1/MSH2/MSH6/PMS2* identified from gene panel test, or by whole genome or whole exome sequencing)
	• microsatellite instability (MSI; instability of 2+ microsatellite markers determined by PCR, including automated MSI tests [e.g., MSISensor], or based on a study-specific definition of MSI based on a gene panel test, whole genome or whole exome sequencing)
	• high tumour mutational burden (TMB, [e.g., ≥10 mutations per Mb or ≥20 mutations per Mb] based on a gene panel test, whole genome or whole exome sequencing)
	
	<u>Additional pre-planned review questions</u>
	• The prevalence of dMMR, MSI and high TMB by cancer type and cancer stage (if available):
	  ○ in adult and paediatric patients at cancer diagnosis prior to cancer treatment;
	  ○ in adult and paediatric patients with advanced cancer whose tumour has progressed following prior systemic treatment;
	  ○ in adult and paediatric patients based on different assays.
	
	Exclusion criteria:
	• Sample size ≤ 50
	• TMB detected from circulating tumour DNA[6]

Context	No limit to any setting
Type of evidence sources and publication status	Inclusion criteria: primary research studies (including case series and analyses of large-scale genomic data [e.g., The Cancer Genome Atlas]), review articles (including scoping reviews, systematic reviews and meta-analyses), letters, opinions and editorials that contain extractable data. Exclusion criteria: • Case reports • Conference abstracts • In vitro studies and in vivo studies • Non-academic literature (e.g., Health Technology Assessment reports)
Publication date	01/01/2018-31/01/2021
Language	English only
Database	MEDLINE and EMBASE
Date of executing final search	01/02/2021

dMMR – mismatch repair deficiency; MSI – microsatellite instability; TMB – tumour mutational burden; PCR = polymerase chain reaction; HIV = human immunodeficiency virus.

3. Data extraction

1) Tumour group categories

Tumour groups were categorised based on the anatomical site where possible, with 13 tumour group categories in total. Haematological tumours and lymphoma (including non-Hodgkin's lymphoma) were excluded from the scoping review. The final classification was based on each included study, as not all studies provided the specific International Classification of Diseases (ICD) codes for included cancer types, and classification of some cancers has changed over time (e.g. gastroesophageal junction cancer was classified as esophageal cancer in the 7th editing of the UICC/AJCC TNM classification, but as gastric cancer in the 8th edition[15]).

Supplementary Table S4. Adult solid tumour group categories

Tumour group	Cancer types and selected caner sub-types included in meta-analyses
Central nervous system tumours	• Brain tumours: low-grade glioma, high-grade glioma, glioblastoma (stage IV glioma)
Skin cancers	• Skin cancers, with the following sub-types in sub-group analyses ○ Melanoma ○ Non-melanoma (including cutaneous squamous cell carcinoma)
Sarcomas	• Sarcomas, with the following sub-types in sub-group analyses ○ Bone sarcoma ○ Soft tissue sarcoma (including liposarcoma, retroperitoneal sarcoma, nerve sheath tumour, uterine sarcoma, gastrointestinal stromal tumour)
Endocrine tumours[a]	• Endocrine tumours, with the following sub-types in sub-group analyses ○ Adrenocortical cancer ○ Thyroid carcinoma
Neuroendocrine tumours[b]	• Neuroendocrine tumours, with the following sub-types in sub-group analyses ○ Carcinoid ○ Gastrointestinal neuroendocrine tumours
Head and neck cancers[c]	• Head and neck cancers, with the following sub-types in sub-group analyses ○ Nasopharyngeal carcinoma ○ Oral cavity carcinoma ○ Salivary gland carcinoma
Thoracic cancers	• Lung cancer, with the following sub-types in sub-group analyses ○ Mesothelioma ○ Small cell lung cancer ○ Non-cell lung cancer • Thymic malignancy
Biliary tract cancers	• Ampullary cancer • Bile duct/gallbladder, with the following sub-types in sub-group analyses ○ Bile duct cancer (intrahepatic/extrahepatic cholangiocarcinoma only): Although intrahepatic cholangiocarcinoma is sometimes classified as a type of liver cancer since it occurs in the parts of the bile ducts within the liver, it is defined as bile duct cancer in our analysis. ○ Gallbladder cancer
Gastrointestinal cancers	• Anal cancer • Appendiceal cancer

Tumour group	Cancer types and selected caner sub-types included in meta-analyses
	• Colon cancer only • Colorectal cancer (any sites in the colon and the rectum) • Esophageal cancer • Gastric cancer (including gastroesophageal junction cancer): Gastroesophageal junction cancer was classified as esophageal cancer in the 7th editing of the UICC/AJCC TNM classification, but as gastric cancer in the 8th edition.[15] Studies of biomarker prevalence in esophageal cancer or gastric cancer also do not always specify whether gastroesophageal junction cancers are included or excluded. • Liver cancer (including hepatocellular carcinoma) • Pancreatic cancer • Rectal cancer only • Small bower cancer
Genitourinary tract cancers	• Bladder/urothelial cancer (including both urothelial carcinoma and upper urinary tract urothelial carcinoma since studies often reported the prevalence in urothelial carcinoma) • Kidney cancer (including renal cell carcinoma) • Penile cancer • Prostate cancer • Testicular cancer
Breast cancer	• Breast cancer
Gynaecological cancers	• Cervical cancer • Endometrial cancer (including endometrioid carcinoma) • Ovarian cancer, with the following sub-types in sub-group analyses only ○ dMMR/MSI enriched histological subtypes (endometroid carcinoma, non-serous/non-mucinous carcinoma, clear cell carcinoma): Guidelines generally recommends tumour testing for dMMR/MSI in these histologic types only.[14] Therefore, studies focused on these histologic sub-types were included in the cancer sub-group analyses only. • Uterine cancer (excluding endometrial cancer): if reported prevalence separately for endometrial cancer and uterine cancer • Vulvar cancer
Others	• Peritoneal cancer • Germ cell tumours • Cancer of unknown primary • Cancer of unknown primary-neuro • Underspecified

dMMR = mismatch repair deficiency; MSI = microsatellite instability.

[a] Of the seven studies reporting the prevalence of dMMR/MSI/high tumour mutational burden (TMB) in endocrine tumours; i) three studies reported the prevalence at this level only, with one study in adrenocortical cancer and three studies in thyroid cancer. Therefore, cancer-specific analysis was performed at this level.

[b] Of the seven studies reporting the prevalence of dMMR/MSI/high TMB in neuroendocrine tumours, three studies reported the prevalence at this level only, with one study in carcinoid and three studies in gastrointestinal neuroendocrine tumours. Therefore, cancer-specific analysis was performed at this level.

[c] Of the 12 studies reporting the prevalence of dMMR/MSI/high TMB in head and neck cancers, five studies reported the prevalence at this level only, with one study each in nasopharyngeal carcinoma and oral cavity carcinoma and two studies in salivary gland carcinoma. Therefore, cancer-specific analysis was performed at this level.

2) Cancer stage categories

Not all studies provided details on how different cancer stages were defined, and the categorisation was not always consistent between studies. As current drug approvals based on dMMR/MSI/high TMB largely focus on unresectable or metastatic solid tumours, we separately considered data on biomarker prevalence for early-stage cancers and advanced-stage cancers where available, as well as data for overall prevalence.

