PET Beta Amyloid Imaging in the Context of Dementia

MEDCAC
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ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Disclosures

- Institute for Clinical and Economic Review
- Basis for my comments:
  - Diagnostic Tests for Alzheimer's Disease: Generating and Evaluating Evidence to Inform Insurance Coverage Policy
- Funding for the white paper
  - Unrestricted funding to Massachusetts General Hospital for ICER activities
    - Aetna
    - Harvard Pilgrim Health Plan
    - HealthPartners
    - Merck
    - National Pharmaceutical Council
    - United Health Foundation

Alzheimer's Dx White Paper

- Genesis and purpose
  - "To define the standards by which evidence will be evaluated for coverage, both at the current time and after the potential advent of more effective treatments. This aim will be accomplished by providing specific research recommendations to help clinical researchers and manufacturers generate the level of evidence required to meet these standards."
- Process
  - ICER recruitment of AD Dx Policy Development Group
    - Clinical researchers
    - Patient organizations (Alzheimer's Association)
    - Public and private health insurers (Aetna, BCBSMA, Kaiser, Wellpoint, CMS)
    - Manufacturers (Avid Radiopharmaceuticals, Johnson & Johnson
- Opinions expressed do not necessarily reflect PDG views

MEDCAC Question

- How confident are you that there is adequate evidence to determine whether or not PET imaging of brain beta amyloid changes health outcomes (improved, equivalent or worsened) in patients who display early symptoms or signs of cognitive dysfunction?
  - If there is adequate evidence, how confident are you that PET imaging of brain beta amyloid improves health outcomes in these patients?

Evolving paradigm of Alzheimer's Disease and the Role of Biomarkers

- Correspondence between AD pathology and symptoms not always consistent.
  - 30% of cognitively normal older adults have "positive" amyloid findings in the brain (Jack, 2009)
- Current dominant view among research community is that amyloid deposition develops first during a 10-15 year preclinical phase, with neurofibrillary pathology beginning later and accelerating before the emergence of symptoms.
- New paradigm at the foundation of new criteria for diagnosis of AD from 2011 workgroup convened by the NIA and the Alzheimer's Association.

Paradigm of evolution of AD and Role of Biomarkers

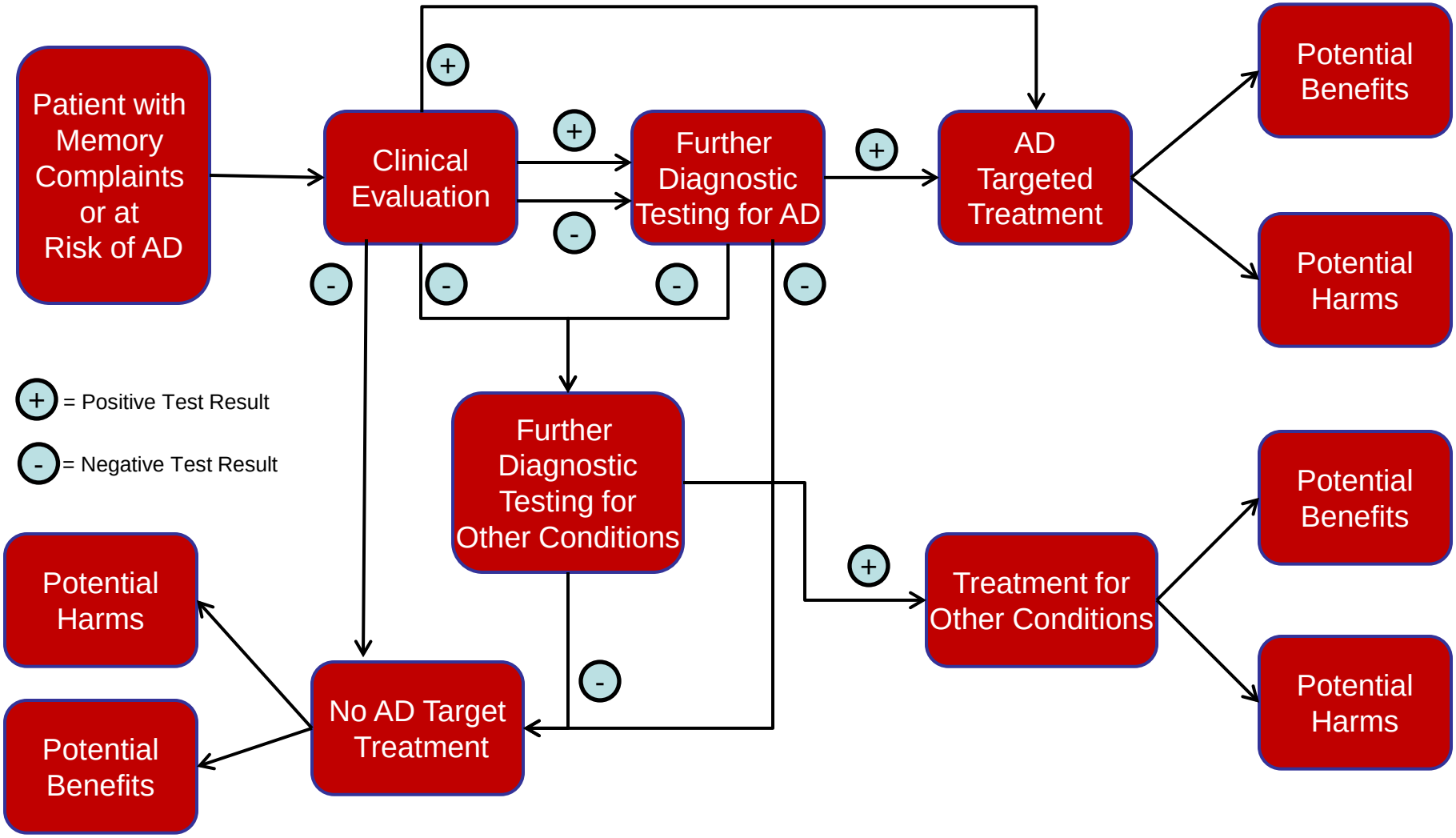
- Pre-clinical Alzheimer's disease ("for research purposes only")
  - Asymptomatic amyloidosis
  - Amyloidosis plus neurodegeneration
  - Amyloidosis plus neurodegeneration plus subtle cognitive decline
- Mild cognitive impairment (MCI)
  - Core clinical criteria
  - Amyloid and neuronal injury tests affect likelihood that MCI is due to AD
- AD dementia
  - Core clinical criteria
  - Biomarker tests: "probable," "possible," and "unlikely" dementia due to AD

