



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

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

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22 **Article type:** Reviews  
23  
24  
25

26 **Abstract**

27

28 **Background**

29 Dementia is caused by a variety of neurodegenerative disease(s) and is associated with a  
30 decline in memory and other cognitive abilities, while inflicting enormous socioeconomic  
31 burden. The complexity of dementia and its associated comorbidities, present immense  
32 challenges for dementia research and care, particularly in clinical decision-making.

33 **Main Body**

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

43 **Conclusion**

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

47

48

49 **Keywords:** Dementia, Alzheimer's disease, dementia care pathway, data science,  
50 computational neurology, computational modelling, computational neuroscience, healthcare  
51 economics, clinical decision support systems

52

## 53 **Background**

54

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

67

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

78

79 Despite the demand for dementia care and treatment, to date, there are no disease modifying  
80 therapies for the most common dementia subtypes. Medications that target particular

81 neurotransmitter systems (e.g. cholinesterase inhibitors) and nutritional supplements have  
82 been proposed to slow the early cognitive decline associated with mild to moderate AD and  
83 Lewy body dementia [9, 10]. Trials investigating disease modifying therapies have mostly  
84 targeted the formation of beta-amyloid plaques, suggested to be one of the neuropathological  
85 hallmarks of AD, but the results have so far been underwhelming [11, 12]. This may be  
86 attributed to testing people with dementia too late; by the time that the clinical symptoms have  
87 manifested themselves, amyloid may have been accumulating in brain structures for several  
88 years [13, 14]. Therapies targeting hyperphosphorylated tau (twisted fibres of tau proteins),  
89 the other main neuropathological substrate of AD, have also failed to demonstrate significant  
90 improvements in clinical outcomes [13, 14]. In all likelihood, AD and other dementia subtypes  
91 are likely to be the product of interactions between multiple factors, including, but not limited  
92 to cholinergic neuronal damage, neuroinflammation, oxidative stress, glucose  
93 hypometabolism, and more recently, gut microbiome perturbations via the immune system,  
94 endocrine system, vagus nerve, and bacteria-derived metabolites [14]. It is also possible that  
95 some of these hypotheses could be related [15] but further confirmatory work is required.

96

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

109 data-driven computational approaches can have an immediate impact on improving dementia  
110 care pathway.