Supplementary Table S5. Cancer stage categories

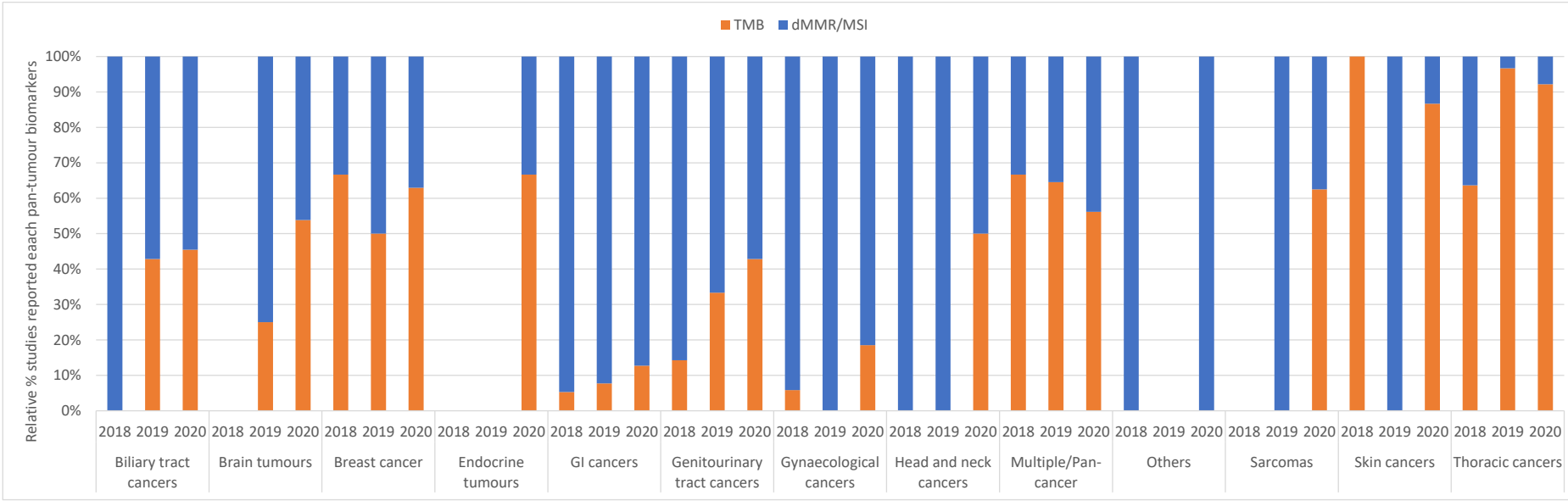
Cancer stage category	Different study-specific definitions
Early-stage	• Stage I, II, III (any of these and their combinations) • Early-stage cancer • For studies of brain cancer: Grade 1 or 2 [low grade]
Advanced-stage	• Stage III/IV • Stage IV • Locally advanced cancer • Advanced cancer • Metastatic cancer • Relapsed and/or refractory cancer • For studies of brain cancer: Grade 3 or 4 [high grade]
Overall	• Not limited to a specific cancer stage, nor restricted to early-stage or advanced-stage cancers

Supplementary Table S6. Minimum sample size thresholds for inclusion of studies in meta-analyses

	Minimum sample size		
Cancer type	**Overall**	**Early-stage**	**Advanced-stage**
Colorectal cancer	1000	400	200
Colon cancer	200	200	200
Endometrial cancer	400	50	50
Lung cancer	200	50	50
Ovarian cancer	100	50	50
Gastric cancer	400	50	50
Other cancers	50	50	50

4. Overview of literature reporting the prevalence of dMMR/MSI/high TMB

Supplementary Fig. S1. Relative proportion of studies reporting the prevalence of high TMB *vs* dMMR/MSI within each tumour group



dMMR = mismatch repair deficiency; MSI = microsatellite instability; TMB = tumour mutational burden. See Supplementary Table S4 for cancer types included in each tumour group.

5. Detailed results

1) Number of prevalence estimates included in each cancer-specific meta-analysis

Supplementary Table S7. Number of prevalence estimates included in each cancer-specific meta-analysis

Cancer	No. of prevalence estimates by pan-tumour biomarker					
	dMMR	MSI	TMB≥10 mut/Mb	TMB≥20 mut/Mb	dMMR/ MSI[a]	Total (column %)
Gastrointestinal cancers (170/412, 41%)						
Anal cancer	-	2	1	1	-	**4 (1%)**
Appendiceal cancer	1	3	-	1	-	**5 (1%)**
Colon cancer[b]	10	7	-	1	1	**19 (5%)**
CRC[b]	14	22	1	1	7	**45 (11%)**
Esophageal cancer	3	3	1	1	-	**8 (2%)**
Gastric cancer	17	24	3	2	-	**46 (11%)**
Liver cancer	1	6	3	1	-	**11 (3%)**
Pancreatic cancer	3	4	1	1	-	**9 (2%)**
Rectal cancer[b]	4	3	-	-	1	**8 (2%)**
Small bowel cancer	7	6	1	1	-	**15 (4%)**
Genitourinary tract cancers (51/412, 12%)						
Bladder/urothelial cancer	6	6	6	6	-	**24 (6%)**
Kidney cancer	1	4	-	1	-	**6 (1%)**
Penile cancer	1	1	-	-	-	**2 (0%)**
Prostate cancer	6	5	3	1	-	**15 (4%)**
Testicular cancer	1	1	1	1	-	**4 (1%)**
Breast and gynaecological cancers (69/412, 17%)						
Breast cancer	3	5	6	2	-	**16 (4%)**
Cervical cancer	1	2	2	1	-	**6 (1%)**
Endometrial cancer (EC)	14	7	2	2	-	**25 (6%)**
Ovarian cancer	11	6	2	-	-	**19 (5%)**
Uterine cancer (excl. EC)	-	1	-	1	-	**2 (0%)**
Vulvar cancer	-	-	1	-	-	**1 (0%)**
Thoracic cancers (28/412, 7%)						
Lung cancer	4	6	13	3	-	**26 (6%)**
Thymic malignancy	1	1	-	-	-	**2 (0%)**
Biliary tract cancers (17/412, 4%)						
Ampullary cancer	1	-	-	-	-	**1 (0%)**
Bile duct/gallbladder	3	9	2	2	-	**16 (4%)**
Head and neck cancers, sarcomas, and skin cancers (39/412, 9%)						
Head and neck cancers	4	3	3	2	-	**12 (3%)**
Sarcomas	2	5	3	1	-	**11 (3%)**
Skin cancers	5	4	3	4	-	**16 (4%)**
CNS tumours, endocrine tumours, neuroendocrine tumours, and other cancers (38/412, 9%)						
Brain tumours	6	3	1	3	-	**13 (3%)**
Endocrine tumours	1	3	2	1	-	**7 (2%)**
Neuroendocrine tumours	1	3	2	1	-	**7 (2%)**
Other cancers[c]	3	5	-	3	-	**11 (3%)**
Total (row %)	**135 (33%)**	**160 (39%)**	**63 (15%)**	**45 (11%)**	**9 (2%)**	**412 (100%)**

MMR = mismatch repair deficiency; MSI = microsatellite instability; TMB = tumour mutational burden; CRC = colorectal cancer; CNS = central nervous system.

[a] Pooled prevalence of dMMR and MSI in colorectal, colon and rectal cancers only using clinical trials and systematic review/meta-analysis given high concordance between dMMR and MSI in these cancer types.

[b] We analysed the pooled prevalence of pan-tumour biomarkers separately based on estimates including 1) colon cancer only, 2) rectal cancer only, and 3) tumours at any sites in the colon and the rectum, obtaining pooled prevalence estimates described as "colon cancer", "rectal cancer", and "colorectal cancer", respectively.

[c] Other caners include cancer of unknown primary, cancer of unknown primary-neuro, germ cell tumour, peritoneal cancer, and underspecified cancer.

Supplementary Table S8. Numbers of prevalence estimates included in stage-specific meta-analyses

	No. of prevalence estimates by stage group (row %)			
Biomarker	**Overall**	**Early-stage**	**Advanced stage**	**Total**
dMMR	93 (69%)	28 (21%)	14 (10%)	135 (100%)
MSI	108 (68%)	29 (18%)	23 (14%)	160 (100%)
TMB≥10 mut/Mb	32 (51%)	2 (3%)	29 (46%)	63 (100%)
TMB≥20 mut/Mb	33 (73%)	1 (2%)	11 (24%)	45 (100%)
dMMR/MSI	3 (33%)	5 (56%)	1 (11%)	9 (100%)
Total	**269 (65%)**	**65 (16%)**	**78 (19%)**	**412 (100%)**

MMR = mismatch repair deficiency; MSI = microsatellite instability; TMB = tumour mutational burden.

