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Roadmap to Alzheimer's Biomarkers in the Clinic

Biomarkers for the diagnosis of Alzheimer's disease in clinical practice: an Italian intersocietal roadmap

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ABSTRACT

Biomarkers of brain amyloidosis and neurodegeneration/synaptic dysfunction are featured in recent diagnostic criteria for Alzheimer's disease. Several gaps in our knowledge, however, need to be filled before they can be adopted clinically. The aim of this article is to describe a roadmap, developed by a multidisciplinary task force, to rationally implement biomarkers for Italian Memory Clinics. This roadmap is based on a framework comprising 5 sequential phases: identification of leads for potentially useful biomarkers; development of clinical assays for clinical disease; evaluation of detection of early stages; definition of operating characteristics in relevant populations; and estimation of reducing disease-associated mortality, morbidity, and disability. The roadmap was devised by identifying current evidence of validity, still missing evidence, and action needed to collect this missing evidence. With appropriate adaptation to local, country-specific circumstances, the roadmap can be translated to other countries.

1. Introduction

New criteria for the in vivo diagnosis of Alzheimer's disease (AD) have been developed by an International Working Group (IWG) (Dubois et al., 2014) and the National Institute of Aging–Alzheimer Association (NIA-AA) task force (Jack et al., 2011a). These criteria postulate that biomarker assessment enhances the accuracy of the AD diagnosis at the predementia and dementia stages. The proposed so-called "core" biomarkers include both laboratory and neuroimaging parameters (Table 1): (1) medial temporal atrophy on high-resolution magnetic resonance (MR); (2) Aβ42, tau, and phospho-tau (p-tau) in the cerebrospinal fluid (CSF); (3) posterior cingulate precuneus and temporoparietal hypometabolism on ^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET); and (4) increased cortical uptake of amyloid ligands evident on PET. Other biomarkers are claimed to rule out frequent differential diagnoses such as dementia with Lewy bodies, and frontotemporal lobar degeneration includes presynaptic dopaminergic imaging with single-photon emission tomography (e.g.,^{123}I-ioflupane) and serum progranulin (Table 1).

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Table 1
Biomarkers for the early and differential diagnosis of Alzheimer's disease

Modality	Analyte/probe	Abnormality	Pathology	Supported diagnosis
Core AD biomarkers				
CSF	Aβ42	↓ Concentration	Brain amyloidosis	AD
CSF	Tau, p-tau	↑ Concentration	Neurodegeneration	AD
PET	^{11}C-Pittsburgh Compound B,^{18}F ligands	↑ Cortical uptake	Brain amyloidosis	AD
PET	^{18}F-fluorodeoxyglucose (FDG)	↓ Metabolism in posterior cingulate-precuneus and temporoparietal cortex	Neurodegeneration	AD
MR	3D T1 weighted	↓ Volume of hippocampus and medial temporal structures	Neurodegeneration	AD
Other biomarkers				
SPECT	^{123}I-ioflupane	↓ Uptake in the striatum	Neurodegeneration of the presynaptic nigrostriatal pathway	Dementia with Lewy bodies
Serum	Progranulin	↓ Concentration	Decreased production of progranulin in the CNS	Frontotemporal degeneration due to granulin gene mutations

Key: AD, Alzheimer's disease; CNS, central nervous system; CSF, cerebrospinal fluid; MR, magnetic resonance; PET, positron emission tomography; SPECT, single-photon emission tomography.

In 2012, the Italian Society for the Study of Dementia issued a position article on IWG criteria, advising caution in the routine clinical use of "instrumental and laboratory markers for the diagnosis of the preclinical and asymptomatic states" of AD (Musicco et al., 2012). However, the article was developed before publication of the NIA-AA criteria in 2011, and recommendations on the clinical, symptomatic, predementia stage (prodromal or mild cognitive impairment [MCI]) were not included.

