

## 医療情報DB推進コンソーシアム

# 国内外のアウトカム定義とバリデーションの比較

- 調査結果の共有 -

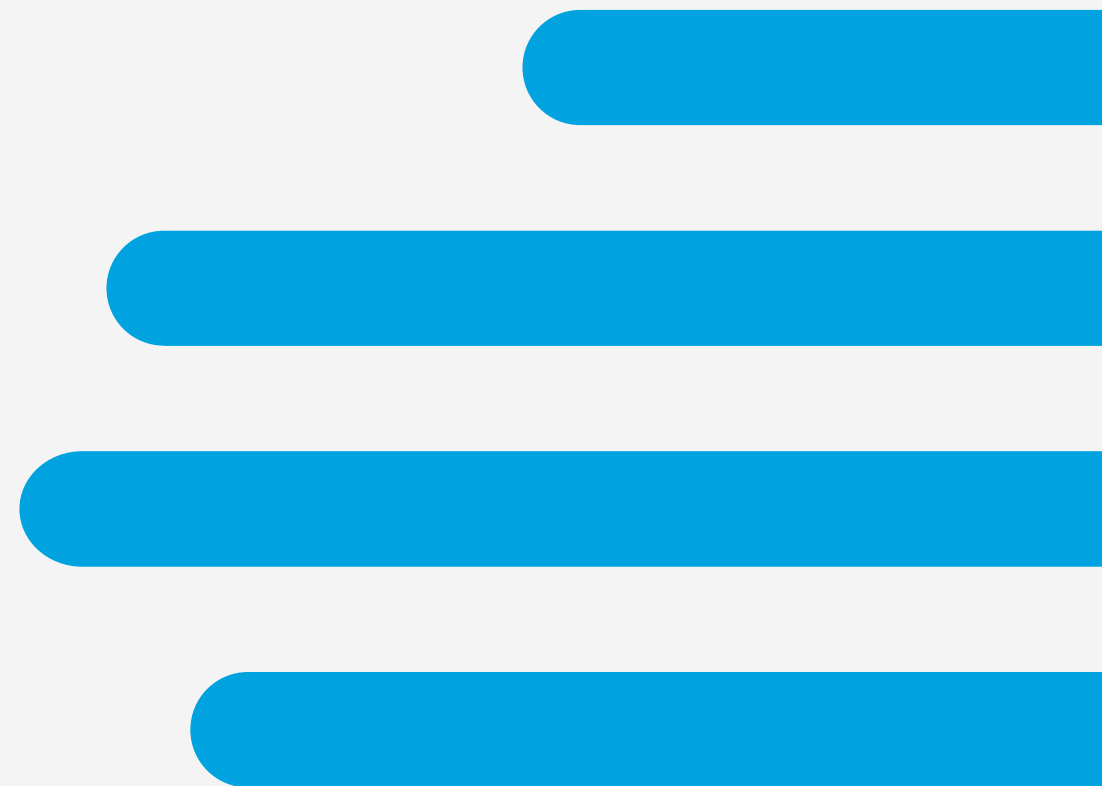
2022年12月5日

IQVIA ソリューションズ ジャパン 株式会社

# 略語一覧

CPRD	Clinical Practice Research Datalink
DNRP	Danish National Registry of Patients
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ICD	International Classification of Diseases
OXMIS	Oxford Medical Information System
PASS	Post-authorisation safety studies
PPV	Positive Predictive Value (陽性的中度)
RMP	Risk Management Plan (リスク管理計画)
SIDIAP	Information System for Research in Primary Care
THIN	The Health Improvement Network

