

Review

Identification of validated case definitions for medical conditions used in primary care electronic medical record databases: a systematic review

Kerry A McBrien,^{1,2} Sepideh Souiri,² Nicola E Symonds,³ Azin Rouhi,⁴
Brendan C Lethebe,² Tyler S Williamson,² Stephanie Garies,^{1,2} Richard Birtwhistle,⁵
Hude Quan,² Gabriel E Fabreau,^{2,6} and Paul E Ronksley²

¹Department of Family Medicine, Cumming School of Medicine, University of Calgary, Calgary, Canada, ²Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Canada, ³Faculty of Science, University of British Columbia, Vancouver, Canada, ⁴Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada, ⁵Department of Family Medicine, Faculty of Health Sciences, Queen's University, Kingston, Canada, and ⁶Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Canada

Corresponding Author: Kerry A. McBrien, MD, MPH, CCFP, 3E20 Teaching, Research & Wellness (TRW) Building, 3280 Hospital Drive NW, Calgary, Alberta T2N 4Z6, Canada (kamcbrie@ucalgary.ca)

Received 18 January 2018; Revised 19 June 2018; Editorial Decision 22 June 2018; Accepted 2 July 2018

ABSTRACT

Objectives: Data derived from primary care electronic medical records (EMRs) are being used for research and surveillance. Case definitions are required to identify patients with specific conditions in EMR data with a degree of accuracy. The purpose of this study is to identify and provide a summary of case definitions that have been validated in primary care EMR data.

Materials and Methods: We searched MEDLINE and Embase (from inception to June 2016) to identify studies that describe case definitions for clinical conditions in EMR data and report on the performance metrics of these definitions.

Results: We identified 40 studies reporting on case definitions for 47 unique clinical conditions. The studies used combinations of International Classification of Disease version 9 (ICD-9) codes, Read codes, laboratory values, and medications in their algorithms. The most common validation metric reported was positive predictive value, with inconsistent reporting of sensitivity and specificity.

Discussion: This review describes validated case definitions derived in primary care EMR data, which can be used to understand disease patterns and prevalence among primary care populations. Limitations include incomplete reporting of performance metrics and uncertainty regarding performance of case definitions across different EMR databases and countries.

Conclusion: Our review found a significant number of validated case definitions with good performance for use in primary care EMR data. These could be applied to other EMR databases in similar contexts and may enable better disease surveillance when using clinical EMR data. Consistent reporting across validation studies using EMR data would facilitate comparison across studies.

Systematic review registration: PROSPERO CRD42016040020 (submitted June 8, 2016, and last revised June 14, 2016)

Key words: systematic review, electronic medical record, case definitions, primary care

BACKGROUND AND SIGNIFICANCE

Rationale

The collection and storage of vast amounts of health data are growing rapidly.¹ These “big data” include electronic medical record (EMR)² data and traditional coded administrative health data, among others. Administrative health data are generated and collected from the administration of the healthcare system, such as hospital discharge abstracts and physician billing claims; these data are routinely used for research and surveillance, as most are population based, relatively inexpensive compared to primary data collection, and exist in a structured format.³

EMRs are commonly used in primary care settings to record patient information and facilitate patient care, and thus contain comprehensive demographic and clinical information about diagnoses, prescriptions, physical measurements, laboratory test results, medical procedures, referrals, and risk factors.⁴ The increased digitization of health information and novel techniques developed for extracting and standardizing data from EMR systems have resulted in many primary care EMR databases being established globally for the purposes of health research and public health surveillance.⁵ A few prominent examples include the Clinical Practice Research Datalink (CPRD)⁶ and The Health Improvement Network (THIN),⁷ both in the UK, as well as the Canadian Primary Care Sentinel Surveillance Network (CPCSSN)⁸ in Canada.

When using administrative or EMR data for secondary purposes, it is important to have the ability to reliably identify cohorts of patients with a specific disease or condition of interest. Case definitions, also referred to as phenotypes, can be constructed from combinations of diagnostic codes, text words, medications, and/or laboratory results found in the patient record.⁵ Ideally, case definitions should be validated against a reference standard for disease identification; in most cases, either a manual review of patient charts or physician confirmation is typically used.

As administrative data have been widely utilized for secondary purposes for many decades, numerous case definitions specific to this data source have been developed and validated in a variety of countries and populations.⁹ EMR data are still a relatively new contribution to disease surveillance and health research, and a full summary of available validated case definitions has not been previously published.

OBJECTIVE

The objective of this study was to identify all case definitions for specific conditions, which have been tested and validated in primary care EMR data.

MATERIALS AND METHODS

We conducted a systematic review of primary studies that reported on the development and validation of case definitions for use in primary care EMR data. We followed a pre-specified protocol,¹⁰ in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.¹¹ All data were obtained from publically available materials and did not require ethics approval from our institutions.

Data sources and search strategy

We searched MEDLINE (Ovid) and Embase (Ovid) with no date, country, or language restrictions. We also searched the bibliogra-

phies of all identified studies. Further, the websites for EMR databases were searched for bibliographic lists (eg, CPRD,⁶ www.cprd.com), and content experts were contacted for information about other potentially ongoing or unpublished studies. The search of online databases included three themes:

1. *Electronic medical records*
2. *Case definition*
3. *Validation study*

We used a comprehensive set of MeSH terms and keyword searches for each of the three themes to ensure we captured all relevant literature. For example, the term “EMR” may be synonymous with a number of relevant keywords (eg, computerized medical records, EHR, etc.). These three search themes were then combined using the Boolean term “AND.” [Supplementary File S1](#) presents our MEDLINE search strategy.

Study selection

Two reviewers independently screened all abstracts. Articles that reported original data for the development and validation of disease case definitions in primary care EMR data were considered for further review. All citations for which either reviewer felt that further review was warranted were kept for full-text review. Bibliographic details from all stages of the review were managed within the *Synthesis* software package.¹²

Two reviewers then scanned full-text articles for the following inclusion criteria:

1. The database under study was a primary care EMR database.
2. There was a description of a computerized case definition for a specific disease or condition.
3. A clearly stated reference standard was used to validate the case definition.
4. Performance metrics were reported (ie, sensitivity, specificity, positive predictive value, negative predictive value, kappa, receiver operating characteristic, likelihood ratio, and their synonyms).

Non-human studies were excluded. Studies reporting on dental health or other non-primary care settings were excluded. We excluded studies in which EMR data were based on patient self-report. We also excluded studies that examined definitions in EMR data linked to administrative health data (though administrative health data used for the reference standard were acceptable). Studies that were not original research and conference abstracts without an adequately detailed description of study methods and results were excluded.

Data extraction

A data extraction form was used to collect information from each included study. The following data elements were extracted: first author, publication year, country, condition(s) under study, sample size and characteristics, cases identified as positive or negative, EMR database or data platform, description of case definition and techniques used to generate it along with fields accessed, reference standard, and performance metrics (eg, sensitivity, specificity, and positive and negative predictive values).

