Appropriate Use Criteria
for Lumbar Puncture and Cerebrospinal Fluid in the Diagnosis of Alzheimer's Disease

Leslie M Shaw

Department of Pathology & Laboratory Medicine

Perelman School of Medicine, University of Pennsylvania

Introduction

- Traditionally clinicians have diagnosed AD using primarily clinical criteria
- CSF AD biomarkers are effective surrogates for neuropathology
- Their use provides for reliable detection of AD earlier in the disease course compared to clinical diagnosis alone
- Reliability of CSF AD biomarker testing for amyloid and tau proteins has advanced considerably within- and across platforms, increasing the likelihood of broad clinical use internationally including in USA where this is typically done in the research realm
- CSF biomarker testing has IVD status in some European countries & used in routine clinical practice & used for patient selection in international treatment trials

Introduction

- A group of experts, a Workgroup, convened by the Alzheimer's Association developed these Appropriate Use Criteria (AUC) to:

  - Assist healthcare practitioners with guidance-based on: **evidence** and the **experience** of the workgroup members, and **ethical standards** for patient care-on the ***Appropriate*** and ***Inappropriate*** use of LP and CSF AD biomarker testing thereby supporting optimal patient safety and care.
  - Builds on the AUC for amyloid PET(Johnson, 2013), these criteria are intended to support clinicians in consistently identifying appropriate patients for LP and CSF testing, while at the same time taking into consideration the cost-effective use of limited healthcare resources.
  - It is hoped that these AUC will be an important resource for policy makers & 3rd party payers

- These AUC ***do not:***

  - Provide recommendations for the research use of CSF biomarker testing
  - Rule out conditions other than AD or MCI-AD as possible causes of cog decline

- While the Workgroup was not charged to make recommendations regarding specific CSF AD biomarkers, when discussing diagnostic value of biomarkers, the document focuses on CSF Aβ42(sometimes normalized to Aβ40), t-tau and p-tau181(and ratios to Aβ42 in some studies).

Evidence discussion

- In Feb 2017 the Workgroup was convened by Alz Assn to develop these AUC

  - Avalere Health provides technical & editorial assistance for this process
  - Teleconference calls, biweekly, through December, 2017; FTF at the London AAIC meeting, July 2017
  - Members include 4 Neurologists, one Neuro-Ethicist, one Lab Medicine physician, one Path & Lab Medicine biomarker researcher
  - Each member had considerable publications on topics relevant to the use of LP, including dementia research, biomarker test validation & clinical utilities, patient care & ethics

- The workgroup defined the scope & parameters of the AUC & key research questions to guide systematic review of published evidence on LP & CSF using the PICOTS (**p**opulation, **i**nterventions, **c**omparisons, **o**utcomes, **t**iming & **s**ettings) framework

AUC Workgroup Members

Workgroup Member*	Affiliation
Jalayne Arias	University of California, San Francisco; Atlantic Fellow, Global Brain Health Institute
Kaj Blennow	Department of Psychiatry & Neurochemistry, University of Gothenberg, Sweden
Douglas Galasko	Department of Neuroscience, UCSD
Jose Luis Molinuevo	Barcelonabeta Brain Research Center, Barcelona, Spain
Stephen Salloway	Memory and Aging Program, Butler Hospital, Brown University
Suzanne Schindler	Department of Neurology, Washington University
Leslie M Shaw	Department of Pathology & Laboratory Medicine, University of Pennsylvania

*Responsible for the scope of evidence reviews & determination of **Indications** for CSF testing and vote on appropriateness or inappropriateness of the **Indications**. All declared conflicts of interest, if any, according to a written policy included in the AUC document.

Five Key Research Questions(KQ1-5)

Key Research Questions	
KQ#1	Safety of Lumbar Puncture in individuals undergoing evaluation for suspected AD
KQ#2	What is the diagnostic accuracy In persons experiencing cog impairment of CSF Aβ42 & tau (t-tau, p-tau) or ratios of analytes as indicators of AD pathology presence or absence?
KQ#3	In persons with little of no cognitive impairment, what is the diagnostic accuracy(sensitivity, specificity) of LP & CSF in assessing CSF amyloid(Aβ42) and tau levels or ratios as indicators of AD pathology presence or absence?
KQ#4	What is the accuracy of CSF amyloid (Aβ42) and tau levels(t-tau, p-tau) or ratios of analytes for predicting progression from MCI to AD? Does the literature report rates of progression from MCI to AD (in individuals with MCI who are found to have amyloid and tau levels in high risk of AD ranges)?
KQ#5	What are the effects of CSF testing for suspected AD on both clinical outcomes (diagnosis) and intermediate outcomes (e.g., management with medications)?

KQ#1 Safety of Lumbar Puncture

- CSF can be collected safely & reliably by LP
  - Documented in >7,000 AD patients in 10 studies
  - Consistent with documented safety record in >30,000 patients with a wide array of neurologic disorders
- Key to maximizing patient safety is recognition of pt- & LP-related risk factors including: contraindications such as use of anticoagulant meds, recent seizures, blood clotting disorders, intracranial lesions, others
- Additional best practices to ensure LP safety:
  - Use of atraumatic narrow bore needle-less risk for PLPH
  - Avoidance of repeated attempts in difficult cases to reduce risk for lower back pain
  - Avoidance of collection of >30 mL
- Fear of the LP procedure is an independent risk factor that can be influenced by the attitude of the clinical staff & can be decreased by providing sensitive, matter-pf-fact, verbal communication about the procedure by clinicians familiar and comfortable with LP

KQ#2: In persons experiencing cognitive impairment, what is the **diagnostic accuracy** of LP & CSF Aβ42 & tau levels(t-tau & p-tau181) or ratios as indicators of AD pathology presence or absence?