# 調査の方法

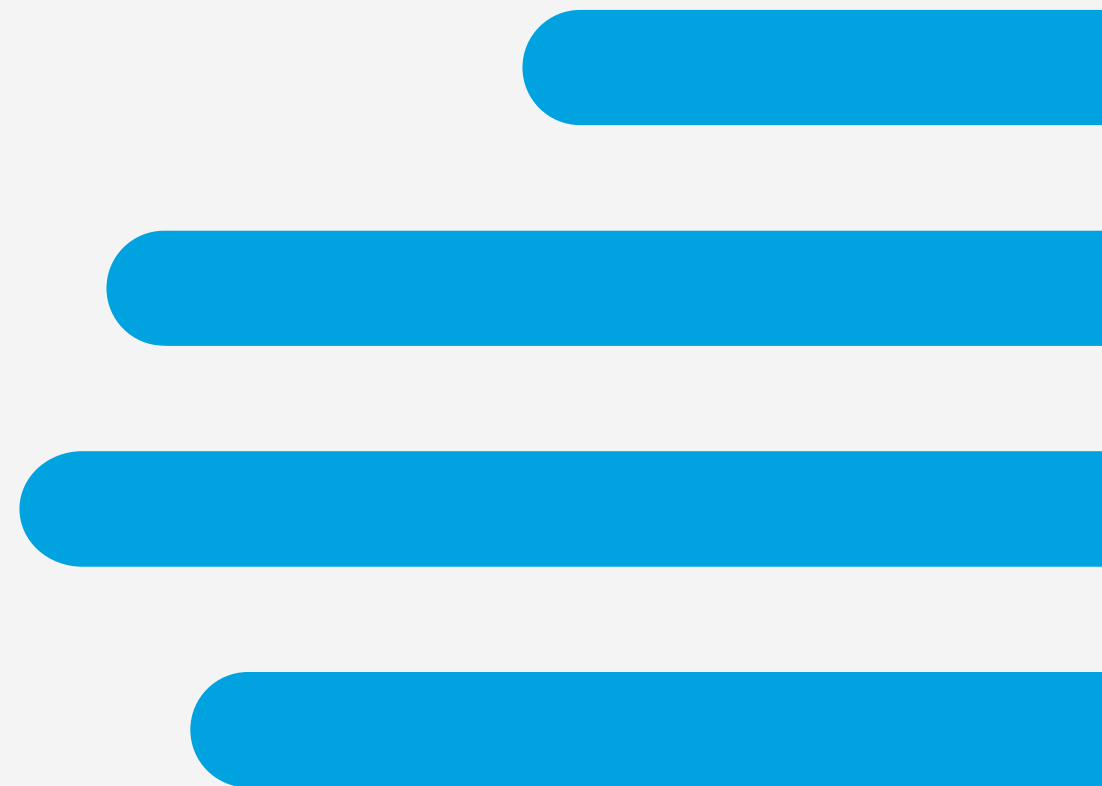


# 昨年度のコンソーシアム調査結果を深掘り（公表済事例の内容を調査）

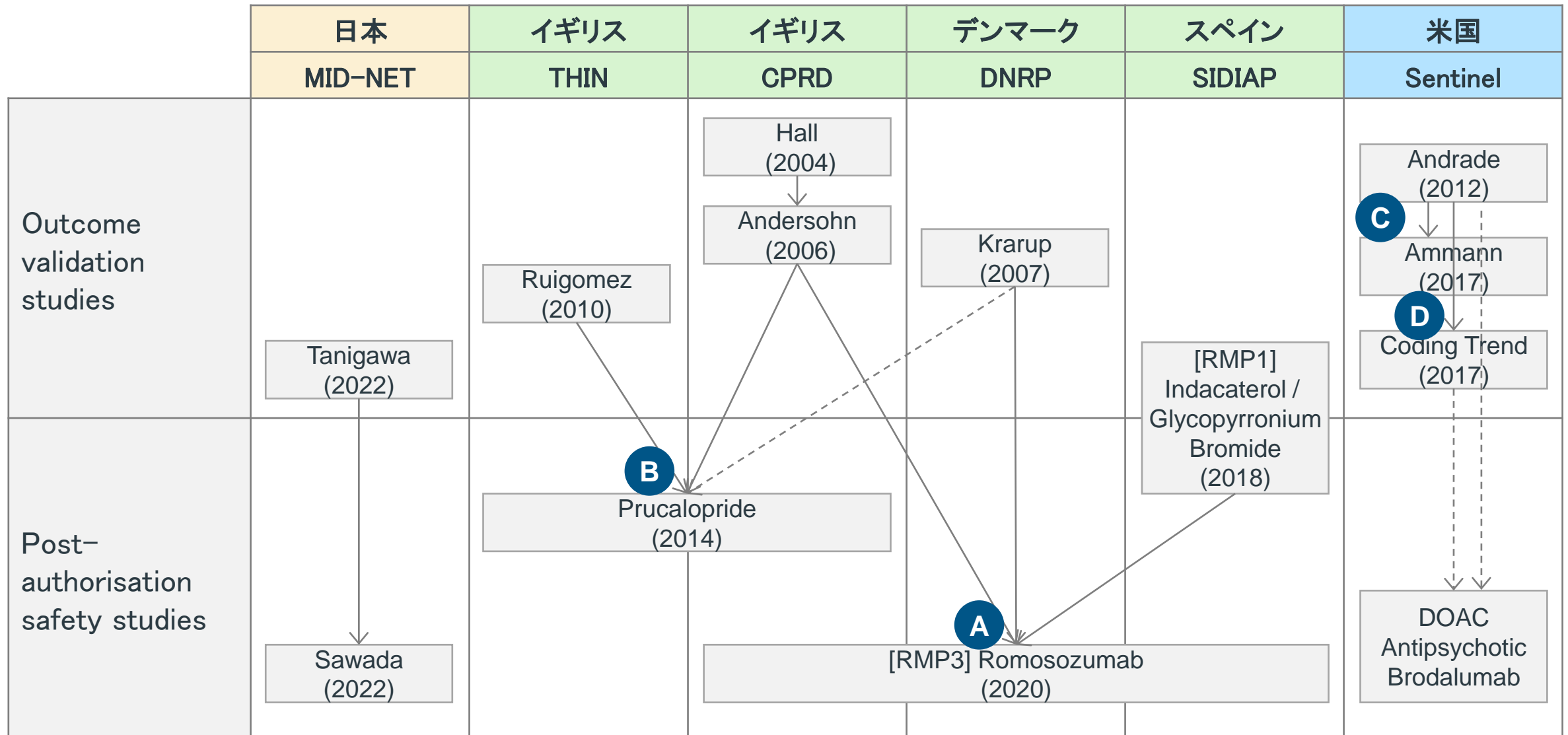
	日本 (PMDA)	欧州 (EMA)	米国 (FDA)
利用データ*1	<p>(n=42)</p>	<p>(n=56)</p>	<p>(n=25)</p>
対象薬剤*2	<p>(n=39)</p>	<p>(n=50)</p>	<p>(n=34)</p>
アウトカム*3	<p>(n=61)</p>	<p>(n=56)</p>	<p>(n=34)</p>

脳梗塞・感染症・悪性腫瘍が対象

# 調査の結果



# 脳梗塞（アウトカムバリデーション研究とPASSの関係性）



# 脳梗塞（欧州における先行研究の活用例）

## A RomosozumabのPASS Protocolへの記載

UCB Non-Interventional PASS Protocol Romosozumab 18 Jun 2020 OP0004

### APPENDIX 4. VALIDATION PROCESS FOR STUDY OUTCOMES

Validation studies will be conducted for each of the study outcomes. A sample of 250 eligible cases will be sampled from the study cohorts for previously unvalidated outcomes. All cases for Objective 3 (amongst eligible users of romosozumab or ALN in the study period) will be individually validated for outcomes where a PPV <75% has been previously demonstrated.

The following table summarizes previous validation studies and the results for each of the contributing data sources.

