Agency Medical Director Comments

Neuroimaging for Dementia

January 16, 2014

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

Agency Medical Directors’ Concerns

- Safety = Medium
- Efficacy = Medium
- Cost = Medium
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.

Meta-analyzed Estimates of Dementia Prevalence (%)

<table>
<thead>
<tr>
<th>Region</th>
<th>Sex</th>
<th>Age group (years)</th>
<th>Std prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>60-64</td>
<td>65-69</td>
</tr>
<tr>
<td>USA</td>
<td>M</td>
<td>1.3</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>1.0</td>
<td>1.8</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>1.1</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Adapted from: Dementia: a public health priority
Neuroimaging for Dementia

Functional Neuroimaging
Modalities of Interest

• Positron emission tomography
  – ¹⁸F-FDG-PET
  – ¹¹C-DTBZ-PET

• Single photon emission computed tomography (SPECT)
  – HMPAO –SPECT
  – ¹²³I-FT-CIT-SPECT

• Functional magnetic resonance imaging (fMRI)

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?
Neuroimaging for Dementia

Current State Agency Policy

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
<th>Medicaid</th>
<th>UMP</th>
<th>DOC</th>
<th>LNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>70554</td>
<td>fMRI, brain, without physician</td>
<td></td>
<td>NC</td>
<td>PA</td>
<td>PA</td>
</tr>
<tr>
<td>70555</td>
<td>fMRI, brain, with physician</td>
<td></td>
<td>NC</td>
<td>PA</td>
<td>PA</td>
</tr>
<tr>
<td>78607</td>
<td>SPECT imaging of brain</td>
<td></td>
<td>C</td>
<td>PA</td>
<td>PA</td>
</tr>
<tr>
<td>78608</td>
<td>PET imaging of brain</td>
<td></td>
<td>PA</td>
<td>PA</td>
<td>PA</td>
</tr>
</tbody>
</table>

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

Neuroimaging for Dementia: State Agency Utilization

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

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

Costs are reported for non-Medicare members only
## Neuroimaging for Dementia: State Agency Utilization

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

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

Costs are reported for Fee for Service clients only.
Gary Franklin, Medical Director
WA - Department of Labor & Industries
January 16, 2015

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**
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.

- **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.
Neuroimaging for Dementia

Diagnostic Accuracy - Cont.

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

- **fMRI**
  - No data

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.
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

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.
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

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.
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.

Neuroimaging for Dementia

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
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

- **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.
Neuroimaging for Dementia

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

Questions?

More Information:

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

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Salary or payments such as consulting fees or honoraria in excess of $10,000.</td>
<td></td>
<td>✓</td>
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<tr>
<td>2. Equity interests such as stocks, stock options or other ownership interests.</td>
<td></td>
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<tr>
<td>3. Status or position as an officer, board member, trustee, owner.</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>4. Loan or intellectual property rights.</td>
<td></td>
<td>✓</td>
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<tr>
<td>5. Research funding.</td>
<td>✓</td>
<td></td>
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<tr>
<td>6. Any other relationship, including travel arrangements.</td>
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If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

NIH

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

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] [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

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 Consulting Staff, Shriners Hospital for Children, Portland, Oregon.
2002-2012 Assistant Professor of Neurology, Oregon Health & Science University
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
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)

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

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
$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 Neurodegenerative 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) 03/01/13-02/28/15 no 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).
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

Clinical Trials (2004 - present): 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 Ila/Ilb, 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

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 Disease. 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

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-Investigator
Sponsor: Janssen

Role: Co-Investigator
Sponsor: Janssen

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 Randomized, Double-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Tolerability of Dimebon (Latrepiridine) 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: Eli Lilly and Company

Role: Co-Investigator
Sponsor: Elan

Role: Co-Investigator
Sponsor: Myriad Pharmaceuticals

Role: Co-Investigator
Sponsor: Ono Pharmaceuticals

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-Controlled, 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

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)

Publications/Creative Work:

Peer-reviewed


3. DB Howieson, PhD, R Camicioli, MD, J Quinn, MD, LC Silbert, MD, B Care, MM Moore, A Dame, G Sexton, PhD, JA Kaye, MD. Natural History of Cognitive Decline in the Old Old. *Neurology. 60:1489-1494, 2003 May.*


7. J.A. Kaye, MD; M.M. Moore, B.S.; D. Galasko, MD; U.K. Craig, PhD; R. Adonay, B.S.; and L. Silbert, MD. Brain Volumes in Guam dementia vs Parkinson dementia complex vs aging Chamorro adults. *Neurology. 69(2):196-9, 2007 July*


24. Hiroko H. Dodge, PhD, 1) 2) Jian Zhu, MS, 3) Danielle Harvey, PhD, 4) Lisa C. Silbert, MD, 1)5) Jeffrey A. Kaye, MD, 1)5), Robert Koepppe, PhD, 6) Roger Albin, MD, 2)7) for the Alzheimer’s Disease Neuroimaging Initiative*. Biomarker Progressions Predict Stage-Specific Cognitive Decline in Alzheimer Disease. Alzheimer’s & Dementia 2014. Conditional acceptance.


