Diagnosing Dementia –
A Guide to Biomarker Testing in the Clinic

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Disclosures

• My family and I have no significant financial or other relationship with the manufacturer of any product or service I may discuss

• Off-label use of antipsychotics for the treatment of behavioral symptoms in dementia may be discussed during Q&A. Use of these medications in dementia patients is the subject of two warnings issued by the U.S. Food and Drug Administration
Agenda

• A standardized approach to diagnosing dementia
• CSF biomarkers in the diagnostic evaluation
• Neuroimaging biomarkers in the diagnostic evaluation
• Structured reporting of brain scans in dementia
• Structural neuroimaging signatures of the dementias
• Functional neuroimaging of the dementias – an introduction
• The “Dementia Protocol”
• Final Word and Take Home Points

A standardized approach to diagnosing dementia
Why use a standardized approach to diagnosis

• The diagnosis is easily missed without a standardized approach
• In an academic primary care practice in one study
  • 76% patients with moderate to severe dementia remained undiagnosed
  • These patients were less likely to receive a full diagnostic work-up
  • In the year after screening, these patients had significantly more hospitalizations, ER visits and mortality, compared to patients with mild or no cognitive impairment
• In the GP-based Delphi-MV study in Germany, those who received a formal diagnosis of dementia had approximately a 180% higher chance of receiving anti-dementia treatment

Callahan et al., 1995; Wucherer et al., 2015

Accuracy of clinical diagnoses

• In the NACC data collected between 2005-2010, a clinical diagnosis of AD dementia was found to have
  • sensitivity of 70-87%
  • specificity of 44-70%
• In the recent Ph 3 trials of bapineuzumab, up to 36% of patients among APOE ε4 non-carriers were noted to have negative amyloid PET scans
• In an analysis of 2357 patients from the Swedish Dementia (SveDem) registry diagnosed with AD dementia in routine clinical practice, about a quarter did not have a typical AD biomarker profile

Beach et al., 2012; Salloway et al., 2014; Rosén et al., 2015
The 2-step approach to diagnosing dementia

- **Syndromal level – does this patient have dementia?**
  - Clinical history and exam – patient, collateral information (informant, medical records)
  - Cognitive screening in the office
  - Functional screening in the office
  - Referral for neuropsychological testing in selected cases

- **Disease level - What is the etiology of the dementia?**
  - Laboratory testing
  - Biomarkers
    - CSF, neuroimaging
  - Genetic studies

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**Does this patient have dementia?**

Dementia is a clinical syndrome which has **3 basic elements**:

- **Cognitive decline** from a previously known or estimated level;
- In someone who is **alert and cooperative**; and
- Which is sufficient to cause **functional impairment**

All formal definitions of dementia are based on these 3 basic elements
The NIA-AA criteria for dementia

The NIA-AA updated criteria for the presence of dementia require:

- Cognitive impairment identified from history taking and objective cognitive assessment
- Minimum of 2 cognitive domains: memory, executive, visuospatial, language, and personality/behavior
- Interference with function at work or usual activities
- Decline from previous levels of function
- Not explained by delirium or a psychiatric disorder

McKhann et al., 2011

The DSM-5 criteria for dementia

- DSM-5 criteria require
  - Subjective concern about cognition by patient/informant/clinician; and
  - Objective evidence of cognitive decline from expected level from testing or clinical assessment
- DSM-5 also distinguishes between Major and Mild NCD (previously Cognitive Disorder NOS) based on ability to function independently in everyday activities
  - Major NCD – cognitive deficits interfere with independent functioning
  - Mild NCD – cognitive deficits do not interfere with independent functioning as individuals are able to compensate

American Psychiatric Association, 2013
DSM-5 criteria – cont’d

- Dementia is subsumed under the Neurocognitive Disorders (NCD) in DSM 5
  - A substantial decline in one single cognitive domain can still receive a diagnosis of NCD
  - The term “dementia” implies degenerative dementias in older individuals
- 2 of 5 cognitive domains in DSM-IV – Memory, aphasia, apraxia, agnosia, executive function
- 1 of 6 cognitive domains in DSM-5 – Learning and memory, complex attention, language, perceptual-motor, social cognition and executive function

American Psychiatric Association, 1994; American Psychiatric Association, 2013

Cognitive domains in DSM-IV v DSM-5

<table>
<thead>
<tr>
<th>DSM-IV</th>
<th>DSM-5</th>
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<tbody>
<tr>
<td>Memory</td>
<td>Learning and memory</td>
</tr>
<tr>
<td>Aphasia</td>
<td>Language</td>
</tr>
<tr>
<td>Apraxia</td>
<td>Perceptual-motor</td>
</tr>
<tr>
<td>Agnosia</td>
<td>• Also visual perception, visuoconstruction</td>
</tr>
<tr>
<td>Executive function</td>
<td>• Executive function</td>
</tr>
<tr>
<td></td>
<td>• Complex attention</td>
</tr>
<tr>
<td></td>
<td>• Sustained, selective, divided</td>
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<tr>
<td></td>
<td>• Social cognition</td>
</tr>
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<td></td>
<td>• Recognition of emotion, Theory of mind (ToM)</td>
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</tbody>
</table>
What is the etiology of the dementia?

“The NCD’s are unique among DSM-5 categories (as they) are syndromes for which the underlying pathology, and frequently the etiology...can potentially be determined”

American Psychiatric Association, 2013

Dementia etiology in DSM-5

- Coding note for the NCD’s
  “Code based on medical or substance etiology” (DSM-5, p 603)
- 10 specific etiological subtypes of dementia in DSM-5
  - 8 of which require an additional medical code based on etiology

American Psychiatric Association, 2013
Importance of etiology to the psychiatrist

- Dementia is the *quintessential neuropsychiatric syndrome of old age*
- 85-100% of dementia patients have psychiatric symptoms during the course of dementia
  - Etiology modulates the psychiatric presentation of the disease
- A long psychiatric prodrome in many dementing disorders is becoming increasingly evident
- Etiology will increasingly determine the choice of medications as disease-specific medications are approved by the FDA
  - Cholinesterase inhibitors – avoid in FTD, use in AD and LBD
  - Pimavanserin (Nuplazid) – first medication approved for psychosis in PD in April 2016

Dementia Quality Measurement Set

- Currently undergoing revision, this establishes the current standard of care for dementia
- "Disclosure of Dementia Diagnosis" is the very first measure
- It measures patients/caregiver dyads who have been told
  - That they have dementia and
  - What disease is responsible
- Diagnosis is defined as the provider’s best current opinion about dementia etiology...may include a disclosure that diagnosis remains unknown or that a previous diagnosis must be revised

*From the AAN-APA Draft for Work Group Review and Public Comment, October 28, 2015*
What does the APA practice guideline say about etiology?

