Research Article

Blueprint for a Brain Health Clinic to Detect and Manage Early-Stage Cognitive Decline: A Consensus Exercise

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Abstract

Background: It is possible that about 30% of all dementia is preventable by addressing many of the modifiable health and lifestyle risks important for overall physical health. Currently, people in the pre-dementia or very early dementia stage who are referred to Memory Assessment Services (MAS) in the UK receive minimal, if any, support and/or intervention. They are typically referred back to primary care until the full syndrome of dementia emerges. This represents a lost opportunity to modify the trajectory of the condition, intervene with disease modifying therapies (DMTs) when available, and delay the onset of a full dementia syndrome.

Objective: We aimed to develop a blueprint for a pragmatic 'Brain Health Clinic' (BHC) that can be implemented alongside, or in conjunction with, conventional MAS.

Methods: Using modified consensus methods, an interdisciplinary task force of clinicians with experience in the diagnosis and care of people with cognitive impairment and dementia, met on several occasions to review existing evidence, share clinical experience, and propose a model for a pragmatic, 'real life' BHC, as an extension of, or embedded within, a current MAS.

Results: The BHC is a systems-based, integrated care approach that uses existing resources, and can be developed by reconfiguring the way current MAS are provided. It can support people with early-stage cognitive impairment to remain well for longer, potentially changing outcomes. The practical, evidence-based and user-friendly blueprint is available as a free online tool (depicted in figures throughout this article). It sets out a vision for managing early-stage cognitive decline using a 'preempt-prevent' approach that maximizes brain health and quality of life for the person at risk and their families. It sets the stage for implementation of validated, clinically useful biomarker batteries and DMT to be introduced when available, fostering personalized cognitive healthcare.

Conclusion: Adapting existing services to address neurodegenerative cognitive decline in the very earliest stages is a key intervention for secondary prevention of dementia.

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Background

According to population and epidemiologic analyses, the number of people with dementia globally is continuing to grow. There are over 46 million people living with dementia worldwide [1] and one in twenty people are diagnosed with 'young onset' dementia [2]. In the United Kingdom (UK), there are currently over 900,000 people living with dementia at a cost of £26 billion per annum [3]. Treatments are currently confined to therapies that ameliorate symptoms for a short period in a sub-group of people. There is hope that by 2025, disease modifying therapies (DMTs) for Alzheimer's disease (AD), the commonest cause of dementia, will be available.

Theoretically, about 30% of all dementia in the population is preventable by reducing many recognized health risks, including hypertension, type 2 diabetes, obesity, smoking, and sedentarism [4], as well as less commonly known factors such as midlife hearing loss, depression and social isolation [4], alcohol misuse [5], head-injury and delirium [6]. Preventative measures through lifestyle and risk factor modification [4] should be aligned with new pharmacological advances that are leading to DMTs in [7], as well as new biomarker-based diagnostic criteria [8] for, AD. Collectively, this presents a compelling case to review our existing model for dementia diagnostic services and to adopt a fresh approach to the diagnosis and management of AD.

This blueprint for a pragmatic Brain Health Clinic (BHC), developed through a consensus process of clinical stakeholders, takes these drivers into consideration and presents a model for detection, diagnosis and management of cognitive impairment in the pre-dementia or very early stage of dementia, with a focus on secondary prevention and intervention. This blueprint complements and extends existing, and more detailed, guidance on the infrastructure required for administration of DMT, when licensed [7]. The blueprint has been created as a free interactive online tool (https://dementiaacademy.co/2019/11/28/a-practical-model-for-dementia-prevention/) to support clinicians seeking to develop a BHC in their locality.

The Need to Reconfigure Memory Assessment Services (MAS)

Memory Assessment Services (MAS), initially established as university-based medication-management clinics in the UK, were introduced to the National Health Service (NHS) in the 1990's when cognitive enhancing drugs were first licensed for AD. Over 200 MAS now exist in the UK as an integral part of most later life mental health services, although very few focus on the prevention of progression from prodromal dementia to the full clinical syndrome of dementia.

At present, patients assessed in the early stages of cognitive decline (i.e. subjective memory complaints (SMC), mild cognitive impairment (MCI), or pre-clinical and prodromal AD), are generally referred back to primary care without further support or intervention. For some, their condition will stabilize or even improve; however, a significant proportion will progress to a full dementia syndrome. At this point, re-referral to MAS for a diagnosis and management plan is often initiated. Unfortunately, some people might not be referred back to a MAS for intervention even if progression has occurred. Furthermore, the diagnosis of MCI or very early stage dementia in MAS is often inconsistent and may not be based on updated biomarker-based diagnostic criteria [8]. This is despite recent evidence that the use of such testing changes treatment plans for up to 30% of MAS attendees [9].

For individuals at risk of dementia, a biomarker-based diagnosis of underlying disease may make a significant difference to life planning and the desire for follow-up. Vos, et al. [10] have demonstrated that those with both positive amyloid and neuronal injury biomarkers have a 20 times higher risk (60% versus 5%) of progression from prodromal disease to dementia over a three-year period. By intervening with 'brain-healthy lifestyle' practices during this three-year period there is an opportunity to potentially modify this outcome, as well as to support a proactive and timely approach to diagnosis and care at the first moment it may be required.

A recent clinical audit conducted in three UK-based National Health Service (NHS) MAS in Manchester informed part of the development of this blueprint. The audit, a snapshot of 379 newly referred and follow-up patients over a three-month period, revealed significant variability in the assessment, diagnosis and management of the 43 (11%) people presenting with MCI or early-stage dementia, both within and across the three sites [11]. Data were gathered on the diagnosis of MCI and its sub-typing (if done), information needed to track 'at-risk' patients, the nature of any follow-up plans, and whether patients had transitioned to dementia. The findings revealed low adherence to evidence-based diagnostic standards, and inconsistent use of biomarkers (neuroimaging and fluid) and predictive risk models. There was inconsistent subtyping of MCI in 50%, and only 26.7% of cases had documentation of accepted criteria. Furthermore, 32.6% of the follow-up patients had been identified with vascular-related MCI, and there was no evidence that their vascular risk factors had been addressed [12].