Supplementary Table S9. Numbers of prevalence estimates included in cancer-specific meta-analyses by pan-tumour biomarker and assays used

	No. of prevalence estimates by pan-tumour biomarker					
Assay	**dMMR**	**MSI**	**TMB≥10 mut/Mb**	**TMB≥20 mut/Mb**	**dMMR/MSI**	**Total**
Gene panel sequencing	28/136 (21%)	77/160 (48%)	41/63 (65%)	42/45 (93%)	0/9 (0%)	188/413 (46%)
IHC	101/135 (75%)	0/160 (0%)	0/63 (0%)	0/45 (0%)	0/9 (0%)	102/413 (25%)
IHC/PCR	0/136 (0%)	0/160 (0%)	0/63 (0%)	0/45 (0%)	8/9 (89%)	8/413 (2%)
N/S	3/136 (2%)	5/160 (3%)	1/63 (2%)	2/45 (4%)	1/9 (11%)	12/413 (3%)
Others	0/136 (0%)	4/160 (3%)	0/63 (0%)	0/45 (0%)	0/9 (0%)	4/413 (1%)
PCR	0/136 (0%)	63/160 (39%)	0/63 (0%)	0/45 (0%)	0/9 (0%)	63/413 (15%)
WES	3/136 (2%)	10/160 (6%)	20/63 (32%)	1/45 (2%)	0/9 (0%)	34/413 (8%)
WGS	0/136 (0%)	1/160 (1%)	1/63 (2%)	0/45 (0%)	0/9 (0%)	2/413 (0%)
Total	**135/135 (100%)**	**160/160 (100%)**	**63/63 (100%)**	**45/45 (100%)**	**9/9 (100%)**	**412/412 (100%)**

MMR = mismatch repair deficiency; MSI = microsatellite instability; TMB = tumour mutational burden; IHC = immunohistochemistry; PCR = polymerase chain reaction; WES = whole exome sequencing; WGS = whole genome sequencing.

Supplementary Table S10. References of studies included in each cancer-specific meta-analysis of dMMR prevalence

Cancer	Overall		Early stage		Advanced stage	
	No. of estimate	References	No. of estimate	References	No. of estimate	References
Gastrointestinal cancers						
Anal cancer	-		-		-	
Appendiceal cancer	1	16	-		-	
Colon cancer[b]	2	17, 18	7	19-25	1	26
CRC[b]	12	16, 27-35	1	35	1	36
Esophageal cancer	3	37-39	-		-	
Gastric cancer	7	39-45	5	46-50	5	40, 41, 50-52
Liver cancer	1	16	-		-	
Pancreatic cancer	2	16, 53	-		1	54
Rectal cancer[b]	-		4	55-58	-	
Small bowel cancer	6	16, 59-63	1	60	-	
Genitourinary tract cancers						
Bladder/urothelial cancer	6	16, 64-68	-		-	
Kidney cancer	1	16	-		-	
Penile cancer	1	69	-		-	
Prostate cancer	5	16, 67, 70-72	-		1	73
Testicular cancer	-		1	74	-	
Breast and gynaecological cancers						
Breast cancer	3	16, 67, 75	-		-	
Cervical cancer	1	16	-		-	
Endometrial cancer	8	16, 76-82	6	78, 80, 83-86	-	
Ovarian cancer[a]	9	16, 42, 87-93	2	90, 94	-	
Uterine cancer (excl. endometrial cancer)	-		-		-	
Vulvar cancer	-		-		-	
Thoracic cancers						
Lung cancer	4	16	-		-	
Thymic malignancy	1	16	-		-	
Biliary tract cancers						
Ampullary cancer	-		1	95	-	
Bile duct/gallbladder	3	16, 96, 97	-		-	
Head and neck cancers, sarcomas, and skin cancers						
Head and neck cancers	4	16, 98-100	-		-	
Sarcomas	2	16	-		-	
Skin cancers	4	16, 67, 101	-		1	102
CNS tumours, endocrine tumours, neuroendocrine tumours, and other cancers						
Brain tumours	2	16, 103	-		4	104-107
Endocrine tumours	1	16	-		-	
Neuroendocrine tumours	1	16	-		-	
Other cancers[b]	3	16, 108	-		-	

dMMR = mismatch repair deficiency; MSI = microsatellite instability.

[a] Including studies included in cancer sub-group analysis only (i.e., dMMR/MSI enriched histologic sub-types, e.g., endometroid carcinoma, non-serous carcinoma, mucinous carcinoma)

[b] We analysed the pooled prevalence of pan-tumour biomarkers separately based on estimates including 1) colon cancer only, 2) rectal cancer only, and 3) tumours at any sites in the colon and the rectum, obtaining pooled prevalence estimates described as “colon cancer”, “rectal cancer”, and “colorectal cancer”, respectively.

[c] Other caners include cancer of unknown primary, cancer of unknown primary-neuro, germ cell tumour, peritoneal cancer, and underspecified cancer.

Supplementary Table S11. References of studies included in each cancer-specific meta-analysis of MSI prevalence

Cancer	Overall		Early stage		Advanced stage	
	No. of estimate	References	No. of estimate	References	No. of estimate	References
Gastrointestinal cancers						
Anal cancer	2	109, 110	-		-	
Appendiceal cancer	2	110, 111	-		1	111
Colon cancer[b]	1	112	6	24, 113-117	-	
CRC[b]	11	32, 109, 110, 118-125	4	118, 119, 126, 127	7	118, 119, 128-132
Esophageal cancer	3	42, 109, 110	-		-	
Gastric cancer	10	42, 109, 110, 121, 123, 133-137	11	138-148	3	149-151
Liver cancer	3	109, 121, 123	-		3	123, 152, 153
Pancreatic cancer	4	109, 110, 154, 155	-		-	
Rectal cancer[b]	-		3	55, 156, 157	-	
Small bowel cancer	4	109, 110, 158, 159	2	160, 161	-	
Genitourinary tract cancers						
Bladder/urothelial cancer	5	67, 68, 109, 110, 162	-		1	163
Kidney cancer	3	109, 110, 164	-		1	165
Penile cancer	1	69	-		-	
Prostate cancer	4	67, 109, 110, 166	-		1	167
Testicular cancer	-		-		1	168
Breast and gynaecological cancers						
Breast cancer	4	67, 109, 110, 123	-		1	169
Cervical cancer	2	110, 170	-		-	
Endometrial cancer	5	80, 81, 110, 121, 171	1	80	1	172
Ovarian cancer[a]	6	42, 90, 109, 110, 173, 174	-		-	
Uterine cancer (excl. endometrial cancer)	1	110	-		-	
Vulvar cancer	-		-		-	
Thoracic cancers						
Lung cancer	5	109, 110, 123	-		1	123
Thymic malignancy	1	109	-		-	
Biliary tract cancers						
Ampullary cancer	-		-		-	
Bile duct/gallbladder	8	97, 110, 175-178	-		1	179
Head and neck cancers, sarcomas, and skin cancers						
Head and neck cancers	3	109, 110, 123	-		-	
Sarcomas	4	67, 109, 110	1	180	-	
Skin cancers	4	67, 109, 110	-		-	
CNS tumours, endocrine tumours, neuroendocrine tumours, and other cancers						
Brain tumours	1	109	1	109	1	109
Endocrine tumours	3	109, 110, 181	-		-	
Neuroendocrine tumours	3	109, 110	-		-	
Other cancers[c]	5	109, 110	-		-	

dMMR = mismatch repair deficiency; MSI = microsatellite instability.

[a] Including studies included in cancer sub-group analysis only (i.e., dMMR/MSI enriched histologic sub-types, e.g., endometroid carcinoma, non-serous carcinoma, mucinous carcinoma)

[b] We analysed the pooled prevalence of pan-tumour biomarkers separately based on estimates including 1) colon cancer only, 2) rectal cancer only, and 3) tumours at any sites in the colon and the rectum, obtaining pooled prevalence estimates described as “colon cancer”, “rectal cancer”, and “colorectal cancer”, respectively.

[c] Other caners include cancer of unknown primary, cancer of unknown primary-neuro, germ cell tumour, peritoneal cancer, and underspecified cancer.

Supplementary Table S12. References of studies included in each cancer-specific meta-analysis of high TMB (≥10 mutations/Mb) prevalence

Cancer	Overall		Early stage		Advanced stage	
	No. of estimate	References	No. of estimate	References	No. of estimate	References
Gastrointestinal cancers						
Anal cancer	-		-		1	182
Appendiceal cancer	-		-		-	
Colon cancer[b]	-		-		-	
CRC[b]	1	123	-		-	
Esophageal cancer	1	183	-		-	
Gastric cancer	1	123	-		2	52, 151
Liver cancer	1	123	-		2	123, 152
Pancreatic cancer	1	123	-		-	
Rectal cancer[b]	-		-		-	
Small bowel cancer	1	159	-		-	
Genitourinary tract cancers						
Bladder/urothelial cancer	3	184-186	1	185	2	163, 185
Kidney cancer	-		-		-	
Penile cancer	-		-		-	
Prostate cancer	2	166, 187	-		1	167
Testicular cancer	-		-		1	168
Breast and gynaecological cancers						
Breast cancer	4	123, 184, 188, 189	-		2	169, 188
Cervical cancer	1	184	-		1	182
Endometrial cancer	1	171	-		1	182
Ovarian cancer[a]	1	174	-		1	173
Uterine cancer (excl. endometrial cancer)	-		-		-	
Vulvar cancer	-		-		1	182
Thoracic cancers						
Lung cancer	4	123, 184, 190, 191	1	192	8	123, 182, 193-196
Thymic malignancy	-		-		-	
Biliary tract cancers						
Ampullary cancer	-		-		-	
Bile duct/gallbladder	1	197	-		1	182
Head and neck cancers, sarcomas, and skin cancers						
Head and neck cancers	2	123, 184	-		1	182
Sarcomas	3	123, 184	-		-	
Skin cancers	1	184	-		2	198, 199
CNS tumours, endocrine tumours, neuroendocrine tumours, and other cancers						
Brain tumours	1	123	-		-	
Endocrine tumours	1	184	-		1	182
Neuroendocrine tumours	1	184	-		1	182
Other cancers[c]	-		-		-	

dMMR = mismatch repair deficiency; MSI = microsatellite instability.

