Shaping a data-driven era in dementia care pathway through computational neurology approaches

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Abstract

Background: Dementia is caused by a variety of neurodegenerative diseases and is associated with a decline in memory and other cognitive abilities, while inflicting an enormous socioeconomic burden. The complexity of dementia and its associated comorbidities presents immense challenges for dementia research and care, particularly in clinical decision-making.

Main body: Despite the lack of disease-modifying therapies, there is an increasing and urgent need to make timely and accurate clinical decisions in dementia diagnosis and prognosis to allow appropriate care and treatment. However, the dementia care pathway is currently suboptimal. We propose that through computational approaches, understanding of dementia aetiology could be improved, and dementia assessments could be more standardised, objective and efficient. In particular, we suggest that these will involve appropriate data infrastructure, the use of data-driven computational neurology approaches and the development of practical clinical decision support systems. We also discuss the technical, structural, economic, political and policy-making challenges that accompany such implementations.

Conclusion: The data-driven era for dementia research has arrived with the potential to transform the healthcare system, creating a more efficient, transparent and personalised service for dementia.

Keywords: Dementia, Alzheimer’s disease, Dementia care pathway, Data science, Computational neurology, Computational modelling, Computational neuroscience, Healthcare economics, Clinical decision support systems

Background

Dementia refers to a clinical syndrome distinct from physiological ageing, caused by one or more pathological processes and characterised by progressive impairment in cognition and everyday functioning [1]. Alzheimer’s disease (AD), typically characterised by impairment in memory, is the most common subtype of dementia, constituting 60–70% of the cases [1]. AD can be categorised as familial AD (with a family history of the disease and early AD onset) and sporadic AD, with the latter overwhelmingly being the most common type [2]. AD may co-exist with pathological processes characteristic of other common dementia subtypes such as vascular dementia, frontotemporal dementia and Lewy body dementia [1]. Further, there may also be co-morbidities with other illnesses such as epilepsy [3]. To add to the complexity, the prodromal stages, or mild cognitive impairment (MCI), associated with some dementia subtypes, can be loosely defined and heterogeneous, particularly when assessments...
are subject to factors like delirium, psychiatric illness and the effects of medication [1, 4].

Globally, it is estimated that there were 47 million people with dementia in 2015, and with a rapidly growing ageing population, this is expected to reach 75 million by 2030 and 132 million by 2050 [5]. Dementia has a considerable impact on the well-being and functioning of those living with the disease, and also on their families and caregivers. Dementia care can place health and social care services under an operational and financial strain, costing an estimated US$ 818 billion in 2015 and estimated US$2 trillion in 2030 [5]. In the UK, dementia costs £26 billion per year. In 2014, 850,000 people in the UK were estimated to be living with dementia, and this may rise to 1.6 million by 2040 [6]. In neighbouring Ireland, there were about 48,000 people with dementia in 2011, and this is projected to increase to 132,000 by 2041, while costing €1.7 billion annually [7, 8].

Despite the demand for dementia care and treatment, to date, there are no disease-modifying therapies for the most common dementia subtypes. Medications that target particular neurotransmitter systems (e.g. cholinesterase inhibitors) and nutritional supplements have been proposed to slow the early cognitive decline associated with mild to moderate AD and Lewy body dementia [9, 10]. Trials investigating disease-modifying therapies have mostly targeted the formation of beta-amyloid plaques, suggested to be one of the neuropathological hallmarks of AD, but the results have so far been underwhelming [11, 12]. This may be attributed to testing people with dementia too late; by the time that the clinical symptoms have manifested themselves, amyloid may have been accumulating in the brain structures for several years [13, 14]. Therapies targeting hyperphosphorylated tau (twisted fibres of tau proteins), the other main neuropathological substrate of AD, have also failed to demonstrate significant improvements in clinical outcomes [13, 14]. In all likelihood, AD and other dementia subtypes are likely to be the product of interactions between multiple factors, including but not limited to cholinergic neuronal damage, neuroinflammation, oxidative stress, glucose hypometabolism and, more recently, gut microbiome perturbations via the immune system, endocrine system, vagus nerve and bacteria-derived metabolites [14]. It is also possible that some of these hypotheses could be related [15], but further confirmatory work is required.

