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The Appropriate Use of Neuroimaging in the Diagnostic Work-Up of Dementia: An Evidence-Based Analysis

Health Quality Ontario

February 2014

Ontario Health Technology Assessment Series; Vol. 14: No. 1, pp. 1–64, February 2014

Suggested Citation

This report should be cited as follows:

Health Quality Ontario. The appropriate use of neuroimaging in the diagnostic work-up of dementia: an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2014 February;14(1):1–64. Available from: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontario-health-technology-assessment-series/imaging-for-dementia.

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Abstract

Background

Diagnosis of dementia is challenging and requires both ruling out potentially treatable underlying causes and ruling in a diagnosis of dementia subtype to manage patients and suitably plan for the future.

Objectives

This analysis sought to determine the appropriate use of neuroimaging during the diagnostic work-up of dementia, including indications for neuroimaging and comparative accuracy of alternative technologies.

Data Sources

A literature search was performed using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published between 2000 and 2013.

Review Methods

Data on diagnostic accuracy and impact on clinical decision making were abstracted from included studies. Quality of evidence was assessed using GRADE.

Results

The search yielded 5,374 citations and 15 studies were included. Approximately 10% of dementia cases are potentially treatable, though less than 1% reverse partially or fully. Neither prediction rules nor clinical indications reliably select the subset of patients who will likely benefit from neuroimaging. Clinical utility is highest in ambiguous cases or where dementia may be mixed, and lowest for clinically diagnosed Alzheimer disease or clinically excluded vascular dementia. There is a lack of evidence that MRI is superior to CT in detecting a vascular component to dementia. Accuracy of structural imaging is moderate to high for discriminating different types of dementia.

Limitations

There was significant heterogeneity in estimates of diagnostic accuracy, which often prohibited a statistical summary of findings. The quality of data reported by studies prohibited calculation of likelihood ratios in the present analysis. No studies from primary care were found; thus, generalizability beyond tertiary care settings may be limited.

Conclusions

A diagnosis of reversible dementia is rare. Imaging has the most clinical utility in cases where there is potentially mixed dementia or ambiguity as to the type of dementia despite prolonged follow-up (e.g., 2 years or more). Both CT and MRI are useful for detecting a vascular component of dementia.

Plain Language Summary

Dementia is a devastating condition of memory loss and behaviour change that affects many Canadians, especially older adults. Diagnosis is complex because symptoms can be caused by different brain diseases, such as Alzheimer disease, and in some cases by other causes such a tumour or cerebrovascular disease. Although dementia rarely improves much, an accurate diagnosis is important because it determines the treatment a patient should receive and helps patients and families understand what the future holds.

Brain imaging, using computed tomography (CT) or magnetic resonance imaging (MRI) scans, may help in the diagnosis by allowing doctors to see changes in brain structure or function that explain the dementia. Unfortunately, it is not well understood which patients will most likely benefit from a brain scan and which type of scan works best to diagnose dementia. This study reviewed the published evidence about these questions.

The study found that relying on specific symptoms to decide who should have a brain scan, rather than imaging all dementia patients, is unreliable and can miss some potentially treatable conditions. The study also found that scans have most value when doctors are uncertain as to the type of dementia despite monitoring the patient for a while (e.g., 2 years) or when the patient may have a combination of dementia types. Brain scans are often less helpful in the diagnosis of Alzheimer disease, and doctors can often use clinical assessment to rule out vascular dementia (another common type of dementia, related to cerebrovascular disease). The evidence also shows that MRI is not better than CT in detecting vascular dementia as a contributing cause. For Alzheimer disease, Creutzfeldt-Jakob disease, and clinically ambiguous dementias, both CT and MRI are highly accurate in correctly ruling out these diagnoses, but both types of scans have only low to moderate ability to correctly identify patients with any of these conditions. Importantly, the quality of the evidence available for this study was limited by considerable differences in research and analysis methods.

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List of Abbreviations

AAN	American Academy of Neurology
AChEI	Acetylcholinesterase inhibitors
AD	Alzheimer disease
AGREE	Appraisal of Guidelines for Research and Evaluation
CCC	Canadian Consensus Conference on the Assessment of Dementia / Canadian Consensus Conference on the Diagnosis and Treatment of Dementia
CI	Confidence interval
CJD	Creutzfeldt-Jakob disease
CT	Computed tomography
DOR	Diagnostic odds ratio
DSM	Diagnostic and Statistical Manual of Mental Disorders
FDG	Fluorodeoxyglucose 18F
FLAIR	Fluid-attenuated inversion recovery
FTD	Frontotemporal dementia
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HQO	Health Quality Ontario
LBD	Lewy body dementia
LR	Likelihood ratio
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
MTA	Medial temporal lobe atrophy
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NP	Neuropsychological
NPH	Normal-pressure hydrocephalus
OHTAC	Ontario Health Technology Advisory Committee
PET	Positron emission tomography
PRC	Potentially reversible cause
RCT	Randomized controlled trial
RDOR	Ratio of diagnostic odds ratios
SH	Subdural hematoma
SOL	Space-occupying lesion
VaD	Vascular dementia
WMH	White matter hyperintensities

Background

Overuse, underuse, and misuse of interventions are important concerns in health care and lead to individuals receiving unnecessary or inappropriate care. In April 2012, under the guidance of the Ontario Health Technology Advisory Committee's Appropriateness Working Group, Health Quality Ontario (HQO) launched its Appropriateness Initiative. The objective of this initiative is to develop a systematic framework for the ongoing identification, prioritization, and assessment of health interventions in Ontario for which there is possible misuse, overuse, or underuse.

For more information on HQO's Appropriateness Initiative, visit our website at www.hqontario.ca.

Objective of Analysis

The objective of this evidence-based analysis was to determine the appropriate use of neuroimaging in the diagnostic work-up of dementia. Structural imaging with computed tomography (CT) and magnetic resonance imaging (MRI), and functional imaging with positron emission tomography (PET) were considered.

Clinical Need and Target Population

Dementia

Dementia is a general term for the condition of memory loss, cognitive impairment, and/or personality and behavioural changes. Nearly 750,000 Canadians were affected by cognitive impairment and dementia in 2011, and the number of prevalent cases is projected to nearly double to 1.4 million by 2031. (1) The various types of dementia result from different underlying brain pathologies (Table 1) and present with variable and typical symptoms that are described below.

Alzheimer Disease

The most common cause of dementia is Alzheimer disease (AD), which accounts for nearly two-thirds of dementia cases in Canada. (2) AD has a gradual onset, primarily affects cognition and memory, and is progressive and neurodegenerative. (3) The incidence of AD doubles every 5 years after age 60, with prevalence hovering around 1 in 8 over the age of 65 and affecting more than half of individuals aged 85 and older. (3) AD brain pathology is characterized by abnormal aggregations of proteins, and these appear pathologically as amyloid plaques and neurofibrillary tangles. (3) While there is a correlation between the hallmark pathological features and symptoms of AD, plaques and tangles have been found at autopsy in approximately 30% of cognitively normal elderly subjects. (4)

Vascular Dementia

Vascular dementia (VaD) refers to cognitive and functional impairment due to strokes caused by cerebrovascular disease. (5) VaD accounts for an estimated 1 in 5 cases. (6) VaD is unique in that its course is not always progressive; there is potential for stabilization of disease course and partial recovery. (5) Three syndromes of VaD are widely accepted: multi-infarct dementia, single-infarct dementia, and small vessel disease. (5) The severity of vascular changes must be detected and assessed relative to the presence of other changes (e.g., neurodegeneration, symptoms) because vascular changes also occur in normal aging. (7) It has been estimated that vascular changes are present upon autopsy in 29% to 41% of community cases of dementia. (7) The concurrent presence of both AD and VaD pathology (e.g., cerebral

infarcts) is referred to as mixed dementia and has been estimated to account for nearly 40% of dementia cases among community-dwelling patients. (8)

Lewy Body Dementia

Lewy body dementia (LBD) is another type of neurodegenerative dementia, and accounts for 5% to 15% of cases. (9) The 3 classic features of LBD are parkinsonism, visual hallucinations, and fluctuating cognition and level of alertness; the presence of dementia and 2 of these features is required for a diagnosis of probable LBD (Table 1). (10) Age of onset ranges from 50 to 83 years, and people can live for up to 20 years after diagnosis. (11)

Frontotemporal Dementia

A common type of dementia, especially among patients younger than age 65, is frontotemporal dementia (FTD). As the name suggests, the frontal and temporal lobes of the cortex are most affected by atrophy and neuronal loss, leading to changes in personality, behaviour, and/or language. (12) The 3 recognized variants of FTD are distinguished by the predominance of any one of the aforementioned features. Behavioural variant FTD is characterised by personality changes and inappropriate social and interpersonal conduct. (12) Semantic dementia patients express speech that is smooth or fluent but devoid of information or specific labels or meanings. (12) In contrast, patients with progressive nonfluent aphasia, the third FTD variant, exhibit hesitant, agrammatical and effortful speech, including problems with finding words and naming objects. (12) Median survival is estimated to be 11 to 12 years. (12)

Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease (CJD) is a rare transmissible prion disease and can present as combinations of cognitive disturbances, visual symptoms, myoclonus and ataxia, psychiatric symptoms, and sleep disturbances. (13) CJD has a number of variants; however all CJD types are usually rapidly fatal, with survival in the order of 4 to 19 months after onset. (13) In Canada, suspected cases of CJD are required to be reported to the CJD Surveillance System operated by the Public Health Agency of Canada to monitor the epidemiology of the disease, promote rapid diagnosis, and reduce risk of the disease among Canadians. (14) In line with the international incidence of 1 to 2 cases per million population, 99 cases of suspected CJD were referred for investigation in Canada in 2012, and 27 deaths occurred among definite and probable cases that year. (15)

Mild Cognitive Impairment

A related but discrete state of cognitive decline, mild cognitive impairment (MCI), has been recognized in the last 2 decades. This preclinical stage of dementia, especially AD, has been the focus of much research aiming to predict progression to dementia. (16) While a clinical diagnosis of MCI is not a necessary precursor to dementia, it is a major risk factor for subsequent progression, with an estimated 12% of MCI patients converting to AD per year. (17) MCI is primarily clinically distinguished by patients' retention of functional independence. (3) As MCI is not considered a type of dementia, it was not included in this analysis.

Table 1: Clinical, Radiological, and Pathological Features of Dementia Types

Dementia Type	Main Clinical Features	Brain Radiological Features via CT, MRI	Pathological Features
Alzheimer disease (3;18)	Insidious, gradual progression Impairment in memory and cognition Loss of functional independence in activities of daily living	Global atrophy, especially medial temporal lobe (hippocampus and parahippocampal gyrus)	Amyloid plaques and neurofibrillary tangles, synapse loss, neurodegeneration
Vascular dementia (5)	Previous strokes or TIAs Sudden or gradual onset Slow or stepwise progression Mild memory impairment Early onset, severe executive function	Infarcts (lacunar, non-lacunar), white matter lesions (basal ganglia, periventricular)	Focal or multifocal atrophy of cortical or subcortical regions Moderate to severe dilation of ventricles Bilateral, large vessel infarcts in thalamus, basal ganglia, capsular genu, angular gyrus Thrombotic plaques and arteriosclerosis in extra- and intracranial vessels
Lewy body dementia (11)	Fluctuating alertness and cognitive impairment (episodic confusion, attentional deficits, visuospatial dysfunction) Visual hallucinations, perceptual difficulties, misidentifications Parkinsonism	Neocortex, limbic cortex, subcortical nuclei, brainstem	Aggregations of α-synuclein and other proteins (e.g., ubiquitin, neurofilament protein, α B crystallin) in neurons (i.e., Lewy bodies, Lewy neurites)
Frontotemporal dementia (12;18)	Insidious, gradual onset Behavioural, emotional, and personality changes Aphasia	Atrophy and neuronal loss of frontal and temporal lobes	Abnormal deposits and neuritic tangles of tau protein
Creutzfeldt-Jakob disease (13)	Cognitive decline Ataxia Psychiatric symptoms Visual signs Aphasia	Asymmetric hyperintensity in 3 or more cortical noncontiguous gyri and striatum (i.e., caudate and rostral putamen) in specific MRI sequences	Aggregation of pathologic prion protein, neuronal loss

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; TIA, transient ischemic attack.

Diagnosis of Dementia

Dementia is provisionally diagnosed clinically and can be confirmed by post-mortem examination; thus, neuroimaging can only play a supporting role to the clinician in determining etiology of clinical symptoms. (19) Standard diagnostic criteria are used to establish the presence of dementia and differentiate subtypes. (7) Some common diagnostic criteria for the various dementias are listed in Table 2. O'Brien and Barber (20) provide a more in-depth overview of clinical criteria.

