The Biomarker-based Diagnosis of Alzheimer's Disease.

1 – Ethical and Societal Issues.

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ABSTRACT

There is great interest in the use of biomarkers to assist **in the timely** identification of Alzheimer's disease (AD) in individuals with mild symptoms.

However, the **inclusion** of AD biomarkers in clinical-criteria poses socio-ethical challenges. The Geneva Task Force for the Roadmap of Alzheimer's Biomarkers was established to deliver a **systematic strategic research agenda (aka roadmap) to promote efficient and effective validation of AD biomarkers and to foster their uptake in clinical practice.**

In this paper we **summarize the workshop discussion of** the Geneva Task Force "Ethical and societal issues" working-group, which comprised bioethicists, clinicians, health economists, and representatives of those affected by AD.

The working-group identified the following key issues that need to be **included in the roadmap: improving access to services through timely diagnosis; the need for a diagnostic research protocol before moving to clinical routine; recruitment in diagnostic research protocols in the absence of effective therapy; respect for the autonomy of the individual with mild cognitive impairment (MCI) in information and consent process and the right not to know biomarkers results; need for counseling programs; disclosure of the diagnosis in a structured environment and the involvement of family members; health policies including the individuals' views and the protection of their interests; and the economic costs for society.**

KEYWORDS

Alzheimer's disease; mild cognitive impairment; informed consent; disclosure of diagnosis; ethics; society.

Introduction

Alzheimer's disease (AD) is a neurodegenerative, progressive and highly disabling disease **of which no effective therapy is currently available**. Approximately 50 million people are currently affected worldwide and, **although dementia incidence may be declining (Satizabal et al., 2016)**, the **prevalence** is expected to increase sharply in the coming decades as a result of population aging **alone** (Prince et al., 2013). AD is largely under-diagnosed amongst those who are affected. Diagnostic criteria based on biomarker data have been proposed by an International Working Group of experts in 2007 (Dubois et al., 2007) and by the National Institute on Aging and Alzheimer's Association task force in 2011 (Albert et al., 2011; McKhann et al., 2011) **mainly for use in research contexts**. These new criteria were **necessary in order** to update the existing ones that date back to 1984 (McKhann et al., 1984), and to **mark the recent** advances in our knowledge and understanding of AD **and its underlying neuropathological features**. Core biomarkers of these features have been intensely investigated in **these last few years and include** medial temporal atrophy on high-resolution magnetic resonance imaging (MRI), temporoparietal hypometabolism on fluorodeoxyglucose positron emission tomography (FDG-PET), Abeta42 and tau in the cerebrospinal fluid (CSF), and increased cortical uptake of amyloid ligands on positron emission tomography (PET) **[Note 1]**. A significant inter-individual variability exists in the extent to which brain and cognitive reserve may buffer the clinical manifestations of the underlying brain damage (Stern, 2012), **with the latter** invariably **increasing** with age **even** in asymptomatic persons (Jack et al., 2014). Nevertheless, the aforementioned core biomarkers have been linked to the clinical expression of AD (Albert et al., 2011; McKhann et al., 2011). Based on the hypothesis that the pathophysiological process of AD begins many years prior to the manifestation of overt clinical symptoms (Jack et al., 2013), biomarkers that capture dementia-related brain damage might also be useful to recognize relevant disease processes in the asymptomatic, preclinical phase of AD (Sperling et al., 2011) and in those with mild cognitive impairment (MCI) – the prodromal stage of AD (Albert et al., 2011). The latter is of potentially great relevance for the development of future disease-modifying drugs **as** these are thought to **exert their efficacy during the long dementia latency period and** mostly at the very early stages of the progression of brain damage. **The authors of the proposed AD diagnostic criteria recommend that** more research work is needed to validate and implement the use of the core-biomarkers in research first and in clinical settings afterwards. **In fact, the current** use of biomarkers in asymptomatic or mildly symptomatic persons

is mainly directed at providing observational evidence that **contributes to establish their validity, and** can be **ultimately** useful to improve diagnosis and/or to monitor progress and treatment of AD in research settings.

In the present paper we focus on the ethical considerations relevant to inform the use of biomarkers in mildly symptomatic individuals who refer to a medical service requesting specialist consultation for cognitive problems. The paper summarizes and reports the discussion of the “Ethical and societal issues” working-group of the Task Force for the Roadmap of Alzheimer’s Biomarkers, which held its first meeting in Geneva on 8-9 December 2014. The working-group was constituted of bioethicists, clinicians, health economists, and representatives from voluntary health associations including the Alzheimer’s Association and Alzheimer Switzerland. **The Task Force for the Roadmap of Alzheimer’s Biomarkers** meeting and the ensuing work had the ultimate aim **of developing a strategic research agenda** to systematize the acquisition of sound empirical evidence to support the **forthcoming** use of biomarkers in the diagnosis of AD in clinical practice taking into consideration **ethical, scientific and** clinical issues (The Lancet Neurology, 2014).

