Washington State Health Care Authority

Agency Medical Director Comments

Neuroimaging for Dementia

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Gary Franklin, MD, MPH
Medical Director, Department of Labor and Industries
Research Professor, University of Washington

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Neuroimaging for Dementia

Agency Medical Directors' Concerns

- **Safety = Medium**

- **Efficacy = Medium**

- **Cost = Medium**

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Neuroimaging for Dementia

Background

- **Dementia**
  - Alzheimer's disease (AD) is the most common type of dementia, accounting for 60-80% of cases.
  - Dementia with Lewy Bodies (DLB) and frontotemporal dementia (FTD) are much less common.

- **Mild cognitive impairment (MCI)**
  - 10-20% people over 65 have MCI.
  - About 12% of MCI patients develop AD each year.

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Neuroimaging for Dementia

Meta-analyzed Estimates of Dementia Prevalence (%)

Region	Sex	Age group (years)							
		60-64	65-69	70-74	75-79	80-84	85-89	90+	Std prevalence
USA	M	1.3	2.1	3.7	6.8	12.3	21.6	45.2	
	F	1.0	1.8	3.3	6.4	12.5	23.2	52.7	
	All	1.1	1.9	3.4	6.3	11.9	21.7	47.5	6.46

Adapted from: **Dementia: a public health priority**
http://www.who.int/mental_health/publications/dementia_report_2012/en

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Functional Neuroimaging Modalities of Interest

- **Positron emission tomography**
  - ^{18}F-FDG-PET
  - ^{11}C-DTBZ-PET

- **Single photon emission computed tomography (SPECT)**
  - HMPAO –SPECT
  - ^{123}I-FT-CIT-SPECT

- **Functional magnetic resonance imaging (fMRI)**

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Key Questions

- **What is the diagnostic accuracy of functional neuroimaging for the differential diagnosis** of AD, FTD, and Lewy body dementia (including DLB and PDD) based on an appropriate gold standard (e.g., autopsy, genetic confirmation)?

- **What is the ability of functional neuroimaging to predict progression** and clinical outcomes? Is one functional test better at predicting progression or clinical outcomes versus another?

- Do the results of functional neuroimaging impact therapeutic decisions or clinical management compared to those made for patients who did not receive functional neuroimaging?

- What are the short and long term harms of diagnostic functional neuroimaging?

- What is the evidence that functional neuroimaging may perform differently in subpopulations (i.e., younger age, presence of comorbidities, etc.)? Consider the impact on disease progression, clinical outcomes, and harms.

- What is the cost-effectiveness of incorporating diagnostic functional neuroimaging into the comprehensive initial diagnostic work-up?

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Current State Agency Policy

CPT	Description	Medicaid	UMP	DOC	LNI
70554	f**MRI**, brain, without physician	NC	PA	PA	NC
70555	f**MRI**, brain, with physician	NC	PA	PA	NC
78607	**SPECT** imaging of brain	C	PA	PA	C
78608	**PET** imaging of brain	PA	PA	PA	PA

C: Covered
NC: Not covered
PA: Prior authorization required

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Public Employee Benefits (PEBB) & Uniform Med Plan (UMP)

	2010	2011	2012	2013	4 Year Total	Avg % Chng
PEBB/UMP Average Annual Members	213,487	212,596	212,684	222,339		1.4%
Dementia Diagnosed Member Counts	1874	2038	2224	2347	5833	6.4%
Cognitive Testing Patients	684	704	767	761	2916	2.4%
Nuclear Imaging (NI) for Dementia count	15	26	21	29	91	
SPECT Scans (78607) (% Medicare)	5 (60%)	2 (50%)	3 (33.3%)	1 (0%)	11 (45.4%)	
PET Scans (78608) (% Medicare)	10 (80%)	24 (66.7%)	18 (77.8%)	28 (75.0%)	80 (73.8%)	
NI Scans Total Cost (Direct cost by code)	**$3,286**	**$7,905**	**$7,122**	**$10,647**	**$28,960**	
NI Scans Total Cost (Day of procedure related charges)	**$5,005**	**$9,264**	**$7,368**	**$10,956**	**$32,593**	

Costs are reported for non-Medicare members only

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Neuroimaging for Dementia:
State Agency Utilization

Medicaid Fee for Service (FFS) & Managed Care (MCO)

	2010	2011	2012	2013	4 Year Total	Avg % Chng
Medicaid Avg Annual Clients (FFS)	474,676	473,356	477,727	442,698		-2.2%
Medicaid Avg Annual Clients (MCO)	680,785	695,591	730,250	800,096		5.6%
Dementia Diagnosed Clients (FFS)	6200	6272	5516	5456	23,444	-1.6%
Dementia Diagnosed Clients (MCO)	1017	1101	1248	1601	4,967	10.3%
Cognitive Testing Patients (FFS + MCO)	69	58	49	72	248	8.8%
Nuclear Imaging (NI) for Dementia	**12**	**15**	**9**	**7**	**43**	
SPECT Scans (78,607)	5	5	4	2	16	
PET Scans (78,608)	**7**	**10**	**5**	**5**	**27**	
NI Scans Total Cost (Direct cost by code)	**$3,876**	**$2,814**	**$851**	**$648**	**$8,189**	
NI Scans Total Cost (Day of procedure related charges)	**$4,110**	**$3,399**	**$1,070**	**$683**	**$9,262**	

Costs are reported for Fee for Service clients only

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Neuroimaging for Dementia:
State Agency Utilization

Agency & Image Type	PEBB/UMP		Medicaid	
	PET	SPECT	PET	SPECT
Day of Service Charge Breakdowns, Allowed Amounts	Non-Medicare Allowed Amounts, n=13	Non-Medicare Allowed Amounts, n=3	FFS only, Allowed Amounts, n=25	FFS only, Allowed Amounts, n=11
by Type of Charge				
Nuclear Imaging	$2,266	$1,359	$1,212	$527
Other Imaging	$19	$590	$7	$264
Other Care/Psych Care	$76	$0	$6	$8
Radiopharmaceuticals	$56	$0	$268	$52
Other Tests	$30	$0	$0	$0
Total	**$2,447**	**$1,949**	**$1,493**	**$851**
by Facility vs Provider				
Facility	$1,989	$1,840	$237	$742
Provider	$458	$109	$1,255	$109
Total	**$2,447**	**$1,949**	**$1,493**	**$851**

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Neuroimaging for Dementia: State Agency Utilization

PEBB/UMP Nuclear Imaging for Dementia by Age/Gender, 2010-2013

	F SPECT	M SPECT	F PET	M PET
■ 80+	0	0	7	9
▥ 65-79	6	2	20	23
▤ 50-64	2	1	12	3
▣ 35-49	0	0	0	1
▢ 21-34	0	0	0	1

Medicaid Nuclear Imaging for Dementia by Age/Gender, 2010-2013

	F SPECT	M SPECT	F PET	M PET
■ 80+	2	0	2	1
▥ 65-79	1	0	3	7
▤ 50-64	5	3	8	3
▣ 35-49	0	1	1	0
▢ 21-34	1	0	0	0

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Neuroimaging for Dementia

Diagnostic Accuracy

- **FDG-PET: AD vs. FTD**
  - Diagnosis of AD with FDG-PET alone (visual assessments)
    - 94-98% sensitivity
    - 73-76% specificity
  - Combination of FDG-PET (visual classification) + clinical diagnosis
    - 90% sensitivity
    - 86% specificity
  - Clinical diagnosis alone
    - 63-100% sensitivity
    - 79-100% specificity

- **FDG-PET may not be superior to clinical diagnosis based on the limited evidence**

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Diagnostic Accuracy – Cont.

- **HMPAO-SPECT: AD vs. FTD**
  - Diagnosis of AD with HMPAO-SPECT alone (visual assessments)
    - 65% sensitivity
    - 72% specificity
  - Combination of HMPAO-SPECT + clinical diagnosis
    - 84% sensitivity
    - 84% specificity
  - Clinical diagnosis alone
    - 77% sensitivity
    - 88% specificity
- HMPAO-SPECT may not be superior to clinical diagnosis based on the limited evidence.

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Diagnostic Accuracy – Cont.

- **FDG-PET: AD vs. DLB**
  - Diagnosis of DLB with FDG-PET alone
    - 80-90% sensitivity
    - 80-100% specificity
  - Combination of FDG-PET + clinical diagnosis
    - 80-90% sensitivity
    - 80-100% specificity
  - Clinical diagnosis alone
    - No data
- There is no evidence to demonstrate that FDG-PET is superior to clinical diagnosis.

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Diagnostic Accuracy – Cont.

- **^{123}I-FP-CIT-SPECT**
  - no data

- **fMRI**
  - No data

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Prognostic Accuracy

- **Patient progression (MCI to AD/dementia conversion)**

  - **FDG-PET** (10 studies: 2 CoE I and 8 CoE III)
    - 92-100% sensitivity
    - 75-89% specificity
  - **SPECT** (3 studies: CoE III)
    - 58% sensitivity
    - 81% specificity
  - **fMRI** (1 study: CoE III)
    - 55% sensitivity
    - 73% specificity

- Moderate evidence shows PET has a reasonable accuracy to predict MCI/AD conversion. The accuracy of SPECT or fMRI is low based on insufficient evidence

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Neuroimaging for Dementia

Fundamental Problems with Studies
- MCI Progression -

- Two COE 1 studies-Drzezga et al 2005 and Fellgiebel et al 2007

- Very narrow populations, with Avg MMSE at baseline in those with + PET @ 25

- In Fellgiebel et al-3/12 (25%) with abn baseline FDG PET did not progress to dementia

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Harms of Functional Neuroimaging

- **Insufficient evidence**
- Radiation exposure concerns related to radiolabeled tracers in PET and SPECT (5.7 – 25 mSv)
    - Administered doses of ^{18}F-FDG range from 185 – 740 MBq (effective dose: 3.5 – 14.1 mSv)
    - Administered doses of Tc-99m HMPAO range from 555 – 1110 MBq (effective dose: 5.2 -10.3 mSv)
- References – an average effective dose associated with
    - A head CT: 2 mSv
    - A chest CT: 7 mSv
- Potential impact
    - The FDA estimates: an amount of 10 mSv increases the risk of death from cancer by 1 in 2,000.

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Cost Effectiveness

- Insufficient evidence. All used simulated cohorts.

- **FDG-PET** – Conflicting results
  - One cost-utility study: NOT cost-effective as an add-on modality to the clinical workup for the diagnosis of AD
  - Two cost-effectiveness studies: being cost-effective
- **SPECT**
  - Two cost-utility studies: NOT cost-effective as an add-on modality
- **DSC-MRI**
  - Two cost utility studies: NOT cost-effective as an add-on modality
- **fMRI**
  - No data

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Private Payer Examples

- Most of the major private payers do **not** cover any of the diagnostic functional neuroimaging modalities, including Aetna, Premera Blue Cross Blue Shield, with one exception.

- Cigna covers SPECT as medically necessary for Alzheimer's disease when other imaging studies are inclusive or contraindicated; however, results should be considered supportive and not diagnostic.

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Neuroimaging for Dementia

Oregon Health Evidence Review Commission
8/9/2012

- Functional neuroimaging (PET, SPECT, or fMRI) should not be covered for screening, diagnosis, or monitoring of dementia;

- In patients with mild cognitive impairment, imaging (structural and functional) should not be used to predict progression of the risk of developing dementia.

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Centers for Medicare & Medicaid Services
- FDG PET -

- April, 2003: Non-covered
- April, 2009:
  - Covers FDG-PET scans for differential diagnosis of FTD and AD under specific requirements; "An FDG PET scan is considered reasonable and necessary in patients with a recent diagnosis of dementia and documented cognitive decline of at least 6 months, who meet diagnostic criteria for both AD and FTD"

  OR

  - The use of FDG-PET in a CMS-approved practical clinical trial focused on its utility in the diagnosis or treatment of dementing neurodegenerative diseases
- Sept, 2013-Beta-amyloid PET: Coverage with evidence development

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Other Considerations

- **Impact of functional neuroimaging on diagnosis of dementia and MCI**
  - A diagnosis is generally able to be made based on an initial workup (a thorough history, detailed cognitive testing, and neurological examination) and structural neuroimaging.
  - Functional neuroimaging is typically not used to diagnose MCI

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Other Considerations

- **Impact of functional neuroimaging on management and treatment of dementia**
  - The addition of functional neuroimaging to structural neuroimaging would not change management and treatment for the majority of patients with typical dementia phenotypes, particularly classic AD
  - For someone with atypical features (younger onset, rapid progression, and symptoms that straddle multiple diagnoses), clarification of AD versus FTD may be helpful in both treatment and counseling/prognosis

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State Agency Recommendation

- **Functional neuroimaging not covered for differential diagnosis or progression of dementia or MCI**

  OR

- **Covered with conditions:**
  - Cover FDG-PET only for differential diagnosis of AD and FTD when clinical diagnosis and structural neuroimaging are inconclusive (use CMS criteria);all other uses for differential dx or progression not covered
  - SPECT and fMRI not covered for any indications related to diagnosis or prognosis in dementia and MCI

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Questions?

More Information:

http://www.hca.wa.gov/hta/Documents/neuro_draft_report_10 2014.pdf

Gary Franklin, MD, MPH
fral235@lni.wa.gov

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Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment

Clinical Expert

Lisa C. Silbert, MD, MCR

Director, Dementia Clinic, Portland Veteran's Affairs Medical Center

Associate Professor of Neurology, Oregon Health & Science University

Director of the Neuroimaging Lab, NIH/NIA Layton Aging & Alzheimer's Disease Center, Oregon Health & Science University

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		✓
2.	Equity interests such as stocks, stock options or other ownership interests.		✓
3.	Status or position as an officer, board member, trustee, owner.		✓
4.	Loan or intellectual property rights.		✓
5.	Research funding.	✓	
6.	Any other relationship, including travel arrangements.		✓

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

_____NIH_____

_____

_____

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	✓	

If yes to #7, provide name and funding Sources: _I am Associate Professor at_
Oregon Health & Science University and Staff Neurologist
at the Portland VA Medical Center. I have research funding
through the NIH.