Table 2: Selected Commonly Used Diagnostic Criteria for Dementias

Dementia Type	Examples of Clinical Diagnostic Criteria
Dementia	DSM-III-R
Alzheimer disease	NINCDS-ADRDA (Possible AD, Probable AD) DSM-III-R (Dementia of the Alzheimer Type)
Vascular dementia	California Criteria NINDS-AIREN MHIS
Lewy body dementia	Consortium for DLB Diagnostic Criteria
Frontotemporal dementia	Lund-Manchester Criteria Consensus diagnostic criteria
Creutzfeldt-Jakob disease	Clinical criteria

Abbreviations: California Criteria, State of California AD Diagnostic and Treatment Centers Criteria; DLB, dementia with Lewy bodies; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised; MHIS, Hachinski Ischemic Score modified by Rosen; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association of Internationale pour la Recherche et l'Enseignement en Neurosciences.
Source: Pitner et al, 2004. (7)

A challenge with the diagnosis of dementia is that impairment in cognition may be produced by a number of underlying pathologies. (21) Neuroimaging has historically played an important role in the exclusion of treatable causes of dementia, such as intracranial masses, subdural hematomas, or normal-pressure hydrocephalus. (21) Neurosyphilis was a commonly encountered reversible cause until the 1940s when the condition began to be successfully treated. (22) Neuroimaging can enable the identification of unsuspected cerebrovascular disease or patterns of cerebral atrophy that can aid in determining the patient's dementia subtype. (20)

Differentiating subtypes of dementia has important implications for patient management. AD patients are often prescribed acetylcholinesterase inhibitors (AChEI), which are ineffective for patients who have normal cholinergic function, such as those with FTD. (12) Treatment plans for patients with VaD may include symptom management similar to AD, as well as secondary prevention of subsequent strokes (e.g., managing hypertension and hyperlipidemia). (5) LBD patients may require management of cognitive impairment, motor symptoms, psychosis and behavioural disturbances, but exhibit sensitivity to the adverse effects of antipsychotic medication, which must be prescribed cautiously. (11) These patients also respond well to AChEIs. In patients with FTD, selective serotonin reuptake inhibitors may be used, or in severe or aggressive cases, antipsychotic medication may be indicated for management of behavioural symptoms. (12) Despite symptom-focused interventions, there are presently no treatments that reverse or modify dementia. (3) A specific diagnosis is important, however, because it can provide information about prognosis for patients and families to help them prepare for disease progression. (21) For untreatable conditions such as dementia, the ability to plan for the future can provide benefits analogous to effective treatment, and the confirmation or ruling-out of a specific diagnosis can improve patients' well-being. (23)

Ontario Context

A study by You and colleagues (24) published in 2008 examined the indications and results of CT and MRI imaging using linked Ontario data from fiscal year 2004/2005. Two hundred consecutive outpatient scans were sampled at 20 randomly selected hospitals in Ontario, each performing CT and MRI for 3 anatomical regions, for a total of 11,824 eligible CT scans and 11,867 MRI eligible scans. Dementia was the fourth most prevalent indication for brain CT, accounting for 9.4% of all brain CTs, and was the 10th

most prevalent indication for brain MRI, accounting for 4.0% of all brain MRIs. (24) These data suggest that imaging for dementia comprises a relatively small proportion of scans in Ontario.

Technologies

Computed Tomography

Computed tomography (CT) is a structural medical imaging method that employs computer-based tomographic reconstruction to delineate bodily structures based on their ability to block an x-ray beam. (19) CT images can identify structural abnormalities, such as space-occupying lesions or intracranial neoplasms, although in less fine detail than newer structural imaging technologies. (19) A standard CT scan of the brain as a supporting component to the clinical diagnosis of dementia would typically include a noncontrast image. (*Personal communication, Expert Advisory Panel for Appropriate Utilization of Medical Imaging for the Diagnostic Work-Up in Patients with Dementia, July 19, 2013*) The radiation exposure during a head CT is typically in the order of 2 to 4 millisieverts (mSv). (25) CT examinations are preferable for patients who are claustrophobic or unable to remain still for longer durations, as is required for MRI imaging. (19)

Magnetic Resonance Imaging

Structural magnetic resonance imaging (MRI) can provide similar structural information as CT. However, MRI provides higher resolution and greater sensitivity to underlying tissue structure and water content, which allows for the detection of subtle anatomical and vascular changes associated with cognitive impairment and dementia. (19;21) MRI imaging is contraindicated in patients with ferromagnetic foreign bodies or medical or biostimulation devices including pacemakers, vagus nerve stimulators, implantable cardioverter-defibrillators, loop recorders, cochlear implants, and insulin pumps. (19)

Positron Emission Tomography

In contrast to CT and MRI, positron emission tomography (PET) is a chemical or functional imaging technique. For example, using a radio-labeled analogue of glucose, fluorodeoxyglucose 18F (FDG), PET depicts regions of cerebral atrophy based on reduced glucose metabolism. (3) The 3-dimensional image reflects the uptake of FDG; increased or atypical uptake may indicate the presence of a neoplasm. (26) Radiation from the FDG injection is estimated to be 0.019 mSv, and precautions must be taken for pregnant and breastfeeding women. (26) A wide variety of other PET ligands exist to examine other aspects of brain biochemistry, but none are commercially available in Canada.

Regulatory Status

CT and MRI imaging have been licensed in Canada since the 1980s. PET machines may be stand-alone devices or combined CT/PET scanners. The radiotracer FDG used for PET scanning is currently available solely through Health Canada via Clinical Trials Application, and the only approved indications for FDG are identification, staging, and detection of metastases of lung and colorectal cancers. (*Personal communication, Health Canada, March 27, 2013*) In light of the regulatory information from Health Canada that FDG is not indicated for brain imaging for dementia in Ontario, PET was removed from the scope of the analysis; it was included in the search strategy as the search was conducted prior to receipt of this information. Thus, in this report the term neuroimaging refers solely to non-contrast, structural CT and MRI.

Evidence-Based Analysis

Research Questions

To determine the appropriate use of imaging during the diagnostic work-up of dementia and to provide context for this issue, the following questions were addressed:

- What is the prevalence and reversibility of potentially reversible (treatable) causes of dementia?
- What are the indications for a structural imaging investigation for dementia diagnosis?
- What is the clinical utility or adjunctive value of neuroimaging for dementia diagnosis?
- When structural imaging is indicated, which modality (CT or MRI) should be used?
- What is the diagnostic accuracy of neuroimaging for discriminating dementia types?

Research Methods

Literature Search

Search Strategy

A literature search was performed on February 20, 2013, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2000, until February 20, 2013. PET was included in the search strategy as the regulatory information indicating its ineligibility was received after the search date; however, articles on PET were excluded. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full reports
- published between January 2000 and February 2013
- symptomatic patients with suspected or established dementia (including Alzheimer disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Creutzfeld-Jakob disease, mixed dementia)
- neuroimaging during diagnosis with structural CT or MRI
- adult, human studies
- randomized controlled trials (RCTs), systematic reviews, meta-analyses, observational studies, diagnostic accuracy studies

Exclusion Criteria

- studies on nondementia patients (e.g., mild cognitive impairment, Parkinson disease, Huntington disease, traumatic brain injury)
- neuroimaging with other modalities (e.g., positron-emission tomography, single-photon emission computed tomography, amyloid imaging) or experimental methods
- studies on asymptomatic populations, genetic testing, predicting future development of dementia, validation of methods of radiographic image interpretation or measurement

- pediatric populations, animal models
- case reports, editorials, commentaries, conference abstracts or proceedings

Outcomes of Interest

The outcomes of interest were adapted from a hierarchy of efficacy for diagnostic tests by Fryback and Thornbury (27) and pertained to diagnostic accuracy, clinical utility, and patient experience and quality of life (when available):

- diagnostic accuracy (e.g., sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios)
- impact on diagnosis (percentage of times clinicians' assessment changed after the test; percentage of cases where the diagnostic test was determined to be useful in making the diagnosis or differential diagnosis)
- impact on therapeutic decisions (percentage of times therapy planned before diagnostic test changed after the test; percentage of times the diagnostic test was determined to be useful in planning patient management/treatment)
- patient outcomes (e.g., percentage of patients who improved with diagnosis by imaging compared to without; morbidity or additional procedures avoided after diagnostic imaging)

Expert Panel

In April 2013, an Expert Advisory Panel for Appropriate Utilization of Medical Imaging for the Diagnostic Work-Up in Patients with Dementia was struck. Members of the panel included family physicians, neurologists, neuro/radiologists, geriatricians and geriatric psychiatrists, personnel from the Ministry of Health and Long-Term Care, and physicians recruited through the Ontario Medical Association.

The role of the expert panel was to contextualize the evidence produced by Health Quality Ontario and provide advice on the appropriate use of diagnostic imaging in dementia diagnosis. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of panel members.

Statistical Analysis

Likelihood Ratios

Where the data allowed, likelihood ratios (LR) were calculated to summarize the predictive value of indications for neuroimaging and similar variables. The likelihood ratio is a measure that combines sensitivity and specificity and provides a summary of how much more or less likely a patient with a disease of interest is to have a given test result (i.e., positive or negative) relative to patients without the disease of interest. (28) The positive likelihood ratio (LR+) is calculated as sensitivity/(1 − specificity), while the negative likelihood ratio (LR-) is calculated as (1 − sensitivity)/specificity. These values allow for the translation of population characteristics (i.e., sensitivity and specificity) to individual patients. (29) A likelihood ratio of 1.0 reflects a lack of diagnostic value, and in general, large LR+ (> 10) and small LR- (< 0.10) significantly increase the probability of disease or virtually rule out the chance the patient has the disease, respectively. (28) Meta-analysis of sensitivity and specificity, where possible, was performed using Meta-DiSc software, version 1.4.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (30) The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials (RCTs) are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose-response gradient, and accounting for all residual confounding factors. (30) For more detailed information, please refer to the latest series of GRADE articles. (30)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

Results of Evidence-Based Analysis

The database search yielded 5,374 citations published between January 1, 2000, and February 19, 2013 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded in the analysis.

Thirteen studies (5 systematic reviews and 8 observational studies) met the inclusion criteria. The references lists of the included studies and health technology assessment websites were hand searched to identify any additional potentially relevant studies falling within the search dates, and 2 additional citations (1 systematic review and 1 observational study) were included for a total of 15 included citations.

For each included study, the study design was identified and is summarized below in Table 3, which is a modified version of a hierarchy of study design by Goodman. (31)

Table 3: Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	
Large RCT	
Small RCT	
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	
Systematic review of non-RCTs with historical controls	6
Non-RCT with historical controls	7
Database, registry, or cross-sectional study	2
Case series	
Retrospective review, modelling	
Studies presented at an international conference	
Expert opinion	
Total	15

Abbreviation: RCT, randomized controlled trial.

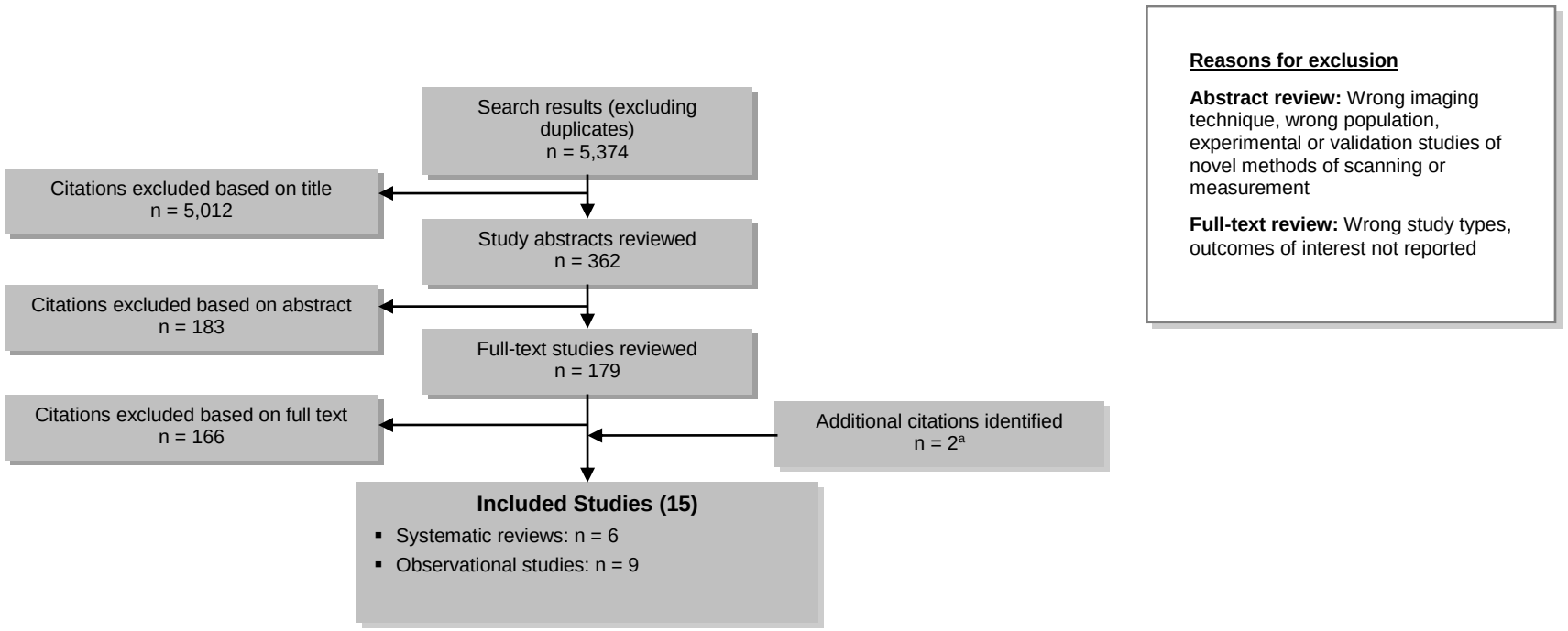

Figure 1: Citation Flow Chart

[a]1 systematic review and 1 observational study were identified via hand searching and bibliographic review.

