Alzheimer-type biomarker changes are identifiable in asymptomatic and mildly symptomatic predementia phases of Alzheimer disease (AD) and AD dementia. The International Work Group (IWG) guidelines for diagnosis identify a unified spectrum of 3 phases. The classic clinical feature that indicates AD is an episodic memory defect of the amnestic type. IWG criteria require biomarker support for the diagnoses of AD at any clinical stage. Pathophysiologic and topographic biomarkers are recognized. These criteria are proposed to allow highly specific diagnosis of AD and assist in identifying patients for clinical trials of AD-related treatments and other types of AD research.

This article gives an updated account of the clinical application of cerebrospinal fluid (CSF) biomarkers for Alzheimer disease (AD). The clinically most relevant biomarkers, total tau, phospho-tau and Aβ42 are discussed, and how they may be used, together with other diagnostic investigations, to make a predementia diagnosis of AD. Recent findings in sporadic and genetic preclinical AD are also discussed and, more specifically, what the biomarkers have taught us on the sequence of events in the pathogenic process underlying AD.

In vivo imaging of amyloid-β (Aβ) with positron emission tomography has moved from the research arena into clinical practice. Clinicians working with cognitive decline and dementia must become familiar with its benefits and limitations. Amyloid imaging allows earlier diagnosis of Alzheimer disease and better differential diagnosis of dementia and provides prognostic information for mild cognitive impairment. It also has an increasingly important role in therapeutic trial recruitment and for evaluation of anti-Aβ treatments. Longitudinal observations are required to elucidate the role of Aβ deposition in the course of Alzheimer disease and provide information needed to fully use the prognostic power of this investigation.
Magnetic resonance imaging (MRI)-based indicators of regional and global brain atrophy and more advanced measures of cortical functional and structural connectivity are among the most promising imaging biomarkers for the characterization of preclinical and prodromal stages of Alzheimer disease (AD). This review presents the current status of available and evolving MRI-based technologies for the early asymptomatic and pre dementia diagnosis of AD, including high-resolution structural MRI of global and regional brain atrophy, diffusion tensor imaging of structural cortical connectivity, and functional MRI during rest and task performance. The selection of an appropriate technique needs to consider its suitability for specific applications.

In this article, cognitive measures in the screening of individuals at risk for Alzheimer disease (AD) are reviewed. Use of cognitive tasks in identifying clinical cases of AD is considered, as well as methods for detecting those in the prodromal stages of the disease, including cognitive screening instruments. Traditional assessments, such as the mini-mental state examination, as well as contemporary computerized screening instruments, are examined. Areas of cognition for investigation in the detection of prodromal AD are recommended. The prospects for general cognitive screening are reviewed, and more engaging technologies to tests individuals at risk for developing AD are recommended.

Effective treatments of Alzheimer disease (AD) dementia are an urgent necessity. There is a growing consensus that effective disease-modifying treatment before the onset of clinical dementia and slowing the progression of mild symptoms are needed after recent setbacks in AD therapeutics. The identification of at-risk and preclinical AD populations is becoming important for targeting primary and secondary prevention clinical trials in AD. This article reviews the strategies and challenges in targeting at-risk and preclinical AD populations for a new generation of AD clinical trials. Design, outcome measures, and complexities in successfully completing a clinical trial targeting this population are reviewed.

This article reviews the current recommendations in early diagnosis and the desires of the patients and their relatives, put in perspective with the reality of the clinical practices. More specific situations covered are: (1) the issue of young diseased patients, taking into account the psychological implications of the early occurrence of the disease in life and of
the longer delay for these patients between the first observable signs and the diagnosis and (2) the issue of genetic testing, taking into account the implications of this extremely early form of bad news on the individual's existence and on the family structure.

Applying the IWG Research Criteria in Clinical Practice: Feasibility and Ethical Issues

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In 2007, new International Working Group research criteria introduced a new conceptualization of Alzheimer disease and created a framework for earlier diagnosis. There is increasing consensus to understand Alzheimer disease as a clinical-biologic entity, in which biomarkers, especially pathophysiologic markers revealing underlying pathology, represent the biologic counterpart of the diagnosis, and specific symptoms, such as episodic memory deficits, account for the clinical one. This article advances and moves forward on this.

FDG-PET in Early AD Diagnosis

Jessica Chew and Daniel H.S. Silverman

18F-fludeoxyglucose positron emission tomography (FDG-PET) is an important tool for detecting the early stages of Alzheimer disease (AD). This article discusses the multiple roles FDG-PET plays in helping to diagnose AD, including detecting the disease in the prodromal and early dementia stages, differential diagnosis of dementia, documenting and quantifying cognitive decline, and predicting progression from mild cognitive impairment to AD. In addition, the role of structural magnetic resonance imaging, underutilization of FDG-PET, and a suggested multimodal approach for early AD diagnosis are discussed.