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X ▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇   LISA SILBERT
    Signature   Date   Print Name

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

CURRICULUM VITAE
OREGON HEALTH & SCIENCE UNIVERSITY

NAME   Lisa C. Silbert, MD, MCR   **DATE**   **04/04/2014**

PRESENT POSITION AND ADDRESS

Academic Rank: **Associate Professor**

Department/Division: **Neurology**

Professional Address: **3181 SW Sam Jackson Park Road, CR-131, Portland, OR 97239**

E-Mail Address: **silbertl@ohsu.edu**

I. BIOGRAPHICAL

Birthdate*:

Marital Status/
Children*:   **Married/1 child**

Home Address*:   **704 SE 29th Ave, Portland, OR 97214**

II. EDUCATION

Undergraduate and Graduate (Include Year, Degree, and Institution):

1992-1996	Indiana University School of Medicine, Indianapolis, Indiana. Medical Degree.
1987-1992	University of California, Los Angeles, Bachelor of Science in Psychobiology.
1991-1992	Certified Emergency Medical Technician: successfully completed a 10-week course in pre-hospital care and emergency medicine, UCLA

Postgraduate (Include Year, Degree, and Institution):

2005-2006	Masters of Clinical Research (M.C.R.), OHSU.
2001-2003	Certificate in Human Investigations, an NIH funded program for clinical investigators, OHSU
2000-2003	Aging and Alzheimer's Fellowship: Oregon Health & Science University and Portland Veteran's Administration Hospital, Portland, Oregon.
2000-2002	Neurophysiology Fellowship: Oregon Health & Science University,

Portland, Oregon. (Board eligible)
1997-2000   Neurology Residency: University of California, Los Angeles Medical Center, Los Angeles, California.
1996-1997   Transitional Internship: Methodist Hospital/Indiana University, Indianapolis, Indiana.

Certification (Include Board, Number, Date, and Recertification):

2002-present   Diplomat, American Board of Psychiatry and Neurology
2000-present   American Heart Association basic life support training

Licenses (Include State, Date, Status, Number, and Renewal Date):

2000-present   Medical License, State of Oregon
2002-2006   Medical License, Guam Board of Medical Examiners
1997-2005   Medical License, State of California.

III. PROFESSIONAL EXPERIENCE

Academic (Include Year, Position, and Institution):

2014-present   Director, Dementia Clinic, Portland Veteran's Affairs Medical Center, Portland, Oregon
2012-present   Associate Professor of Neurology, Oregon Health & Science University
2010-present   Director of the Neuroimaging Lab, NIH/NIA Layton Aging and Alzheimer's Disease Center, Oregon Health & Science University.
2009-present   Consulting Staff, Shriners Hospital for Children, Portland, Oregon.
2000-present   Staff Neurologist, Portland Veteran's Affairs Medical Center, Portland, Oregon.
2002-2012   Assistant Professor of Neurology, Oregon Health & Science University
2002-2005   Consulting Neurologist, University of California, San Diego-University of Guam Lytico-Bodig Research Consortium, Mangilao, Guam.
2000-2002   Senior Instructor of Neurology, Oregon Health & Science University.
May, 2000   Visiting Research Assistant: National Hospital for Neurology and Neurosurgery, Queen Square, London.
1991-1992   Research Assistant to Dr. Jackson Beatty, a behavioral neuroscientist in the psychology department at the University of California, Los Angeles. Involved in research project examining the diagnosis of Alzheimer's disease from T2-weighted images

obtained from Magnetic Resonance Imaging, University of California, Los Angeles.

Administrative (Include Year, Position, and Institution):

2013-present	Career Mentor to junior faculty
2005-2012	Faculty preceptor to Neurology resident. Meets quarterly with resident and semiannually with the residency advisory committee.
2007-present	Faculty interviews with residency candidates (2-3 per year)

Professional Associations

2013-present	Fellow of the American Academy of Neurology (FAAN)
2008-present	International Society to Advance Alzheimer Research and Treatment (ISTAART)
2001-present	American Academy of Neurology Geriatric Neurology section, member.
2001-present	American Academy of Neurology Clinical Neurophysiology section, member.
1999-present	American Academy of Neurology, member.
2003-2004	American Association of Electrodiagnostic Medicine, member

IV. SCHOLARSHIP

Area(s) of Research/Scholarly Interest: My research interests include the effects of subcortical white matter disease on age-related cognitive and motor slowing. I am currently interested in MRI markers of aging and dementia, with a focus on the detection of macro and microvascular changes within the white matter of elderly subjects. In addition, one of my primary research focuses is to establish the relationship between matter change and cognitive and motor function and cerebral perfusion, as determined by arterial spin labeling (ASL).

Grants and Contracts:

Federal (Include Title, Source, PI, Amount Period, and % Effort)

Ongoing Research:

R01 AG036772   Silbert (PI)   03/01/11 – 02/29/16   4.8 calendar
NIH/NIA $205,000
Subcortical Vascular Cognitive Impairment – A Longitudinal Perfusion Imaging Study
Major Goals: This longitudinal study proposes to use high-field MRI measures of perfusion and white matter integrity to determine the mechanisms behind WMH-related cognitive and motor impairment and determine MRI biomarkers to help identify those at risk for cognitive and motor

decline

P30 AG008017   Kaye (PI)   04/01/05-03/31/15   1.8 calendar
"Oregon Alzheimer's Disease Center" $817,392
NIH/NIA
The major goals of this project are to facilitate research in Alzheimer's disease by providing the core resources for clinical and basic research. Six cores (Administrative, Data, Clinical, Genetic, Neuropathology and Education) provide well-characterized subjects and standardized patient and family data, tissue and biological samples for use in a wide range of research projects.
Role: Clinical Core Neurologist; (04/01/08-03/31/09)

P50 NS062684   Montine/Quinn (PI)   2010-2015   1.2 calendar
Pacific Northwest UDALL Center $89,752
NIH/NINDS
The Pacific Northwest Udall Center (PANUC) of Excellence in Parkinson's Disease is a collaborative effort among physicians and scientists at the University of Washington and Oregon Health & Sciences University to investigate cognitive impairment and dementia in Parkinson's disease. Core functions are highly patient-oriented with the goals of clinical service, improving diagnostic tools, and expanding opportunities to participate in clinical research.
Role: Co-Investigator

NIH/NIA R01 – AG043398   Bowman/Shinto (Co-PIs)   09/2013 – 06/2018   1.2 calendar
Omega 3 PUFA for the vascular component of age–related cognitive decline
A phase II randomized and double masked, placebo controlled trial to examine the effects of a supplement on brain structure and function in non-demented older adults at high risk for dementia over 3-years.
Role: Co-Investigator; responsible for MRI analysis of primary outcomes of vascular disease burden.
Total costs: $2,892,505

Completed Research:

   2008-2009   Principal Investigator   0.04 FTE
                 In Vivo diagnosis of Alzheimer's disease using non-invasive high-field magnetic resonance imaging
                 NIH/NIA P30 AG008017 19
                 Start date 4/1/08
                 $30,000

     2004-2009   Principal Investigator   0.85 FTE
                   White Matter Change and CNS Processing in the Elderly
                    Paul B. Beeson Career Development Award in Aging
                 Research Program;
                 NIH K23 AG24826-01
                 Start date: 7/15/04

$839,627

2003-2004   Principal Investigator   0.20 FTE
Altered cortical excitability and CNS processing in the elderly with MRI subcortical white matter signal change.
OHSU General Clinical Research Center
Clinical Research Enhancement Funds Program (CREF)
$20,000

2001-2005   Clinical Consultant   0.02 FTE (PI: Galasko)
Neuroimaging of Aging and Neurodengerative Diseases on Guam
R01 AG143821

State and Local (Include Title, Source, PI, Amount Period, and % Effort)

Ongoing Research:

2014   Principal Investigator   0 FTE   (PI: Silbert)
Innovation Fund Pilot Program
Post-mortem high field imaging of the aging brain for the detection of cerebrovascular injury
Start date: 3/4/14
OHSU School of Medicine
$5,000

Completed Research:

2002-2004   Principal Investigator   .20 FTE
Effects of White Matter change on Cognitive Processing in elderly at highest risk for dementia
Alzheimer's Association
$25,000

Other Support (Include Title, Source, PI, Amount Period, and % Effort)

Ongoing Research:

Storms Family Foundation   Shinto (PI) 03/01/13-02/28/15no associated calendar mo. Lipoic acid and Omega-3 Fatty Acids in Markers of Dementia Risk $64, 000
The goal of this pilot study is to evaluate the effects of lipoic acid combined with omega-3 fatty acids (EPA and DHA) on risk factors for dementia in elderly with hypertension (treated for hypertension). Double-blind, placebo controlled trial with a 1 year treatment period. The primary outcome will be change in executive function over 1 year. Secondary outcomes include change in MRI measures of vascular integrity (white matter hyperintensities, cerebral blood flow).

Role: Co-Investigator

Completed Research:

       1/11 - 6/11   Principal Investigator
          MRI studies on Aging and Alzheimer's disease
          T&J Meyer Family Foundation
          $65,000 unrestricted donation

       1/10 - 12/10 Principal Investigator
          MRI studies on Aging and Alzheimer's disease
          T&J Meyer Family Foundation
          $100,000 unrestricted donation

      1/09-12/10   Principal Investigator
          MRI studies on Aging and Alzheimer's disease
          Max Millis Fund for Neurological Research
          $15,000 unrestricted donation

      1/09-12/10   Principal Investigator
          MRI studies on Aging and Alzheimer's disease
          Storms Family Fund at the Oregon Community Foundation
          $10,000 unrestricted donation

        2004-2005   Principal Investigator   .80 FTE
                 Cortical Excitability and CNS Processing Efficiency in Elderly with
                 Subcortical White Matter Change
                     American Academy of Neurology Foundation
                     Clinical Research Training Fellowship
                     $50,000/yr salary support + $7,000 education
                     Due to acceptance of NIH K grant, could accept funding from
              7/1/04 – 7/15/04
                     $1,923.08

<u>Clinical Trials (2004 - present):</u> I serve as Co-Investigator on numerous clinical trials through the NIH/NIA Layton Aging and Alzheimer's disease Center. As Co-Investigator, my activities have ranged from recruiting and consenting subjects, to performing neurological exams and obtaining more critical components such as primary study outcomes measurements of cognitive and functional abilities.

ACTIVE CLINICAL TRIALS

Randomized, double-blind, parallel-group, placebo-controlled fixed dose study of Lu AE58054 in patients with mild-moderate Alzheimer's disease treated with donepezil
Role: Co-Investigator
Sponsor: Lundbeck LLC

A Seamless Phase IIa/IIb, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial to Evaluate the Efficacy and Safety of MK-7622 as an Adjunctive Therapy to Donepezil for Symptomatic Treatment in Subjects with Alzheimer's Disease. MK-7622-012
Role: Co-Investigator
Sponsor: Merck Sharp & Dohme Corp

Protocol H8A-MC-LZAZ(a)/ASC-040-A4 Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4 Study). 2013
Role: Co-Investigator
Sponsor: Eli Lilly and Company/NIH

Therapeutic effects of intranasally-administered insulin in adults with amnestic mild cognitive impairment (aMCI) or mild Alzheimers disease (AD), ADC-046-INI. 2013
Role: Co-Investigator
Sponsor: NIH

Pilot Study: Lipoic Acid and Omega-3 Fatty Acid for Alzheimer's Disease Prevention 2014
Role: Co-Investigator. 2013
Sponsor: OHSU Foundation

A Pacebo-controlled, double-blind, parallel-group, Bayesian adaptive randomization design and dose regimen-finding study to evaluate safety, tolerability and efficacy of BAN2401 in subjects with early Alzheimer's Disase. BAN2401-G000-201.
Role: Co-Investigator. 2011
Sponsor: Eisai Inc.

OTHER ACTIVE RESEARCH STUDIES

Pacific Northwest UDALL Center (PANUC): Clinical Core and Sample Collection (2011)
Role: Co-Investigator; evaluate and examine Parkinson's subjects
Sponsor: NIH

Diffusion Tensor Imaging in Parkinson's Disease: (2013)
Role: Co-Investigator; assistance in DTI processing through the ADC neuroimaging lab
Sponsor: Unfunded

Markers of Alzheimer's Disease in saliva and urine. (2004)
Role: Co-Investigator
Sponsor: None

COMPLETED CLINICAL TRIALS

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center, Biomarker, Safety, and Pharmacokinetic Study of Bapineuzumab (AAB-001) Administered Subcutaneously at Monthly Intervals in Subjects with Mild to Moderate Alzheimer's Disease (2011)
Role: Co-Investgator
Sponsor: Janssen

A Phase 3 Extension, Multicenter, Double-Blind, Long Term Safety and Tolerability Treatment Trial of Bapineuzumab (AAB-001, ELN115727) in Subjects with Alzheimer's Disease who Participated in Study ELN115727-301 or in Study ELN115727-30 (2009).
Role: Co-Investigator
Sponsor: Janssen

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, Pharmocodynamic and Pharmacokinetic Effects of BMS-708163 in the Treatment of Patients with Prodromal Alzheimer's Disease (2009).
Role: Co-Investigator
Sponsor: Bristol-Myers Squibb

A Randomized, Double-Blind, Placebo-Controlled, Two Dose-Arm, Parallel Study of the Safety and Effectiveness of Immune Globulin Intravenous (Human), 10% (IGIV, 10%) for the Treatment of Mild to Moderate Alzheimer's Disease (2008).
Role: Co-Investigator
Sponsor: Baxter, NIH/NIA ADCS

A Double-Blind, Placebo-Controlled, Randomized, Multicenter Study Evaluating The Efficacy and Safety of Eighteen Months of Treatment With PF-04494700 (TTP488) in Participants With Mild-to-Moderate Alzheimer's Disease (2007).
Role: Co-Investigator
Sponsor: Pfizer, NIH/NIA ADCS

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Efficacy and Safety Trial of Bapineuzumab (AAB-001, ELN115727) in Subjects with Mild to Moderate Alzheimer's Disease who are Apolipoprotein E4 Non-Carriers (2007).
Role: Co-Investigator
Sponsor: Elan

A Randomized, Double-Blind, Placebo-Controlled Trial of the Effects of Docosahexaenoic Acid (DHA) in Slowing the Progression of Alzheimer's Disease (2006).
Role: Co-Investigator
Sponsor: NIH/NIA ADCS

A Randomized, Double-Blind, Placebo-Controlled Trial of the Effects of Docosahexaenoic Acid (DHA) in Slowing the Progression of Alzheimer's Disease (2011).
Role: Co-Investigator
Sponsor: NIH

A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Tolerability of Dimebon (Latrepirdine) in Subjects with Alzheimer's Disease with Reduced CYP2D6 Metabolism (2010)
Role: Co-Investigator
Sponsor: Pfizer

Protocol H6L-MC-LFAN (b): Effect of y-Secretase Inhibition on the Progression of Alzheimer's Disease:

LY450139 versus Placebo (2009)
Role: Co-Investigator
Sponsor: Eli Lilly and Company

ELND005-AD201- A Phase II, Double Blind, Randomized, Placebo Controlled, Multi-Center, Dose Ranging, Parallel-Group, Study to Evaluate the Safety and Efficacy of Oral ELND005 (AZD-103) in Patients with Mild to Moderate Alzheimer's Disease (2008).
Role: Co-Investigator
Sponsor: Elan

AC-3933-271 A Phase II, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Dose-Ranging Study Assessing the Efficacy and Safety of AC-3933 Tablets Twice Daily in Adults with Mild to Moderate Alzheimer's Disease (2007).
Role: Co-Investigator
Sponsor: Dainippon Sumitomo Pharma Amrica, Inc.