- Nothing!!
- The APA practice guideline for treating psychosis and agitation in dementia was released this month
  - Of the 15 “guideline statements”, not one addresses etiology
  - Assessment starts with noting the “type, frequency, severity, pattern, and timing of symptoms”
- Psychiatrists are still being encouraged to practice at the syndromal level!!
  Reus et al., 2016

Role of biomarkers in determining etiology - Lack of clinical-neuropathological concordance

- As one moves from the typical late-onset amnestic AD dementia toward the non-amnestic dementia syndromes:
  - “At the single patient level, no clinical pattern is pathognomonic of a specific neuropathology type, highlighting the critical role of biomarkers”
- Curiously, DSM-5 requires biomarker (neuroimaging) evidence to establish a diagnosis of “probable” FT-NCD and Vascular NCD
- But for “Probable” NCD-AD, biomarker (neuroimaging) evidence is only required to rule out mixed (concurrent vascular) etiology
  Mesulem et al., 2014; American Psychiatric Association, 2013
CSF biomarkers in the diagnostic evaluation

The ideal dementia diagnostic biomarker

Attributes of the ideal ante-mortem dementia biomarker include:

• Ability to detect fundamental features of neuropathology that can be validated at autopsy
• Ability to differentiate one form of dementia from other forms
• Ability to differentiate the stages of disease progression to guide therapy
• Highly reliable, easy to perform, and inexpensive
• Use minimally invasive sample collection, such as from peripheral tissues

Adapted from Khan and Alkon, 2015
Alzheimer's Disease biomarkers
How a clinicopathological entity became clinicobiological

- In 2007, the International Working Group (IWG) for New Research Criteria for the Diagnosis of Alzheimer's Disease (AD) proposed to anchor the diagnosis of AD on the presence of biomarkers
- For the first time, it was proposed that AD could be diagnosed in vivo and independent of the presence of dementia
- The 2011 NIA-AA diagnostic guidelines for AD were based on this framework and incorporated biomarker testing

Dubois et al., 2007; McKhann et al., 2011

AD biomarkers in the IWG and NIA-AA criteria

<table>
<thead>
<tr>
<th>NIA-AA</th>
<th>Biomarkers of brain amyloid Aβ deposition</th>
<th>Biomarkers of downstream neuronal injury</th>
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<tbody>
<tr>
<td>IWG</td>
<td>(Low) CSF Aβ42 (+) Amyloid PET (Elevated) CSF tau (p-tau and t-tau)</td>
<td></td>
</tr>
<tr>
<td>Pathophysiological</td>
<td>(+) FDG-PET (↑) temporal and medial parietal atrophy on structural neuroimaging</td>
<td></td>
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<tr>
<td>Topographical</td>
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Dubois et al., 2010; McKhann et al., 2011; Wellington et al., 2016
Alzheimer’s Biomarkers Standardization Initiative
2014 consensus recommendations

• All three core AD biomarkers (Aβ42, total-tau and phospho-tau$_{181}$) should
be analyzed

• In patients with intermediate phospho-tau$_{181}$ values
  • Adding Aβ40 and Aβ42/Aβ40 ratio improved the sens, spec and diagnostic accuracy to
    80% in differentiating AD from non-AD dementia

• The normal and pathologic reference ranges of AD CSF biomarkers vary up
  to 20-30% between different centers; when in doubt, call the lab
  Molinuevo et al., 2014; Slaets et al., 2013

CSF Biomarkers in AD

• Individually, core biomarkers have a sensitivity of 82-86% for distinguishing
  AD patients from controls or other dementias

• Combinations improve diagnostic accuracy, especially when biomarker
  results are “conflicting”

• Core biomarkers can be combined in several ways
  • Simple ratios e.g. Duits’ total-tau/Aβ42
  • Regression models e.g. Hulstaert formula, Schoonenboom regression
  • Probabilistic models e.g. Spies model, PLM scale
  Hulstaert et al., 1999; Duits et al., 2014; Schoonenboom et al., 2012; Spies et al., 2013; Lehmann et al., 2014
CSF biomarkers in AD – PLM Scale

From Lehmann et al., 2014

Accuracy of CSF biomarkers in AD

From Lehmann et al., 2015
Dynamic biomarker trajectory in AD -2010

Revised biomarker trajectory in AD -2013

From Jack et al., 2010

From Jack et al., 2013
When should clinicians utilize CSF biomarkers?

- The 2011 NIA-AA guidelines do not recommend using the CSF biomarkers for “routine diagnostic purposes”
- 3 situations where their use is suggested are:
  - Investigational studies;
  - Clinical trials; and
  - As optional clinical tools for use where available and when deemed appropriate by the clinician

McKhann et al., 2011

How do clinicians utilize CSF biomarkers?

- CSF biomarker values consistent with AD pathology increase the diagnostic confidence
- In ambiguous cases, clinicians look to the CSF biomarkers to help guide their diagnosis
- In various studies, pre-test diagnoses changed following CSF biomarker testing in 7-27% cases

Duits et al., 2015; Kester et al., 2010; Mouton-Liger et al., 2014

From Gooblar et al., 2015
Indications for ordering CSF biomarkers in AD

- Rates of ordering CSF studies in questionable AD vary depending on the country
  - About 40% patients clinically diagnosed with dementia in Sweden get a spinal tap
- Biomarker testing should be considered in all patients with early onset dementia, MCI (if patient requests) and atypical presentations
- CSF biomarkers in AD are independent of age of onset of disease
  
  Falahati et al., 2014; Molinuevo et al., 2014; Bouwman et al., 2009

CSF AD biomarker testing – nuts and bolts

- Clinical testing for AD CSF biomarkers is available commercially from Athena Diagnostics, Worcester, MA
- To discriminate AD from non-AD, Athena provides
  - Values of Aβ42 and total-tau without reference ranges; and phospho-tau181; with
  - Amyloid Tau Index (ATI) which is the ratio of Aβ42 normalized by the discrimination line
- ATI of <1.0 and p-tau concentration of >61 pg/ml are consistent with AD
  - ATI of 0.8–2.0 and p-tau 54–68 pg/ml are noted to be in a “borderline” range
- Athena reports a sens of 85% to 94% and a spec of 83% to 89% for the ATI
Sample CSF AD biomarker report

CSF AD Biomarkers in non-AD dementias

- Core CSF AD biomarker profile can be found in those with a clinical diagnosis of a non-AD dementia
  - Lewy Body Dementia – 47%
  - Corticobasal Degeneration – 38%
  - FTLD – 30%
  - Vascular Dementia – 30%
  - Psychiatric patients – 8%
- Younger AD dementia and older non-AD dementia patients are more likely to have a CSF AD profile

Schoonenboom et al., 2012
Neuroimaging biomarkers in the **diagnostic** evaluation

**Neuroimaging biomarkers in dementia**

**Current practice guidelines**

- **AAN (2001)** – “…data supports the use of a neuroimaging examination—either a noncontrast CT or MR scan—*under most circumstances at the time of the initial dementia assessment* to identify pathology…” (italics mine)

- **EFNS (2012)** – “Structural imaging should be carried out at least once in the diagnostic work-up of patients with cognitive impairment…*MRI is currently the imaging modality of choice*…” (italics mine)

Knapman et al., 2001; Filippi et al., 2012
Why should all dementia patients have a brain scan?