A framework suggested by Pepe and colleagues (Pepe et al., 2001) for the development of biomarkers for cancer **screening (Tab. 1)** constitutes the methodological reference **used** to accomplish this task. **We transposed the framework from cancer to AD being mindful of biological and methodological differences, including the distinction between screening and diagnostic purposes (Frisoni et al., in this issue; Boccardi et al., in this issue).** We maintain that a **constructive and more comprehensive ethical discussion is favored by this approach based on a number of up-to-date reviews on AD biomarkers, and conducted on the basis of such framework.**

At the present state of **development (Cerami et al. in this issue, Chiotis et al. in this issue, Garibotto et al., in this issue, Mattsson et al., in this issue; Sonni et al., in this issue; Ten Kate et al., in this issue),** the use of **AD** biomarkers for diagnostic purposes raises potential ethical **challenges and** concerns **that deserve careful consideration.** Taking in consideration **Pepe and colleagues’ framework and with specific reference to phases 4 and 5 of biomarkers development,** the working-group identified the following key issues that need to be included in the roadmap: **improving access to services through timely diagnosis; the need for a diagnostic**

research protocol before moving to clinical routine; recruitment in diagnostic research protocols in the absence of effective therapy; respect for the autonomy of the individual with MCI in information and consent process and the right not to know biomarkers results; need for counseling programs; disclosure of the diagnosis in a structured environment and the involvement of family members; health policies including the individuals' views and the protection of their interests; and the economic costs for society that may be incurred through an expanding use of testing in mild or very early stages of the disease (Tab 2).

Criticisms to the use of biomarkers for a diagnosis of AD in the pre-dementia stage of the disease, at which cognitive and functional deficits are mild but subjectively and objectively recognizable, include the potential harm of invasive diagnostic investigations (including adverse psychological outcomes) and the risk to distract collective resources that should be used to support those with manifest dementia amongst whom the need of care is greatest (Le Couter et al., 2013). The clinical utility and the potential psychological strain related to a probabilistic diagnosis **remain uncertain**, and whether the use of core biomarkers can improve the positive predictive value of MCI diagnosis in the general population is not known. Nevertheless, should biomarkers contribute substantially to a **timelier** or even an early diagnosis of AD, the implications for therapeutics, caregiving, legal matters and health care aspects would be enormous (Prince et al., World Alzheimer Report 2011).

Topic 1 - Improving access to services through timely diagnosis

The most salient issue **that emerged** during the working-group discussions **revolved around the persistence of dementia under-diagnosis in the general population. This topic** was mainly brought forward by representatives **of** voluntary health organizations as **being among the** major problems facing people with cognitive **and functional** impairments (Connolly et al., 2011; Koch and Iliffe, 2010). A **significant** number of people, both in high income and low middle income countries, never receive a diagnosis of dementia and, when diagnosis does occur, it is frequently late on in the disease process (Prince et al., World Alzheimer Report 2011). This **acts as a potential barrier towards** improving the quality of life of individuals with dementia and their caregivers.

During the discussions, it became apparent that the development and implementation of biomarkers for AD diagnosis is unlikely perceived *prima facie* as a potential driver of over-diagnosis. Rather, biomarkers may improve timely diagnosis, provided that they have been

validated in phase 1-3 to reliably and accurately detect persons in the prodromal, pre-dementia stage of AD. If biomarkers improve timely diagnosis, they hold the potential to enhance access to services for dementia patients who are currently undiagnosed and thus unable to access help. For this to happen, effective approaches must exist to modify the risk of progressing to dementia or otherwise provide effective early assistance to these individuals.

The values at stake in this context are truthfulness and beneficence. If the preliminary evidence currently available and supporting the reliability of biomarkers for AD is confirmed, it would enable individuals to obtain a more truthful picture of their situation. In addition, if effective early interventions exist, it will become possible to help these individuals more effectively.

There was hope that an improved timely diagnosis might shed a different light on AD through a reduction in the stigma attached to it (Johnson et al., 2015) and correct false beliefs that dementia is a normal part of aging and that nothing can be done. Stigma is still one of the major issues that significantly concern people with dementia (Batsch and Mittelman, World Alzheimer Report 2012), and fear, stigma and false beliefs about dementia are amongst the major causes of under-diagnosis (Brooker et al., 2014).