Risk of bias assessment

Included studies were assessed for quality using a component-based approach. We used relevant items from the Quality Assessment of

Diagnostic Accuracy Studies (QUADAS) quality assessment tool for diagnostic accuracy studies.¹³ This tool includes an assessment of bias in several domains, including patient selection, the validation strategy, and reporting of outcomes. Two authors independently assessed risk of bias in each domain and reported the risk of bias as high, low, or unclear. Disagreements were resolved by discussion or with a third reviewer as needed.

Data synthesis

Included studies were described in detail, including setting, target population, and database accessed. Case definitions were grouped by ICD-9 disease category, and definitions were summarized together with their performance metrics. It was not possible to pool data for specific conditions, given study heterogeneity; however, a qualitative comparison of performance of case definitions across conditions was done and reported narratively. Within disease conditions for which there was more than one validated case definition, we documented performance metrics across case definitions and specifically examined the relative importance of using different data elements in creating case definitions for diabetes. In addition to summarizing case definitions and their performance metrics by disease condition, we also produced a detailed inventory of the combinations of variables used, the data fields accessed, and the computer programming methods used.

RESULTS

Study identification

The initial search produced 8983 abstracts from the two databases; 6664 remained after removing duplicates (Figure 1). After the initial abstract screen, 646 articles went forward to full-text review, of which 40 met criteria for inclusion. Reviewer agreement was good in the full-text review stage, with a kappa value of 0.66. The most common reason for exclusion was setting, ie, not primary care (55.8%). Other reasons for exclusion included: not explicitly stating either the case definitions (23.3%) or validation results (1.5%), not using EMR data exclusively (11.7%), not focusing on a specific medical condition (0.8%), and not having a reference standard (0.5%).

Table 1 describes the characteristics of the studies selected for inclusion ($n=40$). Most studies were published between 2010 and 2016 (82.5%) and were conducted in Europe ($n=25$; 62.5%). Twelve studies (30%) were conducted in North America, and the remaining three studies were from Australia and New Zealand (7.5%). Frequently used databases included the General Practice Research Database (GPRD) and its successor, the CPRD, THIN, Integrated Primary Care Information (IPCI), and CPCSSN. Most of the studies focused on a general clinical population, though some (7.5%) were specific to pediatric, adolescent, or senior groups. Sample sizes ranged between 75 and 190 000 patients, with a per-study median of just under 2000 patients. Figure 2 provides a summary of select study characteristics.

Study quality assessment

Supplementary File S2 reports the study quality assessment. Most studies were of reasonably high quality with three studies meeting all quality criteria and 25 studies missing only one or two components of quality. Twelve studies were of questionable quality with three or more domains either not done or not reported. Most studies

did not use blinding of the results of the case definition or did not report whether blinding was performed (85%). Further, over one-third (35%) of the studies did not report enough information about the case definition to allow for replication; nearly a quarter of the studies (22.5%) lacked adequate details about the reference standard used to validate the definition.

Medical conditions

Case definitions were found for a total of 47 medical conditions, which represented 13 chapters of the ICD-9,⁵³ the most common being respiratory and circulatory conditions. Eight diseases had multiple case definitions: two for colorectal cancer, eight for diabetes, three for depression, six for hypertension, six for chronic obstructive pulmonary disease (COPD), three for asthma (one of which was pediatric asthma), two for skin and soft tissue infections, and five for arthritis (three osteoarthritis, one rheumatoid arthritis, one inflammatory arthritis).

Case definitions and validation

Most case definitions were constructed using diagnostic codes, such as ICD-9⁵³ or Read codes;⁵⁴ these were sometimes supplemented with laboratory values (eg, glycated hemoglobin [HbA1c] for diabetes), medications (eg, metformin for diabetes), or physical measurements (eg, blood pressure, weight) (Table 2). Some studies tested machine learning programs that were also able to access unstructured data elements, such as free text clinical notes.^{14,15,50,55,56}

The reporting of performance metrics was variable across studies, with some describing several metrics and others reporting just one. The most frequently used validation measure was the positive predictive value (PPV); sensitivity and specificity were also frequently measured. Seven studies reported true positives and false positives.^{14,21,33,34,39,42,51} Only one study reported likelihood ratios⁴⁰ (Figure 2 and Table 2). The most common reference standard used was manual chart review, though others included a physician questionnaire, registries based on other data sources, and other diagnostic tests.

Case definitions for malignancies ($n=8$) performed well overall, with mostly high sensitivities, specificities, and PPVs. With respect to chronic illnesses, definitions for diabetes ($n=8$) also performed well across the three metrics. Definitions for hypertension ($n=5$) and ischemic heart disease ($n=3$) had moderate performance, while definitions for heart failure ($n=2$) were highly specific but not very sensitive. Similarly, definitions for COPD ($n=6$), overweight ($n=1$), osteoarthritis ($n=3$), and depression ($n=3$) also had high specificities but low sensitivities. Asthma definitions performed moderately well across sensitivity and specificity. Some less common diseases, ie, dementia, Parkinson's disease, epilepsy, and multiple sclerosis, had definitions with good sensitivities and specificities, but PPVs tended to be moderate. Case definitions for acute infections (otitis media and respiratory infections) had excellent specificities but low sensitivities. Supplementary File S3 contains further detail on the published case definitions.

In the case of diabetes, 19 separate tests of validation were reported across eight studies, three of which were performed at different times in the same database (CPCSSN). These definitions used various elements of EMR data alone or in combination, including diagnostic codes, reason for visit, medications, laboratory data, problems lists, and in one case, free text (Table 3). There are no consistent trends indicating that one or more elements increases performance. However, in the case of Hirsch et al, case definition