- Until 2001, a selective approach using prediction rules had been recommended
- A 2000 analysis of 6 prediction rules found that
  - The rule with the highest sensitivity (87.5-100%) still had low specificity (37.2-52.9%)
  - At a 5% base rate of potentially reversible dementia (PRD), all rules had a PPV < 15%
  - Under-utilization of neuroimaging leads to under-detection of PRD – medico-legal ramifications

  Gifford et al., 2000

Exclusionary approach
Welcome to the 90’s!

- In the 1990’s, the approach was only to rule out acute processes (mostly space occupying lesions)
  - Reversible etiologies must be identified and treated – still holds true
  - In the absence of a reversible etiology, all dementia was “senile” - due to hardening of arteries (arteriosclerosis) which is age-related, inevitable and incurable - so why bother
- This approach provides little additional information over what is identified clinically

  Scheltens, 2001
Inclusionary approach – current practice

The current recommendation is to rule in dementia etiology in order to

• **Guide prognosis and treatment** - of both cognitive and behavioral symptoms in all but the last stages of the disease:
  • Cholinesterase-inhibitor responsive or not
  • Extreme neuroleptic sensitivity or not
  • Anti-amyloid therapy or not (in the near future)
• **Reduce diagnostic uncertainty and provide closure** - families are becoming increasingly aware of the different etiologies of dementia and routinely seek this information
• **Determine need for genetic testing** - of the patient and, at times, of family members

*Adapted from Scheltens, 2001*

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**Neuroimaging modalities**

• **Structural imaging**
  • CT
  • MRI – imaging modality of choice
  • Non conventional MRI – H₁-MRS, DTI, ASL, resting state fMRI

• **Functional imaging**
  • SPECT scan – DaT scan with 123I-ioflupane, MIBG cardiac scan
  • FDG-PET scan (CT or MRI)

• **Molecular imaging**
  • Amyloid imaging
  • Tau imaging - 18F-FDDNP; and many others in development
  • *Future – alpha-synuclein imaging, TdP imaging*
“Senescent changes, nothing acute”

- A brain imaging report by a general radiologist typically contributes little to the diagnostic process in dementia.
- General radiologists routinely miss dementia-related focal atrophy.
  - In one study where 85% of the scans were performed in academic settings, only 10% bv-FTD patients was that diagnosis even considered by the radiologist.
- Calling an atrophy pattern unremarkable leads to:
  - delayed or missed diagnoses
  - unnecessary referrals
  - potentially harmful treatments

Suárez et al., 2009

Senescent changes – cont’d

- Non-psychiatric providers (neurologists, cardiologists) typically order and read their own scans.
  - 24-38% neurologists depend on their own scan readings alone – this group is increasing in size - the rest use a combination approach.
- The referring clinician can best integrate clinical, lab and imaging data meaningfully, improving patient care and safety.
  - We read and interpret our own labs, why not imaging?
- If the patient has received a report of the study, he/she may wish to personally review it with the referring clinician.
- Finally - The referring clinician may potentially be held liable in a malpractice lawsuit for missed findings on the imaging study.
  - That the finding may have been missed by the radiologist as well is not an adequate defense.
AAN membership surveys, 1996 and 2005.
Structural neuroimaging - CT or MRI?

- **MRI is the imaging modality of choice** – different pulse sequences greatly enhance sensitivity to focal lesions and brain stem atrophy, no exposure to radiation
- **CT** still preferred in ER's to rule out large SOL's and bleeds; preferred modality in
  - Quick in and out situations e.g. advanced dementia with agitation
  - Claustrophobic patients and patients sensitive to noise
  - Patients with metal implants and non-MRI compatible devices e.g. pacemakers
  - Patients who cannot afford an MRI (not covered in their insurance plan, self-pay)
- If only CT is possible, obtain a spiral (helical) CT with MPR in the sagittal and coronal planes

Indications for ordering MRI with contrast

- Rapidly progressive dementia in a young patient
- Suspicion of infection – look for contrast enhancement of inflamed areas
- Suspicion of vasculitis – look for vascular and leptomeningeal enhancement

Adapted from Barkhof et al., 2011
**Visual or volumetric analysis?**

- Volumetric analysis of regional brain structures can quantify degree of atrophy
- Currently, volumetric analysis should complement but not replace visual analysis of atrophy
  - Gross pathologic processes such as ICH can interfere with automated segmentation
  - Visual rating has been shown to be superior than volumetric analysis
- EFNS (2012) – “accepted standards for quantitative analysis are lacking”
- **NeuroQuant®**: FDA approved to measure volumes of brain structures in 3D-T1w sagittal non-contrast MRI images [http://www.cortechslabs.com/products/](http://www.cortechslabs.com/products/)
  - Consider using the proprietary software package provided by your MRI vendor or open source software (e.g. SPM8)

Suppa et al., 2015; Brewer et al., 2009; Wahlund et al., 2000; Filippi et al., 2012

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**Structured reporting of brain scans in dementia**
Structured reporting – basic steps

- First, exclude surgically treatable conditions
- Next, assess extent and pattern of brain atrophy
- Finally, assess extent and pattern of “signal change”
- If no abnormality for age, then
  - Reassess after a suitable interval, or
  - Consider CSF biomarker studies or functional imaging

*Adapted from Harper et al., 2014*
Assess the extent and pattern of brain atrophy

- Macrostructural tissue loss (atrophy) is the major substrate of the dementia syndrome
- Atrophy been shown to map accurately to
  - Decline in cognitive performance downstream
  - Microstructural and metabolic changes upstream
- Atrophy can be easily assessed in routine clinical practice
  - Unlike measuring microstructural and metabolic changes in vivo, which require specialized imaging techniques not currently used in clinical practice

