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PERSPECTIVE

Clinical research in dementia: A perspective on implementing innovation

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Abstract

The increasing global prevalence of dementia demands concrete actions that are aimed strategically at optimizing processes that drive clinical innovation. The first step in this direction requires outlining hurdles in the transition from research to practice. The different parties needed to support translational processes have communication mismatches; methodological gaps hamper evidence-based decision-making; and data are insufficient to provide reliable estimates of long-term health benefits and costs in decisional models. Pilot projects are tackling some of these gaps, but appropriate methods often still need to be devised or adapted to the dementia field. A consistent implementation perspective along the whole translational continuum, explicitly defined and shared among the relevant stakeholders, should overcome the

"research-versus-adoption" dichotomy, and tackle the implementation cliff early on. Concrete next steps may consist of providing tools that support the effective participation of heterogeneous stakeholders and agreeing on a definition of clinical significance that facilitates the selection of proper outcome measures.

KEYWORDS
Alzheimer's disease, clinical innovation, dementia, implementation, methodology, neurocognitive disorders, translational research

1 | BACKGROUND

Medical research aims at providing new diagnostics, treatment, and care by testing new knowledge gained in basic research through clinical studies. However, achieving clinical innovation requires specific efforts that bring this new knowledge into practice, an urgently needed step in the field of dementia due to increased life expectancy and the consequent global increase of its prevalence.[1,2] The discrepancy between scientific knowledge production and its adoption in practice is evident from enduring gaps in diagnosis, treatment, and care. The 2020 Alzheimer Europe report on national responses to dementia shows that in half of the European countries, the actions taken to support dementia health care still cover only 40% to 63% of expressed needs (see Figure 17 in[3]). The dementia detection rate itself is estimated to lag well below 70%, even in high-income countries, with imprecise diagnoses despite the availability of etiological biomarkers.[4] Routine clinical use of such biomarkers would increase early and accurate diagnosis. Implementing non-pharmacological treatment would improve the quality of care and of life of patients and caregivers (Table 1). Such actions would contribute to tackling the global priority of dementia concretely, but their implementation depends on proper completion of relevant intermediate steps.

Slow translation of scientific findings into practice is common in many medical fields. The definition of evidence-based clinical procedures requires strict validation studies, quality assessment of produced evidence, and demonstration of impact on relevant outcomes. On the other hand, translation to practice entails obtaining regulatory approval, access and reimbursement, and adoption by clinicians, steps that are hampered by a variety of hurdles rooted in logistical procedures and cultural traditions.[5] We propose that the "implementation cliff"[6] cannot be overcome as long as these two aspects are not considered as the two faces of a single coin.

The World Health Organization (WHO) global action plan[7] inspires local policies to achieve concrete aims, incorporated in the national dementia strategies developed so far.[8] Formal monitoring based on specific indicators[9] helps to assess whether such aims are achieved. However, hurdles between planned aims and their achievement need to be identified to mitigate them and proceed effectively. In this article, we identify some barriers and how they may be tackled to pull scientific advancements beyond publication in scientific journals and reach patients, carers, institutions, and communities. Identifying and overcoming such gaps is a pivotal step that complements and supports the WHO-inspired national dementia strategies.

2 | CHALLENGES BETWEEN RESEARCH AND ADOPTION

The development (eg, definition of procedures, creation of tools, data collection) required to bring a valid and meaningful diagnostic tool or therapy to practice requires collaboration between professionals and researchers from different fields, as well as different entities, such as scientific societies, regulators, and decisionmakers. Consequently, gaps range from concrete methodological faults in the produced studies to the more elusive, but no less relevant, issue of communication among such parties.

2.1 | Challenge 1: Communication

Given their diverse backgrounds and experience, scientists, clinicians, and related professionals, as well as stakeholders, may approach the same topic using different conceptual representations. Taking for granted that others understand exactly what we mean from our words leads to misunderstanding and ineffective collaboration.[10]

2.2 | Within research

Even among researchers, the concept of translational research itself is heterogeneous, covering different steps and aims along the translational continuum (Figure 1), where a unidirectional flow of information from basic research, to clinical studies, to adoption is usually implied. The heterogeneity of terms and concepts is even wider between the research and implementation fields, still considered as separate.[6] Efforts to attenuate this perspective have been made in different contexts, by the National Institutes of Health's medical scientist training program in United States,[11] the European Society for Translational Medicine in Europe,[12] and different formal methodological approachs.[13,14] These underscore the need of a *bi*directional flux of information at all development steps, requiring researchers to overcome hyper-specialization and interact across adjacent research