Open Label Study of the Effect of Daily Treatment with MPC-7869 in Subjects with Dementia of the Alzheimer's Type (2006).
Role: Co-Investigator
Sponsor: Myriad Pharmaceuticals

A double blind, phase II, safety and efficacy evaluation of ONO-2506PO in patients with mild to moderate Alzheimer's Disease (2005).
Role: Co-Investigator
Sponsor: Ono Pharmaceuticals

Evaluation of the safety, tolerability and impact on biomarkers of anti-oxidant treatment of mild to moderate Alzheimer's disease (2005).
Role: Co-Investigator
Sponsor: NIH/NIA ADCS

A long term extension study evaluating the safety and tolerability of BID and QD administration of Memantine in patients with mild to moderate dementia of the alzheimer's type (2005).
Role: Co-Investigator
Sponsor: Forest Laboratories

A multi-center, double-blind, placebo-controlled therapeutic trial to determine whether natural huperzine A improves cognitive function (2005)
Role: Co-Investigator
Sponsor: NIH/NIA ADCS

A Multi-Center Randomized, Double-Blind, Placebo-Controlled Trial of Simvastatin to Slow the Progression of Alzheimer's Disease (2004).
Role: Co-Investigator
Sponsor: NIH

A Phase IIa, Multicenter, Randomized, Double-Blind, Placebo-Controled, Multiple Ascending Dose, Safety, Tolerability, Pharmacokinetic, Pharmacodynamic, and Immunogenicity Trial of AAB-001 in Patients with Mild to Moderate Alzheimer's Disease (2004).
Role: Co-Investigator
Sponsor: Elan

Fish oil & alpha lipoic acid in mild Alzheimer's disease (2004).
Role: Co-Investigator
Sponsor: NIH

High dose supplements to reduce homocysteine and slow the rate of cognitive decline in Alzheimer's Disease (2004).
Role: Co-Investigator
Sponsor: NIH

A prospective, randomized, parallel cohort, multicenter, 13 week, open label comparative study of the effects of exelon (rivastigmine tartrate) 6 to 12 mg/day, aricept (donepezil HCL) 5-10 mg/day and reminyl (galantamine bromide) 16 to 24 mg/day on CSF cholinesterase activity in patients with mild to moderate AD (2004).
Role: Co-Investigator
Sponsor: Novartis

Statin effects on platelet APP ratios and AD dementia (2004).
Role: Co-Investigator
Sponsor: NACC (National Alzheimer's Coordinating Center)

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11. Nichole E Carlson, Mindy Milar Moore, Alison Dame, Diane Howieson, **Lisa C. Silbert**, Joseph Quinn, and Jeffrey Kaye. Trajectories of brain loss in aging and the development of cognitive impairment. Neurology. *Neurology;70:828-833, 2008.*

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25. Giovanni B Frisoni[1,2], Clifford R Jack[3], Martina Bocchetta[1,4], Corinna Bauer[5], Kristian S Frederiksen[6], Yawu Liu[7], Gregory Preboske[3], Tim Swihart[8], Melanie Blair[9], Enrica Cavedo[1], Michel J Grothe[10], Mariangela Lanfredi[11], Oliver Martinez[12], Masami Nishikawa[13], Marileen Portegies[14], Travis Stoub[15], Chadwich Ward[3], Liana G. Apostolova[16], Rossana Ganzola[17], Dominik Wolf[18], Frederik Barkhof[19], George Bartzokis[20], Charles DeCarli[12], John G. Csernansky[21], Leyla deToledo-Morrell[15], Mirjam I. Geerlings[14], Jeffrey Kaye[8], Ronald J Killiany[5], Stephane Lehéricy[22], Hiroshi Matsuda[13], John O'Brien[23], **Lisa C. Silbert**[8], Philip Scheltens[19], Hilkka Soininen[7], Stefan Teipel[10], Gunhild Waldemar[6], Andreas Fellgiebel[18], Josephine Barnes[9], Michael Firbank[24], Lotte Gerritsen[25], Wouter Henneman[19], Nikolai Malykhin[26], Jens C Pruessner[27], Lei Wang[28], Craig Watson[12], Henrike Wolf[29], Mony deLeon[30], Johannes Pantel[31], Clarissa Ferrari[11], Paolo Bosco[1], Patrizio Pasqualetti[32,33], Simon Duchesne[17], Henri Duvernoy[34], Marina Boccardi[1] for the European Alzheimer's Disease Consortium and the Alzheimer's Disease Neuroimaging Initiative[†]. *The EADC-ADNI Harmonized Protocol for Hippocampal Segmentation of Magnetic Resonance: Evidence of Validity*. Journal of Alzheimer's and Dementia 2014. *In submission*.

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Jonathan Nelson[1,4], Jennifer Young[1], Marjorie Grafe[1,2], Randy Woltjer[2], Joseph Quinn[3], Patricia Kramer[3], **Lisa Silbert[3]**, Nabil J. Alkayed[1,4]. Role of Soluble Epoxide Hydrolase in Age-related Vascular Cognitive Decline. Winter Eicosanoid Conference. Baltimore, Maryland, March 2014

Yosef A Berlow, David L Lahna, Daniel L Schwartz, Randall L Woltjer, Robin L Guariglia, **Lisa C. Silbert**, Jeffrey A Kaye, and William D Rooney. Brain Iron Content and Smoking History in Healthy Older Individuals. International Society for Magnetic Resonance in Medicine (ISMRM). Milan Italy, May 2014.

Lisa C. Silbert MD, David Lahna BA, Nutta-on Promjunyakul PhD, William Rooney PhD, Deniz Erten-Lyons MD, Jeffrey Kaye MD. Increased Cerebrovascular Lesions and Reduced Cerebral Blood Flow are Independently Associated with White Matter Integrity In Cognitively Intact Elderly: A Multi-Modal MRI Study. Alzheimer's Association International Conference on Alzheimer's Disease. Copenhagen, Denmark, July 2014.

Meredith Frederick, Randy Woltjer, **Lisa Silbert**, Morad Daniel, Adam Nelson, Carolyn Prince, Deniz Erten-Lyons. Oculopharyngeal muscular dystrophy: a trinucleotide expansion disorder causing dementia. Alzheimer's Association International Conference on Alzheimer's Disease. Copenhagen, Denmark, July 2014.

Marina Boccardi, Clifford R Jack, Martina Bocchetta, Corinna Bauer, Kristian S Frederiksen, Yawu Liu, Gregory Preboske, Tim Swihart, Melanie Blair, Enrica Cavedo, Michel J Grothe, Mariangela Lanfredi, Oliver Martinez, Masami Nishikawa, Marileen Portegies, Travis Stoub, Chadwich Ward , Liana G. Apostolova, Rossana Ganzola, Dominik Wolf, Frederik Barkhof, George Bartzokis, Charles DeCarli, John G. Csernansky, Leyla deToledo-Morrell, Mirjam I. Geerlings, Jeffrey Kaye, Ronald J Killiany, Stephane Lehéricy, Hiroshi Matsuda, John O'Brien, **Lisa C. Silbert**, Philip Scheltens, Hilkka Soininen, Stefan Teipel , Gunhild Waldemar, Andreas Fellgiebel, Josephine Barnes, Michael Firbank, Lotte Gerritsen, Wouter Henneman, Nikolai Malykhin, Jens C Pruessner, Lei Wang, Craig Watson, Henrike Wolf, Mony deLeon, Johannes Pantel, Clarissa Ferrari, Paolo Bosco, Patrizio Pasqualetti, Simon Duchesne, Henri Duvernoy, Giovanni B Frisoni, for the EADC -European Alzheimer's Disease Consortium and the ADNI - Alzheimer's Disease Neuroimaging Initiative. Validation of the eADC-ADNI Harmonized Protocol for Manual Hippocampal Segmentation. Alzheimer's Association International Conference on Alzheimer's Disease. Copenhagen, Denmark, July 2014.

Hiroko H. Dodge PhD, Junko Nishihira MD, **Lisa C. Silbert** MD, Nutta-on Promjunyakul PhD, Takashi Tokashiki MD, Yusuke Oya MD, Roger L Albin MD. Education and cognitive functions among octogenarians in Okinawa, Japan: Does education Matter? International Pschogeriatric Association.

Beijing, China, October 2014. *In submission.*

Invited Lectures and Conference Presentations:

<u>International and National</u>

2014   <u>Longitudinal White Matter Hyperintensity Change: MRI Biomarkers for Clinical Trials.</u> 2014 American Statistical Association Biopharmaceutical Section FDA-Industry Statistics Workshop. Washington, D.C., September 2014.

2014   <u>White Matter Hyperintensity Penumbra: a PASL study</u>. Nutta-on Promjunyakul, David Lahna, Bill Rooney, Deniz Erten-Lyons, Jeffrey Kaye, Lisa Silbert. Alzheimer's Association International Conference on Alzheimer's Disease. Platform Presentation. Copenhagen, Denmark, July 2014.

2013   <u>Link between White Matter Hyperintensities and Cognitive Function</u>. 8th International Congress of Vascular Dementia (ICVD); Invited talk: Session on White Matter Rarefaction. Athens, Greece 2013.

2012   <u>Alzheimer's Disease Pathology Burden Associated with Clinical Dementia Decreases with Age</u>. **LC Silbert**, D Erten-Lyons, JA Kaye, T Huong, S Stanfield, J Quinn, B Oken, K Wild, HH Dodge, R Woltjer. Alzheimer's Association International Conference on Alzheimer's Disease, Platform Presentation. Vancouver BC, August 2012. Alzheimer's & Dementia: The Journal of the Alzheimer's Association - July 2012 (Vol. 8, Issue 4, Supplement, Page P446.

2012   <u>Acceleration of White Matter Hyperintensity Burden Preceding Mild Cognitive Impairment</u>. **Lisa Silbert**, Hiroko Dodge, Louie Perkins, Lena Sherbakov, Deniz Erten-Lyons, Randy Woltjer, Jeffery Kaye. 64rd Annual American Academy of Neurology Meeting; Aging and Dementia: Clinical Aspects and Epidemiology, Platform Presentation. Neurology 2012; 78:S24.006

2011   <u>Trajectory of White Matter Hyperintensity Burden Preceding Mild Cognitive Impairment</u>**.** **Lisa Silbert,** Hiroko Dodge, Louie Perkins, Lena Sherbakov, Jeffrey Kaye. Alzheimer's Association International Conference on Alzheimer's Disease, Imaging Consortium, Platform Presentation. Paris, France, July 2011. Alzheimer's & Dementia: The Journal of the Alzheimer's Association - July 2011 (Vol. 7, Issue 4, Supplement, Page S7.

2011   Effects of Regional White Matter Integrity Disruption on Memory Function in the Elderly. **Lisa Silbert,** Louie Perkins, Lena Sherbakov, Hiroko Dodge, Jeffrey Kaye. 63rd Annual American Academy of Neurology Meeting Platform Presentation. Hawaii, April 2011.

2010   Age-related white matter change and motor dysfunction in the elderly. NIA workshop on Sensory and Motor Dysfunctions in Aging and Alzheimer's Disease (SMAAD). Bethesda, MD

2006   Etiology, Diagnosis, and Treatment of Vascular Cognitive Impairment (9/16/06). Dementia and Neuropsychiatry Conference - An update for Neurologists,Psychiatrists, Geriatricians and Primary Care . The University of Vermont, Burlington, Vermont (1 hr).

Regional and Local

2014   White Matter Hyperintensities: New Insights & Future Directions. 3rd Annual OHSU Stroke Meeting. Oregon Zoo. 3/7; Conference attendees include OHSU faculty researchers, clinician scientists, lab staff and post docs whose research focuses on Stroke (participating OHSU departments include APON, Behavioral Neuroscience, Neurology, Molecular Microbiology and Immunology and the Oregon Stroke Center)

2014   Memory Loss –Mild Cognitive Impairment & Alzheimer's Dementia. Portland VAMC. Video teleconference lecture to 3 Oregon VA sites and rural psychologists. 1/22/14. 1 hr.; attendees: Primary Care physicians, nurse practitioners and neuropsychologists.

2013   Effects of Cerebrovascular disease on cognitive and motor aging; experience form the Oregon Alzheimers Disease Center. Movement Disorders Journal Club. OHSU. 10/31/13

2013   Non- Alzheimer's Dementia. 3rd Annual, Clinical Neuroscience on the Oregon Coast. Salishan, Glenden Beach, OR. 9/7/2013. 1 hr; attendees: primary care physicians.

2013   Work-up and Treatment of Memory Loss. 3rd Annual, Clinical Neuroscience on the Oregon Coast. Salishan, Glenden Beach, Or. 9/7/2013. 1 hr; attendees: primary care physicians.

2013   Challenges in Vascular Dementia Research. OHSU

Anesthesiology Journal Club. 5/29/2013. 1 hr.