Mungas et al., 2002; Frisoni et al., 2010; Logue et al., 2011

Normal senescence

- Global grey matter volume decreases linearly with age at least over the 30–60 year age range (with regional exceptions)
- Grey matter loss appears more prominent in the frontal and parietal cortices
- Ventricular enlargement and hippocampal atrophy rates accelerate after age 70
- White matter volume shows an increase throughout middle adulthood, declining only after the age of 50 years

Whole brain volume across ages 31–84 years

From Scahill et al., 2003
Neuropathological substrate of atrophy

- Best studied for Alzheimer’s Disease dementia
- Multiple pathologies converge on brain structures that mediate cognitive decline
- Cortical atrophy is related to both Alzheimer’s and vascular pathology
- Hippocampal atrophy is related to both Alzheimer’s pathology and hippocampal sclerosis
  - This volume loss is directly related to neuronal loss (not shrinkage) in the hippocampus
  - However, AD is not the only pathology that causes neuronal loss in this region
  - Additional pathologies have cumulative effects on hippocampal volume loss

Jagust et al., 2008; Zarow et al., 2005

Assessing cerebral atrophy in the clinic
Using Visual Rating Scales

- A number of Visual Rating Scales (VRS) have been available since in 1990’s
- While initially constructed for research studies, these can be easily adapted into clinical practice
- VRS focus attention on brain regions particularly susceptible to change in specific dementias

Harper et al., 2015
Why should the radiologist use VRS?

- VRS can be applied directly to clinically acquired images without the use of additional software.
- With suitable training, they can easily be used as an adjunct to standard clinical radiology reports.
- They can be used to enforce structured image reporting.
- They can provide a framework for interpreting imaging findings, making visual assessment more consistent and potentially more sensitive.

Harper et al., 2015

Pasquier’s Generalized Cerebral Atrophy (GCA) scale

- Rated in the transaxial plane in T1 or T2/FLAIR sequences.
- Atrophy is always overestimated in heavily T2-weighted sequences – avoid.
- Estimate the overall atrophy and ignore focal changes when estimating GCA.
- Can be rated on a visual rating scale from 0 (no atrophy) to 3 (knife blade atrophy).

Pasquier et al., 1996
Pasquier’s GCA Scale – cont’d

Davies-Kipps’ Frontotemporal Atrophy (FTA) scale

- Davies and co-workers devised a visual rating scale to rate atrophy in FTD brains based on a prior scheme for staging FTLD neuropathology in autopsy studies
- Kipps and co-workers extended it to include posterior temporal atrophy
- Rating is done on 2 non-contiguous slices in T1w coronal images
- It is a 5-point visual rating scale
  - The overall rating is the highest score amongst the lobar (frontal or temporal) ratings
  - Score of 2 and above is abnormal

Broe et al., 2003; Davies et al., 2006; Kipps et al., 2007
Davies-Kipps’ FTA scale – cont’d

Slice 1 - rate anterior temporal and frontal atrophy at level of temporal pole

Slice 2 - rate posterior temporal atrophy at level of LGN

Davies-Kipps’ FTA scale – cont’d

From Kipps et al., 2007
Imaging the hippocampal formation

The hippocampal axis (D) is slightly oblique to the standard axial slices (B, C). It is best imaged in two planes: parallel to the long axis of the hippocampus and in a slightly oblique coronal plane which is perpendicular to the long axis of the hippocampus.

Szabo et al., 2014; Gardner and Hogan, 2005

Imaging the hippocampal formation – cont’d

Locating the ERC, TRC and PRC on a coronal section at the level of the cornu ammonis.

Kivisaari et al., 2013
Scheltens’ Medial Temporal Atrophy (MTA) scale

- Scheltens’ 5-point scale is based on
  - Width of choroid fissure (C)
  - Width of temporal horn of the lateral ventricle (D)
  - Height of hippocampal formation (A)
- Rated in the coronal plane in T1w images on the slice that best depicts both hippocampal formations

Scheltens et al., 1992; Suppa et al., 2015

Schelten’s MTA scale – cont’d
Duara’s Medial Temporal Atrophy (MTA) scale

- Duara modified Schelten’s MTA scale to include the perirhinal (PRC) and entorhinal (ERC) cortices
- A single coronal slice at the level of the mammillary bodies is used for the rating
- The L or R MTA score is the average score across the 3 structures on that side
- Rating is done on a 5-point score from 0-4
- The sensitivity and specificity values are derived from cut-offs for impairment for either L or R MTA

Duara et al., 2008

Duara’s MTA scale – cont’d

Duara et al., 2008
ERC v ERC

- Relatively normal ERC and PRC
- Atrophied ERC and PRC

Kim’s Medial Temporal Atrophy (MTA) scale

- Kim’s 5-point scale (0-4) is based on
  - Width of the hippocampus + PHG (A’)
  - Width of the perimesencephalic cistern (C’)
  - Width of the temporal horn (D’)
- Obtained by transposing Scheltens’ T1w-coronal rating scale onto T2w axial images
- The authors found a high kappa value between the T1W-axial and T1W-coronal VRS’s

Kim et al., 2014
Kim’s MTA scale – cont’d

- Koedam’s Posterior Atrophy (PA) scale
  - Rated 0-3 by examining T1w images in all 3 planes
    - Width of the PCS
    - Width of the POS
    - Atrophy of the precuneus
    - Sulcal dilatation in the parietal lobes
  - Best used in combination with an MTA scale

Koedam et al., 2011; Lehmann et al., 2012
Assessing the extent and pattern of “signal change”

- Relatively uniform signal intensity within a single tissue type is the norm on MRI
- Regions of hyper or hypo-intensity likely represent pathology
- In dementia patients, such signal change in white or grey matter is usually due to cerebrovascular disease
  - Vascular and degenerative pathology often coexist in dementia patients
  - They share similar risk factors and there is a complex interaction between them
  - Differentiating the contribution of vascular versus degenerative pathology to the cognitive decline is often difficult
- Rarely, such signal change may be due to an inflammatory, metabolic or infective processes (outside the scope of this workshop)

Harper et al., 2014

Cerebrovascular Disease

- Large vessel disease

- Small vessel disease

- Systemic disease

- Small vessel disease includes
  - Recent small subcortical infarcts
  - Lacune of presumed vascular origin
  - White matter hyperintensity of presumed vascular origin
  - Perivascular spaces
  - Cerebral microbleeds
  - Cerebral atrophy

STRIVE nomenclature – Wardlaw et al., 2013
**Definitions**

STandards for Reporting Vascular changes on nEuroimaging (STRIVE v1, 2013)

**White Matter Hyperintensities (WMH)**

- Appears hypo-dense on CT, so termed *leukoaraiosis* in 1987 by Hachinski and colleagues.
- Called *WMH on MRI*, these are lesions of variable size without cavitation.
- Iso-intense on T1; *best seen on T2* weighted images (T2 or T2/FLAIR).
- Population prevalence:
  - 96% in age >65 in the Cardiovascular Health Study.
  - 95% in age 60-90 in the Rotterdam Scan Study.