Over the past few years in the UK, there has been a push to decrease MAS involvement in the post-diagnostic care of those at risk of, or with dementia, and there has been a corresponding increase in the outsourcing of services to non-medical providers. Since the prevalence of MCI is estimated at one-third of the population aged over 60-years [13], and the rate of conversion to dementia from MCI is estimated at about 6 to 15% per year [14], there is a strong case to consider a new approach for how early-stage cognitive decline should be managed. Recent health economic modelling has suggested that a pre-clinical diagnosis of AD and treatment with DMTs could cost health services several million per year; however, the future health and social care (particularly informal) cost savings due to DMTs could be in the billions [15]. This BHC blueprint, using a pragmatic systems-based approach that stretches across primary and secondary care (tertiary care, if indicated), is proposed as a potential solution by extending or adapting currently operating MAS.

Figure 1: Roles and responsibilities in a Brain Health Clinic multidisciplinary team.
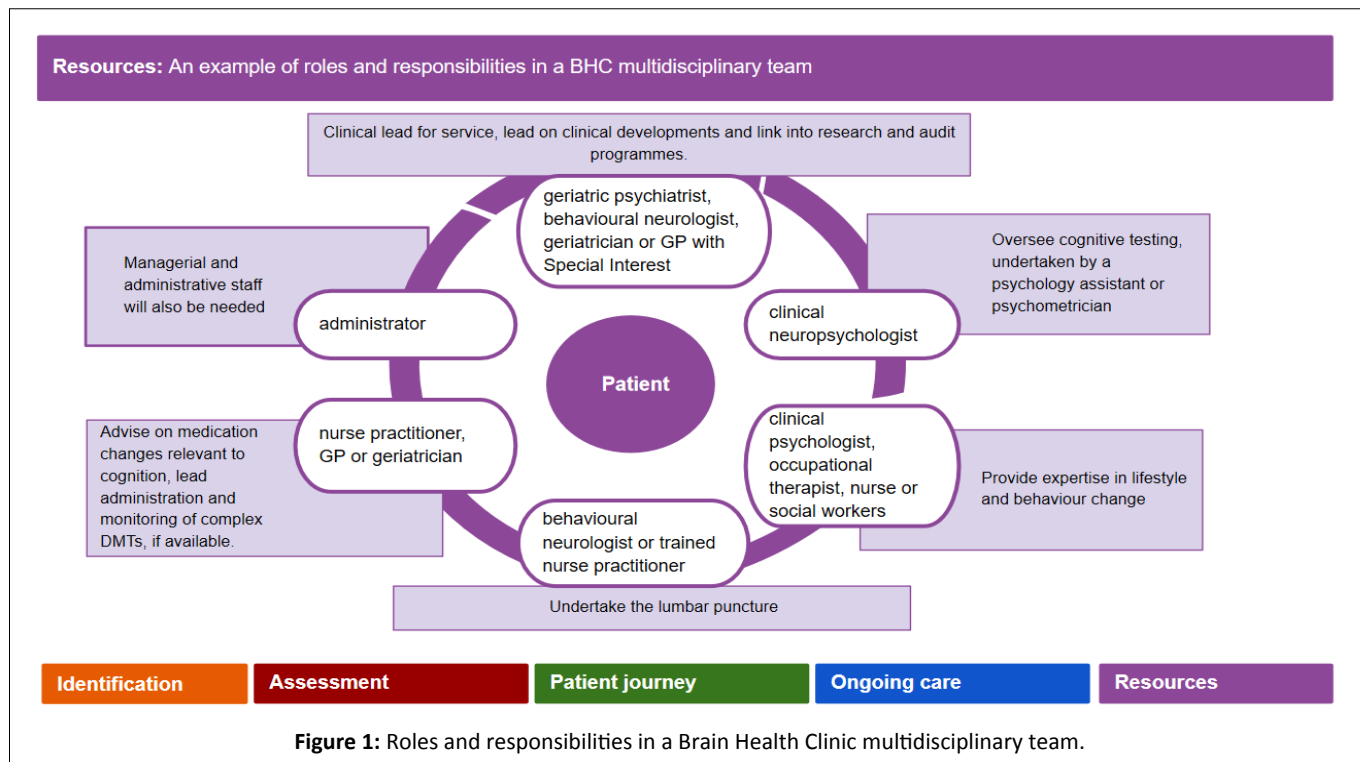
Objectives

The overall aim of a BHC is to lower the prevalence of dementia in the community that it serves. At present, many health services prioritize reactionary approaches and crisis management over preventative support. By risk stratifying all those with early-stage cognitive decline, individualized care is more achievable. This can equip those at low risk with the information and support they need to live ''brain-healthy' lives and can provide those at high risk with early interventions, enabling them to live better for longer (Figure 1).

The specific objective of this blueprint is to outline an approach to early-stage cognitive decline from a secondary prevention perspective, and to maximize brain health and quality of life for those experiencing cognitive decline. The blueprint depicts an integrated service model which is adaptable to local service configuration, utilizes the latest validated assessment methods, and can be emulated nationally in most contexts.

Method

Following the MAS audit [11] to establish a baseline of activity, we used an iterative approach in four stages to develop our blueprint, as outlined in Table 1. We formed a task force involving the expertise of 32 delegates of the 2019 Dementia Masterclass (hosted by Neurology Academy, Sheffield, November 2018) in dialogue-based methods to elicit specialist knowledge and anecdotal clinical experience. From the outset, we established that the BHC blueprint would be based on practical, clinical experience and the emerging evidence base. Health economic aspects were beyond the remit of the project, and wider consultation with patients and care partner stakeholder groups have yet to be conducted during an implementation phase.

Results

The collective input of the taskforce resulted in a blueprint for the BHC, outlined below and depicted in screen shots of the online BHC tool.

Purpose of the Brain Health Clinic (BHC)

- To correctly diagnose patients with early-stage cognitive decline according to updated diagnostic classifications, including the application of biomarker information.

- To identify which patients are at risk of progressing to dementia, compared to those whose condition will remain static or even improve (i.e. risk stratification).

- To prevent and slow the rate of transition from cognitive decline to dementia using varied interventions (i.e. risk modification and disease modification).

