SPECIAL COMMENTARY
750 words, up to 10 references, 1 figure or photo
Deadline for submission: Tuesday Apr 23

In JAMA's issue of April 2nd, Rabinovici et al. published the first results of the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study [A], a large US-based study on amyloid PET for the diagnosis of Alzheimer's disease. They find that "among Medicare beneficiaries with mild cognitive impairment or dementia of uncertain etiology evaluated by dementia specialists, the use of amyloid PET was associated with changes in clinical management within 90 days". These management changes consisted mostly of prescription or discontinuation of ~~counseling and~~ drugs (Alzheimer's drugs, cognitive enhancers, and drugs for mood, behavior, dementia risk factors, and drugs used to treat other neurologic conditions) and counseling. Interestingly, a positive scan is followed by ~~greatly~~ markedly increased prescription of Alzheimer's drugs, while ~~these~~ practitioners hardly budge when the scan is negative. The authors acknowledge that the study does not provide an answer to the key question, i.e. whether the management changes are associated with improved clinical outcomes. The longitudinal component of the IDEAS study, currently ongoing, will collect information on hospital admissions and mortality ~~in order~~ to ~~try and answer~~address these hard end-points and explain why such a huge sample size (n=16.008) is needed~~is very question~~. Impact on diagnostic confidence and drug prescription have previously been shown in much smaller studies such as ABIDE [REF de Wilde], though the magnitude of changes is more impressive in IDEAS.

Amyloid PET has made the dream of dementia specialists come true, i.e. visualizing *in vivo* and with high accuracy the amyloid deposits that Alois Alzheimer described as senile plaques over a century ago and that until recently could be appreciated only post mortem – far too late to be of any practical use. As is often the case, enthusiasm on this technological advancement was followed by more sobering observations. A large proportion (20 to 30%) to of persons of 65 years and over with intact cognitive function living in the community have a positive amyloid PET scan, making the exam more suitable to rule out than rule in the disease (i.e. a negative amyloid PET rules out Alzheimer's pathology as the cause of your patient's cognitive impairment, but a positive scan does not imply that Alzheimer's pathology is the culprit) [B]. ~~Last, a~~Amyloid is just one of the two molecular culprits of Alzheimer's, the other being tau, ~~to~~ which is more closely associated with the onset of symptoms, and for which new ~~amyloid~~ PET tracers are emerging [REF Villemagne]~~is blind~~. In this apparently grim scenario, how can a diagnostic test of brain amyloidosis improve clinical outcomes?

The impact on health outcomes of diagnostic exams allowing to identify conditions amenable to a cure (e.g. gastroscopy for gastric cancer, angiography for cerebral vessel ~~thrombosis~~occlusion, etc.) is obvious. The impact of diagnostic exams for conditions for which only palliative care exists is much more subtle. Medicine is a highly integrated and non-deterministic discipline where biomedical, psychological, psycho-social, and regulatory factors interact with multiple pathways. An uncertain diagnosis can trigger more useless or misleading diagnostic exams, that can trigger ~~useless~~ ineffective or toxic drug interventions,

that can trigger inappropriate management choices, that can trigger adverse health outcomes~~, that can trigger…~~. The causal pathway between diagnosis and outcome is blurred and affected by a number of probabilistic factors that rigorous scientific method can barely measure and control. Despite the hurdles, the Alzheimer and dementia community should strive to provide the best evidence for any medical intervention, be it diagnostic or treatment.

Whatever its pathophysiological role, brain amyloidosis is a major predictor of adverse cognitive outcomes in non-demented persons [F, G], and the current definition of Alzheimer's disease requires brain amyloidosis as a ~~mandatory feature~~necessary – though not sufficient - feature [H, J]. IDEAS is collecting the much-needed hard evidence on the clinical validity and utility of an accurate and reliable amyloid detection tool such as amyloid PET [K]. One of the ~~major~~ weaknesses of IDEAS is ~~however its~~the non-controlled design, as all patient underwent PET. An initiative currently running in Europe (AMYPAD diagnostic and patient management study~~ – DPMS~~) is using a randomized design to study the impact of amyloid PET on diagnostic confidence and patient-related outcomes [D].

While IDEAS and AMYPAD ~~DPMS~~ both focus on amyloid PET, dementia workup makes use of other biomarkers such as metabolic FDG PET and CSF studies; the latter allows simultaneous assessment of amyloid beta 42 and tau proteins and is more popular in (northern) Europe than in the USA. More initiatives ~~expanding the zoom to~~examining the whole diagnostic armamentarium will be needed to develop an evidence-based cost-effective diagnostic workup for patients with cognitive impairment and suspected Alzheimer's disease. However, coordinated and harmonized validation of biomarkers relying on different platforms such as PET and CSF will be a challenge. The Alzheimer's and dementia community has developed a biomarker validation framework that should help precisely achieve this goal [E].

While waiting for drugs able to prevent or delay the progression of Alzheimer's disease, patients have the right to at least know what is affecting their memory, plan for the future, and receive the ~~best available~~most appropriate pharmacologic and non-pharmacologic interventions. IDEAS is a major step in this direction.

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