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# **BMJ Open**

#### Accuracy of Algorithms to Identify Patients With a Diagnosis of Major Cancers and Cancer Related Adverse Events Using Japanese Health Administrative Data

| Journal:                      | BMJ Open  |
|-------------------------------|---|
| Journal.                      |   |
| Manuscript ID                 | bmjopen-2021-055459   |
| Article Type:                 | Original research   |
| Date Submitted by the Author: | 15-Jul-2021   |
| Complete List of Authors:     | Fujiwara, Takashi; Kurashiki Central Hospital, Department of<br>Management, Clinical Research Center; Kurashiki Central Hospital,<br>Department of Otolaryngology/Head and Neck Surgery<br>Kanemitsu, Takashi; Chugai Pharmaceutical Co Ltd, Medical Affairs<br>Division<br>Tajima, Kosei ; Chugai Pharmaceutical Co Ltd, Clinical Development<br>Division<br>Yuri, Akinori; Chugai Pharmaceutical Co Ltd, Drug Safety Division<br>Iwasaku, Masahiro; Kurashiki Central Hospital, Department of<br>Management, Clinical Research Center<br>Okumura, Yasuyuki; Real world Data Co., Ltd.<br>Tokumasu, Hironobu; Kurashiki Central Hospital, Department of<br>Management, Clinical Research Center; Real World Data Co., Ltd. |
| Keywords:                     | Adult oncology < ONCOLOGY, Breast tumours < ONCOLOGY,<br>Gynaecological oncology < GYNAECOLOGY, Respiratory tract tumours <<br>ONCOLOGY, Urological tumours < ONCOLOGY  |
|                               |   |

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# Title page

# Title

Accuracy of Algorithms to Identify Patients With a Diagnosis of Major Cancers and

Cancer-Related Adverse Events Using Japanese Health Administrative Data

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#### **Word count: 3,871**

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#### Abstract

 **Objectives:** Validation studies in oncology are limited in Japan. This study was conducted to evaluate the accuracy of diagnosis and adverse event (AE) definitions for specific cancers in a Japanese health administrative real-world database (RWD).

**Design and setting:** Retrospective observational validation study to assess the diagnostic accuracy of electrical medical records (EMR) and claim coding regarding oncology diagnosis and AEs based on medical record review in the RWD.

**Participants:** The validation cohort included patients with lung (n=2,257), breast (n=1,121), colorectal (n=1,773), ovarian (n=216), and bladder (n=575) cancer who visited the hospital between January 2014 and December 2018, and those with prostate cancer (n=3,491) visiting between January 2009 and December 2018, who were identified using EMRs.

Outcomes: Key outcomes included primary diagnosis, deaths, and AEs.

**Results:** Data on International Classification of Diseases, 10th revision (ICD-10)–definitive diagnosis and death could be extracted with high accuracy. The positive predictive value (PPV; 95% confidence interval [CI]) for primary diagnosis was high (lung, 81.0 [74.9–86.2]; breast, 74.0 [67.3–79.9]; colorectal, 80.5 [74.3–85.8]; ovarian, 49.5 [39.3–59.7]; bladder, 42.0 [32.2–52.3]; prostate, 79.0 [69.7–86.5]). Sensitivity (95% CI) for death was high (lung, 97.0 [84.2–99.9]; breast, 100.0 [1.3–100.0]; colorectal, 100.0 [28.4–100.0]; ovarian, 100.0 [35.9–100.0]; bladder, 100.0 [9.4–100.0]; prostate, 75.0 [19.4–99.4]). Overall, PPV tended to be low, with the definition based on ICD-10 alone for AEs.

**Conclusion:** EMR data were deemed appropriate to comprehensively identify patients with specific cancers or deceased patients using RWD in Japan.

**Trial registration:** University hospital Medical Information Network (UMIN) Clinical Trials Registry; UMIN000039345

### Strengths and limitations of this study

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To our knowledge, this is the first study in oncology in Japan that validates disease • names and adverse event definitions in a health administrative real-world database (RWD) using chart review based on electronic medical records data from a hospital as the reference standard. Validation was performed at a single facility; therefore, there is a possibility of selection bias. Study results are limited by the inherent issues related to the use of an RWD, which • primarily stores medical information for the purpose of insurance claims. The diagnosis and adverse event definitions used in this study may not be the most • suitable; thus, there is an opportunity to further deepen these definitions. Study methods for the consolidation of true positives for events with low incidence • need to be further investigated as it was challenging to investigate outcomes with 21/2 extremely low incidence. **Keywords** database, electronic medical record, health administrative, real-world database, validation study 

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#### INTRODUCTION

In recent years, evidence from routine clinical practice using data from real-world databases (RWDs) has increasingly gained importance in decision-making in healthcare, research, and drug development.[1] In addition, RWD studies can help generate evidence for advancement in precision medicine and facilitation of targeted and efficient patient care.[2] In line with this trend, evidence related to several aspects, such as health technology, expenditure forecasting, survival outcomes, time to therapy, and treatment efficacy, are increasingly being collected from RWD studies in oncology.[3-6]

However, it is important to validate case-identification algorithms to evaluate the accuracy of information sourced from RWDs, which is usually collected for purposes other than research.[7] To this end, several studies have been conducted outside of Japan to evaluate the accuracy of algorithms based on health administrative data in identifying cancer diagnoses or other outcomes using databases, such as registries, population-based cohorts, chart reviews, and electronic medical records (EMRs) as reference standards.[8-17]

The implementation of the revised ordinance of Good Postmarketing Study Practice by the Pharmaceuticals and Medical Devices Agency (PMDA) in 2018 suggests that the importance of using RWDs in post-marketing surveillance to investigate the safety and efficacy of pharmaceutical products is being recognized in Japan as well.[18] To encourage validation studies, the PMDA of Japan and Japan Society for Pharmacoepidemiology established a basic concept for conducting validation studies to verify diagnosis codes and other outcome definitions in Japanese RWDs.[19, 20] However, among the validation studies conducted to date,[21-31] to our knowledge, only one claims-based study reported on outcomes in cancer, more specifically breast cancer; a cancer registry was used as the reference standard in this study.[32] Thus, there is a need to perform validation studies on a wider range of cancer types in Japan using a reliable database as a reference standard. This

 study was conducted for validation of diagnosis and adverse event (AE) definitions for specific cancers in a Japanese RWD using a chart review by EMR.

#### **PATIENTS AND METHODS**

#### Study design

This was a validation study of diagnosis and AE definitions in the health administrative RWD of the Health, Clinic, and Education Information Evaluation Institute (HCEI) conducted by chart review from Kurashiki Central Hospital, Japan, as the reference standard.

#### **Data collection**

Data were collected retrospectively from EMRs at the Kurashiki Central Hospital, Japan (Figure 1), which were the primary data source. All possible cases that met the diagnosis and AE definitions and cases other than all possible cases were identified using International Classification of Diseases, 10th revision (ICD-10) codes (Figures S1–S6) from the EMRs. Further, these cohorts were randomly sampled to verify the diagnoses and related events. EMRs were manually reviewed to verify the diagnosis of all possible cases. This verified data set was anonymized and sent to Real World Data Co. Ltd., the vendor for HCEI. The verified data set was linked deterministically to claims data and EMRs originally derived from the hospital.

#### Chart review based on EMR

A chart review for all possible cases was conducted by medical professionals, including medical doctors involved in the management of cancer patients and four clinical research coordinators (CRCs) at the Kurashiki Central Hospital, Japan. At least two CRCs conducted chart reviews independently. Any disagreements were resolved by discussion between the two CRCs or by a medical doctor if the disagreement was not resolved following a discussion.

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#### HCEI database

HCEI is an integrated RWD initiated in Japan and supported by Real World Data Co., Ltd. (Kyoto).[33] As of August 2020, HCEI was collecting information from approximately 20 million patients from 190 medical institutions in Japan, including Kurashiki Central Hospital. The HCEI database covers 1.2% of the overall Japanese population and includes data from 1.3 million outpatients and 0.21 million inpatients in 2019.[33] Medical information is extracted from EMRs, claims, and Diagnosis Procedure Combination (DPC) in the HCEI database. Patient-level data from DPC, EMRs, and claims are integrated in advance at the hospital, anonymized, linked to a unique code, and standardized (**Figure 1**). The linked data are then provided to HCEI for storage on their server. Information on procedures (such as surgery) is obtained from claims, while information on laboratory tests and treatments is obtained from EMRs. Diagnosis data are obtained from both claims and EMRs. According to HCEI's security policy, personal identifiable information (such as date of birth) is not collected during data extraction. Master lists are constructed based on the national standards of the Ministry of Health, Labour and Welfare (MHLW) of Japan.[34]

#### **Ethics Approval**

This study was approved by the Research Institute of Healthcare Data Science (https://rihds.org/ethic/) (RI2019010) and the institutional ethics committee of Kurashiki Central Hospita (KCH3301) l, and conducted under the tenets of the Declaration of Helsinki, Act on the Protection of Personal Information,[35] and Ethical Guidelines for Medical and Health Research Involving Human Subjects.[36] It was conducted under a joint research agreement between Kurashiki Central Hospital, Chugai Pharmaceutical Co., Ltd., and HCEI, and is registered at the UMIN Clinical Trials Registry (UMIN000039345). Target patients at

Kurashiki Central Hospital had the option, on the hospital's website, to refuse disclosure of their information.

#### Patient and public involvement in research

Patients or the public were not involved in the design or conduct, reporting or dissemination plans of our research.

#### **Patient selection**

Patients with lung, breast, colorectal, ovarian, and bladder cancer who visited Kurashiki Central Hospital between January 2014 and December 2018 (**Figures S1–S5**), and those with prostate cancer (**Figure S6**) who visited the hospital between January 2009 and December 2018 were eligible for inclusion in the study. Patients participating in clinical trials during the data extraction periods and those who were assigned the respective ICD-10 code for lung, colorectal, breast, ovarian, and bladder cancer from January 1, 2014, to January 31, 2014, and from November 1, 2018, to December 31, 2018, and that for prostate cancer from January 1, 2009, to January 31, 2009, and from November 1, 2018, to December 31, 2018, were excluded from the study. Patients diagnosed during these periods were excluded to avoid bias due to the time lag between suspected diagnosis by medical examination and confirmation of diagnosis by biopsy, when the outcome definition was potentially met.

The cohort entry date was the date when the respective cancer was diagnosed— January 2014 for lung, breast, colorectal, ovarian, and bladder cancer and January 2009 for prostate cancer—and the end date was December 31, 2018. To avoid selection of cases diagnosed before the cohort entry date, patients who were assigned the respective ICD-10 code for lung, colorectal, breast, ovarian, and bladder cancer before December 31, 2013, and that for prostate cancer before December 31, 2008, were excluded.

Eligible patients were stratified by random sampling as all possible and not possible

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cases. All possible cases included patients who met the ICD-10 code for the respective support during the specified data extraction period. Patients who were never assigned an ICD-10 code for the respective cancer; those with lung, colorectal, breast, ovarian, and bladder cancer who visited the hospital between January 1, 2014, and December 31, 2018; and those with prostate cancer between January 1, 2009, and December 31, 2018, were stratified as not possible cases. Overall, 200 cases each with lung, breast, or colorectal cancer and 100 cases each with ovarian, bladder, or prostate cancer were targeted and randomly selected from all possible cases for the EMR review, and not possible cases were also randomly selected using the same proportions.

#### Outcomes and assessment of accuracy

 Outcomes for validation included primary diagnosis, performance status (PS)  $\geq 2$ ,[37] first/second/third recurrence or exacerbation, death, and AEs, particularly immune-related AEs (irAEs), associated with new diagnoses for patients with lung, breast, colorectal, ovarian, bladder, and prostate cancer. AEs included interstitial pneumonia, liver dysfunction, colitis/diarrhea, type 1 diabetes mellitus (T1DM), encephalitis/meningitis, nerve disorders (excluding paresthesia), myasthenia gravis, Guillain-Barré syndrome, skin disorder, rhabdomyolysis, myocarditis, perforation of digestive tract/fistula, hypoadrenocorticism, and febrile neutropenia.

Outcomes were defined by separate algorithms (**Tables S1 and S2**) for each cancer type using one variable or a combination of two or more variables, such as diagnoses, treatments, procedures, and laboratory test results. Lung cancer was further classified as primary, non-small cell, and small cell.

#### Statistical analysis

The target sample size for random sampling was determined based on the feasibility of the

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chart review, assuming that the 95% confidence interval (CI) for positive predictive value (PPV) and sensitivity can be estimated with an accuracy of maximum  $\pm 10\%$  if  $\geq 100$  patients met the definition of primary diagnosis and  $\geq 100$  were true positives.[38]

In the data set submitted by HCEI, accuracy for each cancer type was evaluated using sensitivity, specificity, PPV, and negative predictive value (NPV) for primary diagnosis, first recurrence/exacerbation, and death. Other outcomes were evaluated using only PPV to determine if the cases were true for those meeting the outcome definition. AEs were validated in patients with true primary cancer who had received chemotherapy. PPV was calculated only after confirming whether the outcome occurred within (before or after) 30 days of the patient meeting the outcome definition.

All possible cases refer to the population that is assumed to include all true patients,[19, 39-41] and included patients who met the ICD-10 code for the respective cancer in the EMRs during the specified data extraction period. True positives were defined as patients in whom the outcomes occurred based on HCEI information and EMR review. In addition, patients were randomly selected from cases other than all possible cases at the same extraction rate as that for "all possible cases" to calculate the specificity and NPV for primary diagnosis, first recurrence/exacerbation, and death. The data extraction period for different cancer types was estimated based on the national survival rate survey of 2019 conducted by the National Cancer Center Council,[42] in which the survival period was 10 years for prostate cancer and 5 years for other cancer types. Likewise, a longer data extraction period was considered for prostate cancer to allow for the collection of true positives.

The frequency and 95% CIs were calculated for sensitivity, specificity, PPV, and NPV. The degree of agreement between two chart reviewers was evaluated using the kappa coefficient. Extrapolability of the Kurashiki Central Hospital database to that of other hospitals in HCEI database was assessed by comparing the distribution of patient characteristics. Matching was performed through deterministic linkage and statistical analyses were conducted using R-4.0.2 software.

#### RESULTS

#### **Patient disposition**

Of the 256,418 patients who received medical treatment from 2014 to 2018, 2,257 with lung cancer (Figure S1), 1,121 with breast cancer (Figure S2), 1,773 with colorectal cancer (Figure S3), 216 with ovarian cancer (Figure S4), and 575 with bladder cancer (Figure S5) were included as all possible cases (Table 1). From 2009 to 2018, 3,491 patients with prostate cancer of 413,631 patients receiving medical treatment (Figure S6) were included as 0.05 all possible cases (Table 1).

| Table | 1. | Study | cohort |
|-------|----|-------|--------|
|-------|----|-------|--------|

| Cancer type       | Patients who                        | Target      | All possible cases, | True cases, n |
|-------------------|-------------------------------------|-------------|---------------------|---------------|
|                   | underwent medical<br>treatment from | patients, n | n                   |               |
|                   | January 2014 to                     |             |                     |               |
|                   | December 2018,* n                   |             |                     |               |
| Lung cancer       | 256,418                             | 252,847     | 2,257               | 162           |
| Breast cancer     | 256,418                             | 253,358     | 1,121               | 148           |
| Colorectal cancer | 256,418                             | 252,733     | 1,773               | 161           |
| Ovarian cancer    | 256,418                             | 254,995     | 216                 | 49            |
| Bladder cancer    | 256,418                             | 254,520     | 575                 | 42            |
| Prostate cancer   | 413,631                             | 410,356     | 3,491               | 79            |

\*Period: January 2009 to December 2018 for prostate cancer

#### 

#### Lung cancer

The kappa value in chart reviews for diagnosis definitions was 0.982 (95% CI:

0.947–1.017) for primary lung cancer, 0.979 (95% CI: 0.950–1.008) for non-small cell lung cancer (NSCLC), 1.00 for small cell lung cancer (SCLC), and 0.982 (95% CI: 0.947–1.017) for death. There were 30 false negatives and 132 true positives for A1 using DPC diagnosis (**Table 2**). Sensitivity was 100% with A2 using related definitive diagnosis (**Table 2**). Although specificity, PPV, and NPV for NSCLC were high for B1 and B2 using cancer-related diagnosis codes, sensitivity was low (38.3%; **Table S3**). Accuracy was high for all statistical parameters for SCLC (**Table 2**). Data on death could be extracted with high accuracy using EMR definitions (E1; **Table 3**).

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|------|----|----|----|
|------|----|----|----|

|                     |               |               |                            |            |              | 6/bmjopen-2021-055459<br>Specificity     |              |              |
|---------------------|---------------|---------------|----------------------------|------------|--------------|--|--------------|--------------|
| <b>Fable 2.</b> Dia | gnosis defin  | itions with l | high* accura               | acy        |              | 05548                                    |              |              |
| Outcome             | True          | False         | True                       | False      | Sensitivity, | Specificit                               | PPV,         | NPV          |
| definition          | positives,    | positives,    | negatives,                 | negatives, | % (95% CI)   | % (95% <b>Ct</b> )                       | % (95% CI)   | % (95% CI)   |
|                     | n             | n             | n                          | n          |              | uly 2022                                 |              |              |
| Lung cancer         | r             |               |                            |            |              |  |              |              |
| Primary lung        | , cancer      |               | $\boldsymbol{\mathcal{R}}$ |            |              | Dow                                      |              |              |
| A1                  | 132           | 7             | 22,237                     | 30         | 81.5         | 100.0                                    | 95.0         | 99.9         |
|                     |               |               |                            |            | (74.6–87.1)  | (99.9–100.                               | (89.9–98.0)  | (99.8–99.9)  |
| A2                  | 162           | 38            | 22,206                     | 0          | 100.0        | 99.8                                     | 81.0         | 100.0        |
|                     |               |               |                            |            | (96.6–100.0) | (99.8–99.9                               | (74.9–86.2)  | (100.0–100.0 |
| A4                  | 128           | 7             | 22,237                     | 34         | 79.0         | 100.0                                    | 94.8         | 99.8         |
|                     |               |               |                            |            | (71.8–85.0)  | (99.9–100                                | (89.6–97.9)  | (99.8–99.9)  |
| Small cell lu       | ng cancer     |               |                            |            | Via          |  |              |              |
| C1                  | 10            | 0             | 22,395                     | 1          | 90.9         | 100.0                                    | 100.0        | 100.0        |
|                     |               |               |                            |            | (58.7–99.8)  | (100.0- <sup>9</sup>                     | (58.7–100.0) | (100.0–100.0 |
|                     |               |               |                            |            |              | (100.0– <sup>9</sup> April<br>100.0) 111 |              |              |
| Breast cance        | er            |               |                            |            |              | , <b>"</b>                               |              |              |
| Primary brea        | st cancer     |               |                            |            |              | 2024 by                                  |              |              |
| α2                  | 148           | 52            | 45,002                     | 0          | 100.0        | 99.9 g                                   | 74.0         | 100.0        |
|                     |               |               |                            |            | (96.3–100.0) | (99.8–99.9)                              | (67.3–79.9)  | (100.0–100.0 |
| Colorectal c        | ancer         |               |                            |            |              | Protec                                   |              |              |
| Primary colo        | rectal cancer |               |                            |            |              | 99.9<br>99.9                             |              |              |
| β2                  | 161           | 39            | 28,309                     | 0          | 100.0        | 99.9 g                                   | 80.5         | 100.0        |

|              |                  |                     |                 |                     | BMJ Open                    | 6/bmjc                         |             |               |
|--------------|------------------|---------------------|-----------------|---------------------|-----------------------------|--------------------------------|-------------|---------------|
|              |                  |                     |                 |                     |                             | 6/bmjopen-2021                 |             | Page 14 of    |
| Outcome      | True             | False               | True            | False               | Sensitivity,                | <br>Specificity                |             | NPV           |
| definition   | positives,       | positives,          | negatives,      | negatives,          | % (95% CI)                  | % (95% C                       | % (95% CI)  | % (95% CI)    |
|              | n                | n                   | n               | n                   |                             | 13                             |             |               |
|              |                  |                     |                 |                     | (96.6–100.0)                | (99.8–99.9                     | (74.3-85.8) | (100.0–100.0) |
| Ovarian ca   | ancer            |                     |                 |                     |                             | 2022.                          |             |               |
| Primary ov   | arian cancer     |                     |                 |                     |                             | Dow                            |             |               |
| γ1           | 44               | 14                  | 11,692          | 5                   | 89.8                        | 99.9 load                      | 75.9        | 100.0         |
|              |                  |                     |                 | 6                   | (77.8–96.6)                 | (99.8–99. <b>9</b>             | (62.8–86.1) | (99.7–100.0)  |
| Bladder ca   | ancer            |                     |                 | NO                  |                             | h mo                           |             |               |
| Primary bla  | adder cancer     |                     |                 | 91                  | r                           | ttp://t                        |             |               |
| ε1           | 33               | 16                  | 44,206          | 9                   | 78.6                        | 100.0                          | 67.3        | 100.0         |
|              |                  |                     |                 |                     | (63.2–89.7)                 | (99.9–100.0)                   | (52.5-80.1) | (100.0–100.0) |
| Prostate ca  | ancer            |                     |                 |                     | 10.                         | <u>, m</u> i.<br>              |             |               |
|              | ostate cancer    |                     |                 |                     | C/                          | /m/ o                          |             |               |
| δ2           | 79               | 21                  | 11,655          | 0                   | 100.0                       | 99.8 April 1<br>(99.7–99.9) 11 | 79.0        | 100.0         |
|              |                  |                     |                 |                     | (93.2–100.0)                | (99.7–99.9) <u>=</u>           | (69.7–86.5) | (100.0–100.0) |
|              |                  |                     |                 | e; PPV, positive p  |                             | , 202                          |             |               |
| *All accurac | y values include | ed for a definition | ition are appro | oximately 70% or    | more.                       | 2024 by gues                   |             |               |
|              |                  |                     |                 |                     |                             | gues                           |             |               |
|              |                  |                     |                 |                     |                             |                                |             |               |
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| Sahle 3 Deat          | n definitions wi   | ith high* accu      | Iracy              |                     |                            |              | 6/bmjopen-2021-05545          | Page 15 c          |
|-----------------------|--------------------|---------------------|--------------------|---------------------|----------------------------|--------------|-------------------------------|--------------------|
| Outcome<br>definition | True<br>positives, | False<br>positives, | True<br>negatives, | False<br>negatives, | Sensitivity,<br>% (95% CI) |              |                               | NPV,<br>% (95% CI) |
|                       | n                  | n                   | n                  | n                   |                            |              | ず。(95% CI)<br>July 2022.      |                    |
| Lung cancer           |                    |                     | ,                  |                     |                            |              | 22. D                         |                    |
| E1                    | 32                 | 0                   | 40                 | 1                   | 97.0                       | 100.0        | <u>8</u> 00.0                 | 97.6               |
|                       |                    |                     |                    |                     | (84.2–99.9)                | (87.1–100.0) | 84.2-100.0)                   | (87.1–99.9)        |
| E4                    | 32                 | 0                   | 40                 | 1                   | 97.0                       | 100.0        | a<br>a<br>a<br>a<br>a<br>00.0 | 97.6               |
|                       |                    |                     |                    |                     | (84.2–99.9)                | (87.1–100.0) | ∃<br><u>₹</u> 84.2–100.0)     | (87.1–99.9)        |
| Breast cance          | r                  |                     |                    |                     | •                          |              | ,//bm                         |                    |
| E1                    | 1                  | 0                   | 104                | 0                   | 100.0                      | 100.0        | <u>a</u> 00.0                 | 100.0              |
|                       |                    |                     |                    |                     | (1.3–100.0)                | (94.8–100.0) | 1.3–100.0)                    | (94.8–100.0)       |
| E4                    | 1                  | 0                   | 104                | 0                   | 100.0                      | 100.0        | <u> </u>                      | 100.0              |
|                       |                    |                     |                    |                     | (1.3–100.0)                | (94.8–100.0) | °1.3−100.0)                   | (94.8–100.0)       |
| Colorectal ca         | ancer              |                     |                    |                     |                            | b.           | pril 19                       |                    |
| E1                    | 4                  | 0                   | 53                 | 0                   | 100.0                      | 100.0        | 800.0                         | 100.0              |
|                       |                    |                     |                    |                     | (28.4–100.0)               | (90.1–100.0) | \$00.0<br>\$28.4-100.0)       | (90.1–100.0)       |
| E4                    | 4                  | 0                   | 53                 | 0                   | 100.0                      | 100.0        | g<br>g<br>00.0                | 100.0              |
|                       |                    |                     |                    |                     | (28.4–100.0)               | (90.1–100.0) | <u>7</u> 28.4–100.0)          | (90.1–100.0)       |
| Ovarian can           | cer                |                     |                    |                     |                            |              | btected by copyright.         |                    |
| E1                    | 5                  | 0                   | 16                 | 0                   | 100.0                      | 100.0        | <u>–</u><br>म् <u>व</u> 00.0  | 100.0              |

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|-------------|------------|------------|------------|------------|--------------|--------------|----------------------|-------------|
|             |            |            |            |            |              |              | 6/bmjopen-2021-0     | Page 1      |
| Outcome     | True       | False      | True       | False      | Sensitivity, | Specificity, | PV,                  | NPV,        |
| definition  | positives, | positives, | negatives, | negatives, | % (95% CI)   | % (95% CI)   | چ» (95% CI)          | % (95% C    |
|             | n          | n          | n          | n          |              |              | 13 ปเ                |             |
|             |            |            |            |            | (35.9–100.0) | (71.3–100.0) | 35.9-100.0)          | (71.3–100.0 |
| E4          | 5          | 0          | 16         | 0          | 100.0        | 100.0        | 1900.0               | 100.0       |
|             |            |            |            |            | (35.9–100.0) | (71.3–100.0) | <u>§</u> 35.9-100.0) | (71.3–100.0 |
| Bladder ca  | incer      | (          | Jr.        |            |              |              | oaded                |             |
| E1          | 2          | 0          | 8          | 0          | 100.0        | 100.0        |                      | 100.0       |
|             |            |            |            |            | (9.4–100.0)  | (51.8–100.0) | <b>3</b> 9.4–100.0)  | (51.8–100.0 |
| E4          | 2          | 0          | 8          | 0          | 100.0        | 100.0        | <u>a</u> 00.0        | 100.0       |
|             |            |            |            |            | (9.4–100.0)  | (51.8–100.0) | §9.4–100.0)          | (51.8–100.0 |
| Prostate ca | ancer      |            |            |            | 1/0          |              | .bmj.c               |             |
| E1          | 3          | 0          | 32         | 1          | 75.0         | 100.0        | <b>1</b> 00.0        | 97.0        |
|             |            |            |            |            | (19.4–99.4)  | (94.2–100.0) | <u>3</u> 19.4–100.0) | (84.2–99.9) |
| E4          | 3          | 0          | 32         | 1          | 75.0         | 100.0        |                      | 97.0        |
|             |            |            |            |            | (19.4–99.4)  | (94.2–100.0) | ×19.4–100.0)         | (84.2–99.9) |

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#### **Breast cancer**

The kappa value in the chart review for diagnosis definitions was 1.000 and 0.961 (95% CI: 0.917-1.005) for death. The sensitivity was 100% for  $\alpha 2$  using EMR diagnosis (**Table 2**) Sensitivity was as low as 62.8% and there were 55 false negatives in  $\alpha 1$  using DPC diagnosis (Table S3). The accuracy of death definitions for breast cancer was challenging to calculate because outcome events were very few owing to good disease prognosis (Table S4).

#### Colorectal cancer

The kappa value in the chart review for both diagnosis definitions and death was 0.953 (95%) CI: 0.900–1.006). There were 39 false positives in  $\beta 2$  (**Table 2**); 15 were diagnosed with colorectal cancer before 2014, two had malignancies that were excluded, and the remaining patients were diagnosed with another cancer on subsequent examination of EMR. Death occurred in four of 57 target patients, and sensitivity and specificity of E1 were 100% each 2. (Table 3).

#### **Ovarian cancer**

The kappa value in the chart review for diagnosis definitions was 0.920 (95% CI: 0.843–0.997) and 0.940 (95% CI: 0.873–1.007) for death. PPV was higher with γ1 than with  $\gamma 2$  (75.9% vs 49.5%) (**Table S3**). Sensitivity was higher with  $\gamma 2$  than with  $\gamma 1$  (100.0% vs 89.8%) (Table S3). Death occurred in five of 21 target patients, and the sensitivity and specificity of E1 were 100% each (Table 3).

#### **Bladder cancer**

The kappa value in the chart review for diagnosis definitions was 0.898 (95% CI: 0.812-0.985) and 0.878 (95% CI: 0.784-0.973) for death. Sensitivity was 100% in £2, but PPV was as low as 42.0% (Table S3). PPV was higher with  $\varepsilon$ 1 than with  $\varepsilon$ 2 (67.3% vs 42.0%) (Table S3). Death occurred in two of 10 target patients, and the sensitivity and

specificity of E1 were 100% each (Table 3).

#### **Prostate cancer**

The kappa value in the chart review for diagnosis definitions was 0.875 (95% CI: 0.755–0.995) and 0.9045 (95% CI: 0.798–1.011) for death. PPV was 100% in  $\delta$ 1 (**Table S3**), and sensitivity was 100% in  $\delta$ 2 (**Table 2**). Death occurred in four of 36 target patients, and the sensitivity and specificity of E1 were 75% and 100%, respectively (**Table 3**).

#### Adverse events

The overall PPV for all cancer types was <50%: 47.1% for interstitial pneumonia, 34.6% for liver disorders, 25.5% for colitis/diarrhea, and 13.3% for nerve disorders (excluding paresthesia) by related ICD-10 definitive diagnosis. Although PPV was 100% for encephalitis/meningitis and gastrointestinal perforation by related ICD-10 definitive diagnosis, only one case each was identified as these are rare AEs. For skin disorders, PPV was 76.4% by related ICD-10 definitive diagnosis and 70.4% when treatments were combined in the definition. A combination of related ICD-10 definitive diagnosis and treatments resulted in a PPV of 87.5% for liver disorders. By ICD-10-related definitive diagnosis and intravenous antibiotics use, PPV ranged between 76.9% and 100% for febrile neutropenia. The PPV was 0% for T1DM.

No events of myasthenia gravis, Guillain-Barré syndrome, rhabdomyolysis, adrenal hypofunction, and myocarditis were identified in this analysis.

#### **Other outcomes**

Only 1 true positive case was extracted for  $PS \ge 2$  for lung cancer using the definition of rehabilitation status. Although the PPV was high, evaluation was difficult. Similarly, the accuracy of the definition of first recurrence/exacerbation was extremely low for all cancer

types owing to very few true positives. Since the accuracy of the second and third recurrence/exacerbation was calculated based on the number of true positives during first recurrence/exacerbation, it could not be evaluated.

#### Extrapolability of EMR data

Sex and age of all possible cases at the Kurashiki Central hospital and all hospitals were similar (Table

4).

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| Гаble 4. Demograph | ic and observation | n period of study | BMJ Open            |                      | 6/bmjopen-2021-055459 on 13 July             | Page <b>20</b> of . |
|--------------------|--------------------|-------------------|---------------------|----------------------|--|---------------------|
|                    | All possible       | Male, n (%)       | Age (years) at data | Age (years) at the   | <br>Observation period                       | Observation period  |
|                    | cases, n           |                   | extraction,         | time of granting     | (days)                                       | (days)              |
|                    |                    |                   | mean (SD)           | ICD-10,<br>mean (SD) | mean (SD)                                    | person-years        |
| Lung cancer        |                    |                   |                     |                      | oaded fro                                    |                     |
| Kurashiki Central  | 2,477              | 1,728 (69.8)      | 75.0 (9.9)          | 72.8 (10.2)          | 801 4 (626.7)                                | 1,985,024           |
| Hospital           |                    |                   |                     |                      | tp://b                                       |                     |
| All hospitals      | 19,861             | 13,136 (66.1)     | 74.8 (10.2)         | 73.5 (10.4)          | 523 (552.4)                                  | 10,405,993          |
| Breast cancer      |                    |                   | C                   |                      | en.br  |                     |
| Kurashiki Central  | 1,166              | 10 (0.9)          | 67.0 (13.3)         | 64.1 (13.3)          | 1,022.6 (650.8)                              | 1,192,400           |
| Hospital           |                    |                   |                     |                      | m/ or  |                     |
| All hospitals      | 18,289             | 131 (0.7)         | 64.7 (14.1)         | 62.6 (14.1)          | 780 (618.6)                                  | 14,274,791          |
| Colorectal cancer  |                    |                   |                     |                      | ii<br>19,                                    |                     |
| Kurashiki Central  | 1,684              | 989 (58.7)        | 73.6 (11.3)         | 71.1 (11.6)          | 930 (613.5)                                  | 1,566,924           |
| Hospital           |                    |                   |                     |                      | 4 by (                                       |                     |
| All hospitals      | 23,501             | 13,836 (58.9)     | 74.1 (11.3)         | 72.1 (11.5)          | 770 56 (596.2)                               | 18,110,552          |
| Ovarian cancer     |                    |                   |                     |                      | Prot   |                     |
| Kurashiki Central  | 265                | 34 (12.8)         | 66.4 (15.4)         | 63.9 (15.5)          | од<br>8962 (653.5)<br>еб<br>by<br>соругідht. | 237,497             |
|                    |                    |                   |                     |                      | d  |                     |

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| All hospitals<br>Bladder cancer<br>Kurashiki Central | All possible<br>cases, n<br>2,592 | Male, n (%)   | Age (years) at data<br>extraction, | Age (years) at the | 6/bmjopen-2021-0<br>Observation period                  | Page 21 of<br>Observation perio |
|--|-----------------------------------|---------------|------------------------------------|--------------------|---|---------------------------------|
| Bladder cancer                                       | cases, n                          | Male, n (%)   | extraction,                        |                    | Observation period                                      | Observation perio               |
| Bladder cancer                                       |                                   |               | -                                  | time of granting   | (5  |                                 |
| Bladder cancer                                       | 2,592                             |               |                                    | time of granting   | (days)  | (days)                          |
| Bladder cancer                                       | 2,592                             |               | mean (SD)                          | ICD-10,            | mean (SD)   | person-years                    |
| Bladder cancer                                       | 2,592                             |               |                                    | mean (SD)          | July 2  |                                 |
|  |                                   | 145 (5.6)     | 64.1 (14.9)                        | 62.3 (15.1)        | 667 <sup>8</sup> (581.1)                                | 1,729,551                       |
| Kurashiki Central                                    |                                   | 0             |                                    |                    | Dow   |                                 |
|  | 568                               | 446 (78.5)    | 77.6 (10.0)                        | 75.0 (10.5)        | 991 ਛੋੜੇ (611.8)  | 563,042                         |
| Hospital   |                                   |               |                                    |                    | aded  |                                 |
| All hospitals  | 7,408                             | 5,810 (78.4)  | 76.9 (10.4)                        | 74.9 (10.6)        | 7999 (595.8)  | 5,925,496                       |
| Prostate cancer                                      |                                   |               | NO <sub>2</sub>                    |                    | http:/  |                                 |
| Kurashiki Central                                    | 3,131                             | 3,057 (97.6)  | 76.5 (8.4)                         | 71.9 (8.7)         | 1,703   | 5,332,446                       |
| Hospital   |                                   |               |                                    |                    | open  |                                 |
| All hospitals  | 32,136                            | 28,690 (89.3) | 77.7 (8.9)                         | 74.2 (9.2)         | 1,34133 (1,041.6)                                       | 43,105,126                      |
|  |                                   |               |                                    |                    | om/ on April 19, 2024 by guest. Protected by copyright. |                                 |

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#### DISCUSSION

To our knowledge, this is the first study in oncology in Japan that validates disease names and AE definitions in an RWD, using chart review based on EMR as the gold standard. The accuracy of diagnosis definitions by the ICD-10 code in EMRs was high, with a high sensitivity; therefore, diagnosis definitions by ICD-10 may be generalizable. It was expected that both PPV and NPV would increase by using diagnosis definitions with exact matches, but PPV remained stable and sensitivity decreased. Therefore, definitions including related diagnoses were deemed more appropriate. The PPV of diagnosis definition by DPC was relatively high, but sensitivity tended to be low. Although the diagnosis definition using DPC showed false negatives, it can be used for identifying patients with the respective disease. In the definitions using a definitive diagnosis from claims, PPV tended to decrease, but sensitivity tended to increase. This suggests that it is important to select the outcome definition for use according to the purpose of the study.