Prevalence and Reversibility of Potentially Reversible Causes of Dementia

The prevalence of potentially reversible causes of dementia (PRCs) and the extent to which such treatable cases reverse are important contextual factors in determining the appropriate use of imaging in the diagnosis of dementia. Clarfield (32) updated a previous meta-analysis of the prevalence of reversible dementias. The original meta-analysis, (33) which included 32 articles published from 1972 to 1987 focusing on the etiology of dementias, estimated the proportion of cases of dementia that reversed either partially or fully. The update included 39 articles published between 1987 and 2001 and calculated weighted means via inverse-variance weights method, whereas the original study had calculated simple means. An overview of the parameters of both the original and updated analyses is presented in Table 4.

Table 4: Overview of Meta-Analyses on the Etiologies of Dementia

Author, Year	Search Method (Restrictions Applied)	Search Period	No. Studies Included
Clarfield, 2003 (32)	• Index Medicus search • Bibliography review • Consultation of textbooks (neurology, geriatrics, internal medicine, psychiatry) (English language only)	1987–2002	39
Clarfield, 1988 (33)	• Index Medicus search • Bibliography review • Consultation of textbooks (neurology, geriatrics, psychiatry) (Clinical studies only)	1966–1987	32

Abbreviations: No, number.
Source: Clarfield, 2003. (32)

The most commonly cited reversible causes that can be detected with neuroimaging are normal-pressure hydrocephalus (NPH), subdural hematoma (SH), and cerebral tumours. In the update, the author recalculated the simple means from the original meta-analysis (33) using the weighted-means method to facilitate comparison. The prevalence of PRCs and the proportions that reversed fully or partially are presented from each meta-analysis in Table 5.

Table 5: Prevalence and Reversibility of Potentially Reversible Causes of Dementia

Author, Year	No. Patients with Dementia (Total No. Patients)	% Potentially Reversible Cases[a] (% SH, tumour, NPH combined)	% Fully Reversed	% Partially Reversed
Clarfield, 2003 (32)	5,062 (7,042)	9.0 (2.2)	0.3	0.3
Clarfield, 1988 (33)	2,781 (2,889)	13.2 (3.5)	1.3	3.7

Abbreviations: No, number; NPH, normal-pressure hydrocephalus; SH, subdural hematoma.
[a]Calculated using inverse-variance weights method to calculate weighted means.
Source: Clarfield, 2003. (32)

In the updated meta-analysis, of the 9% of dementia cases that were potentially reversible, 0.6% actually reversed either fully or partially. (32) This is in contrast to the original meta-analysis (33) where the prevalence of PRCs was higher (approximately 13%) with 7% actually reversing partially or fully. The author commented that those with reversible causes tended to be younger, have a recent onset, and have milder symptoms, and that such cases were more commonly found among inpatients. (32) The latter point is offered as a potential contributor to the lower prevalence found in more recent observational studies, which were more likely to focus on outpatients (54% of included studies) or community-based settings

(31%), compared to studies in the 1970s and 1980s. (32) The reported information on included studies in this article were used to assess the risk of bias (Appendix 2, Table A6). The GRADE quality assessment can be found in Table A1 (GRADE: Very low).

Indications for Imaging in the Diagnosis of Dementia

Three studies provided some insight into the indications for an imaging investigation during the diagnosis of dementia.

Gifford et al (34) conducted a systematic review of the evidence underlying clinical prediction rules. As an alternative to imaging all patients, clinical prediction rules aim to identify patients with a high pretest probability of a PRC (e.g., tumour, subdural hematoma, normal-pressure hydrocephalus). Such rules tend to be a collection of clinical and/or demographic characteristics that indicate the need for neuroimaging with CT or MRI for the identification of PRCs. Relevant databases were searched for selective neuroimaging criteria published between 1983 and 1998, and the authors identified 7 relevant articles reporting on 6 sets of prediction rules for inclusion in their analysis.

All of the prediction rules included consideration of the duration or acuity of dementia symptoms. The full set of indications included in each prediction rule can be found in Gifford et al. (34) To be included in the systematic review, studies were required to provide sufficient detail on the clinical variables in the rules, information on the outcome in terms of presence or absence of a PRC, and sufficient data to calculate sensitivity and specificity. (For sensitivity, studies had to provide the proportion of patients with positive PRC results on imaging and at least one indication for imaging according to the rule; for specificity, studies had to provide the proportion of patients with no PRC defined on imaging and no indication for imaging according to the rule). Table 6 shows the range of sensitivity and specificity from the primary studies evaluating the prediction rules.

Table 6: Overview of Clinical Prediction Rules for Selective Neuroimaging in Dementia

Prediction Rule	No. Clinical Variables in Rule	Orientation of Prediction Rule	No. Primary Studies Evaluating Rule	Sensitivity Range (%)	Specificity Range (%)
Dietch (35)	11	Identifies patients who do not need a CT scan	2	87.5–100	37.2–52.9
Larson High-Risk (36;37)	3	Identifies patients who should undergo a CT scan	3	25.0–100	64.2–85.7
Larson Low-Risk (36)	3	Identifies patients who do not need a CT scan	2	50.0–100	68.6–76.0
Bradshaw (38)	5	Identifies patients who should undergo a CT scan	2	12.5–67.3	69.2–79.1
AAN (39)	5	Identifies patients who do not need a CT scan	1	66.7	42.1
CCC (40)	10	Identifies patients who should undergo a CT scan	1	83.3	63.2

Abbreviations: AAN, American Academy of Neurology; CCC, Canadian Consensus Conference; CT, computed tomography; No, number.
Source: Gifford et al, 2000. (34)

Diagnostic accuracy of the prediction rules varied considerably, with sensitivities from as low as 12.5% to perfect and specificities also from low to high (37.2–85.7%) depending on the population the rules were applied to. Prevalence of PRCs in the primary studies ranged from 0% to 10.4%. The authors estimated the number of cases that would be missed by applying the prediction rules to a hypothetical cohort of 1,000 dementia patients. The Dietch and Canadian Consensus Conference on the Assessment of Dementia (CCC) prediction rules were found to perform best in terms of fewest cases of PRCs missed among patients identified as not needing a scan. With a prevalence of 1%, the Dietch rules would have missed 1 patient with a PRC, and the CCC rules would result in 2 PRCs being missed. As the prevalence of PRC increased to 5%, 10%, and 15% in the hypothetical cohort, the number of PRC cases missed by the Dietch rules was 6, 13, and 19, respectively. For the Canadian Consensus Conference rules and the same hypothetical prevalences, numbers of missed cases were 8, 17, and 25, respectively. The rules that resulted in the lowest rates of false negatives were also those that would scan the largest proportion of patients (Dietch, 63%; CCC, 58%) relative to the other rules (AAN, 37%; Larson Low-Risk, 36%; Larson High-Risk 24%, Bradshaw 21%).

Sitoh and colleagues (41) tested the ability of a subset of the same clinical prediction rules to identify patients with suspected dementia who would benefit from neuroimaging. Retrospectively reviewing the medical records of 210 outpatients referred to a memory clinic, clinical variables were used to categorize patients as scan indicated or not indicated according to 5 sets of clinical prediction rules. Two definitions of significant findings were used to calculate sensitivity and specificity: i) hydrocephalus, meningiomas, subdural hematomas, subdural hygromas, or any other space-occupying lesions that may be amenable to surgical intervention, or ii) stroke or any of the conditions in the first definition. Table 7 presents likelihood ratios found for the broader, second definition.

Table 7: Likelihood Ratios of Clinical Prediction Rules for Selective Neuroimaging in Dementia

Prediction Rule	Evaluating Studies (First Author, Year)	Patient Population	n	LR+[a]	LR–[a]
Dietch	Sitoh, 2006 (41)	Memory clinic outpatients	210	2.02	0.58
	Martin, 1987 (42)	Geriatric clinic outpatients	204	1.39	0.34
	Dietch, 1983 (35)	VA hospital inpatients	200	2.12	0.0
Larson High-Risk	Sitoh, 2006 (41)	Memory clinic outpatients	210	2.13	0.91
	Martin, 1987 (42)	Geriatric clinic outpatients	204	0.70	1.17
	Larson, 1986 (37)	Dementia clinic outpatients	200	NA	NA
	Larson, 1984 (36)	Dementia clinic outpatients	107	7.0	0.0
Larson Low-Risk	Sitoh, 2006 (41)	Memory clinic outpatients	210	0.80	1.39
	Martin, 1987 (42)	Geriatric clinic outpatients	204	2.08	0.66
	Larson, 1984 (36)	Dementia clinic outpatients	107	3.19	0.0
Bradshaw	Sitoh, 2006 (41)	Memory clinic outpatients	210	1.56	0.87
	Martin, 1987 (42)	Geriatric clinic outpatients	104	0.60	1.10
	Bradshaw, 1983 (38)	Neuroradiological unit outpatients and inpatients	500	2.19	0.47
AAN	Chui, 1997 (39)	Memory clinic outpatients	98	1.15	0.79
CCC	Sitoh, 2006 (41)	Memory clinic outpatients	210	1.0	1.0
	Freter, 1998 (40)	Memory clinic outpatients	196	2.26	0.26

Abbreviations: AAN, American Academy of Neurology; CCC, Canadian Consensus Conference on the Assessment of Dementia; LR, likelihood ratio; VA, Veterans Affairs.
[a]Calculated by authors from sensitivity and specificity values published in the articles; 95% confidence intervals not provided.
Source: Sitoh et al, 2006. (41)

In both the Gifford (34) and Sitoh (41) studies, meta-analysis was not possible due to heterogeneity across studies that compared the same rules. Therefore, no summary accuracy estimates are available. The trends in likelihood ratios for the rules mirror the trends of sensitivity and specificity in the Gifford systematic review: LR+ ranged from lacking diagnostic utility (~1.0) to highly accurate (2.26), as did the LR-. The Sitoh study (41) did not report confidence intervals (CI) around the LR+ and LR- so no indication of the precision of these estimates is available. The author was contacted for raw data but no longer had access to the information.

Condefer and colleagues (43) examined the extent to which clinical indications for neuroimaging were related to the clinical utility of CT scans for memory clinic patients. Two physicians reviewed standardized and anonymized case histories of 146 patients and found that none of the indications from clinical prediction rules were significant predictors of clinical utility (i.e., change in diagnosis or management). Indications assessed were focal neurological signs, age less than 70 years, abrupt onset, noninsidious course, history of head injury, memory loss onset less than 2 years prior to the scan, history of hypertension/bleeding disorder, and physician prediction of an influential scan. Applied to the study sample, the individual indications were not significantly related to the clinical utility of the scan. Sensitivity for change in diagnosis or management ranged from 5% to 59%, and specificities ranged from 43% to 89%. The detection of vascular or structural lesions by CT did not necessarily affect clinical decisions.

Based on the above evidence, prediction rules and individual clinical indications do not appear to significantly predict abnormalities on a CT or MRI scan. Groups of indications (in prediction rules) have variable accuracy in predicting abnormalities, and prediction rules that are most accurate also scan the highest proportions of patients. Clinical indications (individually and together) also do not significantly predict influence on clinical decision making (i.e., diagnosis, treatment/management), nor does the detection of abnormalities always influence these decisions (GRADE: Very low). Details of the GRADE assessment of the quality of the body of evidence for the indications for neuroimaging can be found in Table A2.

Clinical Utility of Neuroimaging

Four studies investigated the clinical utility of CT or MRI imaging in memory clinic patients. (44-47) In these studies, clinical utility refers to the impact of the information obtained from neuroimaging on diagnosis and clinical decisions, as opposed to the diagnostic validity of the imaging for detecting anatomical features. Massoud and colleagues (47) assessed the additive contribution of CT or MRI to clinical diagnosis of mixed dementia (concomitant cerebrovascular and Alzheimer disease) in 61 patients at an Alzheimer research and tertiary care centre. Two patients were suspected to have infarcts based on clinical diagnosis; however, 13 other infarcts that had not been suspected clinically were detected by neuroimaging. The authors concluded that small infarcts (microinfarcts) pose a challenge to clinical detection and that neuroimaging is therefore important. Using pathological diagnosis as a gold standard, the addition of information from neuroimaging increased the sensitivity of clinical diagnosis of cerebrovascular disease by 53% (from 6% to 59%); however, specificity decreased by 17% (from 98% to 81%). For detection of cerebral infarcts only, the sensitivity of clinical diagnosis increased by 46% (from 8% to 54%) and specificity decreased 15% (from 98% to 83%) with the addition of information from neuroimaging.