LC Silbert MDa,b, D Erten-Lyons MDa,b, HH Dodge PhDa, JA Kaye MDa,b, H Tran BSa, S Stanfield BSa, B Oken MDa, K Wild, PhDa, R Woltjer MD, PhDa. Relationship between quantitative Tau, β-amyloid and Age in Alzheimer’s Dementia. In final preparations for submission.

Abstracts


Galasko, D., Salmon, D., Olichney, J., Craig U., Kaye, J., Silbert, L., Thal, L. Diverse Types of Pathology Underlie Dementia in Older Chamorros. Neurology 60 (suppl.1); 2003.

Quinn, J., Silbert, L., Kulhanek, D., Dang, T., Moore, M., Kaye, J. Plasma Beta Amyloid 1-42 Is Stable over 8 weeks in Alzheimer’s Patients Initiated Donepezil. Neurology 60 (suppl.1); 2003.

Kaye, J., Moore, M., Dame, A., Howieson, D., Quinn, J., Silbert, L., Zitelburger, T., Friedman, D. Distinguishing Features of the Oldest Old with Elite Memory. Neurology 60 (suppl.1); 2003.


Kaye, J., Moore, M, Galasko, D., Craig, U., Adonay, R., Silbert, L. Family History of Mariana’s Dementia (MD) or Parkinsonism-Dementia Complexes (PDC) is Associated with Differences in Brain Volume Among Chamorro Adults. Neurology 62 (suppl. 5), 2004.

Erten-Lyons, D., Moore, M, Howieson, D., Quinn, J., Silbert, L., Kaye, J. Rates of Brain Volume Loss Prior to Diagnosis Identify MCI Patients Who are destined to Develop Dementia. Neurology 62 (suppl. 5), 2004.


Kaye JA, Moore MM, Galasko DR, Miller F, Craig UK, Silbert LC, Adonay RS. Healthy Chamorro adults and those with Marianas Dementia (MD) are distinguished by patterns of cortical atrophy which differ from European and African American Elderly. Neurology 64 (suppl. 1), pp A391, April, 2005.

Deniz Erten-Lyons, Felicia Ferguson, Diane Howeison, Milar Moore, Lisa Silbert, Joseph Quinn, Jeffrey Kaye. Elderly with more medical illnesses have smaller brains and are more resistant to cognitive decline. Neurology 64 (suppl. 1), pp A230, April, 2005.


Jonathan Nelson1,4, Jennifer Young1, Marjorie Grafe1,2, Randy Woltjer2, Joseph Quinn3, Patricia Kramer3, Lisa Silbert3, Nabil J. Alkayed1,4. Role of Soluble Epoxide Hydrolase in Age-related Vascular Cognitive Decline. Winter Eicosanoid Conference. Baltimore, Maryland, March 2014


Invited Lectures and Conference Presentations:

International and National


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

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

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)

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.

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

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.

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.

Challenges in Vascular Dementia Research. OHSU
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  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  Chairman’s Roundtable Presentation. Imaging and White Matter Change in Aging and Dementia Research. 2/24/2011, 2 hrs.


2010  When it’s 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  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


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, Physician 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


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


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
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

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.
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; Vancouver 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 Alzheimer’s 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 Alzheimer’s, 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   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.


2002-2003 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.
Order of Scheduled Presentations:

Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment

<table>
<thead>
<tr>
<th>Name</th>
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<td>1 David Djang, MD</td>
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Disclosure
Any unmarked topic will be considered a "Yes"

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<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
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<tr>
<td>1. Salary or payments such as consulting fees or honoraria in excess of $10,000.</td>
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<td>No</td>
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<td>2. Equity interests such as stocks, stock options or other ownership interests.</td>
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<td>3. Status or position as an officer, board member, trustee, owner.</td>
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<td>4. Loan or intellectual property rights.</td>
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<td>5. Research funding.</td>
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<td>6. Any other relationship, including travel arrangements.</td>
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If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

If yes to #7, provide name and funding Sources:

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<th>Potential Conflict Type</th>
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<td>7. Representation: if representing a person or organization, include the name and</td>
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<tr>
<td>funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).</td>
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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.