Lung cancer, SCLC, and NSCLC could be classified with high accuracy using diagnosis codes. However, there were very few true positives with SCLC. Since the database is used primarily for insurance purposes, precise documentation of a histological classification of lung cancer in EMR was likely not deemed important to be recorded by physicians; therefore, the numbers were low. PPV was high, but sensitivity was low for diagnostic codes for NSCLC; therefore, further studies are required to understand how false negatives can be extracted.

The sensitivity for the EMR definition of breast cancer was 100% and DPC definition was as low as 62.8%. However, specificity was high with both EMR and DPC, and PPV ranged between 74.0% and 83.8%. In a previous study,[32] high sensitivity, specificity, and PPV were observed using definitions obtained by combining diagnostic and procedure codes in a Japanese claims database, suggesting that a combination of codes may result in higher

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accuracy.

The accuracy of the evaluation for death was high using the EMR definition for lung cancer. Although sensitivity was high using the EMR definition for other cancers too, further studies are needed in a greater number of cases for confirmation. In cancer types other than lung cancer, which generally have a short prognosis, high sensitivity and PPV were observed for some definitions. However, there were many true negatives because survival was longer than expected and deaths were few, which made evaluation challenging. This could be due to the longer survival of cancer patients at Kurashiki Central Hospital compared with that observed in the national cancer survival rate survey,[42] which was used as a basis for determining the extraction period. Since the survival was long for the hospital database used in this study and fatal events occurred rarely, further investigation is necessary.

Identification of cases with "recurrence/exacerbation" was extremely difficult in all cancer types by definition using items such as diagnoses with "recurrent" as a modifier, pathology-related medical practice code, or relevant surgical history. A previous validation study in breast cancer suggested that the quality of recurrence data may improve by the use of multiple recurrence algorithms in health administrative databases along with selective analysis of medical record data.[17] Another validation study that evaluated breast cancer recurrences achieved high sensitivity and PPV using definitions based on the second round of chemotherapy, diagnostic procedures, treatment, visit to oncologists, patient age, and tumor stage.[15] True positives may be identified if specific therapies are used for the first recurrence/exacerbation, but further investigation is required. Similarly,  $PS \ge 2$ , an important variable for cancer, needs further investigation since it was extremely difficult to identify in this study.

For AEs, PPV tended to be low overall with the definition based on ICD-10 alone, suggesting that a combination of definitions based on specific treatment approaches for AEs

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could be more appropriate. The definitions of febrile neutropenia and skin disorders had high PPVs and therefore, can be generalized. The validation of T1DM as an AE was challenging as it was difficult to differentiate whether it was an existing comorbidity or developed newly. Moreover, T1DM as a primary diagnosis is rarely found, as the treatment usually targets complications of T1DM. For a few AEs, no true positives were identified, which could be because the outcome definition was developed for irAEs. However, owing to the absence of any reference standard for irAEs in clinical practice, a chart review was instead conducted for AEs in general. For AEs with a low incidence, further studies with a greater number of cases and a more appropriate validation method are required.

Since RWDs contain a large volume of information, it is not realistic to perform validation of multiple outcomes using all cases; instead, representative samples should be used as much as possible. However, such investigations are possible only in a small number of medical facilities. A validation data set, which is a compact version of the database of the concerned medical facility and represents the entire database, should be developed to minimize bias. Further, the definition of the disease and outcomes with low incidence should allow for the collection of as many true positives as possible. An optimal validation methodology should be developed in consideration of the above requirements.

In our study, all possible cases were extracted using the related ICD-10 code from medical information available in the study institution. In order to provide health insurance, the Health Insurance Bureau of the MHLW requires that a suspected diagnosis is changed to a definitive diagnosis as soon as a diagnosis is confirmed.[43] Since the RWD used in this study is a health insurance database, patients with a definitive diagnosis identified by ICD-10 code were deemed as all possible cases. To confirm the robustness of this hypothesis, 100 cases for each cancer type were randomly sampled from cases other than all possible cases to ensure that no patients with a primary diagnosis were included. In future, when conducting a

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validation study prior to a pharmacoepidemiology study using information from an RWD, a more efficient method is warranted. In randomized controlled trials (RCTs), the efficacy and safety of treatments are assessed objectively; therefore, assessments are preset. However, in daily clinical practice, treatment decisions are subjective and based on the availability and type of medical resources, capabilities, treatment cost, and patient needs. Therefore, diagnosis and outcome definitions based on efficacy and safety assessments used in RCTs may not be suitable in RWD studies and should be carefully vetted for use in daily clinical practice.

In this study, validation was performed at a single facility; therefore, there is a possibility of selection bias. Further, the results are limited by the inherent issues related to the use of an RWD, which primarily stores medical information for the purpose of insurance claims. Moreover, the diagnosis and AE definitions used in this study may not be the most suitable, and there is an opportunity to further deepen the definitions. For instance, the definition of AE in this study was developed based on treatment-associated irAEs and information on therapeutic agents such as steroids and treatments for allergy; however, definitions based on therapies used for general AE treatment could have been more appropriate. Also, it was challenging to investigate outcomes with extremely low incidence, for example, certain AEs. Therefore, study methods for the consolidation of true positives for events with low incidence need to be investigated.

#### **CONCLUSIONS**

 The results from our study suggest that patient populations with various cancer types and death can be identified with high sensitivity and predictability by the diagnosis and AE definitions used in this study. DPC data could identify only a limited proportion of patients with cancer, while claims or DPC data could identify only a limited proportion of deceased patients. Since the number of cases was limited in this study, further investigation is required to validate the definitions using DPC and claims data. In view of the current claims process in

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Japan, EMR data are deemed appropriate to comprehensively identify patients with cancer or deceased patients for postmarketing surveillance using RWD. Although a high PPV was observed for a few AEs, precision could have been low owing to the low incidence of AEs, and therefore, validation of AEs warrants further investigation.

#### Acknowledgments

The following persons from Kurashiki Central Hospital Clinical Research Center (Department of Management, Clinical Research Center, Kurashiki Central Hospital, Okayama, Japan) provided additional support: Maki Satomi coordinated at the study site for implementation of protocol procedures and Ryo Ishida, Emi Sato, Mami Yamaguchi, and Yuri Komatsubara contributed to the chart review. Takeshi Kimura of Real World Data Co., Ltd. provided support for statistical analysis and Yusuke Miyoshi of Chugai Pharmaceuticals Co., Ltd. provided administrative support. Akihiro Seki of Chugai Pharmaceuticals supported in developing the outcome definitions.

Editorial support in the form of medical writing, assembling tables, and creating high-resolution images based on the authors' detailed directions, collating author comments, copyediting, fact checking, and referencing was provided by Dr. Deepali Garg, MBBS, PGDHA, of Cactus Life Sciences (part of Cactus Communications) and funded by Chugai Pharmaceutical Co., Ltd.

#### Funding

This study was funded by Chugai Pharmaceutical Co., Ltd. The funding did not have Award/Grant numbe.

#### **Competing interests**

TK, KT, and AY are employees of Chugai Pharmaceutical Co., Ltd. TF reports personal fee

for statistical analysis from Real World Data Co., Ltd. during the conduct of the study; personal fee for collaborative research from Chugai Pharmaceutical Co., Ltd.; and personal fee for statistical analysis from Real World Data Co., Ltd. outside the submitted work. MI has nothing to disclose. YO is an employee of Real World Data Co., Ltd. and reports personal fees from MSD K.K., Otsuka Pharmaceutical, and Kurashiki Central Hospital, outside the submitted work. HT reports personal fees for lecture from AYUMI Pharmaceutical Corporation and Chugai Pharmaceutical Co., Ltd., outside the submitted work and is an employee of Kurashiki Central Hospital and the Director of Real World Data, Co., Ltd.

# Author contributions

TF contributed to the study concept and design, and collection, analysis, and interpretation of data. TK, KT, YA and HT contributed to study concept and design, and data interpretation. MI contributed to collection and interpretation of data. YA contributed to analysis and interpretation of data. All authors provided final approval for the version to be published.

#### Data sharing statement

Data are available upon reasonable request.

#### **Figure legend**

**Figure 1.** Health, Clinic, and Education Information Evaluation Institute/real-world database

EMR: Electronic medical records; HCEI: Health, Clinic, and Education Information

Evaluation Institute; KCH: Kurashiki Central Hospital; RWD: real-world database

Figure S1. Patient disposition: Lung cancer

ICD-10, International Classification of Diseases, 10th Revision

\*Including 199 duplicates; #Study observation periods lasted from January 1, 2014, to January 31, 2014, and from November 1, 2018, to December 31, 2018, but were excluded as study washout periods;

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| 100 patients were randomly sampled from patients other than all possible cases (patients given a suspected |
|--|
| diagnosis of related ICD-10) to confirm non-diagnosis of primary cancer                                    |
| Random sampling was performed based on the extraction percentage   |
| Figure S2. Patient disposition: Breast cancer  |
| ICD-10, International Classification of Diseases, 10th Revision  |
| *Including 61 duplicates; #Study observation periods lasted from January 1, 2014 to January 31, 2014, and  |
| from November 1, 2018, to December 31, 2018, but were excluded as study washout periods; 100 patients      |
| were randomly sampled from patients other than all possible cases (patients given a suspected diagnosis of |
| related ICD-10) to confirm non-diagnosis of primary cancer   |
| Random sampling was performed based on the extraction percentage   |
| Figure S3. Patient disposition: Colorectal cancer  |
| ICD-10, International Classification of Diseases, 10th Revision  |
| *Including 61 duplicates; #Study observation periods lasted from January 1 to January 31, 2014, and from   |
| November 1, 2018, to December 31, 2018, but were excluded as study washout periods; 100 patients were      |
| randomly sampled from patients other than all possible cases (patients given a suspected diagnosis of      |
| related ICD-10) to confirm non-diagnosis of primary cancer   |
| Random sampling was performed based on the extraction percentage   |
| Figure S4. Patient disposition: Ovarian cancer   |
| ICD-10, International Classification of Diseases, 10th Revision  |
| *Including three duplicates; #Study observation periods lasted from January 1 to January 31, 2014, and     |
| from November 1, 2018, to December 31, 2018, but were excluded as study washout periods; 100 patients      |
| were randomly sampled from patients other than all possible cases (patients given a suspected diagnosis of |
| related ICD-10) to confirm non-diagnosis of primary cancer   |
| Random sampling was performed based on the extraction percentage   |
| Figure S5. Patient disposition: Bladder cancer   |
|  |

ICD-10, International Classification of Diseases, 10th Revision

\*Including 25 duplicates; #Study observation periods lasted from January 1, 2014, to January 31, 2014, and from November 1, 2018, to December 31, 2018, but were excluded as study washout periods; 100 patients

were randomly sampled from patients other than all possible cases (patients given a suspected diagnosis of related ICD-10) to confirm non-diagnosis of primary cancer
Random sampling was performed based on the extraction percentage
Figure S6. Patient disposition: Prostate cancer
ICD-10, International Classification of Diseases, 10th Revision
\*Including 44 duplicates; #Study observation periods lasted from January 1, 2009, to January 31, 2009, and from November 1, 2018, to December 31, 2018, but were excluded as study washout periods; 100 patients were sampled from patients other than all possible cases (patients given a suspected diagnosis of related ICD-10) to confirm non-diagnosis of primary cancer

Random sampling was performed based on the extraction percentage

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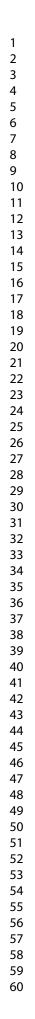
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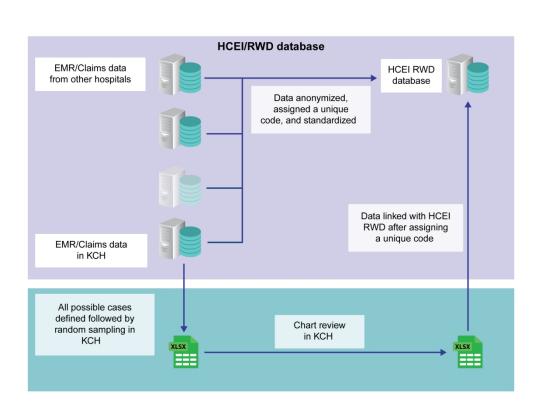
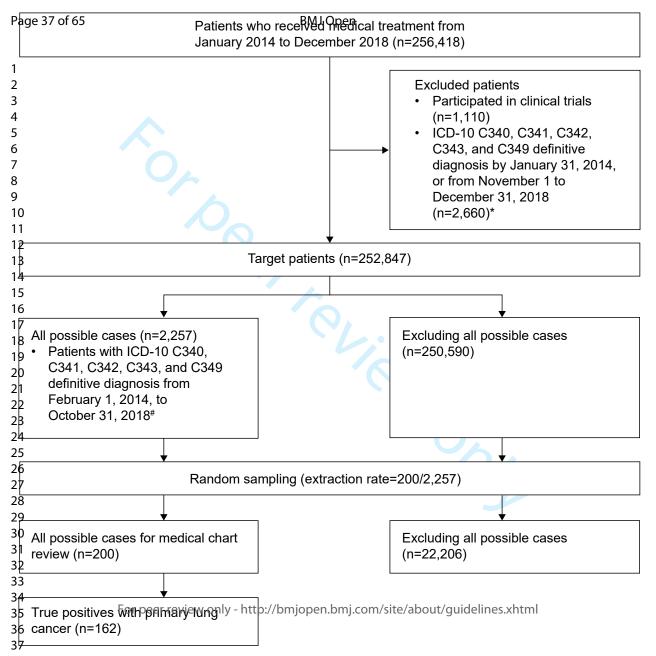
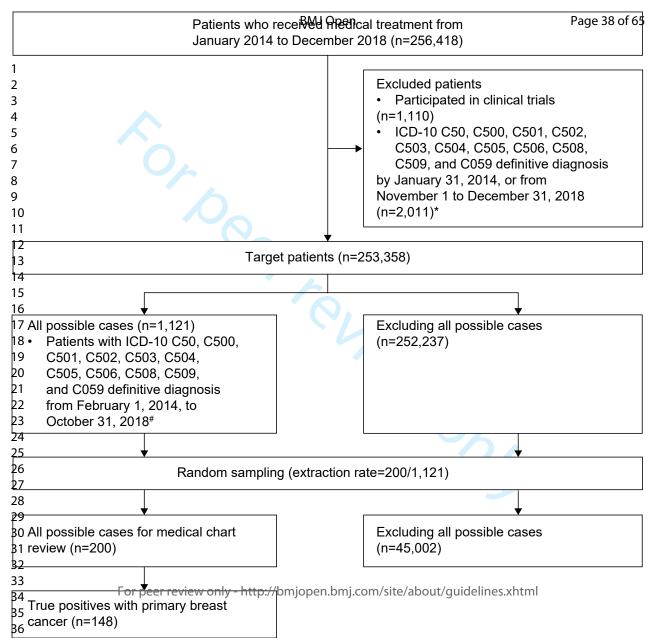
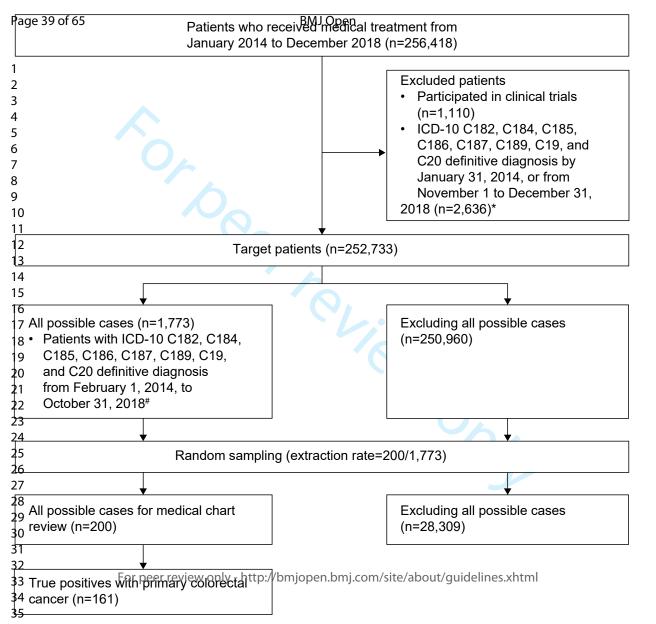


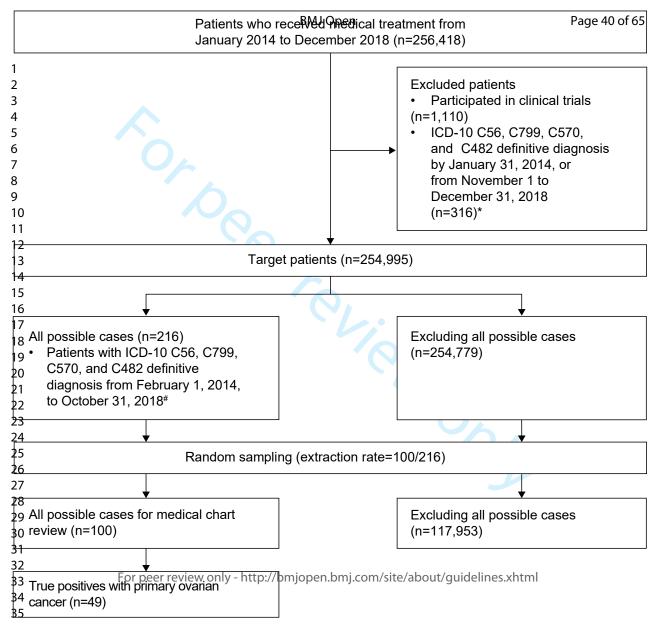
Figure 1. Health, Clinic, and Education Information Evaluation Institute/real-world database EMR: Electronic medical records; HCEI: Health, Clinic, and Education Information Evaluation Institute; KCH: Kurashiki Central Hospital; RWD: real-world database

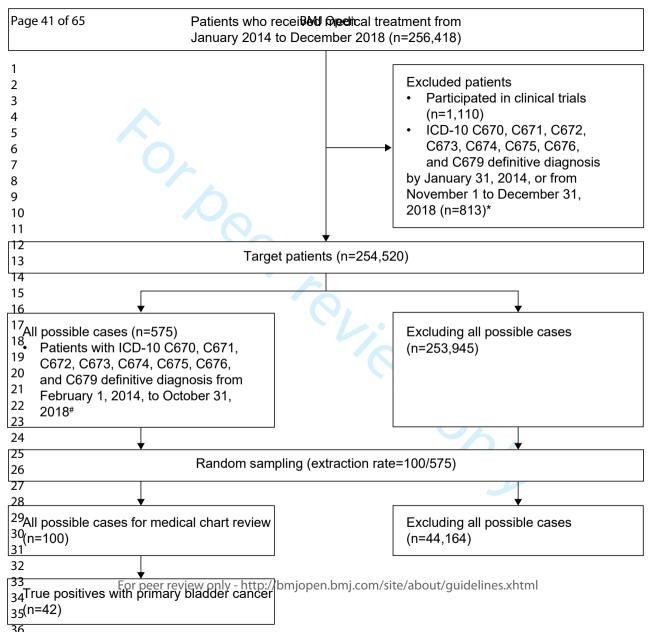
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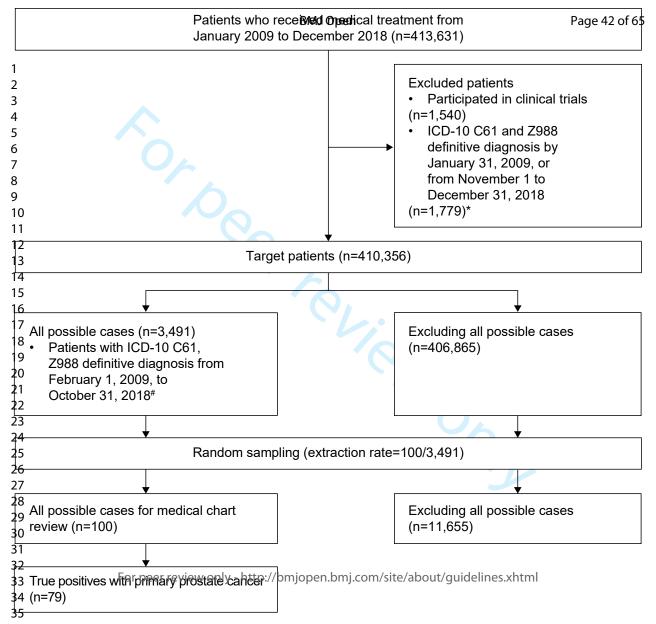












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# **Supplemental Tables**

## Table S1. Outcome definitions

|                               | BMJ Open  |             |
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|                               | en-202  | Page 1 of   |
| Supplemental Tables           | BMJ Open 2021-055459 on 13  |             |
| Table S1. Outcome definitions | 9 on<br>13  |             |
| Outcome                       | Definition  |             |
| A. Primary lung cancer        | • Definitive diagnosis of lung cancer (ICD-10: C340, C341, C342, C343, or C349) recorded be<br>and 2018 in DPC data. Primary diagnosis, admission-precipitating diagnosis, or most resourc  |             |
|                               | A2 • Definitive diagnosis of lung cancer (ICD-10: C340, C341, C342, C343, or C349) recorded be<br>and 2018 in EMR data.   | etween 201  |
|                               | <ul> <li>Diagnosis of lung cancer (Japanese original diagnostic code: 1629003) recorded between 201</li> <li>in EMR data.</li> </ul>  | 14 and 2018 |
|                               | <ul> <li>Definitions written in A1 and specimen examination for laboratory giagnosis (Japanese origin procedural code: 160060170, 160060270, 160171470, 160185110, 50214310, 160209750, 1 160214810, 160190270, 160190370, 160190470, 160190570, 160214470, 160214970, or 160 recorded between 2014 and 2018 in claims data.</li> </ul> | 160214710   |
| B. Non-small cell lung cancer | • Diagnosis of non-small cell lung cancer (Japanese original diagnost code: 8847272, 884773<br>8847598, 8847637, 8847664, or 8842053) recorded between 2014 and 2018 in EMR data.   | 32, 884923  |
|                               | Diagnosis of non-small cell lung cancer (Japanese original diagnost code: 8842835, 884767   | 76, 884767  |

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|                              |        |            | BMJ Open BMJ Open Page 2 o   |
| Outcome                      | Defini | tion       |  |
|                              |        |            | 8847678, 8847679, 8835493, 8847634, 8847635, 8847636, 8847639, 8837666, 8847661, 8847662,  |
|                              |        |            | 8847663, 8847664, 8831458, 8847595, 8847596, 8847597, 884759 <u>8</u> , 8833932, 1629003, 1629006,                               |
|                              |        |            | 1629009, 8838805, 8838844, 8838852, 8838898, 8838901, 884205 8 8842831, 8842832, 8842833,  |
|                              |        |            | 8842834, 8847272, 8847732, 8849238, 8849788, or 2312002) recorded between 2014 and 2018 in EMI                                   |
|                              |        | $\bigcirc$ | data.  |
| C. Small cell lung cancer    | C1     | •          | Diagnosis of small cell lung cancer (Japanese original diagnostic coge: 8847594, 8842185, 8847633,                               |
|                              |        |            | 8847660, or 8847675) recorded between 2014 and 2018 in EMR data.   |
| α. Primary breast cancer     | α1     | •          | Definitive diagnosis of breast cancer (ICD-10: C500, 501, 502, 503 504, 505, 506, 508, 509, or D059)                             |
|                              |        |            | recorded between 2014 and 2018 in DPC data. Primary diagnosis, agmission-precipitating diagnosis, or                             |
|                              |        |            | most resource-consuming diagnosis.   |
|                              | α2     | •          | Definitive diagnosis of breast cancer (ICD-10: C500, 501, 502, 5035504, 505, 506, 508, 509, or D059)                             |
|                              |        |            | recorded between 2014 and 2018 in EMR data.  |
|                              | α3     | •          | Diagnosis of breast cancer (Japanese original diagnostic code: 8849699) recorded between 2014 and 20                             |
|                              |        |            | in EMR data.   |
| β. Primary colorectal cancer | β1     | •          | Definitive diagnosis of colorectal cancer (ICD-10: C179, C182, $C_{\overline{p}}^{\overline{p}}$ 4, C186, C187, C189, C19, or C2 |
|                              |        |            | recorded between 2014 and 2018 in DPC data. Primary diagnosis  |
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| Outcome                    | Defin | nition 55  |
|----------------------------|-------|--|
|                            |       | 45<br>50   |
|                            |       | most resource-consuming diagnosis.   |
|                            | β2    | • Definitive diagnosis of colorectal cancer (ICD-10: C179, C182, C184, C186, C187, C189, C19, or C   |
|                            |       | recorded between 2014 and 2018 in EMR data.  |
|                            | β3    | • Diagnosis of breast cancer (Japanese original diagnostic code: 8847 15 or 8847916) recorded betwee   |
|                            |       | 2014 and 2018 in EMR data.   |
| γ. Primary ovarian cancer  | γ1    | • Definitive diagnosis of ovarian cancer (ICD-10: C56, C799, C570, 🖗 C482) recorded between 2014   |
|                            |       | 2018 in DPC data. Primary diagnosis, admission-precipitating diagnosis, or most resource-consumin  |
|                            |       | diagnosis.   |
|                            |       |  |
|                            | γ2    | • Definitive diagnosis of ovarian cancer (ICD-10: C56, C799, C570, Gr C482) recorded between 2014  |
|                            |       | 2018 in EMR data.  |
| ε. Primary bladder cancer  | ε1    | • Definitive diagnosis of bladder cancer (ICD-10: C670, C671, C672 C673, C674, C675, C676, or C6   |
|                            |       | recorded between 2014 and 2018 in DPC data. Primary diagnosis, admission-precipitating diagnosis,  |
|                            |       |  |
|                            |       |  |
|                            | ε2    | • Definitive diagnosis of bladder cancer (ICD-10: $C6/0$ , $C6/1$ , $C6/2$ , $C6/3$ , $C6/4$ , $C675$ , $C676$ , or $C6$   |
|                            |       | recorded between 2014 and 2018 in EMR data.  |
| δ. Primary prostate cancer | δ1    | most resource-consuming diagnosis.       Image: Construction of the second |
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| Outcome                             | Defini | <u>.</u>   |
|                                     |        | data. Primary diagnosis, admission-precipitating diagnosis, or most gesource-consuming diagnosis.<br>ಹ   |
|                                     | δ2     | Definitive diagnosis of prostate cancer (ICD-10: C61 or Z988) recoeded between 2009 and 2018 in EN   |
|                                     |        | data.  |
| D. Performance status 2 or          | D1     | Medical treatment of rehabilitation for cancer patients (Japanese Striginal diagnostic code: 1800331   |
| higher at the start of chemotherapy |        | of the therapeutic drug described in Table S2.   |
| chemotherapy                        | D2     | <ul> <li>Medical treatment of rehabilitation for disuse syndrome (Japanese original diagnostic code: H001-02,</li> </ul>   |
|                                     |        | عجم المعلى 180044610, 180044710, 180044810, 180044910, 180045010, 1800455110, 180045210, 180045310,  |
|                                     |        | 180045410, 180045530, 180045630, 180045730, 180051530, 1800 <del>5</del> 1630, 180051730, 180051830,   |
|                                     |        | 180051930, 180052030, 180052130, 180052230, 180052330, 180052330, 180052530, or 180052630)   |
|                                     |        | recorded between 2014 and 2018 in claims data, given in the same $\frac{1}{2}$ dex month as the prescription mo  |
|                                     |        | of the therapeutic drug described in Table S2.   |
| E. Death                            | E1     | • Date of death in EMR data.   |
|                                     | E2     | • Date of death in DPC data.   |
|                                     | E3     | <ul> <li>Medical treatment of death for patients (Japanese original diagnostic code: 114007270, 114018670, or<br/>114019970) recorded between 2014 and 2018 in claims data.</li> </ul> |
|                                     | I      | 114019970) recorded between 2014 and 2018 in claims data.  |
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| Outcome                         | Defini | ition | 5545   |
|                                 | E4     | •     | 30 days before and after definitions written in E1.  |
|                                 | E5     | •     | $30 \text{ days before and after definitions written in E2.} \qquad \qquad$ |
|                                 | E6     | •     | 30 days before and after definitions written in E3.  |
| F. First recurrence/progression | F1     | ·     | Date of disease name with "recurrence" as a modifier in Japanese or ginal diagnostic code.   |
|                                 | F2     | ŀ     | Second specimen examination for laboratory diagnosis (Japanese orgginal procedural code: 160060170,  |
|                                 |        |       | $160060270, 160171470, 160185110, 160214310, 160209750, 1602 \vec{\underline{B}4}710, 160214810, 160190270,$   |
|                                 |        |       | 160190370, 160190470, 160190570, 160214470, 160214970, or 160062310) recorded between 2014 and   |
|                                 |        |       | 2018 in claims data.   |
|                                 | F3     | •     | Definitions written in F2 and patients with no history of surgery for the purpose of excision (with or   |
|                                 |        |       | without surgery for the purpose of examination).   |
|                                 | F4     | •     | Month of definitions written in F1.  |
|                                 | F5     | •     | Month of definitions written in F2.  |
|                                 | F6     | •     | Month of definitions written in F3.  |
| G. Second                       | G1     | •     | Date of administration of the drug described in Appendix 2 after de gnitions written in F1.  |
| recurrence/progression          | G2     | •     | Third specimen examination for laboratory diagnosis (Japanese origenal procedural code: 160060170,   |
|                                 |        |       | 160060270, 160171470, 160185110, 160214310, 160209750, 1602 4710, 160214810, 160190270,  |
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| Outcome                   | Defini | <u>0</u>  |
|                           |        | 160190370, 160190470, 160190570, 160214470, 160214970, or 16 <b>9</b> 062310) recorded between 2014                         |
|                           |        | 2018 in claims data.  |
|                           | G3     | Month of definitions written in G1.   |
|                           | G4     | Month of definitions written in G2.   |
| H. Third                  | H1     | • Date of administration of the drug described in Appendix 2 after Gla  |
| recurrence/progression    | H2     | • Forth specimen examination for laboratory diagnosis (Japanese original procedural code: 160060170,                        |
|                           |        | 160060270, 160171470, 160185110, 160214310, 160209750, 16024710, 160214810, 160190270,                                      |
|                           |        | 160190370, 160190470, 160190570, 160214470, 160214970, or 160062310) recorded between 2014                                  |
|                           |        | 2018 in claims data.  |
|                           | Н3     | Month of definitions written in H1.   |
|                           | H4     | Month of definitions written in H2.   |
| Adverse events            |        | 19, 202   |
| I. Interstitial pneumonia | I1     | • Definitive diagnosis of interstitial pneumonia (ICD-10: J702, J703, \$704, J841 or J849) recorded in E                    |
|                           |        | data and Medical treatment (ATC code: H02AB04 or H02AB06 [exectled logs]).  |
|                           | I2     | <ul> <li>Definitive diagnosis of interstitial pneumonia (ICD-10: J448, J700, \$701, J702, J704, J82, J841, J849,</li> </ul> |
|                           |        | M0510) recorded in EMR data.  |
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| Outcome             | Defini | tion | 2021-0<br>021-0<br>55   |
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|                     | Denni  |      | 54<br>59  |
|                     | 13     | •    | Definitions written in I2 plus prescription of methylprednisolone (AGC code: H02AB04) or prednisolon                |
|                     |        |      | (ATC code: H02AB06 with exception of external medicine) record $\underbrace{a}_{\underline{\beta}}$ in claims data. |
| J. Hepatic failure  | J1     | •    | Definitive diagnosis of hepatic failure (ICD-10: K720, K712, or K783) recorded in EMR data plus                     |
|                     |        |      | prescription of methylprednisolone (ATC code: H02AB04) or prednessolone (ATC code: H02AB06 with                     |
|                     |        |      | exception of external medicine) recorded in claims data.  |
|                     | J2     | •    | Laboratory data abnormality in EMR data plus prescription of methylprednisolone (ATC code:                          |
|                     |        |      | H02AB04) or prednisolone (ATC code: H02AB06 with exception of external medicine) recorded in                        |
|                     |        |      | claims data.  |
|                     | J3     | •    | Definitive diagnosis of hepatic failure (ICD:10: K710, K711, K712, K716, K717, K718, K719, K720,                    |
|                     |        |      | K729, K739, K740, K741, K743, K744, K745, K746, K750, K751, K752, K753, K754, K758, K759,                           |
|                     |        |      | K760, K761, K762, K763, K764, K765, K767, K768, K769, R18, R509, R945, or S361) recorded in                         |
|                     |        |      | EMR data.   |
|                     | J4     | •    | Definitions written in J3 plus prescription of medical treatment (ATE code: H02AB04, H02AB06,                       |
|                     |        |      | A05AA02, or A05BA08) recorded in claims data.   |
| K. Colitis•diarrhea | K1     | •    | Definitive diagnosis of colitis • diarrhea (ICD:10: A090 or A099) recorded in EMR data plus prescription            |
|                     |        |      | of methylprednisolone (ATC code: H02AB04) or prednisolone (AT   |
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| Outcome                      | Defini | <u>0</u>  |
|                              |        | external medicine) recorded in claims data.   |
|                              | K2     | • Definitive diagnosis of colitis • diarrhea (ICD-10: A099, K501, $K502$ , K510, K512, K513, K515, K5 |
|                              |        | K519, K521, K522, K528, K529, K550, K551, K552, K559, K566, K591, K628, K638, K921, K922              |
|                              |        | M321, or R101) recorded in EMR data.  |
|                              | K3     | • Definitions written in K2 plus prescription of medical treatment (AFC codes: H02AB04, H02AB06,      |
|                              |        | A07A, A07F, A07E, A07D, or A07X) recorded in claims data.   |
| L. Type 1 diabetes           | L1     | • Prescription of medical treatment (ATC code: A10AB, A10AC, A10AD, or A10AE)                         |
|                              | L2     | • Definitive diagnosis of type 1 diabetes (ICD-10: E10, E100, E101, 102, E103, E104, E105, or E100    |
|                              |        | recorded in EMR data.   |
| M. Encephalitis • meningitis | M1     | • Definitive diagnosis of encephalitis • meningitis (ICD-10: G040, Gg 48, G049, or G934) recorded in  |
|                              |        | EMR data.   |
|                              | M2     | • Definitive diagnosis of encephalitis • meningitis (ICD-10: G040, G948, G049, or G934) recorded in   |
|                              |        | EMR data plus prescription of methylprednisolone (ATC code: H02AB04) or prednisolone (ATC code        |
|                              |        | H02AB06 with exception of external medicine) recorded in claims $\frac{1}{2}$                         |
|                              | M3     | Definitive diagnosis of encephalitis.   |
|                              |        | Definitive diagnosis of encephalitis.     Meningitis (ICD-10: R291) recorded in EMR data.             |
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|                              | F      | or peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml                              |