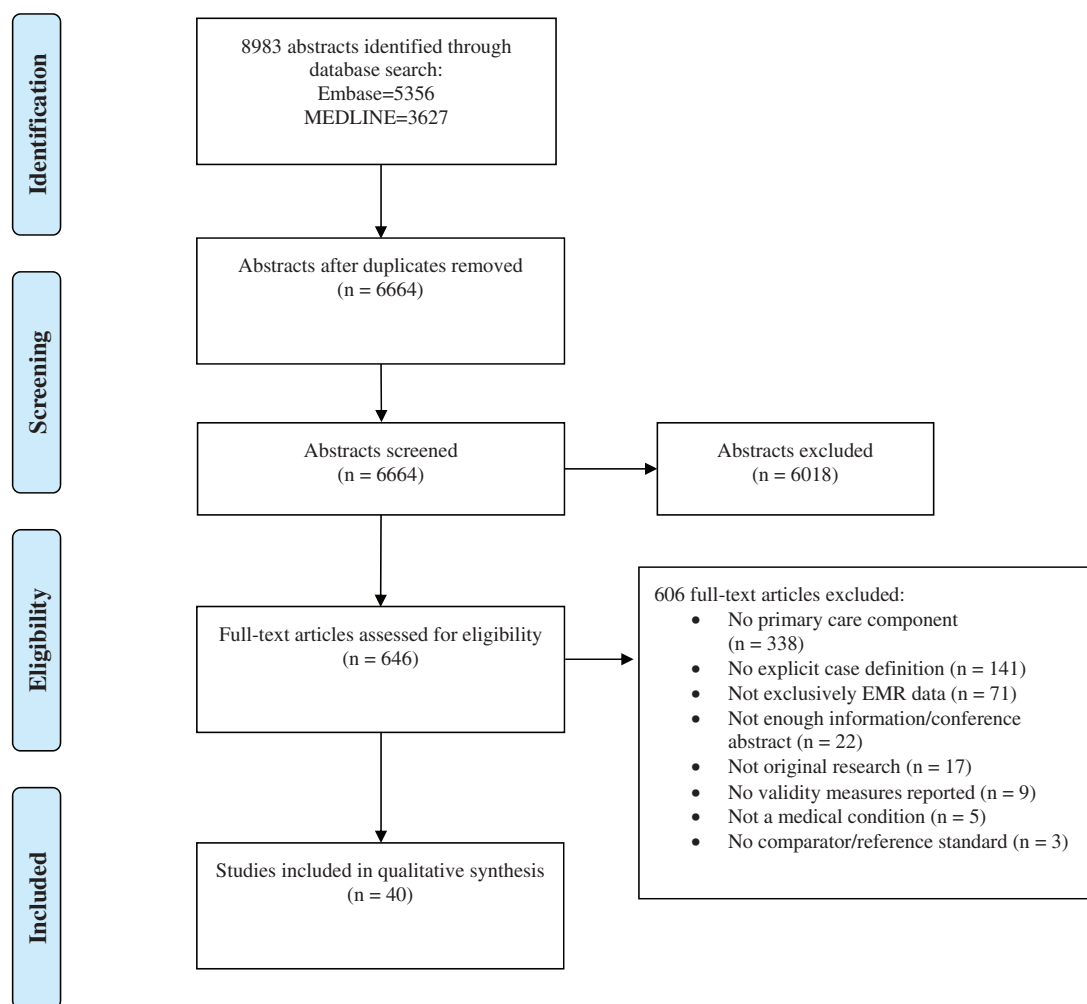


Figure 1. Study selection.

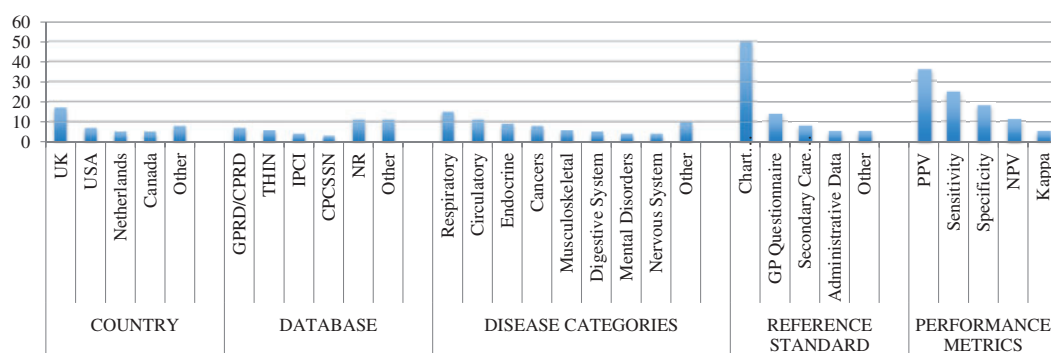


Figure 2. Summary of study characteristics.

performance improved slightly with the addition of other data elements to diagnostic codes. In most cases in which diagnostic codes were not used, performance was markedly lower. Also noted is that PPV decreased slightly when case definition sensitivity increased. Free text was used only in one instance; however, it did not have superior performance to diagnostic codes.

DISCUSSION

Summary of findings

We undertook this project to summarize all studies that have developed and validated case definitions using primary care EMR data. Validated case definitions are important tools, as they can be

Table 1. Study characteristics

First Author	Year	Country	Condition	Patients	EMR Data Source	Sample size
Afzal ¹⁴	2013	Netherlands	Asthma	5 to 18 years; registered in IPCI for at least 6 months	IPCI	5032
Afzal ¹⁵	2013	Netherlands	Hepatobiliary disease; Acute renal failure	All patients registered in IPCI	IPCI	973; 3988
Cea Soriano ¹⁶	2016	UK	Colorectal cancer	40 to 89 years at diagnosis; no record of cancer prescription for low-dose aspirin prior to study entry	THIN	3805
Charlton ¹⁷	2010	UK	Major congenital malformations	Mother-baby pairs; mothers 14 to 49 years at the date of delivery	GPRD	188
Coleman ¹⁸	2015	Canada	Diabetes; Hypertension; Depression; Osteoarthritis; COPD	60 years and over; at least one of the five conditions of interest according to current CPCSSN algorithms	CPCSSN	403
Coloma ¹⁹	2013	Netherlands; Italy	Acute myocardial infarction	>1 year of continuous and valid data	IPCI; Health Search/CSD Patient DB	400; 200
Cowan ²⁰	2014	USA	Asthma	Patients seen in the University of Wisconsin Department of Family Medicine Clinics between 2007-2009	Health Plan Employer Data Information Set (HEDIS)	190 000
de Burgos-Lunar ²¹	2011	Spain	Diabetes mellitus; Hypertension	Over 18 years	Computerized Clinical Records of primary health care clinics in the Spanish National Health System	423
Dregan ²²	2012	UK	Colorectal cancer; Lung cancer; Gastro-oesophageal cancer; Urological cancer	Patients with at least 12 months of follow-up prior to the start of observation and no alarm symptom or cancer diagnosis documented	GPRD	42 556
Dubreuil ²³	2016	UK	Ankylosing spondylitis	18 to 59 years	THIN	85
Faulconer ²⁴	2004	UK	COPD	Over 45 years	EMIS	10 975
Gil Montalban ²⁵	2014	Spain	Diabetes mellitus	30 to 74 years	AP-Madrid	2268
Gray ²⁶	2000	England	Ischaemic heart disease	45 years or over	NR	1680
Gu ²⁷	2015	New Zealand	Skin and Subcutaneous tissue infections	20 years or under	Four New Zealand general practice EMRs	307
Hammad ²⁸	2013	UK	Congenital cardiac malformations	Singleton live-birth babies	CPRD	719
Hammersley ²⁹	2011	UK	Active seasonal allergic rhinitis	15 to 45 years	Anonymized dataset	1092
Hirsch ³⁰	2014	USA	Diabetes	18 years or over; at least 2 outpatient encounters with any GHS provider in 2009	EHR database from Geisinger Health System	499
Kadhim-Saleh ³¹	2013	Canada	Diabetes; Hypertension; Osteoarthritis; COPD; Depression	All patients who attended the Kingston (Ontario) PBRN and all 22 practices within the network	CPCSSN	313
Kang ³²	2015	UK	Glaucoma; Cataract	18 to 80 years	CPRD	863; 986
Krysko ³³	2015	Canada	Multiple sclerosis	20 years or over	EMRALD, EMR only	943
Levine ³⁴	2013	USA	Skin and soft tissue infections	Primary care outpatients in an academic health-care system	Oregon Health & Science University's research data warehouse	731