Regardless of our incomplete understanding of dementia, the rising global population and longer average lifespan [1, 16] make an increasing and urgent case for timely and accurate recognition of dementia and its subtypes, particularly in guiding clinical decision regarding appropriate clinical care. Indeed, it is projected that the direct healthcare costs of early diagnosis may be offset by the cost savings arising from the earlier targeting of patients to the appropriate clinical care pathways [17]. Such savings may be linked to the benefits of earlier delivery of dementia medication and caregiver interventions, and delaying institutionalisation, thereby reducing the overall direct and indirect health and social care cost burden [17]. In addition, early diagnosis and intervention increases the quality of life and care planning for people with dementia and their caregivers, which promote independence [17]. In this context, it is clear that the potential economic and humane benefits of improving the clinical care pathway for dementia are immense. Indeed, as we shall discuss below, the application of data-driven computational approaches can have an immediate impact on improving dementia care pathway.

**Dementia care pathway**

To evaluate the effectiveness of dementia care, we must first assess the current dementia care pathway. As an example, the pre-eminent body in the UK working on clinical guidelines and standardised practices for medical professionals is the National Institute for Health and Care Excellence (NICE), with dementia care guidelines updated in 2018 to reflect the current best practices [18]. The guidelines put forth several strong recommendations for how dementia care should be implemented at the primary care level, at specialist memory assessment services and in the wider community. A schematic of the NICE 2018 recommendations for the dementia care pathway is illustrated in Fig. 1 [19]. Symptoms of dementia are usually first identified by either the individual themselves or a family member of caregiver, before being assessed by general practitioners (GPs). At the primary care level, a major focus is to exclude common and treatable causes of delirium or other disorders. If dementia remains a concern, further investigation and onward referral to secondary care are required, where more detailed assessment by a specialist (e.g. memory clinic) will diagnose dementia, its subtype and initiate treatment [19, 20].

Two major issues that often impede the effectiveness of the dementia care pathway are diagnoses and time delays (Fig. 1, blue and purple text). Regarding the former, the rates of dementia detection (underdiagnosis) can vary considerably [21], and the diagnosis of dementia, and its subtype, can be inaccurate [22, 23]. In one US study, depending on the permissiveness of clinical and neuropathological criteria, AD diagnosis sensitivity (true positive rate) can range between 71 and 97%, while it is between 44 and 71% for specificity (true negative rate) [24]. Suggested reasons for dementia misdiagnosis include physicians/GPs in primary care not being appropriately trained or confident in detecting the disease (within their brief consultation time) and the lack of standardised validated screening protocols and/or routine implementation of screening [22, 25, 26].
There is also a link between early diagnosis and dementia prevalence. It has been estimated that if early identification of risks and diagnosis, leading to proper treatments or interventions, can delay dementia onset by 2 years, the prevalence would reduce by 20%, with a further prevalence reduction of 50% if a delay of 5 years was achieved [27]. Interestingly, to decrease the national dementia underdiagnosis rate, the UK government has introduced the incentivization for GPs dementia diagnosis (paid per case); unintended consequences of the approach include poor patient experience, false-positive diagnosis and negative impacts on waiting lists in memory clinics due to increased numbers of referrals [28–30].

Early and accurate diagnosis, on top of providing timely and appropriate care and treatment and reducing undue psychological stress associated with false-positive diagnosis, also has economic benefits. In particular, past studies have shown that patients with prior AD misdiagnosis (false positive) used substantially more medical services until their (non-comorbidity) vascular dementia diagnosis, leading to increased annual medical costs per patient; following corrected diagnosis, the medical costs converged to patients never diagnosed with AD [31, 32].

Regarding the issue of delays in dementia diagnosis, this can be due to various factors. These include false-negative diagnosis, caregivers’ lack of knowledge or reluctance to seek help, uncertainty from patients and families about when and where to seek help, poor communication and uncertainty from medical doctors [22, 33, 34]. For instance, in one review of services in England, waiting times for assessment can range from 3 to 184 days, while dementia diagnosis from referral could take up to 199 days [34]. Such delays could permit substantial cognitive decline. Further, patients identified with MCI have to wait for a follow-up re-evaluation in either a recommended 6-month time interval or when there is a significant change in status [19].