David Djang

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
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

- 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

- 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

<table>
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<tr>
<th>Symptoms</th>
<th>Pathology</th>
<th>Diagnostic criteria</th>
<th>Treatment</th>
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</table>
| **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 |

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# Mild cognitive impairment

- 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

<table>
<thead>
<tr>
<th>Measures</th>
<th>EFNS 2012 guideline recommendations for use</th>
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| **18F-FDG-PET**           | • 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                                                                                                                                                             |
| **123I-FP-CIT-SPECT**     | • dopaminergic nigrostriatal 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

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

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

Inclusion criteria (PICO)

- **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

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)

<table>
<thead>
<tr>
<th>Quality rating</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>High confidence that the evidence reflects the true effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>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.</td>
</tr>
<tr>
<td>Low</td>
<td>Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.</td>
</tr>
</tbody>
</table>
Provide a summary of the inter-rater and intra-rater diagnostic reliability (reproducibility)

Reliability: Overview of evidence base

- **FDG-PET**: 7 studies (5 CoE I, 1 CoE II, 1 CoE III); N = 45-132
- **11C-DTBZ-PET**: 1 study (CoE II); N = 27
- **HMPAO-SPECT**: 2 studies (CoE III); N = 16-57
- **123I-FT-CIT-SPECT**: 2 studies (CoE I); N = 20-288
- **fMRI**: no evidence
Context Question: Diagnostic Reliability

<table>
<thead>
<tr>
<th>Imaging modality: diagnosis</th>
<th>Inter-rater reliability</th>
<th>Intra-rater reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG-PET: AD vs. FTD</td>
<td>0.72 - 0.81 (3 studies, 2-6 raters, N=45-132)</td>
<td>76% of cases (1 study, 12 raters, N=45)</td>
</tr>
<tr>
<td>FDG-PET: AD vs. other dementias</td>
<td>0.52 - 0.67 (2 studies, 3 raters, N=67-110)</td>
<td>94% of cases (1 study, 2 raters, N=100)</td>
</tr>
<tr>
<td>HMPAO-SPECT: AD vs. FTD</td>
<td>0.48 (1 study, 2 raters, N=16)</td>
<td>35% of cases (1 study, 5 raters, N=57)</td>
</tr>
<tr>
<td>11C-DTBZ-PET: AD vs. FTD vs. DLB</td>
<td>0.85 (1 study, 3 raters, N=27)</td>
<td>NR</td>
</tr>
<tr>
<td>123I-FT-CIT-SPECT: DLB vs. non-DLB dementias</td>
<td>0.87 (1 study, 3 raters, N=288)</td>
<td>75% of cases (1 study, 3 raters, N=20)</td>
</tr>
</tbody>
</table>

- Provide a summary of the sensitivity and specificity based on gold standard
Accuracy: Overview of evidence base

• 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

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

**Results: KQ1**

KQ1: Overview of evidence base

- 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, 11C-DTBZ-PET, 123I-FP-CIT-SPECT**: no evidence
### KQ1: FDG-PET, AD vs. FTD

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

### KQ1: HMPAO-SPECT, AD vs. FTD

<table>
<thead>
<tr>
<th>Imaging (classification)</th>
<th>Patient presentation</th>
<th>Final SoE</th>
<th>Imaging alone (gold standard: autopsy)</th>
<th>Clinical diagnosis alone</th>
<th>Imaging + clinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold standard: autopsy</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AD prevalence: 55%</td>
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</tr>
<tr>
<td>HMPAO-SPECT (visual): AD vs. FTD</td>
<td>AD or FTD</td>
<td>Insufficient</td>
<td>Sensitivity: 65% (1 CoE IV, N=56)</td>
<td>Sensitivity: 84%</td>
<td>Sensitivity: 77%</td>
</tr>
<tr>
<td></td>
<td>Symptom duration: 4.0 yrs. (mean)</td>
<td></td>
<td>Specificity: 72% (1 CoE IV, N=56)</td>
<td>Specificity: 84% (1 CoE IV, N=56)</td>
<td>Specificity: 88%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Diagnosis through comprehensive work-up</td>
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</tr>
</tbody>
</table>
### KQ1: FDG-PET, DLB vs. AD