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|---|-------|-------|---|
| Outcome                                     | Defin | ition |   |
|   | M4    | •     | Definitions written in M3 plus prescription Meningitis (ICD-10: R2 <b>9</b> 1) recorded in EMR data of medical<br>ت<br>treatment (ATC code: J05AB, J01, or J02A) recorded in claims data  |
| N. Nerve<br>disorder (excludes paresthesia) | N1    | •     | Definitive diagnosis of nerve disorder (excludes paresthesia) (ICD- 20: G500, G501, G508, G509, G511, G512, G513, G514, G518, G519, G520, G521, G522, G523, G527, 20: S28, G529, G540, G541, G542,  |
| uisor der (excludes parestiesia)            |       | 0     | G543, G544, G545, G560, G561, G562, G563, G564, G568, G569, a 570, G571, G572, G573, G574,  |
|   |       |       | G575, G576, G579, G580, G587, G588, G589, G603, G608, G609, G618, G620, G622, G629, G64, G723, G810, G811, G819, G820, G821, G822, G823, G824, G825, G830, G831, G832, G833, G839, G900, G902, G903, G904, G908, G909, H812, H919, H933, M7926, M7926, M7929, M8900, M998, R252, R253, or R258) recorded in EMR data. |
|   | N2    | •     | Definitions written in N1 and medical treatment (ATC code H02AB04 or H02AB06) recorded in claims<br>data.   |
| O. Myasthenia gravis                        | 01    | •     | Definitive diagnosis of myasthenia gravis (ICD-10: G700) recorded in EMR data.  |
|   | 02    | •     | Definitive diagnosis of myasthenia gravis (ICD-10: G700) recorded in EMR data plus prescription of<br>methylprednisolone (ATC code: H02AB04) or prednisolone (ATC code: H02AB06 with exception of<br>external medicine) recorded in claims data.  |
|   | 03    | •     | Definitive diagnosis of myasthenia gravis (ICD-10: G700, G701, G609) recorded in EMR data.  |

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| Definit<br>O4<br>P1 | BMJ Open       Page 10         ion       54         • Definitions written in O3 and medical treatment (ATC code: H02AB04, H02AB06, or H07AA02)         recorded in claims data.         • Definitive diagnosis of Guillain-Barré syndrome (ICD-10: G610) resorded in EMR data. |
|---------------------|--|
| O4                  | • Definitions written in O3 and medical treatment (ATC code: H02AB004, H02AB06, or H07AA02)  |
| P1                  | recorded in claims data.   |
|                     |  |
|                     | • Definitive diagnosis of Guillain-Barré syndrome (ICD-10: G610) recorded in EMR data.   |
| P2                  |  |
| 1 2                 | • Definitions written in P1 plus prescription of methylprednisolone (Agence C code: H02AB04) or predniso   |
|                     | (ATC code: H02AB06 with exception of external medicine) recorded in claims data.   |
| P3                  | • Definitions written in P1 plus prescription of methylprednisolone (ATC code: H02AB04), prednisolo  |
|                     | (ATC code: H02AB06 with exception of external medicine), or immunoglobulin recorded in claims of   |
| P4                  | • Definitions written in P1 and medical treatment (ATC code: H02AB06, J06BA, J06BB, o  |
|                     | J06BC) recorded in claims data.  |
| Q1                  | • Definitive diagnosis of skin disorders (ICD-10: H605, H738, I831, 200, L010, L011, L020, L021, L0  |
|                     | L023, L024, L028, L029, L030, L031, L032, L033, L038, L039, L039, L081, L089, L100, L101, L1   |
|                     | L103, L104, L105, L108, L109, L110, L111, L119, L120, L121, L123, L129, L130, L131, L138, L13  |
|                     | L200, L208, L210, L219, L233, L238, L239, L26, L270, L271, L279, L280, L281, L282, L290, L29   |
|                     | L292, L298, L299, L300, L301, L302, L303, L304, L305, L309, L409, L401, L402, L403, L404, L4   |
|                     | L409, L410, L411, L413, L414, L415, L418, L419, L42, L430, L432, L433, L438, L439, L440, L44   |
|                     | للفظي<br>L442, L443, L449, L500, L501, L502, L504, L508, L509, L510, L541, L512, L518, L519, L52, L530   |
|                     | co p   |
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|                     | P4   |

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|-------|--------------|----------------|---|--|
|       |              |                |   | Page 11 of 21  |
| Outco | ome          | Definition     |   | -0<br>5545   |
|       |              |                | L531, L532, L538, L539, L560, L561, L562, L563, L564, L568, L<br>L589, L590, L598, L700, L701, L702, L703, L708, L709, L710, L<br>L739, L80, L810, L811, L812, L813, L814, L816, L817, L818, L8<br>L853, L858, L859, L870, L871, L872, L879, L88, L890, L891, L8<br>L909, L919, L920, L921, L928, L929, L930, L931, L932, L940, L<br>L950, L951, L97, L980, L981, L982, L983, L984, L985, L986, L94<br>in EMR data. | Image: Construct of the system         Image: Construct of the system |
|       |              | Q2 •           | Definitions written in Q1 and medical treatment (ATC codes: H02A<br>[excludes steroidal drugs]) recorded in claims data.  | B04, H02AB06, D04AA, or R01AC  |
| R. Rh | abdomyolysis | R1 •           | "Drug-induced rhabdomyolysis" or "rhabdomyolysis" in definitive<br>M6289) recorded in EMR data.   | diagnosis of rhabdomyolysis (ICD-10:<br>9<br>₽   |
|       |              | R2 •           | Definitive diagnosis of rhabdomyolysis (ICD-10: D868, G718, G72<br>M339, M353, M358, M6019, M6091, M6092, M6095, M6098, M6<br>M6155, M6159, M6289, M7900, M7910, M7911, M7912, M7913,<br>M7979) recorded in EMR data.   | 8<br>1999, M6105, M6109, M6119, M6129,   |
|       |              | R3 •<br>For pe | Definitions written in R2 plus prescription of methylprednisolone (<br>er review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml  |  |
|       |              |                |   |  |

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| Outcome        | <b>Definition</b>  |
|----------------|--|
|                | (ATC code: H02AB06 with exception of external medicine) recorded in claims data.   |
| S. Myocarditis | S1 • Definitive diagnosis of myocarditis (ICD-10: I401, I408, I409, I514) recorded in EMR data.                                      |
|                | S2 • Definitive diagnosis of myocarditis (ICD-10: I401, I408, I409, I514) recorded in EMR data plus                                  |
|                | prescription of methylprednisolone (ATC code: H02AB04) or prednessolone (ATC code: H02AB06 wi  |
|                | exception of external medicine) recorded in claims data.   |
|                | S3 • Definitive diagnosis of myocarditis (ICD-10: D868, E854, E888, E\$9, I010, I011, I012, I018, I019,                              |
|                | 1050, 1051, 1052, 1058, 1059, 1060, 1061, 1062, 1069, 1070, 1071, 1072, 1078, 1079, 1080, 1081, 1082, 108                            |
|                | 1088, 1089, 1090, 1091, 1092, 1099, 1200, 1201, 1208, 1209, 1210, 1219, 1212, 1213, 1214, 1219, 1220, 122                            |
|                | 1228, 1229, 1230, 1231, 1232, 1233, 1234, 1235, 1236, 1238, 1240, 124 <sup>1</sup> / <sub>2</sub> , 1248, 1249, 1251, 1252, 1253, 12 |
|                | 1255, 1256, 1258, 1259, 1300, 1308, 1309, 1319, 1339, 1340, 1341, 1342, 1348, 1350, 1351, 1352, 1358, 13                             |
|                | I360, I361, I362, I369, I370, I371, I372, I379, I38, I401, I408, I40921420, I421, I422, I423, I424, I42                              |
|                | I426, I427, I428, I429, I440, I441, I442, I443, I444, I445, I446, I449, I451, I452, I453, I454, I455, I4                             |
|                | I458, I459, I460, I461, I469, I470, I471, I472, I479, I480, I481, I482, I489, I490, I491, I492, I493, I4                             |
|                | I495, I498, I499, I500, I501, I509, I513, I514, I515, I518, I519, R0 (a), R001, R008, R570, R571, R57                                |
|                | R943) recorded in EMR data.  |
|                | <ul> <li>S4</li> <li>Definitions written in S3 plus prescription of methylprednisolone (AGC code: H02AB04) or prednisol</li> </ul>   |
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|                                   |          |        | BMJ Open<br>Page 13 o   |  |  |  |
| Outcome                           | Defin    | ition  | Q   |  |  |  |
|                                   |          |        | (ATC code: H02AB06 with exception of external medicine) recorded in claims data.  |  |  |  |
| T. Gastrointestinal perforation   | T1       | •      | Definitive diagnosis of gastrointestinal perforation (ICD-10: K255, $\underbrace{\underline{K}}_{\leq}$ 265, K631, K65S, or K639) |  |  |  |
|                                   |          |        | recorded in EMR data.   |  |  |  |
| U. Adrenal insufficiency          | U1       | ·      | Definitive diagnosis of adrenal insufficiency in Japanese original diagnostic code including the words                            |  |  |  |
|                                   |          |        | "autoimmune adrenitis" recorded in claims data and "hypoadrenocorticism" plus medical treatment                                   |  |  |  |
|                                   |          |        | (ATC: code H02AB09) recorded in claims data.  |  |  |  |
|                                   | U2       | •      | Definitive diagnosis of adrenal insufficiency (ICD-10: E271, E272, E273, E274, E275 or E278) recorded                             |  |  |  |
|                                   |          |        | in EMR data.  |  |  |  |
|                                   | U3       | •      | Definitions written in U2 plus medical treatment (ATC code H02AB09) recorded in claims data.                                      |  |  |  |
| X. Febrile neutropenia            | X1       | •      | Definitive diagnosis of febrile neutropenia (ICD-10: D70) recorded in EMR data and medical treatment                              |  |  |  |
|                                   |          |        | (Table S2) recorded in claims data.   |  |  |  |
| ATC, Anatomical Therapeutic Chemi | cal; DPC | C, Dia | agnosis Procedure Combination; EMR, electronic medical record; ICD-10, International Classification                               |  |  |  |
| Diseases, 10th revision           |          |        | 24 by   |  |  |  |
|                                   |          |        | guest   |  |  |  |
|                                   |          |        | t. Protected by copyright.  |  |  |  |
|                                   |          |        | ct<br>ed<br>b   |  |  |  |
|                                   |          |        |   |  |  |  |
|                                   |          |        | yright.   |  |  |  |
|                                   | F        | For pe | eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml  |  |  |  |

### Table S2. Drug codes

|                              | BMJ Open                                   | 6/bmjopen-2021-055459 on 13 July |
|------------------------------|--|----------------------------------|
|                              |  | open Da                          |
|                              |  | Pa<br>20                         |
|                              |  | 21-0                             |
|                              |  | 055                              |
|                              |  | 459                              |
| Table S2.         Drug codes |  | on                               |
| Table 52. Drug codes         |  | 13                               |
| ATC code                     | Common name                                | luly                             |
| L01XC32                      | Atezolizumab                               | 2022.                            |
| L01XC17                      | Nivolumab                                  |                                  |
| L01XC18                      | Pembrolizumab                              | <br>0<br>¥                       |
| L01XC31                      | Avelumab                                   |                                  |
| L01XC28                      | Durvalumab                                 | nloader                          |
| L01XC06                      | Cetuximab                                  |                                  |
| L01XC08                      | Panitumumab                                | from                             |
| L01XE02                      | Gefitinib                                  | http                             |
| L01XE35                      | Osimertinib                                | с//b                             |
| L01XE47                      | Dacomitinib                                | mjo                              |
| L01XE13                      | Afatinib                                   | pen                              |
| L01XE03                      | Erlotinib                                  | .bm                              |
| L01XE36                      | Alectinib                                  | j.<br>co                         |
| L01XE44                      | Lorlatinib                                 | m/                               |
| L01XE28                      | Ceritinib                                  | on                               |
| L01XE16                      | Crizotinib                                 | Apri.                            |
| L01XC07                      | Bevacizumab (includes related biosimilars) | 1 19                             |
| L01XC13                      | Pertuzumab                                 |                                  |
| L01XC14                      | Trastuzumab emtansine                      | 2024                             |
| L01XE07                      | Lapatinib                                  | by (                             |
| L01XE33                      | Palbociclib                                |                                  |
| L01XE50                      | Abemaciclib                                | st. F                            |
| L01XE10, L04AA18             | Everolimus                                 | rot                              |
| L01XX46                      | Olaparib                                   | ecte                             |
| L01XC08                      | Panitumumab                                | Protected by copyright.          |
| L01XE21                      | Regorafenib                                | y oc                             |
|                              |  | γα                               |

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|-------------|----------|--|---------------|
|             |          | BMJ Open BMJ Open Page 15 c  | of <b>2</b> 1 |
|             |          |  |               |
|             | ATC code | Common name  |               |
|             | L01      | Anti-malignant tumor drugs excluding talaporfin sodium (620001918), porfimer sodium (620007468), anagrelide hydrochloride hydrate<br>(622379001), and sterile talc (622293901) 9   | 3             |
|             | L02      | Hormone therapy $\vec{\omega}$   | _             |
|             | L04      | Immunosuppressive drug   |               |
|             | J01CR05  |  | _             |
|             | J01DD02  | Iazobactam and piperacillin     N       Ceftazidime hydrate     N  | _             |
|             | J01DE03  | Cefozopran hydrochloride   | _             |
|             | J01DE01  | Cefepime dihydrochloride hydrate   | _             |
|             | J01DE02  | Cefpirome sulfate  |               |
|             | J01DH05  | Biapenem   |               |
|             | J01DH02  | Meropenem hydrate  | _             |
|             | J01DH51  |  | _             |
|             | J01DH04  | Doripenem hydrate, cilastatin sodium   | _             |
|             | J01DH55  |  |               |
|             |          | Imperem hydrate, citastatin sodium     T       Doripenem hydrate     0       Panipenem and betamipron     0       Imperem 1,0000     00       Imperem 1,0000     00       Imperem and betamipron     0       Imperem 1,0000     00       Imperem 1,0000     00 |               |
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|  |  |                     |                    | BMJ (               | Open                       |                            | 6/bmjopen-2021-055459 on 1       | Page 16 o            |
|--|--|---------------------|--------------------|---------------------|----------------------------|----------------------------|----------------------------------|----------------------|
| able S3. Accura<br>Outcome<br>definition | cy of diagnosis de<br>True<br>positives, | False<br>positives, | True<br>negatives, | False<br>negatives, | Sensitivity,<br>% (95% CI) | Specificity,<br>% (95% CI) | ⊆ PPV,<br>≤ % (95% CI)           | NPV,<br>% (95% CI)   |
| r  | n  | n                   | n                  | n                   |                            |                            | 20222                            |                      |
| <b>Lung cancer</b><br>Primary lung car   | ncer                                     |                     |                    |                     |                            |                            |                                  |                      |
| i innary lung cal                        |  |                     |                    |                     |                            |                            | Down                             |                      |
| A1                                       | 132                                      | 7                   | 22,237             | 30                  | 81.5                       | 100.0                      | ag 95.0                          | 99.9                 |
|  |  |                     |                    |                     | (74.6–87.1)                | (99.9–100.0)               | <u>\u00e4</u> (89.9–98.0)        | (99.8–99.9)          |
| A2                                       | 162                                      | 38                  | 22,206             | 0                   | 100.0                      | 99.8                       | (74.9–86.2)                      | 100.0                |
|  |  |                     |                    | <u> </u>            | (96.6–100.0)               | (99.8–99.9)                |                                  | (100.0–100.0)        |
| A3                                       | 19                                       | 1                   | 22,243             | 143                 | 11.7                       | 100.0                      | <b>5</b> 95.0                    | 99.4                 |
|  | 100                                      |                     | 22.227             |                     | (7.2–17.7)                 | (100.0–100.0)              | <u>(75.1–99.9)</u>               | (99.2–99.5)          |
| A4                                       | 128                                      | 7                   | 22, 237            | 34                  | 79.0<br>(71.8–85.0)        | 100.0<br>(99.9–100)        | 94.8<br>(89.6–97.9)              | 99.8<br>(99.8–99.9)  |
| Non-small cell l                         | ung cancer                               |                     |                    |                     | (11.0-03.0)                | (99.9–100)                 |                                  | (99.0-99.9)          |
|  | -  |                     | 22.202             |                     |                            | 100.0                      | b<br>M                           |                      |
| B1                                       | 46                                       | 6                   | 22,280             | 74                  | 38.3                       | 100.0                      | 88.5                             | 99.7<br>(00.6, 00.7) |
| B2                                       | 46                                       | 6                   | 22.280             | 74                  | (29.6–47.6)<br>38.3        | (99.9–100.0)<br>100.0      | ₹(76.6–95.6)<br>\$ 88.5          | (99.6–99.7)<br>99.7  |
| D2                                       | 40                                       | U                   | 22,280             | /4                  | 38.3<br>(29.6–47.6)        | (99.9–100.0)               | ∃ 88.3<br>≩(76.6–95.6)           | 99.7<br>(99.6–99.7)  |
| Small cell lung o                        | cancer                                   |                     |                    |                     | (27.0 77.0)                | (55.5 100.0)               |                                  | ()).0 )).1)          |
| Ū.                                       |  |                     |                    |                     |                            |                            | 19,                              |                      |
| C1                                       | 10                                       | 0                   | 22,395             | 1                   | 90.9                       | 100.0                      | ×100.0<br>4(58.7–100.0)          | 100.0                |
| D (                                      |  |                     |                    |                     | (58.7–99.8)                | (100.0–100.0)              | <u><del>5</del></u> (58.7–100.0) | (100.0–100.0)        |
| Breast cancer                            |  |                     |                    |                     |                            |                            | by gu                            |                      |
| Primary breast c                         | ancer                                    |                     |                    |                     |                            |                            | guest                            |                      |
| α1                                       | 93                                       | 18                  | 45,036             | 55                  | 62.8                       | 100.0                      | 83.8 פ                           | 99.9                 |
|  |  |                     |                    |                     | (54.5-70.6)                | (99.9–100.0)               | 983.8<br>ספר (75.6–90.1)         | (99.8–99.9)          |
| α2                                       | 148                                      | 52                  | 45,002             | 0                   | 100.0                      | 99.9                       | G 74.0<br>G (67.3–79.9)          | 100.0                |
| 2  | 0  |                     | 45.054             | 1.40                | (96.3–100.0)               | (99.8–99.9)                | <u>(67.3–79.9)</u>               | (100.0–100.0)        |
| α3                                       | 0  | 0                   | 45,054             | 148                 | 0.0                        | 100.0                      | y NA<br>copyright.               | 99.7<br>(00.6, 00.7) |
|  |  |                     |                    |                     | (0.0 - 3.7)                | (100.0-100.0)              | ру                               | (99.6–99.7)          |

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|                       |                     |                     |                    |                     |                            |                            | 6/bmjopen-2021                                  | Page               |
|-----------------------|---------------------|---------------------|--------------------|---------------------|----------------------------|----------------------------|---|--------------------|
| Outcome<br>definition | True<br>positives,  | False<br>positives, | True<br>negatives, | False<br>negatives, | Sensitivity,<br>% (95% CI) | Specificity,<br>% (95% CI) | 55 PPV,<br>55 % (95% CI)                        | NPV,<br>% (95%     |
| Colorectal can        | n<br>ver            | n                   | n                  | n                   |                            |                            |   |                    |
| Primary colorec       |                     |                     |                    |                     |                            |                            | 3 July  |                    |
| β1                    | 108                 | 8                   | 28,340             | 53                  | 67.1<br>(59.2–74.3)        | 100.0<br>(99.9–100.0)      | 893.1<br>N(86.9–97.0)                           | 99.8<br>(99.8–99.9 |
| β2                    | 161                 | 39                  | 28,309             | 0                   | 100.0<br>(96.6–100.0)      | 99.9<br>(99.8–99.9)        | ₽80.5<br>≦(74.3-85.8)                           | 100.0<br>(100.0–10 |
| β3                    | 0                   | 0                   | 28,348             | 161                 | 0.0 (0.0–3.4)              | 100.0<br>(100.0–100.0)     |   | 99.4<br>(99.3–99.  |
| Ovarian cance         |                     |                     |                    |                     |                            |                            | fro   |                    |
| Primary ovarian       | cancer              |                     |                    |                     |                            |                            | m htt   |                    |
| γ1                    | 44                  | 14                  | 11,692             | 5                   | 89.8<br>(77.8–96.6)        | 99.9<br>(99.8–99.9)        | 75.9<br>(62.8–86.1)                             | 100.0<br>(99.7–100 |
| γ2                    | 49                  | 50                  | 11,656             | 0                   | 100.0<br>(89.4–100.0)      | 99.6<br>(99.4–99.7)        | 9 49.5<br>9 (39.3–59.7)                         | 100.0<br>(100.0–10 |
| Bladder cancer        | •                   |                     |                    |                     |                            |                            | bmj   |                    |
| Primary bladder       | cancer              |                     |                    |                     | 191                        |                            | .com  |                    |
| ε1                    | 33                  | 16                  | 44,206             | 9                   | 78.6<br>(63.2–89.7)        | 100.0<br>(99.9–100.0)      | 9 67.3<br>≥(52.5-80.1)                          | 100.0<br>(100.0–10 |
| ε2                    | 42                  | 58                  | 44,164             | 0                   | 100.0<br>(87.7–100.0)      | 99.9<br>(99.8–99.9)        | ≡.42.0<br>,;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;; | 99.9<br>(99.8–99.  |
| Prostate cancer       | r                   |                     |                    |                     |                            |                            | 2024  |                    |
| Primary prostate      | e cancer            |                     |                    |                     |                            |                            | 4 by gu   |                    |
| δ1                    | 17                  | 0                   | 11,676             | 62                  | 21.5<br>(12.1–32.2)        | 100.0<br>(100.0–100.0)     | פָּל 100.0<br>דו(72.7–100.0)                    | 99.5<br>(99.3–99.  |
| δ2                    | 79                  | 21                  | 11,655             | 0                   | 100.0<br>(93.2–100.0)      | 99.8<br>(99.7–99.9)        | ਰੋ 79.0<br>ਉ (69.7–86.5)                        | 100.0<br>(100.0–10 |
| CI, confidence in     | terval; NA, not ava | ailable; NPV, no    | egative predictiv  | e value; PPV, p     | ositive predictive valu    | ue                         | ed by copyright.                                |                    |

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|  |                    |                                       |                    |                     | ВМЈ Оре                    | 'n                         | 6/bmjopen-2021-055459 on 1               | Page <b>18</b> of <b>21</b> |
|--|--------------------|---------------------------------------|--------------------|---------------------|----------------------------|----------------------------|--|-----------------------------|
| <u>Table S4. Ac</u><br>Outcome<br>definition | True<br>positives, | ath definition<br>False<br>positives, | True<br>negatives, | False<br>negatives, | Sensitivity,<br>% (95% CI) | Specificity,<br>% (95% CI) | ĞPPV,<br>≤√% (95% CI)                    | NPV,<br>% (95% CI)          |
| Lung cance                                   | n<br>r             | n                                     | n                  | n                   |                            |                            | 2022.                                    |                             |
| El El  | 32                 | 0                                     | 40                 | 1                   | 97.0<br>(84.2–99.9)        | 100.0<br>(87.1–100.0)      | 0100.0<br>≦(84.2−100.0)                  | 97.6<br>(87.1–99.9)         |
| E2   | 9                  | 0                                     | 40                 | 24                  | 27.3<br>(13.3–45.5)        | 100.0<br>(87.1–100.0)      | <u>ම</u> 100.0<br>ප <u>(</u> 55.5–100.0) | 62.5<br>(49.5–74.3)         |
| E3   | 0                  | 0                                     | 40                 | 33                  | 0.0 (0.0–15.3)             | 100.0<br>(87.1–100.0)      | TNA<br>m                                 | 54.8<br>(4.7–66.5)          |
| E4   | 32                 | 0                                     | 40                 | 1                   | 97.0<br>(84.2–99.9)        | 100.0<br>(87.1–100.0)      | 5100.0<br>(84.2–100.0)                   | 97.6<br>(87.1–99.9)         |
| E5   | 9                  | 0                                     | 40                 | 24                  | 27.3<br>(13.3–45.5)        | 100.0<br>(87.1–100.0)      | ∃100.0<br>₩(55.5–100.0)                  | 62.5<br>(49.5–74.3)         |
| E6   | 0                  | 0                                     | 40                 | 33                  | 0.0<br>(0.0–15.3)          | 100.0<br>(87.1–100.0)      |  | 54.8<br>(4.7–66.5)          |
| Breast can                                   | <u>cer</u>         |                                       | 104                | 2                   | 100.0                      | 100.0                      |  | 100.0                       |
| E1   | 1                  | 0                                     | 104                | 0                   | 100.0<br>(1.3–100.0)       | 100.0<br>(94.8–100.0)      | S100.0<br>(1.3–100.0)                    | 100.0<br>(94.8–100.0)       |
| E2   | 0                  | 0                                     | 104                | 1                   | 0.0<br>(0.0–98.7)          | 100.0<br>(94.8–100.0)      | PNA<br>19                                | 99.0<br>(94.8–100.0)        |
| E3   | 0                  | 0                                     | 104                | 1                   | 0.0<br>(0.0–98.7)          | 100.0<br>(94.8–100.0)      |  | 99.0<br>(94.8–100.0)        |
| E4   | 1                  | 0                                     | 104                | 0                   | 100.0<br>(1.3–100.0)       | 100.0<br>(94.8–100.0)      | توال 100.0%<br>و(1.3–100.0)              | 100.0<br>(94.8–100.0)       |
| E5   | 0                  | 0                                     | 104                | 1                   | 0.0<br>(0.0–98.7)          | 100.0<br>(94.8–100.0)      | Jest. Pr                                 | 99.0<br>(94.8–100.0)        |
| E6   | 0                  | 0                                     | 104                | 1                   | 0.0<br>(0.0–98.7)          | 100.0<br>(94.8–100.0)      | . P<br>ToTNA<br>ctected                  | 99.0<br>(94.8–100.0)        |
| Colorectal                                   |                    |                                       | 50                 | 2                   | 100.0                      | 100.0                      |  | 100.0                       |
| E1   | 4                  | 0                                     | 53                 | 0                   | 100.0<br>(28.4–100.0)      | 100.0<br>(90.1–100.0)      | ₹100.0<br>§(28.4–100.0)                  | 100.0<br>(90.1–100.0)       |

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|                    |                         |                          |                         |                          |   |                            | 6/bmjopen-2021-                    | Page <b>19</b> of <b>2</b> |
|--------------------|-------------------------|--------------------------|-------------------------|--------------------------|---|----------------------------|------------------------------------|----------------------------|
| Outcome definition | True<br>positives,<br>n | False<br>positives,<br>n | True<br>negatives,<br>n | False<br>negatives,<br>n | Sensitivity,<br>% (95% CI)                | Specificity,<br>% (95% CI) | ୁ<br>ଅନ୍ମହ<br>ଅନ୍ତି (95% CI)<br>ବ୍ | NPV,<br>% (95% CI          |
| E2                 | 2                       | 0                        | 53                      | 2                        | 50.0                                      | 100.0                      | $\frac{1}{2}$ 100.0                | 96.4                       |
|                    |                         | -                        |                         |                          | (6.8–93.2)                                | (90.1–100.0)               | <u><u> </u></u>                    | (87.5–99.6)                |
| E3                 | 0                       | 0                        | 53                      | 4                        | 0.0<br>(0.0–71.6)                         | 100.0<br>(90.1–100.0)      | ₩NA<br>202                         | 93.0<br>(83.0–98.1)        |
| E4                 | 4                       | 0                        | 53                      | 0                        | 100.0<br>(28.4–100.0)                     | 100.0<br>(90.1–100.0)      | <sup>№</sup> 100.0<br>(28.4–100.0) | 100.0<br>(90.1–100.0       |
| E5                 | 2                       | 0                        | 53                      | 2                        | 50.0<br>(6.8–93.2)                        | 100.0<br>(90.1–100.0)      | ≦100.0<br>≥(9.4–100.0)             | 96.4<br>(87.5–99.6)        |
| E6                 | 0                       | 0                        | 53                      | 4                        | 0.0                                       | 100.0                      | <u>a</u> NA                        | 93.0                       |
| <u> </u>           |                         |                          |                         |                          | (0.0–71.6)                                | (90.1–100.0)               | fram                               | (83.0–98.1)                |
| Ovarian ca         |                         |                          | 1.6                     |                          | 100.0                                     | 100.0                      |                                    | 100.0                      |
| E1                 | 5                       | 0                        | 16                      | 0                        | 100.0<br>(35.9–100.0)                     | 100.0<br>(71.3–100.0)      | ₹100.0<br>(35.9-100.0)             | 100.0<br>(71.3–100.0)      |
| E2                 | 2                       | 0                        | 16                      | 3                        | 40.0 (5.3-85.3)                           | 100.0<br>(71.3–100.0)      | <u>3</u> 100.0<br>(9.4–100.0)      | 84.2<br>(60.4–96.6)        |
| E3                 | 0                       | 0                        | 16                      | 5                        | 0.0<br>(0.0–64.1)                         | 100.0<br>(71.3–100.0)      |                                    | 76.2<br>(52.8–91.8)        |
| E4                 | 5                       | 0                        | 16                      | 0                        | $\frac{(0.0 \ 04.1)}{100.0}$ (35.9–100.0) | 100.0<br>(71.3–100.0)      | 8100.0<br>(35.9-100.0)             | 100.0                      |
| E5                 | 2                       | 0                        | 16                      | 3                        | 40.0                                      | 100.0                      | <u>9</u> 100.0                     | (71.3–100.0)<br>84.2       |
| E6                 | 0                       | 0                        | 16                      | 5                        | (5.3–85.3)<br>0.0                         | (71.3–100.0)<br>100.0      | <u>ජ</u> (9.4–100.0)<br>, NA       | (60.4–96.6)<br>76.2        |
|                    |                         |                          |                         |                          | (0.0–64.1)                                | (71.3–100.0)               | ,,<br>N2                           | (52.8–91.8)                |
| Bladder ca         |                         |                          |                         |                          | 100.0                                     | 100.0                      | 202<br>4                           |                            |
| E1                 | 2                       | 0                        | 8                       | 0                        | 100.0<br>(9.4–100.0)                      | 100.0<br>(51.8–100.0)      | ⊈100.0<br>(9.4–100.0)              | 100.0<br>(51.8–100.0)      |
| E2                 | 1                       | 0                        | 8                       | 1                        | 50.0<br>(1.3–98.7)                        | 100.0<br>(51.8–100.0)      | ₹100.0<br>(51.8–100.0)             | 100.0<br>(1.3–100.0)       |
| E3                 | 0                       | 0                        | 8                       | 2                        | 0.0 (0.0–90.6)                            | 100.0<br>(51.8–100.0)      |                                    | 80.0<br>(44.4–97.5)        |
| E4                 | 2                       | 0                        | 8                       | 0                        | 100.0<br>(9.4–100.0)                      | 100.0<br>(51.8–100.0)      | ≝100.0<br>₹(9.4–100.0)             | 100.0<br>(51.8–100.0)      |
|                    |                         |                          |                         |                          | (7. <del>7</del> -100.0)                  | (51.0-100.0)               | copyright.                         | (51.0-100.0)               |

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|-----------------------|-------------------------|--------------------------|-------------------------|--------------------------|----------------------------|---------------------------------------|---|----------------------|
|                       |                         |                          |                         |                          |                            |                                       | 6/bmjopen-2021-(  | Page 20 of 21        |
| Outcome<br>definition | True<br>positives,<br>n | False<br>positives,<br>n | True<br>negatives,<br>n | False<br>negatives,<br>n | Sensitivity,<br>% (95% CI) | Specificity,<br>% (95% CI)            | ु<br>अपूर्व (95% CI)<br>अ                               | NPV,<br>% (95% CI)   |
| E5                    | 1                       | 0                        | 8                       | 1                        | 50.0<br>(1.3–98.7)         | 100.0<br>(51.8–100.0)                 | $\frac{3}{2}$<br>$\frac{100.0}{4}$<br>$\frac{100.0}{2}$ | 100.0<br>(1.3–100.0) |
| E6                    | 0                       | 0                        | 8                       | 2                        | 0.0%                       | 100.0                                 |   | 80.0                 |
| Prostate ca           | ncer                    |                          |                         |                          | (0.0–90.6)                 | (51.8–100.0)                          | 0222.   | (44.4–97.5)          |
| E1                    | 3                       | 0                        | 32                      | 1                        | 75.0<br>(19.4–99.4)        | 100.0<br>(94.2–100.0)                 | <u>5</u><br><u>5</u> 100.0<br><u>6</u> (19.4–100.0)     | 97.0<br>(84.2–99.9)  |
| E2                    | 0                       | 0                        | 32                      | 4                        | 0.0<br>(0.0–71.6)          | 100.0<br>(84.2–100.0)                 | ênA<br>≓  | 88.9<br>(73.9–96.9)  |
| E3                    | 0                       | 0                        | 32                      | 4                        | 0.0<br>(0.0–71.6)          | 100.0<br>(84.2–100.0)                 | mNA   | 88.9<br>(73.9–96.9)  |
| E4                    | 3                       | 0                        | 32                      | 1                        | 75.0<br>(19.4–99.4)        | 100.0<br>(94.2–100.0)                 | 100.0<br>(19.4–100.0)                                   | 97.0<br>(84.2–99.9)  |
| E5                    | 0                       | 0                        | 32                      | 4                        | 0.0 (0.0–71.6)             | 100.0<br>(84.2–100.0)                 |   | 88.9<br>(73.9–96.9)  |
| E6                    | 0                       | 0                        | 32                      | 4                        | 0.0<br>(0.0–71.6)          | (84.2-100.0)<br>100.0<br>(84.2-100.0) | <u> </u>  | 88.9<br>(73.9–96.9)  |
|                       |                         |                          |                         |                          | ve value; PPV, posit       |                                       | m/ on April 19, 2024 by guest. Protected by copyright.  |                      |