Topic 2 – The need for a diagnostic research protocol before moving to clinical routine

All AD biomarkers have successfully passed Pepe's phase 1 and most have also met the aims of phase 2, showing preliminary but consistent evidence regarding their diagnostic validity, i.e. their ability to detect subjects with memory impairment who have a high likelihood of exhibiting AD pathology and therefore progressing to dementia. Nevertheless, at the present stage of development, research studies that aim to better establish or further improve the validity and accuracy of these biomarkers are needed, and a sound demonstration of their clinical validity is required before their utility can be established. This implies that a clear distinction between clinical and research settings and applications should be preserved to fulfill the scientific-clinical requirements of biomarkers development and to avoid harm to individuals seeking medical advice. In phase 3, biomarkers are examined in people with memory complaints, the results of which are not used to assist in the diagnostic procedure. However, in the subsequent steps of their validation (see phase 4 and phase 5 in table 1), clinical utility is assessed with the use of biomarkers in a representative clinical population. In these cases, biomarkers are used to improve the diagnostic procedure, further undergoing quantitative assessment, but with an

added advantage of evaluating their performance in the real world. A biomarker-based diagnosis may therefore be performed, if any, only within phase 4 and 5 research studies following a structured diagnostic research protocol, i.e. a protocol investigating the effectiveness and efficiency of the new diagnostic procedure. This will ensure that all scientific and ethical requirements of research studies are met during patient enrollment and data gathering. The controlled environment, typical of research studies, will have the potential of not only increasing systematic knowledge on biomarkers, but also maximizing potential benefits for the individuals and minimizing the risks associated with the new diagnostic procedure.

Topic 3 - Recruitment in diagnostic research protocols in the absence of effective therapy

The scenario **presented** was the encompassing ethics justifying **the** implementation of a diagnostic research protocol for a person complaining of cognitive symptoms and referred to a memory clinic for a specialist consultation. **On the one hand** the physician may **recognize** that the use of biomarkers could improve the diagnostic process. **On the other hand the physician may like to propose participation in a research study that aims to better establish the validity and accuracy of these biomarkers. Potential issues include** the experimental nature of the procedure, the pre-disability stage of the disorder **that** implies the predictive nature of the diagnostic communication, the current lack of effective prevention and **disease-modifying treatment** options, the concern about “catastrophic reactions” **following diagnosis disclosure supported by positive biomarkers results**, and the risk of stigmatization and misuse of diagnostic results by third parties (Gauthier et al., 2011; Karlawish, 2011; Prvulovic and Hampel, 2011; **Sperling et al., 2013**). **Nevertheless**, the value of knowing, the benefit for **future financial and care planning**, and **the possibility** to participate in **phase III** clinical trials **in the event of a positive testing outcome** are reasons in favor of a biomarkers-based diagnosis **in selected individuals**.

Of note is that at the present state of knowledge, both the offering and not offering the opportunity to take part in a research protocol **in order to improve clinical diagnosis carries** ethical implications. The main ethical justification for offering participation in a diagnostic research protocol consists **of the basic principle that considers individuals** as autonomous persons entitled to ask, to know, and to make **present and future** decisions about their health and life **outcomes** (Porteri and Frisoni, 2014). **Interestingly**, preliminary study results show how highly motivated persons with memory impairments and their caregivers are in obtaining unambiguous diagnosis, at the point that one of their primary reasons to participate in a hypothetical **drug** clinical trial

would be to have access to pre-trial screening **that would identify** whether the person's memory problems had an underlying AD pathology (Lawrence et al., 2014).

Topic 4 – Respect for the autonomy of the individual with MCI in the information and consent process

4.1 The research character of the examinations

The **individual should be informed, using lay terminology, that** the scientific community is **collectively** working on biomarkers validation **as these** are potentially useful **in attaining** a more accurate and informed etiologic diagnosis in persons with cognitive concerns and objective mild cognitive deficits. **In addition, the individual needs to be explicitly made aware on the fact that these** biomarkers are currently **still** under study **and that they do** not yet meet the strict requirements for use in routine practice. **However,** this implies that the person **concerned** understands what 'validation' means in general and in this **particular** context. **This is important so that the individual mindful** that what the physician is offering is the participation in an experimental protocol **in order** to collect a variable combination of biomarker examinations with the aim of developing a way to formulate a valid, more accurate and reliable diagnosis for individual participants. For instance, what **is required** to be communicated to participants is that the post-test probability of a positive or negative result for a given biomarker is the research question to be answered, and that the tests results **may** or may not be used to inform and improve the diagnostic accuracy at an individual level.

As such, the physician should make **it** clear that, although the diagnosis will be eventually formulated, its uncertainty could be high. Further explanations would also be needed to **clarify** the nature of this uncertainty, **also** due to the probabilistic nature of any dementia diagnosis.

Physicians must go the extra mile to ensure that difficult information is made more comprehensible for lay people who, in general, find medical uncertainty challenging and hard to deal with. Qualitative evidence suggests that the level of uncertainty that remains regarding the likelihood towards AD progression when biomarkers and clinical information are combined is particularly difficult to explain to people with mild memory (or other cognitive) problems as well as to their carers (Lawrence et al., 2014).