RESEARCH IN CONTEXT

1. **Systematic review**: The evidence supporting the content of this paper was retrieved using three main strategies. a) The coauthors, having relatively heterogeneous backgrounds, could provide direct experience and specialized knowledge regarding the raised issues from different points of view. b) We performed focused searches on PubMed and other online sources. c) We selected and examined literature connected with key contributions through both forwardand backward-strategies (e.g., papers referenced in selected contributions, or by browsing documents identified on Scopus for citing target papers).
2. **Interpretation**: We interpret the retrieved evidence as denoting a fragmented procedure that does not allow translational dementia research to coordinate and converge individual efforts within a consistent framework entailing shared priorities and methods. A more consistent strategy may reduce waste and boost the efficiency of our answer to the global priority of dementia.
3. **Future directions**: We propose that different scientific specialties, professionals, and institutional and societal parties should jointly develop a consistent strategy taking into consideration the constraints for implementing new scientific knowledge from early on in the development phases. Specific tasks entail producing communication tools enabling effective cooperation among heterogeneous parties and professionals, promoting the awareness on, and the use of, the methodology required for later implementation, and improving the quality of input data leading to better decisional models. One overarching goal consists of achieving a consensus definition of clinical significance, as the basis to operationalize the assessment of patient-relevant outcomes.

areas; clinicians to feed-back information from bedside to research; and heterogeneous stakeholders (regulators, decisionmakers, health funders, industry, patients and caregivers, non-governmental organizations [NGOs] and charities; Figure 2) to play an active role.[12,13,5] Achieving such communication flow is challenging and still limited in dementia research.

2.3 | Between research and clinics

Although less critical than lack of approval and reimbursement, often available knowledge is not accessible by clinicians because it is not translated into local or non-specialist language. The current investment on open access publications is a massive step forward. However, it does not overcome the need of being fluent in English or familiar with scientific literature. Moreover, open access publishing is vulnerable to predatory journals,[15] imposing to non-expert readers the additional challenge of identifying high-quality publications. Even if not an issue for academic clinicians, non-academic health care providers cannot benefit from best practices. As a practical example, inconsistent approaches are used to treat people with dementia despite demonstrated validity[16–18] and recommendations[18] supporting non-pharmacological treatment (Table 1). Continuing professional development programs can link research and practice, but need to be structured accordingly. Without such access, reciprocal communication between research and clinics is likely to be insufficient to support the implementation of novel clinical findings.

2.4 | Between research, clinics, and community

Implementation requires efficient cooperation with a broad range of stakeholders, including people with dementia and caregivers, regulators, funding bodies, and policymakers. In addition to considering the wider management context, institutions are meant to ultimately represent the interest of the community. Consistently, active efforts are made to involve citizens in research,[19–21] but their level of empowerment in the field of dementia still seems insufficient for active participation. The additional time required to engage, build capacity among both researchers and citizens, and structure cooperation is rarely funded, which affects the quality and efficiency of clinical research. As an example,[22] outcomes of clinical utility of amyloid positron emission tomography are mostly defined in terms of physicians' diagnostic confidence, a relevant but limited scope of the utility that diagnostic biomarkers should demonstrate.[23,24] Aspects like clinical significance, quality of life, or patient-relevant outcomes require such complex collaboration to select, operationalize, and assess meaningful and measurable variables. Consensus and dialogue are necessary to "upgrade" relevant outcomes, that is, outcomes that matter within a patient-centered approach, to the well-acknowledged status of current precision medicine. Collaboration with institutions and research funders should aim at incentivizing the assessment of such outcomes and the collection of the required evidence enabling to reach patients: this may possibly start a virtuous circle of increasing investment for research able to provide greater return to society. Structuring such collaboration is thus necessary for scientific innovations to be developed,[25,26] approved,[27] and refunded.[28]

2.5 | Challenge 2: Methodology

Sound methodology is required to publish in peer-reviewed journals. However, methodology is not sound per se, but rather context-specific: heterogeneous measurement methods may multiply the chance of new discoveries in basic research, but standardized methods are necessary to pool data, compare study results, and validate measurements for their practical use as biomarkers.

TABLE 1 Examples of practical consequences of hurdles hampering the translational continuum