Assessments in dementia diagnosis
To receive appropriate treatment and support, careful assessment for diagnosing dementia is necessary. Current assessments and their associated ‘markers’ for dementia can comprise several types, from clinical history, biological (e.g. blood- or brain-based) assessment, to neuropsychological and functional assessments (Table 1) [18]. Often, the choice of assessments is based
on factors such as accuracy, sensitivity, specificity, cost-effectiveness, and speed and convenience of use.

Certain assessment types are more costly and less readily available than others. These include cerebrospinal fluid analysis and various neuroimaging modalities in secondary (specialist) care. Moreover, structural neuroimaging is recommended in all cases unless dementia is well advanced and dementia subtype is identified [18]. However, functional neuroimaging is less often conducted to diagnose dementia subtype even though some biomarkers such as beta-amyloid based PET may have the ability to predict the risk of dementia several years prior to the onset of dementia symptoms (albeit with low specificity) [35]. Thus, there is a need to strike a balance among reliable risk prediction, healthcare costs and the inconvenience for the patient. In contrast, blood-based biomarkers have the potential to offer high-throughput data and are easily subjected to repeated measurement even in frail, elderly people. Newer, e.g. neuroinflammatory-based, markers may offer dementia risk prediction at even earlier pre-symptomatic period [14, 36], although the specificity to dementia, and hence practical use, remains unclear.

For cognitive, neuropsychological and functional assessments, some may require the presence of a clinician and nurse, and perhaps caregiver, while others may take a relatively long time to administer; a comprehensive investigation can even go beyond the time frame of a medical appointment [19]. Thus, a balance between convenience and performance of such assessments is required. Interestingly, composite scales, which combine several neurocognitive subscales or with functional activity scales into a single summary score, have recently gathered high interest for preclinical, prodromal and mild AD, especially for early AD therapeutic research [37]. A composite test assesses different domains of cognition and function through the use of discrete subtests and then averages the standard score means from these subsets to yield an overall score [38]. However, it remains unclear whether composites can actually perform better than the current battery of assessments.

In terms of the health economics evidence for these assessments, a number of cost-utility analysis, which report on incremental costs and quality-adjusted life-years (QALYs) analyses, have been conducted [18]. For instance, [39] compared three cognitive and neuropsychological assessments often used by GPs (Mini-Mental State Examination (MMSE), general practitioner assessment of cognition (GPCOG) and 6-item cognitive impairment test (6CIT)) and identified the most cost-effective option (GPCOG), while providing caution regarding the results’ sensitivity to dementia medicines. Similarly, a cost-utility analysis of (beta-amyloid based PET) neuroimaging markers by [40] supported its use in comparison with standard assessment alone or with cerebrospinal fluid (CSF) testing. However, these studies were often limited to a small number of assessments.

Taken together, we have presented several current issues facing dementia assessments and care. In particular, we have emphasised that providing timely and accurate diagnosis is crucial within the dementia care pathway. To improve the effectiveness of dementia diagnosis and care, we shall discuss in the remainder of this review the needs and challenges associated with clinical data transformation and computational approaches in both dementia research and clinical practice. In particular, we shall emphasise the advantages of improving clinical data curation and integration, identifying new dementia markers and assessments through new fundamental sciences and algorithms, and the development of practical decision support systems. These will be discussed along with their challenges.

### Data digitisation, curation and integration

To enable reliable data analyses for evidence-based solutions to improve dementia diagnosis and care, well-curated and “clean” data are necessary. Compliance with some or all of the so-called 5 C’s (clean, consistent, conformed, current and comprehensive) of data quality [41] and appropriate data governance [42] is necessary. Although this is the case in most openly available dementia data acquired within the context of a research study, actual clinical or medical data paints a rather different picture.

A major reason for “dirty” clinical data is due to the lack of standardisation in the dementia care pathway. For instance, in Northern Ireland, although data related

| Primary care diagnosis | Potential diagnostic variables include the following: |
|------------------------|-----------------------------------------------------|
| Diagnostic variables   | • Clinical history                                   |
|                        | • Clinical cognitive assessment                      |
|                        | • Neuropsychological testing                         |
|                        | • Physical examination                               |
|                        | • Medication review                                  |