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| Section & Topic   | No       | Item  | Reported on pag         |
|-------------------|----------|---|-------------------------|
| TITLE OR ABSTRACT |          |   |                         |
|                   | 1        | Identification as a study of diagnostic accuracy using at least one measure of accuracy                           | 3                       |
|                   |          | (such as sensitivity, specificity, predictive values, or AUC)   |                         |
| ABSTRACT          |          |   |                         |
|                   | 2        | Structured summary of study design, methods, results, and conclusions   | 3                       |
|                   |          | (for specific guidance, see STARD for Abstracts)  |                         |
| INTRODUCTION      |          |   |                         |
|                   | 3        | Scientific and clinical background, including the intended use and clinical role of the index test                | 5                       |
|                   | 4        | Study objectives and hypotheses   | 5 and 6                 |
| METHODS           |          |   |                         |
| Study design      | 5        | Whether data collection was planned before the index test and reference standard                                  | 6                       |
|                   |          | were performed (prospective study) or after (retrospective study)   |                         |
| Participants      | 6        | Eligibility criteria  | 8                       |
|                   | 7        | On what basis potentially eligible participants were identified   | 8                       |
|                   |          | (such as symptoms, results from previous tests, inclusion in registry)  | -                       |
|                   | 8        | Where and when potentially eligible participants were identified (setting, location and dates)                    | 8                       |
| <del>-</del>      | 9        | Whether participants formed a consecutive, random or convenience series   | -                       |
| Test methods      | 10a      | Index test, in sufficient detail to allow replication   | 9                       |
|                   | 10b      | Reference standard, in sufficient detail to allow replication   | 6                       |
|                   | 11       | Rationale for choosing the reference standard (if alternatives exist)   | 5                       |
|                   | 12a      | Definition of and rationale for test positivity cut-offs or result categories                                     | 10                      |
|                   |          | of the index test, distinguishing pre-specified from exploratory  |                         |
|                   | 12b      | Definition of and rationale for test positivity cut-offs or result categories                                     | 10                      |
|                   |          | of the reference standard, distinguishing pre-specified from exploratory  | -                       |
|                   | 13a      | Whether clinical information and reference standard results were available  | 8                       |
|                   | 126      | to the performers/readers of the index test<br>Whether clinical information and index test results were available | 0                       |
|                   | 13b      | to the assessors of the reference standard  | 8                       |
| Analysis          | 14       | Methods for estimating or comparing measures of diagnostic accuracy   | 10-11                   |
| Anuiysis          | 14<br>15 | How indeterminate index test or reference standard results were handled   | 10-11                   |
|                   | 15       | How missing data on the index test and reference standard results were handled                                    | 10-11                   |
|                   | 10       | Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from                             | Not applicable          |
|                   | 1/       | exploratory   | Not applicable          |
|                   | 18       | Intended sample size and how it was determined  | Page 9                  |
| RESULTS           | 10       |   |                         |
| Participants      | 19       | Flow of participants, using a diagram   | Supplementary           |
| runticipunts      | 15       |   | figures 1- 6            |
|                   | 20       | Baseline demographic and clinical characteristics of participants   | Table 4                 |
|                   | 21a      | Distribution of severity of disease in those with the target condition  | Not applicable          |
|                   | 21b      | Distribution of alternative diagnoses in those without the target condition                                       | Not applicable          |
|                   | 22       | Time interval and any clinical interventions between index test and reference standard                            |                         |
| Test results      | 23       | Cross tabulation of the index test results (or their distribution)  | Table 2, Table 3,       |
|                   |          | by the results of the reference standard  | Table S3, Table S       |
|                   | 24       | Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)                           | Along with each         |
|                   |          |   | result in               |
|                   |          |   | corresponding<br>tables |
|                   | 25       | Any adverse events from performing the index test or the reference standard                                       | Not applicable          |
| DISCUSSION        | 23       |   |                         |
|                   | 26       | Study limitations, including sources of potential bias, statistical uncertainty, and                              | Page 25                 |
|                   |          | generalisability  | , upc 20                |
|                   | 27       | Implications for practice, including the intended use and clinical role of the index test                         | Page 26                 |
|                   |          | r   |                         |



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| <br>29 | Where the full study protocol can be accessed         | No      |
|--------|---|---------|
|        |   |         |
| <br>30 | Sources of funding and other support; role of funders | Page 26 |
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## STARD 2015

### AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

## EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

### DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <u>http://www.equator-network.org/reporting-guidelines/stard.</u>



## Accuracy of Algorithms to Identify Patients With a Diagnosis of Major Cancers and Cancer Related Adverse Events in an administrative database: A validation study in an acute care hospital in Japan

| Journal:                             | BMJ Open  |  |  |  |  |  |
|--------------------------------------|---|--|--|--|--|--|
| Manuscript ID                        | bmjopen-2021-055459.R1  |  |  |  |  |  |
| Article Type:                        | Original research   |  |  |  |  |  |
| Date Submitted by the Author:        | 22-Jan-2022   |  |  |  |  |  |
| Complete List of Authors:            | Fujiwara, Takashi; Kurashiki Central Hospital, Department of<br>Management, Clinical Research Center; Kurashiki Central Hospital,<br>Department of Otolaryngology/Head and Neck Surgery<br>Kanemitsu, Takashi; Chugai Pharmaceutical Co Ltd, Medical Affairs<br>Division<br>Tajima, Kosei ; Chugai Pharmaceutical Co Ltd, Clinical Development<br>Division<br>Yuri, Akinori; Chugai Pharmaceutical Co Ltd, Drug Safety Division<br>Iwasaku, Masahiro; Kurashiki Central Hospital, Department of<br>Management, Clinical Research Center<br>Okumura, Yasuyuki; Real world Data Co., Ltd.<br>Tokumasu, Hironobu; Kurashiki Central Hospital, Department of<br>Management, Clinical Research Center; Real World Data Co., Ltd. |  |  |  |  |  |
| <b>Primary Subject<br/>Heading</b> : | Oncology  |  |  |  |  |  |
| Secondary Subject Heading:           | Oncology  |  |  |  |  |  |
| Keywords:                            | Adult oncology < ONCOLOGY, Breast tumours < ONCOLOGY,<br>Gynaecological oncology < GYNAECOLOGY, Respiratory tract tumours <<br>ONCOLOGY, Urological tumours < ONCOLOGY  |  |  |  |  |  |
|                                      |   |  |  |  |  |  |

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## Title page

# Title

Accuracy of Algorithms to Identify Patients With a Diagnosis of Major Cancers and Cancer-Related Adverse Events in an administrative database: A validation study in an acute care hospital in Japan

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# Abstract

**Objectives:** Validation studies in oncology are limited in Japan. This study was conducted to evaluate the accuracy of diagnosis and adverse event (AE) definitions for specific cancers in a Japanese health administrative real-world database (RWD).

**Design and setting:** Retrospective observational validation study to assess the diagnostic accuracy of electrical medical records (EMRs) and claim coding regarding oncology diagnosis and AEs based on medical record review in the RWD. The sensitivity and positive predictive value (PPV) with 95% confidence intervals (CIs) were calculated.

**Participants:** The validation cohort included patients with lung (n=2,257), breast (n=1,121), colorectal (n=1,773), ovarian (n=216), and bladder (n=575) cancer who visited the hospital between January 2014 and December 2018, and those with prostate cancer (n=3,491) visiting between January 2009 and December 2018, who were identified using EMRs.

Outcomes: Key outcomes included primary diagnosis, deaths, and AEs.

**Results:** For primary diagnosis, sensitivity and PPV for the respective cancers were as follows: lung, 100.0% (96.6–100.0) and 81.0% (74.9–86.2); breast, 100.0% (96.3–100.0) and 74.0% (67.3–79.9); colorectal, 100.0% (96.6–100.0) and 80.5% (74.3–85.8); ovarian, 89.8% (77.8–96.6) and 75.9 (62.8–86.1); bladder, 78.6% (63.2–89.7) and 67.3% (52.5–80.1); prostate, 100.0% (93.2–100.0) and 79.0% (69.7–86.5). Sensitivity and PPV for death were as follows: lung, 97.0% (84.2–99.9) and 100.0% (84.2–100.0); breast, 100.0% (1.3–100.0) and 100.0% (28.4–100.0); breast, 100.0% (1.3–100.0) and 100.0% (35.9–100.0) and 100.0% (9.4–100.0). ovarian, 100.0% (35.9–100.0) and 100.0% (19.4–100.0). Overall, PPV tended to be low, with the definition based on International Classification of Diseases, 10th revision alone for AEs.

Conclusion: Diagnostic accuracy was not so high, and therefore needs to be further

 investigated.

**Trial registration:** University hospital Medical Information Network (UMIN) Clinical Trials Registry; UMIN000039345.

# Strengths and limitations of this study

- To our knowledge, this is the first study in oncology in Japan that validates disease and adverse event definitions in a health administrative real-world database (RWD) using chart review based on electronic medical records data from a hospital as the reference standard.
- Validation was performed at a single facility, which may limit generalizability and transportability of the results.
- Study results are limited by the inherent issues related to the use of an RWD, which primarily stores medical information for the purpose of insurance claims.
- The diagnosis and adverse event definitions used in this study may not be the most suitable; thus, there is an opportunity to further deepen these definitions.
- Study methods for the consolidation of true positives for events with low incidence need to be further investigated as it was challenging to investigate outcomes with extremely low incidence.

# Keywords

database, electronic medical record, health administrative, real-world database, validation study

# **INTRODUCTION**

In recent years, evidence from routine clinical practice using data from real-world databases (RWDs) has increasingly gained importance in decision-making in healthcare, research, and drug development.[1] In addition, RWD studies can help generate evidence for advancement

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in precision medicine and facilitation of targeted and efficient patient care.[2] In line with this trend, evidence related to several aspects, such as health technology, expenditure forecasting, survival outcomes, time to therapy, and treatment efficacy, is increasingly being collected from RWD studies in oncology.[3-6]

However, it is important to validate case-identification algorithms to evaluate the accuracy of information sourced from RWDs, which is usually collected for purposes other than research.[7] To this end, several studies have been conducted outside of Japan to evaluate the accuracy of algorithms based on health administrative data in identifying cancer diagnoses or other outcomes using databases, such as registries, population-based cohorts, chart reviews, and electronic medical records (EMRs) as reference standards.[8-17]

The implementation of the revised ordinance of Good Postmarketing Study Practice by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan in 2018 suggests that the importance of using RWDs in post-marketing surveillance to investigate the safety and efficacy of pharmaceutical products is being recognized in Japan as well.[18] To encourage validation studies, the PMDA of Japan and Japan Society for Pharmacoepidemiology established a basic concept for conducting validation studies to verify diagnosis codes and other outcome definitions in Japanese RWDs.[19, 20] However, to our knowledge, only a few claims-based validation studies [21-32] have reported on outcomes in cancer [32, 33] to date. Thus, this necessitates validation studies on a wider range of cancer types in Japan using a reliable database as a reference standard. This study was conducted for validation of diagnosis and adverse event (AE) definitions for specific cancers in a Japanese RWD using a chart review by EMR.

# **PATIENTS AND METHODS**

## Study design

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This was a validation study of diagnosis and AE definitions in the health administrative RWD of the Health, Clinic, and Education Information Evaluation Institute (HCEI) conducted by chart review of EMRs from Kurashiki Central Hospital, Japan, as the reference standard.

## **Data collection**

Data were collected retrospectively from EMRs at the Kurashiki Central Hospital, Japan (Figure 1), which were the primary data source. All possible cases that met the diagnosis and AE definitions and cases other than all possible cases were identified using International Classification of Diseases, 10th revision (ICD-10) codes (Figures S1–S6) from the EMRs. Further, these cohorts were randomly sampled to verify the diagnoses and related events. EMRs were manually reviewed to verify the diagnosis of all possible cases. This verified dataset was anonymized and sent to Real World Data Co. Ltd., the vendor for HCEI. The verified dataset was linked deterministically to claims data and EMRs originally derived from erie the hospital.

#### Chart review based on EMR

A chart review for all possible cases was conducted by medical professionals, including medical doctors involved in the management of cancer patients and four clinical research coordinators (CRCs) at the Kurashiki Central Hospital, Japan. The diagnosis of cancer was made primarily by histopathological tests, followed by radiological diagnosis and findings based on the physician's clinical examination. At least two CRCs conducted chart reviews independently. Any disagreements were resolved by the two CRCs and by a medical doctor, if still unresolved.

### **HCEI database**

HCEI is an integrated RWD initiated in Japan and supported by Real World Data Co., Ltd. (Kyoto).[34] As of August 2020, HCEI was collecting information from approximately

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20 million patients from 190 medical institutions in Japan, including Kurashiki Central Hospital. The HCEI database covers 1.2% of the overall Japanese population and includes data from 1.3 million outpatients and 0.21 million inpatients in 2019.[34] Medical information is extracted from EMRs, claims, and Diagnosis Procedure Combination (DPC) in the HCEI database. Patient-level data from DPC, EMRs, and claims are integrated in advance at the hospital, anonymized, linked to a unique code, and standardized (**Figure 1**). The linked data are then provided to HCEI for storage on their server. Information on procedures (such as surgery) is obtained from claims, while information on laboratory tests and treatments is obtained from EMRs. Diagnosis data are obtained from both claims and EMRs. Per HCEI's security policy, personal identifiable information (such as date of birth) is not collected during data extraction. Master lists are constructed based on the national standards of the Ministry of Health, Labour and Welfare (MHLW) of Japan.[35]

# **Study ethics**

This study was approved by the Research Institute of Healthcare Data Science (https://rihds.org/ethic/) (RI2019010) and the institutional ethics committee of Kurashiki Central Hospital (KCH3301), and conducted under the tenets of the Declaration of Helsinki, Act on the Protection of Personal Information,[36] and Ethical Guidelines for Medical and Health Research Involving Human Subjects.[37] It was conducted under a joint research agreement between Kurashiki Central Hospital, Chugai Pharmaceutical Co., Ltd., and HCEI, and is registered at the UMIN Clinical Trials Registry (UMIN000039345). Target patients at Kurashiki Central Hospital could opt, on the hospital's website, to not disclose their information.

## Patient and public involvement in research

Patients or the public were not involved in the design or conduct, reporting or dissemination

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plans of our research.

### **Patient selection**

Patients with lung, breast, colorectal, ovarian, and bladder cancer who visited Kurashiki Central Hospital between January 2014 and December 2018 (**Figures S1–S5**), and those with prostate cancer (**Figure S6**) who visited the hospital between January 2009 and December 2018 were eligible for the study. Further information on inclusion criteria is provided in **Table S1**. Patients participating in clinical trials during the data extraction periods and those who were assigned the respective ICD-10 code for lung, colorectal, breast, ovarian, and bladder cancer from January 1, 2014, to January 31, 2014, and from November 1, 2018, to December 31, 2018, and that for prostate cancer from January 1, 2009, to January 31, 2009, and from November 1, 2018, to December 31, 2018, were excluded from the study. Patients diagnosed during these periods were excluded to avoid bias due to the time lag between suspected diagnosis by medical examination and confirmation of diagnosis by biopsy, when the outcome definition was potentially met.

The cohort entry date was the date when the respective cancer was diagnosed—January 2014 for lung, breast, colorectal, ovarian, and bladder cancer and January 2009 for prostate cancer—and the end date was December 31, 2018. To avoid selection of cases diagnosed before the cohort entry date, patients who were assigned the respective ICD-10 code for lung, colorectal, breast, ovarian, and bladder cancer before December 31, 2013, and that for prostate cancer before December 31, 2008, were excluded.

Eligible patients were stratified by random sampling as all possible and not possible cases. All possible cases included patients who met the ICD-10 code for the respective support during the specified data extraction period. Patients who were never assigned an ICD-10 code for the respective cancer; those with lung, colorectal, breast, ovarian, and bladder cancer who visited the hospital between January 1, 2014, and December 31, 2018;

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and those with prostate cancer between January 1, 2009, and December 31, 2018, were stratified as not possible cases. Overall, 200 cases each with lung, breast, or colorectal cancer and 100 cases each with ovarian, bladder, or prostate cancer were targeted and randomly selected from all possible cases for the EMR review, and not possible cases were also randomly selected using the same proportions.

### Outcomes and assessment of accuracy

Outcomes for validation included primary diagnosis, performance status (PS)  $\geq$ 2,[38] first/second/third recurrence or exacerbation, death, and AEs, particularly immune-related AEs (irAEs), associated with new diagnoses for patients with lung, breast, colorectal, ovarian, bladder, and prostate cancer. AEs included interstitial pneumonia, liver dysfunction, colitis/diarrhea, type 1 diabetes mellitus (T1DM), encephalitis/meningitis, nerve disorders (excluding paresthesia), myasthenia gravis, Guillain-Barré syndrome, skin disorder, rhabdomyolysis, myocarditis, perforation of digestive tract/fistula, hypoadrenocorticism, and febrile neutropenia.

Outcomes were defined by separate algorithms (**Tables S2 and S3**) for each cancer type using one variable or a combination of  $\geq 2$  variables, such as diagnoses, treatments, procedures, and laboratory test results. Lung cancer was further classified as primary, non-small cell, and small cell.

## Statistical analysis

The target sample size for random sampling was determined based on the feasibility of chart review. If  $\geq 100$  patients each meet the definition of primary diagnosis and true positives, the 95% confidence intervals (CIs) for positive predictive value (PPV) and sensitivity can be estimated with a precision of up to  $\pm 10\%$  for lung, breast, and colorectal cancer.[39] The sample size for ovarian, bladder, and prostate cancer was half that for lung, breast, and

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colorectal cancer.

In the dataset submitted by HCEI, accuracy for each cancer type was evaluated using sensitivity, specificity, PPV, and negative predictive value (NPV) for primary diagnosis, first recurrence/exacerbation, and death. Other outcomes were evaluated using only PPV to determine if the cases were true for those meeting the outcome definition. AEs were validated in patients with true primary cancer who had received chemotherapy. PPV was calculated only after confirming whether the outcome occurred within (before or after) 30 days of the patient meeting the outcome definition.

All possible cases refer to the population that is assumed to include all true patients,[19, 40-42] and included patients who met the ICD-10 code for the respective cancer in EMRs during the specified data extraction period. True positives were defined as patients in whom the outcomes occurred based on HCEI information and EMR review. In addition, patients were randomly selected from cases other than all possible cases at the same extraction rate as that for "all possible cases" to calculate the specificity and NPV for primary diagnosis, first recurrence/exacerbation, and death. The data extraction period for different cancer types was estimated based on the national survival rate survey of 2019 conducted by the National Cancer Center Council,[43] in which the survival period was 10 years for prostate cancer and 5 years for other cancer types. Likewise, a longer data extraction period was considered for prostate cancer to allow for the collection of true positives.

The frequency and 95% CIs were calculated for sensitivity, specificity, PPV, and NPV. 95% CIs were calculated by the symmetric CI method. The degree of agreement between two chart reviewers was evaluated using the kappa coefficient. Extrapolability of the Kurashiki Central Hospital database to that of other hospitals in HCEI database was assessed by comparing the distribution of patient characteristics (age at data extraction, sex, age at time of granting ICD10, observation periods). Outcome definitions used for identification of patients were as follows: A1 for lung cancer,  $\alpha 1$  for breast cancer,  $\beta 1$  for colorectal cancer,  $\gamma 1$  for ovarian cancer,  $\epsilon 1$  for bladder cancer, and  $\delta 1$  for prostate cancer (**Table S2**). Statistical analyses were conducted using R-4.0.2 software.

## RESULTS

# **Patient disposition**

Of the 256,418 patients who received medical treatment from 2014 to 2018, 2,257 with lung cancer (**Figure S1**), 1,121 with breast cancer (**Figure S2**), 1,773 with colorectal cancer (**Figure S3**), 216 with ovarian cancer (**Figure S4**), and 575 with bladder cancer (**Figure S5**) were included as all possible cases (**Table 1**). From 2009 to 2018, 3,491 patients with prostate cancer of 413,631 patients receiving medical treatment (**Figure S6**) were included as all possible cases (**Table 1**).

| Table 1. Stu | idy cohort |
|--------------|------------|
|--------------|------------|

| Cancer type     | Study period    | Patients who     | Target    | All possible | True     |
|-----------------|-----------------|------------------|-----------|--------------|----------|
|                 | for patient     | underwent        | patients, | cases, n     | cases, n |
|                 | selection and   | medical          | n         |              |          |
|                 | chart review    | treatment        |           |              |          |
|                 |                 | during the       |           |              |          |
|                 |                 | study periods, n |           |              |          |
| Lung cancer     | January 2014 to | 256,418          | 252,847   | 2,257        | 162      |
|                 | December 2018   |                  |           |              |          |
| Breast cancer   | January 2014 to | 256,418          | 253,358   | 1,121        | 148      |
|                 | December 2018   |                  |           |              |          |
| Colorectal      | January 2014 to | 256,418          | 252,733   | 1,773        | 161      |
| cancer          | December 2018   |                  |           |              |          |
| Ovarian cancer  | January 2014 to | 256,418          | 254,995   | 216          | 49       |
|                 | December 2018   |                  |           |              |          |
| Bladder cancer  | January 2014 to | 256,418          | 254,520   | 575          | 42       |
|                 | December 2018   |                  |           |              |          |
| Prostate cancer | January 2009 to | 413,631          | 410,356   | 3,491        | 79       |
|                 | December 2018   |                  |           |              |          |

For identifying patients with each cancer type, the following outcome definitions were used: A1 for lung cancer,  $\alpha 1$  for breast cancer,  $\beta 1$  for colorectal cancer,  $\gamma 1$  for ovarian cancer,  $\epsilon 1$  for bladder cancer, and  $\delta 1$  for prostate cancer (Table S2).

#### Lung cancer

The kappa value in chart reviews for diagnosis definitions was 0.982 (95% CI:

0.947–1.017) for primary lung cancer, 0.979 (95% CI: 0.950–1.008) for non-small cell lung cancer (NSCLC), 1.00 for small cell lung cancer (SCLC), and 0.982 (95% CI: 0.947–1.017) for death. There were 30 false negatives and 132 true positives for A1 using DPC diagnosis (**Figure 2**). Sensitivity was 100% with A2 using related definitive diagnosis (**Figure 2**). Although specificity, PPV, and NPV for NSCLC were high for B1 and B2 using cancer-related diagnosis codes, sensitivity was low (38.3%; **Table S4**). Accuracy was high for all statistical parameters for SCLC (**Figure 2**). Data on death could be extracted with high accuracy using EMR definitions (E1; **Figure 3**).

## **Breast cancer**

The kappa value in the chart review for diagnosis definitions was 1.000 and 0.961 (95% CI: 0.917–1.005) for death. The sensitivity was 100% for  $\alpha 2$  using EMR diagnosis (**Figure 2**) Sensitivity was as low as 62.8% and there were 55 false negatives in  $\alpha 1$  using DPC diagnosis (**Table S4**). The accuracy of death definitions for breast cancer was challenging to calculate because outcome events were very few owing to good disease prognosis (**Table S5**).

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# **Colorectal cancer**

The kappa value in the chart review for both diagnosis definitions and death was 0.953 (95%) CI: 0.900–1.006). There were 39 false positives in  $\beta$ 2 (Figure 2); 15 were diagnosed with colorectal cancer before 2014, two had malignancies that were excluded, and the remaining patients were diagnosed with another cancer on subsequent EMR examination. Death occurred in 4/57 target patients, and sensitivity and specificity of E1 were 100% each

(Figure 3).

## **Ovarian cancer**

The kappa value in the chart review for diagnosis definitions was 0.920 (95% CI: 0.843-0.997) and 0.940 (95% CI: 0.873-1.007) for death. PPV was higher with  $\gamma 1$  than with  $\gamma 2$  (75.9% vs 49.5%; **Table S4**). Sensitivity was higher with  $\gamma 2$  than with  $\gamma 1$  (100.0% vs 89.8%; Table S4). Death occurred in 5/21 target patients, and the sensitivity and specificity ·Zie of E1 were 100% each (Figure 3).

## **Bladder cancer**

The kappa value in the chart review for diagnosis definitions was 0.898 (95% CI: 0.812–0.985) and 0.878 (95% CI: 0.784–0.973) for death. Sensitivity was 100% in £2, but PPV was as low as 42.0% (Table S4). PPV was higher with  $\varepsilon$ 1 than with  $\varepsilon$ 2 (67.3% vs 42.0%; Table S4). Death occurred in 2/10 target patients, and the sensitivity and specificity of E1 were 100% each (Figure 3).

### **Prostate cancer**

The kappa value in the chart review for diagnosis definitions was 0.875 (95% CI: 0.755– 0.995) and 0.9045 (95% CI: 0.798–1.011) for death. PPV was 100% in δ1 (Table S4), and sensitivity was 100% in  $\delta 2$  (Figure 2). Death occurred in 4/36 target patients, and the sensitivity and specificity of E1 were 75% and 100%, respectively (Figure 3).

#### Adverse events

The overall PPV for all cancer types was <50%: 47.1% for interstitial pneumonia, 34.6% for liver disorders, 25.5% for colitis/diarrhea, and 13.3% for nerve disorders (excluding paresthesia) by related ICD-10 definitive diagnosis. Although PPV was 100% for encephalitis/meningitis and gastrointestinal perforation by related ICD-10 definitive diagnosis, only one case each was identified as these are rare AEs. For skin disorders, PPV was 76.4% by related ICD-10 definitive diagnosis and 70.4% when treatments were combined in the definition. A combination of related ICD-10 definitive diagnosis and treatments resulted in a PPV of 87.5% for liver disorders. By ICD-10-related definitive diagnosis and intravenous antibiotics use, PPV was 76.9%–100% for febrile neutropenia. PPV was 0% for T1DM.

No events of myasthenia gravis, Guillain-Barré syndrome, rhabdomyolysis, adrenal hypofunction, and myocarditis were identified in this analysis.

#### **Other outcomes**

Only one true positive case was extracted for PS  $\geq 2$  for lung cancer using the definition of rehabilitation status. Of 51 patients who had received chemotherapy, the PS was 0–1 for 33 patients, 2–4 for 16 patients, and unclear for two patients. Thus, only 1 (6.3%) true positive case with PS  $\geq 2$  was extracted using the definition of chemotherapy. Therefore, despite a PPV of 100.0%, it could be challenging to use the current definition of PS  $\geq 2$  in an administrative database study. Similarly, the accuracy of the definition of first recurrence/exacerbation was extremely low for all cancer types owing to very few true positives. Since the accuracy of the second and third recurrence/exacerbation was calculated based on the number of true positives during first recurrence/exacerbation, it could not be evaluated.

# Extrapolability of EMR data

Sex and age of all possible cases at the Kurashiki Central Hospital and all hospitals were

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similar (Table 2).

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| Гаble 2. Demograph | ic and observation       | n period of study | BMJ Open                           |                                     | 6/bmjopen-2021-055459 on 13 Ju | Page <b>16</b> of .          |
|--------------------|--------------------------|-------------------|------------------------------------|-------------------------------------|--------------------------------|------------------------------|
|                    | All possible<br>cases, n | Male, n (%)       | Age (years) at data<br>extraction, | Age (years) at the time of granting | Observation period             | Observation period<br>(days) |
|                    |                          |                   | mean (SD)                          | ICD-10,<br>mean (SD)                | mean (SD)                      | person-years                 |
| Lung cancer        |                          |                   |                                    |                                     | ed fro                         |                              |
| Kurashiki Central  | 2,477                    | 1,728 (69.8)      | 75.0 (9.9)                         | 72.8 (10.2)                         | 801 4 (626.7)                  | 1,985,024                    |
| Hospital           |                          |                   |                                    |                                     | tp://b                         |                              |
| All hospitals      | 19,861                   | 13,136 (66.1)     | 74.8 (10.2)                        | 73.5 (10.4)                         | 523 (552.4)                    | 10,405,993                   |
| Breast cancer      |                          |                   | C                                  |                                     | en.br                          |                              |
| Kurashiki Central  | 1,166                    | 10 (0.9)          | 67.0 (13.3)                        | 64.1 (13.3)                         | 1,022.6 (650.8)                | 1,192,400                    |
| Hospital           |                          |                   |                                    |                                     | m∕ or                          |                              |
| All hospitals      | 18,289                   | 131 (0.7)         | 64.7 (14.1)                        | 62.6 (14.1)                         | 780 (618.6)                    | 14,274,791                   |
| Colorectal cancer  |                          |                   |                                    |                                     | ii<br>19,                      |                              |
| Kurashiki Central  | 1,684                    | 989 (58.7)        | 73.6 (11.3)                        | 71.1 (11.6)                         | 930 (613.5)                    | 1,566,924                    |
| Hospital           |                          |                   |                                    |                                     | 4 by g                         |                              |
| All hospitals      | 23,501                   | 13,836 (58.9)     | 74.1 (11.3)                        | 72.1 (11.5)                         | 770 56 (596.2)                 | 18,110,552                   |
| Ovarian cancer     |                          |                   |                                    |                                     | 8962 (653.5)                   |                              |
| Kurashiki Central  | 265                      | 34 (12.8)         | 66.4 (15.4)                        | 63.9 (15.5)                         |                                | 237,497                      |
|                    |                          |                   |                                    |                                     | id by copyright.               |                              |

| All poss<br>cases,All hospitals2,592Bladder cancer7,402Kurashiki Central568Hospital7,402All hospitals7,402Prostate cancer3,13Kurashiki Central3,13Hospital32,13CD-10, International Classification of | n<br>2 145 (5.6)<br>446 (78.5)<br>8 5,810 (78.4)<br>1 3,057 (97.6) | Age (years) at data<br>extraction,<br>mean (SD)<br>64.1 (14.9)<br>77.6 (10.0)<br>76.9 (10.4)<br>76.5 (8.4) | Age (years) at the<br>time of granting<br>ICD-10,<br>mean (SD)<br>62.3 (15.1)<br>75.0 (10.5)<br>74.9 (10.6)<br>71.9 (8.7) | 66/bmjopen-2021-0<br>Observation period<br>67days)<br>mean (SD)<br>Uy<br>667<br>83 (581.1)<br>0<br>991<br>667<br>991<br>667<br>991<br>667<br>799<br>991<br>6611.8)<br>661<br>799<br>991<br>661<br>799<br>991<br>661<br>799<br>799<br>799<br>799<br>799<br>799<br>799<br>79   | Page 17 o<br>Observation perio<br>(days)<br>person-years<br>1,729,551<br>563,042<br>5,925,496<br>5,332,446 |
|---|--|--|---|--|--|
| All hospitals2,592Bladder cancerKurashiki Central568HospitalAll hospitals7,403Prostate cancerKurashiki Central3,13HospitalAll hospitals32,13  | n<br>2 145 (5.6)<br>446 (78.5)<br>8 5,810 (78.4)<br>1 3,057 (97.6) | extraction,<br>mean (SD)<br>64.1 (14.9)<br>77.6 (10.0)<br>76.9 (10.4)                                      | time of granting<br>ICD-10,<br>mean (SD)<br>62.3 (15.1)<br>75.0 (10.5)<br>74.9 (10.6)                                     | Observation period<br>(days)<br>mean (SD)<br>50<br>667<br>53 (581.1)<br>991<br>667<br>53 (581.1)<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | (days)<br>person-years<br>1,729,551<br>563,042<br>5,925,496  |
| All hospitals2,592Bladder cancerKurashiki Central568HospitalAll hospitals7,403Prostate cancerKurashiki Central3,13HospitalAll hospitals32,13  | 2 145 (5.6)<br>446 (78.5)<br>8 5,810 (78.4)<br>1 3,057 (97.6)      | mean (SD)<br>64.1 (14.9)<br>77.6 (10.0)<br>76.9 (10.4)   | ICD-10,<br>mean (SD)<br>62.3 (15.1)<br>75.0 (10.5)<br>74.9 (10.6)   | mæn (SD)   | person-years 1,729,551 563,042 5,925,496   |
| Bladder cancerKurashiki Central568Hospital7,403All hospitals7,403Prostate cancer3,13Kurashiki Central3,13Hospital32,13  | 446 (78.5)<br>8 5,810 (78.4)<br>1 3,057 (97.6)                     | 64.1 (14.9)<br>77.6 (10.0)<br>76.9 (10.4)  | mean (SD)         62.3 (15.1)         75.0 (10.5)         74.9 (10.6)   | 667<br>50<br>991<br>991<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8)<br>6611.8]<br>6611.8]<br>6611.8]<br>6611.8]<br>6611.8]<br>6611.8]<br>66 | 1,729,551<br>563,042<br>5,925,496  |
| Bladder cancerKurashiki Central568Hospital7,403All hospitals7,403Prostate cancer3,13Kurashiki Central3,13Hospital32,13  | 446 (78.5)<br>8 5,810 (78.4)<br>1 3,057 (97.6)                     | 77.6 (10.0)<br>76.9 (10.4)   | 62.3 (15.1)<br>75.0 (10.5)<br>74.9 (10.6)   | 991 (611.8)<br>991 (611.8)<br>799 (595.8)  | 563,042<br>5,925,496   |
| Bladder cancerKurashiki Central568Hospital7,403All hospitals7,403Prostate cancer3,13Kurashiki Central3,13Hospital32,13  | 446 (78.5)<br>8 5,810 (78.4)<br>1 3,057 (97.6)                     | 77.6 (10.0)<br>76.9 (10.4)   | 75.0 (10.5)<br>74.9 (10.6)  | 991 (611.8)<br>991 (611.8)<br>799 (595.8)  | 563,042<br>5,925,496   |
| Kurashiki Central568HospitalAll hospitals <b>Prostate cancer</b> Kurashiki CentralAll hospitalAll hospitals32,13  | 8 5,810 (78.4)<br>1 3,057 (97.6)                                   | 76.9 (10.4)  | 74.9 (10.6)   | 991 (611.8)<br>991 (611.8)<br>799 (595.8)  | 5,925,496  |
| Hospital All hospitals 7,403 Prostate cancer Kurashiki Central 3,13 Hospital All hospitals 32,13  | 8 5,810 (78.4)<br>1 3,057 (97.6)                                   | 76.9 (10.4)  | 74.9 (10.6)   | 991 (611.8)<br>991 (595.8)<br>799 (595.8)<br>1,703 (1,118.3)   | 5,925,496  |
| All hospitals7,403Prostate cancer7,403Kurashiki Central3,13Hospital32,13All hospitals32,13  | 1 3,057 (97.6)   | 904  |   | 7999 (595.8)   |  |
| Prostate cancerKurashiki Central3,13Hospital32,13   | 1 3,057 (97.6)   | 904  |   | 7999 (595.8)   |  |
| Kurashiki Central3,13HospitalAll hospitals32,13   | ,  | 76.5 (8.4)   | 71.9 (8.7)  |  | 5,332,446  |
| Hospital All hospitals 32,13  | ,  | 76.5 (8.4)   | 71.9 (8.7)  |  | 5,332,446  |
| All hospitals 32,13   | 6 28,690 (89.3)  |  |   |  |  |
| -   | 6 28,690 (89.3)  |  |   | open   |  |
| CD-10, International Classification   | ,,   | 77.7 (8.9)   | 74.2 (9.2)  | 1,34133 (1,041.6)  | 43,105,126   |
|   |  |  |   | om/ on April 19, 2024 by guest. Protected by copyright.  |  |

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# DISCUSSION

To our knowledge, this is the first study in oncology in Japan that validates disease names and AE definitions in an RWD by using chart review based on EMR as the gold standard. The diagnostic accuracy of primary diagnosis definitions by ICD-10 code in EMRs and DPC was evaluated. The PPV of diagnosis definition by DPC was relatively high, but sensitivity tended to be low. Although the diagnosis definition using DPC showed false negatives, it can be used for identifying patients with the respective disease. In the definitions using a definitive diagnosis from claims, PPV tended to decrease, but sensitivity tended to increase, thereby suggesting the importance of selecting outcome definition according to the purpose of the study.