(continued)

Table 1. continued

First Author	Year	Country	Condition	Patients	EMR Data Source	Sample size
Lo Re ³⁵	2009	UK	Hepatitis C virus infection; Viral hepatitis	Patients in the database identified with HCV diagnostic codes	THIN	75
MacRae ³⁶	2015	New Zealand	Upper respiratory tract infection; Lower respiratory tract infection; Wheeze illness; Throat infections; Otitis media; Other respiratory	Under 18 years, enrolled in 36 primary care practices	Primary care EHR data	1200
Mamtani ³⁷	2015	UK	Bladder cancer; Muscle-invasive bladder cancer	21 years or over; at least 6 months of follow-up preceding a first diagnostic code for bladder cancer	THIN	87
Margulis ³⁸	2009	UK	Upper gastrointestinal complications; Peptic ulcer	40 to 84 years	THIN	44; 143
Nielen ³⁹	2013	Netherlands	Inflammatory arthritis	30 years or over	LINH	219
Onofrei ⁴⁰	2004	USA	Heart failure: LVEF \leq 55%; LVEF \leq 40%	All patients with an active record	Providence Research Network	1403; 793
Quint ⁴¹	2014	UK	COPD	Over 35 years	CPRD-Gold	704
Rahimi ⁴²	2014	Australia	Type 2 diabetes mellitus	At least 3 visits in a two-year period	ePBRN	908
Rakotz ⁴³	2014	USA	Undiagnosed hypertension	18 to 79 years	NR	1586
Rothnie ⁴⁴	2016	UK	Acute exacerbation of COPD	Over 35 years	CPRD	988
Scott ⁴⁵	2015	UK	Intra-abdominal surgery complications; small bowel obstruction; Lysis of adhesions	18 years or over	THIN	217
Thiru ⁴⁶	2009	UK	Coronary heart disease	35 years or over	EMIS from the Northern Regional Research Network	673
Tian ⁴⁷	2013	USA	Chronic pain	18 years or over	ECW EHR system	381
Turchin ⁴⁸	2005	USA	Diabetes; Hypertension; Overweight	18 years or over	EMR data from four primary care practices at the Brigham & Women's Hospital, Boston MA	150
Valkhoff ⁴⁹	2014	Netherlands; Italy	Upper gastrointestinal bleeding	1- All ages; 2- 15 years or over	IPCI; Health Search/CSD Patient Database (HSD)	400; 200
Wang ⁵⁰	2012	UK	Ovarian cancer diagnosis	40 to 80 years	GPRD	178
Williamson ⁵	2014	Canada	COPD; Dementia; Depression; Diabetes; Hypertension; Osteoarthritis; Parkinsonism; Epilepsy	90% over 60 years	CPCSSN	1920
Xi ⁵¹	2015	Canada	Asthma	16 years or over	Open-source Oscar EMR system	150
Zhou ⁵²	2016	UK	Rheumatoid arthritis	Over 16 years	GP records contained in SAIL	559

Abbreviations: IPCI = Integrated Primary Care Information; THIN = The Health Improvement Network; GPRD = General Practice Research Database; CPCSSN = Canadian Primary Care Sentinel Surveillance Network; COPD = Chronic obstructive pulmonary disease; EMIS = Egton Medical Information System; CPRD = Clinical Practice Research Datalink; HER = Electronic Health Records; EMRALD = Electronic Medical Record Administrative data Linked Database; PHO = Primary Health Organization; LINH = Netherlands Information Network of General Practice; LVEF = Left ventricular ejection fraction; CPRD-Gold = Clinical Practice Research Datalink-Gold; ePBRN = Electronic Practice Based Research Network; ECW = eClinicalWorks; SAIL = Secure Anonymised Information Linkage; NR = Not Reported.

Table 2. Study results grouped by ICD chapter

First Author	Condition	Reference Standard	Validation Results				
			Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
Certain infectious and parasitic diseases							
Lo Re ³⁵	Hepatitis C virus infection	GP questionnaire	.	.	86	.	.
Lo Re ³⁵	Viral hepatitis	GP questionnaire	.	.	76	.	.
Neoplasms							
Cea Soriano ¹⁶	Colorectal cancer	Chart review	.	.	80	.	.
Dregan ²²	Colorectal cancer	Cancer registry data	92	99	98	99*	.
Dregan ²²	Lung cancer	Cancer registry data	94	99	96	99*	.
Dregan ²²	Gastro-esophageal cancer	Cancer registry data	92	99	97	99*	.
Dregan ²²	Urological cancer	Cancer registry data	85	99	93	99*	.
Mamtani ³⁷	Bladder cancer	GP questionnaire and medical reports	.	.	99	.	.
Mamtani ³⁷	Muscle invasive bladder cancer	GP questionnaire and medical reports	.	.	70	.	.
Wang ⁵⁰	Ovarian cancer	Chart review	86	.	74	.	.
Endocrine, nutritional, and metabolic diseases							
Coleman ¹⁸	Diabetes	Chart review	90	97	91	97*	88
de Burgos-Lunar ²¹	Diabetes mellitus	Chart review	100	99	91	100	99
Gil Montalban ²⁵	Diabetes mellitus	Data from PREDIMERC	74	99	88	97	78
Hirsch ³⁰	Diabetes	Chart review	65-99	99-100*	98-100	94-99*	.
Kadhim-Saleh ³¹	Diabetes	Primary audit of EMRs	100	99	95	100	.
Rahimi ⁴²	Type 2 diabetes	Manual audit of EHR	85*	99*	98	99	.
Turchin ⁴⁸	Overweight	Chart and billing code review	74; 14	100	.	.	67
Turchin ⁴⁸	Diabetes	Chart and billing code review	98; 98	98; 98	.	.	94
Williamson ⁵	Diabetes	Chart review	96	97	87	99	.
Mental disorders							
Coleman ¹⁸	Depression	Chart review	73	96	87	90*	72
Kadhim-Saleh ³¹	Depression	Primary audit of EMRs	39	97	79	86	.
Williamson ⁵	Dementia	Chart review	97	98	73	100	.
Williamson ⁵	Depression	Chart review	81	95	80	95	.
Diseases of the nervous system							
Krysko ³³	Multiple sclerosis	Chart review	92	100	99	100	95
Tian ⁴⁷	Chronic pain	Chart review	85	98	91	96	.
Williamson ⁵	Parkinsonism	Chart review	99	99	82	100	.
Williamson ⁵	Epilepsy	Chart review	99	99	86	100	.
Diseases of the eye and adnexa							
Kang ³²	Cataract	GP questionnaire	.	.	92	.	.
Kang ³²	Glaucoma	GP questionnaire	.	.	84	.	.
MacRae ³⁶	Otitis media	Chart review	58	99	90	94	.
Diseases of the circulatory system							
Coleman ¹⁸	Hypertension	Chart review	95	79	93	86*	76
Coloma ¹⁹	Acute myocardial infarction	Chart review/GP questionnaire	.	.	60-97	.	.
de Burgos-Lunar ²¹	Hypertension	Chart review	85	97	85	97	77
Gray ²⁶	Ischemic heart disease	Chart review	47-96	.	33-83	.	.
Kadhim-Saleh ³¹	Hypertension	Primary audit of EMRs	83	98	98	81	.
Onofrei ⁴⁰	Heart failure: LVEF ≤ 55%	Echocardiography database, echo in chart, chart review	44	100	36	100	.
Onofrei ⁴⁰	Heart failure: LVEF ≤ 40%	Echocardiography database, echo in chart, chart review	54	99	25	100	.
Rakotz ⁴³	Undiagnosed hypertension	AOBP measurement	.	.	51-58	.	.
Thiru ⁴⁶	Coronary heart disease	Established EMR definitions	65-98	.	40-74	.	.
Turchin ⁴⁸	Hypertension	Chart and billing code review	91; 74	86; 92	.	.	77
Williamson ⁵	Hypertension	Chart review	85	94	93	86	.
Diseases of the respiratory system							
Afzal ¹⁴	Pediatric asthma	Chart review	95-98	67-95	57-82	.	.
Coleman ¹⁸	COPD	Chart review	72	92	37	98*	44
Cowan ²⁰	Asthma	Expert panel diagnosis	82-92	95-98	.	.	.
Faulconer ²⁴	COPD	Chart review	79	99*	75	99*	.
Hammersley ²⁹	Allergic rhinitis	Chart review	17-85	86-100	15-100	96-99	.