At the time of the writing of this article (June 2014), our expert panel acknowledged that a number of clinical, technical, organizational, and ethical barriers must be overcome before biomarkers can be widely used. This article was produced following a public workshop sponsored by the Italian Ministry of Health, where the authors were representatives of relevant Italian scientific societies (Neurology, Neuroradiology, Nuclear Medicine, Laboratory Medicine, Neuropsychology, Psychogeriatrics, and Bioethics). The aim of the debate was to develop a roadmap to promote the rational and cost-effective implementation and use of biomarkers for the diagnosis of AD in the clinic. This manuscript describes this roadmap. Here, we focus on diagnosis at the predementia and/or MCI stage and differential diagnosis of atypical dementia cases. Instead, diagnosis at the preclinical and asymptomatic stage will not be addressed. This article does not enter the debate on the most appropriate set of diagnostic biomarkers that is currently ongoing between the NIA-AA and IWG task forces proposing core biomarkers and pathophysiologic and/or progression biomarkers, respectively.

The next sections address the clinical context (Section 2), the phases of biomarker development and validation (Section 3), the current state of validation of biomarkers for AD (Section 4), the roadmap for their large-scale implementation in the Italian health care milieu (Section 5), and the translation of the roadmap to other national health systems (Section 6). The intended readership includes: (1) funding agencies of health care research, who are advised to uptake the document to direct resources for action described herein; (2) scientists and scientific societies who take the responsibility to engage in work with funding agencies to achieve the aims of the roadmap; and (3) policymakers, who will be called to action in due time to convert the results of action into routine practice.

2. The clinical context: what is the benefit of earlier and more accurate diagnosis of AD?

The benefit of early diagnosis is a hotly debated issue. Respected researchers have claimed that the emphasis on early diagnosis of AD is diverting attention and resources from the "real" needs of the elderly (comorbidity and palliative care) (Le Couteur et al., 2013). Some patients and their families may become anxious following a diagnosis of AD and may experience feelings of loss, anger, uncertainty, and frustration. Despite these caveats, potential benefits in diagnosing AD early on include the following aspects: therapeutics (obtaining currently available treatment early, participating in clinical trials with potential disease modifiers), care giving (helping the family to understand and accept, enabling the patient and family to make lifestyle choices), legal (financial and legal plans while competent, taking appropriate steps to prevent injury, i.e., driving, handling weapons), as well as health care aspects (getting more timely access to help within the health care system and within communities).

The diagnostic value of biomarker assessment at the stage of overt dementia is related to drug treatment and prognosis. The differential diagnosis of AD dementia from dementia with Lewy bodies or frontotemporal lobar degeneration can at times be challenging. A diagnosis of dementia with Lewy bodies strongly counter indicates the use of neuroleptics due to their potentially devastating effects (Piggott et al., 1998); a diagnosis of frontotemporal lobar degeneration would indicate against the use of cholinesterase inhibitors (Arciniegas and Anderson, 2013; Mendez et al., 2007) and memantine (Boxer et al., 2013); and finally, cholinesterase inhibitors and memantine are not effective in pure vascular dementia (Schneider, 2003).

The authors believe that the benefits of diagnostic biomarkers overcome individual and society costs in most cases, and that, more stringent formalization of their use in the clinic would reduce current gray areas. We believe that the steps toward large-scale implementation of biomarkers described in Section 5 will contribute to achieve this aim.

3. Phases of biomarker development and validation

Drug development has been carried out in structured phases for quite a number of years, which has facilitated coherent, thorough, and efficient development of new therapies (International Conference on Harmonisation E9 Expert Working Group, 1999). A similar approach has been proposed by a group of oncologists for the development of biomarkers for cancer screening (Pepe et al., 2001). Here, phase 1 (preclinical exploratory studies) aims to identify leads for potentially useful biomarkers and prioritize identified leads; phase 2 (clinical assay development for clinical disease) aims to estimate both true- and false-positive rates or receiver operating characteristics curve and assess ability to distinguish subjects with and without the disease; phase 3 (retrospective longitudinal repository studies) aims to evaluate the