[a] Including studies included in cancer sub-group analysis only (i.e., dMMR/MSI enriched histologic sub-types, e.g., endometroid carcinoma, non-serous carcinoma, mucinous carcinoma)

[b] We analysed the pooled prevalence of pan-tumour biomarkers separately based on estimates including 1) colon cancer only, 2) rectal cancer only, and 3) tumours at any sites in the colon and the rectum, obtaining pooled prevalence estimates described as “colon cancer”, “rectal cancer”, and “colorectal cancer”, respectively.

[c] Other caners include cancer of unknown primary, cancer of unknown primary-neuro, germ cell tumour, peritoneal cancer, and underspecified cancer.

Supplementary Table S13. References of studies included in each cancer-specific meta-analysis of high TMB (≥20 mutations/Mb) prevalence

Cancer	Overall		Early stage		Advanced stage	
	No. of estimate	References	No. of estimate	References	No. of estimate	References
Gastrointestinal cancers						
Anal cancer	1	110	-		-	
Appendiceal cancer	1	110	-		-	
Colon cancer[b]	1		-		-	
CRC[b]	1		-		-	
Esophageal cancer	1	110	-		-	
Gastric cancer	1	110	-		1	151
Liver cancer	-		-		1	152
Pancreatic cancer	1	200	-		-	
Rectal cancer[b]	-		-		-	
Small bowel cancer	1	110	-		-	
Genitourinary tract cancers						
Bladder/urothelial cancer	3	110, 185, 186	1	185	2	163, 185
Kidney cancer	1	110	-		-	
Penile cancer	-		-		-	
Prostate cancer	1	110	-		-	
Testicular cancer	-		-		1	168
Breast and gynaecological cancers						
Breast cancer	1	110	-		1	169
Cervical cancer	1	110	-		-	
Endometrial cancer	1	110	-		1	172
Ovarian cancer[a]	-		-		-	
Uterine cancer (excl. endometrial cancer)	1	110	-		-	
Vulvar cancer	-		-		-	
Thoracic cancers						
Lung cancer	2	110	-		1	201
Thymic malignancy	-		-		-	
Biliary tract cancers						
Ampullary cancer	-		-		-	
Bile duct/gallbladder	2	110	-		-	
Head and neck cancers, sarcomas, and skin cancers						
Head and neck cancers	2	110	-		-	
Sarcomas	1	110	-		-	
Skin cancers	2	110	-		2	198, 199
CNS tumours, endocrine tumours, neuroendocrine tumours, and other cancers						
Brain tumours	2	103, 110	-		1	202
Endocrine tumours	1	110	-		-	
Neuroendocrine tumours	1	110	-		-	
Other cancers[c]	3	110	-		-	

dMMR = mismatch repair deficiency; MSI = microsatellite instability.

[a] Including studies included in cancer sub-group analysis only (i.e., dMMR/MSI enriched histologic sub-types, e.g., endometroid carcinoma, non-serous carcinoma, mucinous carcinoma)

[b] We analysed the pooled prevalence of pan-tumour biomarkers separately based on estimates including 1) colon cancer only, 2) rectal cancer only, and 3) tumours at any sites in the colon and the rectum, obtaining pooled prevalence estimates described as “colon cancer”, “rectal cancer”, and “colorectal cancer”, respectively.

[c] Other caners include cancer of unknown primary, cancer of unknown primary-neuro, germ cell tumour, peritoneal cancer, and underspecified cancer.

2) Prevalence of high TMB (≥20 mutations/Mb)

The pooled overall prevalence of high TMB at the ≥20 mutations/Mb threshold was high for skin (43.5%), colon (19.0%), bladder/urothelial (12.0%), endometrial (11.9%) and lung (9.0%) cancers. Considerable variation was found in the pooled overall prevalence of TMB (≥20 mutations/Mb) among gastrointestinal (range: 0.5%-19.0%), gynaecological (range: 3.7%-11.9%) and genitourinary tract cancers (range: 1.5%-12.0%) (Supplementary Table S14). The prevalence of high TMB (≥20 mutations/Mb) also differed by sub-types in skin cancers (54.6% in non-melanoma *vs* 32.9% in melanoma overall) and lung cancers (11.5% in non-small cell lung cancer *vs* 6.7% in small cell lung cancer overall) (Supplementary Table S18).

Supplementary Table S14. Prevalence of high tumour mutational burden (≥20 mutations/Mb) in adult solid tumours by cancer type and stage group

Cancer	Prevalence from random-effect model (95% CI)[a]		
	Overall	Early stage	Advanced stage
Gastrointestinal cancers			
Anal cancer	3.9% (2.5-5.5%)	-	-
Appendiceal cancer	2.0% (1.2-3.0%)	-	-
Colon cancer[c]	19.0% (15.3-23.1%)	-	-
Colorectal cancer[c]	5.1% (4.8-5.4%)	-	-
Esophageal cancer	2.5% (2.1-3.0%)	-	-
Gastric cancer	4.9% (4.2-5.6%)	-	7.4% (1.6-16.2%)
Liver cancer	-	-	0.8% (0.3-1.6%)
Pancreatic cancer	0.5% (0.1-1.0%)	-	-
Rectal cancer[c]	-	-	-
Small bowel cancer	6.1% (4.7-7.7%)	-	-
Genitourinary tract cancers			
Bladder/urothelial cancer	12.0% (6.9-18.3%), I^2=0.93[b]	22.7% (17.0-28.9%)	12.3% (8.8-16.2%), I^2=0.47
Kidney cancer	1.5% (1.1-1.9%)	-	-
Penile cancer	-	-	-
Prostate cancer	3.0% (2.7-3.5%)	-	-
Testicular cancer	-	-	0.9% (0.0-4.0%)
Breast and gynaecological cancers			
Breast cancer	2.6% (2.4-2.8%)	-	2.2% (1.7-2.7%)
Cervical cancer	6.1% (5.0-7.3%)	-	-
Endometrial cancer (EC)	11.9% (11.1-12.8%)	-	13.5% (6.5-22.4%)
Ovarian cancer	-	-	-
Uterine cancer (excl. EC)	3.7% (2.7-4.9%)	-	-
Vulvar cancer	-	-	-
Thoracic cancers			
Lung cancer	9.0% (4.9-14.2%), I^2=0.98[b]	-	11.9% (10.8-13.0%)
Thymic malignancy	-	-	-
Biliary tract cancers			
Ampullary cancer	-	-	-
Bile duct/gallbladder	1.6% (0.8-2.6%), I^2=0.87[b]	-	-
Head and neck cancers, sarcomas, and skin cancers			
Head and neck cancers	7.7% (6.9-8.6%), I^2=0	-	-
Sarcomas	2.8% (2.3-3.3%)	-	-
Skin cancers	43.5% (23.3-64.9%), I^2=0.99[b]	-	19.7% (1.5-50.0%), I^2=0.93[b]
Central nervous system tumours, endocrine tumours, neuroendocrine tumours, and other cancers			
Brain tumours	5.5% (1.4-11.9%), I^2=0.82[b]	-	1.0% (0.0-4.3%)
Endocrine tumours	1.7% (1.0-2.6%)	-	-
Neuroendocrine tumours	3.5% (2.2-5.1%)	-	-
Other cancers[d]	8.9% (6.0-12.2%), I^2=0.94[b]	-	-

[a] Heterogeneity across studies was presented based on the point estimate of I^2 score and heterogeneity test, if ≥2 records were available for each cancer type and stage group.