(continued)

Table 2. continued

First Author	Condition	Reference Standard	Validation Results				
			Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
Kadhim-Saleh ³¹	COPD	Primary audit of EMRs	41	99	80	94	.
Quint ⁴¹	COPD	Chart review/GP questionnaire	.	.	12-89	.	.
Rothnie ⁴⁴	Acute exacerbations of COPD	Chart review/GP questionnaire	52-88	.	64-86	.	.
Williamson ⁵	COPD	Chart review	82	97	72	98	.
Xi ⁵¹	Asthma	Chart review	74-90	84-93	67-81*	90-96*	.
MacRae ³⁶	Upper respiratory tract infection	Chart review	54	98	86	89	.
MacRae ³⁶	Lower respiratory tract infection	Chart review	61	99	76	98	.
MacRae ³⁶	Wheeze illness	Chart review	96	96	70	100	.
MacRae ³⁶	Throat infections	Chart review	50	99	91	95	.
MacRae ³⁶	Other respiratory	Chart review	66	99	68	99	.
Diseases of the digestive system							
Afzal ¹⁵	Hepatobiliary disease	Chart review	89-92	68-79	.	.	.
Margulis ³⁸	Upper gastrointestinal complications	GP questionnaire	.	.	95	.	.
Margulis ³⁸	Peptic ulcer	GP questionnaire	.	.	94	.	.
Valkhoff ⁴⁹	Upper gastrointestinal bleeding	Expert panel review/chart review	.	.	21; 78	.	.
Scott ⁴⁵	Intra-abdominal surgery complications, small bowel obstruction, and lysis of adhesions	GP questionnaire	.	.	86-95	.	.
Diseases of the skin and subcutaneous tissue							
Gu ²⁷	Skin and subcutaneous tissue infections	Chart review	95	98	80	100	.
Levine ³⁴	Skin and soft tissue infections	Chart review	.	.	53-92	.	.
Diseases of the musculoskeletal system and connective tissue							
Coleman ¹⁸	Osteoarthritis	Chart review	63	94	96	51*	46
Dubreuil ²³	Ankylosing spondylitis	GP questionnaire	30-98	.	71-89	.	.
Kadhim-Saleh ³¹	Osteoarthritis	Primary audit of EMRs	45	100	100	68	.
Nielen ³⁹	Inflammatory arthritis	Chart review	.	.	78	.	.
Williamson ⁵	Osteoarthritis	Chart review	78	95	88	90	.
Zhou ⁵²	Rheumatoid arthritis	Secondary care electronic patient records	86-89	91-95	79-86	.	.
Diseases of the genitourinary system							
Afzal ¹⁵	Acute renal failure	Chart review	62-71	88-92	.	.	.
Congenital malformations, deformations, and chromosomal abnormalities							
Charlton ¹⁷	Major congenital malformations	Chart review	.	.	85	.	.
Hammad ²⁸	Congenital cardiac malformations	GP questionnaire	.	.	0-100	.	.

Abbreviations: ICD = International Classification of Diseases; ICD-9-CM = International Classification of Diseases, 9th revision, clinical modification; NPV = negative predictive value; PPV = positive predictive value.

*indicates calculated values based upon published data.

adapted and applied to different EMR databases to conduct research or surveillance. Our review identified 40 studies that validated case definitions for 47 conditions. The most common conditions were diabetes (eight definitions), hypertension (six definitions), and COPD (six definitions), though multiple definitions have also been developed for depression (three definitions), osteoarthritis (three definitions), and asthma and respiratory infections (four definitions). The majority of other conditions was limited to a single case definition.