| Secondary (specialist) care diagnosis | Potential diagnostic variables include the following: |
|--------------------------------------|-----------------------------------------------------|
| Diagnostic variables                 | • Specified diagnostic criteria                      |
|                                     | • Structural imaging (magnetic resonance imaging (MRI) and computed tomography (CT)) |
|                                     | • Single-photon emission computed tomography (SPECT) (e.g. blood flow, dopamine) |
|                                     | • Positron emission tomography (PET) (e.g. fluorodeoxyglucose (FDG), amyloid) |
|                                     | • Cerebrospinal fluid (CSF) examination              |
|                                     | • Electroencephalography (EEG)                       |
|                                     | • Brain biopsy                                       |
|                                     | • Neuropsychological assessment                      |
|                                     | • Functional assessment                              |
|                                     | • Genetic testing                                    |
|                                     | • Neurological examination                           |

Table 1 Summary of the UK’s primary and secondary (specialist) care diagnosis for people aged 40 years old and over with a suspected diagnosis of dementia [18]
to dementia could be formally retrieved and analysed (e.g. through the Health and Social Care Business Services Organisation’s Honest Broker Service), the set of dementia assessments adopted across different practice sites can differ. GPs in England also have similar non-standardisation in dementia assessments [43]. This could be due to the ambiguity within the national (NICE) guidelines, allowing diversity in approaches and locally based “best” practices. When these data are integrated, they can lead to heterogeneity in data variables and systematic missing (“dirty”) data [44–46]. Missing data could also likely arise from other conditions, such as certain individuals being more likely to complete surveys or respond well to questions, individuals late for medical appointments and individuals with severe dementia unable to attend medical appointments altogether. Therefore, practical strategic approaches, e.g. appropriate data cleaning, imputation and harmonisation techniques, are needed before conducting any analysis [47–52]. Indeed, there are some recent and promising large-scale data extraction and integration initiatives such as the UK-CRIS (Clinical Record Interactive Search) system [53] (see below for more examples).

An alternative solution to reduce heterogeneous data is to employ a “small data” approach. As discussed by [54] in this journal’s collection, there are various advantages to this approach, which can uniquely manage complex, dynamic, multi-causal and complex diseases to facilitate individual-level description, prediction and control. Moreover, given the political, institutional and human nature inertia to change, such localisation and decentralisation could actually be a more viable and economical approach, provided the localised data is of sufficient quality. Further, this approach may be suitable to handle known regional variation in the prevalence and detection of dementia associated with the age profile of the population and accessibility to services (see [7, 55] for examples in rural Ireland). Analytical results or models based on such data would also be localised, which may perhaps be more conducive for the practice of personalised or stratified medicine. If data linkages across regional data silos are implemented for analytical models [60, 72, 73].

Increasing use of medical devices such as pervasive (wearable) sensors or detectors that generate continuous data stream and point-of-care technology, real-time signal processing and edge analytics and other big data approaches would be needed [57, 58]. More fundamentally, the way clinical data is captured early on should be changed and formalised to allow better and systematic digitisation of electronic health or medical records. To enable this would require widespread adoption through policy change. Overall, setting a robust and practical data infrastructure is vital for any reliable data analytics or modelling.

Computational neurology, an integrative computational framework

In [59], we introduced the umbrella term computational neurology to embrace not only computational and theoretical neuroscience, which has largely focused on neural mechanistic or probabilistic modelling [60], but also data-driven artificial intelligence (AI) approaches to handle heterogeneous, complex and large data. Computational or theoretical neuroscience usually requires focused and relatively detailed data (e.g. across neighbouring spatial scales) to model, explain and predict specific biophysics of neural tissues, their activities and functions in either healthy or disordered brains, including in AD and dementia (see e.g. [59, 61–68] and references therein). Such causal-based modelling approaches can help to test hypotheses and elucidate the mechanisms of brain disorders and potential therapeutics.

For such approaches, the required detailed (biological) data may not always be readily available. Further, it may take a long time to realistically model or simulate large-scale brain activities for practical clinical purposes, although there are attempts using simpler reduced computational models [69–71]. Moreover, when data is heterogeneous or when biological information is lacking, biologically realistic mechanistic modelling to bridge across scales may not be feasible, and probabilistic or statistical modelling can be applied. Thus, with the unavailability of mechanistic systems models, causality may be inferred, e.g. based on probabilistic models [60, 72, 73].