2013   The Complaint of Memory Loss. 44th annual Primary Care Review Conference, OHSU. The Governor Hotel. Portland, OR. 2/14/2013

2012   Neuroimaging at the Oregon Alzheimer's Disease Center. Advanced Imaging Research Center Seminar. 4/17/12. OHSU. 1 hr.

2011   Prevalence, Clinical Implications, and Imaging of White Matter Change in the Elderly. OHSU Anesthesiology Journal Club. 6/8/11. OHSU. 1 hr.

2011   Guild Medical Chat; For Members of the Sam Jackson Guild and Frank Doernbecker Guild. Advanced Magnetic Resonance Imaging to Detect Alzheimer's Disease and Other Related Dementia's. 3/18/2011. 2 hrs.

2011   Chairmain's Roundtable Presentation. Imaging and White Matter Change in Aging and Dementia Research. 2/24/2011, 2 hrs.

2010   Brain Aging and White Matter Disease: A Common Clinical Problem Meets a Novel Hypothesis. The Synapse Research Symposium.OHSU.

2010   When its Not Alzheimer's Disease: A Closer look at Lewy Body Disease, Parkinson's Disease Dementia, Frontotemporal Lobar Degeneration, and Vascular Cognitive Impairment. 11th Annual Oregon Geriatrics Society Conference. Sunriver, Oregon. 1 hr.

2010   Cognitive Changes in the Aging Brain in Women. Institute of Womens Health & Integrative Medicine Seminar: Midlife Women. Red Lion Hotel, Portland, Oregon. 2 hours.

2010   Neuroimaging and Parkinson's Disease Dementia. Neuroscience Grand Rounds, OHSU, 1 hr.

2010   Brain Perfusion, Ischemia, and Metabolic Dysfunction. The Synapse Research Symposium.OHSU.

2009   "Ask the Expert" panel at the Carl Cotman Aging Brain Plasticity lecture. OHSU Brain Awareness. 1 hr.

2008   Vascular dementia/vascular cognitive impairment:

definitions, pitfalls, and review. Grand Rounds, OHSU. 1 hr.

2008   Impact of white matter hyperintensity volume progression on rate of cognitive and motor decline. Department of Neurology. Synapse research symposium. OHSU.

2007   Clinical Trials in Alzheimers Disease. Pacific Gardens Family Support Group (11/6/07). 1.5 hours.

2006   Update on Alzheimer's Research and Treatments(01/14/06). Encore Senior Village, Portland, OR. 2 hrs.

2005   Aphasia, Apraxia, and Dementia (5/3/05). OHSU, Physican Assistant

2005   Update on Vascular Dementia. First Annual North Pacific Aging and Dementia Symposium (4/16/05), Skamania Lodge, Stevenson, Washington, 1 hr (sponsored by OHSU, University of Washington School of Medicine, University of British Columbia, and the Oregon Geriatric Education Center)

2005   Current Treatment Options for Alzheimer's disease. Seminar on Healthy Brain Aging and Alzheimer's disease (2/5/05). Healthy talks program , OHSU. 1 hr.

2004   Treatment of dementia – An allopathic perspective (12/15/04). Complimentary and Alternative Medicine (CAM) Grand Rounds. OHSU. 1 hr.

2004   Transcranial Magnetic Stimulation: Basic Physiological Mechanisms and Clinical Applications (12/15/04). Neuroscience Grand Rounds, OHSU. 1 hr.

2004   Vascular Dementia Overview. 4th Annual Oregon Geriatrics Society (OGS) meeting, pre-conference symposium on dementia (10/04). Sun River, OR. 1 hr.

2004   Diagnosis, Etiology, and Treatment of Vascular Dementia. Oregon Geriatric Education Center (OGEC) Summer Institute (6/29/04). OHSU. 1 hr.

2004   Vascular Dementia. OHSU Neurology Conference (7/1/04).

2003   Transcranial Magnetic Stimulation and White Matter Change. 4th Annual African American Dementia and Aging Project (AADAPt) Celebration. Holiday Inn, Portland, Oregon (11/1/03). 1

hr.

2003   Why We Slow with Age. Oregon Brain Aging Study (OBAS) and Dementia Prevention Study (DPS) annual appreciation celebration. Willamette View Manor, Portland, Oregon (6/27/03). 1 hr.

2003   Neurologic Diseases of Guam. OHSU Neurology Conference. 1 hr.

2002   Aging, Memory, and Dementia. Maranatha Church Group (Senior's With A Purpose, SWAP). Maranatha Church, Portland, Oregon (6/21/02). 1 hr.

2001   Head Circumference and ICV as measures of Brain Reserve in the Healthy Elderly. OHSU Neurology Conference. 1 hr.

2000   A case of palatal Myoclonus – Hypertrophic Olivary Hypertrophy. OHSU Neurology Conference. 1 hr.

National and International Study participation

2010-2013   Harmonization of Protocols for Manual Hippocamal Volumetry: an EADC-ADNI project; participating imaging center site coordinator.

2010-2013   Vascular Impairment of Cognition Classification Consensus Study (VICCS); Multi-center, international study funded by the Alzheimer's Society.

2012   C9orf72 Neuroimaging Consortium: multi-center consortium to advance the understand of the contribution of C9orf72 genotype to neurodegeneration through the multimodal integration of genetic and neuroimaging datasets. Hosted by the University of Pennsylvania.

V. SERVICE

Membership in Professional Societies:

2013-present   Fellow of the American Academy of Neurology (FAAN)
2012-present   Vas Cog society: The International Society of Behavioural and Cognitive Vascular Disorders, member.
2010-present   ISTAART Profession Interest Area (PIA) in Neuroimaging
2008-present   International Society to Advance Alzheimer Research and Treatment (ISTAART)

2001-present	American Academy of Neurology Geriatric Neurology section, member.
2001-present	American Academy of Neurology Clinical Neurophysiology section, member.
1999-present	American Academy of Neurology, member.
2003-2004	American Association of Electrodiagnostic Medicine, member
1992-1998	American Medical Association, Student member.

Granting Agency Review Work:

2014	Reviewer, National Medical Research Council (NMRC); national funding agency under the Ministry of Health, Singapore Clinical Trial Grant Co-Development Scheme.
2013-2014	Reviewer, USC ADRC Pilot Project Grant Application
2013-2014	Reviewer, Alzheimer's Research UK, Senior Research Fellowship application.
2012	Reviewer, 2012-2015 California Alzheimer's Disease Research Awards
2012	Reviewer, Chief Scientist Office Research Grant Application. Scottish Government.
2011	Reviewer, Oregon Alzheimer's Disease Center Pilot Project Grant Application.
2010	Reviewer, Parkinson's Disease Society Project grant application. Parkinson's Disease Society of the United Kingdom.
2005-2007	Reviewer, OHSU Research Committee, OHSU SOM. Meet quarterly for one full afternoon (3-4 proposal to review per quarter)
2006	Reviewer, The Oregon Partnership for Alzheimer's Research, Oregon Tax Check-off Alzheimer's Research Fund

Editorial and Ad Hoc Review Activities:

2011-2013	Editorial Board Member, ISRN Pathology

Committees:

Regional

2014	Department of Neurology Appointments, Promotion and Tenure Committee, OHSU
2013-present	Oregon Alzheimer Disease Center Executive Committee, OHSU
2013-present	PVAMC Rural Collaborative Management of Dementia Development Team.
2011-2013	Portland VA Medical Center Dementia E-Consult Development Team.

International/National: Peer-reviewed journals

2014	Reviewer, Cerebral Cortex
2004-2014	Reviewer, Neurobiology of Aging (2-3)
2008-2014	Reviewer, Alzheimer's & Dementia (1-2)
2009-2014	Reviewer, Neurology (1-4)
2013	Reviewer, Behavioral and Brain Functions
2013	Reviewer, Frontiers Neuroscience (2)
2013	Reviewer, Brain
2012	Reviewer, Journal of Gerontology: Medical Sciences
2012	Reviewer, PLOS ONE
2012	Reviewer, Environmental Health Perspectives
2012	Reviewer, Alzheimer Disease & Associated Disorders
2011	Reviewer, Archives of Neurology (1-2)
2011	Reviewer, Journal of Applied Physiology (1-2)
2010-2011	Reviewer, Psychiatry Research – Neuroimaging (2-3)
2010-2011	Reviewer, Journal of Neurology, Neurosurgery & Psychiatry (3-4)
2006-2010	Reviewer, Neuropsychologia (1-2)
2009	Reviewer, Journal of the American Geriatrics Society (1-2)
2007-2009	Reviewer, Brain Imaging and Behavior (1-2)
2008	Reviewer, Brain (1-2)
2008	Reviewer, NeuroImage (1-2)
2008	Reviewer, Journal of Alzheimer's Disease (1-2)
2007	Reviewer, Annals of Neurology (1-2)
2007	Reviewer, Brain Research (1-2)
2006	Reviewer, Journal of Neurology (1-2)

International/National: Peer-reviewed on-line publications

2011	Reviewer, Medscape reference, Alzheimer's Review

International/National: Peer-reviewed abstract publications

2013	Reviewer, 2014 AAN abstracts, Aging and Dementia
2012	Reviewer, 2013 AAN abstracts, Aging and Dementia
2009	Reviewer, 2010 AAN abstracts, Aging and Dementia

International: Conference participation

2013	Chair for 8th International Congress of Vascular Dementia, platform session: Chronic Hypoperfusion and Cognitive Impairment; Athens Greece, 2013.
2012	Chair for 2012 Alzheimer's Association International Conference on Alzheimer's Disease platform session: Cellular and Molecular Mechanisms: Neuropathology; Vancounver BC

2011   Chair for 2011 Alzheimer's Association International
Conference on Alzheimer's Disease platform session: Vascular
Disease and Other Pathologies; Paris, France.
2010   Chair for 2010 American Academy of Neurology platform
session; Aging and Dementia: Recognition and Treatment; Toronto,
Canada

Clinical Responsibilities:

2012-Present   Clinical evoked potential interpretation (inpatient and outpatient
SSEP, BAERs and VEPs). OHSU. Two days per week, and every
4th Friday, Saturday, and Sunday.

2010-Present   Cover after-hours and weekend attending Neurologist on call,
inpatient neurology ward service. OHSU. One week per year.

2005-Present   Intraoperative electrophysiology monitoring. OHSU, Shriners, and
DCH. Two days per week, and every 4th Friday, Saturday, and
Sunday.

2000-Present   Geriatric Neurology Clinic. Portland VA Medical Center. One-half
day per week.

2000-Present   Aging and Alzheimer's Clinic. Oregon Health & Science University.
One-half day per week.

2010-2012   Electroencephalogram reading. OHSU. One day per week, and
every 7th weekend.

2007-2010   Electroencephalogram reading. Oregon Health & Science
University. Every 4th Wednesday and every 8th Friday, Saturday,
and Sunday.

2007-2009   Attending Neurologist, inpatient neurology ward service. Oregon
Health & Science University. Two weeks per year.

2004-2006   Attending Neurologist at Emergency Care Unit clinic. Portland
VA Medical Center. One-half day per month.

2001-2006   Attending Neurologist, inpatient neurology ward service. Oregon
Health & Science University. Four weeks per year.

2001-2004   Attending Neurologist at Emergency Care Unit clinic. Portland
VA Medical Center. One-half day per week.

2000-2002   EMG/NCV. Four-half days per week

2000-2002   EEG. Three-half days per week.

Awards:

2011   OHSU Golden Rose Award: Recognizing outstanding service excellence; awarded for service provided in intraoperative neurophysiological monitoring.

VI. TEACHING (OHSU Educator's Portfolio):

Overview of your Role as an Educator: During the course of my OHSU and VA dementia clinics, I regularly provide guidance and education proper technique pertaining to the neurologic exam as well as information regarding the etiology, workup, diagnosis and treatment of dementia patients to psychiatry, gerontology and neurology fellows, neurology residents, and 3rd and 4th year medical students. In addition to this, I give a formal lecture to medical students in their neurology rotation on the diagnosis and treatment of Alzheimers disease approximately 3-4 times per year. I regularly have summer interns working in the Neuroimaging lab and participating in dementia clinic consisting of both college and high school students interested in neuroscience.

Educational Activity (see Appendix A and B):

2014   Dementia Basics: Diagnosis and treatment of Alzheimers, Lewy Body, Vascular, and Frontotemporal Dementias. VA teleconference to primary care physicians: Rural Dementia Care Outreach Program.

2000-Present   Dementia. Lecture for medical students. OHSU. 1 hr., quarterly. (3-4 per year)

2013   Diagnosis and Treatment of Mild Cognitive Impairment and Alzheimer's Dementia. VA teleconference to primary care physicians: Rural Dementia Care Outreach Program.

2013   Vascular Cognitive Impairment, Lewy Body Dementia, and Frontotemporal Lobar Degeneration. Neuroscience of Aging (BEHN 629). OHSU. 6/5/2013. 1 hr.

2013   Developed revised case and evidenced-based Dementia Lecture for 4th year medical students on Neurology Rotation

2012   Dementia Essentials for Neurology Residents and Medical Students. Neurology Resident Noon Conference. OHSU. 1 hr.

2003-2011   Refined History and Examination: Central Nervous System Physical Exam course. Oregon Health and Science University, second year medical school class. 3 hrs., annually.

2011   Parkinson's disease: Cognitive issues and brain exercises. PVAMC auditorium; An education session for VA Parkinson's patients. 5/13/11. 1 hour.

2010   Strategies for Obtaining R01 funding. OCTRI Scholars Meeting. OHSU. 1 hr.

2010   Dementia and Imaging MD/PhD Student CTRC Rotation. OHSU. 3 days a week mentoring/teaching 1 MD/PhD Student on the dementia evaluation and imaging research.

01/2009   Microvascular frontal-subcortical syndrome of aging. Neuroscience of Aging Course (course no. BEHN629). OHSU. 1 hr.

01/2008   Aphasias & Disorders of Cognition: Neuroscience and Behavior Course Small Groups. Medical Students, OHSU. 1 hr

11/2005   What you need to know about applying for a K23 grant. HIP program students, OHSU. 1 hr

2008   What every resident should know about Dementia. Neurology Resident Noon Conference. OHSU. 1 hr.

2002-2007   Alzheimer's Disease. Oregon Health & Science University physician's assistant students. Portland, Oregon. 1 hr., annually.