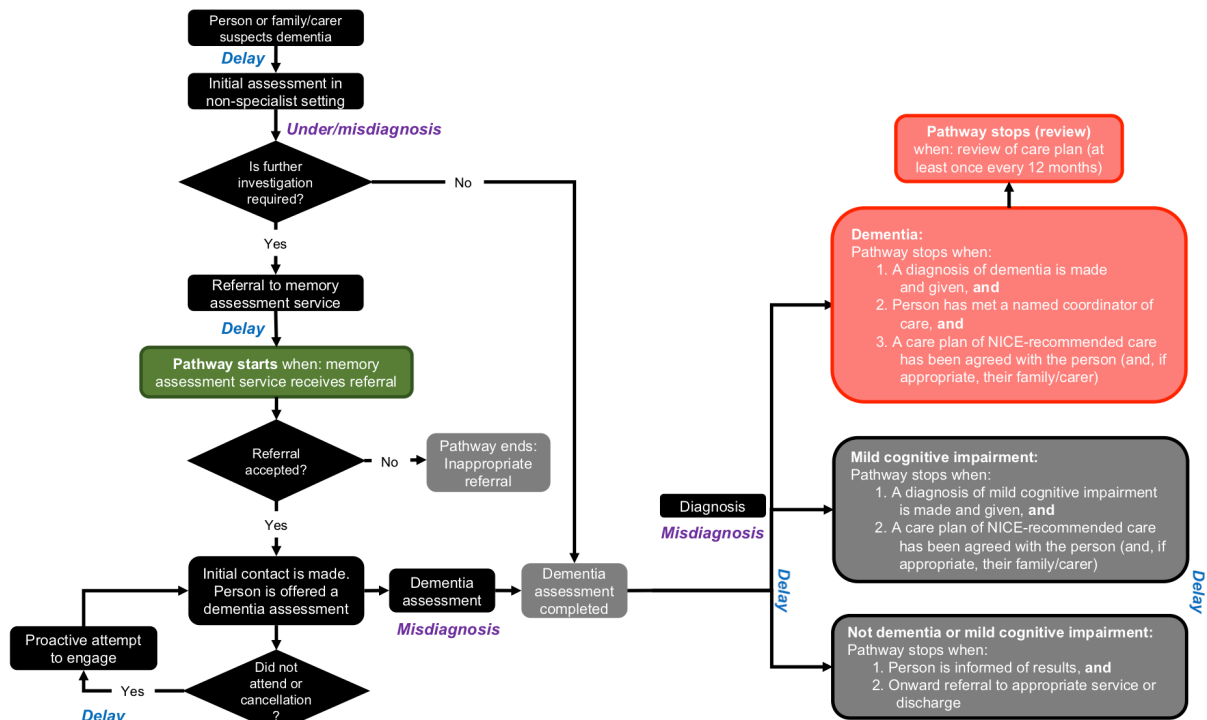
111

## 112 **Dementia care pathway**

113

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

128



129  
 130 **Fig. 1.** Flowchart of the UK dementia care pathway under NICE guidelines, and potential  
 131 disruption. Includes primary and secondary (specialist) care. Blue and purple text: potential  
 132 time delays and under/misdiagnoses; and also opportunities for technologies and novel  
 133 dementia markers. Flowchart based on [19].

134

135 Two major issues that often impede the effectiveness of dementia care pathway are diagnoses  
 136 and time delays (Fig. 1, blue and purple text). Regarding the former, the rates of dementia  
 137 detection (underdiagnosis) can vary considerably [21] and the diagnosis of dementia, and its  
 138 subtype, can be inaccurate [22, 23]. In one US study, depending on the permissiveness of  
 139 clinical and neuropathological criteria, AD diagnosis sensitivity (true positive rate) can range  
 140 between 71% to 97%, while it is between 44% to 71% for specificity (true negative rate) [24].  
 141 Suggested reasons for dementia misdiagnosis include physicians/GPs in primary care not  
 142 being appropriately trained or confident in detecting the disease (within their brief consultation  
 143 time), and lack of standardised validated screening protocols and/or routine implementation  
 144 of screening [25, 22, 26].

146 There is also a link between early diagnosis and dementia prevalence. It has been estimated  
147 that if early identification of risks and diagnosis, leading to proper treatments or interventions,  
148 can delay dementia onset by 2 years, the prevalence would reduce by 20%; with a further  
149 prevalence reduction of 50% if a delay of 5 years was achieved [27]. Interestingly, to decrease  
150 the national dementia underdiagnosis rate, the UK government has introduced the  
151 incentivisation for GPs dementia diagnosis (paid per case); unintended consequences of the  
152 approach include poor patient experience, false-positive diagnosis, and negative impacts on  
153 waiting lists in memory clinics due to increased numbers of referrals [28, 29, 30].

154

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

162

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

172

173 **Assessments in dementia diagnosis**



174

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

181

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

195

196 **Table 1.** Summary of the UK's primary and secondary (specialist) care diagnosis for people  
197 aged 40 years old and over with suspected diagnosis of dementia [18].

**Primary care diagnosis**

<b>Diagnostic variables</b>	Potential diagnostic variables include: <ul style="list-style-type: none"> <li>• Clinical history</li> <li>• Clinical cognitive assessment</li> <li>• Neuropsychological testing</li> <li>• Physical examination</li> <li>• Medication review</li> </ul>
<b>Secondary (specialist) care diagnosis</b>	
<b>Diagnostic variables</b>	Potential diagnostic variables include: <ul style="list-style-type: none"> <li>• Specified diagnostic criteria</li> <li>• Structural imaging (Magnetic Resonance Imaging (MRI) and Computed Tomography (CT))</li> <li>• Single-photon emission computed tomography (SPECT) (e.g. blood flow, dopamine)</li> <li>• Positron emission tomography (PET) (e.g. fluorodeoxyglucose (FDG), amyloid)</li> <li>• Cerebrospinal fluid (CSF) examination</li> <li>• Electroencephalography (EEG)</li> <li>• Brain biopsy</li> <li>• Neuropsychological assessment</li> <li>• Functional assessment</li> <li>• Genetic testing</li> <li>• Neurological examination</li> </ul>