From Wardlaw et al., 2013; Longstreth et al., 1996; de Leeuw et al., 2001.
Imaging WMH

- **Fazekas Scale** is derived from prior scales
- PVWMH and DWMH were separately rated from 0 (absent) to 3 (confluent lesions)
- Fazekas scale itself has been modified to improve inter-rater reliability
- Automated WMH volumetric analyses now allow more precise measurements
- Visual identification of the pattern of WMH distribution may be a clue to the underlying microangiopathy type

Fazekas et al., 1987; Prins and Scheltens, 2015; Charidimou et al., 2016

**Fazekas 0**
- No WMHs

**Fazekas 1**
- Focal or periventricular lesions:
  - Single lesions ≤5mm
  - Grouped lesions ≤20mm

**Fazekas 2**
- Beginning confluent lesions:
  - Single lesions 10–20mm
  - Grouped lesions ≥20mm in any diameter
  - No more than connecting bridges between individual lesions

**Fazekas 3**
- Confluent lesions:
  - Single lesions or confluent areas of hyperintensity ≥20mm in any diameter
  - Abbreviation: WMHs, white matter hypointensities.

*From Prins and Scheltens, 2015*

Imaging WMH – cont’d

- Fazekas grade 3
- **Fazekas grade 3** Coronal view
- Fazekas grade 3 with lacune
Definitions – cont’d

Perivascular (Virchow-Robin) Space (PVS or VRS)

- Fluid filled spaces that follow the course of a vessel with signal intensity similar to CSF (T2w)
- Appear linear (stripes or striations) when imaged parallel to the vessel
- Round or ovoid (<3 mm) when imaged perpendicular (lacunes are usually 3-15 mm)
- Enlarged PVS (ePVS) in the basal ganglia look like a sieve and are called état criblé
- Scored 0 (none) to 4 (>40) separately in the basal ganglia and centrum semiovale on one side based on number, then score added (0-8)

Wardlaw et al., 2013; Doubal et al., 2010
Definitions – cont’d

Cerebral Microbleeds (CMB’s)

- Not visible on T1w, T2w, T2/FLAIR or CT
- Best seen on blood-sensitive T2* GRE or SWI sequences
- Small (2-5 mm, max 10 mm) area of signal void with associated “blooming”
- “Blooming” artifact – Signal void on T2*GRE is larger than the actual hemosiderin deposits
- Size of blooming artifact depends on field strength and pulse sequence, not on size of actual lesion
- Underlying histopathology is heterogeneous

Fisher, 2014; Greenberg et al., 2009; van Veluw et al., 2016
Imaging CMB’s

- Thinner slices, 3D transformation and higher field strength enhances the detection of CMB’s
- Phase and magnitude data can be combined to create Susceptibility Weighted Imaging (SWI)
- Algorithmically transformed into a Minimum Intensity Projection (mIP) to maximize the detection of low intensity CMB’s
- Always watch out for CMB mimics
- CMB count by region is typically used in the clinic
- About a fourth to a third of AD dementia patients have CMB’s
- Risk increases with age, male sex and ApoE ε4 homozygosity

Greenberg et al., 2009; Whitwell et al., 2015; Sveinbjornsdottir et al., 2008

Imaging CMB’s - MARS

From Gregoire et al., 2009
Rating Small vessel Disease
The Total SVD score

- 4-point ordinal scale (0-4) to score total SVD burden:
  - 1 point – 1 or more lacunes
  - 1 point – 1 or more CMBs
  - 1 point – moderate or severe enlargement of PVS in the basal ganglia
  - 1 point – Fazekas gr 3 for PVWMHs, or Fazekas gr 2 or 3 for DWMHs

- Higher total SVD score associated with acute lacunar stroke, older age, male sex, smoking and hypertension

Staals et al., 2014

Structural neuroimaging signatures of the dementias
How to integrate this information to diagnose the degenerative dementias
“Typical” Late-onset AD (LOAD)

- Neurodegeneration begins in the hippocampo-entorhinal region (trans-entorhinal cortex)
- ApoE4 is a major risk factor
- No consistent hemispheric asymmetry is present
- Symptoms usually emerge after the age of 65 (late onset)
- Females tend to be overrepresented
- Core clinical phenotypic criterion – episodic memory profile characterized by a low free recall that is not normalized by cueing (amnestic syndrome of the hippocampal type)
  - Vis-à-vis frontal-related retrieval deficit which is normalized by cueing

Mesulam et al., 2014; Dubois and Albert, 2004

Neuroimaging signature of “typical” LOAD

- 2011 NIA-AA criteria for AD included imaging biomarkers – structural MRI, FDG-PET and Amyloid PET
- MTA is very sensitive but not specific for AD
  - MTA is a sensitive indicator of any underlying hippocampal pathology
  - Right hippocampal atrophy may be more specific for AD than left
- MTA score of >1 is considered abnormal in age <75; score >2 in age above 75

McKhann et al., 2011; Scheltens et al., 1992; Lehmann et al., 2012
The “Atypical” AD spectrum
Early Onset? Non-amnestic? Hippocampal sparing? Type 2?

- Typical AD Dementia is comprised of amnestic (hippocampal) and non-amnestic (focal cortical) deficits
- The 2011 NIA-AA criteria were first to allow 3 non-amnestic presentations of AD
- DSM-5 criteria for NCD-AD do not allow a diagnosis of non-amnestic presentations
- Non-amnestic presentations account for about 6-14% of all AD cases
- Early-onset AD (EOAD) is simply defined as onset before age 65, regardless of the clinical phenotype (more often non-amnestic)
- AD age at onset is a substantially heritable trait; with increasing age at onset, the heritability of AD declines

McKhann et al., 2011; Dubois et al., 2014; Koedam et al., 2010; APA, 2013; Wingo et al., 2012

EOAD – Single disease entity?

From van der Flier et al., 2011
Unlikely!!