2002-2003   Clinical presentation and pathology of Dementia Lecture. Oregon Health & Science University, second year medical school class. 1 hr.

2000-2002   Neurophysiology. Lecture series on EEG and EMG for Oregon Health & Science University residents and medical students. 1 hr, monthly.

Curriculum Development

2014   The medical student 4th year clerkship dementia lecture was completely revised by myself and Dr. Erten-Lyons to reflect updated diagnostic and treatment information and to include case-

study oriented themes. This presentation now serves as the standard dementia lecture for all medical students participating in their 4th year neurology service rotation.

study oriented themes. This presentation now serves as the standard dementia lecture for all medical students participating in their 4th year neurology service rotation.

Order of Scheduled Presentations:

Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment

	Name
1	David Djang, MD

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		No
2.	Equity interests such as stocks, stock options or other ownership interests.		No
3.	Status or position as an officer, board member, trustee, owner.		No
4.	Loan or intellectual property rights.		No
5.	Research funding.		No
6.	Any other relationship, including travel arrangements.		No

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

_____

_____

_____

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		No

If yes to #7, provide name and funding Sources: _____
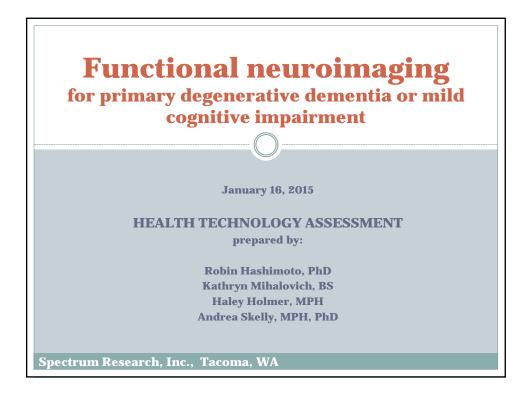
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*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*
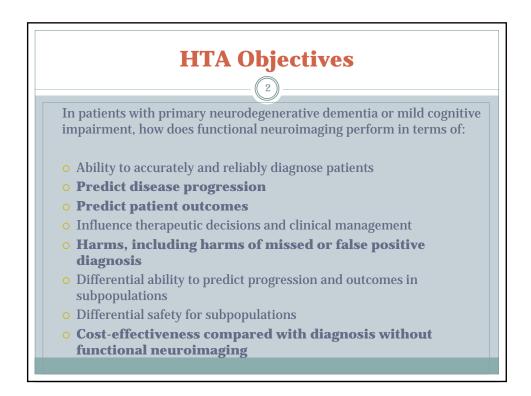
I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.
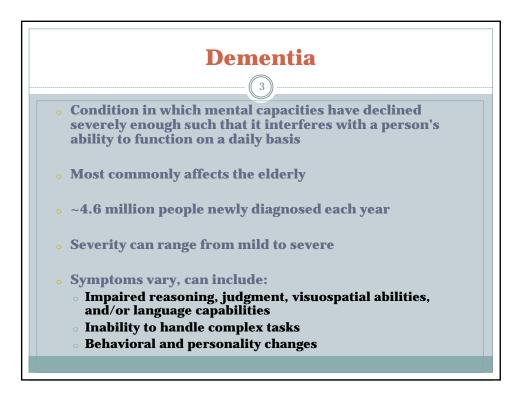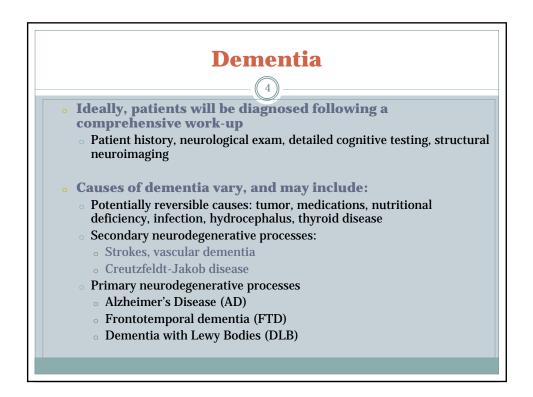
X _____   David Djang
       Signature   Date   Print Name

Mail Address: 1221 Madison St. / Suite 150 / Seattle, WA 98104
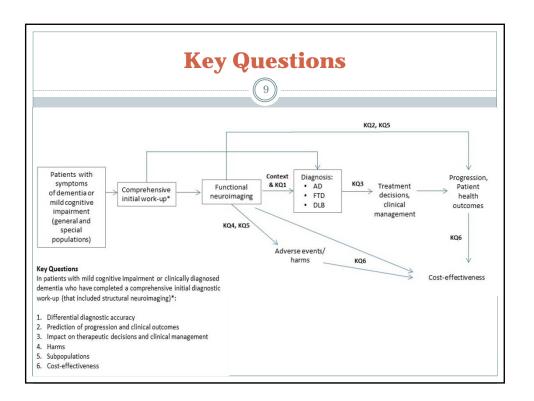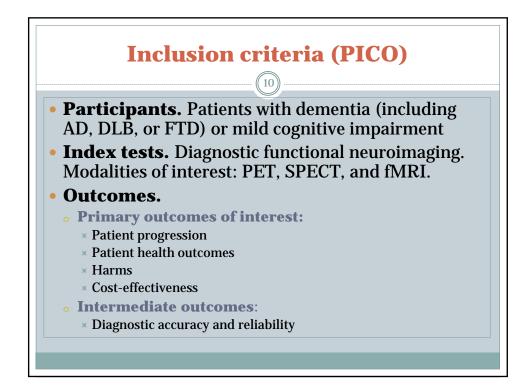
Phone Number: 206 215 3093

Functional neuroimaging
for primary degenerative dementia or mild cognitive impairment

January 16, 2015

HEALTH TECHNOLOGY ASSESSMENT
prepared by:

Robin Hashimoto, PhD
Kathryn Mihalovich, BS
Haley Holmer, MPH
Andrea Skelly, MPH, PhD

Spectrum Research, Inc., Tacoma, WA

HTA Objectives
2

In patients with primary neurodegenerative dementia or mild cognitive impairment, how does functional neuroimaging perform in terms of:

- Ability to accurately and reliably diagnose patients
- **Predict disease progression**
- **Predict patient outcomes**
- Influence therapeutic decisions and clinical management
- **Harms, including harms of missed or false positive diagnosis**
- Differential ability to predict progression and outcomes in subpopulations
- Differential safety for subpopulations
- **Cost-effectiveness compared with diagnosis without functional neuroimaging**

Dementia

(3)

- Condition in which mental capacities have declined severely enough such that it interferes with a person's ability to function on a daily basis

- Most commonly affects the elderly

- ~4.6 million people newly diagnosed each year

- Severity can range from mild to severe

- Symptoms vary, can include:
  - **Impaired reasoning, judgment, visuospatial abilities, and/or language capabilities**
  - **Inability to handle complex tasks**
  - **Behavioral and personality changes**

Dementia

(4)

- Ideally, patients will be diagnosed following a comprehensive work-up
  - Patient history, neurological exam, detailed cognitive testing, structural neuroimaging

- Causes of dementia vary, and may include:
  - Potentially reversible causes: tumor, medications, nutritional deficiency, infection, hydrocephalus, thyroid disease
  - Secondary neurodegenerative processes:
    - Strokes, vascular dementia
    - Creutzfeldt-Jakob disease
  - Primary neurodegenerative processes
    - Alzheimer's Disease (AD)
    - Frontotemporal dementia (FTD)
    - Dementia with Lewy Bodies (DLB)

Dementia

(5)

	Symptoms	Pathology	Diagnostic criteria	Treatment
AD	• Memory loss and impaired learning • Mood, behavior changes • Confusion • Difficulty speaking, swallowing, walking	Atrophy/ neuronal loss in hippocampal and mesial temporal lobe (beta-amyloid plaques, tau tangles)	NINCDS-ADRDA, NIA, DSM-V	Symptom reduction: NMDA antagonists, acetylcholinesterase inhibitors
DLB	• Deficits in attention and executive function • Memory impairment in later stages • Parkinsonism • Hallucinations	Varies (Lewy body deposits)	DLB Consortium, DSM-V	Symptom reduction: cholinesterase inhibitors, SSRIs
FTD	• Inappropriate behaviors • Problems with thinking, concentrating, and with language • Movement	Atrophy/ neuronal loss in frontal and temporal lobes (tau and ubiquitin deposits)	Lund and Manchester, DSM-V	Symptom reduction: SSRIs

Mild cognitive impairment

(6)

- **Not dementia: does not impair a person's functional independence**

- **Affects 10-20% of people aged 65 or older**

- **Can affect memory and/or cognitive function**

- **Associated with increased risk of developing AD or other dementia**

- **Not all people with MCI progress to dementia; some get better**

Functional neuroimaging

(7)

	Measures	EFNS 2012 guideline recommendations for use
^{18}F-FDG-PET	• glucose metabolism	• AD: hypometabolism in temporoparietal cortices • MCI patients with AD phenotype may be predictive of conversion to AD • FTD: hypometabolism in frontotemporal lobe • DLB: hypometabolism possibly present in occipal lobe, but could also be present in AD so not recommended to differentiate AD vs. DLB.
HMPAO-SPECT	• cerebral blood flow	• Hypoperfusion patterns similar to that of hypometabolism seen with FDG-PET
^{123}I-FP-CIT-SPECT	• dopaminergic nigrostriatial denervation	• DLB: positive scan indicative of DLB, but negative scan does not exclude DLB
fMRI	• Cerebral blood flow in real time, usually measured during a task	• Future tool

Harms

(8)

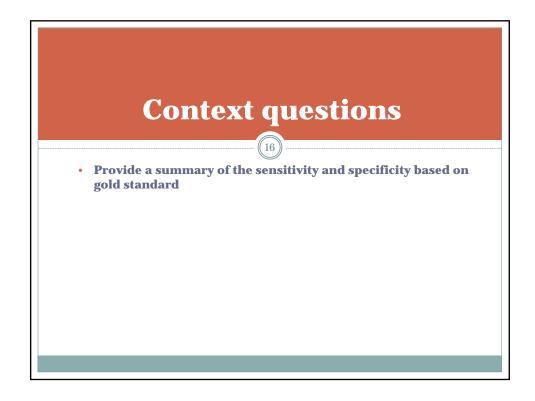| Imaging	Effective radiation dose	Other reported harms
PET and SPECT (general)	5.7 – 25 mSv	
FDG-PET	3.5 – 14.1 mSv	Reported events includetransient hypotension, hypo- or hyperglycemia, allergic reaction, flushing, tachycardia, diaphoresis.
HMPAO-SPECT	5.2 – 10.3 mSv	Reported events include: fever, nausea, flushing, rash, hypo- or hypertension, respiratory reaction, seizure, diaphoresis, cyanosis, anaphylaxis, facial swelling, abdominal pain.
^{123}I-FP-CIT-SPECT	2.3 – 4.4 mSv	Reported events include: headache, vertigo, dry mouth, nausea, dizziness.
fMRI	None	Reported events include: vertigo, tiredness, disorientation, nausea, claustrophobia, anxiety.
CT (head/chest)	2 mSv/ 7 mSv	

FDA estimates that an effective dose of 10 mSV increases the risk of death from cancer by 1 in 2000. The FDA states that the imaging procedure should be considered when medically necessary and if it is believed to do more good than harm.

Key Questions

⑨

KQ2, KQ5

Patients with symptoms of dementia or mild cognitive impairment (general and special populations) → Comprehensive initial work-up* → Functional neuroimaging → Context & KQ1 → Diagnosis:
- AD
- FTD
- DLB
→ KQ3 → Treatment decisions, clinical management → Progression, Patient health outcomes

KQ4, KQ5

Adverse events/ harms → KQ6

KQ6

Cost-effectiveness

Key Questions
In patients with mild cognitive impairment or clinically diagnosed dementia who have completed a comprehensive initial diagnostic work-up (that included structural neuroimaging)*:

1. Differential diagnostic accuracy
2. Prediction of progression and clinical outcomes
3. Impact on therapeutic decisions and clinical management
4. Harms
5. Subpopulations
6. Cost-effectiveness

Inclusion criteria (PICO)

⑩

- **Participants.** Patients with dementia (including AD, DLB, or FTD) or mild cognitive impairment
- **Index tests.** Diagnostic functional neuroimaging. Modalities of interest: PET, SPECT, and fMRI.
- **Outcomes.**
  - Primary outcomes of interest:
    - Patient progression
    - Patient health outcomes
    - Harms
    - Cost-effectiveness
  - Intermediate outcomes:
    - Diagnostic accuracy and reliability

Literature search

(11)

1. Total Citations   (n = 10,049)

2. Title/Abstract exclusion (n = 9935)

3. Retrieved for full-text evaluation   (n = 111)

4. Excluded at full–text review (n = 77)

5. Publications included   (n = 34)
Context questions   (n = 14)
Key question 1   (n = 6)
Key question 2   (n = 13)
Key question 3   (n = 0)
Key question 4   (n = 2)
Key question 5   (n = 0)
Key question 6   (n = 4)

Overall quality of evidence (GRADE)

(12)

Quality rating	Interpretation
High	High confidence that the evidence reflects the true effect.
Moderate	Moderate confidence in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Insufficient	Very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

Context questions

13

- **Provide a summary of the inter-rater and intra-rater diagnostic reliability (reproducibility)**

Reliability: Overview of evidence base

14

- **FDG-PET:** 7 studies (5 CoE I, 1 CoE II, 1 CoE III); N = 45-132

- **[11]C-DTBZ-PET:** 1 study (CoE II); N = 27

- **HMPAO-SPECT:** 2 studies (CoE III); N = 16-57

- **[123]I-FT-CIT-SPECT:** 2 studies (CoE I); N = 20-288

- **fMRI**: no evidence

Context Question: Diagnostic Reliability

15

Imaging modality: diagnosis	Inter-rater reliability		Intra-rater reliability
	Kappa	100% inter-rater agreement	Kappa
FDG-PET: AD vs. FTD	0.72 - 0.81 (3 studies, 2-6 raters, N=45-132)	76% of cases (1 study, 12 raters, N=45)	NR
FDG-PET: AD vs. other dementias	0.52 - 0.67 (2 studies, 3 raters, N=67-110)	94% of cases (1 study, 2 raters, N=100)	0.52 (mean) (1 study, 3 raters, N=110)
HMPAO-SPECT: AD vs. FTD	0.48 (1 study, 2 raters, N=16)	35% of cases (1 study, 5 raters, N=57)	NR
[11]C-DTBZ-PET: AD vs. FTD vs. DLB	0.85 (1 study, 3 raters, N=27)	NR	NR
^{123}I-FT-CIT-SPECT: DLB vs. non-DLB dementias	0.87 (1 study, 3 raters, N=288)	75% of cases (1 study, 3 raters, N=20)	NR