The case definitions we identified may be useful for research or surveillance efforts that require identification of one of the 47 conditions in primary care EMR data. While not all will be easily transferred for use with other data sources, these definitions can serve as an important starting point. Further, for conditions for which we have not identified a case definition, there is an opportunity to develop, test, and publish case definitions so they are available to others. For instance, Barnett et al conducted a literature review, followed by a consensus exercise to identify 40 conditions likely to be

Table 3. Diabetes case definition elements and performance

First Author	Database	Diagnostic Codes	Reason for Visit	Medications	Lab results	Problem List	Classification System	Free Text	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Coleman ¹⁸	CPCSSN	X		X	X				90	97	91	.
de Burgos-Lunar ²¹	EMRs in Spanish National Health System	X							100	99	91	100
Gil Montalban ²⁵	AP-Madrid	X					X		74	99	88	97
Hirsch ³⁰	Geisinger Health System	X							96	.	98	.
Hirsch ³⁰	Geisinger Health System					X			75	.	100	.
Hirsch ³⁰	Geisinger Health System				X				65	.	100	.
Hirsch ³⁰	Geisinger Health System			X					84	.	99	.
Hirsch ³⁰	Geisinger Health System	X				X			96	.	98	.
Hirsch ³⁰	Geisinger Health System	X			X	X			99	.	98	.
Hirsch ³⁰	Geisinger Health System	X		X		X			98	.	98	.
Hirsch ³⁰	Geisinger Health System	X		X	X	X			99	.	98	.
Kadhim-Saleh ³¹	CPCSSN	X		X	X	X			100	99	95	100
Rahimi ⁴²	ePBRN		X						.	.	100	100
Rahimi ⁴²	ePBRN			X					.	.	97	99
Rahimi ⁴²	ePBRN				X				.	.	16	99
Rahimi ⁴²	ePBRN		X	X	X				.	.	98	99
Turchin ⁴⁸	EMR from four practices							X	98	98	.	.
Turchin ⁴⁸	EMR from four practices	X							98	98	.	.
Williamson ⁵	CPCSSN	X		X	X				96	97	87	99

chronic and have significant impact on patients' treatment needs, function, quality of life, morbidity, and mortality.⁵⁷ Tonelli et al identified case definitions with moderate to high validity for use in administrative health data for 30 of these conditions.⁹ Our review identified EMR case definitions for only 16 of these conditions. While it appears that case definitions are created opportunistically for research that focuses on one or more specific conditions, creating case definitions requires considerable effort, and having these available for use and adaptation may facilitate future research.

This review also summarized the methods and data elements used for developing the case definitions. Diagnostic codes were the most common feature used to define the conditions, and also the most simplistic method, as many definitions relied solely on diagnostic codes. While diagnostic codes were highly sensitive and specific for some conditions (eg, cancer), they were much less sensitive for others (eg, heart failure, depression), perhaps due to less specific diagnostic codes for these types of conditions. For instance, heart failure could present as shortness of breath, or together with another condition such as arrhythmia or diabetes. Similarly, depression could present symptomatically as insomnia, fatigue, malaise, etc., and be given a diagnostic code specific to the symptomatology. In several instances, diagnostic codes were augmented with a combination of medications, laboratory data, problem lists, and/or free text searches. In the case of diabetes, these additional data elements were useful in improving the sensitivity and specificity of the case definition.^{5,30} Of note, diabetes case definitions tended to perform better overall than those for COPD, another common chronic condition.

While this may be due to better diagnostic coding on the part of physicians, it is also possible to identify diabetes based on laboratory values. Having additional data elements available for disease identification may improve case definition performance.

Finally, while less common than traditional expert committee created definitions, machine learning programs have been used in an attempt to efficiently identify the best case definitions using multiple data elements.^{5,9} It is difficult to comment on whether these programs perform better, as the only condition for which both methods have been used is diabetes, and both performed similarly, albeit in different databases.^{5,18,21,25,30,31,42,48} That said, machine learning techniques are likely a more efficient way to generate candidate case definitions, and may therefore play an important role in increasing both the number of conditions for which case definitions are available, and their performance, as many more candidate definitions could be tested and validated quickly. The database used is also likely to be an important factor in the performance of case definitions, as data quality influences the predictive accuracy of any one data element for a specific disease. Therefore, while advanced techniques such as machine learning and free text mining may lead to higher performing case definitions, improving the quality and completeness of data within a database is also an important consideration for moving this field forward.

Strengths

Research and surveillance using primary care EMR databases are increasing, as vast amounts of clinical data are becoming available for

secondary purposes. To our knowledge, this is the first systematic review of its kind that describes validated case definitions used in primary care EMR data. These results may improve our ability to more efficiently define cohorts with specific conditions without requiring a full validation exercise, which is resource and time intensive. In addition, this review summarizes the disease conditions for which validated case definitions have been developed and encourages further research to develop and validate case definitions for other disease conditions, for which such definitions do not exist or are lacking.

Limitations

Although this review was thorough in its methods, a lack of detailed reporting in many papers may have led to their exclusion. For instance, 141 papers did not explicitly describe their case finding algorithms, and 22 papers were missing requisite data. Also, 12 studies did not report validity measures (ie, specificity, PPV, etc.) or did not describe a reference standard. Among the studies included in our review, not all metrics of interest were reported. For instance, some studies reported only PPV, which limits our ability to comment on the sensitivity of the case definition, or its performance in a population with a different prevalence of disease. The generalizability of each case definition is also unknown, as they were conducted in a unique variety of populations, settings, healthcare systems, and EMR systems/databases.

Recommendations for reporting of case definition validation studies

Given the variability in reporting, adherence to reporting guidelines, such as those described in the Standards for Reporting of Diagnostic Studies (STARD) statement,⁵⁸ may strengthen this growing field of research. STARD lists the essential elements to be included in a report of a diagnostic accuracy study. STARD contains 30 elements, most of which apply to reporting validation studies of case definitions. However, as most diagnostic accuracy studies are undertaken in a clinical context, with the test under study being one that diagnoses disease in an individual, certain elements should be modified to reflect the unique aspects of case definition validation studies. The following are specific recommendations for reporting of case definition validation studies:

1. Identify the study as a case definition validation study, including the condition(s) in question.
2. Specify the intended use of the case definition (eg, patient identification for clinical purposes, surveillance, research).
3. Describe the database that the case definition was applied to and how the elements populating the database were collected (eg, for clinical care, health care administration, other).
4. Describe how the sample used for validation was selected.
5. Describe the clinical and demographic characteristics of the population whose information is included in the database.
6. Describe the process by which the case definition(s) was/were derived (eg, using statistical methods or machine learning, expert opinion, other).
7. Clearly describe the case definition(s) under study in sufficient detail to allow others to replicate their implementation.
8. Clearly describe the reference standard used to verify the performance of the case definition(s) and rationale for its use.
9. State whether the reference standard was applied independently of the case definition.
10. In studies in which the case definition(s) is/are derived from data using machine learning or other statistical methods, the testing dataset and validation dataset should be clearly described.
11. Clearly describe the methods for assessing performance and the specific metrics used (eg, sensitivity, specificity, PPV, negative predictive value [NPV], other), including how missing or indeterminate data were handled.
12. Presentation of results should include cross tabulation of the case definition(s) results by the reference standard results as well as the performance metrics and their 95% confidence intervals.

CONCLUSION

Data collected in primary care electronic medical records are becoming an important resource for conducting research and understanding disease patterns and prevalence. This review provides a summary of validated case definitions for a number of clinical conditions in primary care EMR data, most of which identify conditions with relatively good accuracy. The case definitions identified through this review may be used as a starting point for research and disease surveillance that require the identification of medical conditions in primary care EMR data. However, there are a number of conditions for which no case definition has been reported in the peer-reviewed literature. To improve the utility of future studies, authors publishing on case definitions with validity outcomes should adhere to detailed reporting standards.