From Mendez, 2012

Parietal atrophy and EOAD

• Age at onset modulates the distribution of cortical involvement
• In one study of autopsy-confirmed AD
  • 33% of EOAD subjects had PA only (v. 18% LOAD subjects)
  • 9% EOAD subjects had MTA only (v. 46% LOAD subjects)
  • 24% EOAD subjects had no atrophy (v. 0% LOAD subjects)
• Adding PA scores to MTA ratings significantly improved the discrimination
  • of EOAD from age matched controls
  • but not of LOAD from controls

Karas et al., 2007; Lehmann et al., 2012; Filippi et al., 2012
52 y o female with AD and APOE ε3/ε3 genotype

From van der Flier et al., 2011

The Non-amnestic → Amnestic AD continuum

<table>
<thead>
<tr>
<th>Younger age</th>
<th>Older</th>
<th>Oldest-old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-amnestic (~60%)</td>
<td>Amnesia + focal cortical deficits</td>
<td>Non-amnestic (~6%) “Preserved social graces”</td>
</tr>
<tr>
<td>Predominantly male</td>
<td>Male and female</td>
<td>Predominantly female</td>
</tr>
<tr>
<td>Rapid progression</td>
<td>Slow progression</td>
<td>Very gradual progression</td>
</tr>
<tr>
<td>PA &gt;&gt; MTA</td>
<td>PA and MTA</td>
<td>Severe MTA</td>
</tr>
<tr>
<td>Heritability 92-100% - 10% AD; rest AR?</td>
<td>Heritability 60-80% - highly polygenic</td>
<td>Phenocopies include HS, PART, AGD</td>
</tr>
<tr>
<td>Phenocopies include amnestic-FTD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Parkinsonian syndromes

- Synucleinopathies
  - Dementia with Lewy Bodies (DLB) and Parkinson’s Disease Dementia (PDD)
  - Multisystem atrophy (MSA)
- Tauopathies
  - Corticobasal syndrome (CBS) and corticobasal degeneration (CBD)
  - Progressive supranuclear plasy (PSP)
  - Frontotemporal dementia with parkinsonism (FTDP-17)
  - Pick’s disease

Modified from Boeve, 2007

Neuroimaging in DLB

- There is no structural neuroimaging signature of DLB
- In pure DLB cases, there is relative preservation of medial temporal lobe structures compared to AD of comparable clinical severity on CT/MRI
- Other (non-structural) imaging strategies listed in the 2005 DLB diagnostic criteria
  - Low dopamine transported uptake in the basal ganglia (DaT scan, PET)
  - Reduced occipital activity on PET/SPECT
  - Abnormal myocardial MIBG scintigraphy
- FDG-PET scan can be diagnostic, but CMS does not reimburse
  - Occipital FDG-PET hypometabolism accurately classifies coincident DLB (80% sens and 100% spec)

Filippi et al., 2012; McKeith et al., 2005; Toledo et al., 2013
The Frontotemporal Lobar Degeneration (FTLD) spectrum

- Behavioral variant FTD (bv-FTD)
  - Including the benign (phenocopy) and late-onset variants
- The language dementias - Primary Progressive Aphasia (PPA)
  - Including right temporal variant FTD (rtv-FTD) – sv-PPA or orphan syndrome?
- FTD with motor features
  - FTD-ALS
  - FTD with atypical parkinsonism – PSP, CBD

Modified from Miller, 2014

Diagnosing behavioral variant-FTD

- DSM-5 criteria for FT-NCD only include a behavioral and a language variant
  - In at least 10% of autopsy-proven bv-FTD subjects, an amnestic presentation has been reported (usually C9ORF72 mutation)
  - In another 10% patients, the bv-FTD phenotype IS due to AD
  - If prominent axial rigidity and gaze disturbance, think CBD or PSP
- Presence of signature neuroimaging findings is necessary for “probable” FT-NCD
- A phenocopy syndrome (male predominance with negative early imaging findings) appears to have a slowly progressive course and better overall prognosis

APA, 2013; Hodges et al., 2004; Chare et al., 2014; Davies et al., 2006; Gossink et al., 2016
Diagnosing language variant-FTD
Primary Progressive Aphasia (PPA)

- 2011 PPA classification included 3 subtypes (including lv-PPA for the first time, did not include PPAOS)
  - “Aphasia must be the most prominent deficit at symptom onset and for the initial phases... in the absence of prominent initial episodic memory, visual memory, visuospatial and behavioral disturbances... that cause impaired ADLs... not accounted for by other disorders”
  
  Mesulam, 2013; Gorno-Tempini et al., 2011

PPA subtypes

- 3 PPA subtypes in the 2011 PPA classification
  - **Non-fluent or agrammatic** variant (nfv-PPA or PPA-G)
  - **Semantic** variant (sv-PPA or PPA-S)
  - **Logopenic** variant (lv-PPA or PPA-L) – usually due to AD
- Primary Progressive Apraxia of Speech (PPAOS)
- **DSM-5** has a “language variant” of FT-NCD with a very basic definition
  - The subtypes of PPA are mentioned only in the text
  - Ignores the fact that about 40% of PPA patients have Alzheimer’s and not FTLD pathology

Gorno-Tempini et al., 2011; American Psychiatric Association, 2013; Whitwell, 2015
Imaging the FTD subtypes – Step 1
Obtain a detailed history from patient and informant

- Disinhibition, obsessions, eating → bv-FTD
- Agrammatism → nfv-PPA
- Loss of empathy, prosopagnosia → rtv-FTD
- Naming, single word comprehension → sv-PPA

Imaging FTD – Step 2
Obtain a detailed family history

- About 40% of FTLD cases are familial (FH of dementia/ALS/neuropsychiatric disorder/movement disorder)
- 10% FTD cases are autosomal dominant
  - 3 or more family members affected across successive generations, and
  - 2 first degree relatives of the index patient are affected
- 3 major genes – MAPT, GRN and C9ORF72 – and many minor genes are implicated
  - FTLD gene mutations are also found in 7-14% "sporadic" cases (mostly C9ORF72)
- 3 major proteins – tau (~40%), TDP-43 (~45%) and FUS (~5%)
- There is no 1:1 concordance between gene → proteinopathy → neuroimaging findings → clinical phenotype

Miller, 2014; Le Ber et al., 2013; Whitwell, 2015
Imaging FTD – Step 3
Assess the overall pattern of atrophy using the FTA scale

Rate frontal, anterior temporal and posterior temporal for each hemisphere separately, which allows focal presentations of FTLD to be identified

Imaging FTD – Step 4
Neuroimaging signatures of the sporadic FTD subtypes
## Sporadic FTD subtypes – cont’d

![bv-FTD](image), ![nfv-PPA](image), ![sv-PPA](image), ![rtv-PPA](image)