Context questions

16

- **Provide a summary of the sensitivity and specificity based on gold standard**

Accuracy: Overview of evidence base

17

- **All studies used autopsy as gold standard**

- **FDG-PET:** 2 retrospective studies (one CoE II, one CoE IV); N = 55-138

- **HMPAO-SPECT:** 1 retrospective study (CoE IV); N = 73

- **[123]I-FT-CIT-SPECT:** 1 prospective study (CoE I); N = 20

- **fMRI, ^{11}C-DTBZ-PET**: no evidence

Context Question: Diagnostic Accuracy

18

Imaging modality: diagnosis	Patient presentation	Imaging alone (gold standard: autopsy)	Clinical diagnosis alone	Imaging + clinical diagnosis
FDG-PET (visual): AD	**Dementia** (ranged in severity from questionable/mild to severe dementia)	Sensitivity: 93-95% Specificity: 63-73% (2 studies, N=55-138)	Sensitivity: 79% Specificity: 88% (1 study, N=55) Probable or possible AD using NINCDS-ADRDA	NR
HMPAO-SPECT (visual): AD	**Dementia**	Sensitivity: 93% Specificity: 85% (1 study, N=73)	NR	NR
^{123}I-FT-CIT-SPECT (visual): DLB	**Dementia**	Sensitivity: 88% Specificity: 83% (1 study, N=20)	Sensitivity: 75% Specificity: 42% (1 study, N=20) (Consensus DLB criteria)	NR
^{123}I-FT-CIT-SPECT (semi-quantitative): DLB	"	Sensitivity: 88% Specificity: 100% (1 study, N=20)	"	NR

Results: KQ1

19

KQ1. What is the diagnostic accuracy of functional neuroimaging for the differential diagnosis of AD, FTD, and Lewy body dementia based on gold standard (autopsy)?

KQ1: Overview of evidence base

20

- **All studies used autopsy as gold standard**

- **FDG-PET, AD vs. FTD:** 3 retrospective studies (two CoE II, one CoE III); N = 10-45

- **HMPAO-SPECT, AD vs. FTD:** 1 retrospective study (CoE IV); N = 56

- **FDG-PET, AD vs. DLB:** 2 retrospective studies (CoE III); N = 11-21

- **fMRI, ^{11}C-DTBZ-PET, ^{123}I-FP-CIT-SPECT**: no evidence

KQ1: FDG-PET, AD vs. FTD

21

Imaging (classification)	Patient presentation	Final SoE	Imaging alone (gold standard: autopsy)	Clinical diagnosis alone	Imaging + clinical diagnosis
Gold standard: autopsy AD prevalence: 30-68%					
FDG-PET (visual): AD vs. FTD	AD or FTD Symptom duration: 5 yrs. (mean)	**Low**	Sensitivity: 94-98% (2 CoE II, N=90) Specificity: 73-76% (2 CoE II, N=100)	Sensitivity: 63-89% Specificity: 79-86% (2 CoE II, N=90) Diagnosis with "clinical scenario"	Sensitivity: 90% Specificity: 86% (1 CoE II, N=45) Diagnosis with "clinical scenario"
FDG-PET (automated): AD vs. FTD	AD or FTD Symptom duration: NR	**Insufficient**	Sensitivity: 67% Specificity: 100% (1 CoE III, N=10)	Sensitivity: 100% Specificity: 100% (1 CoE III, N=10)	NR

KQ1: HMPAO-SPECT, AD vs. FTD

22

Imaging (classification)	Patient presentation	Final SoE	Imaging alone (gold standard: autopsy)	Clinical diagnosis alone	Imaging + clinical diagnosis
Gold standard: autopsy AD prevalence: 55%					
HMPAO-SPECT (visual): AD vs. FTD	AD or FTD Symptom duration: 4.0 yrs. (mean)	**Insufficient**	Sensitivity: 65% Specificity: 72% (1 CoE IV, N=56)	Sensitivity: 84% Specificity: 84% (1 CoE IV, N=56) Diagnosis through comprehensive work-up	Sensitivity: 77% Specificity: 88% (1 CoE IV, N=56) Diagnosis through comprehensive work-up

KQ1: FDG-PET, DLB vs. AD

23

Imaging (classification)	Patient presentation	Final SoE	Imaging alone (gold standard: autopsy)	Clinical diagnosis alone	Imaging + clinical diagnosis
Gold standard: autopsy DLB prevalence: 45-52%					
FDG-PET (automated): DLB vs. AD	DLB or AD Symptom duration: 3.4 yrs. (mean from 1 study, other study NR)	**Insufficient**	Sensitivity: 80-90% Specificity: 80-100% (2 CoE III, N=32)	NR	NR

Results: KQ2

24

KQ2. **What is the ability of functional neuroimaging to predict progression and clinical outcomes? Is one test better at predicting progression or clinical outcomes versus another?**

KQ2: FDG-PET

25

Imaging (classification)	Outcome	Studies (CoE)	Findings	Final SoE
FDG-PET: Patient progression (MCI to AD/dementia conversion) Reference standard: AD/dementia at follow-up				
FDG-PET (visual)	Sensitivity	2 CoE II N = 47 F/U: 1.3-1.6 yrs.	92-100%	Moderate
	Specificity	"	75-89%	Moderate
FDG-PET (automated)	Sensitivity	3 CoE III N = 136 F/U: 1.3-3 yrs.	33-45%	Insufficient
	Specificity	"	43-93%	Insufficient

KQ2: FDG-PET

26

Imaging (classification)	Outcome	Studies (CoE)	Findings	Final SoE
FDG-PET: Patient progression (MCI to progressive cognitive decline) Reference standard: progressive cognitive decline at follow-up				
FDG-PET (visual)	Sensitivity	1 CoE I N = 17 F/U: 1.6 yrs.	75%	Low
	Specificity	"	88%	Low

KQ2: FDG-PET

27

Imaging (classification)	Outcome	Studies (CoE)	Findings	Final SoE
FDG-PET: Cognitive decline				
FDG-PET (visual)	Cognition (MMSE scores)	1 CoE III N = 95 F/U: 3.5±1.0 yrs.	Progressive (n=67) vs. nonprogressive dementia (n=28) predicted by FDG-PET : MMSE scores of ~18 vs. ~25.5 ($P < 0.05$)	Insufficient

FDG-PET: prediction of outcomes related to function, behavior, psychological status, depression, caregiver burden, and global health:
No evidence (insufficient SoE)

KQ2: HMPAO- or IMP-SPECT

28

Imaging (classification)	Outcome	Studies (CoE)	Findings	Final SoE
HMPAO- or IMP-SPECT: Patient progression (MCI to AD/dementia conversion) Reference standard: AD/dementia at follow-up				
SPECT (automated)	Sensitivity	1 CoE III N = 316 F/U: 3 yrs.	58%	Insufficient
	Specificity	"	81%	Insufficient
SPECT (visual)	Sensitivity	3 CoE III N = 454 F/U: 1.3-4.1 yrs.	36-76%	Insufficient
	Specificity	"	39-82%	Insufficient

SPECT: prediction of outcomes related to function, behavior, cognition, psychological status, depression, caregiver burden, and global health:
No evidence (insufficient evidence).

KQ2: fMRI

(29)

Imaging (classification)	Outcome	Studies (CoE)	Findings	Final SoE
fMRI: Patient progression (MCI to dementia conversion) **Reference standard: dementia at follow-up**				
fMRI	Sensitivity	1 CoE III N = 33 F/U: 2.5±0.8 yrs.	55%	Insufficient
	Specificity	"	73%	Insufficient

fMRI: prediction of outcomes related to function, behavior, cognition, psychological status, depression, caregiver burden, and global health:
No evidence (insufficient evidence).

No evidence:
FP-CIT-SPECT, DTBZ-PET, or comparison of different types of functional neuroimaging to predict progression or patient outcomes

Results: KQ3

(30)

KQ3. Do the results of functional neuroimaging impact therapeutic decisions or clinical management compared to those made for patients who did not receive functional neuroimaging?

No evidence.

Results: KQ4

31

KQ4. **What are the short- and long-term harms of diagnostic functional neuroimaging?**

KQ4: Harms

32

Imaging (classification)	Outcome	Studies (CoE)	Findings	Final SoE
FDG-PET	Injection-related harms	1 CoE III N = 36 Short-term	0%	Insufficient
^{123}I-FP-CIT-SPECT	Injection-related harms	1 CoE III N = 326 Procedural/ Post-procedural	2.8% patients (10 events)	Insufficient
FDG-PET, ^{123}I-FP-CIT-SPECT	Other harms (long-term harms, harms of missed diagnosis or false positive)	0 studies		Insufficient

No evidence: HMPAO-SPECT, DTBZ-PET, fMRI

Results: KQ5

(33)

KQ5. **What is the evidence that functional neuroimaging may perform differently in subpopulations (i.e., younger age, presence of comorbidities, etc.)? Consider the impact on disease progression, clinical outcomes, and harms.**

No evidence.

Results: KQ6

(34)

KQ6. **What is the cost-effectiveness of incorporating diagnostic functional neuroimaging into the comprehensive initial diagnostic work-up?**

KQ6: FDG-PET

35

- **Evidence base**: 3 studies (1 cost-utility, 2 cost-effectiveness studies, all moderately well-conducted)
- **Population:** simulated cohort of hypothetical mild to moderate dementia patients
- **Diagnostic test:** comprehensive diagnostic work-up ± FDG-PET
- **Diagnosis:** AD

- **Cost-utility study (reports cost per QALY)**
  - US perspective
  - 18-month time horizon
  - Costs included patient care (home care or nursing home) and medication
  - Addition of FDG-PET was more costly and did not improve QALYs

- **Cost-effectiveness studies (reports cost per improved outcome)**
  - Study A: US perspective, 6-month time horizon
  - Study B: European perspective, time horizon not reported
  - Cost of care not included unless there was a false-negative diagnosis
  - Addition of FDG-PET was cost-effective
    - Less costly overall; increased accuracy vs. conventional work-up alone

KQ6: SPECT

36

- **Evidence base**: 2 cost-utility studies (both moderately well-conducted; report cost per QALY)
- **Population:** simulated cohort of hypothetical mild or moderate dementia patients referred to a specialty AD clinic
- **Diagnostic test:** comprehensive diagnostic work-up ± SPECT
- **Diagnosis:** AD

- US perspective
- 18-month time horizon
- Costs included patient care (home care or nursing home) and medication
- SPECT associated with slightly higher costs overall
- Addition of SPECT did not result in increased QALYs
- Conclusion: SPECT not cost-effective as an add-on to the conventional clinical work-up in the diagnosis of AD

Gaps in the evidence

37

Imaging modality	Gaps in evidence
All	Prediction of outcomes related to cognition, function, behavior, psychological status, depression, caregiver burden, and global health
All	How one type of functional neuroimaging compares to another in terms of prediction of patient outcomes
All	Impact on therapeutic decisions and clinical management compared with diagnostic work-up without functional neuroimagin
All	Impact of missed diagnosis or false positive diagnosis
fMRI	Accuracy and reliability of diagnosis

Thank you.

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Questions?

HTCC Coverage and Reimbursement Determination
Analytic Tool

> HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries
> of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards[2]:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.

- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.

- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.

- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms[3]:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.

- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.

- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.

- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.

- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely

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[1] Based on Legislative mandate: See RCW 70.14.100(2).

[2] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.

- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. *Availability of Evidence:*

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. *Sufficiency of the Evidence:*

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

3. *Factors for Consideration - Importance*

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;

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[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Discussion Document:

What are the key factors and health outcomes and what evidence is there?

Safety Outcomes	Safety Evidence
Injection related harms	
Missed/false diagnosis	
Other harms	
Efficacy – Effectiveness Outcomes	**Efficacy / Effectiveness Evidence**
Sensitivity	
Specificity	
Disease progression	
Other clinical outcomes	
Cognition (MMSE Score)	
Special Population / Considerations Outcomes	**Special Populations/ Considerations Evidence**
Cost	**Cost Evidence**
Cost	
Cost-effectiveness	
Cost-utility	

Medicare Coverage and Guidelines

[From page 78 of the evidence report]

1.1. *Medicare and Representative Private Insurer Coverage Policies*

Payer websites were searched for coverage decisions on the use of functional neuroimaging in the diagnosis of dementia. Eleven policies were identified for selected bell-weather payers and coverage policies are consistent for non-coverage of functional neuroimaging. Generally speaking, the payers will not provide coverage for any of the diagnostic functional neuroimaging modalities, with the exception of two policies:

- Centers for Medicare and Medicaid Services (CMS) will provide coverage for FDG-PET scans for either the differential diagnosis of FTD and AD under specific requirements; OR, the use of FDG-PET in a CMS-approved practical clinical trial focused on its utility in the diagnosis or treatment of dementing neurodegenerative diseases.
- Cigna covers SPECT as medically necessary for Alzheimer's disease when other imaging studies are inconclusive or contraindicated; however, results should be considered supportive and not diagnostic.

Coverage decisions are summarized briefly below and policy details are provided in Table 5.

Centers for Medicare and Medicaid Services (CMS) National Coverage Determinations

National Coverage Determination (NCD) for FDG PET for Dementia and Neurodegenerative Diseases (220.6.13)

Medicare covers FDG Positron Emission Tomography (FDG-PET) scans for either the differential diagnosis of FTD and AD under specific requirements (see Table 5); OR, for use in a CMS-approved practical clinical trial focused on the utility of FDG-PET in the diagnosis or treatment of dementing neurodegenerative diseases. All other uses of FDG-PET for patients with a presumptive diagnosis of dementia-causing neurodegenerative disease (e.g., possible or probable AD, clinically typical FTD, dementia of Lewy bodies) for which CMS has not specifically indicated coverage continue to be noncovered.