- To provide resources to patients and their families about brain health, the risks of dementia and how personal interventions (i.e. lifestyle changes) might alleviate such risks.

Approach to the Brain Health Clinic (BHC) and team

The BHC is designed as a pragmatic, integrated care approach that can be embedded into existing services or work in collaboration or consultation with external services [16]. It can seamlessly incorporate the support and expertise of primary through to tertiary care. The BHC blueprint can be adapted to any one of the three integrated care approaches. Embedded approaches usually involve different members of a team working in the same physical space, where consultative or collaborative approaches may involve pro-

Table 1: Outline of method for developing the blueprint for a Brain Health Clinic.

Project timeline:	• November 2018, project launch and work-groups form • March 2019, first full group videoconference • April - August 2019, follow-up full group videoconference • September - December 2019, iterative development and pilot testing of the tool • February 2020, launch of Brain Health Clinic blueprint on-line tool
Setting and procedures:	• Baseline clinical audit of three representative Memory Assessment Services in Manchester, UK to describe current clinical practice • Initial contact with professional stakeholders via a two-day Dementia Academy clinical masterclass hosted by Neurology Academy (www.neurologyacademy.org), Sheffield, UK (11/2018) to form a project task force • Project orientation session introducing aims, method and timeline • Five delegate workgroups formed; each assigned a sub-section of the tool • Workgroup video-linked meeting every two months to draft the blueprint • Fourth draft presented for consultation to new delegates of Dementia Academy masterclass, Sheffield, UK, June 2019 • Sixth and seventh iterations developed by the workgroup • Final version launched on-line, February 2020
Task force participants	Delegates attending the Dementia Academy masterclass were 32 practicing clinicians with the following backgrounds: • geriatric psychiatry (n = 1) • geriatrics or medicine for the elderly (n = 15) • specialist registrars (senior clinical trainees) in geriatrics, neurology and geriatric psychiatry (n = 5) • orthogeriatrics (n = 1) • mental health nursing (n = 1) • neuroscience nursing (n = 4) • general practice (n = 2) • neuroradiology (n = 1) • clinical research in ageing (n = 1)
Facilitators:	• The project lead and Dementia Academy director (IL) facilitated the group sessions and video-linked meetings • Each workgroup was facilitated by a Dementia Academy faculty member • Each workgroup appointed a designated lead to coordinate work
Data collected to develop the blueprint for the Brain Health Clinic:	• **Stage 1:** Audit of MCI diagnosis and patient journey in NHS UK MAS's (11) • **Stage 2:** Expert consultation, divided into five work workgroups to develop the components of the BHC: • Aim and ethos of the BHC • Characteristics of the typical BHC attendee • Steps in a diagnostic work-up to establish a meaningful diagnosis of prodromal dementia, including the sub-type, and risk stratification • Types of interventions (pharmacological and non-pharmacological) and the infrastructure to support them • Patient journey through and beyond the BHC • **Stage 3:** Consultation with experts of the draft tool • **Stage 4:** On-line launch of the tool, Blueprint for a BHC

fessionals from different services all working together in a systems-based manner towards a common goal, stretching across tiers of the health and social care system. A key focus of the BHC is to support and empower individuals to navigate around existing health and social care systems, enabling them to tailor their healthcare to meet their needs and achieve the outcomes they choose.

Brain Health Clinic (BHC) team

The core BHC team comprises professionals from different disciplines across the primary to tertiary care spectrum, each with different roles and responsibilities (Figure 1). Whilst the specialist assessments and initial interventions will be undertaken by members of the core team, they will link in with a range of services and providers both internal and external to the host organization (usually a local MAS). The

team can meet in person or virtually for multi-disciplinary team meetings (MDTs). Communication among professionals involved and movement of the patient between components can be regulated by a 'brain health guide', MDT coordinator or a non-specialist case manager.

Patient inclusion criteria for the Brain Health Clinic (BHC)

The BHC will accept referrals directly from primary care, secondary acute care (in- or out-patient), as well as conventional MAS.

- Adult age (above 18)[a]

- Self- or informant-reported cognitive complaint

- Subjective or objective cognitive impairment not meeting criteria for a clinical syndrome of dementia (i.e. preserved or relatively preserved independence in functional abilities (defined by 'activities of daily living')[b]

- First-degree relative of people with dementia or diagnosis of a cognitive neurodegenerative disorder

- Episode of delirium within the past six months

[a]It is expected that almost all referrals will be people of the age of 55, but clinicians should be vigilant for young-onset dementia.

[b]It is expected that most referrals will have some degree of subtle functional impairment.

Exclusion Criteria for the Service

- Non-degenerative cognitive impairment due to another identified cause at the point of referral (e.g. depression, alcohol and drug misuse), which requires first line treatment first line; if the cognitive complaint persists after

effective treatment of primary illness, the referral can be considered.

Components of the Brain Health clinic (BHC)

The blueprint illustrates the component parts of the BHC, giving clear recommendations on how to operationalize the service model, including information about existing resources. The BHC has four main components (outlined below), which are identification (Figure 2), assessment (Figure 3), patient journey (in three intervention streams) (Figures 4, Figure 5, Figure 6), and ongoing care (Figure 7).

Identification: *This involves assessing and identifying appropriate referrals, using assessment tools* (Figure 2). At the point of referral, it is expected that a basic medical and cognitive work-up will have been completed to rule out reversible causes for cognitive complaints (e.g. depression and thyroid dysfunction) and to establish that the patient is in the pre-dementia stage. The initial tier of cognitive testing will depend on whether the patient is referred directly from primary care (e.g. screening tools such as the *General Practitioner Assessment of Cognition* (GPCOG; [17]) and *the 6-item Cognitive Impairment Test* (6CIT; [18]) may be useful) or a secondary care MAS (e.g. *Addenbrooke's Cognitive Evaluation-III, ACE-III; [19] or the Montreal Cognitive Assessment*, MoCA; [20]). A staging tool should also be applied to ascertain whether the patient falls into the preclinical or prodromal stage of dementia (i.e. Clinical Dementia Rating Scale (CDR) [21] score of 0 to 0.5).