	MI	Stroke	All-cause death	CV death
SIDIAP (ES)	91.3%	75.7%	>90%	53.1%
CPRD (UK)	92.2% <sup>a</sup>	90% <sup>b</sup>	NA	NA
SNDS (FR)	85.0%	>85%	NA	NA
HSD (IT)	69.6%			40%
IPCI (NL)	75%	89.7%		38%
Nationwide linked Danish registries (DK)	>95%	>97%	NA	NA
GePaRD (DE)			>83% <sup>c</sup>	

CPRD=Clinical Practice Research Datalink; CV=cardiovascular; DE=Germany; DK=Denmark; ES=Spain; FR=France; GePaRD=German Pharmacoepidemiological Research Database; HSD=Health Search Database; IPCI=Integrated Primary Care Information Project; IT=Italy; MI=myocardial infarction; NL=Netherlands; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; SNDS=Systeme National Des Données de Santé  
Note: NA=Validation not necessary as information is obtained directly from mortality records.

<sup>a</sup> Herrett et al, 2013

<sup>b</sup> Andersohn et al, 2006

<sup>c</sup> Ohlmeier et al, 2016

<https://www.encepp.eu/encepp/openAttachment/fullProtocol/37345.jsessionid=HNM7lSuUpU2i9PWfiLaS1ETzPHPoAmSAPGgMb0SUs6ybQ1T0vhx0!-1345876343>

## B PrucaloprideのPASS Protocolへの記載

Table 3: Summary of Case Finding Algorithms for Each of the Endpoints of Interest

Hospitalizations for AMI	Hospitalizations for Stroke
Case finding: ICD-10 hospital discharge codes for all data sources	
(Joensen et al. (2009); Pajunen et al. (2005))	(Andrade et al. (2012); Flynn et al. (2010); Kirkman et al. (2009); Kokotailo and Hill (2005); Krarup et al. (2007); Roumie et al. (2008a))
<ul style="list-style-type: none"> <li>I21, Acute myocardial infarction</li> </ul>	<ul style="list-style-type: none"> <li>I60, Subarachnoid hemorrhage</li> <li>I61, Intracerebral hemorrhage</li> <li>I63, Cerebral infarction</li> <li>I64, Stroke, not specified as hemorrhage or infarction</li> </ul>
Hospitalizations for AMI	Hospitalizations for Stroke
Case finding for THIN, CPRD (without HES linkage): Read codes, electronic patient profiles, free-text search	
(Fireman et al. (2012); Garcia Rodríguez et al. (2004); Hammad et al. (2008b); McAlpine et al. (1998); Varas-Lorenzo et al. (2000))	(Andersohn et al. (2006); Arana et al. (2006); Gaist et al. (2013); Ray et al. (2009); Roumie et al. (2008a); Ruigómez et al. (2010))
AMI/chest pain Read code with hospitalization and documentation that any of the following occurred: <sup>a</sup> <ul style="list-style-type: none"> <li>Record of ECG or location of infarction</li> <li>Death within 1 month</li> <li>Coronary revascularization procedure (i.e., CABG or stent)</li> <li>Positive cardiac enzymes recorded</li> <li>Thrombolytic therapy</li> </ul>	Stroke Read code AND hospitalization and any of the following <sup>a</sup> : <ul style="list-style-type: none"> <li>Record of CT, NMR, EEG, or location of infarction</li> <li>Death within 1 month</li> <li>Stroke-related surgery/procedure</li> <li>Thrombolytic therapy</li> <li>Evidence of residual damage <ul style="list-style-type: none"> <li>Parésis, numbness</li> <li>Speech, vision, swallowing problems</li> <li>Rehabilitation or physiotherapy</li> </ul> </li> </ul>

SPD555-802: Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort (encepp.eu)