When the data gets sufficiently large and complex, the applications of data mining, AI or machine learning become essential. This is especially the case for big data generated by new technologies, as discussed previously. Some of the wider perspectives on this topic have already been discussed in this journal’s collection [74, 75]. Notable open big data initiatives include those for fundamental brain sciences such as the Allen Brain Map [76], Collation of Connectivity Data for the Macaque (CoCoMac) database [77] and Human Connectome Project (HCP) [78], and for clinical and translational sciences, including the Cambridge Centre for Ageing Neuroscience (Cam-CAN)
dataset inventory [79], Alzheimer’s Disease Neuroimaging Initiative (ADNI) [80], the National Alzheimer’s Coordinating Center (NACC) [81], UK Biobank [82] and the Dementias Platform UK (DPUK) [83]. Other large-scale projects include those coordinated by the Innovative Medicines Initiative (IMI), e.g. the European Medical Information Framework (EMIF) [84], the European Prevention of Alzheimer’s Dementia Consortium (EPAD) [85], AETIONOMY (Organising mechanistic knowledge about neurodegenerative diseases for the improvement of drug development and therapy) [86] and Neuronet (Efficiently Networking European Neurodegeneration Research) [87].

Importantly, these databases and platforms now enable researchers, particularly those with computational or theoretical inclination, to perform large-scale quantitative analyses to enable wider and more direct research impact (e.g. see [88]). There are also opportunities for researchers to link across mechanistic and data-driven computational approaches (e.g. see [89, 90]). Figure 2 summarises the possible interactions of these various modelling approaches with different data types. Together, these computational approaches can be applied for a deeper understanding of dementia, test potential therapeutics and for detecting and predicting dementia.

**Computationally derived and other novel markers of dementia**

Computational neurology applied to dementia can potentially solve some of the issues facing dementia diagnosis and prognosis. Particularly, data-driven models can provide more objective methods for detection and risk prediction of dementia. For some applications, the detection accuracy can be higher than that of humans. For instance, in the sub-area of computational neuroimaging, advanced techniques such as deep learning have led to very high accuracy for identifying dementia severity, outperforming human experts [91]. Some neuroimaging work, e.g. [92], has also combined multiple neuroimaging modalities to further enhance dementia predictive accuracy. However, to convince relevant stakeholders of their use in clinical practice, cost-utility analysis of these computational approaches and their identified markers may be needed.

As compared to the current battery of dementia assessments, including recently suggested use of composite scales, computational researchers can now use algorithms to perform unbiased and automated selection of the most relevant assessments or variables, and their (optimal) combinations, for predicting dementia severity and risk (e.g. [73, 88]). Such data-driven approaches may reveal markers that can lie beyond human intuition. Moreover, these computationally derived markers often consist of a smaller number of variables than standard assessments, while still able to provide reasonable (or higher) accurate prediction of dementia. Thus, there is potential that their use can lead to more effective dementia diagnosis.

Novel biomarkers using newer technologies, not currently deployed in the dementia care pathway, may also have the potential to transform dementia diagnosis and prognosis. These include readily accessible novel blood-based markers (using high-throughput next-generation DNA sequencing, proteomic and metabolomic technologies) permitting identification of protein concentrations/activity/isoforms and post-translational modifications, metabolic products, such as amino acids, carbohydrates, lipids, organic acids and nucleic acids (single nucleotide polymorphisms (SNPs)) [93]. Similar data analytical, e.g. feature selection and dimensional reduction, methods can be used to home in and identify key markers [94, 95].

Although not currently part of the dementia care pathway, magnetoencephalography (MEG), with its high temporal resolution, can more directly identify novel biomarkers for dementia and its prodromal stage. They can come in the form of abstract machine learning or functional brain
connectivity-based markers [96–99]. Given that electroencephalography (EEG), with poorer spatial localisation than MEG, has already been incorporated in dementia diagnosis (Table 1) [18], it may perhaps be not too inconceivable to also include MEG. Further, MEG, with its ease of use, may be more favourable for frail, elderly or demented participants owing to the avoidance of cumbersome procedures, e.g. preparation of the electrodes and conducting gel as required for EEG. However, the current high costs associated with the acquisition and maintenance of MEG instrumentation impede its widespread use.