Assessment: *This involves a detailed assessment including biomarkers and risk detection modelling to ensure sub-typing and prognosis of early stage cognitive decline* (Figure 3). This includes clinical, lifestyle, behavioral, functional and cognitive assessments as well as biomarker detection. The outcome of the assessment will enable patients to be assigned to one of three risk-based 'streams' exemplified in the 'patient journey'
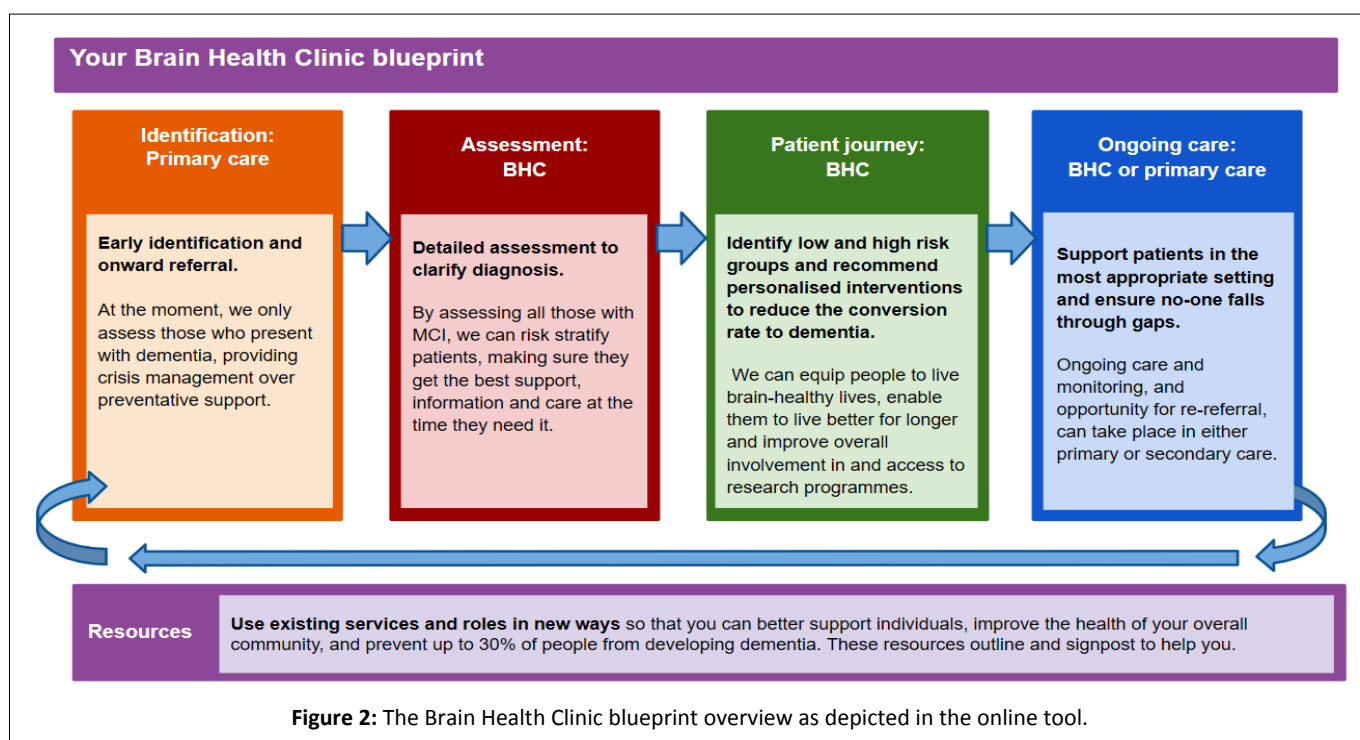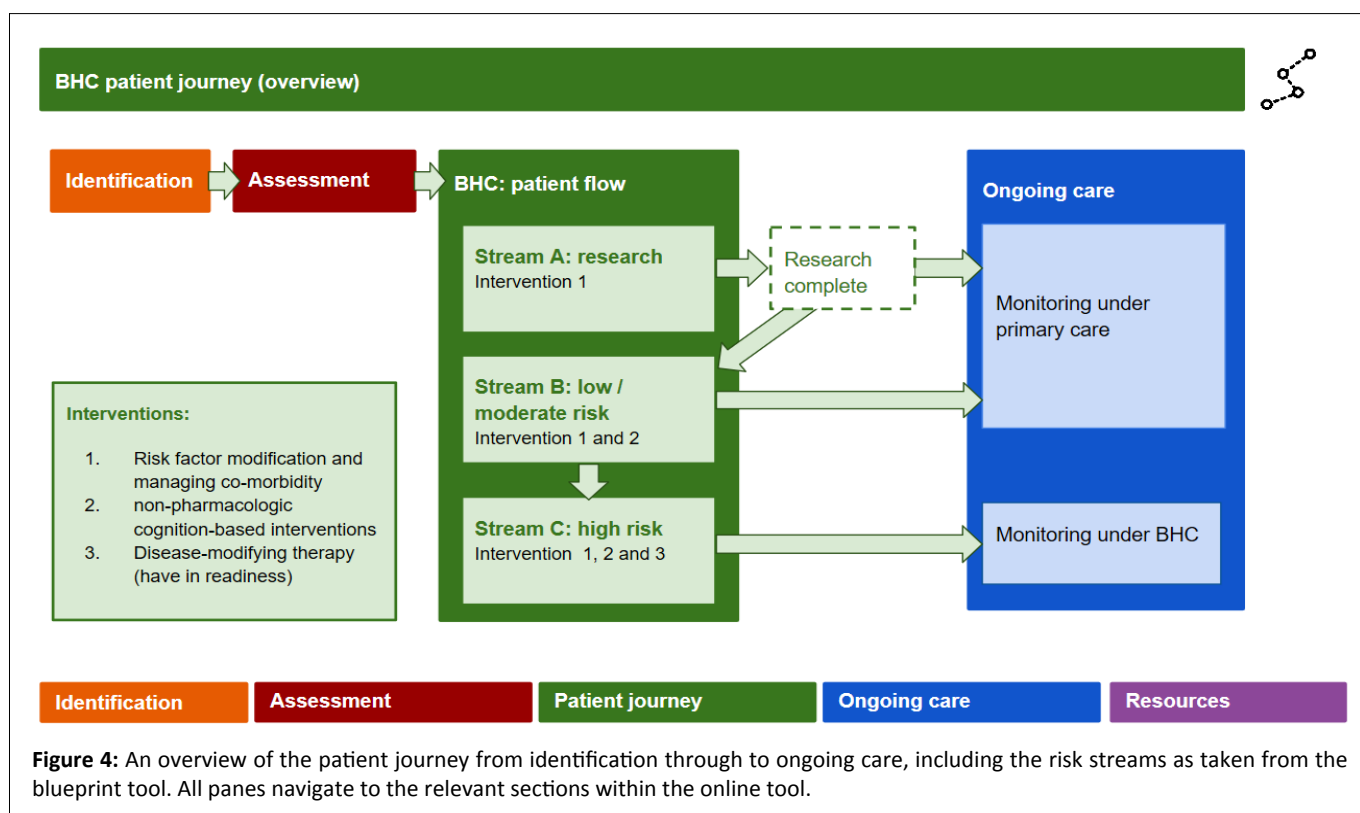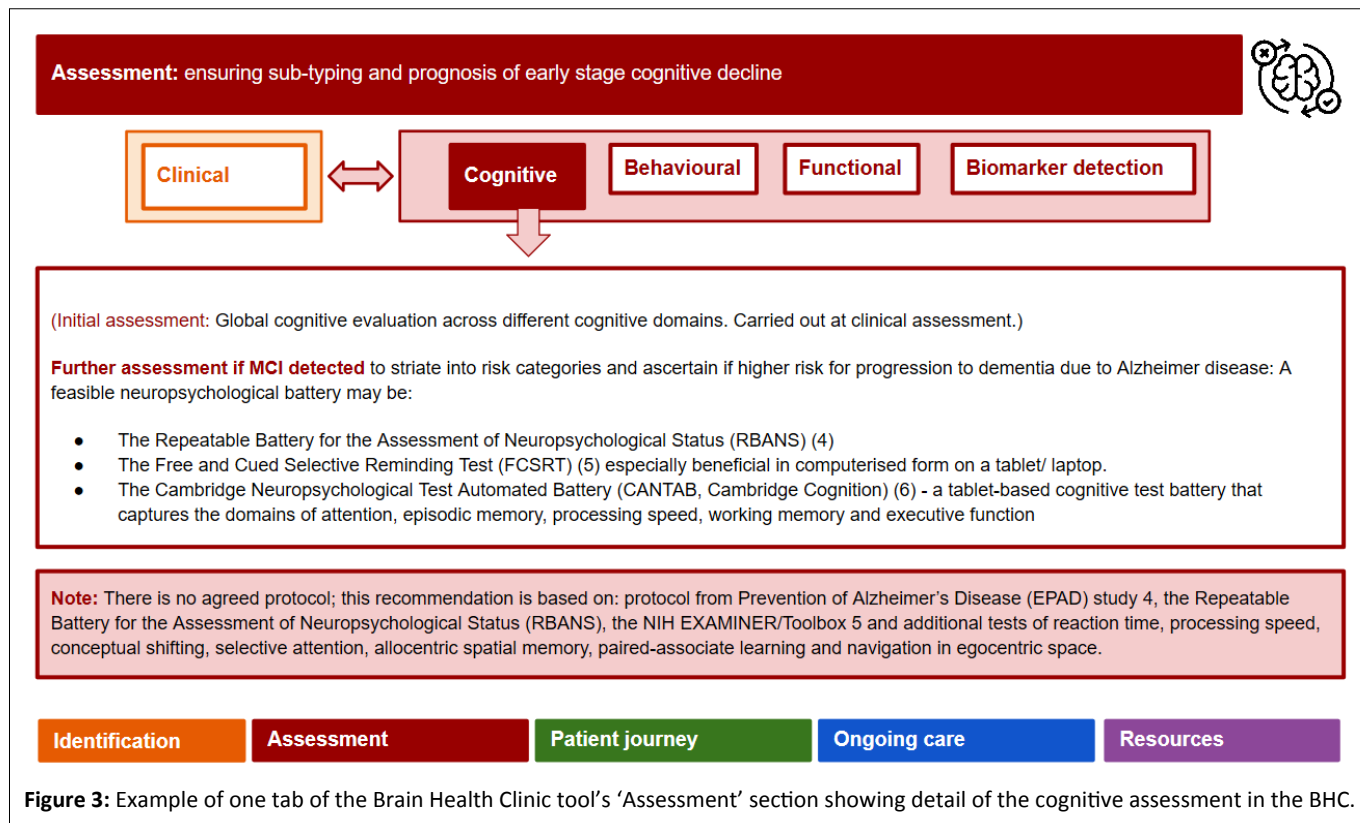