Field	Implementable resource	Aim	Background problem	Practical consequence	Impact	Way forward
Treatment	Non-pharmacological treatment is demonstrated to be more effective than currently available pharmacological treatment, and recommended in combination with drugs, by a Cochrane review.[73] Additional investigation in a second Cochrane review confirmed positive results, although the methodology of original studies should be improved to provide firmer recommendations.[74] A GRADE analysis showed that improvement of many dimensions was supported by studies with up to moderate quality of evidence.[75]	Reduce and prevent excess disability. Potentiate interpersonal and social interactions. Slow down progression. Improve quality of life. Provide patient-centered and possibly tailored treatment. Facilitate and improve the interactions with caregivers.	Cultural bias toward the pharmacological approach.[37] The "effect" of non-pharmacological treatment and rehabilitation is seen as negligible, since they cannot revert to full health, although reverting to full health is not (always) the actual target of drugs or of rehabilitation, in dementia as in other fields. Being performed by personnel, non-pharmacological care is considered "expensive" relative to pharmacological intervention. However, this computation considers only the cost of the treatments themselves, and not the value of their impact. Similar considerations apply for investment in training for informal caregivers.The methodological quality of many many of non-pharmacological intervention studies is considered low. Although often true, this does not differ from other sectors traditionally considered "sound" (see FDG-PET example in this table), and studies provided anyway a good level of evidence overall.[74,75]	Patients cannot benefit from the available non-pharmacological treatment. Substituting non-pharmacological with pharmacological treatment means impoverishing patients' resources for interpersonal interactions. This increases their social isolation, with dubious ethical validity. BPSD increase, with consequent increase of antipsychotic administration (see BPSD in this table for their consequences on health). The above adds to the deleterious effects of the neurodegenerative disease itself, increasing excess disability and distress in a vicious circle. Lack of education and training contributes to both lack of impact and perceived lack of impact of such intervention. Society develops a worse concept of dementia than it may be with a higher level of non-pharmacological care.	Excess disability adds to the direct consequences of dementia, affecting both patients and caregivers.[75] Society develops fear and stigmatization of dementia and related disorders.	Improve modelling of costs and benefits and feed more representative computations of costs. Incorporate ethical considerations by allowing participation at many steps, from research to decision-making.

(Continues)

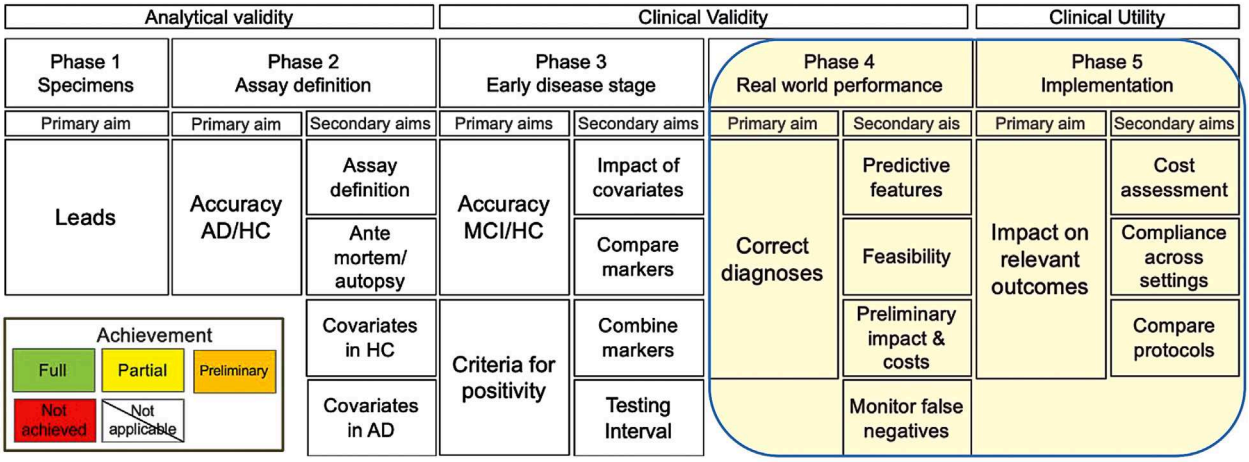
TABLE 1 (Continued)

Field	Implementable resource	Aim	Background problem	Practical consequence	Impact	Way forward
BPSD	Non-pharmacological intervention is recommended as first-line intervention against BPSD.[76]	Reducing BPSD by interacting personally with the patient. This allows identification of the cause of distress, supports the patient in the experience of the effects of neurodegeneration, improves the relationship with the caregiver and restores meaningful relationships and a sense of everyday life.	Non-pharmacological intervention is more complex than administering a drug, and apparently more expensive, as it implies personnel time and an individualized approach.[77]	Antipsychotics cause serious adverse effects including death, and their effect on BPSD is not sufficiently demonstrated.[78] Personal interaction as from column II has greater potential to reduce BPSD[79] and no side effects.	Although apparently sparing time and money, drugs actually amplify the problem by damaging health. Ethical implications. Societal development of fear for these conditions.	The personnel or caregivers already taking care of patients should be properly assisted to understand the nature and how to deal with BPSD based on non-pharmacological strategies. Beyond time and cost of the treatment per se, all the dimensions of the problem should be modeled and operationalized, to improve studies comparing cost-effectiveness.
AD Biomarkers	Use of etiological biomarkers in the diagnostic procedure of neurocognitive disorders	Providing early and accurate diagnosis of neurocognitive disorders	Validation is not yet completed, and regulators and health payers lack complete data for approving, recommending, and reimbursing their clinical use.	Biomarkers in the course of validation are inconsistently incorporated in clinical procedures.[80] Appropriateness of use and of information to consumers is inconsistent across clinical centers.	Costs and ethical consequences: inconsistent procedures make results from different centers not comparable; lack of an optimal diagnostic algorithm may lead to superfluous examinations; patients not fully informed about the experimental value of biomarkers have even more limited understanding of results.[81,82]	A methodological framework was provided to help comply with a methodology leading effectively to approval and refund (Strategic Biomarker Roadmap;[83] Figure 1; Glossary). Keeping this methodology into account in translational studies allows completion of the translational continuum while minimizing gaps and effort. Data so produced are eligible for EtD for clinical, regulatory, and policy decision-making. The methodology itself still needs fine-tuning, especially for later implementation steps, and the definition and assessment of patient-relevant outcomes.[84]