National Coverage Determination (NCD) for Single Photon Emission Computed Tomography (SPECT) (220.12)

Medicare does not include MCI, dementia, AD, FTD, DLB etc. in the list of conditions for which SPECT is covered.

Table 5. Overview of payer technology assessments and policies for functional neuroimaging

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments

Center for Medicare & Medicaid Services (CMS) (2009)
 	
National Coverage Determination (NCD) for FDG PET for Dementia and Neurodegenerative Diseases
 	
Manual Section #: 220.6.13
 	
Effective Date: 04/03/2009
Implementation Date: 10/30/2009
	NR	NR	Medicare covers FDG-PET scans for either the differential diagnosis of FTD and AD under specific requirements; OR, its use in a CMS-approved practical clinical trial focused on the utility of FDG-PET in the diagnosis or treatment of dementing neurodegenerative diseases. Specific requirements for each indication are clarified below:
			
			FDG-PET Requirements for Coverage in the Differential Diagnosis of AD and FTD:
			1. In patients with a recent diagnosis of dementia and documented cognitive decline of at least 6 months, who meet diagnostic criteria for both AD and FTD. These patients have been evaluated for specific alternate neurodegenerative diseases or other causative factors, but the cause of the clinical symptoms remains uncertain, and:
			
			  • The patient's onset, clinical presentation, or course of cognitive impairment is such that FTD is suspected as an alternative neurodegenerative cause of the cognitive decline
			  • The patient has had a comprehensive clinical evaluation (as defined by AAN), physical and mental status examination aided by cognitive scales or neuropsychological testing, laboratory tests, and structural imaging
			  • The evaluation of the patient has been conducted by a physician experienced in the diagnosis and assessment of dementia
			  • The evaluation of the patient did not clearly determine a specific neurodegenerative disease or other cause for the clinical
				NR

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
			symptoms, and information available through FDG-PET is reasonably expected to help clarify the diagnosis between FTD and AD and help guide future treatment • The FDG-PET scan is performed in a facility that has all the accreditation necessary to operate nuclear medicine equipment. The reading of the scan should be done by an expert in nuclear medicine, radiology, neurology, or psychiatry, with experience interpreting such scans in the presence of dementia • A brain SPECT or FDG-PET scan has not been obtained for the same indication • The referring and billing provider(s) have documented the appropriate evaluation of the Medicare beneficiary 2. FDG-PET Requirements for Coverage in the Context of a CMS-approved Practical Clinical Trial Utilizing a Specific Protocol to Demonstrate the Utility of FDG-PET in the Diagnosis, and Treatment of Neurodegenerative Dementing Diseases: • Only in the context of an approved clinical trial that contains patient safeguards and protections to ensure proper administration, use and evaluation of the FDG-PET scan All other uses of FDG-PET for patients with a presumptive diagnosis of dementia-causing neurodegenerative disease (e.g., possible or probable AD, clinically typical FTD, DLB) for which CMS has not specifically indicated coverage continue to be non-covered.	

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
Center for Medicare & Medicaid Services (2002) *National Coverage Determination for Single Photon Emission Computed Tomography (SPECT)* Manual Section #: 220.12 Effective Date: 10/01/2002 Implementation Date: 10/01/2002	NR	NR	Medicare does not include MCI, dementia, AD, FTD, DLB etc. in the list of conditions for which SPECT is covered. There is no specific indication of non-coverage.	NR
Oregon HERC (2012)	NR	1 meta-analysis, 6 case series. Complete evidence base NR.	Functional neuroimaging (PET, SPECT or fMRI) should not be covered for screening, diagnosis, or monitoring of dementia. In patients with mild cognitive impairment, imaging should not be used to predict progression of the risk of developing dementia.	No evidence for improved outcomes from any functional neuroimaging intervention.
Aetna (2013) *Clinical Policy Bulletin: Functional Magnetic Resonance Imaging* POLICY #: 0739 Effective Date: 11/09/2007 Last Review Date: 11/21/2013 Next Review Date: 09/04/2014	NR	This policy is based on 1 RCT.	Aetna considers fMRI experimental and investigational for the diagnosis, monitoring, or prognosis of AD and PD.	Further validation of the use of fMRI is warranted.

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
Aetna (2014) *Clinical Policy Bulletin: Positron Emission Tomography (PET)** POLICY #: 0071 Effective Date: 10/23/1995 Last Review Date: 03/28/2014 Next Review Date: 01/22/2015	NR	NR for neurologic indications.	Aetna considers PET scans experimental and investigational for AD (including the use of florbetapir-PET for imaging beta-amyloid), dementia, Parkinson's disease, or for other neurologic indications not listed as medically necessary in this policy because of insufficient evidence of its effectiveness.	There is insufficient evidence of effectiveness for PET scanning.
Aetna (2013) *Clinical Policy Bulletin: Single Photon Emission Computed Tomography (SPECT)* POLICY #: 0376 Effective Date: 03/08/2000 Last Review Date: 07/12/2013 Next Review Date: 04/24/2014	NR	NR	Aetna considers SPECT experimental and investigational the following in these situations: • Initial or differential diagnosis of members with suspected dementia (e.g., AD, DLB, FTD).	The diagnostic value of SPECT has not been established in the peer-reviewed medical literature.
Cigna (2006) *Nuclear Imaging including Single-Photon Emission Computed Tomography (SPECT)* POLICY #: 0169 Effective Date: 09/15/2004 Revised Date: 10/15/2006	NR	This policy is based on 14 reports examining neuroimaging in the brain, as well as information from multiple professional societies/ organizations.	Cigna covers SPECT as medically necessary for dementia (including AD) when other imaging studies are inconclusive or contraindicated.	Characteristic patterns have been described in AD but have not been fully substantiated with clinicopathologic correlations. At this stage, results should be considered supportive but not diagnostic.

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
Cigna (2012) *Functional Magnetic Resonance Imaging (fMRI)* POLICY #: 0478 Effective Date: 07/15/2012 Next Review Date: 07/15/2013	NR	NR	Cigna considers fMRI for the diagnosis of dementia, AD, and PD to be investigational.	fMRI is not routinely employed in clinical practice for diagnosis of dementia, AD, and PD.
Cigna (2006) *Positron Emission Tomography (PET)** POLICY #: 0091 Effective Date: 06/15/2006 Original Effective Date: 06/15/2004	NR	This policy is based on 13 reports, including one systematic review, a 2001 AHRQ HTA, a CMS NCD, and information from multiple professional societies/organizations.	Cigna considers PET-based diagnosis of dementia, PD, and AD to be experimental.	Cigna cites a lack of demonstrated diagnostic specificity and sensitivity in the current literature.
Premera Blue Cross Blue Shield (2013) *Dopamine Transporter Imaging with Single -Photon Emission Computed Tomography (DAT-SPECT)* POLICY #: 6.01.54 Effective Date: 9/27/2013 Last Review Date: 5/28/2013	Through 5/28/2013	"Published peer-reviewed literature"	Dopamine transporter imaging with DAT-SPECT is investigational for all indications, including but not limited to: • Aiding in the diagnosis of patients with clinically uncertain parkinsonian syndromes • DLB • Monitoring of disease progression	• In the absence of comparisons with the gold standard (neuropathological exam), long-term clinical follow-up may be used as a surrogate standard to evaluate the ability of DAT-SPECT to discriminate degenerative PS from normality or from non-degenerative disorders that present with similar symptoms, and to discriminate DLB from AD.

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
Premera Blue Cross Blue Shield (2013) *Functional Magnetic Resonance Imaging (fMRI)* POLICY #: 6.01.47 Effective Date: 08/16/2013 Last Review Date: 08/12/2013	NR	NR	fMRI is considered investigational for all indications other than for preoperative investigation for neurosurgery candidates.	NR

Clinical Guidelines

The National Guideline Clearinghouse (NGC), major bibliographic databases, professional societies, and Medline were searched for guidelines related to functional neuroimaging for the diagnosis of dementia. Key word searches were performed: "functional neuroimaging" OR "functional imaging" OR "PET" OR "positron emission tomography" OR "Positron-Emission Tomography" OR "SPECT" OR (Single AND Photon AND Emission AND Computed AND Tomography) OR "Tomography, Emission-Computed, Single-Photon" OR "fMRI" OR "functional MRI" OR "functional magnetic resonance imaging." Sixteen documents were recovered that contained specific recommendations regarding this topic.

Guidelines from the following sources are summarized:

- European Federation of the Neurological Societies
- The National Institute on Aging, Alzheimer's Association
- Canadian Consensus Conference on Diagnosis and Treatment of Dementia (imaging group)
- National Guideline Clearinghouse

In addition, one guideline was identified during the literature search and was included, and one statement was identified from the "Choosing Wisely" campaign and is noted below.

A brief synopsis of each guideline is included below. Details of each included recommendation for functional neuroimaging, including the class/grade of recommendation and the level of evidence, can be found in Table 3 that follows.

The Society of Nuclear Medicine, 2012[38]: SNM Practice Guideline for Dopamine Transporter Imaging with ^{123}I-ioflupane SPECT 1.0. DaT-SPECT is recommended for differentiating between dementia with Lewy Bodies or Alzheimer's disease.

European Federation of the Neurological Societies, 2012[51]: EFNS task force: the use of neuroimaging in the diagnosis of dementia. Routine functional neuroimaging may not be beneficial in typical cases of dementia, but are recommended in cases where the diagnosis remains in doubt after clinical and structural imaging. Functional neuroimaging may help to differential different kinds of dementia from other pathologies.

The National Institute on Aging, Alzheimer's Association, 2011[97]: The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Biomarker evidence from FDG-PET imaging are not recommended for the diagnosis of AD.

The National Institute on Aging, Alzheimer's Association, 2011[9]: The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. The definitive absence of evidence of neuronal injury (FDG-PET) strongly suggests that the MCI syndrome is not due to AD.

Clinical Research Center for Dementia of South Korea, 2011[113]: Clinical Practice Guideline for Dementia; Part I: Diagnosis and Evaluation. Functional imaging is not recommended as the only

imaging measure, but may be useful in cases where diagnostic uncertainty remains after other work up.

National Institute for Health and Clinical Excellence, Social Care Institute for Excellence, 2007[14]: *A NICE-SCIE Guideline on supporting people with dementia and their caregivers in health and social care.* Functional neuroimaging is recommended for use in differentiating different types of dementia, if the diagnosis is in doubt.

American College of Radiology, 2010[112]: *ACR Appropriateness Criteria dementia and movement disorders.* FDG-PET and HMPAO SPECT may be appropriate in cases of probable and possible Alzheimer's disease, suspected frontotemporal dementia and suspected vascular dementia (or mixed VAD and AD), for "problem solving." fMRI is usually not appropriate.

Scottish Intercollegiate Guidelines Network, 2006[119]: *Management of patients with dementia. A national clinical guideline.* SPECT may be used with CT to aid in the differential diagnosis of dementia, when in doubt.

Regional Health Council (Italy), 2011[115]: *Dementia. Diagnosis and Treatment.* PET and SPECT should not be routinely used in assessing dementia.

European Federation of Neurological Societies, 2010[70]: *EFNS guidelines for the diagnosis and management of Alzheimer's disease.* FDG-PET and SPECT are recommended adjuncts when the diagnosis remains in doubt. Dopaminergic SPECT is useful to differentiate AD from DLB. EEG is recommended in differential diagnosis of atypical clinical presentations of AD.

European Federation of Neurological Societies, 2012[167]: *EFNS guidelines on the diagnosis and management of disorders associated with dementia.* SPECT is recommended for distinguishing DLB and AD dementias. SPECT and PET techniques are useful in FTLD diagnosis.

Diagnostic Pathway Expert Reference Group, 2013[125]: *Guidance on the use of neuroimaging in the assessment of dementia in Primary Care (NHS-England).* FDG-PET, HMPAO-SPECT and DaTscans can assist in the diagnosis of dementia, but due to the cost of these interventions they recommended reserving their use in a specialist memory assessment service.

Canadian Consensus Conference on Diagnosis and Treatment of Dementia (imaging group), 2013[168]: *Clinical applications of neuroimaging in patients with Alzheimer's disease: a review from the Fourth CCCDTD 2012.* FDG-PET is recommended for differential diagnosis purposes; SPECT rCBF if an FDG-PET scan is not available. There was inadequate consensus on imaging for the use of a functional imaging modality in patients with MCI.

Canadian Consensus Conference on Diagnosis and Treatment of Dementia (imaging group), 2013[27]: *Role of emerging neuroimaging modalities in patients with cognitive impairment: a review from the CCCDTD 2012.* fMRI is not recommended for the clinical investigation of patients presenting with cognitive impairment.

Dementia with Lewy bodies Consortium, 2005[22]: *Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium.* SPECT and PET imaging is recommended, based on their suggestive and supportive features towards DLB diagnosis. DAT scanning is useful to distinguish DLB and AD disorders.

"Choosing Wisely" statement from The Society of Nuclear Medicine and Molecular Imaging, 2013[30]: *Five things physicians and patients should question:* Don't use PET imaging in the

evaluation of patients with dementia unless the patient has been assessed by a specialist in this field. Without objective evidence of dementia, the potential benefit of PET is unlikely to justify the cost or radiation risk. Dementia subtypes have overlapping patterns in PET imaging. Clinical evaluation and imaging often provide additive information and should be assessed together to make a reliable diagnosis and plan care.