[b] Statistically significant heterogeneity across studies (p<0.05).

[b] We analysed the pooled prevalence of pan-tumour biomarkers separately based on estimates including 1) colon cancer only, 2) rectal cancer only, and 3) tumours at any sites in the colon and the rectum, obtaining pooled prevalence estimates described as “colon cancer”, “rectal cancer”, and “colorectal cancer”, respectively.

[d] Other caners include cancer of unknown primary, cancer of unknown primary-neuro, germ cell tumour, peritoneal cancer, and underspecified cancer.

Note: See Supplementary Table S10 and Supplementary Table S13 for the number of records included in the analysis and the references.

3) Sub-group analyses of the prevalence of dMMR/MSI/high TMB

Supplementary Table S15. Prevalence of dMMR in adult solid tumours by cancer sub-type and stage group

Cancer sub-type	Prevalence from random-effects model (95% CI)[a]		
	Overall	Early stage	Advanced stage
Gynaecological cancers			
Ovarian cancer (dMMR/MSI enriched sub-types)[c]	11.8% (5.9-19.3%), I^2=0.87[b]	13.7% (9.4-18.7%)	-
Thoracic cancers			
Mesothelioma	0.8% (0.0-2.5%)	-	-
NSCLC	1.2% (0.8-1.6%)	-	-
SCLC	0.8% (0.0-3.5%)	-	-
Biliary tract cancers			
Cholangiocarcinoma	6.3% (2.1-12.1%)	-	-
Gallbladder cancer	-	-	-
Head and neck cancers			
Nasopharyngeal carcinoma	2.0% (0.0-5.8%)	-	-
Oral cavity carcinoma	7.4% (4.6-10.7%)	-	-
Salivary gland carcinoma	0.0% (0.0-3.3%)	-	-
Sarcomas			
Bone sarcoma	-	-	-
Soft tissue sarcoma	1.2% (0.6-1.9%)	-	-
Skin cancers			
Melanoma	6.7% (0.0-37.5%), I^2=0.98[b]	-	-
Non-melanoma	2.0% (0.4-4.4%)	-	9.1% (5.2-13.8%)
Endocrine tumours			
Adrenocortical cancers	-	-	-
Thyroid carcinoma	0.7% (0.1-1.7%)	-	-
Neuroendocrine tumours			
Carcinoid	-	-	-
GI neuroendocrine tumour	0.0% (0.0-1.2%)	-	-
Other cancers			
Cancer of unknown primary	2.3% (1.3-3.6%)	-	-
Germ cell tumour	0.0% (0.0-1.5%)	-	-
Peritoneal cancer	6.3% (2.7-11.4%)	-	-
Underspecified	-	-	-
Cancer of unknown primary-neuro	-	-	-

dMMR = mismatch repair deficiency; MSI = microsatellite instability; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

[a] Heterogeneity across studies was presented based on the point estimate of I^2 score and heterogeneity test, if ≥2 records were available for each cancer type and stage group.

[b] Statistically significant heterogeneity across studies ($p<0.05$).

[c] dMMR/MSI enriched histologic sub-types: endometroid carcinoma, non-serous carcinoma, mucinous carcinoma.

Supplementary Table S16. Prevalence of MSI in adult solid tumours by cancer sub-type and stage group

Cancer sub-type	Prevalence from random-effects model (95% CI)[a]		
	Overall	Early stage	Advanced stage
Gynaecological cancers			
Ovarian cancer (dMMR/MSI enriched sub-types)[c]	14.4% (8.9-20.9%), I^2=0.5	-	-
Thoracic cancers			
Mesothelioma	-	-	-
NSCLC	0.5% (0.2-0.9%), I^2=0.92[b]	-	-
SCLC	0.5% (0.3-0.8%), I^2=0	-	-
Biliary tract cancers			
Cholangiocarcinoma	1.8% (0.7-3.3%), I^2=0.72[b]	-	-
Gallbladder cancer	1.4% (0.0-6.1%)	-	-
Head and neck cancers			
Nasopharyngeal carcinoma	-	-	-
Oral cavity carcinoma	-	-	-
Salivary gland carcinoma	-	-	-
Sarcomas			
Bone sarcoma	0.3% (0.0-1.0%)	-	-
Soft tissue sarcoma	2.6% (0.0-11.3%), I^2=0.96[b]	1.4% (0.0-5.7%)	-
Skin cancers			
Melanoma	0.0% (0.0-0.2%)	-	-
Non-melanoma	1.9% (1.2-2.9%), I^2=0	-	-
Endocrine tumours			
Adrenocortical cancers	1.1% (0.0-4.5%)	-	-
Thyroid carcinoma	1.9% (0.0-5.5%)	-	-
Neuroendocrine tumours			
Carcinoid	0.4% (0.0-1.1%)	-	-
GI neuroendocrine tumour	2.0% (1.0-3.3%)	-	-
Other cancers			
Cancer of unknown primary	2.2% (1.0-3.8%), I^2=0.85[b]	-	-
Germ cell tumour	-	-	-
Peritoneal cancer	0.3% (0.0-0.9%)	-	-
Underspecified	1.8% (0.9-2.8%)	-	-
Cancer of unknown primary-neuro	0.9% (0.4-1.4%)	-	-

dMMR = mismatch repair deficiency; MSI = microsatellite instability; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

[a] Heterogeneity across studies was presented based on the point estimate of I^2 score and heterogeneity test, if ≥2 records were available for each cancer type and stage group.

[b] Statistically significant heterogeneity across studies ($p<0.05$).

[c] dMMR/MSI enriched histologic sub-types: endometroid carcinoma, non-serous carcinoma, mucinous carcinoma.

Supplementary Table S17. Prevalence of high TMB (≥10 mutations/Mb) in adult solid tumours by cancer sub-type and stage group

Cancer sub-type	Prevalence from random-effects model (95% CI)[a]		
	Overall	Early stage	Advanced stage
Gynaecological cancers			
Ovarian cancer (dMMR/MSI enriched sub-types)[c]	11.6% (6.3-18.3%)	-	-
Thoracic cancers			
Mesothelioma	-	-	1.2% (0.0-5.0%)
NSCLC	33.6% (28.1-39.2%), I^2=0.88[b]	58.7% (52.4-65.0%)	42.3% (35.1-49.6%), I^2=0.92[b]
SCLC	-	-	38.6% (29.1-48.6%), I^2=0.59
Biliary tract cancers			
Cholangiocarcinoma	9.5% (3.3-18.2%)	-	-
Gallbladder cancer	-	-	-
Head and neck cancers			
Nasopharyngeal carcinoma	-	-	-
Oral cavity carcinoma	-	-	-
Salivary gland carcinoma	-	-	3.7% (0.5-9.1%)
Sarcomas			
Bone sarcoma	-	-	-
Soft tissue sarcoma	1.3% (0.0-4.8%), I^2=0.57	-	-
Skin cancers			
Melanoma	52.6% (49.7-55.5%)	-	28.0% (18.8-38.3%)
Non-melanoma	-	-	58.2% (44.8-71.0%)
Endocrine tumours			
Adrenocortical cancers	-	-	-
Thyroid carcinoma	-	-	2.5% (0.0-7.4%)
Neuroendocrine tumours			
Carcinoid	-	-	-
GI neuroendocrine tumour	-	-	-
Other cancers			
Cancer of unknown primary	-	-	-
Germ cell tumour	-	-	-
Peritoneal cancer	-	-	-
Underspecified	-	-	-
Cancer of unknown primary-neuro	-	-	-

dMMR = mismatch repair deficiency; MSI = microsatellite instability; TMB = tumour mutational burden; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

[a] Heterogeneity across studies was presented based on the point estimate of I^2 score and heterogeneity test, if ≥2 records were available for each cancer type and stage group.

[b] Statistically significant heterogeneity across studies ($p<0.05$).

[c] dMMR/MSI enriched histologic sub-types: endometroid carcinoma, non-serous carcinoma, mucinous carcinoma.