- "There was a broad consensus within all three workgroups that much additional work is needed to validate the application of biomarkers for diagnostic purposes."

Conceptual Approaches to Evaluating Evidence on AD Diagnostic Tests

- Analytic Framework
- Evidence Hierarchy
- Analytic validity, clinical validity, clinical utility

Simplified Analytic Framework: Diagnostic Testing for Alzheimer's Disease



Potential Benefits and Harms of PET-amyloid imaging

Potential Benefits of Positive Test	Potential Harms of Positive or False Positive Test
Ability to start AD-specific treatment earlier	Additional patients started on drugs of limited or no benefit
Ability to plan more effectively for the future	Discrimination/difficulty obtaining long-term care or life insurance
Ability to seek clinical trials	
Potential Benefits of Negative Test	**Potential Harms of Negative or False Negative Test**
Promotes consideration of alternative, perhaps more treatable causes	Aggressive additional diagnostic testing that does not lead to improved outcomes and may present unnecessary risks and costs
Patient reassurance	False patient reassurance (false negative)
Reduction in number of patients continued on or started on AD drugs	

Evidence Hierarchies for Diagnostics

Diagnostic Imaging Evidence Hierarchy Level	Genetic Testing Evidence Category	Example of Outcome Measures
1. Technical Efficacy	1. Analytic validity	Interpretable scan resolution, accuracy and reliability of tests of CSF proteins to measure CSF protein levels, inter-reader and inter-laboratory reliability of test results
2. Diagnostic Accuracy	2. Clinical validity	Sensitivity/specificity vs. gold standard test or vs. some other standard
3. Diagnostic Impression		Change in presumptive diagnosis following introduction of new test results
4. Diagnostic Action		Initiation or cessation of treatment; impact on use of additional diagnostic studies
5. Patient Outcomes	3. Clinical utility	**Potential Harms and Benefits**
6. Societal Outcomes		Cost-effectiveness of testing

Review of Current Evidence

- Literature search January 2000 – March 2012
- 575 articles on all types of Dx evaluated

Study Level	Number of studies
Technical Efficacy (Analytic Validity)	17
Diagnostic Accuracy (Clinical Validity)	553
Diagnostic Impression	5
Diagnostic Action	None
Patient Outcomes (Clinical Utility)	None
Societal Outcomes	None

Focus on PET-amyloid imaging

- 15 articles identified, including 2 new since March 2012

Study Level	Number of studies
Technical Efficacy (Analytic Validity)	
Diagnostic Accuracy (Clinical Validity)	14
Diagnostic Impression	1
Diagnostic Action	None
Patient Outcomes (Clinical Utility)	None
Societal Outcomes	None