(Continues)

TABLE 1 (Continued)

Field	Implementable resource	Aim	Background problem	Practical consequence	Impact	Way forward
Diagnostic procedure of neurocognitive disorders	^{18F}FDG-PET	Help confirm neurodegeneration and support an etiological diagnostic hypothesis	Systematic procedures to recommend the exam based on evidence found that available data cannot support any recommendation	Validation studies often did not comply with EtD requirements[85] or entailed too large a variability,[86,87] due to faults along the validation steps	^{18F}FDG-PET is used based on a clinician's own advice. The exam is not systematically recommended or reimbursed for diagnosing neurocognitive disorders.	- Make sure that validation studies comply with the methodology required by EtD procedures - Adhere to reporting guidelines - Adapt reporting guidelines to specific fields if necessary or helpful
Possible screening biomarkers	Plasma biomarkers	Support the diagnostic procedure to exclude further unnecessary examination Population screening to assess eligibility for treatment and prevention intervention at the population level	Screening biomarkers need high specificity.[88] If the validation studies contain methodological faults, as in the case of diagnostic biomarkers[83] (AD biomarkers in this table), the screening may lead to ahigh number of false positives.	False positives lead to unnecessary examination. Faulty methodology would unnecessarily amplify this problem.	Unjustified costs, as in the previous case of PSA.[89] Possible ethical issues.	Adapt the Strategic Biomarker Roadmap for the validation of diagnostic biomarkers[69,83] to the screening context of use, to improve validation of screening biomarkers at the best of current possibilities.
Methodology	Defined standard operating procedures for both research (where appropriate) and clinical context.	Make studies comparable; allow pooling of data from different data sets; reduce noise obscuring signal across studies; align clinical procedures with research findings	Different research groups, as well as clinical centers, have logistical reasons to stick with local procedures	Clinical data are not consistent across centers. - Clinical impact: higher costs (patients need to re-run the same analysis to get the baseline in a new center); clinical procedures not aligned with the value demonstrated in research studies. Research: data cannot be pooled; studies cannot be compared; evidence assessment procedures find exceeding variability of findings, obscuring signal and supporting decision-making.	Low reliability and cost-effectiveness of both research and clinical procedures.	Import implementation methods to facilitate bottom-up implementation of standard operating procedures. Identify the stakeholders most interested in cost-effectiveness of clinical and research activities, to contribute with top-down implementation.



Examples of validation steps requiring further structuring

- Phase 4, Primary aim (Ph4, PA, "Correct diagnoses"): Real world patients are not selected as in clinical studies; usage protocol may not be complied with the same accuracy. Is the tested biomarker still valid and reliable despite comorbidity or multiple pharmacological treatment of patient, or constraints in everyday clinical routine?
- Ph4, SA2, "Feasibility": methods from implementation science allow to structure this step systematically, but need being adapted to the specific field of investigation
- Ph4, SA3 and Ph5, SA1 ("Cost assessment"): are patients, caregivers and community values and preferences taken into account in the computation of costs and benefits?
- Ph5, PA ("Impact on relevant outcomes"): how and by whom are "relevant outcomes" defined? Is a system for direct interaction of researchers, patients/caregivers and regulators in place to collaborate on this sort of issues?

So far, only preliminary and inconsistent initiatives have addressed these issues.

FIGURE 1 Strategic Biomarker Roadmap (modified from[32]). Methodological framework for the validation of diagnostic biomarkers for neurocognitive disorders. Validation steps must be achieved in the outlined sequence (left to right) to generate data that is eligible for evidence-to-decision procedures. Proper structuring of the latest development steps, devoted to ascertaining reliability, feasibility, and so on, in the real world, is still required in dementia research. (See also Glossary)

Methodological issues in clinical studies are diverse:[29] disregarding standardized methods prevents reproducibility, comparisons, and meta-analyses, and incorporates unwanted variability; poor study designs fail to test relevant hypotheses. Independent evidence assessments of studies of ^{18F}fluorodeoxyglucose (FDG)–PET in the diagnosis of dementia failed to lead to any clinical recommendation due to exceedingly large variability of results,[30] and to study designs not addressing the target assessment. Indeed, the *incremental* diagnostic value of FDG-PET could not be computed, since the accuracy of clinical diagnosis alone was not assessed.[31] The adoption of proper methodology requires that researchers, research funders, and publishers be aware of the kind of data necessary for decision-making.