The diagnostic accuracy of lung cancer by histological classification varied, with a sensitivity of 90.9% and PPV of 100.0% for SCLC and a sensitivity of 38.3% and PPV of 88.5% for NSCLC. Since the database is used primarily for insurance purposes, precise histological classification of lung cancer in EMR was likely not considered an important documentation item by physicians; therefore, only 38.3% of NSCLC patients received ICD-10 code of NSCLC. In SCLC, further studies to investigate improved methods of extracting false negatives are warranted.

The sensitivity for the EMR definition of breast cancer was 100% and DPC definition was as low as 62.8%. However, specificity was high with both EMR and DPC, and PPV ranged between 74.0% and 83.8%. In a previous study,[33] high sensitivity, specificity, and PPV were observed using definitions obtained by combining diagnostic and procedure codes in a Japanese claims database, suggesting that a combination of codes may result in higher accuracy.

The accuracy of the evaluation for death was high (97.0% sensitivity and 100.0% PPV) using the EMR definition for lung cancer. Although the sensitivity was high using the

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EMR definition for other cancers as well, further studies with a larger sample size are needed for confirmation. In cancer types other than lung cancer, which generally have a short survival according to the national cancer survival rate survey,[43] high sensitivity and PPV were observed with some definitions. The number of true negatives was high due to a longer survival at Kurashiki Central Hospital than expected, resulting in fewer deaths, which made the evaluation challenging. Thus, further investigation is necessary. In Japan, a death notification is submitted to the city office in case of death, but it is not linked to the hospital information system and EMRs. Therefore, there is a high likelihood of death data getting missed. However, Kurashiki Central Hospital follows up patients to check their health status, including death, and the likelihood of missing death data was therefore minimal.

Identification of cases with "recurrence/exacerbation" was extremely difficult in all cancer types by definition using items such as diagnoses with "recurrent" as a modifier, pathology-related medical practice code, or relevant surgical history. A previous validation study in breast cancer conducted using cancer registry and health maintenance organization data in the United States suggested that the quality of recurrence data may improve by using multiple recurrence algorithms, and a second cancer record in a cancer registry may potentially improve the diagnostic accuracy of recurrence [17] In another validation study conducted in Canada, Xu et al assessed the recurrence of breast cancer using data extracted from discharge abstracts, physician billing claims, and the National Ambulatory Care Reporting System.[15] They achieved a sensitivity of 94.2% and a PPV of 79.2% using definitions based on second round of chemotherapy, diagnostic procedures, treatment, visit to oncologists, patient age, and tumor stage.[15] True positives may be identified if specific therapies are used for the first recurrence/exacerbation, but further investigation is required. Similarly, PS  $\geq$ 2, an important variable for cancer, needs further investigation as it was extremely difficult to identify in this study.

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For AEs, PPV tended to be low overall with a definition based on ICD-10 alone, suggesting that a combination of definitions based on specific treatment modalities for AEs could be more appropriate. The definitions of febrile neutropenia and skin disorders had high PPVs and, therefore, can be generalized. The validation of T1DM as an AE was challenging as it was difficult to differentiate whether it was an existing comorbidity or developed newly. Moreover, T1DM as a primary diagnosis is rarely found, as the treatment usually targets complications of T1DM. For a few AEs, no true positives were identified, possibly because the outcome definition was developed for irAEs. However, owing to the absence of any reference standard for irAEs in clinical practice, chart review was instead conducted for AEs in general. For AEs with a low incidence, further large studies with a more appropriate validation method are required.

Since RWDs contain a large volume of information, it is not realistic to perform validation of multiple outcomes using all cases; instead, representative samples should be used as much as possible. However, such investigations are possible only in a small number of medical facilities. An efficient and precise validation dataset that comprehensively represents the database of a medical facility is required to minimize bias. Furthermore, definition of the disease and outcomes with low incidence should allow for the collection of as many true positives as possible.

In our study, all possible cases were extracted using the related ICD-10 code from medical information available in the study institution. The Health Insurance Bureau of the MHLW requires that a suspected diagnosis is changed to a definitive diagnosis as soon as a diagnosis is confirmed.[44] Since the RWD used in this study is a health insurance database, patients with a definitive diagnosis identified by ICD-10 code were deemed as all possible cases. To confirm the robustness of this hypothesis, 100 cases for each cancer type were randomly sampled from cases other than all possible cases to ensure that no patients with a

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primary diagnosis were included. A more efficient method is warranted for validation before a pharmacoepidemiology study using information from an RWD. In randomized controlled trials (RCTs), the efficacy and safety of treatments are assessed objectively; therefore, assessments are preset. However, in daily clinical practice, treatment decisions are subjective and based on the availability and type of medical resources, capabilities, treatment cost, and patient needs. Therefore, diagnosis and outcome definitions based on efficacy and safety assessments used in RCTs may not be suitable in RWD studies and should be carefully evaluated for use in daily clinical practice.

In this study, validation was performed at a single facility, potentially limiting generalizability and transportability of the results. Further, the results are limited by the inherent issues related to use of an RWD, which primarily stores medical information for the purpose of insurance claims. Moreover, ICD-10 codes for patients diagnosed or treated in other hospitals could be missing from EMRs at Kurashiki Central Hospital. Furthermore, chart review of all patients was not conducted in this study. Therefore, patients with a primary diagnosis among other than all possible cases could have been misclassified as true negatives, potentially underestimating the number of false negatives. Moreover, the diagnosis and AE definitions used in this study may not be the most suitable, and there is an opportunity to further deepen the definitions. For instance, the definition of AE in this study was developed based on treatment-associated irAEs and information on therapeutic agents such as steroids and treatments for allergy; however, definitions based on therapies used for general AE treatment could have been more appropriate. Furthermore, it was challenging to investigate outcomes with an extremely low incidence, for example, certain AEs. Therefore, study methods for consolidation of true positives for events with low incidence need to be investigated.

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# CONCLUSIONS

The results from our study suggest that diagnostic accuracy was not so high. DPC data could identify only a limited proportion of patients with cancer, while claims or DPC data could identify only a limited proportion of deceased patients. Since the number of cases was limited in this study, further investigation is required to validate the definitions using DPC and claims data. In view of the current claims process in Japan, EMR data are deemed appropriate to comprehensively identify patients with cancer or deceased patients for postmarketing surveillance using RWD. Although a high PPV was observed for a few AEs, precision could have been low owing to the low incidence of AEs, and therefore, validation of AEs warrants further investigation.

# Acknowledgments

The following persons from Kurashiki Central Hospital Clinical Research Center (Department of Management, Clinical Research Center, Kurashiki Central Hospital, Okayama, Japan) provided additional support: Maki Satomi coordinated at the study site for implementation of protocol procedures and Ryo Ishida, Emi Sato, Mami Yamaguchi, and Yuri Komatsubara contributed to the chart review. Takeshi Kimura of Real World Data Co., Ltd. provided support for statistical analysis and Yusuke Miyoshi of Chugai Pharmaceuticals Co., Ltd. provided administrative support. Akihiro Seki of Chugai Pharmaceuticals supported in developing the outcome definitions.

Editorial support in the form of medical writing, assembling tables, and creating high-resolution images based on the authors' detailed directions, collating author comments, copyediting, fact checking, and referencing was provided by Dr. Deepali Garg, MBBS, PGDHA, of Cactus Life Sciences (part of Cactus Communications) and funded by Chugai Pharmaceutical Co., Ltd.

# Funding

This study was funded by Chugai Pharmaceutical Co., Ltd.

# **Competing interests**

TK, KT, and AY are employees of Chugai Pharmaceutical Co., Ltd. TF reports personal fee for statistical analysis from Real World Data Co., Ltd. during the conduct of the study; personal fee for collaborative research from Chugai Pharmaceutical Co., Ltd.; and personal fee for statistical analysis from Real World Data Co., Ltd. outside the submitted work. MI has nothing to disclose. YO is an employee of Real World Data Co., Ltd. and reports personal fees from MSD K.K., Otsuka Pharmaceutical, and Kurashiki Central Hospital, outside the submitted work. HT reports personal fees for lecture from AYUMI Pharmaceutical Corporation and Chugai Pharmaceutical Co., Ltd., outside the submitted work and is an employee of Kurashiki Central Hospital and the Director of Real World Data, Co., Ltd.

# **Author contributions**

TF contributed to the study concept and design, and collection, analysis, and interpretation of data. TK, KT, YA and HT contributed to study concept and design, and data interpretation. MI contributed to collection and interpretation of data. YO and YA contributed to analysis and interpretation of data. All authors provided final approval for the version to be published.

# **Data sharing statement**

Data are available upon reasonable request.

# **Figure legends**

**Figure 1.** Health, Clinic, and Education Information Evaluation Institute/real-world database EMR, electronic medical record; HCEI, Health, Clinic, and Education Information Evaluation Institute; KCH, Kurashiki Central Hospital; RWD, real-world database

| Figure 2. Diagnosis definitions with high* accuracy  |
|--|
| CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value                    |
| *All accuracy values included for a definition are approximately 70% or more.                              |
|  |
| Figure 3. Death definitions with high* accuracy  |
| CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value                    |
| *All accuracy values included for a definition are >70%.   |
| Figure S1. Patient disposition: Lung cancer  |
| ICD-10, International Classification of Diseases, 10th Revision  |
| *Including 199 duplicates; #Study observation periods lasted from January 1, 2014, to January 31, 2014,    |
| and from November 1, 2018, to December 31, 2018, but were excluded as study washout periods;               |
| 100 patients were randomly sampled from patients other than all possible cases (patients given a suspected |
| diagnosis of related ICD-10) to confirm non-diagnosis of primary cancer.                                   |
| Random sampling was performed based on the extraction percentage.  |
| Figure S2. Patient disposition: Breast cancer  |
| ICD-10, International Classification of Diseases, 10th Revision  |
| *Including 61 duplicates; #Study observation periods lasted from January 1, 2014 to January 31, 2014, and  |
| from November 1, 2018, to December 31, 2018, but were excluded as study washout periods; 100 patients      |
| were randomly sampled from patients other than all possible cases (patients given a suspected diagnosis of |
| related ICD-10) to confirm non-diagnosis of primary cancer.  |
| Random sampling was performed based on the extraction percentage.  |
| Figure S3. Patient disposition: Colorectal cancer  |
| ICD-10, International Classification of Diseases, 10th Revision  |
| *Including 61 duplicates; #Study observation periods lasted from January 1 to January 31, 2014, and from   |
| November 1, 2018, to December 31, 2018, but were excluded as study washout periods; 100 patients were      |
| randomly sampled from patients other than all possible cases (patients given a suspected diagnosis of      |
| related ICD-10) to confirm non-diagnosis of primary cancer.  |
| Random sampling was performed based on the extraction percentage.  |
|  |

Figure S4. Patient disposition: Ovarian cancer

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ICD-10, International Classification of Diseases, 10th Revision

\*Including three duplicates; #Study observation periods lasted from January 1 to January 31, 2014, and from November 1, 2018, to December 31, 2018, but were excluded as study washout periods; 100 patients were randomly sampled from patients other than all possible cases (patients given a suspected diagnosis of related ICD-10) to confirm non-diagnosis of primary cancer.

Random sampling was performed based on the extraction percentage.

Figure S5. Patient disposition: Bladder cancer

ICD-10, International Classification of Diseases, 10th Revision

\*Including 25 duplicates; <sup>#</sup>Study observation periods lasted from January 1, 2014, to January 31, 2014, and from November 1, 2018, to December 31, 2018, but were excluded as study washout periods; 100 patients were randomly sampled from patients other than all possible cases (patients given a suspected diagnosis of related ICD-10) to confirm non-diagnosis of primary cancer.

Random sampling was performed based on the extraction percentage.

Figure S6. Patient disposition: Prostate cancer

ICD-10, International Classification of Diseases, 10th Revision

\*Including 44 duplicates; <sup>#</sup>Study observation periods lasted from January 1, 2009, to January 31, 2009, and from November 1, 2018, to December 31, 2018, but were excluded as study washout periods; 100 patients were sampled from patients other than all possible cases (patients given a suspected diagnosis of related

ICD-10) to confirm non-diagnosis of primary cancer.

Random sampling was performed based on the extraction percentage.

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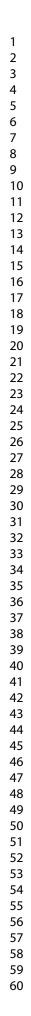
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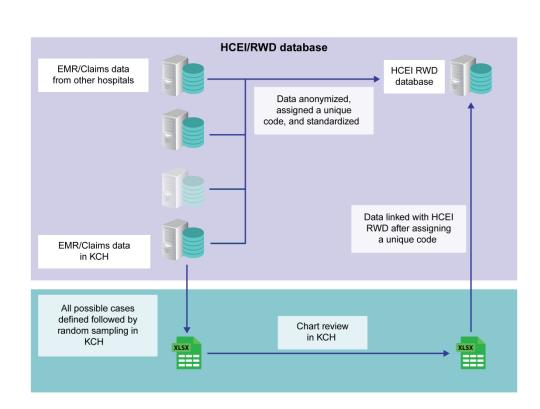


Figure 1. Health, Clinic, and Education Information Evaluation Institute/real-world database EMR: Electronic medical records; HCEI: Health, Clinic, and Education Information Evaluation Institute; KCH: Kurashiki Central Hospital; RWD: real-world database

|   |  |   |   |  | Index to  | est (A                                 | .1)   |  |   | ]   |   |
|---|--|---|---|--|---|--|---|--|---|---|---|
|   |  |   |   | Positive (r  | 1)  |  |   | Negative (n)   |   |   |   |
| Reference   | P  | Positive (n)  |   | 132  |   |  |   | 7  |   |   | (%) = 95.0<br>Cl: 89.9–98.0   |
| standard  |  | legative (n)  |   | 30   |   | 22,237                                 |   |  |   | NPV   | (%) = 99.9<br>Cl: 99.8–99.9   |
|   |  |   |   | Sensitivity (%)<br>95% CI: 74.6-   |   |  |   | ecificity (%) = 100.0<br>5% CI: 99.9–100.0   |   |   |   |
|   |  |   |   | 0070 01. 74.0  | Index to  | est (A                                 |   | 070 01. 00.0 100.0   |   | ]<br>]  |   |
|   |  |   |   | Positive (r  |   |  | -/  | Negative (n)   |   | 1   |   |
| Reference   | P  | ositive (n)   |   | 162  |   |  |   | 38   |   |   | (%) = 81.0<br>Cl: 74.9–86.2   |
| standard  |  | legative (n)  |   | 0  |   |  |   | 22,206   |   | NPV   | (%) = 100.0<br>: 100.0–100.0  |
|   | _  |   |   | Sensitivity (%) =<br>95% CI: 96.6-   |   |  |   | ecificity (%) = 99.8<br>95% CI: 99.8–99.9  |   |   |   |
|   |  |   |   |  | Index to  | est (A                                 | .4)   |  |   | i   |   |
|   |  |   |   | Positive (r  |   |  |   | Negative (n)   |   | 1   |   |
| Reference   | , P  | Positive (n)  |   | 128  |   |  |   | 7  |   |   | (%) = 94.8<br>Cl: 89.6–97.9   |
| standard  |  | legative (n)  |   | 34   |   |  |   | 22,237   |   | NPV (%) = 99.8<br>95% CI: 99.8–99.9   |   |
|   | _  |   |   | Sensitivity (%)  | - 70  |  | Spe   | cificity (%) = 100.0   |   |   |   |
| Small ce  | ll lun   | g cancer (Kapp  | ba value  | 95% CI: 71.8-  | -85.0   | C. P                                   | g   | 5% CI: 99.9–100<br>st cancer (Kappa value  | e [95% Cl]:<br>test (α2)  | 1.000 [1.000  | 0–1.000])   |
| . Small ce  | ll lun   | g cancer (Kapp<br>Positive (  | Index to  | 95% CI: 71.8-  | -85.0   | C. P                                   | g   | 5% CI: 99.9–100<br>st cancer (Kappa value  | test (α2)   | 1.000 [1.000  | 0–1.000])<br>]  |
|   |  |   | Index to  | 95% CI: 71.8-<br>[95% CI]: 1.000 [1.000<br>est (C1)  | -85.0<br>D-1.000])<br>PPV (%) = 100.0   |  | rimary breas  | 15% Cl: 99.9–100<br>st cancer (Kappa value<br>Index  | test (α2)<br>Nega   |   | PPV (%) = 3   |
|   | e (n)  | Positive (  | Index to  | 95% CI: 71.8-<br>[95% CI]: 1.000 [1.000<br>est (C1)<br>Negative (n)  | -85.0<br>-1.000])<br>PPV (%) = 100.0<br>95% CI: 58.7–100.0<br>NPV (%) = 100.0   |  | rimary breas  | st cancer (Kappa value<br>Index<br>Positive (n)  | test (α2)<br>Nega   | tive (n)  | PPV (%) = 3<br>95% CI: 67.3<br>NPV (%) = 1  |
| Positiv   | e (n)  | Positive (  | Index to<br>(n)<br>) = 90.9   | 95% CI: 71.8-<br>[95% CI]: 1.000 [1.00(<br>est (C1)<br>Negative (n)<br>0   | 85.0<br><b>PPV (%)</b> = 100.0<br><b>95%</b> CI: 58.7–100.0<br><b>NPV (%)</b> = 100.0<br><b>95%</b> CI: 100.0–100.0   | Reference                              | rimary breas  | st cancer (Kappa value<br>Index<br>Positive (n)  | test (α2)<br>Nega<br>45<br>Specificit   | tive (n)<br>52<br>5,002   | <b>PPV (%)</b> = 1<br>95% CI: 67.3  |
| Positiv<br>Negati                                 | e (n)<br>ve (n)                                      | Positive (<br>10<br>1<br>Sensitivity (%)<br>95% CI: 58.7  | Index to<br>(n)<br>= 90.9<br>-99.8  | 95% CI: 71.8-<br>[95% CI]: 1.000 [1.000<br>est (C1)<br>Negative (n)<br>0<br>22,395<br>Specificity (%) = 100.0  | -1.000]) PPV (%) = 100.0 95% CI: 58.7−100.0 NPV (%) = 100.0 95% CI: 100.0−100.0   | Reference<br>standard                  | rimary breas<br>Positive (n)<br>Negative (n)  | 15% Cl. 99.9–100           st cancer (Kappa value           Index           Positive (n)           148           0           Sensitivity (%) = 100.0   | test (α2)<br>Nega<br>45<br>Specificit<br>95% Cl:  | <b>ttive (n)</b><br>52<br>5,002<br><b>y (%) =</b> 99.9<br>99.8–99.9   | <b>PPV (%)</b> =<br>95% Cl: 67.3<br><b>NPV (%)</b> = 1<br>95% Cl: 100.0-  |
| Positiv<br>Negati                                 | e (n)<br>ve (n)                                      | Positive (<br>10<br>1<br>Sensitivity (%)<br>95% CI: 58.7  | Index to<br>(n)<br>) = 90.9<br>-99.8<br>Cappa va  | 95% CI: 71.8-<br>[95% CI]: 1.000 [1.000<br>ast (C1)<br>Negative (n)<br>0<br>22,395<br>Specificity (%) = 100.0<br>95% CI: 100.0-100.0   | -1.000]) PPV (%) = 100.0 95% CI: 58.7−100.0 NPV (%) = 100.0 95% CI: 100.0−100.0   | Reference<br>standard                  | rimary breas<br>Positive (n)<br>Negative (n)  | 55% CI: 99.9–100           st cancer (Kappa value           Positive (n)           148           0           Sensitivity (%) = 100.0           95% CI: 96.3–100.0           an cancer (Kappa value)  | test (α2)<br>Nega<br>45<br>Specificit<br>95% Cl:  | <b>ttive (n)</b><br>52<br>5,002<br><b>y (%) =</b> 99.9<br>99.8–99.9   | <b>PPV (%)</b> =<br>95% Cl: 67.3<br><b>NPV (%)</b> = 1<br>95% Cl: 100.0-  |
| Positiv<br>Positiv<br>Negati<br>Primary           | e (n)<br>ve (n)                                      | Positive (<br>10<br>1<br>Sensitivity (%)<br>95% CI: 58.7  | Index to<br>(n)<br>= 90.9<br>-99.8<br>Cappa va<br>Index t   | 95% CI; 71.8-<br>[95% CI]: 1.000 [1.000<br>ast (C1)<br>Negative (n)<br>0<br>22,395<br>Specificity (%) = 100.0<br>95% CI: 100.0-100.0<br>alue [95% CI]: 0.953 [0  | -1.000]) PPV (%) = 100.0 95% CI: 58.7−100.0 NPV (%) = 100.0 95% CI: 100.0−100.0   | Э Reference<br>standard                | rimary breas<br>Positive (n)<br>Negative (n)  | 55% CI: 99.9–100           st cancer (Kappa value           Positive (n)           148           0           Sensitivity (%) = 100.0           95% CI: 96.3–100.0           an cancer (Kappa value)  | test (α2)<br>Nega<br>45<br>Specificit<br>95% Cl:<br>ue [95% Cl]<br>test (γ1)  | <b>ttive (n)</b><br>52<br>5,002<br><b>y (%) =</b> 99.9<br>99.8–99.9   | <b>PPV (%)</b> =<br>95% Cl: 67.3<br><b>NPV (%)</b> = 1<br>95% Cl: 100.0-  |
| Positiv<br>Positiv<br>Negati<br>Primary           | e (n)<br>ve (n)<br>color                             | Positive (<br>10<br>1<br>Sensitivity (%)<br>95% CI: 58.7<br>ectal cancer (K   | Index to<br>(n)<br>= 90.9<br>-99.8<br>Cappa va<br>Index t   | 95% Cl; 71.8-<br>[95% Cl]: 1.000 [1.000<br>est (C1)<br>Negative (n)<br>0<br>22,395<br>Specificity (%) = 100.0<br>95% Cl: 100.0-100.0<br>slue [95% Cl]: 0.953 [0<br>est (β2)  | -1.000]) PPV (%) = 100.0 95% CI: 58.7−100.0 NPV (%) = 100.0 95% CI: 100.0−100.0   | Э Reference<br>standard                | rimary breas<br>Positive (n)<br>Negative (n)  | 55% CI: 99.9–100           st cancer (Kappa value           Index           Positive (n)           148           0           Sensitivity (%) = 100.0           95% CI: 96.3–100.0           an cancer (Kappa value           Index   | test (α2)<br>Nega<br>45<br>Specificit<br>95% Cl:<br>μe [95% Cl]<br>test (γ1)<br>Nega  | tive (n)<br>52<br>5,002<br>y (%) = 99.9<br>99.8–99.9<br>]: 0.920 [0.8   | <b>PPV (%)</b> =<br>95% Cl: 67.3<br><b>NPV (%)</b> = 1<br>95% Cl: 100.0-  |
| Positiv<br>Positiv<br>Negati<br>Primary           | e (n)<br>ve (n)<br>color<br>e (n)                    | Positive (<br>10<br>1<br>Sensitivity (%)<br>95% CI: 58.7<br>ectal cancer (K<br>Positive (<br>161  | Index to<br>(n)<br>= 90.9<br>-99.8<br>Cappa va<br>Index t   | 95% Cl; 71.8-<br>[95% Cl]: 1.000 [1.000<br>est (C1)<br>Negative (n)<br>0<br>22,395<br>Specificity (%) = 100.0<br>95% Cl: 100.0-100.0<br>hlue [95% Cl]: 0.953 [0<br>est (β2)<br>Negative (n)  | .85.0<br>→1.000])<br>PPV (%) = 100.0<br>95% CI: 58.7-100.0<br>95% CI: 100.0-100.0<br>95% CI: 100.0-100.0<br>.900-1.006])<br>PPV (%) = 80.5  | Э Reference<br>standard                | rimary breas<br>Positive (n)<br>Negative (n)  | 55% CI: 99.9–100           st cancer (Kappa value           Index           Positive (n)           148           0           Sensitivity (%) = 100.0           95% CI: 96.3–100.0           an cancer (Kappa value           Index           Positive (n)           44   | test (α2)<br>Nega<br>45<br>Specificit<br>95% Cl:<br>με [95% Cl]<br>test (γ1)<br>Nega  | tive (n)<br>52<br>5,002<br>y (%) = 99.9<br>99.8–99.9<br>]: 0.920 [0.8<br>tive (n)   | PPV (%) = 1<br>95% CI: 67.3<br>NPV (%) = 1<br>95% CI: 100.0-<br>43-0.997])  |
| Primary   | e (n)<br>ve (n)<br>color<br>e (n)                    | Positive (           10           1           Sensitivity (%)           95% CI: 58.7           ectal cancer (K           Positive (           161           0 | Index to<br>(n)<br>= 90.9<br>-99.8<br>(appa va<br>Index t<br>(n)<br>= 100.0                                 | 95% Cl; 71.8-<br>[95% Cl]: 1.000 [1.000<br>ast (C1)<br>0<br>22,395<br>Specificity (%) = 100.0<br>95% Cl: 100.0-100.0<br>stue [95% Cl]: 0.953 [0<br>est (β2)<br>Negative (n)<br>39  | -85.0<br>-1.000])<br>PPV (%) = 100.0<br>95% CI: 58.7−100.0<br>NPV (%) = 100.0<br>95% CI: 100.0−100.0<br>95% CI: 100.0−100.0<br>95% CI: 14.3−86.8<br>NPV (%) = 80.5<br>95% CI: 74.3−86.8                                   | Reference<br>standard                  | rimary breas<br>Positive (n)<br>Negative (n)  | 55% CI: 99.9–100           st cancer (Kappa value           Index           Positive (n)           148           0           Sensitivity (%) = 100.0           95% CI: 96.3–100.0           an cancer (Kappa value           Index           Positive (n)           44           5   | test (α2)<br>Nega<br>45<br>Specificit<br>95% Cl]<br>test (γ1)<br>Nega<br>11<br>Specificit   | tive (n)<br>52<br>5,002<br>y (%) = 99.9<br>99.8–99.9<br>]: 0.920 [0.8<br>tive (n)<br>14   | PPV (%) = 1<br>95% CI: 67.3<br>NPV (%) = 1<br>95% CI: 100.0-<br>43-0.997])<br>PPV (%) = 1<br>95% CI: 62.8<br>NPV (%) = 1  |
| Positiv<br>Negati<br>Primary<br>Positiv<br>Negati | e (n)<br>ve (n)<br>color<br>e (n)<br>ve (n)          | Positive (<br>10 1 Sensitivity (%) 95% CI: 58.7 ectal cancer (K Positive ( 161 0 Sensitivity (%) 95% CI: 96.6-  | Index to<br>(n)<br>= 90.9<br>-99.8<br>Cappa va<br>Index t<br>(n)<br>= 100.0<br>-100.0                       | 95% CI; 71.8-<br>[95% CI; 1.000 [1.000<br>est (C1)<br>Negative (n)<br>0<br>22,395<br>Specificity (%) = 100.0<br>95% CI: 100.0-100.0<br>alue [95% CI]: 0.953 [0<br>est (β2)<br>Negative (n)<br>39<br>28,309<br>Specificity (%) = 99.9   | .85.0<br>→1.000])<br>PPV (%) = 100.0<br>95% CI: 58.7-100.0<br>NPV (%) = 100.0<br>95% CI: 100.0-100.0<br>95% CI: 74.3-85.8<br>NPV (%) = 100.0<br>95% CI: 74.3-85.8<br>NPV (%) = 100.0<br>95% CI: 100.0-100.0               | Reference Reference standard           | Positive (n)<br>Negative (n)<br>rimary ovari<br>Positive (n)<br>Negative (n)                  | 55% CI: 99.9–100<br>st cancer (Kappa value<br>Positive (n)<br>148<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 96.3–100.0<br>an cancer (Kappa valu<br>Positive (n)<br>44<br>5<br>Sensitivity (%) = 89.8  | test (α2)<br>Nega<br>45<br>Specificit<br>95% Cl:<br>ie [95% Cl]<br>test (γ1)<br>Nega<br>11<br>Specificit<br>95% Cl:   | tive (n)<br>52<br>5002<br>y (%) = 99.9<br>99.8–99.9<br>j: 0.920 [0.8<br>tive (n)<br>14<br>.692<br>y (%) = 99.9<br>99.8–99.9                                   | PPV (%) = 1<br>95% C1: 67: 3<br>NPV (%) = 1<br>95% C1: 1000-<br>43-0.997])<br>PPV (%) = 1<br>95% C1: 62.8<br>NPV (%) = 1<br>95% C1: 99.7-   |
| Positiv<br>Negati<br>Primary<br>Positiv<br>Negati | e (n)<br>ve (n)<br>color<br>e (n)<br>ve (n)          | Positive (<br>10 1 Sensitivity (%) 95% CI: 58.7 ectal cancer (K Positive ( 161 0 Sensitivity (%) 95% CI: 96.6-  | Index to<br>(n)<br>-90.9<br>-99.8<br>Cappa va<br>Index t<br>(n)<br>= 100.0<br>-100.0<br>pa value            | 95% Cl; 71.8-<br>[95% Cl; 1.000 [1.000<br>est (C1)<br>Negative (n)<br>0<br>22,395<br>Specificity (%) = 100.0<br>95% Cl; 100.0-100.0<br>stored (β2)<br>Negative (n)<br>39<br>28,309<br>Specificity (%) = 99.9<br>95% Cl; 99.8-99.9  | .85.0<br>→1.000])<br>PPV (%) = 100.0<br>95% CI: 58.7-100.0<br>NPV (%) = 100.0<br>95% CI: 100.0-100.0<br>95% CI: 74.3-85.8<br>NPV (%) = 100.0<br>95% CI: 74.3-85.8<br>NPV (%) = 100.0<br>95% CI: 100.0-100.0               | Reference Reference standard           | Positive (n)<br>Negative (n)<br>rimary ovari<br>Positive (n)<br>Negative (n)                  | 55% CI: 99.9–100           st cancer (Kappa value           Index           Positive (n)           148           0           Sensitivity (%) = 100.0           95% CI: 96.3–100.0           an cancer (Kappa value           Index           Positive (n)           44           5           Sensitivity (%) = 89.8           95% CI: 77.8–96.6           tate cancer (Kappa value)  | test (α2)<br>Nega<br>45<br>Specificit<br>95% Cl:<br>ie [95% Cl]<br>test (γ1)<br>Nega<br>11<br>Specificit<br>95% Cl:   | tive (n)<br>52<br>5002<br>y (%) = 99.9<br>99.8–99.9<br>j: 0.920 [0.8<br>tive (n)<br>14<br>.692<br>y (%) = 99.9<br>99.8–99.9                                   | PPV (%) = 1<br>95% C1: 67: 3<br>NPV (%) = 1<br>95% C1: 1000-<br>43-0.997])<br>PPV (%) = 1<br>95% C1: 62.8<br>NPV (%) = 1<br>95% C1: 99.7-   |
| Positiv<br>Negati<br>Primary<br>Positiv<br>Negati | e (n)<br>ve (n)<br>color<br>e (n)<br>ve (n)          | Positive (<br>10 1 Sensitivity (%) 95% CI: 58.7 ectal cancer (K Positive ( 161 0 Sensitivity (%) 95% CI: 96.6-  | Index to<br>(n)<br>-90.9<br>-99.8<br>Cappa va<br>Index t<br>(n)<br>= 100.0<br>-100.0<br>pa value<br>Index t | 95% CI: 71.8-<br>[95% CI; 1.000 [1.000<br>est (C1)<br>Negative (n)<br>0<br>22,395<br>Specificity (%) = 100.0<br>95% CI: 100.0-100.0<br>store (β2)<br>Negative (n)<br>39<br>28,309<br>Specificity (%) = 99.9<br>95% CI: 99.8-99.9<br>95% CI: 99.8-99.9  | .85.0<br>→1.000])<br>PPV (%) = 100.0<br>95% CI: 58.7-100.0<br>NPV (%) = 100.0<br>95% CI: 100.0-100.0<br>95% CI: 74.3-85.8<br>NPV (%) = 100.0<br>95% CI: 74.3-85.8<br>NPV (%) = 100.0<br>95% CI: 100.0-100.0               | Reference Reference standard           | Positive (n)<br>Negative (n)<br>rimary ovari<br>Positive (n)<br>Negative (n)                  | 55% CI: 99.9–100           st cancer (Kappa value           Index           Positive (n)           148           0           Sensitivity (%) = 100.0           95% CI: 96.3–100.0           an cancer (Kappa value           Index           Positive (n)           44           5           Sensitivity (%) = 89.8           95% CI: 77.8–96.6           tate cancer (Kappa value)  | test (a2)<br>Nega<br>45<br>Specificit<br>95% Ci<br>test (y1)<br>Nega<br>11<br>Specificit<br>95% Ci<br>tue [95% Ci<br>tue [95% Ci  | tive (n)<br>52<br>5002<br>y (%) = 99.9<br>99.8–99.9<br>j: 0.920 [0.8<br>tive (n)<br>14<br>.692<br>y (%) = 99.9<br>99.8–99.9                                   | PPV (%) = 1<br>95% C1: 67: 3<br>NPV (%) = 1<br>95% C1: 1000-<br>43-0.997])<br>PPV (%) = 1<br>95% C1: 62.8<br>NPV (%) = 1<br>95% C1: 99.7-   |
| Primary I<br>Primary I                            | e (n)<br>ve (n)<br>color<br>e (n)<br>ve (n)          | Positive (<br>10 1 Sensitivity (%) 95% CI: 58.7 ectal cancer (K Positive ( 161 0 Sensitivity (%) 95% CI: 96.6 er cancer (Kap                                  | Index to<br>(n)<br>-90.9<br>-99.8<br>Cappa va<br>Index t<br>(n)<br>= 100.0<br>-100.0<br>pa value<br>Index t | 95% CI; 71.8-<br>[95% CI; 1.000 [1.000<br>est (C1)<br>Negative (n)<br>0<br>22.395<br>Specificity (%) = 100.0<br>95% CI: 100.0-100.0<br>hlue [95% CI]: 0.953 [0<br>est (β2)<br>Negative (n)<br>39<br>28,309<br>Specificity (%) = 99.9<br>95% CI: 99.8-99.9<br>a [95% CI]: 0.898 [0.8]<br>est (ε1)                 | .85.0<br>→1.000])<br>PPV (%) = 100.0<br>95% CI: 58.7-100.0<br>NPV (%) = 100.0<br>95% CI: 100.0-100.0<br>95% CI: 74.3-85.8<br>NPV (%) = 100.0<br>95% CI: 74.3-85.8<br>NPV (%) = 100.0<br>95% CI: 100.0-100.0               | G Reference<br>A standard - d standard | rimary breast<br>Positive (n)<br>Negative (n)<br>rimary ovari<br>Negative (n)<br>Negative (n) | 55% CI: 99.9–100           st cancer (Kappa value           Index           Positive (n)           148           0           Sensitivity (%) = 100.0           95% CI: 96.3–100.0           an cancer (Kappa value           Index           Positive (n)           44           5           Sensitivity (%) = 89.8           95% CI: 77.8–96.6           tate cancer (Kappa value           Index I                                     | test (a2)<br>Nega<br>95% Cl:<br>10 [95% Cl]<br>test (y1)<br>Nega<br>11<br>Specificit<br>95% Cl:<br>11ue [95% Cl<br>11ue [95% Cl]<br>Nega  | ttive (n)<br>52<br>;002<br>y (%) = 99.9<br>99.8–99.9<br>]: 0.920 [0.8<br>ttive (n)<br>14<br>.692<br>y (%) = 99.9<br>99.8–99.9<br>i]: 0.875 [0.7               | PPV (%) = '<br>95% C1: 67.3<br>NPV (%) = 1<br>95% C1: 100.0<br>43-0.997])<br>PPV (%) = '<br>95% C1: 62.8<br>NPV (%) = 1<br>95% C1: 99.7-<br>95% C1: 99.7-<br>95% C1: 99.7-<br>95% C1: 99.7-<br>95% C1: 99.7-<br>95% C1: 99.7-<br>95% C1: 90.7-<br>95% |
| Primary I<br>Primary I                            | e (n)<br>ve (n)<br>color<br>e (n)<br>ve (n)<br>bladd | Positive (<br>10 1 Sensitivity (%) 95% CI: 58.7 ectal cancer (K Positive ( 161 0 Sensitivity (%) 95% CI: 96.6 er cancer (Kap Positive ( 33                    | Index to<br>(n)<br>-90.9<br>-99.8<br>Cappa va<br>Index t<br>(n)<br>= 100.0<br>-100.0<br>pa value<br>Index t | 95% CI; 71.8-<br>[95% CI; 1.000 [1.000<br>est (C1)<br>Negative (n)<br>0<br>22.395<br>Specificity (%) = 100.0<br>95% CI: 100.0-100.0<br>hlue [95% CI]: 0.953 [0<br>est (β2)<br>Negative (n)<br>39<br>28,309<br>Specificity (%) = 99.9<br>95% CI: 99.8-99.9<br>a [95% CI]: 0.898 [0.8]<br>est (ε1)<br>Negative (n) | -85.0<br>→1.000])<br>PPV (%) = 100.0<br>95% CI: 58.7-100.0<br>NPV (%) = 100.0<br>95% CI: 100.0-100.0<br>95% CI: 74.3-85.8<br>NPV (%) = 100.0<br>95% CI: 74.3-85.8<br>NPV (%) = 100.0<br>95% CI: 100.0-100.0<br>12-0.985]) | Reference Reference standard           | rimary breast<br>Positive (n)<br>Negative (n)<br>rimary ovari<br>Negative (n)<br>Negative (n) | 55% CI: 99.9–100           st cancer (Kappa value           Index           Positive (n)           148           0           Sensitivity (%) = 100.0           95% CI: 96.3–100.0           an cancer (Kappa value           Index           Positive (n)           44           5           Sensitivity (%) = 89.8           95% CI: 77.8–96.6           tate cancer (Kappa value           Index t           Positive (n)           79 | test (a2)<br>Nega<br>95% Cl:<br>10 [95% Cl]<br>test (γ1)<br>Nega<br>95% Cl:<br>11<br>Specificit<br>95% Cl:<br>12 [95% Cl]<br>14 [95% Cl]<br>15 [95% Cl]<br>14 [95% Cl]<br>15 [95% Cl]<br>15 [95% Cl]<br>16 [95% Cl]<br>17 [95% Cl]<br>17 [95% Cl]<br>17 [95% Cl]<br>17 [95% Cl]<br>17 [95% Cl]<br>18 [95% Cl]<br>19 [95% Cl]<br>19 [95% Cl]<br>10 [95% Cl | ttive (n)<br>52<br>;002<br>y (%) = 99.9<br>99.8–99.9<br>i: 0.920 [0.8<br>ttive (n)<br>14<br>.692<br>y (%) = 99.9<br>99.8–99.9<br>ii]: 0.875 [0.7<br>ttive (n) | PPV (%) = 1<br>95% C1: 67: 3<br>NPV (%) = 1<br>95% C1: 1000-<br>43-0.997])<br>PPV (%) = 1<br>95% C1: 62.8<br>NPV (%) = 1<br>95% C1: 99.7-   |