Table 3. Clinical Guidelines

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
The Society of Nuclear Medicine (SNM) *SNM Practice Guideline for Dopamine Transporter Imaging with ^{123}I-ioflupane SPECT 1.0 (2012)[38]*	No systematic literature search performed	^{123}I-ioflupane SPECT Diagnoses included: DLB, AD	NR	^{123}I-ioflupane SPECT can be used to help differentiate between DLB and AD. - AD exhibits normal to mildly diminished striatal binding - DLB exhibits significantly decreased striatal binding	NR	NR
European Federation of the Neurological Societies (EFNS) *EFNS task force: the use of neuroimaging in the diagnosis of dementia (2012)[51]*	Through April 2012	Functional neuroimaging (SPECT, PET) Diagnoses included: Alzheimer's disease (AD), vascular brain diseases, dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), primary progressive aphasia (PPA)	Articles published in English (including but not limited to meta-analyses, systematic reviews, and evidence-based management guidelines.	Consensus recommendations were given and graded according to the EFNS guidance regulations. "Good practice points" were stated as opinion when there was lack of evidence but consensus amongst experts was reached. **Recommendations for functional imaging:** 1. Although typical cases of dementia may not benefit from routine SPECT or PET imaging, these tools are recommended in those cases where diagnosis remains in doubt after clinical and structural MRI work-up and in particular clinical settings. 2. Functional imaging can be of value to diagnose (or exclude) a neurodegenerative dementia in those subjects with cognitive impairment presenting with severe psychiatric disturbances (including depression and agitation) and in cases where proper cognitive	NR* Good practice point	class II, level A* NR

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Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
				testing is difficult, that is, with no language in common with the patient.		
				3. Normal FDG PET scan findings, in the presence of the suspicion of dementia, make a neurodegenerative diagnosis less likely.	NR	class II, level A
				4. The overall regional pattern of metabolic impairment of the posterior cingulate/precuneus and lateral temporoparietal cortices, more accentuated than frontal cortex deficits, together with the relative preservation of the primary sensorimotor and visual cortices, basal ganglia and cerebellum defines the distinct metabolic phenotype of AD.	NR	class II, level A
				5. AD-like metabolic patterns in patients with MCI are predictive of conversion to AD within several years.	NR	class II, level A
				6. Occipital hypometabolism, particularly in the primary visual cortex, may be more common in DLB than AD on a group basis. However, on individual scans, the appearance of DLB and AD can be identical. Moreover, occipital hypometabolism is not a specific marker for DLB and can be associated with AD.	NR Good practice point	class II, level B NR
				7. Although an overlap of functional abnormalities between FTD and AD has been shown to occur, the presence of posterior temporal and parietal brain hypoperfusion or hypometabolism is predictive of a pathological diagnosis of AD, whereas a disproportionate reduction in frontal perfusion/metabolism is more common in FTD.	NR	class II, level A

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
				8. In PPA patients, bilateral posterior temporoparietal hypometabolism (PET) or hypoperfusion (SPECT) is predictive of AD pathology; normal bilateral posterior tempoparietal function is specific for FTLD.	NR	class III, level C
				9. Dopaminergic SPECT is useful to distinguish DLB from AD, especially when there are no clear extrapyramidal symptoms and signs. However a negative 123I-FP-CIT scan does not necessarily exclude a diagnosis of probable DLB, as around 20% of individuals with probable DLB appear to have normal.	NR NR	class I, level A class I, level A
				10. Dopaminergic SPECT can be useful in differentiating DLB from long-term psychiatric patients on neuroleptic drugs, who's parkinsonism may be drug-induced.	Good practice point	NR
				Recommendations for non-conventional MRI: 1. At present, advanced MRI techniques do not have a role in the diagnosis or routine assessment or monitoring of neurodegenerative dementia.	Good practice point	Class IV
				2. The reliability and reproducibility of advanced MRI techniques requires further evaluation, and serious efforts are under way to achieve harmonization of both acquisition and post-processing procedures.	NR	NR
The National Institute on Aging The Alzheimer's Association	No systematic literature search performed	PET Diagnoses included: AD	NR	**Recommendations for functional imaging:** In persons who meet the core clinical criteria for probable AD dementia **biomarker evidence (i.e.,** biomarkers of downstream neuronal degeneration such as **FDG-PET)** may increase the certainty that the basis of the clinical dementia syndrome is the	NR	NR

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
The diagnosis of dementia due to Alzheimer's disease: Recommenda-tions from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease (2011)[97]				AD pathophysiological process. However, **we do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time for the following reasons:** 1. The core clinical criteria provide very good diagnostic accuracy and utility in most patients; 2. More research needs to be done to ensure that criteria that include the use of biomarkers has been appropriately designed; 3. There is limited standardization of biomarkers from one locale to another; 4. Access to biomarkers is limited to varying degrees in community settings. Presently, the use of biomarkers to enhance certainty of AD pathophysiological process may be useful in three circumstances: • Investigational studies • Clinical trials • Optional clinical tools for use where available and when deemed appropriate by the clinician. Further studies are needed to prioritize biomarkers and to determine their value and validity in practice and research settings.		
The National Institute on Aging The Alzheimer's Association The diagnosis of	No systematic literature search performed	FDG-PET, SPECT Diagnoses included: MCI due to AD	NR	For MCI subjects whose clinical and cognitive MCI syndrome is consistent with AD as the etiology, the addition of biomarkers (e.g. biomarkers of neuronal injury such as hypometabolism or hypoperfusion on **PET** or **SPECT**) may affect levels of certainty that the AD pathophysiological process is the underlying cause of the MCI syndrome.	NR	NR

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease (2011)[9]				The definitive absence of evidence of neuronal injury strongly suggests that the MCI syndrome is not due to AD. In such situations, search for biomarkers that reflect alternative pathological processes should be considered. Such biomarkers are not as well established as those for AD. They may include: **(1)** prominent frontal or frontotemporal hypometabolism, hypoperfusion, or atrophy that often reflects frontotemporal lobar degeneration, **(2)** loss of dopamine transporters seen with SPECT imaging, often seen in DLB.		
Clinical Research Center for Dementia of South Korea

Clinical Practice Guideline for Dementia; Part I: Diagnosis and Evaluation (2011)[113] | CPGs: 1997-2007

SRs: 2007-NR | FDG-PET, SPECT

Diagnoses included: AD, VaD, DLB, FTD, Huntington's disease, NPH | 4 CPGs selected to adapt to the guideline (of 22 CPGs reviewed), SRs | Structural and functional brain imaging should be performed for the diagnosis of dementia. As functional brain imaging, (FDG) PET or (HMPAO) SPECT can be used together with structural imaging. | NR | A[†] |
| | | | | Functional imaging may be useful in those cases where diagnostic uncertainty remains after clinical and structural imaging work up. They should not be used as the only imaging measure. | NR | B |
| National Institute for Health and Clinical Excellence – Social Care Institute for Excellence (NICE-SCIE) | Database inception-March 2006 | FDG-PET, SPECT, FP-CIT SPECT

Diagnoses included: AD, VaD, DLB, FTD, delirium | Observational case-control and cohort studies, details NR | Perfusion HMPAO SPECT should be used to help differentiate AD, VaD and FTD if the diagnosis is in doubt. | NR | NR |
| | | | | FDG-PET should be used to help differentiate AD, VaD and FTD if the diagnosis is in doubt and HMPAO SPECT is unavailable. | NR | NR |

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
A NICE-SCIE Guideline on supporting people with dementia and their carers in health and social care (2007)[14]				FP-CIT SPECT should be used to help establish the diagnosis in those with suspected dementia with DLB if the diagnosis is in doubt.	NR	NR
				EEG should not be used as a routine investigation in people with dementia.	NR	NR
				EEG should be considered if a diagnosis of delirium or FTD is suspected, or in the assessment of associated seizure disorder in those with dementia.	NR	NR
American College of Radiology ACR Appropriateness Criteria dementia and movement disorders (2010)[112]	Dates NR	fMRI, FDG-PET, HMPAO SPECT Diagnoses included: AD, FTD, DLB, VaD	NR	FDG-PET may be appropriate in cases of probable AD, for "problem solving".	6*	NR
				FDG-PET is usually appropriate in cases of possible AD, for "problem solving".	7	NR
				HMPAO SPECT may be appropriate in cases of probable AD, for "problem solving".	5	NR
				HMPAO SPECT may be appropriate in cases of possible AD, for "problem solving".	6	NR
				fMRI is usually not appropriate in cases of probable AD, for "research purposes".	2	NR
				fMRI is usually not appropriate in cases of possible AD.	2	NR
				FDG-PET is usually appropriate in cases of suspected FTD, for "problem solving".	7	NR
				HMPAO SPECT may be appropriate in cases of	6	NR

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
				suspected FTD, for "problem solving".		
				fMRI is usually not appropriate in patients with suspected FTD.	2	NR
				FDG-PET is usually appropriate in cases of suspected DLB, for "problem solving".	7	NR
				HMPAO SPECT is usually appropriate in cases of suspected DLB, for "problem solving".	7	NR
				fMRI is usually not appropriate in cases of suspected DLB.	2	NR
				FDG-PET may be appropriate in cases of suspected VaD or mixed VaD and AD, for "problem solving".	6	NR
				HMPAO SPECT may be appropriate in cases of suspected VaD or mixed VaD and AD, for "problem solving".	5	NR
				fMRI is usually not appropriate in cases of suspected VaD or mixed VaD and AD.	2	NR
Scottish Intercollegiate Guidelines Network (SIGN) Management of patients with dementia. A national clinical	1994-2004	SPECT, EEG Diagnoses included: AD, VaD, DLB, FTD	SRs and cohort studies, details NR	SPECT may be used in combination with CT to aid the differential diagnosis of dementia when the diagnosis is in doubt.	C[§]	2+ to 2++[§]
				There is not enough evidence to support the routine use of EEG to assess dementia.	B[§]	2+[§]

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
guideline (2006)[119]						
Regional Health Council (Italy) Dementia. Diagnosis and treatment (2011)[115]	No systematic search performed	PET, SPECT Diagnoses included: NR	DSM-IV	PET and SPECT should not be routinely used in assessing dementia.	NR	NR**
European Federation of Neurological Societies (EFNS) EFNS guidelines for the diagnosis and management of Alzheimer's disease (2010)[70]	Before May 2009	FDG-PET, SPECT, EEG Diagnoses included: AD, DLB	Original research articles, meta-analysis, and systematic reviews; details NR	FDG-PET and perfusion SPECT are useful adjuncts when diagnosis remains in doubt. Dopaminergic SPECT is useful to differentiate AD from DLB. EEG is recommended in differential diagnosis of atypical clinical presentations of AD.	B* A NR	NR* NR Good practice point
European Federation of Neurological Societies (EFNS) EFNS guidelines on the diagnosis and management of disorders associated with dementia (2012)[167]	Before June 2011	SPECT, PET Diagnoses included: AD, FTD, FTLD, DLB	NR	SPECT perfusion is useful to distinguish DLB and CBS from AD. SPECT pre-synaptic dopamine transporter imaging is useful to distinguish DLB from non-DLB dementias.	NR B	Good practice point NR
				SPECT and PET perfusion and metabolic techniques are highly useful in FTLD (other dementia) diagnosis.	C	III

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
Diagnostic Pathway Expert Reference Group (DPERG){NHS England: Strategic Clinical Networks Guidance on the use of neuro-imaging in the assessment of dementia in Primary Care (NHS-England) (2013){NHS England: Strategic Clinical Networks (South West), 2013 #19656}	No systematic search performed	FDG-PET, HMPAO-SPECT Diagnoses included: AD, FTD, DLB	NR	FDG-PET or HMPAO-SPECT can help in diagnosing and differentiating AD from FTD and DaTscans™ can assist in the diagnosis of DLB. Given the cost of these interventions, we would suggest they are reserved for use in a specialist memory assessment service.	NR	NR
Canadian Consensus Conference on Diagnosis and Treatment of Dementia, imaging group (CCCDTD) Clinical applications of neuroimaging in patients with Alzheimer's disease: a review	January 2006 – January 2012	FDG-PET, SPECT, PET amyloid imaging, dopamine presynaptic imaging agents Diagnoses included: AD	208 articles for PET and 98 articles for SPECT	For a patient whose underlying pathological process is still unclear (after clinical and structural imaging evaluations), preventing adequate clinical management, we recommend that the specialist obtains an 18F-FDG PET scan for differential diagnosis purposes.	Grade 1B[**]	NR[**]
				If such a patient cannot be practically referred for a FDG-PET scan, we recommend that a SPECT rCBF study be performed for differential diagnosis purposes.	Grade 2C	NR
				There was only partial consensus for the proposition that for a patient with MCI evaluated	NR	NR

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
from the Fourth CCCDTD 2012 (2013)[168]				by a dementia specialist and in whom clinical management would be influenced by evidence of an underlying neurodegenerative process, an ^{18}F-FDG PET scan be performed or, if not available, then a SPECT rCBF study be performed.		
Canadian Consensus Conference on Diagnosis and Treatment of Dementia, imaging group (CCCDTD) Role of emerging neuroimaging modalities in patients with cognitive impairment: a review from the CCCDTD 2012 (2013)[27]	January 2006 – April 2012	fMRI Diagnoses evaluated: AD, MCI	NR	fMRI is not currently recommended for the clinical investigation of patients presenting with cognitive impairment.	NR NR NR	3b[††] 3b 3b
Dementia with Lewy bodies Consortium (DLB) Diagnosis and management of dementia with Lewy bodies: third report of the DLB	No systematic search performed	DAT, PET, SPECT Diagnoses evaluated: DLB	NR	Suggestive features for DLB[‡‡]: • Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging	NR	NR
				Supportive features for DLB[§§]: • Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity	NR	NR

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
Consortium (2005)[22]				Low striatal DAT activity also occurs in DLB but is normal in AD, making DAT scanning particularly useful in distinguishing between the two disorders.	NR	NR

Clinical Committee Findings and Decisions

Efficacy Considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening.
- Other morbidity concerns
- Short term or direct complication versus long term complications
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost Impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next Step: Cover or No Cover

If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover with Conditions

If covered with conditions, the Committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?

- Refer to evidence identification document and discussion.
- Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
- Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:

- What are the known conditions/criteria and evidence state
- What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical Committee Evidence Votes

First Voting Question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Is there sufficient evidence under some or all situations that the technology is:

	Unproven (no)	Equivalent (yes)	Less (yes)	More (yes)
Effective				
Safe				
Cost-effective				

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;

- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective

- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;

- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

_____Not Covered _____ Covered Unconditionally _____ Covered Under Certain Conditions

Discussion Item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next Step: Proposed Findings and Decision and Public Comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?

2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next Step: Final Determination

Following review of the proposed findings and decision document and public comments:

Final Vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes the process is concluded.

If no, or an unclear (i.e., tie) outcome Chair will lead discussion to determine next steps.