Computed Tomography

Condefer et al (44) evaluated the clinical utility of CT via retrospective review of the case histories of 146 patients 65 years and older who met the DSM-IV criteria for dementia. Two geriatricians independently assigned diagnoses to standardized and anonymized cases following a review of complete medical

history, physical and neurological examination, functional assessment (activities of daily living, instrumental activities of daily living), a full neuropsychological exam, routine blood chemistries, and a noncontrast CT scan. First, clinical diagnoses and provisional treatment plans were made using research criteria for AD, LBD, and VaD based on all clinical information except the CT. Second, physicians reviewed the radiologist's report on the CT with the diagnosis and treatment plan from the clinical evaluation and specified if and how the results of the CT influenced diagnosis or treatment. Overall, CT information led to revision of diagnosis and treatment decisions in approximately 10% of cases. Diagnosis was revised in 12% (+/- 2%) of cases; the most common changes were either the exclusion or inclusion of a vascular component and, less frequently, confirmation of atypical AD or identification of a structural lesion. (44) Changes to treatment decisions occurred in 11% (+/- 2%) of cases and most commonly involved the addition of low-dose aspirin or AChEI or referral to further neuroimaging or neurosurgery. (44)

Magnetic Resonance Imaging

Using similar methods, clinical utility of MRI was quantified in a study by Hentschel et al. (45) A prospective cohort of 106 consecutive patients referred to a memory clinic with a primary care diagnosis of dementia underwent a full clinical evaluation (history, neurological, psychiatric exam) and subsequent MRI investigation and neuropsychological testing. The initial and final diagnoses after all assessments were categorized as shown in Table 8.

Table 8: Categories of MRI Imaging, Neuropsychological Results, and Final Diagnosis

MRI Sequence Results	Neuropsychological Test Results	Final Diagnostic Group	Patient Types Included in Final Diagnosis
Findings compatible with neurodegenerative dementia[a]	Cognitive disturbances suggesting neurodegenerative dementia	Neurodegenerative dementia (ND)	AD[b] LBD FTD
Findings compatible with vascular dementia[c]	Cognitive disturbances suggesting vascular dementia	Vascular dementia (VaD)	VaD[d]
No findings characteristic of neurodegenerative or vascular dementia	No cognitive disturbances compatible with dementia	No dementia (XD)	MCI No cognitive disturbances

Abbreviations: AD, Alzheimer disease; LBD, Lewy body dementia; FTD, frontotemporal dementia; MCI, mild cognitive impairment; MRI, magnetic resonance; VaD, vascular dementia.
[a]Alzheimer disease, frontotemporal dementia, or Lewy body dementia based on analysis of atrophy patterns of frontal and temporal cerebral cortex, enorhinal and amygdala region, and hippocampus.
[b]Fulfilling the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD.
[c]Based on assessment of subcortical microangiopathic white matter lesions visible on T1, double echo plus fluid-attenuated inversion recovery (FLAIR) MRI sequences.
[d]Including definite, probable, and possible vascular dementia according to the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria
Source: Hentschel et al, 2005. (45)

After consideration of both MRI and neuropsychological (NP) test results, the initial clinical diagnosis changed for 26% of patients (95% CI, 17–35). Using 3-dimensional contingency tables, the authors analyzed the independent influence of the neuroradiological and NP test findings on the final comprehensive diagnosis, which was based on all information (reference standard). Though the influence of MRI alone on diagnosis cannot be teased out from these results, both the main effect of neuroimaging and neuropsychological diagnosis on final diagnosis were statistically significant ($P < 0.01$). Table 9 summarizes the influence of MRI and NP findings on final diagnosis.

Table 9: Influence and Accuracy of NP and MRI Relative to Final Comprehensive Diagnosis

Diagnosis	Initial Diagnoses (% of cases)	% Change after MRI and NP Results (– or +)	MRI Sensitivity (%)	MRI Specificity (%)	MRI PPV (%)
ND	27	+ 3	93	96	78
VaD	28	– 8	90	79	51
XD	45	+ 5	55	96	93

Abbreviations: MRI, magnetic resonance imaging; ND, neurodegenerative dementia; NP, neuropsychological test; PPV, positive predictive value; VaD, vascular dementia; XD, no dementia.
Source: Hentschel et al, 2005. (45)

The authors advocate for the inclusion of neuroimaging for the investigation of mild to moderate cases in light of the change in final diagnosis of more than a quarter of patients in the study and the congruence between their results with MRI and similar results with CT by Condefer et al. (44) Hentschel et al (45) did not comment on or assess the influence of MRI on treatment decisions for patients.

Jani and colleagues (46) investigated the relationship between clinical and radiological diagnoses in elderly inpatients and outpatients referred to a psychiatric hospital for an MRI investigation of cognitive impairment. A sample of 104 patients age 65 years and older received a clinical and MRI evaluation and separate diagnoses based on each set of information. The agreement between the clinical and radiological diagnoses was assessed.

Overall, correlations between clinical and radiological diagnoses were weak. MRI and clinical diagnosis were concordant in 11 cases of AD and 2 cases of VaD. "Other" diagnoses were facilitated by MRI in 2 cases, and 29 patients who had been clinically diagnosed with dementia were found on MRI to have normal age-related changes. MRI enabled the determination of a more specific diagnosis in the 63 patients (60.6%) previously assigned a clinical diagnosis of unspecified dementia: 28 cases (44.4%) were revised to AD, 17 cases each (27%) were revised to VaD or normal aging, and 1 case was found to have a subdural hematoma. Even among the patients who had been diagnosed clinically with AD or VaD, the diagnosis was revised in 3 (11.1%) and 5 (62.5%) patients, respectively, in light of MRI results.

In summary, the clinical utility of neuroimaging in these studies is variable. Information from CT or MRI scans may result in revision of clinical diagnosis in as few as 10% to nearly two-thirds of patients, depending on the type and severity of dementia (GRADE: Low). Details of the GRADE assessment of the quality of the body of evidence for the clinical utility for neuroimaging can be found in Table A3.

Comparative Accuracy of CT and MRI

No studies directly answered the research question of which modality should be used when structural imaging is indicated. However, a systematic review by Beynon and colleagues (48) assessed the comparative accuracy of CT and MRI for the detection of a vascular component to dementia. The parameters of the review are summarized in Table 10.

Table 10: Overview of Systematic Review Parameters

Databases	Search Dates	Inclusion Criteria[a]	No. of Citations Reviewed (Included)
MEDLINE Embase BIOSIS Science Citation Index Zetoc NTIS Dissertation Abstracts GrayLit network	Database inception to February 2011	Assessing: CT or MRI imaging for the detection of cerebrovascular changes Target conditions: VaD (all subtypes), AD, mixed dementia Reference standards: autopsy, NINCDS-ADRDA for AD, NINDS-AIREN for VaD, DSM-III/DSM-III R/DSM-IV, ADDTC, ICD-10, any reference standard for mixed dementia Reporting: 2 x 2 data for test accuracy for ≥ 1 of general infarcts, lacunar infarcts, nonlacunar infarcts, WMH, PVH, BGH, global assessment	19,669 (38)

Abbreviations: AD, Alzheimer disease; ADDTC, State of California AD Diagnostic and Treatment Centers Criteria; BGH, basal ganglia hyperintensities; CT, computed tomography; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; MRI, magnetic resonance imaging; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; No., number; NTIS, National Technical Information Service; PVH, periventricular hyperintensities; VaD, vascular dementia; WMH, white matter hyperintensities.
[a]No language or methodological restrictions were applied.
Source: Beynon et al, 2012. (48)

Of the 38 included studies, 26 studies assessed CT, 16 MRI, and 4 both. All of the included studies were observational (20 prospective cohorts, 6 retrospective cohorts, 12 case control studies), and most (n = 31) used clinical criteria as a reference standard, with the remaining 7 comparing to autopsy. The results are presented as a diagnostic odds ratio (DOR) and, for comparative accuracy, the ratio of the DORs (RDOR) for MRI to CT. The DOR is a useful measure of a diagnostic test's performance that is not dependent on the prevalence of the condition being tested for, and it compares the odds of positivity among the diseased to the odds of positivity among the non-diseased. (49) Only one study evaluated MRI against autopsy; thus DOR to summarize test performance could only be compared between CT and MRI from studies using clinical criteria as a reference standard. RDORs were calculated for each of the following: general infarcts, lacunar infarcts, nonlacunar infarcts, white matter hyperintensities, periventricular hyperintensities, basal ganglia hyperintensities, and global assessment.

Although MRI appeared to have greater accuracy (RDOR > 1.0) for all of the imaging findings with the exception of general infarcts (RDOR = 0.57; 95% CI, 0.03–10.5, $P = 0.64$), none of the RDORs reached statistical significance and confidence intervals were very wide. The authors report that the results of the 4 studies providing direct comparisons were similar to the indirect comparisons, though RDORs from direct comparisons tended to be smaller. (48) Limitations of the meta-analyzed studies include generally small sample sizes, especially among autopsy studies (sample size range, 31–53; median, 44) and to a lesser extent among nonautopsy studies (sample size range, 43–683; median, 70). There was considerable variability across studies in terms of findings reported, and only 4 studies provided a direct comparison of CT and MRI. Other limitations include the small number of studies using autopsy as a reference standard, as opposed to using clinical diagnostic criteria. The composition of "global assessments" of neuroimaging varied as well. Detailed results for all vascular changes assessed by included studies can be found in Beynon et al. (48)

The quality of included studies was evaluated by the authors using the QUADAS tool, a 14-item qualitative assessment of methodological considerations of diagnostic accuracy studies. (50) The authors state that most studies were likely to result in biased or less applicable estimates as they did not enrol an appropriate spectrum of patients. Despite these challenges, a meta-regression to assess the potential impact of incorporation bias (which results when the index test is used to establish final diagnosis) and

selection bias (when the sample does not include a representative spectrum of patients) revealed no significant influence on the RDORs, which were similar in both the presence and absence of these factors.

The supplementary table of characteristics of included studies (study design, imaging modality, diagnostic accuracy findings) provided by the authors was used to assess risk of bias, and original studies were sought for further details as needed. For the detection of a vascular component to dementia, there is a lack of evidence that MRI is superior to CT (GRADE: Very low). The GRADE quality assessment for this body of evidence is shown in Table A4.

Diagnostic Accuracy of Neuroimaging for Distinguishing Types of Dementia

Alzheimer Disease

Three systematic reviews report on the sensitivity and specificity of neuroimaging for differential or confirmatory diagnosis of AD. (51-53) The parameters of the reviews are outlined in Table 11.

Table 11: Systematic Reviews of Diagnostic Accuracy of Neuroimaging for Alzheimer Disease

Author, Year	Databases (Limits, if Applicable)	Search Dates	Inclusion Criteria	No. of Citations Retrieved (Included)
Bloudek et al, 2011 (51)	MEDLINE (English)	January 1990–March 2010	Assessing: MRI, CT, SPECT, FDG-PET, CSF analysis Reference standards: clinical or histopathological diagnosis Reporting: sensitivity and specificity for diagnosis compared to MCI, other dementias, or controls without dementia Study design features: excludes MRI imaging sequences that are experimental or investigational and not routinely used	2,137[a] (119)
Wahlund et al, 2005 (52)	MEDLINE (English)	1980–2004	Assessing: MRI Reference standards: clinical or neuropathological criteria Reporting: data allowing for calculation of sensitivity, specificity, and likelihood ratios compared to normal and other diseased controls Study design features: at least 20 cases and controls each or, where controls were inappropriate, at least 30 cases; meta-analyses excluded	434 (36)
Wollman and Prohovnik, 2003 (53)	MEDLINE	August 1998–August 2001	Assessing: CT, MRI, PET, SPECT Reference standard: clinical criteria Reporting: sensitivity and specificity for diagnosis or differentiation from normal or other diseases using MTL width (CT); hippocampal volume (MRI); MTL volume (MRI) Study design features: None reported	NR (13)

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; FDG-PET, fluorodeoxyglucose 18F positron emission tomography; MCI, mild cognitive impairment; MTAL medial temporal lobe; MRI, magnetic resonance imaging; No., number; NR, not reported; PET, positron emission tomography; SPECT, single photon emission computed tomography.
[a]1,840 unique articles, 22 additional identified via bibliographic search.

The review by Wahlund et al (52) included 36 articles on MRI, and LR+ and LR- were calculated based on reported sensitivity and specificity in the primary articles. The results are presented separately by comparison group used (healthy controls, other dementias, mild cognitive impairment [MCI]), method of estimation of brain volume (visual rating, linear measurement, volumetry, other) and brain region assessed (entorhinal cortex, hippocampus).

The authors assessed the quality of included studies based on study design, patient selection, comparison groups, and setting. The strength of evidence was also evaluated based on individual study quality and results for studies meeting the authors' "evidence criteria" (sensitivity and specificity > 80% and LR+ > 5). Of the 36 included studies, 30 (83%) fell within the lowest 3 quality categories. For full details see Wahlund et al. (52)

There was no meta-analysis conducted or any synthesis of findings, and the authors report that conclusive information could not be systematically extracted from the literature due to the variety of methods used in studying this topic, and thus no conclusions could be drawn.

The second review by Bloudek and colleagues (51) synthesized accuracy estimates for both CT and MRI and conducted sensitivity analysis to assess the impact of the variability in study methods. Despite accounting for the correlation between sensitivity and specificity using a mixed-effects binary regression, they found significant unexplained heterogeneity in sensitivity (I^2 = 89.8%) and specificity (I^2 = 58.5%) of CT, and Cochran's Q statistic for heterogeneity was significant for both estimates (P < 0.01, 0.03, respectively). Similarly, there was significant unexplained heterogeneity in sensitivity (I^2 = 64.3%) and specificity (I^2 = 84.2%) for MRI, and Cochran's Q statistic for heterogeneity was significant for both estimates (P < 0.05 for all).