Figure 2. Diagnosis definitions with high\* accuracy

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value \*All accuracy values included for a definition are approximately 70% or more.

189x198mm (300 x 300 DPI)

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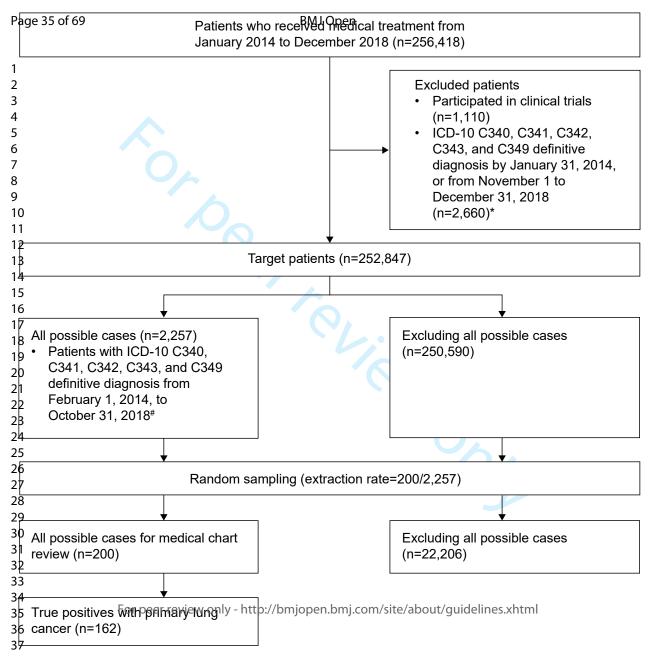
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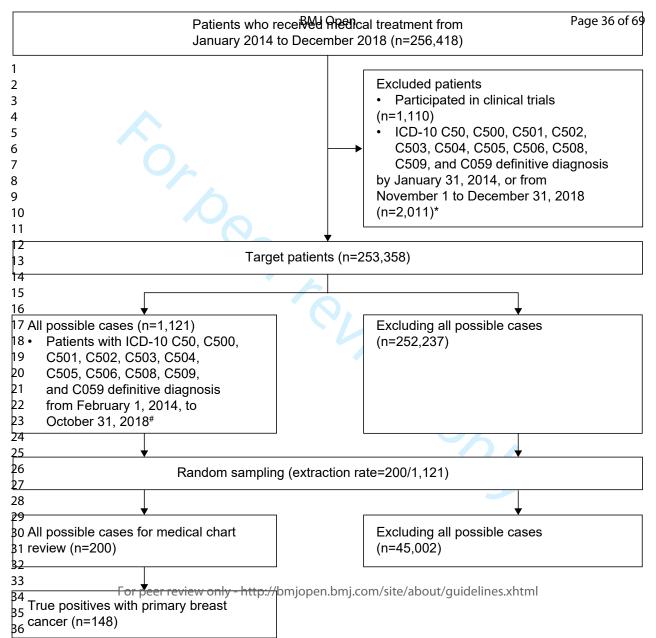
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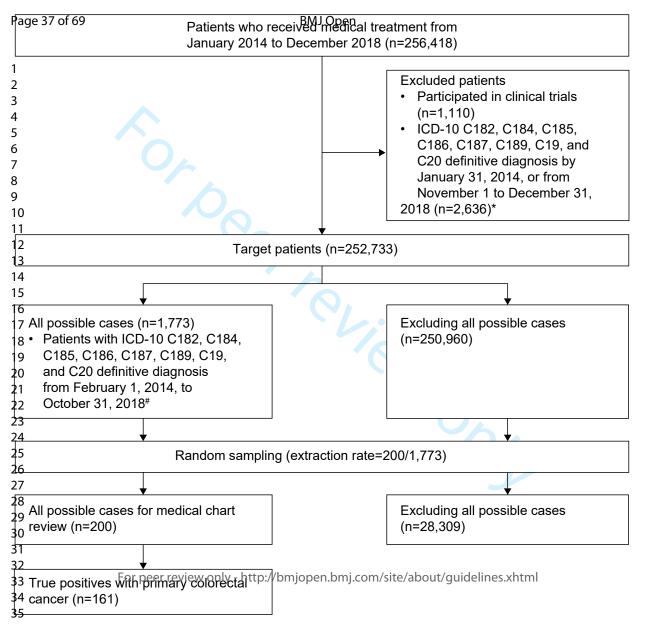
|                          |  | Index   | test (E1)  |  |  |  | Index   | test (E4)  |  |
|--------------------------|--|---|--|--|--|--|---|--|--|
|                          |  | Positive (n)  | Negative (n)   | 1  |  |  | Positive (n)  | Negative (n)   | 1  |
| dard                     | Positive (n)   | 32  | 0  | <b>PPV (%)</b> = 100.0<br>95% CI: 84.2–100.0   | Reference<br>standard<br>Z J   | ositive (n)  | 32  | 0  | PPV (%) = 100<br>95% CI: 84.2–10   |
| standard                 | Negative (n)   | 1   | 40   | NPV (%) = 97.6<br>95% CI: 87.1–99.9  | Refer<br>stan  | legative (n)   | 1   | 40   | NPV (%) = 97.<br>95% CI: 87.1–99   |
|                          |  | Sensitivity (%) = 97.0<br>95% CI: 84.2–99.9   | Specificity (%) = 100.0<br>95% CI: 87.1–100.0  |  |  |  | Sensitivity (%) = 97.0<br>95% CI: 84.2-99.9   | Specificity (%) = 100.0<br>95% CI: 87.1–100.0  |  |
| Br                       | reast cancer   | r (Kappa value [95% Cl  | ]: 0.961 [0.917–1.005]   | )  |  |  |   |  |  |
|                          |  | Index 1   | test (E1)  | ]  |  |  | Index   | test (E4)  |  |
|                          |  | Positive (n)  | Negative (n)   | ]  |  |  | Positive (n)  | Negative (n)   |  |
| standard                 | Positive (n)   | 1   | 0  | <b>PPV (%)</b> = 100.0<br>95% CI: 1.3–100.0  | Reference<br>standard<br>Z J   | ositive (n)  | 1   | 0  | <b>PPV (%)</b> = 100<br>95% CI: 1.3–10   |
| star                     | Negative (n)   | 0   | 104  | NPV (%) = 100.0<br>95% CI: 94.8–100.0  | Refe<br>star<br>z  | legative (n)   | 0   | 104  | NPV (%) = 100<br>95% CI: 94.8–10   |
|                          |  | Sensitivity (%) = 100.0<br>95% CI: 1.3–100.0  | Specificity (%) = 100.0<br>95% CI: 94.8–100.0  |  |  |  | Sensitivity (%) = 100.0<br>95% CI: 1.3–100.0  | Specificity (%) = 100.0<br>95% CI: 94.8–100.0  |  |
| Co                       | olorectal ca   | ncer (Kappa value [95%  | % CI]: 0.953 [0.900-1.0  | 00])   |  |  |   |  |  |
|                          |  | Index   | test (E1)  | ]  |  |  | Index   | test (E4)  |  |
|                          |  | Positive (n)  | Negative (n)   | 1  |  |  | Positive (n)  | Negative (n)   | 1  |
| dard                     | Positive (n)<br>Negative (n)   | 4   | 0  | <b>PPV (%)</b> = 100.0<br>95% CI: 28.4–100.0   | ence<br>dard   | Positive (n)<br>legative (n)                                 | 4   | 0  | PPV (%) = 100<br>95% CI: 28.4–10   |
| đ                        | Negative (n)   | 0   | 53   | NPV (%) =100.0   | l a el l   | legative (n)   | 0   | 53   | NPV (%) = 100  |
| S                        | Negative (II)  | 0   |  | 95% CI: 90.1-100.0   | st Re  | regative (ii)  |   |  | 95% CI: 90.1–10  |
| S                        | Negative (II)  | Sensitivity (%) = 100.0<br>95% CI: 28.4–100.0   |  |  | st<br>st   | iegauve (ii)   | Sensitivity (%) = 100.0<br>95% CI: 28.4–100.0   | Specificity (%) = 100.0<br>95% CI: 90.1–100.0  | 95% CI: 90.1–10  |
|                          |  | Sensitivity (%) = 100.0   | Specificity (%) = 100.0<br>95% CI: 90.1–100.0  |  | St St  |  |   |  | 95% CI: 90.1–10  |
|                          |  | Sensitivity (%) = 100.0<br>95% CI: 28.4–100.0<br>er (Kappa value [95% C   | Specificity (%) = 100.0<br>95% CI: 90.1–100.0  |  | st   |  | 95% CI: 28.4–100.0  |  | 95% CI: 90.1–10  |
| 0                        |  | Sensitivity (%) = 100.0<br>95% CI: 28.4–100.0<br>er (Kappa value [95% C   | Specificity (%) = 100.0<br>95% Cl: 90.1–100.0<br>Cl]: 0.940 [0.873–1.007   | (r<br>)<br>  |  |  | 95% CI: 28.4–100.0  | 95% CI: 90.1–100.0   | 95% CI: 90.1–10  |
| 0                        |  | Sensitivity (%) = 100.0<br>95% CI: 28.4–100.0<br>er (Kappa value [95% C   | Specificity (%) = 100.0<br>95% Cl: 90.1–100.0<br>Cl]: 0.940 [0.873–1.007<br>test (E1)  | <b>PPV (%)</b> = 100.0<br>95% CI: 35.9–100.0   |  |  | 95% CI: 28.4–100.0  | 95% CI: 90.1-100.0   | <b>PPV (%)</b> = 100<br>95% CI: 35.9–10  |
| ndard                    | varian cance   | Sensitivity (%) = 100.0<br>95% Cl: 28.4–100.0<br>er (Kappa value [95% C<br>Index 1<br>Positive (n)  | Specificity (%) = 100.0<br>95% CI: 90.1–100.0<br>Ci]: 0.940 [0.873–1.007<br>test (E1)<br>Negative (n)  | ])<br>PPV (%) = 100.0  |  | Positive (n)<br>legative (n)                                 | 95% CI: 28.4–100.0<br>Index t<br>Positive (n)   | 95% CI: 90.1–100.0   | <b>PPV (%)</b> = 100<br>95% CI: 35.9–10<br><b>NPV (%)</b> = 100  |
| 0                        | <b>varian cance</b><br>Positive (n)  | Sensitivity (%) = 100.0<br>95% Cl: 28.4–100.0<br>er (Kappa value [95% C<br>Index t<br>Positive (n)<br>5   | Specificity (%) = 100.0<br>95% CI: 90.1–100.0<br>CI]: 0.940 [0.873–1.007<br>test (E1)<br>Negative (n)<br>0<br>16   | ])<br><b>PPV (%)</b> = 100.0<br>95% Ci: 35.9-100.0<br><b>NPV (%)</b> = 100.0<br>95% Ci: 71.3-100.0   |  |  | 95% CI: 28.4–100.0<br>Index t<br>Positive (n)<br>5<br>0   | 95% CI: 90.1–100.0<br>test (E4)<br>Negative (n)<br>0   | 95% CI: 90.1-10<br>PPV (%) = 100<br>95% CI: 35.9-10<br>NPV (%) = 100<br>95% CI: 71.3-10  |
| standard                 | varian cance<br>Positive (n)<br>Negative (n)   | Sensitivity (%) = 100.0<br>95% Cl: 28.4–100.0<br>er (Kappa value [95% C<br>Index t<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0   | Specificity (%) = 100.0<br>95% Ci: 90.1–100.0<br>Ci]: 0.940 [0.873–1.007<br>test (E1)<br>Negative (n)<br>0<br>16<br>Specificity (%) = 100.0<br>95% Ci: 71.3–100.0  | ))<br>PPV (%) = 100.0<br>95% Cl: 35.9-100.0<br>NPV (%) = 100.0<br>95% Cl: 71.3-100.0   |  |  | 95% CI: 28.4–100.0<br>Index 1<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0  | 95% CI: 90.1–100.0<br>iest (E4)<br>Negative (n)<br>0<br>16<br>Specificity (%) = 100.0  | <b>PPV (%)</b> = 100<br>95% CI: 35.9–10<br><b>NPV (%)</b> = 100  |
| standard                 | varian cance<br>Positive (n)<br>Negative (n)   | Sensitivity (%) = 100.0<br>95% Cl: 28.4–100.0<br>er (Kappa value [95% C<br>Index t<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% Cl: 35.9–100.0<br>r (Kappa value [95% C  | Specificity (%) = 100.0<br>95% Ci: 90.1–100.0<br>Ci]: 0.940 [0.873–1.007<br>test (E1)<br>Negative (n)<br>0<br>16<br>Specificity (%) = 100.0<br>95% Ci: 71.3–100.0  | ))<br>PPV (%) = 100.0<br>95% Cl: 35.9-100.0<br>NPV (%) = 100.0<br>95% Cl: 71.3-100.0   |  |  | 95% CI: 28.4–100.0<br>Index 1<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0  | 95% CI: 90.1–100.0<br>iest (E4)<br>Negative (n)<br>0<br>16<br>Specificity (%) = 100.0  | <b>PPV (%)</b> = 100<br>95% CI: 35.9–10<br><b>NPV (%)</b> = 100  |
| standard                 | varian cance<br>Positive (n)<br>Negative (n)   | Sensitivity (%) = 100.0<br>95% Cl: 28.4–100.0<br>er (Kappa value [95% C<br>Index t<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% Cl: 35.9–100.0<br>r (Kappa value [95% C  | Specificity (%) = 100.0<br>95% Ci: 90.1–100.0<br>Ci]: 0.940 [0.873–1.007<br>test (E1)<br>Negative (n)<br>0<br>16<br>Specificity (%) = 100.0<br>95% Ci: 71.3–100.0<br>Ci]: 0.878 [0.784-0.973]  | ))<br>PPV (%) = 100.0<br>95% Cl: 35.9-100.0<br>NPV (%) = 100.0<br>95% Cl: 71.3-100.0   | Reference<br>standard<br>Z 0   | ²ositive (n)<br>legative (n)                                 | 95% CI: 28.4–100.0<br>Index 1<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0  | 95% CI: 90.1–100.0<br>test (E4)<br>Negative (n)<br>0<br>16<br>Specificity (%) = 100.0<br>95% CI: 71.3–100.0  | <b>PPV (%) =</b> 100<br>95% CI: 35.9–10<br><b>NPV (%) =</b> 100  |
| g standard O             | varian cance<br>Positive (n)<br>Negative (n)   | Sensitivity (%) = 100.0<br>95% CI: 28.4–100.0<br>er (Kappa value [95% C<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0<br>er (Kappa value [95% C  | Specificity (%) = 100.0<br>95% CI: 90.1–100.0<br>CI]: 0.940 [0.873–1.007<br>test (E1)<br>Negative (n)<br>0<br>16<br>Specificity (%) = 100.0<br>95% CI: 71.3–100.0<br>CI]: 0.878 [0.784-0.973]<br>test (E1)   | <ul> <li><b>PPV (%)</b> = 100.0</li> <li>95% CI: 35.9-100.0</li> <li>95% CI: 71.3-100.0</li> <li>95% CI: 71.3-100.0</li> <li>95% CI: 9.4-100.0</li> </ul>  | Reference<br>standard<br>Z 0   | ²ositive (n)<br>legative (n)                                 | 95% CI: 28.4–100.0<br>Index 1<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0  | 95% CI: 90.1–100.0<br>test (E4)<br>Negative (n)<br>0<br>16<br>Specificity (%) = 100.0<br>95% CI: 71.3–100.0<br>test (E4)   | <b>PPV (%)</b> = 100<br>95% CI: 35.9–10<br>95% CI: 71.3–10<br>95% CI: 71.3–10<br>95% CI: 9.4–10  |
| ndard E standard O       | varian canco<br>Positive (n)<br>Negative (n)<br>adder cance  | Sensitivity (%) = 100.0<br>95% Cl: 28.4–100.0<br>er (Kappa value [95% C<br>Index 1<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% Cl: 35.9–100.0<br>er (Kappa value [95% C<br>Index 1<br>Positive (n)<br>2<br>0  | Specificity (%) = 100.0<br>95% Ci: 90.1–100.0<br>Ci]: 0.940 [0.873–1.007<br>test (E1)<br>0<br>Specificity (%) = 100.0<br>95% Ci: 71.3–100.0<br>Si]: 0.878 [0.784-0.973]<br>test (E1)<br>Negative (n)<br>0<br>8   | ))<br>PPV (%) = 100.0<br>95% CI: 35.9-100.0<br>NPV (%) = 100.0<br>95% CI: 71.3-100.0<br>95% CI: 9.4-100.0<br>95% CI: 51.8-100.0<br>95% CI: 51.8-100.0  | Reference<br>standard<br>Z 0   |  | 95% CI: 28.4–100.0<br>Index 1<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0<br>Index 1<br>Positive (n)<br>2<br>0   | 95% CI: 90.1–100.0<br>test (E4)<br>0<br>16<br>Specificity (%) = 100.0<br>95% CI: 71.3–100.0<br>test (E4)<br>Negative (n)<br>0<br>8   | PPV (%) = 100<br>95% CI: 35.9–10<br>95% CI: 71.3–10<br>95% CI: 71.3–10<br>95% CI: 9.4–10<br>95% CI: 9.4–10<br>95% CI: 9.4–10                   |
| g standard O             | Positive (n)<br>Negative (n)<br>adder cance  | Sensitivity (%) = 100.0<br>95% Cl: 28.4–100.0<br>er (Kappa value [95% C<br>Index I<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% Cl: 35.9–100.0<br>er (Kappa value [95% C<br>Index I<br>Positive (n)<br>2   | Specificity (%) = 100.0<br>95% Ci: 90.1–100.0<br>Ci]: 0.940 [0.873–1.007<br>test (E1)<br>0<br>Specificity (%) = 100.0<br>95% Ci: 71.3–100.0<br>Si]: 0.878 [0.784-0.973]<br>test (E1)<br>Negative (n)<br>0<br>8   | ))<br>PPV (%) = 100.0<br>95% CI: 35.9-100.0<br>NPV (%) = 100.0<br>95% CI: 71.3-100.0<br>95% CI: 9.4-100.0<br>95% CI: 51.8-100.0<br>95% CI: 51.8-100.0  | Reference<br>standard<br>Z 0   | ²ositive (n)<br>legative (n)                                 | 95% CI: 28.4–100.0<br>Index 1<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0<br>Index 1<br>Positive (n)<br>2  | 95% CI: 90.1–100.0<br>test (E4)<br>0<br>16<br>Specificity (%) = 100.0<br>95% CI: 71.3–100.0<br>test (E4)<br>Negative (n)<br>0<br>8   | PPV (%) = 100<br>95% CI: 35.9–10<br>95% CI: 71.3–10<br>95% CI: 71.3–10<br>95% CI: 9.4–10<br>95% CI: 9.4–10<br>95% CI: 9.4–10                   |
| standard B standard O    | Positive (n)<br>Negative (n)<br>adder cance<br>Positive (n)<br>Negative (n)                                | Sensitivity (%) = 100.0<br>95% CI: 28.4–100.0<br>er (Kappa value [95% C<br>95% CI: 28.4–100.0<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0<br>er (Kappa value [95% C<br>95% CI: 9.4–100.0<br>95% CI: 9.4–100.0  | Specificity (%) = 100.0<br>95% CI: 90.1–100.0<br>CI]: 0.940 [0.873–1.007<br>test (E1)<br>0<br>Specificity (%) = 100.0<br>95% CI: 71.3–100.0<br>CI]: 0.878 [0.784-0.973]<br>test (E1)<br>Negative (n)<br>0<br>8<br>Specificity (%) = 100.0<br>95% CI: 51.8–100.0  | PPV (%) = 100.0         95% CI: 35.9-100.0         95% CI: 91.00.0         95% CI: 91.00.0         95% CI: 94.4-100.0         95% CI: 91.4-100.0         95% CI: 51.8-100.0  | Reference<br>standard<br>Z 0   | ²ositive (n)<br>legative (n)                                 | 95% CI: 28.4–100.0<br>Index I<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0<br>Index I<br>Positive (n)<br>2<br>0<br>Sensitivity (%) = 100.0                      | 95% CI: 90.1–100.0<br>test (E4)<br>Negative (n)<br>0<br>16<br>Specificity (%) = 100.0<br>95% CI: 71.3–100.0<br>test (E4)<br>Negative (n)<br>0<br>8<br>Specificity (%) = 100.0  | <b>PPV (%) =</b> 100<br>95% CI: 35.9–10<br><b>NPV (%) =</b> 100  |
| standard B standard O    | Positive (n)<br>Negative (n)<br>adder cance<br>Positive (n)<br>Negative (n)                                | Sensitivity (%) = 100.0<br>95% CI: 28.4–100.0<br>er (Kappa value [95% C<br>95% CI: 28.4–100.0<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0<br>er (Kappa value [95% C<br>95% CI: 9.4–100.0<br>95% CI: 9.4–100.0  | Specificity (%) = 100.0<br>95% CI: 90.1–100.0<br>CI]: 0.940 [0.873–1.007<br>test (E1)<br>0<br>Specificity (%) = 100.0<br>95% CI: 71.3–100.0<br>CI]: 0.878 [0.784-0.973]<br>test (E1)<br>Negative (n)<br>0<br>8<br>Specificity (%) = 100.0<br>95% CI: 51.8–100.0  | PPV (%) = 100.0         95% CI: 35.9-100.0         95% CI: 91.00.0         95% CI: 91.00.0         95% CI: 94.4-100.0         95% CI: 91.4-100.0         95% CI: 51.8-100.0  | Reference<br>standard<br>Z 0   | ²ositive (n)<br>legative (n)                                 | 95% CI: 28.4-100.0<br>Index 1<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9-100.0<br>Index 1<br>Positive (n)<br>2<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 9.4-100.0 | 95% CI: 90.1–100.0<br>test (E4)<br>Negative (n)<br>0<br>16<br>Specificity (%) = 100.0<br>95% CI: 71.3–100.0<br>test (E4)<br>Negative (n)<br>0<br>8<br>Specificity (%) = 100.0  | PPV (%) = 100<br>95% CI: 35.9–10<br>95% CI: 71.3–10<br>95% CI: 71.3–10<br>95% CI: 9.4–10<br>95% CI: 9.4–10<br>95% CI: 9.4–10                   |
| La standard B standard O | Positive (n)<br>Negative (n)<br>adder cance<br>Positive (n)<br>Negative (n)                                | Sensitivity (%) = 100.0<br>95% CI: 28.4–100.0<br>er (Kappa value [95% C<br>95% CI: 28.4–100.0<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0<br>er (Kappa value [95% C<br>95% CI: 9.4–100.0<br>95% CI: 9.4–100.0  | Specificity (%) = 100.0<br>95% CI: 90.1–100.0<br>CI]: 0.940 [0.873–1.007<br>test (E1)<br>0<br>Specificity (%) = 100.0<br>95% CI: 71.3–100.0<br>CI]: 0.878 [0.784-0.973]<br>test (E1)<br>Negative (n)<br>0<br>8<br>Specificity (%) = 100.0<br>95% CI: 51.8–100.0  | <ul> <li><b>PPV (%)</b> = 100.0</li> <li>95% CI: 35.9−100.0</li> <li><b>PPV (%)</b> = 100.0</li> <li>95% CI: 71.3−100.0</li> <li>95% CI: 9.4−100.0</li> <li>95% CI: 9.4−100.0</li> <li><b>PPV (%)</b> = 100.0</li> <li>95% CI: 51.8−100.0</li> </ul>   | Reference<br>standard <u>z v</u>   | ²ositive (n)<br>legative (n)                                 | 95% CI: 28.4-100.0<br>Index 1<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9-100.0<br>Index 1<br>Positive (n)<br>2<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 9.4-100.0 | 95% CI: 90.1–100.0<br>test (E4)<br>Negative (n)<br>0<br>16<br>Specificity (%) = 100.0<br>95% CI: 71.3–100.0<br>test (E4)<br>Negative (n)<br>0<br>8<br>Specificity (%) = 100.0<br>95% CI: 51.8–100.0  | <b>PPV (%)</b> = 100<br>95% CI: 35.9–10<br><b>NPV (%)</b> = 100<br>95% CI: 9.1–10<br>95% CI: 9.4–10<br><b>NPV (%)</b> = 100<br>95% CI: 51.8–10 |
| La standard B standard O | Positive (n)<br>Negative (n)<br>adder cance<br>Positive (n)<br>Negative (n)                                | Sensitivity (%) = 100.0<br>95% CI: 28.4–100.0<br>er (Kappa value [95% C<br>0<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0<br>er (Kappa value [95% C<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 9.4–100.0<br>er (Kappa value [95% C  | Specificity (%) = 100.0<br>95% CI: 90.1–100.0<br>CI]: 0.940 [0.873–1.007<br>test (E1)<br>0<br>16<br>Specificity (%) = 100.0<br>95% CI: 71.3–100.0<br>CI]: 0.878 [0.784-0.973<br>test (E1)<br>Negative (n)<br>0<br>8<br>Specificity (%) = 100.0<br>95% CI: 51.8–100.0<br>CI]: 0.905 [0.798–1.01 <sup>-1</sup><br>test (E1)                | PPV (%) = 100.0           95% CI: 35.9-100.0           95% CI: 91.00.0   | Reference<br>standard <u>z v</u>   | ²ositive (n)<br>legative (n)                                 | 95% CI: 28.4–100.0<br>Index 1<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0<br>Index 1<br>Positive (n)<br>2<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 9.4–100.0 | 95% CI: 90.1-100.0<br>test (E4)<br>0<br>16<br>Specificity (%) = 100.0<br>95% CI: 71.3-100.0<br>test (E4)<br>Specificity (%) = 100.0<br>8<br>Specificity (%) = 100.0<br>95% CI: 51.8-100.0  | PPV (%) = 100<br>95% CI: 35.9–10<br>95% CI: 71.3–10<br>95% CI: 91.4–10<br>95% CI: 94–10<br>95% CI: 94–10<br>95% CI: 51.8–10<br>95% CI: 51.8–10 |
| La standard g Standard O | varian cance<br>Positive (n)<br>Negative (n)<br>adder cance<br>Positive (n)<br>Negative (n)<br>ostate canc | Sensitivity (%) = 100.0<br>95% CI: 28.4–100.0<br>er (Kappa value [95% C<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0<br>er (Kappa value [95% C<br>Sensitivity (%) = 100.0<br>95% CI: 9.4–100.0<br>95% CI: 9.4–100.0<br>95% CI: 9.4–100.0<br>95% CI: 9.4–100.0<br>95% CI: 9.4–100.0<br>95% CI: 9.4–100.0<br>95% CI: 9.4–100.0 | Specificity (%) = 100.0<br>95% CI: 90.1–100.0<br>CI]: 0.940 [0.873–1.007<br>test (E1)<br>Negative (n)<br>0<br>16<br>Specificity (%) = 100.0<br>95% CI: 71.3–100.0<br>CI]: 0.878 [0.784-0.973]<br>test (E1)<br>Negative (n)<br>0<br>Specificity (%) = 100.0<br>95% CI: 51.8–100.0<br>CI]: 0.905 [0.798–1.01]<br>test (E1)<br>Negative (n) | PPV (%) = 100.0           95% CI: 35.9-100.0           95% CI: 91.00.0           95% CI: 92.00.0           95% CI: 92.00.0 | erence<br>ndard standard z<br>z nd<br>z z nd<br>z nd | Positive (n)<br>legative (n)<br>Positive (n)<br>legative (n) | 95% CI: 28.4–100.0<br>Index 1<br>Positive (n)<br>5<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 35.9–100.0<br>Index 1<br>Positive (n)<br>2<br>0<br>Sensitivity (%) = 100.0<br>95% CI: 9.4–100.0 | 95% CI: 90.1-100.0<br>test (E4)<br>0<br>16<br>Specificity (%) = 100.0<br>95% CI: 71.3-100.0<br>test (E4)<br>Specificity (%) = 100.0<br>8<br>Specificity (%) = 100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>100.0<br>10 | PPV (%) = 100<br>95% CI: 35.9–1<br>NPV (%) = 100<br>95% CI: 71.3–10<br>PPV (%) = 100<br>95% CI: 51.8–10<br>PPV (%) = 100                       |

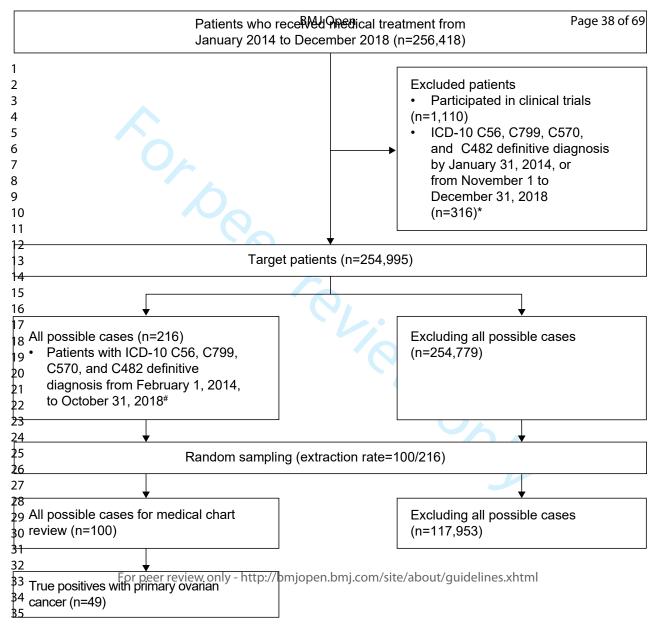
Figure 3. Death definitions with high\* accuracy CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value \*All accuracy values included for a definition are >70%.