Amyvid Diagnostic Accuracy/ Clinical Validity

- Diagnostic accuracy: Comparing scan reading to pathology
- Prevalence of positive histopathology: 39/59 (66%)

Test Performance		In-person Training	Electronic Media Training
Sensitivity	Median	92	82
	Range among 5 readers	(69-95)	(69-92)
Specificity	Median	95	95
	Range among 5 readers	(90-100)	(90-100)

False Positives: 1-2 per reader out of 59 scans

False Negatives:

In-person training: 2-5 per reader/59 scans

Electronic training: 3-12 per reader/59 scans

Amyvid prognostic clinical validity

- Industry funded and co-authored*
- 151 subjects with PET amyloid imaging followed longitudinally
  - 69 cognitively normal, 51 MCI, 31 clinically diagnosed AD dementia
- Aβ+ scans associated with greater decline in multiple cognitive outcome measures
- MCI conversion to dementia at 18-month f/u:
  - 29% of Aβ+ converted vs. 10% of Aβ-
- Questions:
  - Majority reading of scans may enhance prognostic accuracy
  - ? Clinical significance of magnitude of the difference in prognosis
  - "The present data are insufficient to predict whether, or when, cognitive deterioration will occur in individual Aβ+ cognitively normal patients."

*Doraiswamy et al, Neurology 2012;79:1636-1644.

Amyvid diagnostic impression/action

- Industry-sponsored and co-authored*
- 229 patients selected by memory-disorder specialists
- Clinicians gave working diagnosis and management plan pre-PET amyloid testing and then afterward
- Diagnosis changed in 55% of cases, diagnostic confidence increased, 87% had changes to diagnostic/mgmt. plan
- Questions
  - "Not due to AD" and "indeterminate" diagnoses changing to "due to AD" on basis of scan
  - 10 (12%) of 86 thought "due to AD" had negative scans
  - Adding AD drugs to amyloid-positive patients: correct?
  - Negative scans: 50% to 25% of patients on AD drugs
  - Drop in other testing for patients with positive scans: makes sense but correct?
  - Similar drop in other testing for patients with negative scans: why?

* Grundman et al. Alzheimer Dis Assoc Disord 2012.

What Insurers Will Be Looking For: Evidence on Clinical Effectiveness

- Persuasive evidence that diagnostic tests improve patient outcomes, particularly when current treatments have limited benefits and may present harms and unnecessary costs.

- FDA approval if under FDA jurisdiction
  - But not the same evidence standards
  - "the FDA did not require clinical data assessing the effect of florbetapir imaging on clinical management or patients' health."

- Positive test results difficult to demonstrate improved outcomes without effective treatments

- Negative test results: insurers will want studies that measure potential benefits and potential harms

Recommendations for Future Research and Research Design

- *In the current era of AD treatments of limited effectiveness, randomized controlled trials should be performed to evaluate diagnostic tests with potential overall net health benefits.*
  - Outcomes should ideally include true patient-centered outcomes but measurement of impact of testing on subsequent clinician diagnosis and management may give important insight into patient outcomes.

- *Develop consensus standards for biomarker test deployment and interpretation.*

- *In therapeutic studies that have used positive biomarker tests as inclusion criteria (enrichment design studies), include in baseline tests other potential biomarkers that can also be evaluated (nested marker-by-treatment-interaction studies). Ideally, always include additional test options that would be simpler, more accessible, and less expensive than the "gold standard" set of biomarkers used to qualify for inclusion.*

Recommendations for Future Research and Research Design

- *Retrospective assessment of a prognostic biomarker can only be done using data from well-conducted randomized controlled trials and with 1) prospectively stated hypotheses, analysis techniques, and patient populations; and 2) with a pre-defined and standardized assay and scoring system for "positive" results. In other words: data mining should not be done to search retrospectively for combinations of clinical characteristics and biomarker results that are correlated with positive treatment outcomes.*

- *Given that many important clinical and economic outcomes occur years after diagnostic testing, a broad research agenda will benefit from the use of simulation modeling (decision analysis).*

Additional slides

Psychological outcomes

- Psychological well-being, changes in health behaviors, future planning not unique to AD
- REVEAL study of APOE status found no evidence of differences between patients who learned their risk for future AD.
  - Positive test results followed by increased stress for six months, after which declined
  - More participants with APOE-positive status reported changes in AD “prevention activities” compared to non-disclosure counterparts at one year
  - APOE-positive status correlated with “thinking about” or making changes to long-term care insurance