In an effort to account for some of the heterogeneity, the authors conducted subgroup analyses by comparison group (no dementia, dementia controls including MCI, and dementia excluding MCI), standard of truth (autopsy, clinical, combined), and severity (mild, moderate, combined). For MRI, a small proportion of between-study heterogeneity was found to be due to threshold effect; however I^2 in all subgroup analyses was high (87%–90%). There were insufficient studies (n < 4) to conduct any subanalysis for CT or for MRI results using autopsy as reference standard. Subgroup analysis revealed that accuracy of MRI was highest when no-dementia controls were the comparison group, compared to dementia including or excluding MCI. Compared to the combined reference standard (clinical plus autopsy), autopsy alone had slightly higher sensitivity and slightly lower specificity. Accuracy was generally lower for mild cases compared to moderate dementia. Detailed results can be found in the original article. (51)

Wollman and Prohovnik (53) compared neuroimaging to current standards of clinical diagnosis for AD with the aim of making recommendations for its role in practice. The authors did not perform meta-analysis, but instead reported sensitivity and specificity individually for each study identified. The review included studies that assessed the accuracy of neuroimaging in combination with other measurements (e.g., regional cerebral blood flow, cognitive tests), and the accuracy estimates compared to clinical criteria from the studies assessing only neuroimaging are presented. Based on these studies, false-negative rates ranged from 15% to 25% for CT and from 5% to 10% for MRI.

Table 12 summarizes the accuracy estimates for CT and MRI (if reported) from the 3 systematic reviews described above. Compared to clinical or autopsy diagnosis, CT has moderate to high sensitivity and specificity for differentiating AD from MCI, other types of dementias, and healthy aging. MRI also has good accuracy, although there appears to be a wide range in both accuracy estimates due to variability in cortical structures assessed, comparison groups, and methods of assessment (quantitative, visual assessment, volumetric) (GRADE: Very low).

Table 12: Reported Accuracy of Neuroimaging for Diagnosis of Alzheimer Disease

Author, Year	No. Studies	Imaging Technique	Comparison Population(s)	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)
Bloudek et al, 2011 (51)	26	MRI	No dementia, MCI, other dementias (combined)	0.83 (0.79–0.87)	0.85 (0.80–0.89)
	6	CT	No dementia, depression, other dementias (combined)	0.80 (0.68–0.88)	0.87 (0.78–0.93)
Wahlund et al, 2005 (52)	36	MRI	Healthy controls, other dementias	NR	NR
Wollman and Prohovnik, 2003 (53)	2	MRI	Normal controls	0.90[a] 0.95[a]	0.94[a] 0.92[a]
	2	CT	Normal controls Other diseases (VaD depression, paraphrenia)	0.85[a] 0.75[a]	0.90[a] 0.90[a]

Abbreviations: CI, confidence interval; CT, computed tomography; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; No, number; NR, not reported; VaD, vascular.

[a]Confidence intervals not reported.

Creutzfeldt-Jakob Disease

Two studies by Schroter (54) and Tschampa (55) examined the diagnostic accuracy of high signal intensity in the basal ganglia for the diagnosis of CJD. These studies utilized a number of MRI sequences including T2-weighted, T1-weighted, proton-density-weighted, diffusion-weighted, and fluid-attenuated inversion recovery (FLAIR) MRI scans, each of which alter the contrast of free water, damaged tissue, and water- and fat-containing tissues to visualize pathology. Sensitivity and specificity from the studies and summary accuracy measures are presented in Table 13.

Table 13: Reported Accuracy of MRI for Diagnosis of Creutzfeldt-Jakob Disease

Author, Year	MRI Sequence	Comparison Population(s)	Reference Standard	Sensitivity (95% CI)	Specificity (95% CI)
Schroter et al, 2000 (54)	T2-weighted	AD, unclassified dementias, CVD, chronic encephalitis of unknown cause, PD, psychiatric diseases, paraneoplastic syndromes, others	Autopsy or clinical diagnosis	67.3% (59.5–74.4)	93.1% (83.3–98.1)
Tschampa et al, 2005[a] (55)	T2-weighted, diffusion-weighted, FLAIR, proton-density-weighted (overall)	NA	Autopsy or clinical diagnosis[b]	59.7% (51.6–67.4) 58.3% (50.2–66.1) 70.8% (62.9–77.6)	84.2% (69.6–92.6) 89.5% (75.9–95.8) 81.6% (66.6–90.8)

Abbreviations: AD, Alzheimer disease; CI, confidence interval; CVD, cerebrovascular disease; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance; NA, not applicable; PD, Parkinson disease.

[a]Three raters interpreted MRI scans, and accuracy was calculated for each rater independently.

[b]Autopsy results from the German Reference Center for spongiform encephalopathies; clinical diagnosis includes "probable" defined according to World Health Organization criteria for CJD.

Meta-DiSc software, version 1.4, was used to generate summary sensitivity and specificity from these studies. Point estimates and 95% CIs were obtained via a DerSimonian-Laird random effects model. There was no significant heterogeneity, and results are presented in Table 14.

Table 14: Summary Accuracy of MRI for Diagnosis of Creutzfeldt-Jakob Disease

Studies	Summary Sensitivity (95% CI)	I^2 Sensitivity (X^2, P)	Summary Specificity (95% CI)	I^2 Specificity (X^2, P)
Tschampa et al, 2005[a] (55); Schroter et al, 2000 (54)	0.64 (0.58–0.69)	46.9% (1.89, 0.1698)	0.90 (0.82–0.95)	47.3% (1.90, 0.1685)

Abbreviations: CI, confidence interval.
[a]Sensitivity and specificity were calculated based on 3 raters' assessments of MRI images in this study and no summary estimate was calculated across raters; therefore, for the meta-analysis, data from the rater with middle values for both sensitivity and specificity were included to calculate summary estimates.

MRI has high specificity and moderate sensitivity for the diagnosis of CJD. There is some potential influence of the specific MRI sequence on accuracy, and some authors (55) recommend diffusion-weighted and FLAIR MRI sequences to visualize the pathological changes (GRADE: Low).

Clinically Ambiguous Dementia

One study assessed the value of MRI for the differential diagnosis of clinically ambiguous dementia. (56) The study included 69 initially "unclassifiable" patients presenting to a neurological memory centre, and was designed to mimic the reality of memory clinics using widely available tools (i.e., not research-grade technology). All patients met the DSM-IV criteria for dementia; scored 18 or greater on the Mini-Mental State Examination; did not fulfill the criteria for FTD, VaD, Parkinson disease, LBD, or progressive supranuclear palsy/corticobasal degeneration spectrum; and had at least one of the NINCDS-ADRDA "atypical" features of AD. MRI scans were performed at baseline and blind-analyzed retrospectively after 2 years of follow-up for medial temporal lobe atrophy (MTA, assessed using Scheltens scale) to identify AD, and for white matter hyperintensities (WMH) to identify vascular changes and VaD (Fazekas scale). Table 15 shows the accuracy of MRI for differentially diagnosing these patients relative to clinical diagnosis at follow-up.

Table 15: Diagnostic Accuracy of MRI for Diagnosis of Dementia in Clinically Ambiguous Cases

Radiological Assessment	n	Sensitivity	Specificity	AUC (95% CI)	*P*
MTA – AD	60[a]	56%[b]	86%	0.68 (0.51–0.85)	0.0402
WMH – VaD		88%[c]	75%	NR	NR

Abbreviations: AD, Alzheimer disease; AUC, area under the curve; CI, confidence interval; MTA, medial temporal lobe atrophy; NR, not reported; VaD, vascular dementia; WMH, white matter hyperintensities.
[a]9 patients were lost to follow-up; 3 died before 24-month follow-up assessment.
[b]Reference standard NINCDS-ADRDA clinical criteria and MTA rated with Scheltens visual rating scale with threshold ≥ 2.
[c]Reference standard NINCDS-AIREN clinical criteria and WMH rated with Fazekas scale with threshold of Fazekas grade 3.
Source: Boutoleau-Bretonniere et al, 2012. (56)

Among the 60 patients who reached the study end point, 80% of the clinically ambiguous cases had a diagnosis assigned after 2 years of follow-up. Based on all clinical information, 18 patients were diagnosed with AD, 11 with FTD, 8 with VaD, 7 with psychiatric disorders, 4 with other diagnoses, and 12 remained unclassifiable. Using receiver operating characteristic curve analysis, it was found that MRI contributed reliably and significantly to the diagnosis of VaD, and provided a limited but statistically significant contribution to the diagnosis of AD in clinically ambiguous cases. The authors suggest that the

latter finding may be due to the poor specificity of MTA for AD as it is a consistent feature of FTD and other dementias as well. MTA was quite reliable in discriminating organic dementia cases from controls with psychiatric conditions (area under the curve = 0.87, $P < 0.01$). MRI did not contribute to the diagnosis of FTD. MRI has high sensitivity for differentiating clinically ambiguous dementias, moderate specificity for discriminating VaD, and moderate sensitivity but high specificity for discriminating AD (GRADE: Very low).

Limitations

Limitations of this evidence and analysis include:

- Study design limitations
    - No RCTs
    - Lack of diagnostic uncertainty, few prospective studies, inconsistent cohorts from consecutive patients, incorporation bias of imaging into the reference standard
- Generalizability issues
    - Research from tertiary/specialized care; no studies from primary care
- Accuracy issues
    - Diagnostic accuracy as a surrogate for patient-centred outcomes such as patient function, patient and family quality of life
- Heterogeneity
    - Variability in imaging modality, imaging sequences, patient populations, reference standard, brain structure evaluated, methods of assessing scans, and methods of interpreting radiological findings, among other factors
- Imprecision
    - Dichotomized dementia types instead of acknowledgment of concurrence
    - Imprecision of clinical criteria as a reference standard
    - Autopsy available in few studies, with small sample sizes and highly selected populations

Conclusions

- With the exception of dementia related to vascular disease, prevalence of potentially treatable dementias is low (< 10%), and improvement after treatment of the underlying condition is less than 1% (GRADE: Very low).
- Prediction rules and individual clinical indications do not reliably predict abnormalities or influence diagnosis or treatment (GRADE: Very low).
- The clinical utility of structural neuroimaging is:
    - high for patients with potentially mixed dementia
    - high for patients where there is uncertainty for 2 years or more about the type of dementia
    - low for patients with Alzheimer disease clinically diagnosed by follow-up over time (e.g., 1 year)
    - low for patients where vascular dementia has been clinically excluded (GRADE: Low)
- For the detection of a vascular component to dementia, there is a lack of evidence that MRI is superior to CT (GRADE: Low).
- In terms of diagnostic accuracy, structural neuroimaging has low to moderate sensitivity and high specificity for discriminating Alzheimer disease, Creutzfeldt-Jakob disease, and clinically ambiguous cases (GRADE: Low to Very low).

Expert Panel Comments

The Expert Advisory Panel for Appropriate Utilization of Medical Imaging for the Diagnostic Work-Up in Patients with Dementia provided these additional insights into the use of neuroimaging in the diagnosis of dementia in Ontario:

- There is a surprising lack of high-quality evidence on which to base recommendations and there is a need for well-designed and executed studies on practices that are currently considered routine or standard.
- A number of quality issues limit the current clinical validity and utility of CT and MRI. To address these issues, the panel suggests:
    - development of a dementia protocol and reporting standards for neuro/radiologists to improve quality assurance
    - review of ordering processes for imaging, such as electronic ordering systems, to avoid unnecessary repeat scans
- Family physicians in particular emphasize the need for a high level of certainty in making a definitive diagnosis and the key role of neuroimaging in this capacity.
- It is generally agreed that there is little additional value in imaging patients with a chronic disease course (e.g., long-term care patients) as dementia may be pre-existing or identified during a medical visit for other reasons (e.g., falls).
- Much of the available evidence comes from tertiary centres where prior knowledge of neuroimaging may be assumed and/or patients are highly selected (e.g., Alzheimer disease centres), and there is no evidence from primary care settings where many dementia cases in Ontario are managed.
- There are limitations in examining imaging in isolation, rather than in the full context of dementia management; a province-wide expert panel on dementia with a more encompassing scope to facilitate an analysis of dementia management would be beneficial.

Existing Guidelines for Neuroimaging

Table 16 summarizes the wide variation in existing clinical practice guidelines for the use of structural CT or MRI in the evaluation of dementia. The table provides an overview of the recommendations and cited reasons for the final recommendation statement from each guideline.

Table 16: Existing Guidelines for the Use of Neuroimaging in the Evaluation of Dementia

Guideline, Year	Recommendation			Cited Reason(s)	
	Image All	Selective Imaging	MRI Preferred	Detect PRCs	Determine Subtype
4th Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD4), 2012 (57)		✓	✓		✓
European Federation of Neurological Societies (EFNS) Task Force on Imaging in Dementia, 2012 (58)	✓		✓	✓	✓
National Institute for Health and Clinical Excellence (NICE), 2006 (59)	✓		✓	✓	✓
Scottish Intercollegiate Guidelines Network (SIGN), 2005 (60)	✓			NR	NR
American Academy of Neurology (AAN), 2004 (61)	✓				✓

Abbreviations: MRI, magnetic resonance imaging; NR, not reported; PRC, potentially reversible causes of dementia.