The above requires **that** the physician **not only possesses the necessary** expertise in the assessment and diagnosis of AD, but also a **thorough understanding** of the revised diagnostic

guidelines and the role that biomarkers play **in current diagnostic criteria of MCI due to AD that clearly distinguish clinical and research settings. As such,** the study of biomarkers **is best** implemented in qualified clinics able to provide the **individuals** with the best possible information **at all the stages of the investigation process.**

4.2 The added value of biomarkers

A clarification on the added value of the tests should be part of the communication **strategy.** This refers to the potential **incremental** level of accuracy of the diagnosis, and to the consequent possible benefit of receiving the results. **These** benefits may be more relevant in the case of prodromal AD, **where individuals themselves** can personally take relevant decisions and plan for their future before and if cognitive deterioration occurs.

The argument for a **timely** detection of cognitive impairment **that might occur as the result of the insidious underlying AD neuropathology** is supported **by evidence from** population-based studies **that show that it is possible to effectively modify** lifestyles (including physical activity and diet) and **cardiovascular risk** factors (i.e. hypertension, diabetes, smoking, obesity, hyperlipidemia) **exposure in older adults in which a higher dementia risk is present.** The Finnish geriatric intervention study (FINGER) **that looked at the prevention of** cognitive impairment and disability (Ngandu et al., 2015) **was** the first large, long-term RCT showing that a multi-domain intervention can maintain cognitive function and reduce cognitive decline in older at-risk individuals.

Enrollment in clinical trials of cutting edge experimental treatments or other prevention trials currently under way or in preparation (Carrillo et al., 2013) might be offered.

Negative consequences of the biomarker disclosure of information **in terms of** a more accurate diagnosis **for** medical records **purposes** should be discussed (**Arias and Karlawish, 2014**). This is most relevant in countries where health/life insurance contracts could be influenced by biomarker status, or legal and professional decisions *compos mentis* could be challenged. The stigmatization and **potential disease-related** discrimination on work places should also be mentioned, although an individual should be protected by their right to confidentiality and privacy. In most countries, these rights are protected to a large extent, but information will need to take local circumstances into account. Even in countries offering substantial protections, such that nobody can give information on the individual's health to third parties unless authorized by the individual and participation in research study is protected, some risk may nevertheless exist.

Topic 5 - The right not to know biomarkers results

Although information is a pre-condition for the **individuals'** ability to make their own choices and decisions based on their own priorities and views, **individuals'** self-determination **extends to what information to have (Kiltzman et al., 2007), when to know (Scully et al., 2007), and the right not to know.** This **implies** that the physician **must** ensure **that** individual results are available if they are deemed to have clinical relevance, but cannot force subjects to receive them. The decision to undergo examination in a context of research **aiming at increasing knowledge about the validity of biomarkers may not necessarily imply diagnosis disclosure based on tests results.** People may participate in a study in which biomarker data are collected for standardization purposes **only (contributing to analytical validity),** or to refine diagnostic criteria algorithms **(clinical validity),** and individuals **can** opt to receive no or limited feedback on biomarker results.

Furthermore, physicians who conduct research should reassure the individual that the quality of the care they receive is not influenced by their decision to take part into any proposed study. Similarly, the right to withdraw from the study must be guaranteed at all stages, with equal reassurance that this would not influence the quality of care received by the participant (WMA Helsinki Declaration, 2013; CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, 2002) and European regulations (Directive 2001/20/EC; Additional protocol to the convention on human rights and biomedicine, concerning biomedical research, 2005; Regulation (EU) No 536/2014).

Participating in research does not solely depend on the prospect of a personal benefit (Edwards et al., 1998). Altruism is largely present and may predominate (Advisory committee on human radiation experiments, 1996).

Topic 6 - The need for counseling programs

A counseling program, **i.e. interventions of information and support pre and post diagnosis disclosure, should be** an essential requirement for memory clinics implementing biomarkers-based diagnosis of AD. **Without counseling, the complexity of the information to be provided to the individual in a diagnostic research context and the predictive character of the diagnosis will both represent obstacles to the person's understanding and self-determination.** In addition, it seems reasonable, although evidence is lacking, that counseling programs might have greater impact on people and their caregivers at earlier stages of the disease **as a result** of better

cognitive status and greater insight. As **highlighted** by representatives from voluntary health and advocacy organizations, the disclosure of a diagnosis **should be regarded as** the beginning of a journey, and people need support and resources to address the challenges they will face **living** with the disease, as an individual, and as a family.

Although the evidence on the effectiveness of psychosocial interventions for people with dementia and their caregivers is not conclusive (Phung et al., 2013) and somewhat patchy on the benefits of interventions aimed at supporting and/or providing information (Thompson et al., 2007), **some positive experiences already exist (Alzheimer Scotland, 2011). Consequently,** investments in individual and caregiver support programs should not be hindered.