To improve the methodology of diagnostic biomarker validation, a European consortium defined a systematic methodology,[23,26,32] known as the "Strategic Biomarker Roadmap" (SBR) (Figure 1; Glossary). The initiative adapted to the dementia field a methodological framework similar to that of drug development, and previously adapted to diagnostic biomarkers in oncology. The SBR details the methodological requirements of each development step along the whole translational continuum, from analytical validity to implementation. The latest steps assess clinical validity and utility by ascertaining whether the knowledge developed in the laboratory and validated in patient cohorts would still be valid and useful in real-world clinical contexts, despite patients having comorbidities, and clinics having constraints in adhering to protocols. This validation method allowed great progress in oncology: new biomarkers, developed more efficiently, benefitted from quick qualification, and boosted the development of treatment in a context of progressing precision medicine.[33] Its use in dementia research may achieve similar results, but getting there requires adopting such methodology with a resolute implementation-oriented attitude. Indeed, the SBR steps related to later implementation, like the assessment of feasibility or computation of costs (Figure 1), are still limitedly structured, and concrete studies are still weak in our field.

2.6 | Challenge 3: Models for decision-making

Evidence is important to support regulatory or clinical decisions on new treatments or diagnostics (Figure 1), or on whether to use scarce health care resources for reimbursing them. Such evidence should reflect the impact on patient-relevant outcomes, like disease symptoms, quality of life, functional autonomy, social engagement,[34] and the use of services in the long term. Decision-analytic models (Glossary) generate such evidence by extrapolating trial outcomes and synthesizing them with current models of natural progression, health impact, service use, and mortality. The transparency and credibility of these

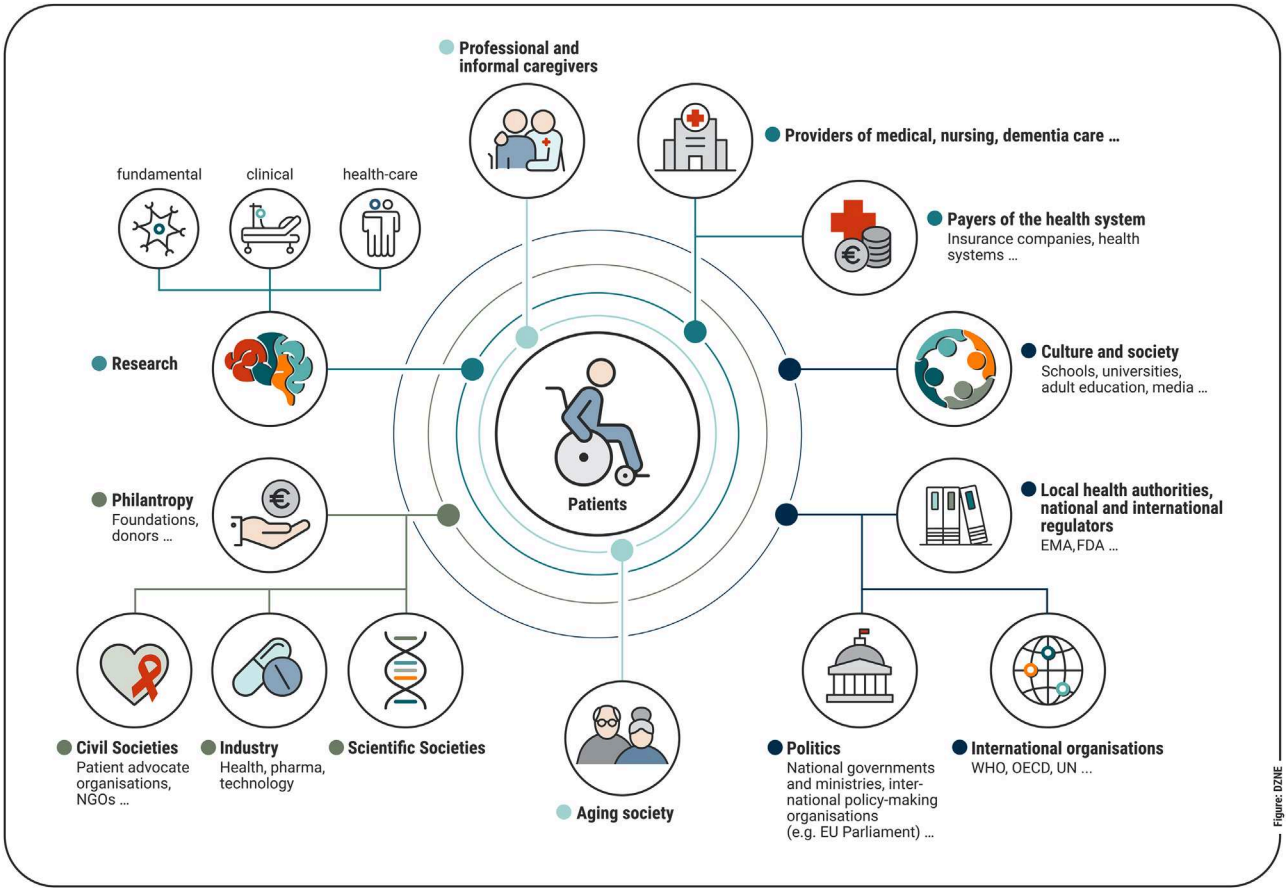


FIGURE 2 **Stakeholders of research on neurocognitive disorders**. Mapping interests and structuring stakeholder participation is required for an effective translational and implementation strategy

models is crucial for decision-makers.[35] A variety of challenges relate to decision-analytic modeling. Herein, we consider the issue from the perspective of cost-effectiveness assessment.