# 脳梗塞（米国におけるアウトカム定義の変遷）

## C 過去のバリデーション研究のSystematic review ⇒ Sentinelでのバリデーション研究の実施

### A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data

Susan E. Andrade, Leslie R. Harrold, Jennifer Tjia, Sarah L. Cutrona, Jane S. Saczynski, Katherine S. Dodd, Robert J. Goldberg, Jerry H. Gurwitz

#### Stroke (ischemic, hemorrhagic and unspecified)

##### Validation algorithms

In general, studies that evaluated the validity of three-digit, four-digit, or five-digit International Classification of Diseases, Ninth Revision, (ICD-9) codes in the range 430.x to 438.x reported the highest PPVs for codes 430.x, 431.x, 434.x, and 436.x. For most studies evaluating codes 430.x, 431.x, or 434.x separately, the reported PPVs were 80% or higher (Table 1). For most studies evaluating code 436.x, the PPVs were 70% or higher. Whereas most studies reported low PPVs for code 433.x, one study that evaluated hospital discharge codes 433.x1 separately from 433.x0 reported a much higher PPV for codes 433.x1 (71% compared with 13%).<sup>38</sup> The fifth digit specification of 0 indicates that the diagnosis of occlusion and stenosis of precerebral arteries occurred without mention of cerebral infarction.

Table 1. Positive predictive values of algorithms to identify cerebrovascular accident/stroke

Citation	Study population and period	Description of outcome studied	Algorithm	Validation/adjudication procedure and operational definition
Goldstein et al. <sup>21</sup>	Hospitalizations from the Durham Veterans Affairs Medical Center, 1995–1997	Hospitalizations (acute ischemic stroke)	Primary diagnosis of ICD-9-CM codes 433, 434, and 436	Medical record review was conducted (N = 175). Outcome was confirmed based upon evidence in discharge summary.  Overall PPV = 61%

A Systematic Review of Validated Methods for Identifying Cerebrovascular Accident or Transient Ischemic Attack using Administrative Data | Sentinel Initiative

### Chart validation of inpatient ICD-9-CM administrative diagnosis codes for ischemic stroke among IGIV users in the Sentinel Distributed Database

Ammann, Eric M. PhD<sup>a</sup>; Leira, Enrique C. MD MS<sup>a,b</sup>; Winiiecki, Scott K. MD<sup>c</sup>; Nagaraja, Nandakumar MD<sup>b</sup>; Dandapat, Sudeepta MD<sup>b</sup>; Carnahan, Ryan M. PharmD, MS<sup>a</sup>; Schweizer, Marin L. PhD<sup>b,d</sup>; Torner, James C. PhD<sup>a</sup>; Fuller, Candace C. PhD<sup>e</sup>; Leonard, Charles E. PharmD, MSCE<sup>f</sup>; Garcia, Crystal MPH<sup>e</sup>; Pimentel, Madelyn MSN<sup>e</sup>; Chrischilles, Elizabeth A. PhD<sup>a</sup>

#### 1 Introduction

In this study, we evaluated the positive predictive value (PPV) of inpatient diagnosis codes for acute ischemic stroke (AIS) in the Sentinel Distributed Database (SDD). The SDD is a large database of longitudinal, patient-level medical and prescription data from a variety of data sources (primarily, billing data from large health insurers and administrative data from integrated healthcare delivery systems) that are converted to a common data format. The SDD and the Sentinel program are sponsored by the U.S. Food and Drug Administration (FDA) for active safety surveillance of marketed medical products. For 2000 to 2016, the SDD has 425 million person-years of longitudinal patient-level data from 223 million health plan members.<sup>[1]</sup> Because AIS is a frequent endpoint for studies conducted in the SDD and other administrative databases, it is important that validation studies be conducted on an ongoing basis to establish the PPV of AIS administrative diagnoses.