The need for better evidence should be a stimulus for implementing better counseling programs, involving different professional expertise and tailored on the individual's and family needs, in terms of content, frequency and duration, while also evaluating their effectiveness. Relevant endpoints in any such research may encompass validated scales that capture individuals' feeling of improved self-esteem and better ability to manage their daily life and social relations, as well as caregivers' feeling **of being** more confident and competent with their role (Phung et al., 2013) and be less burdened and depressed (Schoenmakers et al., 2010).

Topic 7 - The disclosure of diagnosis in a structured environment

7.1 Reasons for and against disclosure

In the case of **MCI due to AD** diagnosis based on the revised criteria unique challenges in disclosing a diagnosis **exist** (Porteri et al., 2010; **Gauthier et al., 2013**), **but AD disclosure is difficult in any case**. Reasons reported in the literature and experienced in clinical practice for and against the disclosure of an AD diagnosis include, on the one hand, the individual's "right to know the truth" and the need to allow the individual to plan for the future; on the other hand, concerns about harming the individual and the intention to protect the individual from potentially adverse psychological effects, including anxiety, depression and **suicidal thoughts** or attempts. **Both** the principle of respect for autonomy and the principle of non-maleficence/beneficence play a major role in deciding in favor or against full disclosure.

The findings from research studies may add elements to the discussion on when and how to disclose the diagnosis. **For instance, studies show that anxiety does not increase after diagnostic feedback (Carpenter et al., 2008), but feelings of loss are experienced after disclosure (Mitchell**

et al., 2013). However, whether disclosing a diagnosis of AD is harmful to the person at a time when symptoms are mild and the individual is not yet demented is still being debated.

Reaction to information on the risk to develop AD rather than being diagnosed with AD has been studied by the REVEAL study group focusing on the effect of APOE genotyping disclosure in asymptomatic adults with a parent suffering from AD (Green et al., 2009). Results showed no significant difference between the disclosure and the non-disclosure group on measures of anxiety, depression and test-related distress. However, the APOE e4-negative subgroup had a significantly lower level of test-related distress than did the APOE e4-positive subgroup. Moreover, persons with high levels of emotional distress prior to undergoing genetic testing were more likely to have emotional difficulties following disclosure.

In addition, because recent studies show that beta-amyloidosis and neurodegeneration are common in individuals without cognitive impairment (Jack et al., 2014), it is plausible that the earlier the detection of prodromal AD, the lower its prognostic utility with respect to the clinical onset of AD. This uncertainty may *per se* be anxiogenic (Wimo and Winblad, 2015).

Disclosure is, however, an important requirement for self-determination, including for non-medical decisions regarding the person's life choices. Truthfulness and respect for autonomy thus require it.

7.2 The need for guidelines

Guidelines for the disclosure of the diagnosis emphasize that informing individuals on their status in a sensitive way should be the usual practice in order to allow them to preserve their quality of life and ensure that they play an active role in planning their future (Alzheimer Europe, 2009; Alzheimer's Association, 2011). The Alzheimer's Association Early Stage Advisory Group, including individuals living with Alzheimer's disease, developed a tool of Principles for a Dignified Diagnosis (Alzheimer's Association, 2014) that outlines practices that should be employed in this process. Nevertheless, there is wide variability in physicians' attitudes and behaviors regarding the practice of disclosing a diagnosis of AD to the individual (Bamford et al., 2004; Werner et al., 2013). In European countries practices based on local cultural values and traditions often prevail. Concerns to avoid harming individuals should act as a basis for a shared, evidence-based guideline for the disclosure of the diagnosis in a pre-dementia stage of the disease. Structured training for medical doctors on how to communicate the diagnosis to the individual should also be promoted.

Topic 8 - The involvement of the person's family members

Different from those with severe cognitive impairments, people complaining of initial memory problems **may** autonomously decide to attend the memory clinic alone. **This is mostly because their independence is still intact or minimally affected. However,** individuals **are concerned** about sharing medical results, and **the** fear that family members may no longer consider them to be fully competent **following diagnostic disclosure** cannot be excluded. Relevant cultural and **subjective** differences likely exist on how next of kin and family members may react to a clinical diagnosis even in the absence of overt symptoms (Blendon et al., 2012).

Attending the clinic without **the support of family members** represents an additional potential level of complexity for both the physician and the individual. Ideally, in order to improve the accuracy of the diagnostic process, the physician should explore the person's willingness to involve a family member or a close friend whenever possible. In fact, an active involvement of a next of kin or close acquaintance from the beginning of the process can **support both individual's autonomy and beneficence**, providing the person with the necessary support during and after the disclosure of diagnosis, and **allowing** the family to understand the situation and assist the individual in making relevant decision and timely choices. Yet, **the person's choices as regards confidentiality and proxy identification** need to be **respected**.