* bv-FTD case courtesy of Dr Frank Gaillard, Radiopaedia.org

## Neuroimaging signatures of the major FTD genes

<table>
<thead>
<tr>
<th>FTD Gene</th>
<th>Clinical phenotype</th>
<th>Neuroimaging signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9ORF72</td>
<td>Mostly bv-FTD</td>
<td>Symmetric atrophy of dorsolateral, medial and orbitofrontal lobes, with additional widespread neuronal loss in anterior temporal, parietal and occipital lobes and cerebellum</td>
</tr>
<tr>
<td>MAPT</td>
<td>Mostly bv-FTD</td>
<td>R-dominant or relatively symmetric atrophy of the anterior temporal lobes, accompanied by lesser atrophy of orbitofrontal and lateral prefrontal cortices</td>
</tr>
<tr>
<td>GRN</td>
<td>Mostly bv-FTD</td>
<td>Markedly asymmetric (L or R) atrophy of the posterior temporal, inferior frontal and inferior parietal lobes; fastest rate of atrophy</td>
</tr>
</tbody>
</table>

*From Ghetti et al., 2015; Miller, 2014; Whitwell et al., 2015; Whitwell, 2015*
Imaging FTD – Step 5

Familial v sporadic bv-FTD

Clinical phenotype bv-FTD

FTA scale shows predominantly temporal atrophy

FTA scale shows striking, often symmetric dorsolateral frontal atrophy

Adapted from Whitwell et al., 2012; Whitwell et al., 2015; Le Ber, 2013; Ghetti et al., 2015

Symmetric MTA may suggest AD

Asymmetric temporal involvement may suggest sv-PPA

Vascular Cognitive Impairment (VCI)

- The term VCI was adopted in 2003 by the International Psychogeriatric Association after a consensus meeting
- It is an umbrella term for all forms of cognitive impairment “associated with and presumed to be caused by cerebrovascular disease”
- Vascular dementia is a more restrictive diagnosis under this umbrella
- Any diagnostic workup of VCI necessarily includes structural brain imaging
  - NINDS-AIREN (1993) – “structural brain imaging is an essential element for the diagnosis of vascular dementia, and without it vascular dementia will be ‘possible’ at best” (italics mine)
  - Neuroimaging evidence is a criteria for diagnosing “probable” Vascular NCD in DSM-5

O’Brien et al., 2003; Gorelick et al., 2011; Wright and Flores, 2015; Román et al., 1993; APA, 2013
Diagnosing Vascular Cognitive Impairment (VCI)

- Post-stroke dementia (PSD) – vast majority is delayed onset PSD
- Vascular dementia (VaD)
  - Multi-infarct (cortical) dementia (MID) – VaD type I
  - Subcortical ischemic vascular dementia (SIVD) – VaD type II
  - Strategic infarct dementia (SID) – VaD type III
  - Hypoperfusion dementia – VaD type IV
  - Hemorrhagic dementia – VaD type V
  - Dementia caused by specific arteriopathies (e.g. CADASIL)
- Mixed (Alzheimer’s disease and Vascular) dementia – VaD type VI
- Vascular MCI (minor NCD)

Adapted from O’Brien et al., 2003; O’Brien, 2006

Diagnosing Vascular Dementia (VaD)

- An operational clinical definition of what constitutes “vascular dementia” remains elusive
- Non-memory domains (processing speed, executive function) are typically affected
  - Memory impairment was essential for diagnosing a dementia syndrome before DSM-5
- A relationship must be demonstrated between cognitive decline and vascular pathology
  - DSM-5 criteria state there must be “evidence of ... cerebrovascular disease” from history, physical exam and/or neuroimaging...”
  - 2011 AHA/ASA criteria state there must be a “clear temporal relationship”

American Psychiatric Association, 2013; Gorelick et al., 2011
Diagnosing VaD – cont’d

• Vascular lesions noted on structural brain scans are often mistakenly thought to be pathophysiologically relevant, leading to a high rate of overdiagnosis of VaD
• In an autopsy-based study of 71 dementia patients
  • A clinical diagnosis of probable or possible VaD was made in 27 patients
  • A diagnosis of VaD was confirmed on autopsy in only 5 of these 27 patients (19%)
  • None of the cases that were clinically diagnosed as probable VaD were neuropathologically confirmed as VaD.
  • 1 patient with probable AD/ DLB was also found to have neuropathologically confirmed VaD

Niemantsverdriet et al., 2015

Vascular contribution to the degenerative dementias

• Much more commonly seen in clinical practice
• In the largest autopsy based study to date, cerebrovascular disease
  • Was shown to increase with age
  • Was more prevalent in AD patients vis-à-vis the other degenerative dementias
  • Increases the deleterious effect of AD pathology on cognition
  • Had an even larger effect size on cognition in Lewy body disease than in AD

Toledo et al., 2013
Neuroimaging in VaD – pearls

- A diagnosis of VaD cannot be made without neuroimaging
- Use of a WMH rating scale is recommended for quantifying the WMH burden
- White matter changes are best seen on T2 and T2/FLAIR sequences on MRI
- The T2/FLAIR sequence is best for identifying cystic lesions
- T2w images are better than T2/FLAIR for identifying thalamic lesions
- In the absence of tissue necrosis, WMH’s are iso-intense on T1w images

Barkhof et al., 2011; Logue et al., 2011

MRI-defined Subcortical Ischemic Vascular Disease (SIVD)

- Diffuse confluent WMH’s (Fazekas gr 3) and état criblé are abnormal at any age
- Isolated gr 1-2 deep WMH’s is a normal finding in older adults
- In the LADIS study, SIVD was defined as
  - Fazekas gr 3 WMHs plus at least 1 lacune; or
  - Fazekas gr 2 WMHs plus >5 lacunes
- MRI-defined SIVD has been operationalized as
  - Extensive periventricular white matter lesions involving at least 1/4 of the total white matter
  - Multiple basal ganglia, thalamic, internal capsule and frontal lacunes in the absence of gr 2-3 WMH’s
  - Bilateral thalamic lesions – at least 1 lesion in each thalamus

Barkhof et al., 2011; van Straaten et al, 2003; Jokinen et al., 2009
Importance of cerebral atrophy in VaD

- Even in VCI, including CADASIL, hippocampal (and cortical) atrophy appears to be the substrate for the dementia syndrome
- Hippocampal atrophy may result from a mixture of ischemic and degenerative pathologies
- Entorhinal cortex is spared in the absence of AD pathology
- Caution: All these studies used pre-DSM-5 criteria to diagnose “vascular” dementia

Fein et al., 2000; O’Sullivan et al., 2007; Gemmell et al., 2012

Cerebral atrophy plays a central role in VCI

From O'Brien, 2006
Functional neuroimaging of the dementias

Advantages of functional imaging

- It complements structural imaging and increases diagnostic certainty
- FDG-PET is 15-20% more accurate than SPECT (better resolution, higher signal magnitude)
  - Caregivers may prefer SPECT over PET so that they can be with the patient
- Visual interpretation of an FDG-PET scan after brief training has almost a 90% accuracy rate in differentiating FTD from AD

Messa et al., 1994; Foster et al., 2007; Bamford et al., 2016
Advantages – cont’d