2.7 | Methodology and validity

Recent systematic reviews on the methodology of decision-analytic models in general[36] and for non-pharmacological interventions[37] highlighted an over-simplified model structure of natural disease progression. Often, progression is classified into three states of mild, moderate, and severe cognitive impairment and does not include the impactful domains of function and behavior, or the underlying biological disease process.[38,39] Models are often re-used or adapted. Those focusing on pharmacological interventions may not be appropriate for non-pharmacological intervention[37] or anyway convey a partial perspective.[37,39] Even benefitting from disease modifiers, not all patients may be eligible for treatment and some may still progress to more severe cognitive, functional, and behavioral symptoms that need being managed to maintain a decent quality of life. Thus, evaluating modifiable factors affecting dimensions like pain, boredom, or social isolation is necessary, but the typical models fail to account for them. These models do not reflect more comprehensive sets of strategies, like combined pharmacological and non-pharmacological intervention or their multi-dimensional effects and costs. Indeed, more time needed by professionals to de-escalate behavioral disturbances may be compensated by lower side-effects or personnel sick leave. Similarly, few models are available for evaluating the cost-effectiveness of primary prevention programs based on intervention on lifestyle or risk factors.[40] In general, limited evidence has been reported on the external validation of decision models.

2.8 | Assumptions and input data

Decision-model predictions are based on extrapolating short-term trial outcomes to a lifetime horizon. Indeed, the largest health benefit and care savings are obtained by postponing moderate-to-severe dementia stages, which have the highest impact on health and care use, and mortality.[41] Estimating the impact of early diagnosis or preclinical interventions requires additional assumptions on translating surrogate outcomes, like physicians' diagnostic confidence, amyloid load, or cognitive scores into patient- or caregiver-relevant outcomes. Finally, models are also affected by the limitations of input data, deriving from the mentioned low-dementia detection,[1,4] the unbalanced representation of ethnicity or socioeconomic status of study participants, the

TABLE 2 Defining a common language for inter-stakeholder participation. AD, Alzheimer's disease; BPSD, behavioral and psychological symptoms in dementia; EtD, evidence to decision procedures; ^{18F}FDG-PET, 18F-fluorodeoxyglucose positron-emission tomography; PSA, prostate specific antigen

Domain	Guiding principle	Examples of recommendations	Gaps
Talking about dementia	Avoid pessimistic or disempowering terms	"A form of dementia" rather than "dementing illness"	"Dementia" does not include conditions like mild cognitive impairment (MCI) or subjective cognitive decline (SCD), affecting the community and object of medical treatment and research
Talking about people with dementia	Avoid defining persons or life based on the condition	"A person with dementia" rather than "dements," "sufferers," etc.	Need to define people attending memory clinics without a diagnosis of dementia. "Patients," "consumers," "end-users" are all not considered suitable by either the community or physicians/researchers
Talking about carers	Avoid assumptions: carers have different experiences	"A person living alongside someone who has dementia" rather than "someone carrying the burden of caring"	Research may need very short and direct terms. This needs to be respectful, but directedness may not be considered as assuming or judgmental in specific contexts
Talking about symptoms and behavioral disturbances	Try to describe it objectively and avoid negatively connoted terms	"Behavioral and psychiatric symptoms" rather than "challenging behaviors"	
In research	Address the condition or people as participants	"Person living with dementia" rather than "subject"	Need to include other conditions than dementia (MCI, SCD). Terms used in research contexts should be considered as elements in mathematical formulas; they need being short and precise without conveying judgmental assumptions. Agreement may need to be found specific to this context
In medical practice	Address the condition avoiding apparently degrading terms	"Person living with dementia" rather than "case," or rather than abbreviations like "PWD"	

A language guideline has been proposed by the Australian Alzheimer's Association (https://www.dementia.org.au/files/resources/dementia-language-guidelines.pdf) and translated into different languages. This can be used as the basis for an update, like incorporating conditions like mild cognitive impairment (MCI) and adaptation to specific contexts of use. For example, research needs precise and direct terms that should be chosen among those not perceived as diminishing, if possible. However, understanding the context of use should also enable access to direct terms used in research as not necessarily assuming or judgmental. This requires communication and agreement among different parties.

scanty inclusion of the real range of comorbidities and clinical diversity of patients. Moreover, collecting such data focusing on contexts of specific resources and needs, rather than relative to dementia as an illness, would provide implementation-relevant information.