Figure 2: The Brain Health Clinic blueprint overview as depicted in the online tool.

Figure 3: Example of one tab of the Brain Health Clinic tool's 'Assessment' section showing detail of the cognitive assessment in the BHC.

Figure 4: An overview of the patient journey from identification through to ongoing care, including the risk streams as taken from the blueprint tool. All panes navigate to the relevant sections within the online tool.

(Figures 4, Figures 5, Figures 6).

Clinical and lifestyle profile: Here, key potentially reversible risk factors are ascertained to inform risk-based decision making, and can include evaluations of vascular health status (e.g. diabetes, hypertension), sensory function (i.e. hearing and vision [22]), mental health status (e.g. depression), so-cial circumstances (e.g. isolation, loneliness, support network [23]), and lifestyle profile (e.g. activity, diet).

Cognitive profile: More detailed neuropsychological test-ing may include *Repeatable Battery for Neuropsychological Status* (RBANS; [24]), *Free and Cued Selective Recall Test* (FCS-
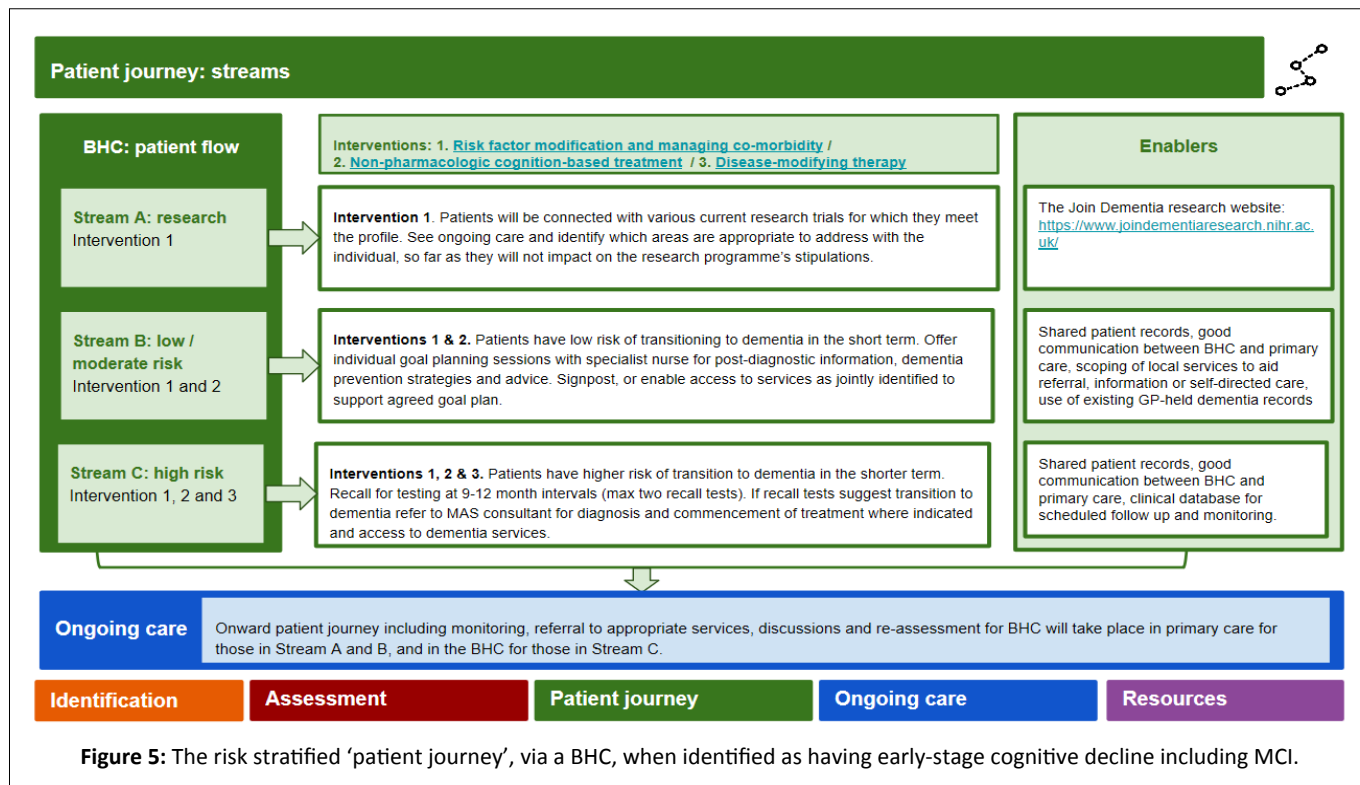
Figure 5: The risk stratified 'patient journey', via a BHC, when identified as having early-stage cognitive decline including MCI.
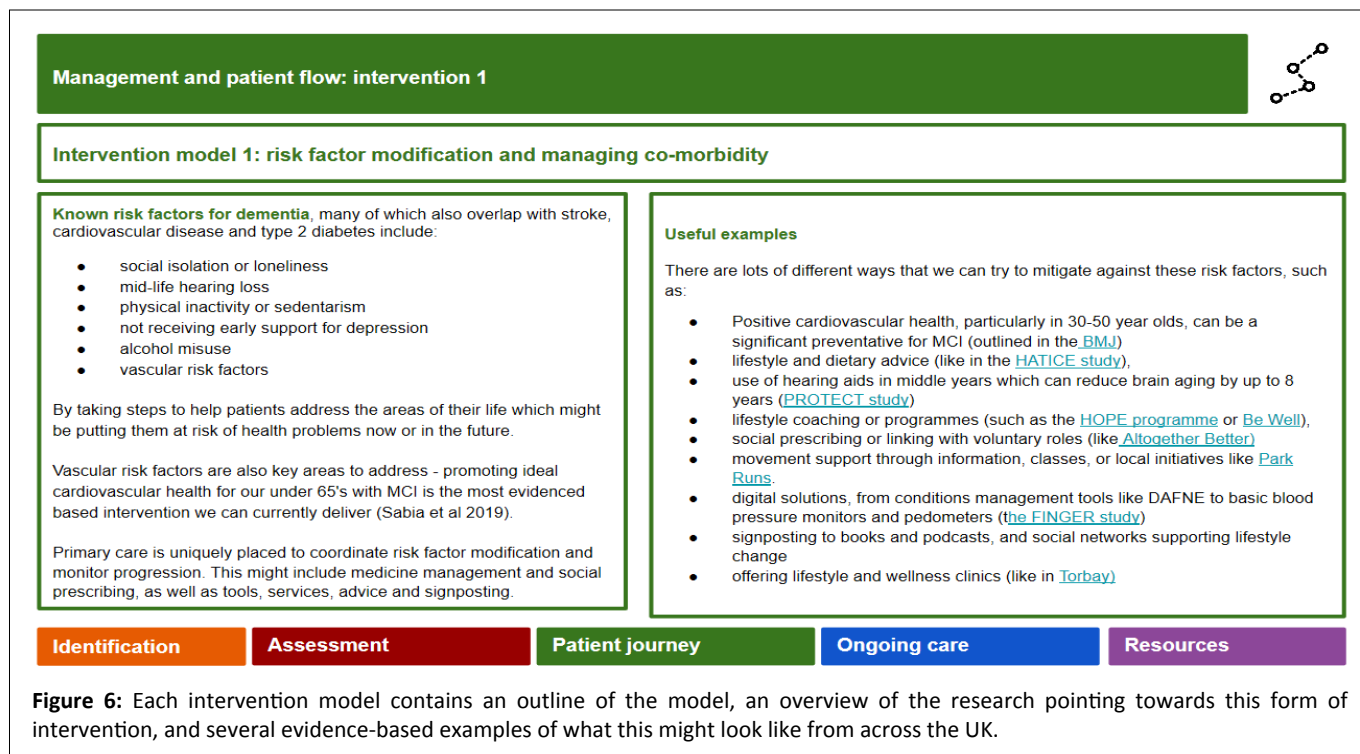

Figure 6: Each intervention model contains an outline of the model, an overview of the research pointing towards this form of intervention, and several evidence-based examples of what this might look like from across the UK.