Topic 9 - Health policies including individuals' views and the protection of their interests

9.1 Individuals' preferences

Individuals should be enabled to collectively play a central role in informing policies on communication and disclosure of diagnosis, which may not always concur with those of clinicians, researchers and other relevant stakeholders (Milne, 2010). Data should be actively and routinely collected on their views and attitudes regarding the implementation of a research diagnostic protocol in the specific case of AD, and on the content and modalities of communication. Experiences of an individual living with AD or related dementia are significantly important in policy related discussions, which already exist across Europe and the United States. This level of engagement appears for instance in the Charter of rights for people with dementia and their carers in Scotland (Cross-party group on Alzheimer's, 2009) and in the Scotland's National Dementia strategy (Scottish Government, 2010), as well as in the National Dementia Strategy for England (Department of Health, 2009), in the French National plan for Alzheimer and related

diseases (Républic Francaise, 2008), and in the Swiss National Dementia Strategy (Office fédéral de la santé publique et Conférence suisse des directrices et directeurs cantonaux de la santé, 2013).

9.2 Criteria for the access to a biomarker based diagnosis

Criteria for **people's** access to the diagnostic protocol during the **present** research phase and then in the clinical **routine** practice also need to be developed to ensure **fairness in access to prospective direct benefits of research and to clinical procedures once they are validated as such**. A clear identification of criteria would also avoid misuse of technologies that are becoming more widely available. As the report on the appropriate use criteria for amyloid PET shows (Johnson et al., 2013a; Johnson et al., 2013b), a careful definition of possible clinical utility of the examinations is needed.

9.3 Adaptation of policies and law

As the diagnosis of prodromal AD will enter clinical practice, professional practices, social policies, and law will need to adapt to the change in the meaning of AD label, which does not necessarily equate to disability (Karlavish, 2011). Health policies should protect the privacy and interests of people who may access biomarker diagnosis against discrimination in health insurance, employment and civil rights in general. At present, regulations, **including** the Genetic information non-discrimination act (GINA) in US (Senate and House of Representatives of the United States of America, 2008) and the Swiss Federal act on human genetic testing (Federal Assembly of the Swiss Confederation, 2004), only apply to genetic information. Moreover, they may, as GINA, cover health but not life, disability or long-term care insurance. This needs to be **clearly explained** to the individual and the carers community as they **need to** fully understand the consequences of biomarkers testing before consenting. More importantly, however, if ways of making predictive/preclinical diagnosis different from those based on genetic information are implemented in the clinic, it is fundamental to **initiate** a public debate for extending people's guarantee of non-discrimination beyond the genetic field.

Topic 10 - Economic cost for society

At present, biomarkers are still under validation. **Distributive justice requires that funds not be divested from proven effective diagnostic and health care interventions towards unproven procedures. As experimental tests, biomarkers costs are therefore currently covered solely by research grants or *ad hoc* funds.**

The ability to make a diagnosis of AD at an early stage is regarded as a fundamental step **in reducing** both the burdens of suffering and costs for families and society, estimated to reach \$1 trillion worldwide by 2018 for AD and related dementias (Prince et al., World Alzheimer report 2015). Economic models suggest that the costs associated with an earlier dementia diagnosis are more than offset by the costs saving from the benefits of anti-dementia drugs and caregiver interventions (Prince et al., World Alzheimer report 2011). **In this context**, early diagnosis is in fact ‘timely diagnosis’, as this corresponds to the “time when the person first meets all the current diagnostic criteria for dementia”. The assumption here is that no additional costs are attached to a more timely diagnosis **as** the procedures and criteria do not vary; they are simply applied earlier in the course of the disease. A diagnosis of prodromal AD may be regarded as an early diagnosis only by extending meaning of disease course. **However, if and when biomarker validation is successfully achieved and the added value of biomarkers to the validity and utility of AD diagnosis is demonstrated in samples drawn from the general population**, considerations regarding the economic benefit of making an early diagnosis are likely to be **also** valid for prodromal AD but would need a further demonstration. **Determining the economic benefit of a biomarker-based diagnosis and whether biomarkers coverage will adhere to fair resource allocation will require econometric analysis (for example in the context of Health Technology Assessment)**, taking into account **all aspects of benefits for patients and their self-determination, as well as** the higher economic direct costs of a diagnosis made using biomarkers and the current lack of **disease modifiers**. Finally, the costs attached to the psychological distress that may unnecessarily be caused to all those who will not eventually develop dementia are **difficult** to predict. However, **if biomarkers are confirmed to be reliable and accurate**, these indirect costs would not differ conceptually from those linked to a number of screening procedures that are in use **today** to favor early diagnosis.