There is variation across guidelines in the recommendations for imaging patients for dementia investigation, including a preferred modality. The methodological rigour and transparency of clinical practice guidelines was evaluated by use of the Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument. (62) AGREE II comprises 23 items organized into 6 quality domains—scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence. (62) The AGREE domain scores provide information about the relative quality of the guideline; a score of 1 indicates an absence of information or poor reporting, while a score of 7 indicates exceptional reporting that meets all criteria. AGREE II scores for these guidelines can be found in Appendix 2, Table A14.

Acknowledgements

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Expert Advisory Panel for Appropriate Utilization of Medical Imaging for the Diagnostic Work-Up in Patients with Dementia

Panel Members	Affiliation(s)	Appointments(s)
Chair		
Dr Sandra Black	Sunnybrook Health Sciences Centre	Director, Brain Sciences Research Program
Neurology		
Dr James Sahlas	McMaster University, Division of Neurology, Department of Medicine	Associate Professor
Dr Morris Freedman	Baycrest Centre for Geriatric Care; University of Toronto	Head of Neurology; Director of the Brain Health Centre Memory Clinic
Dr Stephen Pasternak	University of Western Ontario	Assistant Professor of Neurology
Diagnostic Radiology		
Dr Sean Symons	Sunnybrook Health Sciences Centre, Department of Medical Imaging; Ontario Medical Association (OMA)	Head, Division of Neuroradiology; Chair, OMA Section of Neuroradiology
Dr Lisa Ehrlich	Sunnybrook Health Sciences Centre	Clinical Head of Nuclear Medicine
Dr Donald Lee	University of Western Ontario; University Hospital	Professor; Neuroradiologist
Primary Care		
Dr Linda Lee	Centre for Family Medicine Family Health Team; McMaster University	Associate Clinical Professor
Dr Andrea Moser	Canadian Research Network for Care in the Community	President, Ontario Long Term Care Physicians (OLTCP)
Psychiatry		
Dr Nathan Herrmann	Sunnybrook Health Sciences Centre	Head, Division of Geriatric Psychiatry
Geriatric Medicine		
Dr Sudeep Gill	Queens University, Division of Geriatric Medicine, Department of Medicine	Associate Professor
Ministry of Health Representative		
Dr Garry Salisbury	Ministry of Health and Long-Term Care, Division of Negotiation and Accountability Management	Senior Medical Consultant

Appendices

Appendix 1: Literature Search Strategies

Search date: February 19, 2013
Databases searched: Ovid MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, Embase; Cochrane; Centre for Reviews and Dissemination (CRD) database
Limits: 2000-present; English; NOT case reports, comments, editorials, letters
Filters: none
Question:
Appropriate use of imaging in the diagnostic work-up for dementia

Database: Ovid MEDLINE(R) <1946 to February Week 1 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 15, 2013>, Embase <1980 to 2013 Week 07>
Search Strategy:

#	Searches	Results
1	exp Dementia/	312729
2	exp Cognition Disorders/ use mesz	54585
3	exp cognitive defect/ use emez	84437
4	(dementi* or alzheimer* or predementia* or pre-dementia* or ((dementia* or alzheimer*) adj2 (revers* or early))).ti,ab.	273469
5	or/1-4	468895
6	exp Tomography, X-Ray Computed/ use mesz or exp computer assisted tomography/ use emez	817213
7	exp Magnetic Resonance Imaging/ use mesz or exp nuclear magnetic resonance imaging/ use emez	747046
8	exp Positron-Emission Tomography/	99499
9	exp Neuroimaging/	160053
10	(computed tomograph* or fluorodeoxyglucose* or fludeoxyglucose* or neuroimag* or 18F-FDG or FDG-PET or ct scan* or EBCT or MDCT).ti,ab.	497288
11	or/6-10	1647431
12	5 and 11	51982
13	exp "Predictive Value of Tests"/ use mesz or exp predictive value/ use emez	155007
14	exp Decision Support Techniques/ use mesz or exp medical decision making/ use emez	116708
15	exp Disease Progression/ use mesz	104008
16	exp Early Diagnosis/	75321
17	exp Likelihood Functions/ use mesz or exp maximum likelihood method/ use emez	19682
18	exp odds ratio/ use mesz	51073
19	exp Diagnosis, Differential/ use mesz or exp differential diagnosis/ use emez	663277
20	*"Sensitivity and Specificity"/	848
21	exp Decision Trees/	13374
22	(predict* or decision making or decision support* or likelihood ratio* or clinical utilit* or differential diagnos* or early diagno*).ti,ab.	2278119
23	or/13-22	3130041
24	12 and 23	12268
24	limit 23 to english language	10715
25	limit 24 to (case reports or comment or congresses or editorial or letter or conference abstract or conference paper or conference proceeding) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,Embase; records were retained]	2397
26	24 not 25	8318
27	limit 26 to yr="2000 -Current"	7113
28	limit 27 to yr="2007 -Current"	4847
29	remove duplicates from 28	3662
30	limit 27 to yr="2000 - 2006"	2271
31	remove duplicates from 30	1758
32	29 or 31	5418

Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Dementia] explode all trees	3282
#2	MeSH descriptor: [Cognition Disorders] explode all trees	2279
#3	(dementi* or alzheimer* or predementia* or pre-dementia* or ((dementia* or alzheimer*) near/2 (revers* or early))):ti (Word variations have been searched)	5324
#4	#1 or #2 or #3	7838
#5	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees	3221
#6	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees	4548
#7	MeSH descriptor: [Positron-Emission Tomography] explode all trees	755
#8	MeSH descriptor: [Neuroimaging] explode all trees	1745
#9	(computed tomograph* or fluorodeoxyglucose* or fludeoxyglucose* or neuroimag* or 18F-FDG or FDG-PET or ct scan* or EBCT or MDCT):ti (Word variations have been searched)	1496
#10	#5 or #6 or #7 or #8 or #9	9428
#11	MeSH descriptor: [Predictive Value of Tests] explode all trees	5118
#12	MeSH descriptor: [Decision Support Techniques] explode all trees	2714
#13	MeSH descriptor: [Disease Progression] explode all trees	4529
#14	MeSH descriptor: [Early Diagnosis] explode all trees	556
#15	MeSH descriptor: [Likelihood Functions] explode all trees	314
#16	MeSH descriptor: [Odds Ratio] explode all trees	2622
#17	MeSH descriptor: [Diagnosis, Differential] explode all trees	1345
#18	MeSH descriptor: [Sensitivity and Specificity] explode all trees	13747
#19	MeSH descriptor: [Decision Trees] explode all trees	766
#20	(predict* or decision making or decision support* or likelihood ratio* or clinical utilit* or differential diagnos* or early diagno*):ti (Word variations have been searched)	8446
#21	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20	30739
#22	#4 and #10 and #21 from 2000 to 2013	109

CRD

Line	Search	Hits
1	MeSH DESCRIPTOR dementia EXPLODE ALL TREES	394
2	MeSH DESCRIPTOR cognition disorders EXPLODE ALL TREES	157
3	(dementi* or alzheimer* or predementia* or pre-dementia* or ((dementia* or alzheimer*) adj2 (revers* or early))):TI	492
4	#1 OR #2 OR #3	659
5	MeSH DESCRIPTOR tomography, x-ray computed EXPLODE ALL TREES	667
6	MeSH DESCRIPTOR magnetic resonance imaging EXPLODE ALL TREES	531
7	MeSH DESCRIPTOR positron-emission tomography EXPLODE ALL TREES	237
8	MeSH DESCRIPTOR neuroimaging EXPLODE ALL TREES	50
9	(computed tomograph* or fluorodeoxyglucose* or fludeoxyglucose* or neuroimag* or 18F-FDG or FDG-PET or ct scan* or EBCT or MDCT):TI	442
10	#5 OR #6 OR #7 OR #8 OR #9	1339
11	MeSH DESCRIPTOR predictive value of tests EXPLODE ALL TREES	723
12	MeSH DESCRIPTOR decision support techniques EXPLODE ALL TREES	1231
13	MeSH DESCRIPTOR disease progression EXPLODE ALL TREES	439
14	MeSH DESCRIPTOR early diagnosis EXPLODE ALL TREES	176
15	MeSH DESCRIPTOR likelihood functions EXPLODE ALL TREES	65
16	MeSH DESCRIPTOR odds ratio EXPLODE ALL TREES	841
17	MeSH DESCRIPTOR diagnosis, differential EXPLODE ALL TREES	171
18	MeSH DESCRIPTOR sensitivity and specificity EXPLODE ALL TREES	2947
19	MeSH DESCRIPTOR decision trees EXPLODE ALL TREES	668
20	(predict* or decision making or decision support* or likelihood ratio* or clinical utilit* or differential diagnos* or early diagno*):TI	656
21	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	5942
22	#4 AND #10 AND #21	8
23	(#22):TI FROM 2000 TO 2013	8

Appendix 2: Quality Assessment Tables

Table A1: GRADE Evidence Profile for the Prevalence and Reversibility of Dementia

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Prevalence and Reversibility of Potential Reversible Dementias							
1 (systematic review of 39 observational studies)	Serious limitations (-1)[a]	No serious limitations[b]	No serious limitations	No serious limitations	Undetected[c]	None	⊕ Very low

[a]Evidence for this outcome started as low quality as it is comprised of observational studies. All were cohort studies (10 retrospective and 29 prospective) from a variety of inpatient, outpatient and community-based settings. Only 33 of 39 studies (85%) reported the prevalence of potentially reversible dementias and 23 studies (58%) had sufficient follow-up to actually determine reversibility.

[b]Prevalence estimates ranged from 0% to 18% across studies that reported this information; however, pooled prevalence was estimated using weighted means with inverse-variance weights to minimize the variance.

[c]The possibility of publication bias cannot be ruled out. English language was an inclusion criterion, though there is representation from 17 different countries and this evidence is comprised of both large and small studies.

Table A2: GRADE Evidence Profile for Clinical Indications for Neuroimaging in Dementia Diagnosis

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Diagnostic Accuracy of Clinical Prediction Rules - FN (patients without clinical indications but abnormal scans)							
4 studies (1 systematic review of 7 accuracy studies, 3 accuracy)	Serious limitations (-1)[a]	Serious limitations (-1)[b]	Serious limitations (-1)[c]	Serious limitations (-1)[d]	Undetected[e]	None	⊕ Very Low
Diagnostic Accuracy of Clinical Prediction Rules - FP (patients with clinical indication but normal scans)							
4 studies (1 systematic review of 7 accuracy studies, 3 accuracy)	Serious limitations (-1)[a]	Serious limitations (-1)[b]	Serious limitations (-1)[c]	Serious limitations (-1)[d]	Undetected[e]	None	⊕ Very Low
Diagnostic Accuracy of Clinical Prediction Rules -TP (patients with clinical indications and abnormal scans)							
4 studies (1 systematic review of 7 accuracy studies, 3 accuracy)	Serious limitations (-1)[a]	Serious limitations (-1)[b]	Serious limitations (-1)[c]	Serious limitations (-1)[d]	Undetected[e]	None	⊕ Very Low
Diagnostic Accuracy of Clinical Prediction Rules -TN (patients without clinical indications and normal scans)							
4 studies (1 systematic review of 7 accuracy studies, 3 accuracy)	Serious limitations (-1)[a]	Serious limitations (-1)[b]	Serious limitations (-1)[c]	Serious limitations (-1)[d]	Undetected[e]	None	⊕ Very Low

Abbreviations: FN, false negative; FP, false positive; TN, true negative; TP, true positive.

[a]Evidence for this outcome started as high quality due to study design features. See Table A7 for Risk of Bias assessment.

[b]Inconsistency between accuracy estimates was an issue and prohibited the systematic review from performing meta-analysis. There were large difference in point estimates of sensitivity, specificity, and false negative rates between studies even for the same prediction rule.

[c]Diagnostic accuracy is a surrogate for patient-important outcomes. The samples studied are similar to those presenting to tertiary care centres, however there was no data from primary care.

[d]Confidence intervals for sensitivity and specificity were very wide in all studies and spanned the entire range of possible values depending on the prediction rule and population it was applied to, which may influence the conclusions and recommendations pertaining to the use of the prediction rules.

[e]The possibility of publication bias cannot be ruled out, however, sample sizes were generally moderate in size (i.e., n >100 patients) with the exception of 1, (39) and of the 6 studies reporting funding sources, all were reported to be supported by research grants.

Table A3: GRADE Evidence Profile for Clinical Utility of Neuroimaging in Dementia Diagnosis

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Change of Diagnosis							
4 (accuracy)	Serious limitations (-1)[a]	Serious limitations (-1)[b]	Serious limitations (-1)[c]	No serious limitations[d]	Undetected[e]	None	⊕⊕ Low
Change of Management/Treatment							
1 (accuracy)	Serious limitations (-1)[a]	No serious limitations	Serious limitations (-1)[f]	No serious limitations[g]	Undetected[h]	None	⊕⊕ Low

[a]Evidence for this outcome started as high quality due to study design features. See Table A8 for assessment of risk of bias.