LIST OF ABBREVIATIONS

COPD:	Chronic Obstructive Pulmonary Disease
CPCSSN:	Canadian Primary Care Sentinel Surveillance Network
CPRD:	Clinical Practice Research Datalink
EHR:	Electronic Health Record
EMR:	Electronic Medical Record
GPRD:	General Practice Research Database
ICD-9:	International Classification of Disease version 9
IPCI:	Integrated Primary Care Information
NPV:	Negative Predictive Value
PPV:	Positive Predictive Value
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-analyses
QUADAS:	Quality Assessment of Diagnostic Accuracy Studies
STARD:	Standards for Reporting of Diagnostic Accuracy Studies
THIN:	The Health Improvement Network

ACKNOWLEDGMENTS

Not applicable.

FUNDING

This was an investigator-initiated project. No sources of funding are related to the research reported.

AUTHORS' CONTRIBUTIONS

This review was conceived by PER, TSW, GEF, and KAM, and the protocol was designed with input by SS, NES, AR, BCL, SG, RB, and HQ. NES, AR, BCL, SG, and KAM designed the search strategy. RB and HQ contributed as knowledge users. SS, NES, AR, BCL, PER, and KAM drafted the manuscript, and all authors critically revised it and approved the final version. KAM will act as the guarantor for this review.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Journal of the American Medical Informatics Association* online.

Conflict of interest statement. The authors declare that they have no competing interests.

REFERENCES

- Murdoch TB, Detsky AS. The inevitable application of big data to health care. *JAMA* 2013; 309 (13): 1351–2.
- Deniz S, Şengül A, Aydemir Y, Çeldir Emre J, Özhan MH. Clinical factors and comorbidities affecting the cost of hospital-treated COPD. *Int J Chron Obstruct Pulmon Dis* 2016; 11 (1): 3023–30.
- Quan H, Smith M, Bartlett-Esquilant G, Johansen H, Tu K, Lix L. Mining administrative health databases to advance medical science: geographical considerations and untapped potential in Canada. *Can J Cardiol* 2012; 28 (2): 152–4.
- Biro SC, Barber DT, Kotecha JA. Trends in the use of electronic medical records. *Can Fam Physician* 2012; 58 (1): e21.
- Williamson T, Green ME, Birtwhistle R, et al. Validating the 8 CPCSSN case definitions for chronic disease surveillance in a primary care database of electronic health records. *Ann Fam Med* 2014; 12 (4): 367–72.
- Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; 44 (3): 827–36.
- Blak B, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care* 2011; 19 (4): 251–5.
- Garies S, Birtwhistle R, Drummond N, Queenan J, Williamson T. Data resource profile: national electronic medical record data from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). *Int J Epidemiol* 2017; 46 (4): 1091–2f.
- Tonelli M, Wiebe N, Fortin M. Methods for identifying 30 chronic conditions: application to administrative data. *BMC Med Inform Decis Mak* 2015; 15: 31.
- Souri S, Symonds NE, Rouhi A, et al. Identification of validated case definitions for chronic disease using electronic medical records: a systematic review protocol. *Syst Rev* 2017; 6 (1): 38.
- Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151 (4): 264–9, W64.
- Yergens D. Synthesis v2.4 and v3.0. 2015. <http://www.synthesis.info>. Accessed June 1, 2015.
- Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003; 3 (1): 25.
- Afzal Z, Engelkes M, Verhamme KM, et al. Automatic generation of case-detection algorithms to identify children with asthma from large electronic health record databases. *Pharmacoepidemiol Drug Saf* 2013; 22 (8): 826–33.
- Afzal Z, Schuemie MJ, van Blijderveen JC, Sen EF, Sturkenboom MC, Kors JA. Improving sensitivity of machine learning methods for automated case identification from free-text electronic medical records. *BMC Med Inform Decis Mak* 2013; 13 (1): 30.
- Cea Soriano L, Soriano-Gabarro M, Garcia Rodriguez LA. Validity and completeness of colorectal cancer diagnoses in a primary care database in the United Kingdom. *Pharmacoepidemiol Drug Saf* 2016; 25 (4): 385–91.
- Charlton RA, Weil JG, Cunningham MC, de Vries CS. Identifying major congenital malformations in the UK General Practice Research Database (GPRD): a study reporting on the sensitivity and added value of photocopied medical records and free text in the GPRD. *Drug Saf* 2010; 33 (9): 741–50.
- Coleman KJ, Lutsky MA, Yau V, et al. Validation of autism spectrum disorder diagnoses in large healthcare systems with electronic medical records. *J Autism Dev Disord* 2015; 45 (7): 1989–96.
- Coloma PM, Valkhoff VE, Mazzaglia G, et al. Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. *BMJ Open* 2013; 3 (6): e002862.
- Cowan K, Tandias A, Arndt B, Hanrahan L, Mundt M, Guilbert T. Defining asthma: validating automated electronic health record algorithm with expert panel diagnosis. *Am J Respir Clin Care Med* 2014; 189: A2297.
- de Burgos-Lunar C, Salinero-Fort MA, Cardenas-Valladolid J, et al. Validation of diabetes mellitus and hypertension diagnosis in computerized medical records in primary health care. *BMC Med Res Methodol* 2011; 11 (1): 146.
- Dregan A, Moller H, Murray-Thomas T, Gulliford MC. Validity of cancer diagnosis in a primary care database compared with linked cancer registrations in England. Population-based cohort study. *Cancer Epidemiol* 2012; 36 (5): 425–9.
- Dubreuil M, Peloquin C, Zhang Y, Choi HK, Inman RD, Neogi T. Validity of ankylosing spondylitis diagnoses in The Health Improvement Network. *Pharmacoepidemiol Drug Saf* 2016; 25 (4): 399–404.
- Faulconer E, DeLusignan S. An eight-step method for assessing diagnostic data quality in practice: chronic obstructive pulmonary disease as an exemplar. *Inform Prim Care* 2004; 12 (4): 243–54.
- Gil Montalbán E, Ortiz Marrón H, López-Gay Lucio-Villegas D, Zorrilla Torrás B, Arrieta Blanco F, Nogales Aguado P. [Validity and concordance of electronic health records in primary care (AP-Madrid) for surveillance of diabetes mellitus. PREDIMERC study]. *Gac Sanit* 2014; 28 (5): 393–6.
- Gray J, Majeed A, Kerry S, Rowlands G. Identifying patients with ischaemic heart disease in general practice: cross sectional study of paper and computerised medical records. *BMJ* 2000; 321 (7260): 548–50.
- Gu Y, Kennelly J, Warren J, Nathani P, Boyce T. Automatic detection of skin and subcutaneous tissue infections from primary care electronic medical records. *Stud Health Technol Inform* 2015; 214: 74–80.
- Hammad TA, Margulis AV, Ding Y, Strazzeri MM, Epperly H. Determining the predictive value of Read codes to identify congenital cardiac malformations in the UK Clinical Practice Research Datalink. *Pharmacoepidemiol Drug Saf* 2013; 22 (11): 1233–8.
- Hammersley V, Flint R, Pinnock H, Sheikh A. Developing and testing search strategies to identify patients with active seasonal allergic rhinitis in general practice. *Prim Care Respir J* 2010; 20 (1): 71–4.
- Hirsch AG, Scheck McAlearney A. Measuring diabetes care performance using electronic health record data: the impact of diabetes definitions on performance measure outcomes. *Am J Med Qual* 2014; 29 (4): 292–9.
- Kadhim-Saleh A, Green M, Williamson T, Hunter D, Birtwhistle R. Validation of the diagnostic algorithms for 5 chronic conditions in the Canadian Primary Care Sentinel Surveillance Network (CPCSSN): a Kingston Practice-based Research Network (PBRN) report. *J Am Board Fam Med* 2013; 26 (2): 159–67.
- Kang EM, Pinheiro SP, Hammad TA, Abou-Ali A. Evaluating the validity of clinical codes to identify cataract and glaucoma in the UK Clinical Practice Research Datalink. *Pharmacoepidemiol Drug Saf* 2015; 24 (1): 38–44.
- Krysko KM, Ivers NM, Young J, O'Connor P, Tu K. Identifying individuals with multiple sclerosis in an electronic medical record. *Mult Scler* 2015; 21 (2): 217–24.
- Levine PJ, Elman MR, Kullar R, et al. Use of electronic health record data to identify skin and soft tissue infections in primary care settings: a validation study. *BMC Infect Dis* 2013; 13 (1)