Post-clinical validation of computationally derived and other novel markers should be followed by discussion among policymakers, researchers and other stakeholders to allow their assimilation into the current dementia care pathway. For instance, in conjunction with the traditional set of assessments, assessment for novel blood-based markers could be performed using point-of-care technologies within primary care, while MEG assessment conducted at secondary care.

**Practical clinical decision support systems**

As of now, and in the foreseeable future, clinicians make an informed clinical diagnosis after weighing over all available diagnostic evidence. Given the complexity of the data forming such evidence and the decision-making processes required, computerised decision support systems (CDSSs) can act as tools to assist human experts with interpretation, diagnosis and treatment [100]. A CDSS may consist of a highly specialised computational model, e.g. for discriminating specific neuroimaging data [101]. It may also consist of systems-based computational model that embraces a wide variety of data types or markers [88, 102]. Crucially, CDSS can act as a bridge from fundamental, data-driven research towards clinical application (Fig. 2).

CDSSs can be useful to solve the underdiagnosis or misdiagnosis of dementia within primary care settings, thereby reducing the load at the secondary care level. In fact, a criticism of the UK’s National Dementia Strategy has suggested that more diagnosis should take place in primary care [34]. Moreover, CDSSs can also provide more effective (e.g. neuroimaging) assessments within secondary care. Further, adoption of a common CDSS platform may promote more standardisation of dementia assessments. When incorporated into the telemedicine scene, the adoption of CDSS could be accelerated through awareness of its resolving of issues in financial costs, delays and accessibility (e.g. in an infectious disease pandemic) related to dementia diagnosis and care. In fact, with the widespread use of smartphones, some dementia assessments may perhaps be digitised and conducted within the CDSS in mobile devices (e.g. the IMI RADAR-AD (Remote Assessment of Disease and Relapse – Alzheimer’s Disease) project [103] and the EDoN (Early Detection of Neurodegenerative diseases) project [104]), increasing accessibility to assessments and expediting early diagnoses in cognitive decline and dementia and other supporting services [105–109]. However, this may also lead to potential data security and privacy issues [58].

While developing computational models for CDSSs, care has to be taken as the models trained in e.g. open dementia datasets may consist of variables (e.g. specific cognitive assessments) that may not be the same as that in clinical practice. Also, individual cases are often not considered in analysis and model validation (but see, e.g. [88]). In longitudinal studies for risk prediction, models need to take into account appropriate time trajectories [110] and trajectory heterogeneity [111]. Thus, many current models’ decisions may have an inappropriate estimation of their predictive precisions for actual clinical practice. Moreover, in open dementia datasets, the proportion of MCI or dementia individuals may not necessarily reflect the actual proportion in society. Thus, an appropriate adjustment may be necessary before translational deployment. In addition, many computational modelling studies often struggle with obtaining high detection accuracy when dealing with MCI cases, regardless of the intrinsic strength of the models (e.g. [91]). This may be due to the studies failing to differentiate the subtypes of MCIs (e.g. amnestic MCI) or the ill-defined general term of MCI [112]. Fundamentally related to this is that the clinical classification of the disease is often mixed. We suggest that the next stage for dementia classification would arise from data-driven computational modelling rather than the standard labels in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Particularly, computational neurology could follow the path of computational psychiatry for mental health in the identification of disease categorisation and stages, e.g. through data-driven dimensional or network-based approaches [113, 114].

**Conclusion**

Currently, our understanding of dementia is lacking, and the dementia care pathway is suboptimal. We propose that computational neurology approaches can offer specific solutions. With mechanistic biologically based modelling, it can provide insights into the underlying neural mechanisms and assist in dementia therapeutics research. Supported by appropriate data infrastructure, data-driven modelling and CDSS can provide immediate improvements through better dementia diagnosis and prognosis, and improve related care pathways, while potentially reducing delays and health and social care costs. New markers may be elucidated based on algorithms
and new technologies, which may complement the current diagnostic and prognostic processes.

However, such benefits may only be realised if computational models and CDSSs are appropriately evaluated and adopted by users. Obstacles to implementation in clinical practice may be explained by the general lack of engagement from clinicians, physicians and health specialists [115]. Indeed, many computational models of dementia may perhaps be too ‘academic’ and lack translational characteristics. To move the field forward, it is imperative that computational researchers, informaticians, clinicians, patients, health institutions, policymakers and other stakeholders should work synergistically together.

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