<table>
<thead>
<tr>
<th>Imaging (classification)</th>
<th>Patient presentation</th>
<th>Final SoE</th>
<th>Imaging alone (gold standard: autopsy)</th>
<th>Clinical diagnosis alone</th>
<th>Imaging + clinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold standard: autopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLB prevalence: 45-52%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>FDG-PET (automated):</td>
<td></td>
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</tr>
<tr>
<td>DLB or AD</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Symptom duration: 3.4 yrs. (mean from 1 study, other study NR)</td>
<td>Insufficient</td>
<td>Sensitivity: 80-90%</td>
<td>NR</td>
<td>NR</td>
<td></td>
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</tbody>
</table>

Results: KQ2

**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

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

### KQ2: FDG-PET

<table>
<thead>
<tr>
<th>Imaging (classification)</th>
<th>Outcome</th>
<th>Studies (CoE)</th>
<th>Findings</th>
<th>Final SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG-PET: Patient progression (MCI to progressive cognitive decline)</td>
<td>Reference standard: progressive cognitive decline at follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDG-PET (visual)</td>
<td>Sensitivity</td>
<td>1 CoE I N = 17 F/U: 1.6 yrs.</td>
<td>75%</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>&quot;</td>
<td>88%</td>
<td>Low</td>
</tr>
</tbody>
</table>
### KQ2: FDG-PET

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

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

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

SPECT: prediction of outcomes related to function, behavior, cognition, psychological status, depression, caregiver burden, and global health:
No evidence (insufficient evidence).
**KQ2: fMRI**

<table>
<thead>
<tr>
<th>Imaging (classification)</th>
<th>Outcome Studies (CoE)</th>
<th>Findings</th>
<th>Final SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>fMRI: Patient progression (MCI to dementia conversion)</strong></td>
<td>1 CoE III</td>
<td>55%</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Reference standard: dementia at follow-up</td>
<td>N = 33 F/U: 2.5±0.8 yrs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>fMRI: prediction of outcomes related to function, behavior, cognition, psychological status, depression, caregiver burden, and global health:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No evidence (insufficient evidence).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No evidence: FP-CIT-SPECT, DTBZ-PET, or comparison of different types of functional neuroimaging to predict progression or patient outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Results: KQ3**

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

**Results: KQ4**

KQ4. Harms

<table>
<thead>
<tr>
<th>Imaging (classification)</th>
<th>Outcome</th>
<th>Studies (CoE)</th>
<th>Findings</th>
<th>Final SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG-PET</td>
<td>Injection-related harms</td>
<td>1 CoE III N = 36 Short-term</td>
<td>0%</td>
<td>Insufficient</td>
</tr>
<tr>
<td>[123I-FP-CIT-SPECT]</td>
<td>Injection-related harms</td>
<td>1 CoE III N = 326 Procedural/Post-procedural</td>
<td>2.8% patients (10 events)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>FDG-PET, [123I-FP-CIT-SPECT]</td>
<td>Other harms (long-term harms, harms of missed diagnosis or false positive)</td>
<td>0 studies</td>
<td></td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

No evidence: HMPAO-SPECT, DTBZ-PET, fMRI
**Results: KQ5**

**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**

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

- **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**

- **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

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

---

Thank you.

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 as expressed by the following standards:

- 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:

- 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

---

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 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.

<table>
<thead>
<tr>
<th>Not Confident</th>
<th>Confident</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.</td>
<td>Very certain of evidentiary support. Further information is unlikely to change confidence</td>
</tr>
</tbody>
</table>

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;

---

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

<table>
<thead>
<tr>
<th>Safety Outcomes</th>
<th>Safety Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection related harms</td>
<td></td>
</tr>
<tr>
<td>Missed/false diagnosis</td>
<td></td>
</tr>
<tr>
<td>Other harms</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy – Effectiveness Outcomes</th>
<th>Efficacy / Effectiveness Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
</tr>
<tr>
<td>Disease progression</td>
<td></td>
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<tr>
<td>Other clinical outcomes</td>
<td></td>
</tr>
<tr>
<td>Cognition (MMSE Score)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Special Population / Considerations Outcomes</th>
<th>Special Populations/ Considerations Evidence</th>
</tr>
</thead>
<tbody>
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</table>