198

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

210

211 In terms of the health economics evidence for these assessments, a number of cost-utility  
212 analysis, which report on incremental costs and quality-adjusted life years (QALYs) analyses  
213 have been conducted [18]. For instance, [39] compared three cognitive and  
214 neuropsychological assessments often used by GPs (Mini-Mental State Examination (MMSE),  
215 general practitioner assessment of cognition (GPCOG), and 6-item cognitive impairment test  
216 (6CIT) and identified the most cost-effective option (GPCOG), while providing caution  
217 regarding the results' sensitivity to dementia medicines. Similarly, a cost-utility analysis of  
218 (beta-amyloid based PET) neuroimaging markers by [40] supported its use in comparison to  
219 standard assessment alone or with cerebrospinal fluid (CSF) testing. However, these studies  
220 were often limited to a small number of assessments.

221

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

231

## 232 **Data digitisation, curation and integration**

233

234 To enable reliable data analyses for evidence-based solutions to improve dementia diagnosis  
235 and care, well curated and “clean” data are necessary. Compliance with some or all of the so-  
236 called 5 C's (clean, consistent, conformed, current, and comprehensive) of data quality [41]  
237 and appropriate data governance [42] is necessary. Although this is the case in most openly

238 available dementia data acquired within the context of a research study, actual clinical or  
239 medical data paints a rather different picture.

240

241 A major reason for “dirty” clinical data is due to the lack of standardisation in the dementia  
242 care pathway. For instance, in Northern Ireland, although data related to dementia could be  
243 formally retrieved and analysed (e.g. through the Health and Social Care Business Services  
244 Organisation’s Honest Broker Service), the set of dementia assessments adopted across  
245 different practice sites can differ. GPs in England also have similar non-standardisation in  
246 dementia assessments [43]. This could be due to the ambiguity within the national (NICE)  
247 guidelines, allowing diversity in approaches and locally based “best” practices. When these  
248 data are integrated, they can lead to heterogeneity in data variables and systematic missing  
249 (“dirty”) data [44, 45, 46]. Missing data could also likely arise from other conditions, such as  
250 certain individuals being more likely to complete surveys or respond well to questions,  
251 individuals late for medical appointments, and individuals with severe dementia unable to  
252 attend medical appointments altogether. Therefore, practical strategic approaches e.g.  
253 appropriate data cleaning, imputation and harmonisation techniques, are needed before  
254 conducting any analysis [47, 48, 49, 50, 51, 52]. Indeed, there are some recent and promising  
255 large-scale data extraction and integration initiatives such as the UK-CRIS (Clinical Record  
256 Interactive Search) system [53] (see below for more examples).

257

258 An alternative solution to reduce heterogeneous data is to employ a “small data” approach.  
259 As discussed by [54] in this journal’s Collection, there are various advantages to this approach,  
260 which can uniquely manage complex, dynamic, multi-causal and complex diseases to facilitate  
261 individual-level description, prediction and control. Moreover, given the political, institutional  
262 and human-nature inertia to change, such localisation and decentralisation could actually be  
263 a more viable and economical approach, provided the localised data is of sufficient quality.  
264 Further, this approach may be suitable to handle known regional variation in the prevalence  
265 and detection of dementia associated with the age profile of the population and accessibility

266 to services (e.g. see [7, 55] for examples in rural Ireland). Analytical results or models based  
267 on such data would also be localised, which may perhaps be more conducive for the practice  
268 of personalised or stratified medicine. If data linkages across regional data silos are  
269 implemented for analytical insights into wider patterns or trends, similar issues on data  
270 integration could arise, as discussed previously.

271

272 Clinical or medical data may include unstructured or semi-structured data. For instance,  
273 transcription from handwritten notes from clinicians and nurses to consistent digital formats is  
274 needed before storing in operational data storage or data mart, and for use in analysis. With  
275 the advent of robust handwriting recognition algorithms, especially deep learning [56], this can  
276 be solved to some extent, but medical (e.g. International Classification of Diseases, ICD)  
277 codes may still need to be further decoded in an efficient way. Also, with increasing use of  
278 medical devices such as pervasive (wearable) sensors or detectors that generate continuous  
279 data stream and point-of-care technology, real-time signal processing and edge analytics, and  
280 other big data approaches would be needed [57, 58]. More fundamentally, the way clinical  
281 data is captured early on should be changed and formalised to allow better and systematic  
282 digitisation of electronic health or medical records. To enable this would require widespread  
283 adoption through policy change. Overall, setting a robust and practical data infrastructure is  
284 vital for any reliable data analytics or modelling.