Prior validation studies conducted outside the SDD indicate that hospital discharge diagnosis codes for AIS generally have high PPVs (80% or higher), with principal-position diagnoses performing somewhat better than secondary diagnoses.<sup>[2]</sup> However, to date, no validation studies of AIS diagnosis codes have been performed within the SDD. In addition, medical coding guidelines for AIS were modified in the mid-2000s,<sup>[3]</sup> potentially affecting the validity of AIS-related administrative diagnosis codes. To inform the design and interpretation of future studies of AIS based on records from the SDD and other administrative databases, we report on the PPVs associated with inpatient diagnosis codes for AIS recorded during the years 2006 to 2012. Possible cases included in this chart validation study were identified from the SDD as part of a safety assessment of thromboembolic event (TEE) risk following intravenous immune globulin (IGIV).

Chart validation of inpatient ICD-9-CM administrative diagnosis codes for ischemic stroke among IGIV users in the Sentinel Distributed Database (www.com)



# 脳梗塞（米国におけるアウトカム定義の変遷）

## D ICD-9からICD-10への移行と変換



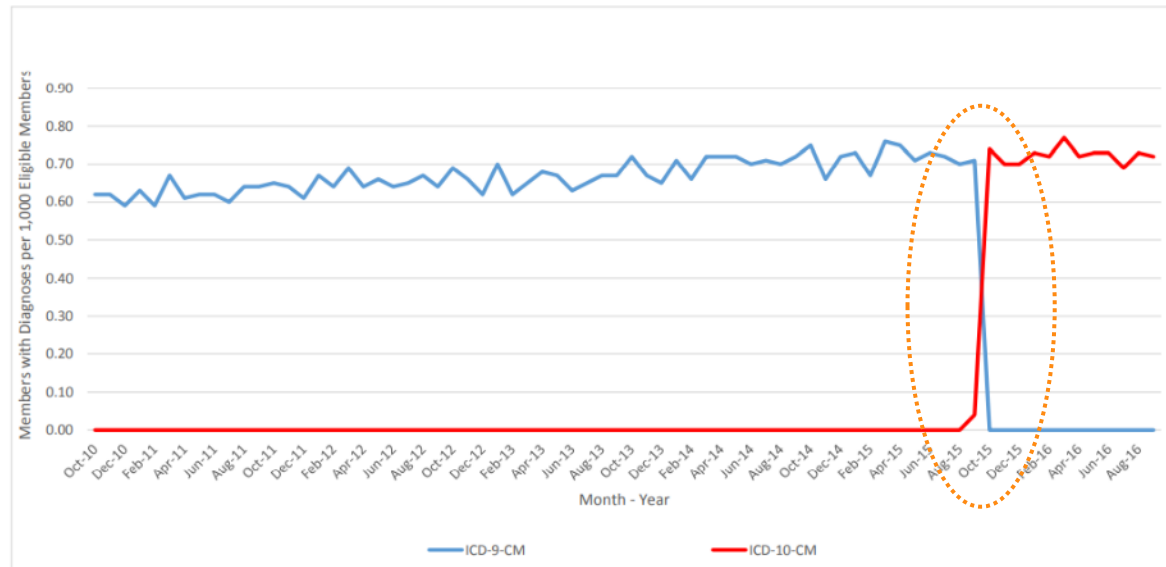
Appendix B. List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes Used to Define Ischemic Stroke

**Overview**

**Date Run:** October 25, 2017

**Request Description:** The purpose of this report was to compare the frequency of diagnoses for ischemic stroke using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) versus International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes. ICD-10-CM code definitions were determined by mapping from ICD-9-CM code definitions using the Centers for Medicare and Medicaid Services (CMS) General Equivalence Mappings (GEMs). Forward-backward mapping (FBM) was used to map ICD-9-CM to ICD-10-CM codes.<sup>1</sup>

Figure 1. Incidence of Ischemic Stroke Diagnoses per 1,000 Eligible Members from October 2010 - September 2016 by Code Type, 183-Day Washout



[Ischemic Stroke Final Trend Report.pdf \(sentinelinitiative.org\)](https://www.sentinelinitiative.org/Ischemic-Stroke-Final-Trend-Report.pdf)