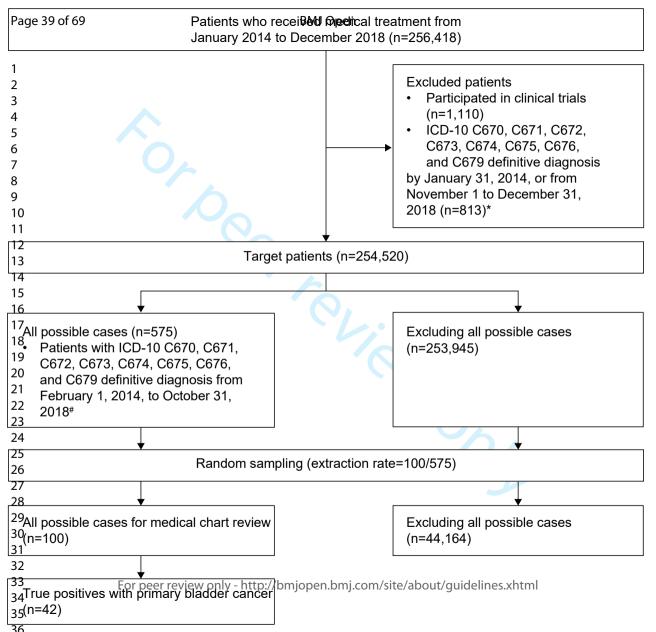
189x206mm (300 x 300 DPI)

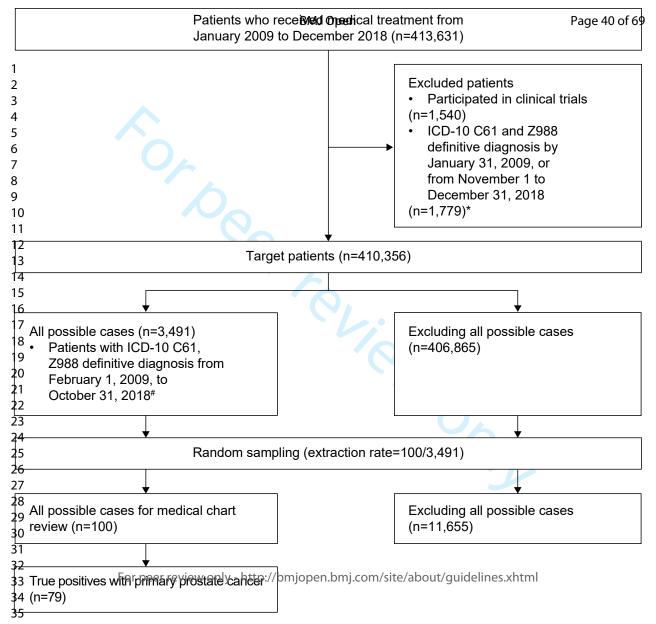












# **Supplemental Tables**

Table S1. Inclusion criteria for lung, breast, colorectal, ovarian, bladder, and prostate cancer

| Conventional classification     | WHO classification                  | Patient criteria  |
|---------------------------------|-------------------------------------|---|
| True primary lung cancer in thi | s study*                            |   |
| Lung tumor                      | Tumors of the lung                  |   |
| Epithelial tumor                | Epithelial tumors                   |   |
| Adenocarcinoma                  | Adenocarcinoma                      | Inclusion as non-small<br>cell carcinoma (excluding<br>atypical adenomatoid<br>familial of pre-invasive<br>lesions) |
| Squamous cell carcinoma         | Squamous cell carcinoma             | Inclusion as non-small<br>cell carcinoma (excluding<br>atypia of pre-invasive<br>lesions)                           |
| Neuroendocrine tumors           | Neuroendocrine tumors               |   |
| Small cell carcinoma            | Small cell carcinoma                | Inclusion as small cell cancer  |
| Large cell neuroendocarcinoma   | Large cell neuroendocrine carcinoma | Exclusion   |
| Carcinoid tumor                 | Carcinoid tumors                    | Exclusion   |
| Pre-invasive lesion             | Preinvasive lesion                  | Exclusion   |
| Large cell carcinoma            | Large cell carcinoma                | Inclusion as non-small cell carcinoma   |
| Adenosquamous carcinoma         | Adenosquamous carcinoma             | Inclusion as non-small cell carcinoma   |
| Sarcomatoid carcinoma           | Sarcomatoid carcinoma               | Inclusion as non-small cell carcinoma   |
| Unclassified carcinoma          | Other and unclassified carcinoma    | Exclusion   |
| Salivary gland type tumor       | Salivary gland-type tumors          | Exclusion   |
| Papilloma                       | Papillomas                          | Exclusion   |
| Adenoma                         | Adenomas                            | Exclusion   |
| Mesenchymal tumor               | Mesenchymal tumors                  | Exclusion   |
| Lymphohistiocytic tumor         | Lymphohistiocytic tumors            | Exclusion   |
| Tumors of ectopic origin        | Tumors of ectopic origin            | Exclusion   |

| Lung metastases                        | Metastases to the lung                        | Exclusion |
|--|---|-----------|
| Pleural tumor                          | Tumor of the pleura                           |           |
| Mesothelial tumor                      | Mesothelial tumors                            | Exclusion |
| Lymphoproliferative disorders          | Lymphoproliferative disorders                 | Exclusion |
| Mesenchymal tumor                      | Mesenchymal tumors                            | Exclusion |
| True primary breast cancer in th       | is study <sup>#</sup>                         |           |
| Mammary gland tumor                    |   |           |
| Epithelial tumor                       | Epithelial tumors                             |           |
| Benign tumor                           | Benign tumors                                 | Exclusion |
| Malignant tumor                        | Malignant tumors (carcinomas)                 |           |
| Noninfiltrating carcinoma              | Noninvasive carcinoma                         | Exclusion |
| Microinvasive carcinoma                | Microinvasive carcinoma                       | Inclusion |
| Invasive carcinoma                     | Invasive breast carcinoma                     | Inclusion |
| Paget's disease                        | Paget's disease of the nipple                 | Exclusion |
| Mixed connective and epithelial tumors | Mixed connective tissue and epithelial tumors | Exclusion |
| Nonepithelial tumor                    | Nonepithelial tumors                          | Exclusion |
| Other                                  | Others  | Exclusion |
| So-called mammary gland disease        | So-called mastopathy                          | Exclusion |
| Hamartoma                              | Hamartoma                                     | Exclusion |
| Inflammatory lesions                   | Inflammatory lesion                           | Exclusion |
| Mammary fibrosis                       | Fibrous disease                               | Exclusion |
| Gynecomastia                           | Gynecomastia                                  | Exclusion |
| Accessory milk                         | Accessory mammary gland                       | Exclusion |
| Metastatic tumors                      | Metastatic tumor                              | Exclusion |
| Other                                  | Others  | Exclusion |
| True primary colorectal cancer in      | n this study <sup>†</sup>                     | 1         |
| Benign epithelial tumor                |   | Exclusion |
| Malignant epithelial tumor             |   |           |
| Adenocarcinoma<br>(adenocarcinoma)     |   | Inclusion |

| Adenosquamous carcinoma<br>(adenosquamous carcinoma)                                  |                         | Inclusion |
|---|-------------------------|-----------|
| Squamous cell carcinoma<br>(squamous carcinoma)                                       |                         | Inclusion |
| Carcinoid tumour (carcinoid tumor)  |                         | Exclusion |
| Endocrine carcinoma (endocrine cell carcinoma)  |                         | Exclusion |
| Miscellaneous (miscellaneous<br>histological types of malignant<br>epithelial tumors) |                         | Exclusion |
| Nonepithelial tumor   |                         | Exclusion |
| Lymphoma (lymphoma)   |                         | Exclusion |
| Unclassifiable tumor  |                         | Exclusion |
| Metastatic tumors   | 6                       | Exclusion |
| Tumor-like lesions  |                         | Exclusion |
| Hereditary neoplasms and gastrointestinal polyposis                                   | C.                      | Exclusion |
| Appendix  | 4.                      | Exclusion |
| Anal canal (including perianal skin)  | 0                       | Exclusion |
| True primary ovarian cancer in  | this study <sup>‡</sup> | 1         |
| Ovarian tumor   | Ovarian tumors          |           |
| Epithelial tumor  | Epithelial tumors       |           |
| Serous tumor  | Serous tumors           | 4         |
| Benign  | Benign                  | Exclusion |
| Borderline malignancy   | Borderline              | Exclusion |
| Malignant   | Malignant               | Inclusion |
| Mucinous neoplasms  | Mucinous tumors         |           |
| Benign  | Benign                  | Exclusion |
| Borderline malignancy   | Borderline              | Exclusion |
| Malignant   | Malignant               | Inclusion |

| Mesothelial tumor   | Mesothelial tumors  | Exclusion |
|---|---|-----------|
| Other tumors  | Miscellaneous tumors  | Exclusion |
| Germ cell and policy stromal tumors   | Germ cell-sex cord-stromal<br>tumors  | Exclusion |
| Somatic tumors associated with<br>monodermal teratomas and<br>dermoid cysts | Monodermal teratoma and<br>somatic-type tumors arising from<br>dermoid cyst | Exclusion |
| Germ cell tumor   | Germ cell tumors  | Exclusion |
| Mixed sex cord-stromal tumor  | Mixed sex cord-stromal tumors   | Exclusion |
| Sex cord–stromal tumor  | Sex cord–stromal tumors   | Exclusion |
| Mixed epithelial mesenchymal tumor  | Mixed epithelial and<br>Mesenchymal tumors                                  | Exclusion |
| Mesenchymal tumor   | Mesenchymal tumors  | Exclusion |
| Anaplastic Carcinoma  | Undifferentiated carcinoma  | Inclusion |
| Malignant   | Malignant   | Inclusion |
| Borderline malignancy   | Borderline  | Exclusion |
| Benign  | Benign  | Exclusion |
| Seromucosal tumor   | Seromucinous tumors   |           |
| Malignant   | Malignant   | Inclusion |
| Borderline malignancy   | Borderline  | Exclusion |
| Benign  | Benign  | Exclusion |
| Brenner's tumor   | Brenner tumors  |           |
| Malignant   | Malignant   | Inclusion |
| Borderline malignancy   | Borderline  | Exclusion |
| Benign  | Benign  | Exclusion |
| Clear cell tumors   | Clear cell tumors   |           |
| Malignant   | Malignant   | Inclusion |
| Borderline malignancy   | Borderline  | Exclusion |
| Benign  | Benign  | Exclusion |
| Endometrioid tumor  | Endometrioid tumors   |           |

| Soft tissue                                    | Soft tissue tumors             | Exclusion              |
|--|--------------------------------|------------------------|
| Neoplastic lesions                             | Tumor-like lesions             | Exclusion              |
| Lymphoid and myeloid neoplasms                 | Lymphoid and myeloid tumors    | Exclusion              |
| Secondary tumors                               | Secondary tumors               | Exclusion              |
| Tubal tumor                                    | Tubal tumors                   | Inclusion              |
| Peritoneal tumor                               | Peritoneal tumors              | Inclusion              |
| Epithelial tumor                               | Epithelial tumors              | Inclusion*             |
| Mesothelial tumor                              | Mesothelial tumors             | Exclusion              |
| Smooth muscle tumors                           | Smooth muscle tumors           | Exclusion              |
| Tumors of unknown origin                       | Tumors of uncertain origin     | Exclusion              |
| Other primary tumors                           | Miscellaneous primary tumors   | Exclusion              |
| Secondary tumors                               | Secondary tumors               | Exclusion              |
| True primary prostate cancer in                | this study <sup>£</sup>        |                        |
| Malignant tumor                                |                                |                        |
| Adenocarcinoma                                 | Adenocarcinoma                 | Inclusion              |
| Rare adenocarcinoma                            | Adenocarcinoma rare type       | Inclusion              |
| Urothelial carcinoma                           | Urothelial carcinoma           | Inclusion              |
| Squamous cell carcinoma                        | Squamous carcinoma             | Inclusion              |
| Adenosquamous carcinoma                        | Adenosquamous carcinoma        | Inclusion              |
| Basal cell carcinoma                           | Basal cell carcinoma           | Inclusion              |
| Small cell carcinoma                           | Small cell carcinoma           | Inclusion              |
|  | Undifferentiated carcinoma     | Inclusion              |
| Anaplastic carcinoma                           |                                |                        |
| Anaplastic carcinoma<br>Other malignant tumors | Other malignant tumors         |                        |
| -  |                                | Exclusion              |
| Other malignant tumors                         | Other malignant tumors         | Exclusion<br>Exclusion |
| Other malignant tumors Sarcoma                 | Other malignant tumors Sarcoma |                        |

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| Malignant tumor   |                            |           |
|---|----------------------------|-----------|
| Adenocarcinoma  | Adenocarcinoma             | Inclusion |
| Rare adenocarcinoma   | Adenocarcinoma rare type   | Inclusion |
| Urothelial carcinoma  | Urothelial carcinoma       | Inclusion |
| Squamous cell carcinoma   | Squamous carcinoma         | Inclusion |
| Adenosquamous carcinoma   | Adenosquamous carcinoma    | Inclusion |
| Basal cell carcinoma  | Basal cell carcinoma       | Inclusion |
| Small cell carcinoma  | Small cell carcinoma       | Inclusion |
| Anaplastic carcinoma  | Undifferentiated carcinoma | Inclusion |
| Other malignant tumors  | Other malignant tumors     |           |
| Sarcoma   | Sarcoma                    | Exclusion |
| Metastatic tumors   | Metastatic tumor           | Exclusion |
| Tumor unclassifiable  | Unclassified tumor         | Exclusion |
| Borderline and associated lesions   |                            | Exclusion |
| Frue primary bladder cancer in t  | this study                 |           |
| Bladder cancer  |                            |           |
| Urothelial tumors   |                            |           |
| Noninvasive flat urothelial<br>carcinoma in situ (urothelial<br>carcinoma in situ)        | 0                          | Exclusion |
| Papillary urothelial carcinoma in<br>situ (noninvasive papillary<br>urothelial carcinoma) |                            | Exclusion |
| nvasive urothelial carcinoma<br>invasive urothelial carcinoma)                            |                            | Inclusion |
| Squamous cell neoplasia   |                            | Inclusion |
| Glandular tumors  |                            | Inclusion |
| Fumors related to the ureteral  |                            | Inclusion |
| membrane  |                            |           |

| Anaplastic carcinoma       | Exclusion |
|----------------------------|-----------|
| Pigmented tumor            | Exclusion |
| Mesenchymal tumor          | Exclusion |
| Lymphohematopoietic tumors | Exclusion |

\*For true primary lung cancer, based on the classification tables (p70-73) of the 8th edition of the Clinical/Pathological Handling Code of the Japanese Lung Cancer Society (original publication 2016).

<sup>#</sup>For true primary breast cancer, based on the histological classification table (p24-25) of the 18th Edition of the Clinical and Pathological Handling Code of the Japanese Breast Cancer Society " (Gold Original Publication 2018) and the comparison table (P65-67) between the WHO classification and the handling conventional classification of the year of publication. <sup>†</sup>For true primary colorectal cancers, based on the classification tables (p30-31) of the 9th edition of the Clinical/Pathological Handling Code (original publication 2018) of the Colon Cancer Study Group

<sup>‡</sup>For true primary ovarian cancers, based on the classification tables (p22-27) of the first edition of the Clinical and Pathological Handling Code (original publication 2016) of the Japanese Society of Obstetrics and Gynecology/Japanese Society of Pathology

<sup>£</sup>For true primary prostate cancer, based on the classification table (p.61) of the Japanese Society of Urological Sciences/Japan Society of Pathology/Japan Society of Medical Radiology, 4th edition of the Covenant on Clinical and Pathological Handling (Kanehara Publishing, 2010).

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### Table S2. Outcome definitions

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| BMJ Open       Page 8 of         nition       9         • Definitive diagnosis of lung cancer (ICD-10: C340, C341, C342, C 233, or C349) recorded between 2014 and 2018 in DPC data. Primary diagnosis, admission-precipitating diagnosis, or most resource-consumin diagnosis.       0         • Definitive diagnosis of lung cancer (ICD-10: C340, C341, C342, C 243, or C349) recorded between 2014 and 2018 in EMR data.       0         • Diagnosis of lung cancer (Japanese original diagnostic code: 1629003) recorded between 2014 and 2018       0 |
|---|
| nition       9<br>3         • Definitive diagnosis of lung cancer (ICD-10: C340, C341, C342, C = 3, or C349) recorded between 2014<br>and 2018 in DPC data. Primary diagnosis, admission-precipitating diagnosis, or most resource-consumin<br>diagnosis.         • Definitive diagnosis of lung cancer (ICD-10: C340, C341, C342, C = 43, or C349) recorded between 2014<br>and 2018 in EMR data.         • Diagnosis of lung cancer (Japanese original diagnostic code: 16290 = 3) recorded between 2014 and 2018   |
| <ul> <li>Definitive diagnosis of lung cancer (ICD-10: C340, C341, C342, C 33, or C349) recorded between 2014 and 2018 in DPC data. Primary diagnosis, admission-precipitating diagnosis, or most resource-consumin diagnosis.</li> <li>Definitive diagnosis of lung cancer (ICD-10: C340, C341, C342, C 343, or C349) recorded between 2014 and 2018 in EMR data.</li> <li>Diagnosis of lung cancer (Japanese original diagnostic code: 1629003) recorded between 2014 and 2018</li> </ul>  |
| <ul> <li>and 2018 in EMR data.</li> <li>Diagnosis of lung cancer (Japanese original diagnostic code: 1629093) recorded between 2014 and 2018</li> </ul>   |
|   |
| in EMR data.  |
| Definitions written in A1 and specimen examination for laboratory diagnosis (Japanese original procedural code: 160060170, 160060270, 160171470, 160185110, 160209750, 160214710, 160214810, 160190270, 160190370, 160190470, 160190570, 1602 €4470, 160214970, or 160062310) recorded between 2014 and 2018 in claims data.  |
| <ul> <li>Diagnosis of non-small cell lung cancer (Japanese original diagnostic code: 8847272, 8847732, 884923</li> <li>8847598, 8847637, 8847664, or 8842053) recorded between 2014 and 2018 in EMR data.</li> </ul>  |
| <ul> <li>Diagnosis of non-small cell lung cancer (Japanese original diagnostic code: 8842835, 8847676, 8847677</li> <li>8847678, 8847679, 8835493, 8847634, 8847635, 8847636, 8847636, 8847666, 8847661, 8847662,</li> </ul>  |
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| Defin | ition                |   |
|       |                      | 8847663, 8847664, 8831458, 8847595, 8847596, 8847597, 8847598, 8833932, 1629003, 1629006,<br>1629009, 8838805, 8838844, 8838852, 8838898, 8838901, 884205 , 8842831, 8842832, 8842833,  |
|       |                      | 8842834, 8847272, 8847732, 8849238, 8849788, or 2312002) recorded between 2014 and 2018 in EMF data.  |
| C1    |                      | Diagnosis of small cell lung cancer (Japanese original diagnostic code: 8847594, 8842185, 8847633, 8847660, or 8847675) recorded between 2014 and 2018 in EMR data.   |
| α1    |                      | Definitive diagnosis of breast cancer (ICD-10: C500, 501, 502, 503, 504, 505, 506, 508, 509, or D059)<br>recorded between 2014 and 2018 in DPC data. Primary diagnosis, admission-precipitating diagnosis, or<br>most resource-consuming diagnosis. |
| α2    |                      | Definitive diagnosis of breast cancer (ICD-10: C500, 501, 502, 503, 504, 505, 506, 508, 509, or D059)<br>recorded between 2014 and 2018 in EMR data.  |
| α3    |                      | Diagnosis of breast cancer (Japanese original diagnostic code: 8849899) recorded between 2014 and 20<br>in EMR data.  |
| β1    |                      | Definitive diagnosis of colorectal cancer (ICD-10: C179, C182, C184, C186, C187, C189, C19, or C2 recorded between 2014 and 2018 in DPC data. Primary diagnosis admission-precipitating diagnosis, most resource-consuming diagnosis.               |
|       | C1<br>α1<br>α2<br>α3 | C1       •         α1       •         α2       •         α3       •         β1       •  |

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| Outcome                    | Defini | ition |  |
|                            | β2     | •     | Definitive diagnosis of colorectal cancer (ICD-10: C179, C182, C184, C186, C187, C189, C19, or C20   |
|                            |        |       | recorded between 2014 and 2018 in EMR data.  |
|                            | β3     | •     | Diagnosis of breast cancer (Japanese original diagnostic code: 8847815 or 8847916) recorded between  |
|                            |        |       | 2014 and 2018 in EMR data.   |
| γ. Primary ovarian cancer  | γ1     | •     | Definitive diagnosis of ovarian cancer (ICD-10: C56, C799, C570, ar C482) recorded between 2014 an   |
|                            |        |       | 2018 in DPC data. Primary diagnosis, admission-precipitating diagrapsis, or most resource-consuming  |
|                            |        |       | diagnosis.   |
|                            | γ2     | •     | Definitive diagnosis of ovarian cancer (ICD-10: C56, C799, C570, or C482) recorded between 2014 an   |
|                            |        |       | 2018 in EMR data.  |
| ε. Primary bladder cancer  | ε1     | •     | Definitive diagnosis of bladder cancer (ICD-10: C670, C671, C672, C673, C674, C675, C676, or C679    |
|                            |        |       | recorded between 2014 and 2018 in DPC data. Primary diagnosis, admission-precipitating diagnosis, or |
|                            |        |       | most resource-consuming diagnosis.   |
|                            | ε2     | •     | Definitive diagnosis of bladder cancer (ICD-10: C670, C671, C672, C673, C674, C675, C676, or C679    |
|                            |        |       | recorded between 2014 and 2018 in EMR data.  |
| δ. Primary prostate cancer | δ1     | •     | Definitive diagnosis of prostate cancer (ICD-10: C61 or Z988) recorded between 2009 and 2018 in DPC  |
|                            |        |       | data. Primary diagnosis, admission-precipitating diagnosis, or most desource-consuming diagnosis.    |
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| Outcome                    | Definit | <u>Ó</u>  |
|                            | δ2      | Definitive diagnosis of prostate cancer (ICD-10: C61 or Z988) recogded between 2009 and 2018 in EMR   |
|                            |         | data.   |
| D. Performance status 2 or | D1      | Medical treatment of rehabilitation for cancer patients (Japanese Briginal diagnostic code: 180033110   |
| higher at the start of     |         | recorded between 2014 and 2018 in claims data, given in the same and the month as the prescription mont   |
| chemotherapy               |         | of the therapeutic drug described in Table S3.  |
|                            | D2      | • Medical treatment of rehabilitation for disuse syndrome (Japanese diginal diagnostic code: H001-02,   |
|                            |         | 180044610, 180044710, 180044810, 180044910, 180045010, 180055110, 180045210, 180045310,   |
|                            |         | 180045410, 180045530, 180045630, 180045730, 180051530, 1800 <mark>5</mark> 1630, 180051730, 180051830,  |
|                            |         | 180051930, 180052030, 180052130, 180052230, 180052330, 180052330, 180052530, or 180052630)  |
|                            |         | recorded between 2014 and 2018 in claims data, given in the same nedex month as the prescription month  |
|                            |         | of the therapeutic drug described in Table S3.  |
| E. Death                   | E1      | Date of death in EMR data.  |
|                            | E2      | • Date of death in DPC data.  |
|                            | E3      | • Medical treatment of death for patients (Japanese original diagnostion code: 114007270, 114018670, or   |
|                            |         | 114019970) recorded between 2014 and 2018 in claims data.       Press         • 30 days before and after definitions written in E1.       Between 2014 and 2018 in claims data. |
|                            | E4      | • 30 days before and after definitions written in E1.   |
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|                            |         | rig<br>ht   |

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| Outcome                         | Defin | 0  |
|                                 | E5    | 30 days before and after definitions written in E2.  |
|                                 | E6    | • 30 days before and after definitions written in E3. $\overleftarrow{\Box}$                           |
| F. First recurrence/progression | F1    | Date of disease name with "recurrence" as a modifier in Japanese original diagnostic code.             |
|                                 | F2    | Second specimen examination for laboratory diagnosis (Japanese orgginal procedural code: 160060170     |
|                                 |       | 160060270, 160171470, 160185110, 160214310, 160209750, 1602 84710, 160214810, 160190270,               |
|                                 |       | 160190370, 160190470, 160190570, 160214470, 160214970, or 16 062310) recorded between 2014 a           |
|                                 |       | 2018 in claims data.   |
|                                 | F3    | Definitions written in F2 and patients with no history of surgery for the purpose of excision (with or |
|                                 |       | without surgery for the purpose of examination).   |
|                                 | F4    | Month of definitions written in F1.  |
|                                 | F5    | Month of definitions written in F2.  |
|                                 | F6    | Month of definitions written in F3.  |
| G. Second                       | G1    | • Date of administration of the drug described in Appendix 2 after definitions written in F1.          |
| recurrence/progression          | G2    | Third specimen examination for laboratory diagnosis (Japanese original procedural code: 160060170,     |
|                                 |       | $160060270, 160171470, 160185110, 160214310, 160209750, 1602 \frac{1}{2}4710, 160214810, 160190270,$   |
|                                 |       | 160190370, 160190470, 160190570, 160214470, 160214970, or 16000000000000000000000000000000000000       |
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| Outcome                   | Definition 54  |
|                           | 2018 in claims data.   |
|                           | $\begin{array}{c c} & & & \\ \hline G3 & \bullet & \text{Month of definitions written in G1.} & & \\ \hline \xi & & \\ \hline \end{array}$ |
|                           | G4     • Month of definitions written in G2.   |
| H. Third                  | H1 • Date of administration of the drug described in Appendix 2 after G1   |
| recurrence/progression    | H2 • Forth specimen examination for laboratory diagnosis (Japanese origenal procedural code: 160060170,                                    |
|                           | 160060270, 160171470, 160185110, 160214310, 160209750, 1602 <b>4</b> 710, 160214810, 160190270,  |
|                           | 160190370, 160190470, 160190570, 160214470, 160214970, or 160062310) recorded between 2014 and   |
|                           | 2018 in claims data.   |
|                           | H3 • Month of definitions written in H1.   |
|                           | H4 • Month of definitions written in H2.   |
| Adverse events            | April  |
| I. Interstitial pneumonia | II • Definitive diagnosis of interstitial pneumonia (ICD-10: J702, J703, 17/04, J841 or J849) recorded in EMR                              |
|                           | data and Medical treatment (ATC code: H02AB04 or H02AB06 [excludes topical drugs]).  |
|                           | I2 • Definitive diagnosis of interstitial pneumonia (ICD-10: J448, J700, \$701, J702, J704, J82, J841, J849, or                            |
|                           | M0510) recorded in EMR data.   |
|                           | 13       • Definitions written in I2 plus prescription of methylprednisolone (Age C code: H02AB04) or prednisolone                         |
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| Outcome             | Defini | tion 5<br>5<br>5<br>5  |
|                     |        | (ATC code: H02AB06 with exception of external medicine) recorded in claims data. $\vec{A}$   |
| J. Hepatic failure  | J1     | <ul> <li>Definitive diagnosis of hepatic failure (ICD-10: K720, K712, or K7±3) recorded in EMR data plus prescription of methylprednisolone (ATC code: H02AB04) or prednessolone (ATC code: H02AB06 with exception of external medicine) recorded in claims data.</li> </ul>   |
|                     | J2     | <ul> <li>Laboratory data abnormality in EMR data plus prescription of methol prednisolone (ATC code:<br/>H02AB04) or prednisolone (ATC code: H02AB06 with exception of external medicine) recorded in</li> </ul>   |
|                     |        | claims data.   |
|                     | J3     | <ul> <li>Definitive diagnosis of hepatic failure (ICD-10: K710, K711, K712 K716, K717, K718, K719, K720, K729, K739, K740, K741, K743, K744, K745, K746, K750, K751, K752, K753, K754, K758, K759, K760, K760, K761, K760, K760,</li></ul> |
|                     |        | K760, K761, K762, K763, K764, K765, K767, K768, K769, R18, R609, R945, or S361) recorded in<br>EMR data.   |
|                     | J4     | Definitions written in J3 plus prescription of medical treatment (ATE code: H02AB04, H02AB06, A05AA02, or A05BA08) recorded in claims data.  |
| K. Colitis•diarrhea | K1     | <ul> <li>Definitive diagnosis of colitis • diarrhea (ICD-10: A090 or A099) recorded in EMR data plus prescriptic of methylprednisolone (ATC code: H02AB04) or prednisolone (ATC code: H02AB06 with exception of external medicine) recorded in claims data.</li> </ul>   |

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| Outcome                      | Defin | ition |   |
|                              | K2    | •     | Definitive diagnosis of colitis • diarrhea (ICD-10: A099, K501, K5⊕, K510, K512, K513, K515, K51<br>K519, K521, K522, K528, K529, K550, K551, K552, K559, K566, €591, K628, K638, K921, K922,<br>M321, or R101) recorded in EMR data.   |
|                              | К3    | Ò     | Definitions written in K2 plus prescription of medical treatment (ATEC codes: H02AB04, H02AB06, A07A, A07F, A07E, A07D, or A07X) recorded in claims data.   |
| L. Type 1 diabetes           | L1    | •     | Prescription of medical treatment (ATC code: A10AB, A10AC, A10AD, or A10AE)   |
|                              | L2    | •     | Definitive diagnosis of type 1 diabetes (ICD-10: E10, E100, E101, E102, E103, E104, E105, or E106)<br>recorded in EMR data.   |
| M. Encephalitis • meningitis | M1    | •     | Definitive diagnosis of encephalitis • meningitis (ICD-10: G040, G648, G049, or G934) recorded in EMR data.   |
|                              | M2    | •     | Definitive diagnosis of encephalitis • meningitis (ICD-10: G040, G48, G049, or G934) recorded in<br>EMR data plus prescription of methylprednisolone (ATC code: H022, B04) or prednisolone (ATC code<br>H02AB06 with exception of external medicine) recorded in claims data. |
|                              | M3    | •     | Definitive diagnosis of encephalitis.   |
|                              | M4    | •     | Definitions written in M3 plus prescription Meningitis (ICD-10: R291) recorded in EMR data of medio   |

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|                                 |        |       | BMJ Open BMJ Open Page 16   |
| Outcome                         | Defini | ition |   |
|                                 |        |       | treatment (ATC code: J05AB, J01, or J02A) recorded in claims datag  |
| N. Nerve                        | N1     | •     | Definitive diagnosis of nerve disorder (excludes paresthesia) (ICD- $\underbrace{\underline{\mu}}$ : G500, G501, G508, G509, G5 |
| disorder (excludes paresthesia) |        |       | G512, G513, G514, G518, G519, G520, G521, G522, G523, G527, S528, G529, G540, G541, G542,                                       |
|                                 |        |       | G543, G544, G545, G560, G561, G562, G563, G564, G568, G569, S570, G571, G572, G573, G574,                                       |
|                                 |        | O     | G575, G576, G579, G580, G587, G588, G589, G603, G608, G609, a G620, G622, G629, G64,  |
|                                 |        |       | G723, G810, G811, G819, G820, G821, G822, G823, G824, G825, 🕏 830, G831, G832, G833, G839,                                      |
|                                 |        |       | G900, G902, G903, G904, G908, G909, H812, H919, H933, M7924, M7926, M7929, M8900, M998,   |
|                                 |        |       | R252, R253, or R258) recorded in EMR data.  |
|                                 | N2     | •     | Definitions written in N1 and medical treatment (ATC code H02AB04 or H02AB06) recorded in claim                                 |
|                                 |        |       | data.   |
| O. Myasthenia gravis            | 01     | •     | Definitive diagnosis of myasthenia gravis (ICD-10: G700) recorded in EMR data.  |
|                                 | 02     | •     | Definitive diagnosis of myasthenia gravis (ICD-10: G700) recorded in EMR data plus prescription of                              |
|                                 |        |       | methylprednisolone (ATC code: H02AB04) or prednisolone (ATC code: H02AB06 with exception of                                     |
|                                 |        |       | external medicine) recorded in claims data.   |
|                                 | 03     | •     | Definitive diagnosis of myasthenia gravis (ICD-10: G700, G701, $G_{\overline{Q}}^{\overline{Q}}$ 09) recorded in EMR data.      |
|                                 | 04     | •     | Definitions written in O3 and medical treatment (ATC code: H02AB04, H02AB06, or H07AA02)  |
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| Outcome                    | Defin | ition  | -0554   |                            |
|                            |       |        | recorded in claims data.  |                            |
| P. Guillain-Barré syndrome | P1    | •      | تع<br>Definitive diagnosis of Guillain-Barré syndrome (ICD-10: G610) re           | data.                      |
|                            | P2    | •      | Definitions written in P1 plus prescription of methylprednisolone (ATC code: H02/ | AB04) or prednisolone      |
|                            |       |        | (ATC code: H02AB06 with exception of external medicine) recorded in claims data   | 1.                         |
|                            | P3    | •      | Definitions written in P1 plus prescription of methylprednisolone (AFC code: H02A | AB04), prednisolone        |
|                            |       |        | (ATC code: H02AB06 with exception of external medicine), or imnum inoglobulin re  | corded in claims data.     |
|                            | P4    | •      | Definitions written in P1 and medical treatment (ATC code: H02AB04, H02AB06,      | J06BA, J06BB, or           |
|                            |       |        | J06BC) recorded in claims data.   |                            |
| Q. Skin disorders          | Q1    | •      | Definitive diagnosis of skin disorders (ICD-10: H605, H738, I831, 500, L010, L01  | 1, L020, L021, L022,       |
|                            |       |        | L023, L024, L028, L029, L030, L031, L032, L033, L038, L039, L080, L081, L089      | , L100, L101, L102,        |
|                            |       |        | L103, L104, L105, L108, L109, L110, L111, L119, L120, L121, L123, L129, L130      | , L131, L138, L139,        |
|                            |       |        | L200, L208, L210, L219, L233, L238, L239, L26, L270, L271, L279, L280, L281,      | L282, L290, L291,          |
|                            |       |        | L292, L298, L299, L300, L301, L302, L303, L304, L305, L309, L400, L401, L402      | , L403, L404, L408,        |
|                            |       |        | L409, L410, L411, L413, L414, L415, L418, L419, L42, L430, L439, L433, L438,      | L439, L440, L441,          |
|                            |       |        | L442, L443, L449, L500, L501, L502, L504, L508, L509, L510, L512, L518            | , L519, L52, L530,         |
|                            |       |        | L531, L532, L538, L539, L560, L561, L562, L563, L564, L568, L520, L571, L572      | , L574, L578, L580,        |
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| Outcome           | Definition   |  |
|                   | L739, L8<br>L853, L8<br>L909, L9<br>L950, L9<br>in EMR<br>Q2 • Definitio | 90, L598, L700, L701, L702, L703, L708, L709, L710, L71, L718, L719, L730, L731, L738<br>10, L810, L811, L812, L813, L814, L816, L817, L818, L819, L82, L83, L850, L851, L852,<br>58, L859, L870, L871, L872, L879, L88, L890, L891, L892, L893, L899, L900, L906, L908,<br>19, L920, L921, L928, L929, L930, L931, L932, L940, L994, L942, L943, L944, L945, L946<br>51, L97, L980, L981, L982, L983, L984, L985, L986, L998, R02, R21, R238, or T783) record<br>data.<br>ns written in Q1 and medical treatment (ATC codes: H02A904, H02AB06, D04AA, or R01A<br>s steroidal drugs]) recorded in claims data. |
| R. Rhabdomyolysis | R1 • "Drug-in  | duced rhabdomyolysis" or "rhabdomyolysis" in definitive giagnosis of rhabdomyolysis (ICD-  |
|                   | M339, M<br>M6155, I  | e diagnosis of rhabdomyolysis (ICD-10: D868, G718, G729, G722, G724, G729, M331, M33<br>1353, M358, M6019, M6091, M6092, M6095, M6098, M6099, M6105, M6109, M6119, M61<br>M6159, M6289, M7900, M7910, M7911, M7912, M7913, M7915, M7916, M7918, M7919, or<br>recorded in EMR data.   |
|                   |  | ns written in R2 plus prescription of methylprednisolone (ATC code: H02AB04) or prednisolo<br>de: H02AB06 with exception of external medicine) recorded in claims data.  |