285

## 286 **Computational Neurology, an integrative computational framework**

287

288 In [59], we introduced the umbrella term Computational Neurology to embrace not only  
289 Computational and Theoretical Neuroscience, which has largely focused on neural  
290 mechanistic or probabilistic modelling [60], but also data-driven artificial intelligence (AI)  
291 approaches to handle heterogeneous, complex and large data. Computational or Theoretical  
292 Neuroscience usually requires focused and relatively detailed data (e.g. across neighbouring  
293 spatial scales) to model, explain and predict specific biophysics of neural tissues, their

294 activities and functions in either healthy or disordered brains, including in AD and dementia  
295 (see e.g. [59, 61-68] and references therein). Such causal based modelling approaches can  
296 help to test hypotheses and elucidate the mechanisms of brain disorders and potential  
297 therapeutics.

298

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

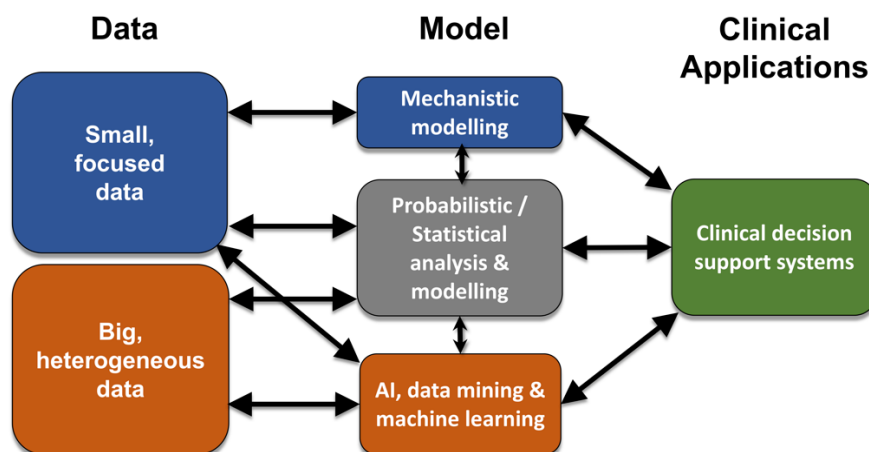
307

308 When the data gets sufficiently large and complex, the applications of data mining, AI or  
309 machine learning become essential. This is especially the case for big data generated by new  
310 technologies, as discussed previously. Some of the wider perspectives on this topic have  
311 already been discussed in this journal's Collection [74, 75]. Notable open big data initiatives  
312 include those for fundamental brain sciences such as the Allen Brain Map [76], Collation of  
313 Connectivity Data for the Macaque (CoCoMac) database [77], Human Connectome Project  
314 (HCP) [78], and for clinical and translational sciences, include the Cambridge Centre for  
315 Ageing Neuroscience (Cam-CAN) dataset inventory [79], Alzheimer's Disease Neuroimaging  
316 Initiative (ADNI) [80], the National Alzheimer's Coordinating Center (NACC) [81], UK Biobank  
317 [82], and the Dementias Platform UK (DPUK) [83]. Other large-scale projects include those  
318 coordinated by Innovative Medicines Initiative (IMI), e.g. the European Medical Information  
319 Framework (EMIF) [84], the European Prevention of Alzheimer's Dementia Consortium  
320 (EPAD) [85], AETIONOMY (Organising mechanistic knowledge about neurodegenerative

321 diseases for the improvement of drug development and therapy) [86], and Neuronet  
322 (Efficiently Networking European Neurodegeneration Research) [87].

323  
324 Importantly, these databases and platforms now enable researchers, particularly those with  
325 computational or theoretical inclination, to perform large-scale quantitative analyses to enable  
326 wider and more direct research impact (e.g. see [88]). There are also opportunities for  
327 researchers to link across mechanistic and data-driven computational approaches (e.g. see  
328 [89, 90]). Fig. 2 summarises the possible interactions of these various modelling approaches  
329 with different data types. Together, these computational approaches can be applied for deeper  
330 understanding of dementia, test potential therapeutics, and for detecting and predicting  
331 dementia.