Code	Description	Code Type
<b>ICD-9-CM</b>		
433.01	Occlusion and stenosis of basilar artery with cerebral infarction	ICD-9-CM
433.11	Occlusion and stenosis of carotid artery with cerebral infarction	ICD-9-CM
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction	ICD-9-CM
433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction	ICD-9-CM
433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction	ICD-9-CM
433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction	ICD-9-CM
434.01	Cerebral thrombosis with cerebral infarction	ICD-9-CM
434.11	Cerebral embolism with cerebral infarction	ICD-9-CM
434.91	Unspecified cerebral artery occlusion with cerebral infarction	ICD-9-CM
436	Acute, but ill-defined, cerebrovascular disease	ICD-9-CM
<b>ICD-10-CM</b>		
163.22	Cerebral infarction due to unspecified occlusion or stenosis of basilar arteries	ICD-10-CM
163.139	Cerebral infarction due to embolism of unspecified carotid artery	ICD-10-CM
163.239	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid arteries	ICD-10-CM
163.019	Cerebral infarction due to thrombosis of unspecified vertebral artery	ICD-10-CM
163.119	Cerebral infarction due to embolism of unspecified vertebral artery	ICD-10-CM
163.219	Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral arteries	ICD-10-CM
163.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery	ICD-10-CM
163.20	Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries	ICD-10-CM
163.30	Cerebral infarction due to thrombosis of unspecified cerebral artery	ICD-10-CM
163.40	Cerebral infarction due to embolism of unspecified cerebral artery	ICD-10-CM
163.50	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery	ICD-10-CM
167.89	Other cerebrovascular disease	ICD-10-CM
163.00	Cerebral infarction due to thrombosis of unspecified precerebral artery	ICD-10-CM
163.011	Cerebral infarction due to thrombosis of right vertebral artery	ICD-10-CM

# 脳梗塞（アウトカムバリデーション研究の比較）

		日本	イギリス	イギリス	デンマーク	スペイン	米国	
		MID-NET	THIN	CPRD	DNRP	SIDIAP	Sentinel	
情報元 (DOI)		Tanigawa (10.1002/pds.5423)	Ruigomez (10.1002/pds.1919)	Hall (10.1212/01.wnl.000011 0312.36809.7f)	Krarpup (10.1159/000102143)	Indacaterol/ Glycopyrronium Bromide	Ammann (10.1097/MD.000000000 0009440)	Coding Trend Fung
種類		acute ischemic stroke	ischemic stroke /TIA	stroke	ischemic stroke	stroke	acute ischemic stroke	ischemic stroke
定義	概要	傷病名＋入院 ＋検査＋薬剤 (Algorithms 8)	傷病名＋入院 ＋フリーテキスト (Read Code)	傷病名 (Read/OXMIS Code)	傷病名＋入院 (ICD10)	傷病名 (ICD10)	傷病名＋入院 (ICD9)	傷病名 (ICD9/ICD10)
	詳細	I63.X/G08 CT/MRI/MRA 抗血栓薬	G63-G67 /F423600	NA	I63.X	I60-I69 /G46/Z86	433.x1/434.xx/436	433.x1/434.xx/436 ↓ I63.X
方法	対象	一般集団	一般集団	片頭痛患者	一般集団	COPD患者	IGIV投与者	-
	手順	カルテレビュー (3施設)  ①Possible Caseから サンプリング (366例) ②2人の医師による 真偽判定 ③11種類の定義別 でPPV算出 (1施設で感度算出)	医師への調査票  ①アウトカム定義群 からサンプリング (245例) ②医師に調査票を 送付して真偽判定 (161例の回答) ③PPV算出	データリンク (Written recordsと)  ①アウトカム定義群 からサンプリング (339例) ②Written recordsの 取得(215例) ③Computerized recordsとの比較で 真偽判定 ④PPV算出(78/88)	データリンク (コホート研究と)  ①アウトカム定義群 をCopenhagen City Heart Study とクロスリンクし、 詳細な情報を入手 (236例) ②2人の評価者による 真偽判定 ③PPV算出(32/33)	データリンク (入院情報と)  ①アウトカム定義群 を抽出(144例) ②リンクした入院情報 で真偽判定 ③リンク無しの症例 は医療記録を マニュアルレビュー ④PPV算出	カルテレビュー (13のSDD Partner)  ①アウトカム定義群 からサンプリング (128例) ②数名の医師による 真偽判定 ③病名ポジション別 (principal/secondary) にPPV算出	2015年10月の ICD9からICD10 への移行を機に、 そのマッピング方法 および移行状況を 解析 (脳卒中の発生率 推移を解析した所、 移行前後での差異 はなかった)
結果	PPV	84.3% (Algorithms 8)	85.7%	89%	>97%	75.7%	60% (Principal position)	-
	感度	88.9% (Algorithms 8)	-	-	-	-	-	-