Conclusion

The working-group extensively explored, evaluated and discussed the major potential ethical and societal issues related to the use of biomarkers in the diagnosis of Alzheimer’s disease at the prodromal stage, **which** is before the overt clinical symptoms of the disease begin. Although some considerations would **also** be pertinent in a context of established biomarkers’ validity, the discussion **specifically** related to the current time window where the diagnostic validity of biomarkers **still** needs to be demonstrated. Therefore, this contribution is an integral part of the

wider initiative, technically consisting in drawing the roadmap for an effective and appropriate validation of biomarkers for future **routine** clinical use. Should the new AD criteria that incorporate not yet validated biomarkers become more broadly applicable with additional studies and greater understanding of the disease pathophysiology across the continuum, the risk-benefit ratio of biomarkers-based diagnosis of AD would be different and the diagnostic process would be implemented with higher confidence. A substantially different scenario would take place once a disease modifying drug becomes available, as many hope it will. This situation is likely to bear some similarity to the application of other, as yet, incompletely explored diagnostic interventions.

Note 1: Recently, new ligands enabling to visualize tau accumulation at PET imaging have also been developed. Although their use is still very innovative, they offer a promising tool in identifying the abnormal tau deposits typically associated to AD and, with different topography, to other disorders.

ACKNOWLEDGEMENTS

The *Geneva Task Force for the Roadmap of Alzheimer's Biomarkers* includes the participants to a workshop held in Geneva on December 8-9, 2014. The P.I. of the Geneva Roadmap effort is Giovanni B Frisoni, with Bengt Winblad and Clifford R Jack Jr as co-PIs. The task force includes experts in biomarker development from the oncology community; experts on diagnostic AD biomarkers from Switzerland and Europe; representatives of pertinent scientific societies (Federation of European Societies of Neuropsychology - FENS, European Nuclear Society - ENS, International Foundation of Clinical Chemistry and Laboratory Medicine - IFCCCLM, European Association of Nuclear Medicine - EANM, and Swiss Federation of Clinical Neuro Societies - SFCNS); representatives of patient advocates, bioethicists and regulatory agencies, and early career researchers. The Geneva Task Force has been endorsed by the EADC – European Alzheimer's Disease Consortium.

The workshop was funded thanks to a competitive grant by the Swiss National Science Foundation and unrestricted grants from: Alzheimer Forum Switzerland, Association pour la Recherche sur

Alzheimer, Genève; Piramal, Eli Lilly & Company, General Electric, Guerbet, TEVA Pharma; Academie Suisse de Sciences Médicales, Vifor Pharma Switzerland., Novartis, Siemens, and IXICO. The Alzheimer's Association hosted the first follow-up meeting of the initiative at the 2015 AAIC congress in Washington. We acknowledge the help from Margherita Mauri and Daria Gennaro (IRCCS Fatebenefratelli, Brescia, Italy) and Agnese Picco (Università di Genova, Genova, Italy) who took care of the logistics of the workshop.

The following scientific societies took part to the Geneva Workshop for the Roadmap of Alzheimer's Biomarkers on December 8-9 2014. Flavio Nobili was delegate from the European Association of Nuclear Medicine (EANM) Neuroimaging Committee. Kaj Blennow was delegate and Chair of the International Federation of Clinical Chemistry and Laboratory Medicine Working Group for CSF proteins (IFCC WG-CSF). Frederik Barkhof was delegate from the European Society of Neuroradiology (ESNR). Stefano Cappa was delegate and Chair of the Federation of European Societies of Neuropsychology (FENS). Urs Mosimann was delegate from the Swiss Federation of Clinical Neuro Societies (SFCNS). The content of this paper represents the opinion of the individual authors and is not necessarily endorsed by the scientific societies which took part to the Geneva Workshop for the Roadmap of Alzheimer's Biomarkers

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Phase 1 – Preclinical Exploratory Studies	Primary Aims: To identify leads for potentially useful biomarkers and prioritize identified leads.
Phase 2 – Clinical Assay Development for Clinical Disease	Primary Aim: to estimate the true and false positive rate to distinguish subjects with and without the disease.
Phase 3 – Retrospective Longitudinal Repository Studies	Primary Aims: To evaluate the capacity of the biomarker to detect disease at preclinical/early stage and define criteria for a positive screening test in preparation for phase 4.
Phase 4 – Prospective Screening Studies	Primary Aim: to determine the operating characteristics of the biomarker in a real life setting (detection rate, false referral rate) and explore impact on health outcomes.
Phase 5 – Disease Control Studies	Primary Aim: to estimate the reductions in disease-associated mortality, morbidity, and disability afforded by the screening test.