[b]Estimated proportions of cases with change in diagnosis ranged from as few as 1 in 10 patients to nearly half of cases. MRI changed diagnosis in up to nearly half of cases (26–44%), (45;46) combined CT or MRI changed 26%, (47) while CT influenced 10% to 14% of diagnoses. (44)

[c]Change in diagnosis is a surrogate for patient-important outcomes as it remains unknown if or how change in diagnosis influenced treatment, patient experience, or quality of life in a meaningful way.

[d]The proportion of cases for which neuroimaging resulted in revision of clinical diagnosis was presented in 3 studies as a point estimate only; except for one study, (44) the standard deviation was narrow (e.g., 2%).

[e]The possibility of publication bias cannot be excluded, however research was funded by grants for 2 of 4 studies (45;46) and sample sizes ranged from 60 to 150 which is large for diagnostic studies.

[f]Change in treatment is a surrogate for patient-important outcomes as it remains unknown if or how change in treatment influences patient experience or quality of life in a meaningful way.

[g]The standard deviation of the proportion of cases in which management was changed due to radiological information was very narrow (e.g., 2%).

[h]The possibility of publication bias cannot be ruled out; however, no conflicts of interest or funding source were disclosed.

Table A4: GRADE Evidence Profile for Comparative Accuracy of MRI vs. CT for Detection of a Vascular Component to Dementia

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Comparative Accuracy of MRI Versus CT							
1 (systematic review of 38 accuracy studies)	Very serious limitations (-2)[a]	Serious limitations (-1)[b]	Serious limitations (-1)[c]	Serious limitations (-1)[d]	Undetected[e]	NA	⊕ Very low

Abbreviations: CT, computed tomography; DOR, diagnostic odds ratio; MRI, magnetic resonance imaging; NA, not available; RDOR, ratio of diagnostic odds ratios; vs., versus.

[a]Evidence for this outcome started at low quality due to study design limitations. See Table A9 for assessment of risk of bias.

[b]Studies showed very heterogeneous results; significant unexplained heterogeneity; large differences in point estimates; and lack of consistency in sensitivity, specificity, and positive and negative likelihood ratios. Results of nonautopsy studies could not be meta-analyzed due to significant heterogeneity.

[c]Diagnostic accuracy is a surrogate for patient-important outcomes. In most studies (25 of 38; 65.8%) there were no important differences between the populations studied and those that recommendations would apply to; all studies provided a direct comparison to an appropriate reference standard, though the standard varied across studies; there was no indication that the level of diagnostic expertise applied in the studies differed significantly from expertise in practice.

[d]Confidence intervals (CIs) for summary estimates from the meta-analysis were variable and some very wide, as were the CIs around DORs and RDORs for CT and MRI for specific brain areas assessed.

[e]The possibility of publication bias cannot be ruled out. Authors did not formally assess publication bias; however, no language or publication status restrictions were applied to the search strategy, articles in foreign languages were translated, and raw data were obtained to facilitate inclusion.

Table A5: GRADE Evidence Profile for Diagnostic Accuracy of Neuroimaging in Dementia Diagnosis

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Diagnostic Accuracy of CT for Differential Diagnosis of Alzheimer Disease							
6 (accuracy)	Serious limitations (-1)[a]	Serious limitations (-1)[b]	Serious limitations (-1)[c]	Serious limitations (-1)[d]	Undetected[e]	None	⊕ Very low
Diagnostic Accuracy of MRI for Differential Diagnosis of Alzheimer Disease							
28 (accuracy; 26 from 1 systematic review, 2 from another)	Serious limitations (-1)[f]	Serious limitations (-1)[g]	No serious limitations[h]	Serious limitations (-1)[i]	Undetected[j]	None	⊕ Very low
Diagnostic Accuracy of MRI for Differential Diagnosis of Creutzfeldt-Jakob Disease							
2 (accuracy)	Serious limitations (-1)[k]	No serious limitations[l]	Serious limitations (-1)[m]	No serious limitations[n]	Undetected[o]	None	⊕⊕ Low
Diagnostic Accuracy of MRI for Differential Diagnosis of Clinically Ambiguous Dementias							
1 (accuracy)	Serious limitations (-1)[p]	No serious limitations	Serious limitations (-1)[q]	Serious limitations (-1)[r]	Undetected[s]	None	⊕ Very low

Abbreviations: AD, Alzheimer disease; AUC, area under the curve; CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging.

[a]Evidence for this outcome started at low quality due to study design limitations. See Table A10 for assessment of risk of bias.

[b]A mixed-effects binary regression model was used to account for the correlation between sensitivity and specificity, yet significant unexplained heterogeneity remained in sensitivity (I^2 = 89.2%) and specificity (I^2 = 58.5%). Cochran's Q statistic for homogeneity was statistically significant for both estimates (P < 0.01, P = 0.03, respectively); subgroup analysis to explore heterogeneity also had significant heterogeneity (I^2 ≈ 87%–90%).

[c]Diagnostic accuracy is a surrogate for patient-important outcomes.

[d]The rate of false positives and false negatives varied from as many as 1 in 5 to approximately 1 in 10, which may influence the conclusions and recommendations pertaining to the use of the prediction rules.

[e]The possibility of publication bias cannot be ruled out. Although all studies received some or all funding from research organizations, foundations, or grants, 2 (63;64) had co-funding support from industry.

[f]Evidence for this outcome started at low quality due to study design limitations. See Table A11 for assessment of risk of bias.

[g]A mixed-effects binary regression model was used to account for the correlation between sensitivity and specificity, yet significant unexplained heterogeneity in sensitivity (I^2 = 64.3%) and specificity (I^2 = 84.2%). Cochran's Q statistic for homogeneity was statistically significant for both estimates (P < 0.01 for all); subgroup analysis to explore heterogeneity also had statistically significant heterogeneity (I^2 ≈ 87%–90%).

[h]Only 2 studies (65;66) excluded patients with evidence of vascular changes which may not reflect the reality of patients to whom the diagnostic test will be applied; however, most studies included tertiary and some community-dwelling patients and employed widely available MRI sequences and interpretation methods (e.g., radiologist or neuroradiologist reports).

[i]The confidence intervals around the summary estimates were within 10%, though confidence intervals for individual sensitivity estimates spanned 20%–50%, and for specificity most intervals varied across a span of approximately 30%.

[j]The possibility of publication bias cannot be ruled out; however, there was no indication of industry sponsorship, sample sizes included both small and large studies, and most studies received some or all funding from independent grants or research organizations, although source of support was not stated for 4 studies (66-70).

[k]Evidence for this outcome started at high quality due to study design features. See Table A12 for assessment of risk of bias.

[l]Meta-analysis revealed heterogeneity in estimates of sensitivity (I^2 = 46.9%, p = 0.1698) and specificity (I^2 = 47.3%, p = 0.1685) that was not statistically significant.

[m]Diagnostic accuracy is a surrogate for patient-important outcomes. Demographics of patients were only reported in one study (54).

[n]Confidence intervals for point estimates of sensitivity and specificity were relatively narrow, and varied across approximately 10% to 15%.

[o]Both studies were funded by national grants and had relatively large sample sizes (i.e., ~200 participants).

[p]Evidence for this outcome started at high quality as due to study design features. See Table A13 for assessment of risk of bias.

[q]Diagnostic accuracy is a surrogate for patient-important outcomes.

[r]The 95% CI around the AUC for differentiating AD from non-AD dementias was wide and ranged from almost random chance to very useful (0.51–0.85).

[s]Support for the research was provided by a local grant and no authors declared anything in the statement of disclosure.

Table A6: Risk of Bias Among Observational Studies in a Systematic Review Estimating the Prevalence of PRCs of Dementia

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Clarfield, 2003 (32)	No limitations[a]	No limitations[b]	No limitations[b]	No limitations[c]	Limitations[d]

Abbreviation: PRC, potentially reversible cause.

[a]All were cohort studies (10 retrospective and 29 prospective) from a variety of inpatient, outpatient, and community-based settings.

[b]No indication of differential surveillance among included studies.

[c]Reported prevalence subgrouped by some known differences in prognostic factors (i.e., inpatient versus outpatient versus community-based; study design with and without follow-up; age groups; sex; severity).

[d]33 of 39 studies (84.6%) reported the prevalence of potentially reversible dementias and 23 studies (59.0%) had sufficient follow-up to determine reversibility.

Table A7: Risk of Bias Among Accuracy Studies for Indications for Neuroimaging in Dementia Diagnosis

First Author, Year	Representative Patients/Diagnostic Uncertainty	Direct Comparison to Reference Standard	Consecutive Patients	Selection/Referral Process Clearly Described	Tests on All Patients	Blind Outcome Evaluation
Condefer, 2004 (44)	No limitations	No limitations	Limitations[a]	Limitations[b]	No limitations	No limitations
Sitoh, 2006 (41)	No limitations	No limitations	Limitations[a]	No limitations	No limitations	No limitations
Condefer, 2003 (43)	No limitations	No limitations	Limitations[a]	Limitations[b]	No limitations	No limitations
Martin, 1987[c,d] (42)	No limitations	No limitations	No limitations	No limitations	No limitations	No limitations
Dietch, 1983[c,d] (35)	No limitations	No limitations	Limitations[a]	No limitations	No limitations	Limitations[e]
Larson, 1986[c,d] (37)	No limitations	No limitations	No limitations	No limitations	No limitations	Limitations[e]
Larson, 1984[c] (36)	No limitations	No limitations	No limitations	No limitations	No limitations	Limitations[e]
Bradshaw, 1983[c,d] (38)	No limitations	No limitations	No limitations	No limitations	No limitations	Limitations[e]
Chui, 1997[c] (39)	No limitations	No limitations	No limitations	No limitations	No limitations	Limitations[e]
Freter, 1998[c] (40)	Limitations[f]	No limitations	No limitations	No limitations	No limitations	Limitations[e]

[a]The study cohort was selected from patient population rather than formed by consecutive patients.

[b]The referral process was not clearly described.

[c]Included in Gifford et al systematic review. (34)

[d]Included in Sitoh et al study. (41)

[e]One or more evaluators were not blinded to results during outcome assessment.

[f]Diagnostic uncertainty was considered to be present when patients were investigated for general cognitive complaints or suspected dementia; or had not yet received a clinical assessment to determine type of dementia; and/or had not yet been diagnosed as having a particular dementia type. Previously diagnosed patients and/or normal controls were recruited for comparison.

Table A8: Risk of Bias Among Accuracy Studies for Clinical Utility of Neuroimaging in Dementia Diagnosis

First Author, Year	Representative Patients/Diagnostic Uncertainty	Direct Comparison to Reference Standard	Consecutive Patients	Selection/Referral Process Clearly Described	Tests on All Patients	Blind Outcome Evaluation
Hentschel, 2005 (45)	No limitations[a]	No limitations	No limitations	No limitations	No limitations	Limitations[b]
Condefer, 2004 (44)	No limitations[a]	No limitations	Limitations[c]	Limitations[d]	No limitations	No limitations
Jani 2000, (46)	No limitations[a]	No limitations	No limitations	No limitations	No limitations	No limitations
Massoud, 2000 (47)	No limitations[a]	No limitations	No limitations	Limitations[d]	No limitations	Limitations[b]

[a]Diagnostic uncertainty was considered to be present when patients were investigated for general cognitive complaints or suspected dementia; or had not yet received a clinical assessment to determine type of dementia; and/or had not yet been diagnosed as having a particular dementia type.

[b]One or more evaluators were not blinded to results during outcome assessment.

[c]The study cohort was selected from patient population rather than formed by consecutive patients.

[d]The referral process was not clearly described.