3 | POSSIBLE WAYS FORWARD

What strategies can address the requirements of implementation and bridge research, clinics, and routine care providers in the dementia field? Useful methods can be adapted from theory-driven approaches,[42] experience from other fields like oncology or coronavirus disease 2019 (COVID-19), along with formal methods from implementation science or from industry and technology (eg, technology readiness level assessment; Glossary). Here, we propose possible ways forward (Tables 1 and 2; Figure 3). These should be considered within the need to establish sustainable structures ensuring the identification, involvement, and concerted effort of all relevant parties.

3.1 | Communication

A first step implies sustainable structural support and standard procedures to get aligned on a common concept of translational research[12] among researchers first. Being aware of the different meanings that the same words may have for different sub-communities or different parties may motivate to specify them into context-specific glossaries, rather than taking them for granted. Adopting terms that are clear and accepted by all parties may also facilitate participatory approaches, empowering the community. Expanding and adapting the document produced by Dementia Australia[43] (Table 2) to specific contexts can

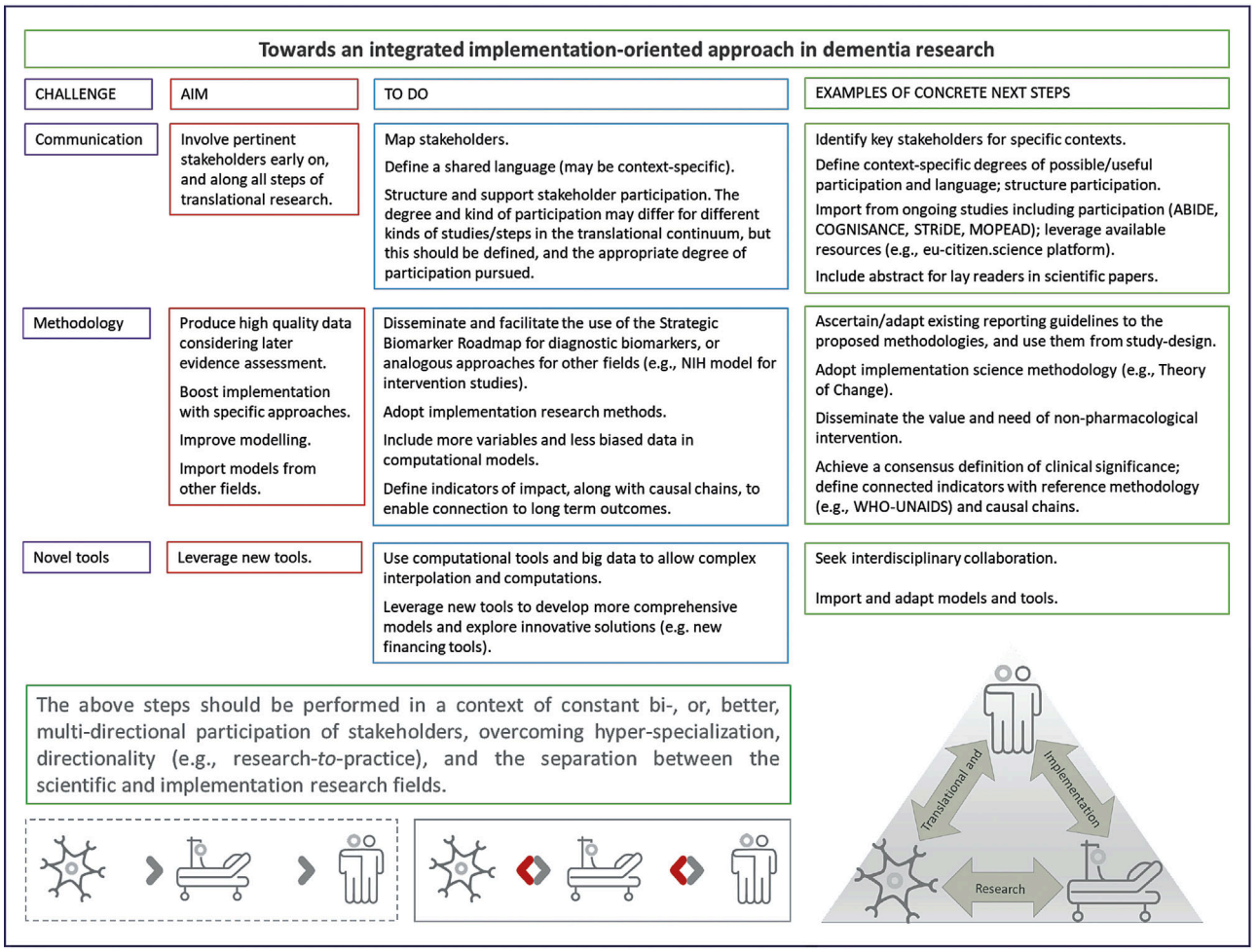


FIGURE 3 **Possible next steps**. Immediate next steps that may address the gaps between research and clinical innovation, within an integrated implementation-oriented perspective

be a first step, before addressing other hurdles to effective participation, such as facilitators and barriers to participation of specific communities.[44] This should not disregard the needs and constraints of researchers themselves: only *reciprocal* interactions can guarantee efficient collaboration at all steps of development.