Supplementary Table S18. Prevalence of high TMB (≥20 mutations/Mb) in adult solid tumours by cancer sub-type and stage group

Cancer sub-type	Prevalence from random-effects model (95% CI)[a]		
	Overall	Early stage	Advanced stage
Gynaecological cancers			
Ovarian cancer (dMMR/MSI enriched sub-types)[c]	-	-	-
Thoracic cancers			
Mesothelioma	-	-	-
NSCLC	11.5% (11.2-11.8%)	-	11.9% (10.8-13.0%)
SCLC	6.7% (5.8-7.7%)	-	-
Biliary tract cancers			
Cholangiocarcinoma	1.2% (0.8-1.5%)	-	-
Gallbladder cancer	-	-	-
Head and neck cancers			
Nasopharyngeal carcinoma	-	-	-
Oral cavity carcinoma	-	-	-
Salivary gland carcinoma	7.1% (5.5-8.8%)	-	-
Sarcomas			
Bone sarcoma	-	-	-
Soft tissue sarcoma	2.8% (2.3-3.3%)	-	-
Skin cancers			
Melanoma	32.9% (31.7-34.1%)	-	8.5% (3.3-15.7%)
Non-melanoma	54.6% (51.4-57.8%)	-	34.5% (22.5-47.7%)
Endocrine tumours			
Adrenocortical cancers	-	-	-
Thyroid carcinoma	-	-	-
Neuroendocrine tumours			
Carcinoid	-	-	-
GI neuroendocrine tumour	3.5% (2.2-5.1%)	-	-
Other cancers			
Cancer of unknown primary	8.7% (8.2-9.2%)	-	-
Germ cell tumour	-	-	-
Peritoneal cancer	-	-	-
Underspecified	13.1% (10.8-15.6%)	-	-
Cancer of unknown primary-neuro	5.7% (4.5-7.0%)	-	-

dMMR = mismatch repair deficiency; MSI = microsatellite instability; TMB = tumour mutational burden; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

[a] Heterogeneity across studies was presented based on the point estimate of I^2 score and heterogeneity test, if ≥2 records were available for each cancer type and stage group.

[b] Statistically significant heterogeneity across studies ($p<0.05$).

[c] dMMR/MSI enriched histologic sub-types: endometroid carcinoma, non-serous carcinoma, mucinous carcinoma.

Supplementary Table S19. Prevalence of dMMR/MSI/high TMB by tumour group, based on studies reporting prevalence estimates on tumour group level only

Tumour group	Prevalence from random-effects model (95% CI)[a]		
	dMMR	MSI	TMB (≥10 mutations/Mb)
GI cancers[16, 67, 184]	8.1% (0.8-21.6%), I^2=0.95[b]		6.8% (6.3-7.3%)
Genitourinary tract cancers[16]			5.5% (4.6-6.4%)
Gynaecological cancers[67, 184]	6.0% (3.1-9.7%)	5.0% (2.3-8.5%)	9.5% (8.8-10.3%)
Central nervous system tumours[16]			5.4% (3.9-7.2%)

dMMR = mismatch repair deficiency; MSI = microsatellite instability; TMB = tumour mutational burden.

[a] Heterogeneity across studies was presented based on the point estimate of I^2 score and heterogeneity test, if ≥2 records were available for each cancer type and stage group.

[b] Statistically significant heterogeneity across studies (p<0.05).

Supplementary Table S20. Pooled prevalence of dMMR/MSI in colorectal, colon and rectal cancers

Cancer[c]	Prevalence from random-effects model (95% CI)[a]		
	Overall	Early stage	Advanced stage
Colorectal cancer[203-208]	8.4% (4.9-12.8%), I^2=0.98[b]	17.0% (12.6-21.9%), I^2=0.99[b]	9.7% (8.7-10.8%)
Colon cancer[209]	-	11.9% (11.0-13.0%)	-
Rectal cancer[210]	-	13.7% (12.9-14.6%)	-

dMMR = mismatch repair deficiency; MSI = microsatellite instability.

[a] Heterogeneity across studies was presented based on the point estimate of I^2 score and heterogeneity test, if ≥2 records were available for each cancer type and stage group.

[b] Statistically significant heterogeneity across studies (p<0.05).

[c] We analysed the pooled prevalence of pan-tumour biomarkers separately based on estimates including 1) colon cancer only, 2) rectal cancer only, and 3) tumours at any sites in the colon and the rectum, obtaining pooled prevalence estimates described as “colon cancer”, “rectal cancer”, and “colorectal cancer”, respectively.

Note: Pooled prevalence of dMMR and MSI in colorectal, colon and rectal cancers only using clinical trials and systematic review/meta-analysis given high concordance between dMMR and MSI in these cancer types.

4) Sensitivity analyses of the prevalence of dMMR/MSI/high TMB

Supplementary Table S21. Prevalence of MSI/high TMB by assays used

Pan-tumour biomarker	Cancer†	Stage	Prevalence from random-effects model (95% CI)[a]		
			PCR	Selected gene panel sequencing	Whole exome sequencing
MSI	Colorectal cancer[109, 110, 118-122, 124, 125, 127, 129-131]	Overall	11.7% (9.0-14.8%), I^2=0.97[b]	6.9% (4.3-10.0), I^2=0.98[b]	-
MSI	Gastric cancer[42, 109, 110, 121, 134-137]	Overall	9.7% (6.2-13.9%), I^2=0.95[b]	5.5% (3.9-7.4), I^2=0.72[b]	--
High TMB (≥10 mut/MB)	Lung cancer[123, 182, 193, 195, 196]	Advanced	-	32.7% (17.9-49.5%), I^2=0.96[b]	22.6% (5.3-47.2%), I^2=0.98[b]

MSI = microsatellite instability; TMB = tumour mutational burden.

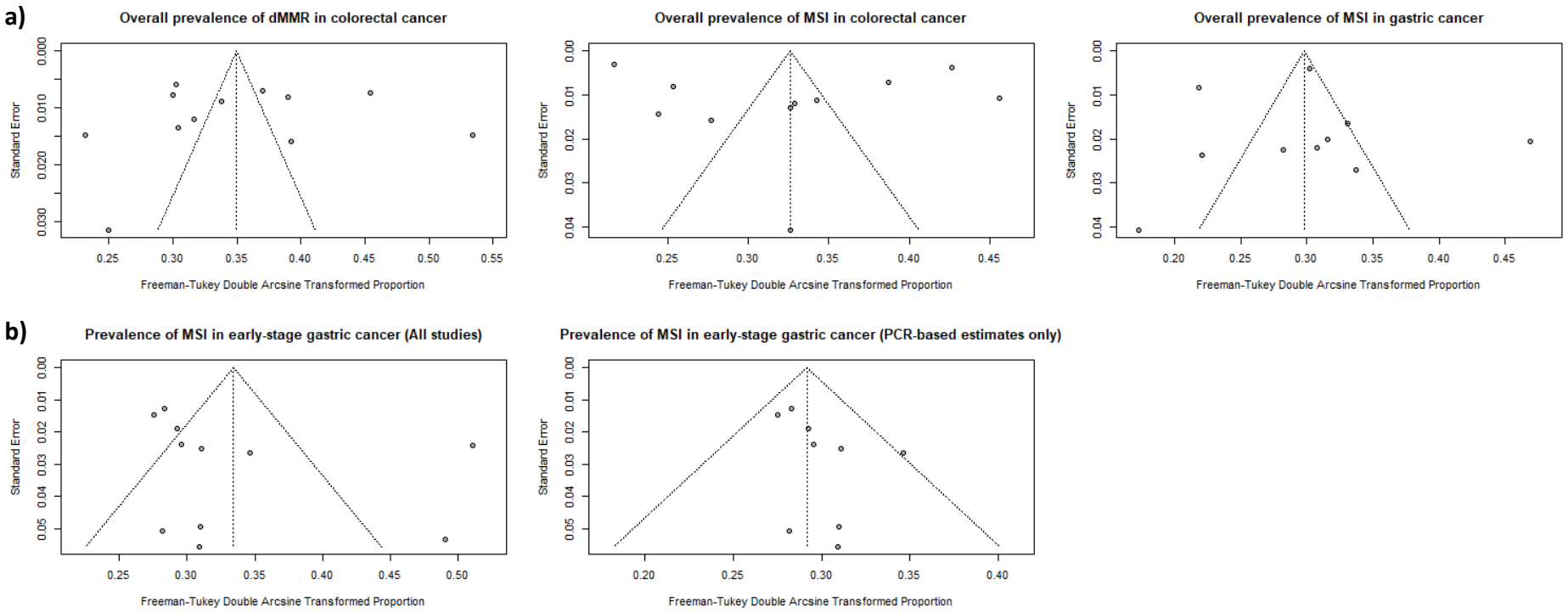
a Heterogeneity across studies was presented based on the point estimate of I^2 score and heterogeneity test, if ≥2 records were available for each cancer type and stage group.

[b] Statistically significant heterogeneity across studies ($p<0.05$).