- Obtaining an FDG-PET at initial clinical eval (IE) improved the diagnostic accuracy of AD equivalent to a mean of 4.1 (SD 2.7) yrs of follow up
- When FDG-PET and IE results were discordant, the correct pathologic diagnosis was more likely to be congruent with the FDG-PET diagnosis
- It may be especially useful in detecting AD in challenging focal dementia presentations

<table>
<thead>
<tr>
<th></th>
<th>+ve FDG-PET</th>
<th>-ve FDG-PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD at IE</td>
<td>+14% likelihood</td>
<td>-39% likelihood</td>
</tr>
<tr>
<td>Not AD at IE</td>
<td>+35% likelihood</td>
<td>-18% likelihood</td>
</tr>
</tbody>
</table>

FDG-PET in the diagnosis of AD

<table>
<thead>
<tr>
<th></th>
<th>Pooled Sensitivity</th>
<th>Pooled Specificity</th>
<th>Pooled Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD v controls</td>
<td>96%</td>
<td>90%</td>
<td>93%</td>
</tr>
<tr>
<td>AD v non-AD dementias</td>
<td>87%</td>
<td>81%</td>
<td>85%</td>
</tr>
</tbody>
</table>

From Bohnen et al., 2012
Use of the 18-FDG tracer

- The brain accounts for about 20% of the oxygen and calories consumed by the body
- Most of this activity is due to oxidation of glucose to produce ATP
- About 85% of this energy is used to sustain postsynaptic action potentials
- 18-FDG is a measure of cerebral glucose consumption i.e. postsynaptic activity
- In healthy aging, metabolic rates are relatively stable over time
- Synaptic damage occurs early in neurodegenerative diseases and probably underlies the initial clinical features
- Neurofibrillary tangles, amyloid plaques, and Lewy bodies don’t directly affect synaptic function
- Hypometabolism in dementia on FDG-PET therefore directly measures loss of brain post-synaptic function and density

Attwell and Iadecola, 2002; Bartlett et al., 1991

Patient preparation before FDG-PET scanning

- Fasting for at least 4 to 6 hours
- Oral hydration with water should be encouraged
- Avoid caffeine, alcohol, or drugs that may affect cerebral glucose metabolism
- Check blood glucose level (ideally not greater than 150–200 mg/dL)
- Environmental conditions: resting state, patient with eyes open and ears unoccluded in a quiet, dimly lit room, with minimal background noise

Berti et al., 2014
Reimbursement issues

- In 2004, the US Centers for Medicare and Medicaid Services approved reimbursement of FDG-PET only for the purposes of differential diagnosis of AD v FTD
- FDG-PET is not approved by CMS for any other clinical indication yet
- It is often impossible to obtain authorization from private insurers for FDG-PET in patients younger than Medicare-eligible age (in whom it may be most useful)

Dickerson, 2012

Cost-benefit analysis

The total charges associated with performance of a dedicated brain FDG-PET amount to less than the cost of 1 year of unnecessary pharmacotherapy for treatment of a misdiagnosed patient

Silverman et al., 1999
The UCLA Department of Nuclear Medicine (Neuronuclear Imaging Section) has developed a checklist to help determine whether the FDG-PET Dementia Evaluation is indicated and covered by Medicare.

Other Nuclear Imaging departments use similar checklists to make sure that coverage for the FDG-PET scan is not denied by CMS.

Check with your Nuclear Imaging department to see what they use.

**UCLA checklist – cont’d**

Checklist courtesy Dr. Dan Silverman
What about Amyloid PET?

- 3 amyloid PET ligands are now commercially available for clinical use
  - 18F-Florbetapir (2012), 18F-Flutemetamol (2013) and 18F-Florbetaben (2014)
- The 2013 CMS National Coverage Decision (NCD) on amyloid PET imaging in dementia and neurodegenerative disease (CAG 00431N) allows coverage of a single amyloid PET scan per patient through the coverage with evidence development (CED) process
  - “...evidence is insufficient to conclude that the use of PET amyloid-beta imaging is reasonable and necessary for the diagnosis or treatment of illness or injury”
- The IDEAS study (now recruiting) aims to study the impact of amyloid PET in the average clinic patient [link](https://www.snmmilearningcenter.org/Activity/3690043/Detail.aspx)

The “Dementia protocol”
Common MRI protocols

Neuroimaging departments typically have many protocols e.g.

- Stroke protocol (non-contrast)
- ICH protocol (contrast)
- Tumor protocol (contrast)
- MS protocol (contrast)

BUT NO DEMENTIA PROTOCOL!!

OHSU MRI dementia protocol
(Special thanks to Dr Jeff Pollock!)

- Uploaded into Epic smart order sets (Ambulatory MRI Brain Imaging) at OHSU in Nov 2015
- Option of choosing MRI brain wo or wwo contrast
OHSU MRI dementia protocol – nuts and bolts

- 3D T1 sagittal with multiplanar reconstructions (cor, sag)
  - use the Neuroquant protocol so one can potentially do volumetrics
- 3D Sag Flair with axial MPR
- Axial T2 (T)SE
- Axial SWI
- Axial DWI with ADC map

*Modified from Barkhof et al., 2011*

Final word and take home points
Occam’s razor or Hickam’s dictum?

- “Patients can have as many diseases as they d--- well please” (John Hickam, MD)
- Look for multiplicity, not a unifying hypothesis – the principle of parsimony does not apply in geriatrics
- Autopsy study of first 22 consecutive ADNI subjects diagnosed with AD dementia or AD-MCI
  - Amnestic, cognitively impaired, subjects without any cognitive signs or symptoms suggestive of non-AD pathologies and a low vascular risk profile
  - Only 4 were found to have a “pure” AD pathology on autopsy
  - 45% had comorbid Lewy Body disease, 23% had comorbid vascular pathology and 40% had comorbid mixed pathology
- Paradoxically, in the 90+ autopsy study, no neuropathology was found in 22% of 63 patients with DSM-IV dementia
  
  Toledo et al., 2013; Corrada et al., 2012

Take home points

- A good dementia work-up must include 1 or more biomarkers
- History and exam with an MRI using the dementia protocol, is usually adequate
- In young-onset and questionable cases, use of 2 disparate biomarkers is advised
- Clinicians must know how and when to order and how to interpret biomarkers if you work with dementia patients
  - Even if you are “opposed” to ordering them in your own practice, patients will come to you with biomarker study reports from other centers and expect you to interpret them
- Structural and functional neuroimaging reports by community radiologists have variable reliability in dementia cases
- The final responsibility (clinical, legal and ethical) rests with the clinician who must know how to integrate biomarker results with clinical and other diagnostic data