# 感染症（アウトカムバリデーション研究の比較）

		日本	デンマーク	米国
		MDV	DNRP	Sentinel
情報元 (DOI)		Nishikawa (2021) (10.37737/ace.22004)	Holland (2014) (10.1016/j.annepidem.2014.05.011)	Lo Re (2021) (10.1002/pds.5253)
種類		serious infection	serious infection	serious infection
定義	概要	傷病名＋入院＋検査 (Algorithms 1)	傷病名＋入院 (ICD10)	「傷病名＋入院」＋ 「入院前の傷病名or抗菌薬」(ICD10)
	詳細	A/B/D/E/G/H/I/J/K/L/M/N/O/R/T 免疫学的検査 (Category D)	A/B/H/I/J/K/L/M/N	A/B/D/G/H/I/J/K/L/M/N/P/R
方法	対象	一般集団	固形癌患者	生物学的製剤投与者
	手順	カルテレビュー（2施設） ①Possible Caseからサンプリング（200例） ②2人の医師による真偽判定 ③15種類の定義別でPPVと感度を算出 (pseudosenstivity)	カルテレビュー（Aalborg大学病院） データリンク（カルテと） ①アウトカム定義群からサンプリング (272例) ②リンクしたカルテ情報を基にした 医師による真偽判定 ③PPVを算出	カルテレビュー（6のSDD Partner） ①アウトカム定義群からサンプリング (223例) ②2人の医師による真偽判定 ③PPVを算出
結果	PPV	85.6% (Algorithms 1)	80%	93.7% (Unweighted) 80.2% (Weighted)
	感度	100% (Algorithms 1)	-	-

# 悪性腫瘍（アウトカムバリデーション研究の比較）

		日本	英国
		MDV	CPRD
情報元 (DOI)		Nishikawa (2021) (10.37737/ace.22004)	Dregan (2012) (10.1016/j.canep.2012.05.013)
種類		malignant tumors	malignant tumors
定義	概要	傷病名 + 検査 (Algorithms 4)	傷病名 (Read/OXMIS Code)
	詳細	B/C/D/R/T 画像診断 (category E)	C/D
方法	対象	一般集団	一般集団
	手順	カルテレレビュー (2施設) ① Possible Case からサンプリング (180例) ② 2人の医師による真偽判定 ③ 18種類の定義別でPPVと感度を算出 (pseudosenstivity)	データリンク (Cancer Registerと) ① Possible Case を抽出 (42,556例) ② リンクしたCancer Register (5,650例) を基にした 2人の評価者による真偽判定 ③ PPVと感度と特異度を算出
結果	PPV	64.1% (Algorithms 4)	98% (Colorectal) 96% (Lung) 97% (Gastro) 92% (Urological)
	感度	90.7% (Algorithms 4)	92% (Colorectal) 94% (Lung) 92% (Gastro) 85% (Urological)