35. Lo Re V, 3rd, Haynes K, Forde KA, Localio AR, Schinnar R, Lewis JD. Validity of The Health Improvement Network (THIN) for epidemiologic studies of hepatitis C virus infection. *Pharmacoepidemiol Drug Saf* 2009; 18 (9): 807–14.
36. MacRae J, Darlow B, McBain L, *et al.* Accessing primary care Big Data: the development of a software algorithm to explore the rich content of consultation records. *BMJ Open* 2015; 5 (8): e008160.
37. Mamtani R, Haynes K, Boursi B, *et al.* Validation of a coding algorithm to identify bladder cancer and distinguish stage in an electronic medical records database. *Cancer Epidemiol Biomarkers Prev* 2015; 24 (1): 303–7.
38. Margulis AV, Garcia Rodriguez LA, Hernandez-Diaz S. Positive predictive value of computerized medical records for uncomplicated and complicated upper gastrointestinal ulcer. *Pharmacoepidemiol Drug Saf* 2009; 18 (10): 900–9.
39. Nielsen MM, Ursum J, Schellevis FG, Korevaar JC. The validity of the diagnosis of inflammatory arthritis in a large population-based primary care database. *BMC Fam Pract* 2013; 14 (1): 79.
40. Onofrei M, Hunt J, Siemenczuk J, Touchette D, Middleton B. A first step towards translating evidence into practice: heart failure in a community practice-based research network. *Inform Prim Care* 2004; 12 (3): 139–45.
41. Quint JK, Mullerova H, DiSantostefano RL, *et al.* Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). *BMJ Open* 2014; 4 (7): e005540.
42. Rahimi A, Liaw ST, Taggart J, Ray P, Yu H. Validating an ontology-based algorithm to identify patients with type 2 diabetes mellitus in electronic health records. *Int J Med Inform* 2014; 83 (10): 768–78.
43. Rakotz MK, Ewigman BG, Sarav M, *et al.* A technology-based quality innovation to identify undiagnosed hypertension among active primary care patients. *Ann Fam Med* 2014; 12 (4): 352–8.
44. Rothnie KJ, Müllerová H, Hurst JR, *et al.* Validation of the recording of acute exacerbations of copd in uk primary care electronic healthcare records. *PloS One* 2016; 11 (3): e0151357.
45. Scott FI, Mamtani R, Haynes K, Goldberg DS, Mahmoud NN, Lewis JD. Validation of a coding algorithm for intra-abdominal surgeries and adhesion-related complications in an electronic medical records database. *Pharmacoepidemiol Drug Saf* 2016; 25 (4): 405–12.
46. Thiru K, Donnan P, Weller P, Sullivan F. Identifying the optimal search strategy for coronary heart disease patients in primary care electronic patient record systems. *Inform Prim Care* 2009; 17 (4): 215–24.
47. Tian TY, Zlateva I, Anderson DR. Using electronic health records data to identify patients with chronic pain in a primary care setting. *J Am Med Inform Assoc* 2013; 20 (e2): e275–80.
48. Turchin A, Pendergrass ML, Kohane IS. DITTO- a tool for identification of patient cohorts from the text of physician notes in the electronic medical record. *AMIA Annu Symp Proc.* 2005; 2005: 744–8.
49. Valkhoff VE, Coloma PM, Masclee GMC, *et al.* Validation study in four health-care databases: upper gastrointestinal bleeding misclassification affects precision but not magnitude of drug-related upper gastrointestinal bleeding risk. *J Clin Epidemiol* 2014; 67 (8): 921–31.
50. Wang Z, Shah AD, Tate AR, Denaxas S, Shawe-Taylor J, Hemingway H. Extracting diagnoses and investigation results from unstructured text in electronic health records by semi-supervised machine learning. *PloS One* 2012; 7 (1): e30412.
51. Xi NW, R.; Agarwal G, Chan D, Gershon A, Gupta S. Identifying patients with asthma in primary care electronic medical record systems chart analysis-based electronic algorithm validation study. *Can Fam Physician* 2015; 6 (10): 474–83.
52. Zhou S-M, Fernandez-Gutierrez F, Kennedy J, *et al.* Defining disease phenotypes in primary care electronic health records by a machine learning approach: a case study in identifying rheumatoid arthritis. *PloS One* 2016; 11 (5): e0154515.
53. World Health Organization. *International Classification of Disease*. Geneva: World Health Organization; 1979.
54. O'Neil M, Payne C, Read J. Read Codes Version 3: a user led terminology. *Methods In Med* 1995; 34 (1–2): 187–92.
55. Hripcsak G, Bakken S, Stetson PD, Patel VL. Mining complex clinical data for patient safety research: a framework for event discovery. *J Biomed Inform* 2003;36 (1–2): 120–30.
56. Denny JC, Miller RA, Johnson KB, Spickard A. Development and evaluation of a clinical note section header terminology. *AMIA Annu Symp Proc* 2008; 2008: 156–60.
57. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012; 380 (9836): 37–43.
58. Cohen JF, Korevaar DA, Altman DG, *et al.* STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open* 2016; 6 (11): e012799.