<table>
<thead>
<tr>
<th>Cost</th>
<th>Cost Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td></td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td></td>
</tr>
<tr>
<td>Cost-utility</td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Payer (Year)</th>
<th>Lit Search Dates</th>
<th>Evidence Base Available</th>
<th>Policy</th>
<th>Rationale/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center for Medicare &amp; Medicaid Services (CMS) (2009)</td>
<td>NR</td>
<td>NR</td>
<td>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:</td>
<td>NR</td>
</tr>
<tr>
<td>National Coverage Determination (NCD) for FDG PET for Dementia and Neurodegenerative Diseases</td>
<td></td>
<td></td>
<td>FDG-PET Requirements for Coverage in the Differential Diagnosis of AD and FTD:</td>
<td></td>
</tr>
<tr>
<td>Manual Section #: 220.6.13</td>
<td></td>
<td></td>
<td>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:</td>
<td></td>
</tr>
<tr>
<td>Effective Date: 04/03/2009</td>
<td></td>
<td></td>
<td>• 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</td>
<td></td>
</tr>
<tr>
<td>Implementation Date: 10/30/2009</td>
<td></td>
<td></td>
<td>• 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</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• The evaluation of the patient has been conducted by a physician experienced in the diagnosis and assessment of dementia</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• The evaluation of the patient did not clearly determine a specific neurodegenerative disease or other cause for the clinical</td>
<td></td>
</tr>
<tr>
<td>Payer (Year)</td>
<td>Lit Search Dates</td>
<td>Evidence Base Available</td>
<td>Policy</td>
<td>Rationale/Comments</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>symptoms, and information available through FDG-PET is reasonably expected to help clarify the diagnosis between FTD and AD and help guide future treatment</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A brain SPECT or FDG-PET scan has not been obtained for the same indication</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The referring and billing provider(s) have documented the appropriate evaluation of the Medicare beneficiary</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>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:</td>
<td></td>
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</tr>
<tr>
<td>Payer (Year)</td>
<td>Lit Search Dates</td>
<td>Evidence Base Available</td>
<td>Policy</td>
<td>Rationale/Comments</td>
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<td>-------------------</td>
</tr>
<tr>
<td>Center for Medicare &amp; Medicaid Services (2002)</td>
<td>NR</td>
<td>NR</td>
<td>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.</td>
<td>NR</td>
</tr>
<tr>
<td>National Coverage Determination for Single Photon Emission Computed Tomography (SPECT) Manual Section #: 220.12 Effective Date: 10/01/2002 Implementation Date: 10/01/2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oregon HERC (2012)</td>
<td>NR</td>
<td>1 meta-analysis, 6 case series. Complete evidence base NR.</td>
<td>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.</td>
<td>No evidence for improved outcomes from any functional neuroimaging intervention.</td>
</tr>
<tr>
<td>Aetna (2013)</td>
<td>NR</td>
<td>This policy is based on 1 RCT.</td>
<td>Aetna considers fMRI experimental and investigational for the diagnosis, monitoring, or prognosis of AD and PD.</td>
<td>Further validation of the use of fMRI is warranted.</td>
</tr>
<tr>
<td>Payer (Year)</td>
<td>Lit Search Dates</td>
<td>Evidence Base Available</td>
<td>Policy</td>
<td>Rationale/Comments</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
</tbody>
</table>
| **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. |
<table>
<thead>
<tr>
<th>Payer (Year)</th>
<th>Lit Search Dates</th>
<th>Evidence Base Available</th>
<th>Policy</th>
<th>Rationale/ Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigna (2012)</td>
<td>NR</td>
<td>NR</td>
<td>Cigna considers fMRI for the diagnosis of dementia, AD, and PD to be investigational.</td>
<td>fMRI is not routinely employed in clinical practice for diagnosis of dementia, AD, and PD.</td>
</tr>
<tr>
<td><em>Functional Magnetic Resonance Imaging (fMRI)</em></td>
<td>POLICY #: 0478</td>
<td>Effective Date: 07/15/2012</td>
<td>Next Review Date: 07/15/2013</td>
<td></td>
</tr>
<tr>
<td>Cigna (2006)</td>
<td>NR</td>
<td>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.</td>
<td>Cigna considers PET-based diagnosis of dementia, PD, and AD to be experimental.</td>
<td>Cigna cites a lack of demonstrated diagnostic specificity and sensitivity in the current literature.</td>
</tr>
<tr>
<td><em>Positron Emission Tomography (PET)</em></td>
<td>POLICY #: 0091</td>
<td>Effective Date: 06/15/2006</td>
<td>Original Effective Date: 06/15/2004</td>
<td></td>
</tr>
<tr>
<td>Premera Blue Cross Blue Shield (2013)</td>
<td>Through 5/28/2013</td>
<td>&quot;Published peer-reviewed literature&quot;</td>
<td>Dopamine transporter imaging with DAT-SPECT is investigational for all indications, including but not limited to:</td>
<td>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.</td>
</tr>
<tr>
<td><em>Dopamine Transporter Imaging with Single -Photon Emission Computed Tomography (DAT-SPECT)</em></td>
<td>POLICY #: 6.01.54</td>
<td>Effective Date: 9/27/2013</td>
<td>Last Review Date: 5/28/2013</td>
<td></td>
</tr>
<tr>
<td>Payer (Year)</td>
<td>Lit Search Dates</td>
<td>Evidence Base Available</td>
<td>Policy</td>
<td>Rationale/Comments</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
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</tr>
<tr>
<td>Premera Blue Cross Blue Shield (2013)</td>
<td>NR</td>
<td>NR</td>
<td>fMRI is considered investigational for all indications other than for preoperative investigation for neurosurgery candidates.</td>
<td>NR</td>
</tr>
<tr>
<td><em>Functional Magnetic Resonance Imaging (fMRI)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POLICY #: 6.01.47</td>
<td></td>
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<tr>
<td>Effective Date: 08/16/2013</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Last Review Date: 08/12/2013</td>
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</tr>
</tbody>
</table>
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-iodioflupane 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**: 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**: 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**: 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**: Dementia. Diagnosis and Treatment. PET and SPECT should not be routinely used in assessing dementia.