Tab 1 – Phases of biomarker development for early detection of cancer (Pepe et al., Journal of the National Cancer Institute, 2001)

ETHICAL ISSUE	RECOMMENDATION
1. Improving access to services through timely diagnosis	<p>Biomarkers may improve timely diagnosis. For this to happen, the following condition must be met: i) biomarkers must have been validated in phases 1-3 to reliably and accurately detect persons in the prodromal, pre-dementia stage of AD.</p> <p>If biomarkers improve timely diagnosis, they hold the potential to enhance access to services for dementia patients who are currently undiagnosed and thus unable to access help. For this to happen, the following additional condition must be met: ii) effective approaches must exist to modify the risk of progressing to dementia or otherwise provide effective early assistance to these individuals.</p> <p>The values at stake here are <i>truthfulness</i> and <i>beneficence</i>. If the preliminary evidence currently available and supporting the reliability of biomarkers for AD is confirmed, it would enable individuals to obtain a more truthful picture of their situation. In addition, if effective early interventions exist, it will become possible to help these individuals more effectively.</p>
2. The need for a diagnostic research protocol before moving to clinical routine	<p>At the present stage of development, a sound demonstration of the clinical validity of AD biomarkers is required and a clear distinction between clinical and research settings and applications is needed.</p> <p>A biomarker-based diagnosis may therefore be performed only within phase 4 and 5 research studies, following a structured diagnostic research protocol, i.e. a protocol investigating the effectiveness and efficiency of the new diagnostic procedure.</p> <p>The controlled environment, typical of research studies, will maximize possible benefits for the individuals and minimize the risks associated with the new diagnostic procedure.</p>
3. Recruitment in diagnostic research protocols in the absence of effective therapy	<p>Offering participation in a diagnostic research protocol is ethically justified when the usual ethical requirements for research participants are met.</p> <p>Recruitment into such studies is justified even in the absence of effective therapies, to allow scientific validation of diagnostic tests and because participants are autonomous persons entitled to ask, to know, and to make decisions about their health and life for the present time and the future.</p>
4. Respect for the autonomy of the individual with MCI in the information and consent process	<p>As with any experimental procedure, clear and loyal communication about the research character of the examinations, the changing degree of scientific uncertainty, as well as the degree and nature of added value of the tests, are paramount to respect the person's self-determination.</p> <p>The added value of the tests refers to the potential incremental level of accuracy of the diagnosis and the consequent possible benefit of</p>

	receiving results at a time when the individuals themselves can personally take relevant decisions and plan for their future before and if cognitive deterioration occurs. Enrolment in prevention trials might also be offered.
5. The right not to know the biomarker results	Despite unlikely for person seeking help in memory clinics, the person who does not wish to receive individual diagnostic results should be given the opportunity, and maintain their right, to participate in a study in which biomarker data are collected for standardization purposes only, or to refine diagnostic criteria algorithms, and individuals can opt to receive no or limited feedback on biomarker results.
6. The need for counseling programs	<p>A counseling program is an essential requirement for memory clinics that are implementing the biomarker-based diagnosis of AD.</p> <p>Without counselling, the complexity of the information to be provided to the individual in a diagnostic research context and the predictive character of the diagnosis will both represent obstacles to the person's understanding and self-determination.</p>
7. The disclosure of diagnosis in a structured environment	<p>Although the findings from research studies may add elements to the discussion on when and how to disclose the diagnosis, whether disclosing a diagnosis of AD is harmful to the person at a time when symptoms are mild and the individual is not yet demented is still being debated.</p> <p>Disclosure is, however, an important requirement for self-determination, including for non-medical decisions regarding the person's life choices. <i>Truthfulness</i> and <i>respect for autonomy</i> thus require it.</p> <p>Concerns to <i>avoid harming individuals</i> should act as a basis for a shared, evidence-based guideline on how to disclose such information.</p>
8. The involvement of the person's family members	When biomarkers are positive, the physician should explore the person's willingness to involve a family member or a close friend whenever possible and respect her choices as regards confidentiality and proxy identification. Early active involvement of a next of kin or close acquaintance can support both the individual's autonomy and beneficence. As such, it can be encouraged.
9. Health policies including individuals' views and the protection of their interests	<p>Individuals should be enabled to collectively play a central role in informing policies on communication and disclosure of diagnosis.</p> <p>Criteria for individuals' access to the diagnostic protocol during the research phase and then in the clinical practice need to be developed to ensure fairness in access to prospective direct benefits of research and to clinical procedures once they are validated as such.</p> <p>Health policies should be adapted to protect the privacy and interests of people who may access biomarker diagnosis against discrimination in</p>

	health insurance, employment and civil rights in general.
10. Economic cost for society	<p>Distributive justice requires that funds not be divested from proven effective procedures towards unproven ones. As experimental tests, biomarkers costs are currently covered by research grants or ad hoc funds.</p> <p>If biomarkers are confirmed to be reliable and accurate, determining whether their coverage adheres to fair resource allocation will require econometric analysis (for example in the context of Health Technology Assessment) taking into account all aspects of benefits for patients and their self-determination, as well as the higher economic direct costs of a diagnosis made using biomarkers and the current lack of disease modifiers.</p>

Tab 2. Ethical issues needing to be addressed in phase 4 and phase 5 research studies of biomarkers for the timely diagnosis of Alzheimer’s disease, and recommendations.