RT [25]) and the *NIH Examiner* [26]. These will support identification of the 'at risk' cohort (i.e. detecting a 'hippocampal signature' characteristic of amnestic MCI, indicative of possible or probable AD and progression to dementia).

Behavioral and functional profiling: In the pre-dementia stage, subtle behavioral and functional changes may be present and be harbingers of later decline [27]. Thus, assessment tools sensitive enough to detect these changes can be used, including the *Mild Behavioral Impairment Checklist* (MBI-C;

[28]) for neuropsychiatric symptoms, the *Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q;* [29]), and the *Neuropsychiatric Inventory* (NPI; [30-32]). Cut-off scores for the MBI-C have yet to be established and its predictive value regarding progression to dementia is still unclear. However, it can be useful in providing a baseline measure of behavioral symptoms. The Amsterdam IADL scale differs from standard ADL measures by detecting deficits in cognitively complex IADLS (e.g. grocery shopping, managing
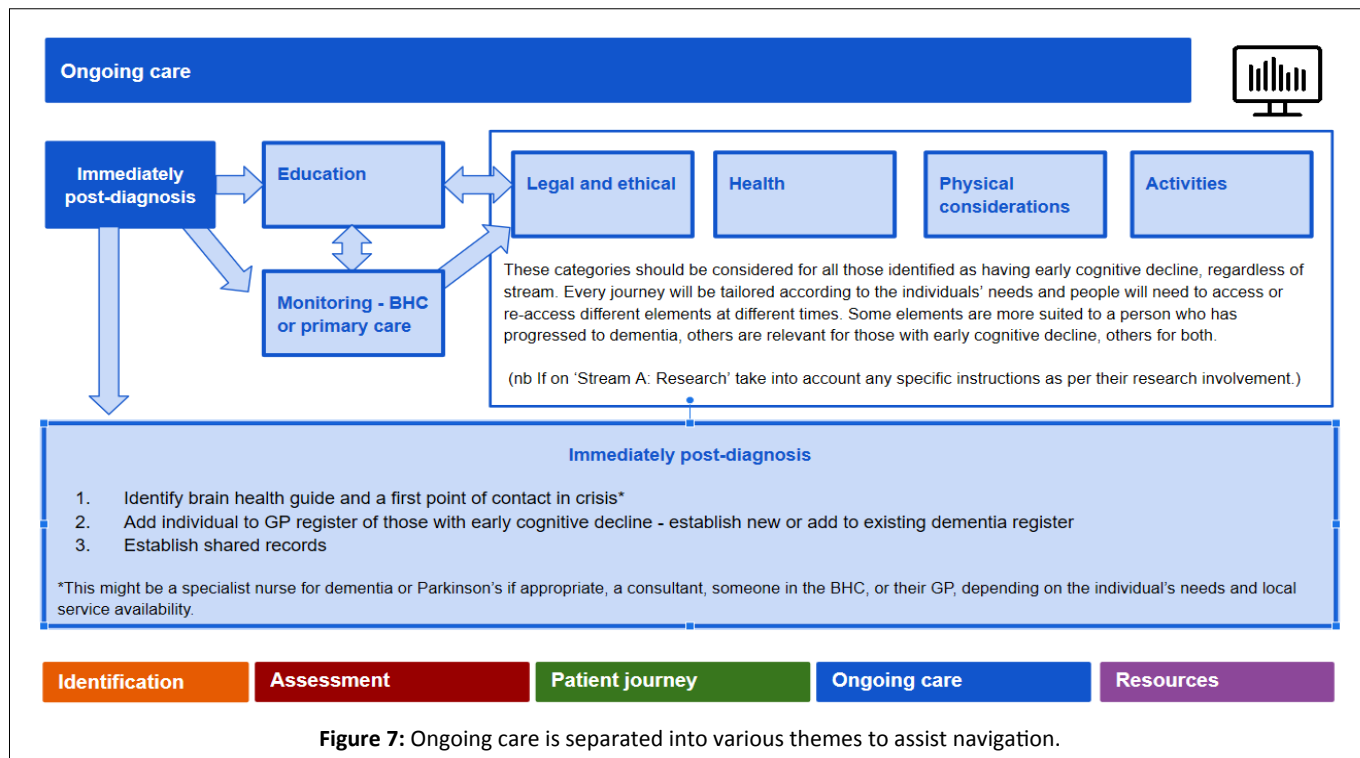
Figure 7: Ongoing care is separated into various themes to assist navigation.

personal finances and using new personal technology) which may be indicators of impending dementia [33]. The Amsterdam IADL scale has undergone international validation studies [34,35].

Biomarker detection: Details of an approach to brain health management in preparation for use of the new DMTs has already been outlined in detail by the Edinburgh Consensus initiative [7] and will thus not be repeated in full here. Instead, key biomarkers, as recommended under the International Working Group (IWG-2) criteria for AD [36] are briefly outlined. The use of biomarkers in the diagnosis of AD in the pre-dementia stage has altered the characterization of AD from being a syndrome-based diagnosis to a biologically based diagnosis.

Biomarkers include those involving β amyloid (A) deposition, pathologic tau (T), and neurodegeneration (N), or the ATN classification, detected by fluid and neuroimaging measures. However, the 'biological' diagnosis of AD is recommended for research settings and is not yet widely used clinically, although the UK's NICE guidance (2018) recommends lumbar puncture for the diagnosis of AD in people with MCI whose diagnosis may be unclear [37]. Finally, genetic testing for AD risk using the apolipoprotein (APOE) genotype is not widely recommended in clinical settings despite being more readily available. Practice guidelines for the use of APOE testing have been published [38].