**European Federation of Neurological Societies, 2010**: 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 DBL. EEG is recommended in differential diagnosis of atypical clinical presentations of AD.

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

**Diagnostic Pathway Expert Reference Group, 2013**: 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**: 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**: Role of emerging neuroimaging modalities in patients with cognitive impairment: a review from the CCCD'TD 2012. fMRI is not recommended for the clinical investigation of patients presenting with cognitive impairment.

**Dementia with Lewy bodies Consortium, 2005**: 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 DBL and AD disorders.

**“Choosing Wisely” statement from The Society of Nuclear Medicine and Molecular Imaging, 2013**: 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

<table>
<thead>
<tr>
<th>Organization(S)</th>
<th>Title (Year)</th>
<th>Search Dates</th>
<th>Functional Neuroimaging; Diagnosis Evaluated</th>
<th>Evidence Base Available</th>
<th>Recommendations</th>
<th>Class/ Grade Of Recommendation</th>
<th>Level Of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Society of Nuclear Medicine (SNM)</td>
<td>SNM Practice Guideline for Dopamine Transporter Imaging with $^{123}$I-ioflupane SPECT 1.0 (2012) $^{38}$</td>
<td>No systematic literature search performed</td>
<td>$^{123}$I-ioflupane SPECT Diagnoses included: DLB, AD</td>
<td>NR</td>
<td>$^{123}$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</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>European Federation of the Neurological Societies (EFNS)</td>
<td>EFNS task force: the use of neuroimaging in the diagnosis of dementia (2012) $^{51}$</td>
<td>Through April 2012</td>
<td>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.)</td>
<td>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.</td>
<td>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</td>
<td>NR*</td>
<td>class II, level A*</td>
</tr>
</tbody>
</table>

* | Good practice point | | | | | | |

14
<table>
<thead>
<tr>
<th>Organization(S)</th>
<th>Search Dates</th>
<th>Functional Neuroimaging; Diagnosis Evaluated</th>
<th>Evidence Base Available</th>
<th>Recommendations</th>
<th>Class/ Grade Of Recommendation</th>
<th>Level Of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>testing is difficult, that is, with no language in common with the patient.</td>
<td>NR</td>
<td>class II, level A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. Normal FDG PET scan findings, in the presence of the suspicion of dementia, make a neurodegenerative diagnosis less likely.</td>
<td>NR</td>
<td>class II, level A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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.</td>
<td>NR</td>
<td>class II, level A</td>
</tr>
<tr>
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<td>5. AD-like metabolic patterns in patients with MCI are predictive of conversion to AD within several years.</td>
<td>NR</td>
<td>class II, level A</td>
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<td>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.</td>
<td>Good practice point</td>
<td>class II, level B</td>
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<td>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.</td>
<td>NR</td>
<td>class II, level A</td>
</tr>
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<td>Organization(S)</td>
<td>Search Dates</td>
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</table>
| The National Institute on Aging | No systematic literature search performed | PET | NR | **Recommendations for non-conventional MRI:**
| | | Diagnoses included: AD | | 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 Alzheimer’s Association | | | | **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 |

8. In PPA patients, bilateral posterior temporoparietal hypometabolism (PET) or hypoperfusion (SPECT) is predictive of AD pathology; normal bilateral posterior temporoparietal function is specific for FTLD.

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.

10. Dopaminergic SPECT can be useful in differentiating DLB from long-term psychiatric patients on neuroleptic drugs, who’s parkinsonism may be drug-induced.