Table A9: Risk of Bias Among Accuracy Studies for Comparative Accuracy of MRI Versus CT

First Author, Year	Representative Patients/Diagnostic Uncertainty	Direct Comparison to Reference Standard	Consecutive Patients	Selection/Referral Process Clearly Described	Tests on All Patients	Blind Outcome Evaluation
Barclay, 1992 (71)	No limitations[a]	No limitations	No limitations	Limitations[b]	No limitations	No limitations
Del Ser, 2005 (72)	Limitations[a]	No limitations	No limitations	Limitations[b]	No limitations	Limitations[c]
Ettlin, 1989 (73)	Limitations[a]	No limitations	Limitations[d]	No limitations	No limitations	No limitations
Erkinjuntti, 1988 (74)	No limitations	No limitations	No limitations	Limitations[b]	No limitations	No limitations
Kondo, 1995[e] (75)	No limitations	No limitations	No limitations	Limitations[b]	No limitations	Limitations[c]
Meguro, 1994[e] (76)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	Limitations[f]	Limitations[c]
Crum, 2003 (77)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	No limitations	No limitations
Amar, 1995 (78)	No limitations	No limitations	Limitations[d]	Limitations[b]	No limitations	No limitations
Barber, 1999 (79)	Limitations[a]	No limitations	Limitations[d]	No limitations	No limitations	No limitations
Charletta, 1995 (80)	Limitations[a]	No limitations	No limitations	Limitations[b]	Limitations[f]	No limitations
Chen, 1992[e] (81)	No limitations	No limitations	No limitations	Limitations[b]	No limitations	Limitations[c]
Engel, 1992 (82)	No limitations	No limitations	No limitations	Limitations[b]	No limitations	Limitations[c]
Erkinjuntti, 1987a (83)	No limitations	No limitations	No limitations	Limitations[b]	No limitations	No limitations
Erkinjuntti, 1987b (84)	No limitations	No limitations	No limitations	Limitations[b]	No limitations	No limitations
Frisoni, 1995 (85)	No limitations	No limitations	No limitations	Limitations[b]	Limitations[f]	No limitations
Hagiwara, 1990[e] (86)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	Limitations[f]	No limitations
Kertesz, 1990 (87)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	No limitations	No limitations
Nagga, 2004 (88)	No limitations	No limitations	No limitations	Limitations[b]	No limitations	No limitations
Purandare, 2008 (89)	Limitations[a]	No limitations	Limitations[d]	No limitations	No limitations	No limitations
Scheltens, 2000 (90)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	No limitations	No limitations
Schroder, 1989[e] (91)	No limitations	No limitations	No limitations	Limitations[b]	No limitations	Limitations[c]
Skoog, 1994 (92)	No limitations	No limitations	Limitations[d]	No limitations	Limitations[f]	No limitations
Staekenborg, 2009 (93)	No limitations	No limitations	No limitations	Limitations[b]	No limitations	Limitations[c]
Steingart, 1987 (94)	No limitations	No limitations	Limitations[d]	No limitations	No limitations	No limitations
Wahlund, 1994 (95)	No limitations	No limitations	No limitations	Limitations[b]	No limitations	No limitations
Wallin, 1989 (96)	No limitations	No limitations	No limitations	Limitations[b]	No limitations	Limitations[c]

First Author, Year	Representative Patients/Diagnostic Uncertainty	Direct Comparison to Reference Standard	Consecutive Patients	Selection/Referral Process Clearly Described	Tests on All Patients	Blind Outcome Evaluation
Zimny, 2007 (97)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	No limitations	Limitations[c]
Aharon-Peretz, 1988 (98)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	No limitations	No limitations
Butler, 1995 (99)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	No limitations	No limitations
Du, 2005 (100)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	No limitations	Limitations[c]
Ebmeier, 1987 (101)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	No limitations	Limitations[c]
Endo, 1989[g] (102)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	Limitations[f]	Limitations[c]
Kobari, 1990(a) (103)	Limitations[a]	No limitations	Limitations[d]	No limitations	No limitations	No limitations
Kobari, 1990(b)[e] (104)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	Limitations[f]	Limitations[c]
Lechner, 1991[e] (105)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	Limitations[f]	Limitations[c]
London, 1986 (106)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	Limitations[e]	No limitations
Patankar, 2005 (107)	Limitations[a]	No limitations	Limitations[d]	No limitations	No limitations	No limitations
Schmidt, 1992[e] (108)	Limitations[a]	No limitations	Limitations[d]	Limitations[b]	No limitations	Limitations[c]

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

[a]Diagnostic uncertainty was considered to be present when patients were investigated for general cognitive complaints or suspected dementia; or had not yet received a clinical assessment to determine type of dementia; and/or had not yet been diagnosed as having a particular dementia type. Previously diagnosed patients and/or normal controls were recruited for comparison.

[b]The selection and/or referral process was not clearly described.

[c]One or more evaluators were not blinded to results during outcome assessment.

[d]The study sample was selected from patient population rather than formed by consecutive patients.

[e]Abstract only available; assessed based on information within abstract.

[f]Both the new and reference test were not performed on all patients in the sample population, and/or it was unclear if these criteria were met.

[g]No abstract or article available; assessed based on information in systematic review only.

Table A10: Risk of Bias Among Accuracy Studies of CT for Diagnosing Alzheimer Disease

First Author, Year	Representative Patients/Diagnostic Uncertainty	Direct Comparison to Reference Standard	Consecutive Patients	Selection/Referral Process Clearly Described	Tests on All Patients	Blind Outcome Evaluation
Jobst, 1998[a] (63)	Limitations[b]	No limitations	Limitations[c]	No limitations	No limitations	No limitations
Rossi, 2004[a] (64)	Limitations[b]	No limitations	No limitations	Limitations[d]	No limitations	No limitations
Frisoni, 2002[a] (109)	No limitations	No limitations	No limitations	No limitations	No limitations	No limitations
Pasquier, 1997[a] (110)	No limitations	No limitations	No limitations	Limitations[d]	No limitations	No limitations
O'Brien, 2000[a,e] (20)	No limitations	No limitations	No limitations	No limitations	No limitations	No limitations
Denihan, 2000[a,e] (111)	Limitations[b]	No limitations	Limitations[c]	Limitations[d]	No limitations	No limitations

Abbreviations: CT, computed tomography.

[a]Included in Bloudek et al systematic review. (51)

[b]Diagnostic uncertainty was considered to be present when patients were investigated for general cognitive complaints or suspected dementia; or had not yet received a clinical assessment to determine type of dementia; and/or had not yet been diagnosed as having a particular dementia type. Previously diagnosed patients and/or normal controls were recruited for comparison.

[c]The study sample was selected from patient population rather than formed by consecutive patients.

[d]The referral process was not clearly described.

[e]Included in Wollman and Pohovnik systematic review. (53)

Table A11: Risk of Bias Among Accuracy Studies of MRI for Diagnosing Alzheimer Disease

First Author, Year	Representative Patients/Diagnostic Uncertainty	Direct Comparison to Reference Standard	Consecutive Patients	Selection/Referral Process Clearly Described	Tests on All Patients	Blind Outcome Evaluation
Killiany, 2000[a] (112)	Limitations[b]	No limitations	Limitations[c]	Limitations[d]	No limitations	No limitations
Erkinjuntti, 1993[a] (113)	No limitations	No limitations	Limitations[c]	No limitations	No limitations	No limitations
Scheltens, 1997[a] (114)	Limitations[b]	No limitations	Limitations[c]	No limitations	No limitations	No limitations
O'Brien, 2001[a] (115)	Limitations[b]	No limitations	Limitations[c]	Limitations[d]	No limitations	No limitations
Frisoni, 1996[a] (116)	Limitations[b]	No limitations	No limitations	Limitations[d]	No limitations	No limitations
Vemuri, 2009[a] (117)	Limitations[b]	No limitations	Limitations[c]	Limitations[d]	No limitations	No limitations
Duara, 2008[a] (118)	Limitations[b]	No limitations	Limitations[c]	Limitations[d]	Limitations[e]	Limitations[f]
Hanyu, 2001[a] (66)	Limitations[b]	No limitations	Limitations[c]	Limitations[d]	No limitations	No limitations
Frisoni, 2002[a] (109)	Limitations[b]	No limitations	No limitations	Limitations[d]	No limitations	No limitations
Matsunari, 2007[a] (119)	Limitations[b]	No limitations	Limitations[c]	Limitations[d]	No limitations	Limitations[f]
Desmond, 1994 [a,g] (120)	Limitations[b]	No limitations	Limitations[c]	Limitations[d]	No limitations	No limitations
Scheltens, 1992[a] (69)	Limitations[b]	No limitations	Limitations[c]	Limitations[d]	No limitations	No limitations
McEvoy, 2009[a] (121)	Limitations[b]	No limitations	Limitations[c]	Limitations[d]	No limitations	No limitations
Barkhof, 2007[a] (122)	No limitations	No limitations	Limitations[c]	Limitations[d]	No limitations	No limitations
Laakso, 1998[a] (123)	Limitations[b]	No limitations	Limitations[c]	Limitations[d]	No limitations	No limitations
Bottino, 2002[a] (65)	No limitations	No limitations	No limitations	Limitations[d]	No limitations	No limitations
Colliot, 2008[a] (67)	Limitations[b]	No limitations	No limitations	Limitations[d]	No limitations	No limitations
Brys, 2009[a] (124)	No limitations	No limitations	No limitations	Limitations[d]	No limitations	No limitations
Burton, 2009[a] (125)	Limitations[b]	No limitations	Limitations[c]	No limitations	No limitations	No limitations
O'Brien, 1997[a] (126)	Limitations[b]	No limitations	Limitations[c]	Limitations[d]	No limitations	No limitations
Pucci, 1998[a,g] (127)	Limitations[b]	No limitations	No limitations	Limitations[d]	No limitations	No limitations
Varma, 2002[a] (70)	No limitations	No limitations	No limitations	Limitations[d]	No limitations	No limitations
Frisoni, 2009[a] (128)	No limitations	No limitations	Limitations[c]	No limitations	Limitations[e]	Limitations[f]
Hanyu, 2005[a] (68)	Limitations[b]	No limitations	Limitations[c]	Limitations[d]	No limitations	No limitations
Wang, 2004[a] (129)	Limitations[b]	No limitations	No limitations	Limitations[d]	Limitations[e]	Limitations[f]
Juottonen, 1999[h] (130)	Limitations[b]	Limitations[i]	Limitations[c]	Limitations[d]	No limitations	No limitations

First Author, Year	Representative Patients/Diagnostic Uncertainty	Direct Comparison to Reference Standard	Consecutive Patients	Selection/Referral Process Clearly Described	Tests on All Patients	Blind Outcome Evaluation
Golebiowki, 1999[a,h] (131)	Limitations[b]	Limitations[i]	Limitations[c]	Limitations[d]	No limitations	No limitations

Abbreviations: MRI, magnetic resonance imaging.

[a]Included in Bloudek et al systematic review. (51)

[b]Diagnostic uncertainty was considered to be present when patients were investigated for general cognitive complaints or suspected dementia; had not yet received a clinical assessment to determine type of dementia; and/or had not yet been diagnosed as having a particular dementia type. Previously diagnosed patients and/or normal controls were recruited for comparison.

[c]The study sample was selected from patient population rather than formed by consecutive patients.

[d]The selection and/or referral process was not clearly described.

[e]Both the new and reference test were not performed on all patients in the sample population, and/or it was unclear if these criteria were met.

[f]One or more evaluators were not blinded to results during outcome assessment and/or semi-automated outcome assessment was used and potential role of evaluator or bias was unclear.

[g]Included in Wollman and Pohovnik systematic review. (53)

[h]Abstract only available; assessed based on information within abstract.

[i]Studies compared results of new test between subgroups of patients rather than directly comparing new tests and reference standard.

Table A12: Risk of Bias Among Accuracy Studies of MRI for Diagnosing Creutzfeldt-Jakob Disease

First Author, Year	Representative Patients/Diagnostic Uncertainty	Direct Comparison to Reference Standard	Consecutive Patients	Selection/Referral Process Clearly Described	Tests on All Patients	Blind Outcome Evaluation
Tschampa, 2005 (55)	No limitations	No limitations	No limitations	No limitations	No limitations	No limitations
Schroter, 2000 (54)	Limitations[a]	No limitations	No limitations	Limitations[b]	No limitations	No limitations

Abbreviations: CJD, Creutzfeldt-Jakob disease; MRI, magnetic resonance imaging.
[a]Diagnostic uncertainty was considered to be present when patients were investigated for general cognitive complaints or suspected dementia; or had not yet received a clinical assessment to determine type of dementia; and/or had not yet been confirmed as having CJD. Patients had been diagnosed and/or normal controls were recruited for comparison.
[b]The study sample was selected from patient population into case-control design as opposed to a cohort formed by consecutive patients.

Table A13: Risk of Bias Among Accuracy Studies of MRI for Diagnosing Clinically Ambiguous Dementias

First Author, Year	Representative Patients/Diagnostic Uncertainty	Direct Comparison to Reference Standard	Consecutive Patients	Selection/Referral Process Clearly Described	Tests on All Patients	Blind Outcome Evaluation
Boutoleau-Bretonniere, 2012 (56)	No limitations[a]	No limitations	Limitations[b]	No limitations	Limitations[c]	No limitations

Abbreviations: MRI, magnetic resonance imaging.
[a]Diagnostic uncertainty was considered to be present when patients were investigated for general cognitive complaints or suspected dementia; or had not yet received a clinical assessment to determine type of dementia; and/or had not yet been diagnosed as having a particular dementia type.
[b]Unclear if the study sample was selected from patient population as opposed to formed by consecutive patients.
[c]Two different MRI sequences were used, one on all patients and another on 55 of 60 patients (91.7%) who were not lost to follow-up (9 of 69).

Table A14: AGREE II Domain Scores for Guidelines on Neuroimaging in the Evaluation of Dementia

Source, Year	AGREE II Domains					
	Scope and Purpose	Stakeholder Involvement	Rigour	Clarity	Applicability	Editorial Independence
CCCDTD4, 2012 (57)	12	8	21	15	7	9
EFNS Task Force, 2012 (58)	15	4	14	16	4	7
NICE, 2007 (59)	20	18	40	12	10	7
SIGN, 2006 (60)	12	18	43	8	11	4
AAN, 2001 (61)	15	9	29	7	4	2
Maximum Possible Score	21	21	56	21	28	14

Abbreviations: AAN, American Academy of Neurology; CCCDTD4, 4th Canadian Consensus Conference on Diagnosis and Treatment of Dementia; EFNS, European Federation of Neurological Societies; NICE, National Institute for Health and Clinical Excellence; SIGN, Scottish Intercollegiate Guidelines Network.

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ISSN 1915-7398 (online)
ISBN 978-1-4606-3643-5 (PDF)