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| Outcome        | Definition 55  |
| S. Myocarditis | S1 • Definitive diagnosis of myocarditis (ICD-10: I401, I408, I409, I5149 recorded in EMR data.                          |
|                | S2 • Definitive diagnosis of myocarditis (ICD-10: I401, I408, I409, I514) recorded in EMR data plus                      |
|                | prescription of methylprednisolone (ATC code: H02AB04) or prednysolone (ATC code: H02AB06 with                           |
|                | exception of external medicine) recorded in claims data.   |
|                | S3 • Definitive diagnosis of myocarditis (ICD-10: D868, E854, E888, E89, I010, I011, I012, I018, I019,                   |
|                | 1050, 1051, 1052, 1058, 1059, 1060, 1061, 1062, 1069, 1070, 1071, 1072, 1078, 1079, 1080, 1081, 1082, 1083,              |
|                | 1088, 1089, 1090, 1091, 1092, 1099, 1200, 1201, 1208, 1209, 1210, 1211, 1212, 1213, 1214, 1219, 1220, 1221,              |
|                | 1228, 1229, 1230, 1231, 1232, 1233, 1234, 1235, 1236, 1238, 1240, 1249, 1249, 1251, 1252, 1253, 1254,                    |
|                | 1255, 1256, 1258, 1259, 1300, 1308, 1309, 1319, 1339, 1340, 1341, 134 <sup>2</sup> , 1348, 1350, 1351, 1352, 1358, 1359, |
|                | I360, I361, I362, I369, I370, I371, I372, I379, I38, I401, I408, I409 I420, I421, I422, I423, I424, I425,                |
|                | I426, I427, I428, I429, I440, I441, I442, I443, I444, I445, I446, I442, I451, I452, I453, I454, I455, I456,              |
|                | I458, I459, I460, I461, I469, I470, I471, I472, I479, I480, I481, I482, I489, I490, I491, I492, I493, I494,              |
|                | 1495, 1498, 1499, 1500, 1501, 1509, 1513, 1514, 1515, 1518, 1519, R000, R001, R008, R570, R571, R579,                    |
|                | R943) recorded in EMR data.  |
|                | S4 • Definitions written in S3 plus prescription of methylprednisolone (ASIC code: H02AB04) or prednisolon               |
|                | (ATC code: H02AB06 with exception of external medicine) recorded in claims data.   |
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|                |  |

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| Outcome                           | Defini   | -0-554<br>554<br>554   |                       |
| T. Gastrointestinal perforation   | T1       | Definitive diagnosis of gastrointestinal perforation (ICD-10: K255, <b>\$</b> 265, K631, K65S, o | or K639)              |
|                                   |          | recorded in EMR data.  |                       |
| U. Adrenal insufficiency          | U1       | Definitive diagnosis of adrenal insufficiency in Japanese original diagnostic code includi       | ng the words          |
|                                   |          | "autoimmune adrenitis" recorded in claims data and "hypoadrenocosticism" plus medica             | l treatment           |
|                                   |          | (ATC: code H02AB09) recorded in claims data.   |                       |
|                                   | U2       | Definitive diagnosis of adrenal insufficiency (ICD-10: E271, E272, E273, E274, E275 or           | r E278) recorded      |
|                                   |          | in EMR data.   |                       |
|                                   | U3       | Definitions written in U2 plus medical treatment (ATC code H02AB09) recorded in clair            | ns data.              |
| X. Febrile neutropenia            | X1       | Definitive diagnosis of febrile neutropenia (ICD-10: D70) recorded in EMR data and me            | dical treatment       |
|                                   |          | (Table S3) recorded in claims data.  |                       |
| ATC, Anatomical Therapeutic Chemi | cal; DPC | agnosis Procedure Combination; EMR, electronic medical record; ICD-12, ICD-10, Internation       | nal Classification of |
| Diseases, 10th revision           |          | 19, 2024 by gues   |                       |
|                                   |          | y gue  |                       |
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|                                   | F        | eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml                             |                       |

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| 1                                |                      | Page 21 of 27   |
| 2                                |                      | 21-0  |
| 3<br>4                           | Table S3. Drug codes | 2021-055459   |
| 5                                | ATC code             | Common name g   |
| 6                                | L01XC32              | Atezolizumab $\vec{a}$  |
| 7                                | L01XC17              | Nivolumab   |
| 8<br>9                           | L01XC18              | Pembrolizumab   |
| 10                               | L01XC31              | Avelumab  |
| 11                               | L01XC28              | Durvalumab 🗸  |
| 12                               | L01XC06              | Cetuximab   |
| 13                               | L01XC08              | Panitumumab   |
| 14<br>15                         | L01XE02              | Gefitinib   |
| 15<br>16                         | L01XE35              | Osimertinib   |
| 17                               | L01XE47              | Dacomitinib   |
| 18                               | L01XE13              | Afatinib  |
| 19                               | L01XE03              | Erlotinib   |
| 20                               | L01XE36              | Alectinib   |
| 21<br>22                         | L01XE44              | Lorlatinib  |
| 22                               | L01XE28              | Ceritinib   |
| 24                               | L01XE16              | Crizotinib  |
| 25                               | L01XC07              | Bevacizumab (includes related biosimilars)  |
| 26                               | L01XC13              | Pertuzumab >  |
| 27                               | L01XC14              | Trastuzumab emtansine   |
| 28<br>29                         | L01XE07              | Lapatinib   |
| 29<br>30                         | L01XE33              | Palbociclib   |
| 31                               | L01XE50              | Abemaciclib $\frac{4}{\sigma}$  |
| 32                               | L01XE10, L04AA18     | Everolimus  |
| 33                               | L01XX46              | Olaparib  |
| 34                               | L01XC08              | Panitumumab T   |
| 35<br>36                         | L01XE21              | Regorafenib   |
| 37<br>38                         | L01                  | Anti-malignant tumor drugs excluding talaporfin sodium (620001918), porfimer sodium (620007468), anagrelide hydrochloride hydrate (622379001), and sterile talc (622293901) |
| 39                               | L02                  | Hormone therapy 8   |
| 40<br>41<br>42<br>43<br>44<br>45 |                      | (6223/9001), and sterile tale (622293901)       Hormone therapy       For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml                             |
| J.                               |                      |   |

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| L04ImmJ01CR05TazoJ01DD02CeftaJ01DE03CefoJ01DE01CefeJ01DE02CefpJ01DH05BiapJ01DH02MeroJ01DH51ImipJ01DH04Dori | mmon name         munosuppressive drug         zobactam and piperacillin         ftazidime hydrate         fozopran hydrochloride         fepime dihydrochloride hydrate         fpirome sulfate         apenem         eropenem hydrate, cilastatin sodium         ripenem hydrate         nipenem and betamipron |          | 021-055459 on 13 July 2022. Downloaded  |
|--|--|----------|---|
| J01CR05TazoJ01DD02CeftaJ01DE03CefoJ01DE01CefeJ01DE02CefpJ01DH05BiapJ01DH02MeroJ01DH51ImipJ01DH04Dori       | zobactam and piperacillin<br>ftazidime hydrate<br>fozopran hydrochloride<br>fepime dihydrochloride hydrate<br>fpirome sulfate<br>apenem  |          | on 13 July 2022.<br>Download  |
| J01DD02CeftsJ01DE03CefoJ01DE01CefeJ01DE02CefpJ01DH05BiapJ01DH02MeroJ01DH51ImipJ01DH04Dori                  | ftazidime hydrate<br>fozopran hydrochloride<br>fepime dihydrochloride hydrate<br>fpirome sulfate<br>apenem   |          | 13 July 2022.<br>Download   |
| J01DE03CefoJ01DE01CefeJ01DE02CefpJ01DH05BiapJ01DH02MeroJ01DH51ImipJ01DH04Dori                              | fozopran hydrochloride<br>fepime dihydrochloride hydrate<br>fpirome sulfate<br>apenem  |          | July 2022. Download   |
| J01DE01CefeJ01DE02CefpJ01DH05BiapJ01DH02MeroJ01DH51ImipJ01DH04Dori   | fepime dihydrochloride hydrate<br>fpirome sulfate<br>apenem  |          | 2022. Download  |
| J01DE02CefpJ01DH05BiapJ01DH02MercJ01DH51ImipJ01DH04Dori  | fpirome sulfate appenem  |          | 22. Download  |
| J01DH05BiapJ01DH02MeroJ01DH51ImipJ01DH04Dori   | apenem   |          | Download  |
| J01DH02MerceJ01DH51ImipJ01DH04Dori   | ·  |          | And   |
| J01DH51 Imip<br>J01DH04 Dori   | eropenem hydrate<br>ipenem hydrate, cilastatin sodium<br>ripenem hydrate<br>nipenem and betamipron   |          | vnlpadec  |
| J01DH04 Dori   | ipenem hydrate, cilastatin sodium<br>ripenem hydrate<br>nipenem and betamipron   |          | ad ec   |
|  | ripenem hydrate  |          | 00  |
| J01DH55 Pani   | nipenem and betamipron   |          | <u>×</u><br><del>1</del>  |
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|-----------------------|-------------------------|--------------------------|-------------------------|--------------------------|----------------------------|----------------------------|---------------------------------|-----------------------|
| Fable S4. Accura      | icy of diagnosis de     | finitions                |                         |                          |                            |                            | 021-055                         |                       |
| Outcome<br>definition | True<br>positives,<br>n | False<br>positives,<br>n | True<br>negatives,<br>n | False<br>negatives,<br>n | Sensitivity,<br>% (95% CI) | Specificity,<br>% (95% CI) | 55 PPV,<br>9 % (95% CI)         | NPV,<br>% (95% C      |
| Lung cancer           | н                       |                          |                         |                          |                            |                            |                                 |                       |
| Primary lung ca       | ncer                    |                          |                         |                          |                            |                            | July 202                        |                       |
| Al                    | 132                     | 7                        | 22,237                  | 30                       | 81.5<br>(74.6–87.1)        | 100.0<br>(99.9–100.0)      |                                 | 99.9<br>(99.8–99.9)   |
| A2                    | 162                     | 38                       | 22,206                  | 0                        | 100.0<br>(96.6–100.0)      | 99.8<br>(99.8–99.9)        | 10<br>81.0<br>8(74.9-86.2)      | 100.0<br>(100.0–100.  |
| A3                    | 19                      | 1                        | 22,243                  | 143                      | 11.7<br>(7.2–17.7)         | 100.0<br>(100.0–100.0)     | ष 95.0<br>हु (75.1–99.9)        | 99.4<br>(99.2–99.5)   |
| A4                    | 128                     | 7                        | 22, 237                 | 34                       | 79.0<br>(71.8–85.0)        | 100.0<br>(99.9–100)        | 94.8<br>(89.6–97.9)             | 99.8<br>(99.8–99.9)   |
| Non-small cell l      | ung cancer              |                          |                         | 1                        | (,110,0010)                | ()))) 100)                 |                                 | ())(0))               |
| B1                    | 46                      | 6                        | 22,280                  | 74                       | 38.3<br>(29.6–47.6)        | 100.0<br>(99.9–100.0)      | <b>88.5</b><br>(76.6–95.6)      | 99.7<br>(99.6–99.7)   |
| B2                    | 46                      | 6                        | 22,280                  | 74                       | 38.3<br>(29.6–47.6)        | 100.0 (99.9–100.0)         | <u>3</u> .88.5<br>8 (76.6–95.6) | 99.7<br>(99.6–99.7)   |
| Small cell lung       | cancer                  |                          |                         |                          | N/                         |                            |                                 |                       |
| C1                    | 10                      | 0                        | 22,395                  | 1                        | 90.9<br>(58.7–99.8)        | 100.0<br>(100.0–100.0)     | ≥100.0<br>=:(58.7-100.0)        | 100.0<br>(100.0–100.0 |
| Breast cancer         |                         |                          |                         |                          |                            |                            | 19,                             |                       |
| Primary breast c      | cancer                  |                          |                         |                          |                            |                            | 2024                            |                       |
| α1                    | 93                      | 18                       | 45,036                  | 55                       | 62.8<br>(54.5–70.6)        | 100.0<br>(99.9–100.0)      | ₹83.8<br>€(75.6–90.1)           | 99.9<br>(99.8–99.9)   |
| α2                    | 148                     | 52                       | 45,002                  | 0                        | 100.0<br>(96.3–100.0)      | 99.9<br>(99.8–99.9)        |                                 | 100.0<br>(100.0–100.9 |
| α3                    | 0                       | 0                        | 45,054                  | 148                      | 0.0 (0.0–3.7)              | 100.0<br>(100.0–100.0)     |                                 | 99.7<br>(99.6–99.7)   |
| Colorectal cano       |                         |                          |                         |                          |                            |                            | <u>b</u>                        |                       |
| Primary colorec       | tai cancer              |                          |                         |                          |                            |                            | copyright                       |                       |
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|-----------------------|-------------------------|--------------------------|-------------------------|--------------------------|--------------------------------------|-------------------------------------|--|---------------------------------------|
| Outcome<br>definition | True<br>positives,<br>n | False<br>positives,<br>n | True<br>negatives,<br>n | False<br>negatives,<br>n | Sensitivity,<br>% (95% CI)           | Specificity,<br>% (95% CI)          | 55 PPV,<br>55 % (95% CI)                 | NPV,<br>% (95% CI)                    |
| β1                    | 108                     | 8                        | 28,340                  | 53                       | 67.1                                 | 100.0                               | <u>ຊ</u><br>ສ <sup>3</sup> 93.1          | 99.8                                  |
| β2                    | 161                     | 39                       | 28,309                  | 0                        | (59.2–74.3)<br>100.0<br>(96.6–100.0) | (99.9–100.0)<br>99.9<br>(99.8–99.9) | ⊆ (86.9–97.0)<br>≤ 80.5<br>≥ (74.3–85.8) | (99.8–99.9)<br>100.0<br>(100.0–100.0) |
| β3                    | 0                       | 0                        | 28,348                  | 161                      | 0.0 (0.0–3.4)                        | 100.0<br>(100.0–100.0)              | NA<br>0                                  | 99.4<br>(99.3–99.5)                   |
| Ovarian cancer        |                         |                          |                         |                          |                                      |                                     | nv                                       | ,/                                    |
| Primary ovarian ca    | ncer                    |                          |                         |                          |                                      |                                     | oade                                     |                                       |
| γ1                    | 44                      | 14                       | 11,692                  | 5                        | 89.8<br>(77.8–96.6)                  | 99.9<br>(99.8–99.9)                 | 175.9<br>5 (62.8–86.1)                   | 100.0<br>(99.7–100.0)                 |
| γ2                    | 49                      | 50                       | 11,656                  | 0                        | 100.0<br>(89.4–100.0)                | 99.6<br>(99.4–99.7)                 | 49.5<br>(39.3–59.7)                      | 100.0<br>(100.0–100.0)                |
| Bladder cancer        |                         |                          |                         | r.                       |                                      |                                     | omjo                                     |                                       |
| Primary bladder car   | ncer                    |                          |                         |                          |                                      |                                     | open                                     |                                       |
| ε1                    | 33                      | 16                       | 44,206                  | 9                        | 78.6<br>(63.2–89.7)                  | 100.0<br>(99.9–100.0)               | <u>5</u> 67.3<br><u>6</u> (52.5–80.1)    | 100.0<br>(100.0–100.0)                |
| ε2                    | 42                      | 58                       | 44,164                  | 0                        | 100.0<br>(87.7–100.0)                | 99.9<br>(99.8–99.9)                 | ₹42.0<br>9 (32.2–52.3)                   | 99.9<br>(99.8–99.9)                   |
| Prostate cancer       |                         |                          |                         |                          | •                                    |                                     | April                                    |                                       |
| Primary prostate ca   | ncer                    |                          |                         |                          |                                      | 7/                                  | 19,                                      |                                       |
| δ1                    | 17                      | 0                        | 11,676                  | 62                       | 21.5<br>(12.1–32.2)                  | 100.0<br>(100.0–100.0)              | N<br>4100.0<br>5 (72.7–100.0)            | 99.5<br>(99.3–99.6)                   |
| δ2                    | 79                      | 21                       | 11,655                  | 0                        | 100.0<br>(93.2–100.0)                | 99.8<br>(99.7–99.9)                 | ୱ 79.0<br>ଝୁ (69.7–86.5)                 | 100.0<br>(100.0–100.0)                |
| 1, confidence interv  | ai, ina, not ava        | maure, inr v, ne         | gauve predictive        | value, PP v, po          | ositive predictive valu              | IC                                  | Protected by copyright                   |                                       |

|                                       |  |  |                              |                          |  |                            | 6/bmjopen-2021-055                           | Page <b>25</b> of <b>2</b> |
|---------------------------------------|--|--|------------------------------|--------------------------|--|----------------------------|--|----------------------------|
| Table S5. Ac<br>Outcome<br>definition | ccuracy of de<br>True<br>positives,<br>n | ath definition<br>False<br>positives,<br>n | s<br>True<br>negatives,<br>n | False<br>negatives,<br>n | Sensitivity,<br>% (95% CI)             | Specificity,<br>% (95% CI) | 55<br>57<br>9% (95% CI)                      | NPV,<br>% (95% CI          |
| Lung canc                             | er                                       |  |                              |                          |  |                            |  |                            |
| E1                                    | 32                                       | 0  | 40                           | 1                        | 97.0<br>(84.2–99.9)                    | 100.0<br>(87.1–100.0)      | ₹100.0<br>8(84.2−100.0)                      | 97.6<br>(87.1–99.9)        |
| E2                                    | 9  | 0  | 40                           | 24                       | 27.3<br>(13.3–45.5)                    | 100.0<br>(87.1–100.0)      | (55.5–100.0)                                 | 62.5<br>(49.5–74.3)        |
| E3                                    | 0  | 0  | 40                           | 33                       | 0.0 (0.0–15.3)                         | 100.0<br>(87.1–100.0)      | A A A A A A A A A A A A A A A A A A A        | 54.8<br>(4.7–66.5)         |
| E4                                    | 32                                       | 0  | 40                           | 1                        | 97.0<br>(84.2–99.9)                    | 100.0<br>(87.1–100.0)      | ≅100.0<br>ā(84.2−100.0)                      | 97.6<br>(87.1–99.9)        |
| E5                                    | 9  | 0  | 40                           | 24                       | 27.3<br>(13.3–45.5)                    | 100.0<br>(87.1–100.0)      | 3100.0<br>(55.5–100.0)                       | 62.5<br>(49.5–74.3)        |
| E6                                    | 0  | 0  | 40                           | 33                       | 0.0 (0.0–15.3)                         | 100.0<br>(87.1–100.0)      | <br>NA<br>                                   | 54.8<br>(4.7–66.5)         |
| Breast can                            | cer                                      |  |                              |                          | (0.0-15.5)                             | (87.1-100.0)               | j <del>o</del> pe                            | (4.7-00.3)                 |
| E1                                    | 1  | 0  | 104                          | 0                        | 100.0<br>(1.3–100.0)                   | 100.0<br>(94.8–100.0)      | 5100.0<br>(1.3–100.0)                        | 100.0<br>(94.8–100.0       |
| E2                                    | 0  | 0  | 104                          | 1                        | 0.0 (0.0–98.7)                         | 100.0<br>(94.8–100.0)      | en la    | 99.0<br>(94.8–100.0        |
| E3                                    | 0  | 0  | 104                          | 1                        | 0.0 (0.0–98.7)                         | 100.0<br>(94.8–100.0)      |  | 99.0<br>(94.8–100.0        |
| E4                                    | 1  | 0  | 104                          | 0                        | $\frac{(0.0-90.7)}{100.0}$ (1.3-100.0) | 100.0<br>(94.8–100.0)      | $\vec{a}^{100.0\%}$<br>$\vec{a}^{101.0.0\%}$ | 100.0<br>(94.8–100.0       |
| E5                                    | 0  | 0  | 104                          | 1                        | 0.0 (0.0–98.7)                         | 100.0<br>(94.8–100.0)      | NA NA  | 99.0<br>(94.8–100.0        |
| E6                                    | 0  | 0  | 104                          | 1                        | 0.0<br>(0.0–98.7)                      | 100.0<br>(94.8–100.0)      | gNA<br>guest                                 | 99.0<br>(94.8–100.0        |
| Colorectal                            | cancer                                   |  |                              |                          | (0.0-20.7)                             | (74.0-100.0)               |  | (74.0-100.0                |
| E1                                    | 4  | 0  | 53                           | 0                        | 100.0<br>(28.4–100.0)                  | 100.0<br>(90.1–100.0)      | ਕੋ100.0<br>ਉ(28.4–100.0)                     | 100.0<br>(90.1–100.0       |
| E2                                    | 2  | 0  | 53                           | 2                        | 50.0<br>(6.8–93.2)                     | 100.0<br>(90.1–100.0)      | (20.1 100.0)<br>§100.0<br>§(9.4–100.0)       | 96.4<br>(87.5–99.6)        |

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|------|----|--------------|
|------|----|--------------|

|                       |                    |                     |                    |                     |                            |                            | 6/bmjopen-2021-              | Page <b>26</b> of <b>27</b> |
|-----------------------|--------------------|---------------------|--------------------|---------------------|----------------------------|----------------------------|------------------------------|-----------------------------|
| Outcome<br>definition | True<br>positives, | False<br>positives, | True<br>negatives, | False<br>negatives, | Sensitivity,<br>% (95% CI) | Specificity,<br>% (95% CI) | Эрру,<br>д% (95% СІ)         | NPV,<br>% (95% CI)          |
| E3                    | <b>n</b><br>0      | <u>n</u><br>0       | <u>n</u><br>53     | <u>n</u><br>4       | 0.0                        | 100.0                      | S<br>S<br>S<br>S<br>NA       | 93.0                        |
| 15                    | 0                  | 0                   | 55                 | •                   | (0.0-71.6)                 | (90.1–100.0)               |                              | (83.0–98.1)                 |
| E4                    | 4                  | 0                   | 53                 | 0                   | 100.0                      | 100.0                      | <u>د</u><br>ج100.0           | 100.0                       |
|                       |                    |                     |                    |                     | (28.4 - 100.0)             | (90.1–100.0)               | S(28.4–100.0)                | (90.1–100.0)                |
| E5                    | 2                  | 0                   | 53                 | 2                   | 50.0                       | 100.0                      | <u>N</u> 100.0               | 96.4                        |
|                       |                    |                     |                    |                     | (6.8–93.2)                 | (90.1–100.0)               | 3(9.4–100.0)                 | (87.5–99.6)                 |
| E6                    | 0                  | 0                   | 53                 | 4                   | 0.0                        | 100.0                      | <u>Š</u> NA                  | 93.0                        |
|                       |                    |                     |                    |                     | (0.0-71.6)                 | (90.1–100.0)               | oac                          | (83.0–98.1)                 |
| Ovarian ca            | ancer              |                     |                    |                     | · · · ·                    | \$ 6                       | NA<br>DNA<br>ed              | · · · · · ·                 |
| E1                    | 5                  | 0                   | 16                 | 0                   | 100.0                      | 100.0                      | ₹100.0                       | 100.0                       |
|                       |                    |                     |                    |                     | (35.9–100.0)               | (71.3–100.0)               | <u>=</u> (35.9-100.0)        | (71.3–100.0)                |
| E2                    | 2                  | 0                   | 16                 | 3                   | 40.0                       | 100.0                      | <b></b>                      | 84.2                        |
|                       |                    |                     |                    |                     | (5.3 - 85.3)               | (71.3–100.0)               | (9.4–100.0)                  | (60.4–96.6)                 |
| E3                    | 0                  | 0                   | 16                 | 5                   | 0.0                        | 100.0                      | JA<br>8                      | 76.2                        |
|                       |                    |                     |                    |                     | (0.0-64.1)                 | (71.3–100.0)               | ор<br>е                      | (52.8–91.8)                 |
| E4                    | 5                  | 0                   | 16                 | 0                   | 100.0                      | 100.0                      | <b>2</b> 100.0               | 100.0                       |
|                       |                    |                     |                    |                     | (35.9–100.0)               | (71.3–100.0)               | (35.9-100.0)                 | (71.3–100.0)                |
| E5                    | 2                  | 0                   | 16                 | 3                   | 40.0                       | 100.0                      | <u>§</u> 100.0               | 84.2                        |
|                       |                    |                     |                    |                     | (5.3-85.3)                 | (71.3–100.0)               | ₹(9.4–100.0)                 | (60.4–96.6)                 |
| E6                    | 0                  | 0                   | 16                 | 5                   | 0.0                        | 100.0                      |                              | 76.2                        |
|                       |                    |                     |                    |                     | (0.0-64.1)                 | (71.3–100.0)               | pri-                         | (52.8–91.8)                 |
| Bladder ca            |                    |                     |                    |                     | 100.0                      | 100.0                      |                              | 100.0                       |
| E1                    | 2                  | 0                   | 8                  | 0                   | 100.0                      | 100.0                      | <u>,</u><br>100.0            | 100.0                       |
| 50                    | - 1                | 0                   | 0                  | 1                   | (9.4–100.0)                | (51.8–100.0)               | <u>8</u> 9.4–100.0)          | (51.8–100.0)                |
| E2                    | 1                  | 0                   | 8                  | 1                   | 50.0                       | 100.0                      |                              | 100.0                       |
| E3                    | 0                  | 0                   | 0                  | 2                   | (1.3–98.7)<br>0.0          | (51.8–100.0)<br>100.0      | <u>(51.8–100.0)</u>          | <u>(1.3–100.0)</u><br>80.0  |
| ЕĴ                    | 0                  | 0                   | 8                  | 2                   | (0.0–90.6)                 |                            | ben<br>St.                   |                             |
| E4                    | 2                  | 0                   | 8                  | 0                   | (0.0-90.6)<br>100.0        | (51.8–100.0)<br>100.0      | <u> </u>                     | <u>(44.4–97.5)</u><br>100.0 |
| 1.4                   | L                  | 0                   | 0                  | 0                   | (9.4–100.0)                | (51.8–100.0)               | 8(9.4–100.0)                 | (51.8-100.0)                |
| E5                    | 1                  | 0                   | 8                  | 1                   | 50.0                       | 100.0                      | <u>(9.4–100.0)</u><br>2100.0 | 100.0                       |
| LJ                    | 1                  | 0                   | 0                  | 1                   | (1.3–98.7)                 | (51.8–100.0)               | ₹(51.8–100.0)                | (1.3-100.0)                 |
|                       |                    |                     |                    |                     | (1.5-70.7)                 | (31.0-100.0)               | copyright.                   | (1.3-100.0)                 |

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|                       |                         |                          |                         |                          |                            |                              | 6/bmjopen-2021-C  | Page 27 of 27              |
|-----------------------|-------------------------|--------------------------|-------------------------|--------------------------|----------------------------|------------------------------|---|----------------------------|
| Outcome<br>definition | True<br>positives,<br>n | False<br>positives,<br>n | True<br>negatives,<br>n | False<br>negatives,<br>n | Sensitivity,<br>% (95% CI) | Specificity,<br>% (95% CI)   | Ğ₽₽V,<br>₫% (95% CI)  | NPV,<br>% (95% CI)         |
| E6                    | 0                       | 0                        | 8                       | 2                        | 0.0%                       | 100.0                        | <u>9</u><br>NA  | 80.0                       |
| Prostate ca           | ncer                    |                          |                         |                          | (0.0–90.6)                 | (51.8–100.0)                 |   | (44.4–97.5)                |
|                       |                         |                          |                         |                          |                            |                              | <u>N</u><br>N100.0  |                            |
| E1                    | 3                       | 0                        | 32                      | 1                        | 75.0                       | 100.0                        |   | 97.0                       |
| E2                    | 0                       | 0                        | 32                      | 4                        | (19.4–99.4)<br>0.0         | <u>(94.2–100.0)</u><br>100.0 | <u>(19.4–100.0)</u>   | <u>(84.2–99.9)</u><br>88.9 |
| ΕZ                    | 0                       | 0                        | 32                      | 4                        | (0.0–71.6)                 | (84.2–100.0)                 | <u>S</u> INA<br><u>S</u>  | (73.9–96.9)                |
| E3                    | 0                       | 0                        | 32                      | 4                        | 0.0                        | 100.0                        |   | 88.9                       |
|                       |                         |                          |                         |                          | (0.0–71.6)                 | (84.2–100.0)                 |   | (73.9–96.9)                |
| E4                    | 3                       | 0                        | 32                      |                          | 75.0                       | 100.0                        | <u>5</u><br><u>100.0</u>  | 97.0                       |
| F.6                   | 0                       | 0                        | 22                      |                          | (19.4–99.4)                | (94.2–100.0)                 | <u>(19.4–100.0)</u>   | (84.2–99.9)                |
| E5                    | 0                       | 0                        | 32                      | 4                        | 0.0 (0.0–71.6)             | 100.0<br>(84.2–100.0)        | NA  | 88.9<br>(73.9–96.9)        |
| E6                    | 0                       | 0                        | 32                      | 4                        | 0.0                        | 100.0                        |   | 88.9                       |
| -                     |                         |                          | -                       |                          | (0.0–71.6)                 | (84.2–100.0)                 | ě.  | (73.9–96.9)                |
|                       |                         |                          |                         |                          |                            |                              | NA<br>Open.pmj.com/ on April 19, 2024 by guest. Protected by copyright. |                            |

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| Section & Topic   | No         | Item   | Reported on pag                      |
|-------------------|------------|--|--------------------------------------|
| TITLE OR ABSTRACT |            |  |                                      |
|                   | 1          | Identification as a study of diagnostic accuracy using at least one measure of accuracy  | 3                                    |
|                   |            | (such as sensitivity, specificity, predictive values, or AUC)  |                                      |
| ABSTRACT          |            |  |                                      |
|                   | 2          | Structured summary of study design, methods, results, and conclusions  | 3                                    |
|                   |            | (for specific guidance, see STARD for Abstracts)   |                                      |
| INTRODUCTION      |            |  |                                      |
|                   | 3          | Scientific and clinical background, including the intended use and clinical role of the index test   | 5                                    |
|                   | 4          | Study objectives and hypotheses  | 5 and 6                              |
| METHODS           |            |  |                                      |
| Study design      | 5          | Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study) | 6                                    |
| Participants      | 6          | Eligibility criteria   | 8                                    |
|                   | 7          | On what basis potentially eligible participants were identified  | 8                                    |
|                   |            | (such as symptoms, results from previous tests, inclusion in registry)   |                                      |
|                   | 8          | Where and when potentially eligible participants were identified (setting, location and dates)   | 8                                    |
|                   | 9          | Whether participants formed a consecutive, random or convenience series  |                                      |
| Test methods      | 10a        | Index test, in sufficient detail to allow replication  | 9                                    |
|                   | 10b        | Reference standard, in sufficient detail to allow replication  | 6                                    |
|                   | 11         | Rationale for choosing the reference standard (if alternatives exist)  | 5                                    |
|                   | 12a        | Definition of and rationale for test positivity cut-offs or result categories  | 10                                   |
|                   |            | of the index test, distinguishing pre-specified from exploratory   |                                      |
|                   | 12b        | Definition of and rationale for test positivity cut-offs or result categories  | 10                                   |
|                   |            | of the reference standard, distinguishing pre-specified from exploratory   |                                      |
|                   | 13a        | Whether clinical information and reference standard results were available   | 8                                    |
|                   |            | to the performers/readers of the index test  |                                      |
|                   | 13b        | Whether clinical information and index test results were available   | 8                                    |
|                   |            | to the assessors of the reference standard   | ļ                                    |
| Analysis          | 14         | Methods for estimating or comparing measures of diagnostic accuracy  | 10-11                                |
|                   | 15         | How indeterminate index test or reference standard results were handled  | 10-11                                |
|                   | 16         | How missing data on the index test and reference standard were handled   | 10-11                                |
|                   | 17         | Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from  | Not applicable                       |
|                   |            | exploratory  |                                      |
|                   | 18         | Intended sample size and how it was determined   | Page 9                               |
| RESULTS           |            |  |                                      |
| Participants      | 19         | Flow of participants, using a diagram  | Supplementary                        |
|                   | 20         | Baseline demographic and clinical characteristics of participants  | figures 1- 6<br>Table 4              |
|                   | 20<br>21a  | Distribution of severity of disease in those with the target condition   | Not applicable                       |
|                   | 21a<br>21b | Distribution of alternative diagnoses in those without the target condition  | Not applicable                       |
|                   | 210        | Time interval and any clinical interventions between index test and reference standard   |                                      |
| Test results      | 23         | Cross tabulation of the index test results (or their distribution)   | Table 2, Table 3,                    |
| restresuits       | 25         | by the results of the reference standard   | Table S3, Table S                    |
|                   | 24         | Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)  | Along with each                      |
|                   |            |  | result in<br>corresponding<br>tables |
|                   | 25         | Any adverse events from performing the index test or the reference standard  | Not applicable                       |
| DISCUSSION        | -          |  | PP 10010                             |
|                   | 26         | Study limitations, including sources of potential bias, statistical uncertainty, and   | Page 25                              |
|                   | -          | generalisability   | <b>U</b> -                           |
|                   | 27         | Implications for practice, including the intended use and clinical role of the index test  | Page 26                              |
| OTHER             |            |  | -                                    |
| INFORMATION       |            | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml  |                                      |



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|        | 28     | Registration number and name of registry                                  | Page 8  |
|--------|--------|---|---------|
|        | <br>29 | Where the full study protocol can be accessed                             | No      |
|        | 30     | Sources of funding and other support; role of funders                     | Page 26 |
| -      |        |   |         |
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|        |        |   |         |

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## STARD 2015

#### AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

### EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

#### DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <u>http://www.equator-network.org/reporting-guidelines/stard.</u>