**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...
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 (2011)\textsuperscript{97}

<table>
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<th>Organization(S)</th>
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<th>Evidence Base Available</th>
<th>Recommendations</th>
<th>Class/ Grade Of Recommendation</th>
<th>Level Of Evidence</th>
</tr>
</thead>
</table>
| The National Institute on Aging | No systematic literature search performed | FDG-PET, SPECT Diagnoses included: MCI due to AD | NR | 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. | NR | NR | NR | NR |
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<tr>
<th>Organization(S)</th>
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<tbody>
<tr>
<td>Clinical Research Center for Dementia of South Korea Clinical Practice Guideline for Dementia; Part I: Diagnosis and Evaluation (2011)¹²³</td>
<td>CPGs: 1997-2007 SRs: 2007-NR</td>
<td>FDG-PET, SPECT Diagnoses included: AD, VaD, DLB, FTD, Huntington’s disease, NPH</td>
<td>4 CPGs selected to adapt to the guideline (of 22 CPGs reviewed), SRs</td>
<td>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. 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.</td>
<td>NR</td>
<td>A¹</td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence – Social Care Institute for Excellence (NICE-SCIE) Database inception-March 2006</td>
<td>FDG-PET, SPECT, FP-CIT SPECT Diagnoses included: AD, VaD, DLB, FTD, delirium</td>
<td>Observational case-control and cohort studies, details NR</td>
<td>Perfusion HMPAO SPECT should be used to help differentiate AD, VaD and FTD if the diagnosis is in doubt. FDG-PET should be used to help differentiate AD, VaD and FTD if the diagnosis is in doubt and HMPAO SPECT is unavailable.</td>
<td>NR</td>
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</table>