β amyloid (A) and pathological tau (T) deposition: These can be detected either by CSF lumbar puncture [39] or PET scans with amyloid or tau tracers [40,41]. Additionally, detection in elevated CSF levels of neurofilament light chain (NFL) protein, a marker for neuroaxonal damage due to AD may add to the sensitivity and specificity of the biological diagnosis [42]. Its levels are elevated in the CSF of patients

with AD and other neurological conditions as compared with healthy controls. A recent meta-analysis by Olsson, et al. recommends using CSF Aß42, T-tau, P-tau and NFL levels as a panel of diagnostic biomarkers for AD in both clinical practice and research [42].

Neurodegeneration (N): This can be detected by structural neuroimaging using magnetic resonance imaging (MRI) to detect such changes as medial temporal atrophy, suggestive of AD [43,44] and changes indicative of cerebrovascular disease (quantified using Fazekas scores).

Assigning the patient intervention stream ('patient journey'): (Figures 4, Figures 5 and Figures 6) *This involves stratifying into three 'streams' according to the patient's risk of progressing to dementia (low vs high) and being offered three multimodal intervention approaches designed to slow or even prevent the transition from early stage cognitive decline to dementia.* Patients can move among streams if their risk profile changes due to successful risk modification. Additionally, the interventions are tailored to the individual's requirements and preferences.

The three streams are: A. *Research stream*, for those meeting eligibility criteria for ongoing research studies and who are interested and willing to participate. In the UK, potential participants can sign up to a research register (www.joindementiaresearch.nihr.ac.uk); B. *Low/moderate risk stream* to receive interventions 1 and 2; and C. *High risk stream* to receive interventions 1, 2 and 3. The nature of the interventions is outlined below:

Intervention 1: Lifestyle risk factor modification, medication rationalization, and managing co-morbidity (includes both pharmacologic and non-pharmacologic interventions pertaining to risk factors) will be offered to patients in the high risk and low risk streams.

Lifestyle risk factor modification: Support to make relevant lifestyle changes to foster brain health and modify risk will be offered, with focus on nutrition, alcohol, sleep, smoking and movement. Emerging evidence from international studies such as the FINGER trial [45] suggests that multi-modal interventions simultaneously targeting vascular and other lifestyle changes in older people with higher risk of AD (i.e. APOE4 positive) may have a slower rate of cognitive decline. Ideally, the lifestyle changes should be framed by evidence-based behavioral psychology approaches to ensure uptake and long-term adherence with the changes.

Medication rationalization: A key aspect at this stage will be a thorough review of medications to ensure that they are not the cause of the cognitive impairment, nor are increasing the risk of cognitive decline. Benzodiazepines, opioid analgesics, certain psychotropics, and medications with high anticholinergic loads should be reviewed and rationalized, if possible [46,47].

Managing co-morbidity: Addressing medical comorbidity, particularly vascular risks, sensory functioning (hearing and vision impairment) and other potential physical causes of cognitive decline need to be carefully addressed, establishing a baseline for ongoing monitoring of medical risk factors and potential modification.

Intervention 2: Non-pharmacologic cognition-based interventions, such as brain training and cognitive stimulation, have been evaluated in the context of dementia due to AD and MCI and have demonstrated improvements in memory in healthy older people and people with MCI [48-51]. The theoretical basis for such cognition-based interventions includes the restoration or activation of compensatory brain mechanisms to improve specific cognitive functions or adapting training to accommodate cognitive impairment by using contextualized perspectives [52].

Intervention 3: DMTs, which have yet to be clinically licensed for therapeutic use, will be the final intervention mode for the BHC as they need to be administered in the very earliest phases of the disease before neuronal degeneration is widespread. These therapies will likely involve different mechanisms of actions such as anti-amyloid and anti-tau antibody-based agents, and anti-inflammatory agents inhibiting pathological cascades.

Ongoing care: *Here the blueprint outlines suggested monitoring and follow-on care, either in primary care or under the BHC, depending on the patient's risk of developing dementia* (Figure 7). Those in the low risk stream and who have less chance of conversion to dementia within three to five years may have less frequent follow-up (i.e. every two years). In contrast, those in the higher risk stream will have more frequent follow-up, at least every six months, with the potential for flexibility should progression appear to be faster or slower. Initially this will be clinic-based, but, as remote monitoring of continuous functions with clinical significance emerge (i.e. using passive and semi-passive monitoring systems of daily functions and activities), such monitoring will be home-based or even self-regulated.

Discussion

We have presented a proposal for a pragmatic, integrated care BHC that can be developed as an extension of, or adaptation to MAS, using existing resources and services. This represents a step forward in the clinical approach to dementia which needs to move beyond diagnosing and supporting people with existing dementia. It urgently needs to focus on prevention, delaying the onset of dementia, and very early identification of individuals at risk of progressing from early-stage cognitive decline to dementia. This can best be done in the setting of a BHC using an integrated or multidisciplinary care approach.

A key challenge in developing a BHC is the need to strike a balance between the emerging evidence regarding risk stratification and risk modification, and what is practical, cost-effective and feasible to undertake in standard clinical settings. Currently, no specific risk stratification tool has been approved for clinical use [53], although an increasing number of tools are being published and validated. Most tools include age, education, and measures of cognition and health, but It is increasingly likely that the most useful tools, once fully validated, will involve multivariable risk prediction models based on demographic, genetic, cognitive, health and lifestyle measures. Furthermore, while lifestyle and health status are emerging as powerful risk factors, apart from a few exceptions such as the FINGER trial [54] and ongoing efforts such as the European Prevention of Alzheimer Disease (EPAD) initiative [55], Level I evidence for risk modification is still lacking. Nonetheless, considering the long 'tail' of disease progression in the preclinical stage of AD and other neurodegenerative conditions leading to dementia, it is prudent to adopt a common-sense approach by instituting changes in existing MAS.

As pointed out by the 2017 Lancet Commission [4], 'acting now on dementia prevention, intervention, and care will vastly improve living and dying for individuals with dementia and their families, and in doing so, will transform the future for society'. The next step will be to consult patient and family care stakeholders, and evaluate implementation, including economic modelling. Approaches such as this, which enable tailoring to the needs of the individual, are essential to ensure the best possible care for an aging population with enduring healthcare concerns, and can begin to address the prevalence of dementia in our society.

Acknowledgement

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