Note: Cancer types with ≥3 records per each pan-tumour biomarker and assay were included in the analysis.

5) Publication bias

Supplementary Fig. S2. Funnel plots for meta-analyses pooling 10+ estimates, showing the transformed proportions and their standard errors. a) Overall prevalence of dMMR and MSI in colorectal cancer and MSI in gastric cancer; b) Prevalence of MSI in early-stage gastric cancer



The funnel plots show the Freeman-Tukey double arcsine transformed prevalence. The vertical and diagonal dashed lines represent the pooled estimate for the transformed proportion and the corresponding 95% confidence interval, respectively. Each point represents the estimate from one study.

6) Illustrative example: estimated numbers of gastric and lung cancer patients with dMMR and, separately, high TMB tumours for two cancer types in Australia in 2021

Supplementary Table S22. Estimated numbers of gastric and lung cancer patients with dMMR and, separately, with high TMB (≥10 mutations/Mb) tumours in Australia in 2021

			Mismatch repair deficiency			High tumour mutational burden (≥10 mutations/Mb)		
Cancer type	Incidence (Estimated in 2021 in Australia)[211]	% distant cases[212]	Overall prevalence [a]	Estimated no. of all cases (Australia 2021)	Estimated no. of distant cases (Australia 2021)	Overall prevalence[*]	Estimated no. of all cases (Australia 2021)	Estimated no. of distant cases (Australia 2021)
Gastric cancer	2,392	38.0%	8.7%	208	79	13.9%	332	126
Lung cancer	13,810	53.6%	1.6%	221	118	25.7%	3,549	1,902

[a] Overall prevalence from random-effect model in our study.

6. Comparison with prior reviews reporting the prevalence of dMMR/MSI/high TMB

Past reviews of dMMR/MSI prevalence have typically focused on a single cancer type, with only two existing structured/systematic reviews consolidating evidence for multiple different cancers.[42, 213]

Lorenzi et al. reported the pooled prevalence of dMMR and MSI across all solid tumours and for six selected tumour types (endometrial, ovarian, gastric, colorectal, esophageal and renal cancers).[42] A systematic search was performed for all studies reporting the prevalence of dMMR or MSI by immunohistochemistry or polymerase chain replication techniques on 26/10/2017, with targeted hand searches for colorectal cancer and pan-tumour genomic studies. A total of 156 studies were included in this structured review, including 103 studies reporting the prevalence of MSI, 48 studies reporting the prevalence of dMMR, and 5 pan-tumour studies. The included studies mostly focused on endometrial (n=53), gastric (n=39), ovarian (n=23), renal (n=9), esophageal (n=6) and colorectal (n=12) cancers. The pooled prevalence of dMMR across the 13 tumour types was 16% (95% CI: 11%-22%) and the pooled prevalence of MSI across 25 tumours was 14% (95% CI: 10%-19%). These pooled prevalence estimates are substantially higher than the pooled pan-cancer prevalence estimates in the current scoping review (dMMR: 2.9% [95% CI: 2.7%-3.1%]; and MSI: 2.7% [95% CI: 2.1%-3.4%]), which is likely due to almost two-thirds of the studies in the previous review focusing on colorectal, endometrial and stomach cancers (where dMMR and MSI are more common). For stage I/II, III and IV cancers, the pooled prevalence estimated in the previous review was 15% (95% CI: 8%–23%), 9% (95% CI: 3%–17%) and 3% (95% CI: 1%–7%), respectively.

Luchini et al. carried out a systematic review of studies that reported test results for high TMB, MSI/dMMR (which were not explicitly differentiated in that work), and PD-1/PD-L1 expression in the same samples, identifying 18 studies on 17 cohorts published to September 2018, of which 10 cohorts were focused on specifically on cancers of the digestive system. In total, the review summarised that a total of 4186 patients from all cohorts combined were positive for at least one of the three biomarkers, and 2.9% of these patients had tumours with high TMB, MSI, and PD-1/PD-L1 expression. Based on Figure 1, there were a total of 913 patients (21.8% of 4186) whose tumours exhibited MSI/dMMR or high TMB, of whom 45.9% exhibited both MSI/dMMR and high TMB, while 42.2% exhibited high TMB only and 11.9% exhibited MSI/dMMR only. However, there were differences in concordance of individual-level biomarker presence between different cancer types, so these results would also be influenced by the cancer type composition of the cohorts underlying the estimates.

Luchini et al. also reported the pooled cancer-specific prevalence of dMMR/MSI (which were not explicitly differentiated in that work) for 14 different cancer types based on six systematic reviews/meta-analyses on MSI published to 15 September 2018, the ESMO factsheet plus one additional study from a hand-search.[213] This study was performed as part of the collaborative project by the ESMO Translational Research and Precision Medicine Working Group, to generate consensus recommendations on the definitions of dMMR/MSI, methods of dMMR/MSI testing, and relationships between MSI, TMB and PD-1/PD-L1 expression. The estimated cancer-specific pooled overall prevalence for the 14 included cancer types was generally similar to our meta-analyses (see Supplementary Table S23).

Supplementary Table S23. Comparison of the prevalence of dMMR/MSI between a prior systematic review and the current analysis

Cancer type(s)	Luchini et al.[213]	Current analysis	
	Overall prevalence of dMMR/ MSI	Overall prevalence of dMMR (95% CI)	Overall prevalence of MSI (95% CI)
Colorectal cancer	17%	11.7% (9.3-14.4%)	10.2% (6.6-14.5%)
Endometrial cancer	20%	26.8% (23.3-30.5%)	21.9% (15.1-29.6%)
Gastric-esophageal cancer	13%	Gastric: 8.7% (7.6-9.9%) Esophageal: 3.8% (1.1-7.8%)	Gastric: 8.5% (6.4-10.9%) Esophageal: 2.4% (1.1-4.2%)
Small bowel cancer	8.3%	21.0% (15.8-26.7%)	14.3% (5.4-26.3%)
Ovarian cancer	3.5%-10%	2.4% (0.5-5.5%)	1.7% (0.0-5.4%)
Glioblastoma	6%-13%	5.1% (3.0-7.7%)	0.6% (0.2-1.3%)
Cancer of unknown primary	1.8%	2.3% (1.3-3.6%)	2.2% (1.0-3.8%)
Cervical cancer	4%	1.9% (0.0-5.8%)	1.5% (0.7-2.6%)
Extrahepatic bile duct cancer	3.4%	3.8% (1.5-7.0%)	1.6% (1.0-2.3%)
Pancreatic cancer	1%-7%	1.5% (0.6-2.7%)	0.9% (0.4-1.5%)
Non-small-cell lung cancer	<1%	1.2% (0.8-1.6%)	0.5% (0.2-0.9%)
Head and neck cancer	<1%	2.2% (0.1-6.1%)	0.5% (0.3-0.7%)
Sarcomas	2%	0.5% (0.0-2.1%)	1.8% (0.0-6.0%)

dMMR = mismatch repair deficiency; MSI = microsatellite instability; CI = confidence interval.

7. Studies reporting the overlap between high TMB and dMMR/MSI status in individual tumours

Of the 85 studies reporting the prevalence of both high TMB and at least one of dMMR/MSI, we identified 17 studies reporting the overlap between high TMB (at different cut-offs) and dMMR/MSI status in individual tumours, including five studies reporting the overall overlap across all cancers and eight studies for gastrointestinal cancers (see Supplementary Table S24). In particular, Vanderwalde et al. reported the prevalence of MSI, high TMB (≥17 mutations/Mb) and PD-L1 in 11,348 cancer cases and the overlap between these pan-tumour biomarkers across all cancers and by 30+ different cancer types, with overlap depending on cancer types and generally high in gastrointestinal cancers (see Supplementary Table S25).[214] We did not identify any large-scale study reporting the overlap in individual tumours in 10+ cancer types based on high TMB cut-offs of ≥10 mutations/Mb or ≥20 mutations/Mb. We also did not identify any large-scale original study reporting the estimated overlap of all three pan-tumour biomarkers (dMMR, MSI, high TMB) in the same tumours, making this a key area for future research.