- Assessment of accuracy of a test depends on the "trueness" of the reference standard the test is compared against. For many disease conditions, an accurate reference is not available & the assessment depends on expert clinical diagnosis or consensus clinical diagnosis.

- For AD, diagnostic accuracy based on clinical criteria is not optimal:
  - sensitivity & specificity are ~80% & 70%, respectively, at expert centers.
  - At earlier disease stages the accuracy is substantially lower
    - eg, at the MCI stage: clinical symptoms overlap with those of other NDs
    - co-pathologies add to the uncertainty.

- More objective detection of AD disease presence or absence is obtained using amyloid PET or neuropathologic evaluation
  - Amyloid PET ligands have been approved by the FDA & EMA to identify/rule out brain amyloidosis based on validation against brain autopsy
  - 19 studies using amyloid PET as reference standard were identified (N=3,697)
  - There were 5 studies that used autopsy diagnosis as the reference standard (N=764)

KQ#2: In persons experiencing cognitive impairment, what is the **diagnostic accuracy** of LP & CSF Aβ42 & tau levels(t-tau & p-tau181) or ratios as indicators of AD pathology presence or absence?

- Sensitivity & specificity; *AUC* across the studies:

- 88-93% & 84-85%; *AUC*= 0.90-0.93,   for Aβ42 alone   [N=3,094]

- 96% & 88-91%;   *AUC*=0.93-0.96,   for Aβ42/Aβ40   [N=515]

- 92.1 & 86.3;   *AUC*=0.95   for t-tau/Aβ42   [N=1,526]

- 91.1 & 89.8;   *AUC*=0.96   for p-tau181/Aβ42   [N=1,453]

KQ#3: In persons with little of no cognitive impairment, what is the diagnostic accuracy(sensitivity, specificity) of LP & CSF in assessing CSF amyloid(Aβ42) and tau levels or ratios as indicators of AD pathology presence or absence?

- Accuracy for detection of AD presence or absence in persons with little or no cognitive impairment is comparable to that described in KQ2, although in a smaller number of study subjects

KQ#4: What is the accuracy of CSF amyloid (Aβ42) and tau levels(t-tau, p-tau) or ratios of analytes for predicting progression from MCI to AD? Does the literature report rates of progression from MCI to AD (in individuals with MCI who are found to have amyloid and tau levels in high risk of AD ranges)?

- When MCI is associated with AD pathology based on positive AD biomarkers, the risk for progression to a clinical diagnosis of AD dementia is higher than when CSF Aβ42 and tau biomarkers are normal.

- Conversely, individuals whose CSF Aβ42 and tau biomarkers are non-pathologic have a high likelihood of remaining free from AD dementia over the time of observation, up to 10 years thus far.

- The wide range of specificity values across studies that document predictive performance of thee CSF biomarkers likely due to:
  - Differences in longitudinal observation time ranging from 1 to 10+ years from time of MCI diagnosis to the time limit of the study
  - Patient age and disease heterogeneity likely impact rates of progression in an individual patient
  - Prolonged follow-up studies for at least 5 years, and ideally longer, are needed to provide robust estimates of predictive performance in clinical practice.

Implementation of these AUC

- Discussion of appropriateness or inappropriateness of **Indications** intended to:
    - assist dementia experts on decisions regarding testing and
    - assist primary or other providers in determining when to refer to a dementia expert for more specialized testing.
- Workgroup(WG) described 6 clinical Indications where CSF biomarker testing is believed to be appropriate; these are largely consistent with those proposed by the PET amyloid imaging AUC:
    - WG recommends Appropriate for CSF biomarker testing for pts. With **progressive & unexplained MCI**
    - Pts with **possible AD** where co-morbidities often make diagnosis uncertain
    - In cases with early **onset (<65 yrs) MCI and dementia**
- WG also describes 3 appropriate Indications that differ from the AUC for amyloid PET:
    - Pts meeting core clinical criteria for **probable AD** with typical age of onset
    - Individuals experiencing SCD but who score within normal range on cog. Testing & considered to be at increased risk for AD
    - Pts whose dominant symptom is a change in behavior & where an AD diagnosis is being considered.
    - We adopt the recommendation that CSF testing should be conducted by dementia experts.

Further research questions

- Studies using "next-generation" CSF biomarker assays will have less center to center variability, together with large sets of comparisons to amyloid PET & autopsy brain examination:
  - More precise sensitivity/specificity, more consistent cutpoints and grayzones around them
  - Optimization of pre-analytical factors is a key requirement to achieve the above
  - Further studies of ratios in comparison to Ab42 alone are warranted
- Candidate new biomarkers
- Long-term follow-up with CSF biomarker positive and negative needed
- Studies to determine added value of CSF biomarkers analogous to the amyloid PET IDEAS study
- Acceptability of LP in diverse settings
- Estimations of risks of future cognitive decline in persons who test positive needed as prevention trials for AD are pursued.