332



333  
334

335 **Fig. 2.** Schematic of computational and theoretical approaches in Computational Neurology:  
336 from fundamental research towards clinical applications. Blue boxes: Small or focused data;  
337 brown: larger or more heterogeneous data. Arrows: Relationships. Sometimes artificial  
338 intelligence (AI), data mining and machine learning methods are also used in relatively smaller  
339 or less heterogeneous data to guide mechanistic modelling (not shown).

340

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

342

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

353

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

362

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



371

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

382

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

389

### 390 **Practical clinical decision support systems**

391

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

399 Crucially, CDSS can act as a bridge from fundamental, data-driven research towards clinical  
400 application (Fig. 2).

401

402 CDSSs can be useful to solve the underdiagnosis or misdiagnosis of dementia within primary  
403 care settings, thereby reducing the load at secondary care level. In fact, a criticism of the UK's  
404 National Dementia Strategy has suggested that more diagnosis should take place in primary  
405 care [34]. Moreover, CDSSs can also provide more effective (e.g. neuroimaging) assessments  
406 within secondary care. Further, adoption of a common CDSS platform may promote more  
407 standardisation of dementia assessments. When incorporated into the telemedicine scene,  
408 the adoption of CDSS could be accelerated through awareness of its resolving of issues in  
409 financial costs, delays and accessibility (e.g. in an infectious disease pandemic) related to  
410 dementia diagnosis and care. In fact, with widespread use of smart phones, some dementia  
411 assessments may perhaps be digitised and conducted within the CDSS in mobile devices  
412 (e.g. the IMI RADAR-AD (Remote Assessment of Disease and Relapse – Alzheimer's  
413 Disease) project [103], and the EDoN (Early Detection of Neurodegenerative diseases) project  
414 [104]), increasing accessibility to assessments, and expediting early diagnoses in cognitive  
415 decline and dementia and other supporting services [105-109]. However, this may also lead  
416 to potential data security and privacy issues [58].

417

418 While developing computational models for CDSSs, care has to be taken as the models  
419 trained in e.g. open dementia datasets may consist of variables (e.g. specific cognitive  
420 assessments) that may not be the same as that in clinical practice. Also, individual cases are  
421 often not considered in analysis and model validation (but see e.g. [88]). In longitudinal studies  
422 for risk prediction, models need to take into account appropriate time trajectories [110] and  
423 trajectory heterogeneity [111]). Thus, many current models' decisions may have inappropriate  
424 estimation of their predictive precisions for actual clinical practice. Moreover, in open dementia  
425 datasets the proportion of MCI or dementia individuals may not necessarily reflect the actual  
426 proportion in society. Thus, appropriate adjustment may be necessary before translational

427 deployment. In addition, many computational modelling studies often struggle with obtaining  
428 high detection accuracy when dealing with MCI cases, regardless of the intrinsic strength of  
429 the models (e.g. [91]). This may be due to the studies failing to differentiate the subtypes of  
430 MCIs (e.g. amnesic MCI) or the ill-defined general term of MCI [112]. Fundamentally related  
431 to this is that the clinical classification of the disease is often mixed. We suggest that a next  
432 stage for dementia classification would arise from data-driven computational modelling rather  
433 than the standard labels in the Diagnostic and Statistical Manual of Mental Disorders (DSM-  
434 5). Particularly, Computational Neurology could follow the path of Computational Psychiatry  
435 for mental health in the identification of disease categorisation and stages e.g. through data-  
436 driven dimensional or network-based approaches [113, 114].

437

## 438 **Conclusion**

439

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

449

450 However, such benefits may only be realised if computational models and CDSSs are  
451 appropriately evaluated and adopted by users. Obstacles to implementation in clinical practice  
452 may be explained by general lack of engagement from clinicians, physicians and health  
453 specialists [115]. Indeed, many computational models of dementia may perhaps be too  
454 'academic' and lack translational characteristics. To move the field forward, it is imperative

455 that computational researchers, informaticians, clinicians, patients, health institutions, policy  
456 makers, and other stakeholders should work synergistically together.

457

458

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783 The authors declare that they have no competing interests.

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796 KW-L drafted the initial manuscript. PLM, NM, DK, JMS-B, ST, EOS, PG, ST, DPF, AJ, JK,  
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