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.
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<tr>
<th>Organization(S)</th>
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</thead>
<tbody>
<tr>
<td>A NICE-SCIE Guideline on supporting people with dementia and their carers in health and social care (2007)</td>
<td>FP-CIT SPECT should be used to help establish the diagnosis in those with suspected dementia with DLB if the diagnosis is in doubt.</td>
<td>NR</td>
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<td>EEG should not be used as a routine investigation in people with dementia.</td>
<td>NR</td>
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<td></td>
<td>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.</td>
<td>NR</td>
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<tr>
<td>American College of Radiology</td>
<td>ACR Appropriateness Criteria dementia and movement disorders (2010)</td>
<td>Dates NR</td>
<td>fMRI, FDG-PET, HMPAO SPECT Diagnoses included: AD, FTD, DLB, VaD</td>
<td>NR</td>
<td>FDG-PET may be appropriate in cases of probable AD, for “problem solving”.</td>
<td>6*</td>
<td>NR</td>
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<td>FDG-PET is usually appropriate in cases of possible AD, for “problem solving”.</td>
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<td>HMPAO SPECT may be appropriate in cases of probable AD, for “problem solving”.</td>
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<td>HMPAO SPECT may be appropriate in cases of possible AD, for “problem solving”.</td>
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<td></td>
<td>fMRI is usually not appropriate in cases of probable AD, for “research purposes”.</td>
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<td>fMRI is usually not appropriate in cases of possible AD.</td>
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<td>FDG-PET is usually appropriate in cases of suspected FTD, for “problem solving”.</td>
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<td>HMPAO SPECT may be appropriate in cases of</td>
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<tr>
<td>Scottish Intercollegiate Guidelines Network (SIGN) Management of patients with dementia. A national clinical guideline</td>
<td>1994-2004</td>
<td>SPECT, EEG Diagnoses included: AD, VaD, DLB, FTD</td>
<td>SRs and cohort studies, details NR</td>
<td>suspected FTD, for “problem solving”. fMRI is usually not appropriate in patients with suspected FTD. FDG-PET is usually appropriate in cases of suspected DLB, for “problem solving”. HMPAO SPECT is usually appropriate in cases of suspected DLB, for “problem solving”. fMRI is usually not appropriate in cases of suspected DLB. FDG-PET may be appropriate in cases of suspected VaD or mixed VaD and AD, for “problem solving”. HMPAO SPECT may be appropriate in cases of suspected VaD or mixed VaD and AD, for “problem solving”. fMRI is usually not appropriate in cases of suspected VaD or mixed VaD and AD.</td>
<td>C^5</td>
<td>2 to 2++^5</td>
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<td>There is not enough evidence to support the routine use of EEG to assess dementia.</td>
<td>B^6</td>
<td>2+^6</td>
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<td>Organization(S)</td>
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<tr>
<td>Regional Health Council (Italy)</td>
<td>Dementia. Diagnosis and treatment (2011)</td>
<td>No systematic search performed</td>
<td>PET, SPECT Diagnoses included: NR</td>
<td>DSM-IV</td>
<td>PET and SPECT should not be routinely used in assessing dementia.</td>
<td>NR</td>
<td>NR**</td>
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<tr>
<td>European Federation of Neurological Societies (EFNS)</td>
<td>EFNS guidelines for the diagnosis and management of Alzheimer’s disease (2010)</td>
<td>Before May 2009</td>
<td>FDG-PET, SPECT, EEG Diagnoses included: AD, DLB</td>
<td>Original research articles, meta-analysis, and systematic reviews; details NR</td>
<td>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.</td>
<td>B’</td>
<td>NR*</td>
</tr>
<tr>
<td>European Federation of Neurological Societies (EFNS)</td>
<td>EFNS guidelines on the diagnosis and management of disorders associated with dementia (2012)</td>
<td>Before June 2011</td>
<td>SPECT, PET Diagnoses included: AD, FTD, FTLD, DLB</td>
<td>NR</td>
<td>SPECT perfusion is useful to distinguish DLB and CBS from AD. SPECT pre-synaptic dopamine transporter imaging is useful to distinguish DBL from non-DLB dementias. SPECT and PET perfusion and metabolic techniques are highly useful in FTLD (other dementia) diagnosis.</td>
<td>B</td>
<td>Good practice point</td>
</tr>
<tr>
<td>European Federation of Neurological Societies (EFNS)</td>
<td>EFNS guidelines for the diagnosis and management of disorders associated with dementia (2012)</td>
<td>Before June 2011</td>
<td>SPECT, PET Diagnoses included: AD, FTD, FTLD, DLB</td>
<td>NR</td>
<td>SPECT perfusion is useful to distinguish DLB and CBS from AD. SPECT pre-synaptic dopamine transporter imaging is useful to distinguish DBL from non-DLB dementias. SPECT and PET perfusion and metabolic techniques are highly useful in FTLD (other dementia) diagnosis.</td>
<td>C</td>
<td>III</td>
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<td>Organization(S)</td>
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<tr>
<td>Diagnostic Pathway Expert Reference Group (DPERG)(NHS England: Strategic Clinical Networks)</td>
<td>No systematic search performed</td>
<td>FDG-PET, HMPAO-SPECT Diagnoses included: AD, FTD, DLB</td>
<td>NR</td>
<td>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.</td>
<td>NR</td>
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<tr>
<td>Canadian Consensus Conference on Diagnosis and Treatment of Dementia, imaging group (CCCDTD)</td>
<td>January 2006 – January 2012</td>
<td>FDG-PET, SPECT, PET amyloid imaging, dopamine presynaptic imaging agents Diagnoses included: AD</td>
<td>208 articles for PET and 98 articles for SPECT</td>
<td>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. 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. There was only partial consensus for the proposition that for a patient with MCI evaluated</td>
<td>Grade 1B**</td>
<td>NR**</td>
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**NR** = Not available
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<tr>
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<td>from the Fourth CCCDTD 2012 (2013)</td>
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<td>by a dementia specialist and in whom clinical management would be influenced by evidence of an underlying neurodegenerative process, an ¹⁸F-FDG PET scan be performed or, if not available, then a SPECT rCBF study be performed.</td>
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<tr>
<td>Canadian Consensus Conference on Diagnosis and Treatment of Dementia, imaging group (CCCDTD)</td>
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<td>fMRI is not currently recommended for the clinical investigation of patients presenting with cognitive impairment.</td>
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<td>Dementia with Lewy bodies Consortium (DLB)</td>
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<td>Diagnoses evaluated: AD, MCI</td>
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<tr>
<td>No systematic search performed</td>
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<td>DAT, PET, SPECT</td>
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<td>Suggestive features for DLB:</td>
<td>NR</td>
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<td></td>
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<td>Diagnoses evaluated: DLB</td>
<td></td>
<td>• Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging</td>
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<td>Supportive features for DLB:</td>
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<td>• Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity</td>
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†† Indicates Class 3b
††† Indicates grade 3b
NR Indicates not recommended/available
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<tr>
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<td>Consortium (2005)\textsuperscript{22}</td>
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<td>Low striatal DAT activity also occurs in DLB but is normal in AD, making DAT scanning particularly useful in distinguishing between the two disorders.</td>
<td>NR</td>
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</table>
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:

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<tr>
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<th>Unproven (no)</th>
<th>Equivalent (yes)</th>
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<th>More (yes)</th>
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<tr>
<td>Effective</td>
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<td>Safe</td>
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<td>Cost-effective</td>
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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.