Supplementary Table S24. Studies reporting the concordance between high TMB and dMMR/MSI status in individual tumours

Author (year)	Cancer type	Overlap between high TMB and dMMR/MSI status
High TMB (≥8 mutations/Mb)		
Lee (2019)[215]	Colorectal cancer	• Of 66 tumours with high TMB and MSI, 42.4% exhibited both markers, while 40.9% exhibited high TMB only and 16.7% MSI only
High TMB (≥10 mutations/Mb)		
Marabelle (2020)[182]	Pan-cancer (advanced incurable solid tumours)	• Phase 2 KEYNOTE-158 cohort • Of 95 tumours with high TMB and/or MSI, 14.7% exhibited both markers, while 85.3% exhibited high TMB only and 0% MSI only
Huang (2020)[184]	Pan-cancer	• Of 48782 tumours, 34.2% was NSCLC (where high TMB without exhibiting dMMR/MSI is common) • Of 10291 tumours with high TMB and/or MSI, 8.8% exhibited both markers, while 91.0% exhibited TMB only and 0.2% MSI only
Echejoh (2020)[216]	Colon cancer	• Of 16 tumours with high TMB, 81.3% exhibited both MSI and dMMR
Wirta (2020)[159]	Small bowel cancer	• Of 94 tumours with high TMB and/or MSI, 77.8% exhibited both markers, while 22.2% exhibited high TMB only and 0.0% MSI only
Jones (2020)[171]	Endometrial cancer	• Of 253 tumours with high TMB and/or MSI, 67.6% exhibited both markers, while 26.9% exhibited high TMB only and 5.5% MSI only
Abida (2019)[166]	Prostate cancer	• Of 47 tumours with high TMB and/or MSI, 48.9% exhibited both markers, while 51.1% exhibited high TMB only and 0.0% MSI only
High TMB (≥10.5 mutations/Mb)		
Cho (2019)[217]	Gastric cancer	• Of 330 tumours with high TMB and/or MSI, 51.4% exhibited both markers, while 48.6% exhibited high TMB only and 0.0% MSI only
High TMB (≥12 mutations/Mb)		
Fabrizio (2018)[218]	Colorectal cancer	• Of 466 tumours with high TMB and/or MSI, 64.6% exhibited both markers, while 35.2% exhibited high TMB only and 0.2% MSI only
High TMB (≥17 mutations/Mb)		
Vanderwalde (2018)[214]	• Pan-cancer • Cancer-specific	• Relationship between MSI, high TMB (≥17 mut/Mb) and PD-L1 was presented across all cancers and by cancer type (see

<table>
<tr><th>Author (year)</th><th>Cancer type</th><th>Overlap between high TMB and dMMR/MSI status</th></tr>
<tr><td></td><td></td><td>Supplementary Table S25 for individual-level overlap between high TMB (≥17 mutations/Mb) and MSI tumour status)</td></tr>
<tr><td>Nikanjam (2020)[109]</td><td>Pan-cancer</td><td>• Overlap between MSI, high TMB (≥17 mut/Mb) and PD-L1 across all cancers
• Of 2603 tumours with high TMB and/or MSI, 25.4% exhibited both markers, while 64.5% exhibited high TMB only and 10.1% MSI only</td></tr>
<tr><td>Salem (2018)[219]</td><td>Gastrointestinal cancers (across 14 cancer types)</td><td>• Of 209 tumours with high TMB and/or MSI, 64.1% exhibited both markers, while 27.3% exhibited high TMB only and 8.6% MSI only</td></tr>
<tr><td>Weinberg (2018)[220]</td><td>Gastrointestinal cancers</td><td>• Of 47 tumours with high TMB and/or MSI, 70.2% exhibited both markers, while 14.9% exhibited high TMB only and 14.9% MSI only</td></tr>
<tr><td colspan="3">High TMB (≥20 mutations/Mb)</td></tr>
<tr><td>Harthimmer (2019)[221]</td><td>Ampullary carcinoma</td><td>• Of the 4 samples with MSI, 100% exhibited high TMB (≥20 mut/Mb)</td></tr>
<tr><td>Singhi (2019)[200]</td><td>Pancreatic cancer</td><td>• Of 6 tumours with high TMB and/or MSI, 33.3% exhibited both markers, while 50.0% exhibited high TMB only and 16.7% MSI only</td></tr>
<tr><td>Chung (2019)[187]</td><td>Prostate cancer</td><td>• Of 11 tumours with high TMB, 71.2% exhibited MSI</td></tr>
<tr><td colspan="3">High TMB (≥17 mutations/Mb or ≥20 mutations/Mb)</td></tr>
<tr><td>Luchini (2019)[213]</td><td>Multiple cancer types</td><td>• Systematic review of the association between MSI, TMB and PD-L1, including Vanderwalde et al.[214], Salem et al.[219] and Weinberg et al.[220]
<table>
<tr><th></th><th>Of all cases exhibiting any of MSI, high TMB, and/or PD-L1 expression</th><th colspan="3">Of all cases exhibiting both MSI and/or high TMB</th></tr>
<tr><th>Cancer</th><th>MSI and/or high TMB</th><th>Both MSI and high TMB</th><th>MSI only</th><th>high TMB only</th></tr>
<tr><td>All cancers</td><td>21.8%</td><td>45.9%</td><td>11.9%</td><td>42.2%</td></tr>
<tr><td>CRC</td><td>54.6%</td><td>81.0%</td><td>3.1%</td><td>15.9%</td></tr>
<tr><td>EC</td><td>63.4%</td><td>60.9%</td><td>31.4%</td><td>7.7%</td></tr>
<tr><td>EGA</td><td>36.5%</td><td>75.9%</td><td>14.0%</td><td>10.1%</td></tr>
<tr><td>Melanoma</td><td>29.1%</td><td>0.0%</td><td>0.0%</td><td>100.0%</td></tr>
<tr><td>NSCLC</td><td>11.5%</td><td>9.6%</td><td>0.0%</td><td>90.4%</td></tr>
</table></td></tr>
</table>

dMMR = mismatch repair deficiency; MSI = microsatellite instability; MSS = microsatellite stables; TMB = tumour mutational burden; EC = endometrial cancer; EGA = esophagogastric adenocarcinoma; NSCLC = non-small cell lung cancer.

Supplementary Table S25. Individual-level overlap between high TMB (≥17 mutations/Mb) and MSI tumour status as reported in Vanderwalde et al. (Cancer Medicine 2018)

Tumour group	Cancer type	Overlap % (n/N)[a]
All cancer types	All cancer types	24.5% (240/979)
Biliary tract cancers	Cholangiocarcinoma	42.9% (3/7)
	Extrahepatic bile duct adenocarcinoma	100.0% (1/1)
Breast and gynaecological cancers	Breast carcinoma	12.1% (4/33)
	Cervical cancer	11.8% (2/17)
	Endometrial carcinoma	50.6% (89/176)
	Nonepithelial ovarian cancer	0.0% (0/1)
	Ovarian surface epithelial carcinomas	46.4% (13/28)
	Other female genital tract malignancies	25.0% (1/4)
Central nervous system tumours	Glioblastoma	20.0% (3/15)
	Low-grade glioma	0.0% (0/1)
Endocrine tumours	Thyroid carcinoma	100.0% (1/1)
Gastrointestinal cancers	Colorectal adenocarcinoma	78.4% (76/97)
	Esophageal and esophagogastric junction carcinoma	0.0% (0/1)
	Gastric adenocarcinoma	88.2% (15/17)
	Liver hepatocellular carcinoma	50.0% (1/2)
	Pancreatic adenocarcinoma	50.0% (4/8)
	Small intestinal malignancies	71.4% (5/7)
Genitourinary tract cancers	Bladder cancer	0.0% (0/24)
	Kidney cancer	0.0% (0/2)
	Prostatic adenocarcinoma	80.0% (4/5)
Head and neck cancers	Head and neck squamous carcinoma	0.0% (0/6)
Neuroendocrine tumours	Neuroendocrine tumours	27.3% (3/11)
Sarcomas	Soft tissue tumours	0.0% (0/12)
	Uterine sarcoma	20.0% (1/5)
Skin cancers	Melanoma	0.0% (0/126)
	Merkel cell carcinoma	0.0% (0/2)
	Uveal melanoma	100.0% (1/1)
Thoracic cancers	Non-small cell lung cancer	3.4% (9/267)
	Small cell lung cancer	0.0% (0/5)
	Thymic carcinoma	0.0% (0/1)

MSI = microsatellite instability; TMB = tumour mutational burden.

[a] Source: Cancer Medicine 2018. Vanderwalde et al.[214] Overlap was calculated by dividing the number of cases with both MSI and high TMB (≥17 mutations/Mb) by the total number of cases with MSI only, high TMB (≥17 mutations/Mb) only and both MSI and high TMB (≥17 mutations/Mb).

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