Communication strategies may entail complementing scientific papers with lay abstracts for the general audience (see Supplemental abstract), as already required by some grant frameworks and journals. The participation of parties who are not experts in research needs to be structured and supported. Ongoing projects, including ABIDE (Alzheimer's biomarkers in daily practice), COGNISANCE (Co-designing Dementia Diagnosis and Post-Diagnostic Care), STRiDE (Strengthening responses to dementia in developing countries), MOPEAD (Models of Patient Engagement for Alzheimer's Disease) (Glossary) enable the participation of citizens, also with cognitive impairment, or stakeholders informing about constraints, needs, and preferences or contributing to concerted action. Using such methods and increasing participation can increase transparency, balance lobbying and representation, and start a virtuous circle supporting effective development of implementable deliverables. An overarching goal achievable with such methods may consist of defining clinical significance, in order to build better clinical studies, feed more appropriate models, and answer the requirements of regulators with information more concretely related to the community's well-being.

3.2 | Methodology

Increased awareness about the methodological requirements for effective implementation and collaboration with experts of implementation science can help produce clinical data that are usable at all steps of the translational continuum. For example, methods like process evaluation for complex medical interventions and theory of change[42] can help structure the implementation plan for complex interventions systematically, to prevent critical gaps; new study designs, like the embedded pragmatic clinical trials,[45] can increase the generalizability of experimental results to real-life contexts by addressing the trade-off between scientific rigor and practical limitations and constraints in clinics, for example, accounting for variables like polypharmacy or multi-morbidity, normally excluded in clinical trials (eg, IMPACT,

Glossary). Reporting guidelines for different kinds of studies are available[46] that should be taken into account from the definition of study design, to guarantee that no relevant parameter be omitted in the study itself. The consistency of available reporting guidelines with methodologies like the SBR has not yet been assessed, and neither is the actual impact of compliance with such guidelines. Defining context-specific indicators of impact would help us understand how to improve methods at different steps, from development in research to implementation in clinics. Indicators of impact on patients and society should be consistent with a definition of clinical significance that incorporates community values and needs. This requires the adoption of community-engaged research and community-based participatory approaches, which can facilitate knowledge transfer between community members and other stakeholders (researchers, care providers, policymakers); ensure that community members are part of the decision-making process; and ensure incorporation of the preferences and priorities of impacted communities into proposed solutions.[47–50]

3.3 | Modeling

Many of the limitations related to decision-analytic models originate from a lack of high-quality data. Nevertheless, some models have incorporated multi-domain designs,[51,52] sometimes devised for non-pharmacological interventions, and including comorbidities, gender, and ethnicity,[53] to allow better definitions of relevant outcomes and better representation of the overall patient population than allowed by clinical trial samples. Relevant data are increasingly available from registries or pooled cohorts (eg, emif-catalogue.eu), from memory clinics, or from claims data, although these are likely challenged with selective drop-out[54] and limited patient-relevant outcomes such as cognition, function, behavior, autonomy, or social engagement. Performing extensive measurements for such outcomes in a random selection of persons in registries, like JPND's ADDITION project,[55] or with a low-labor intensive digital follow-up protocol in memory clinic or care organizations could connect surrogate outcomes with actual long-term patient-relevant outcomes and thus support decision-models that avoid extrapolations based on strong assumptions.

The development of open-source models is an important step toward transparency.[56] It stimulates critical appraisal and helps improving rather than replicating models. Model credibility could also be improved, as studies conducted independently of industry or health-technology assessment authority showed less-favorable conclusions related to the health-economic outcomes of some interventions.[36] In addition, comparing models that evaluate the same intervention and report on standardized outcomes, like life expectancy and time spent in mild cognitive impairment (MCI), and mild, moderate, and severe dementia, supports their understanding and credibility. An example is the International Pharmaco-Economic Collaboration on Alzheimer's Disease,[57] that developed an open-source model[51] and performed model comparisons.

Innovative technology can of course contribute coordination platforms and computational power to interpolate missing information and process big data sources. Still, they cannot compensate per se for the outlined methodological gaps.

4 | DISCUSSION

In this article we have outlined some hurdles that hamper the transfer of new research findings to clinical practice in the field of dementia, and we have proposed possible ways forward. Resolute efforts to improve our ability to bring clinical innovation are necessary to tackle the global increase of dementia prevalence. The investment in dementia research is lower than in other fields, like oncology. However, more effective implementation of interventions that are able to improve patients' well-being would provide a sizeable return of such investment to society, possibly starting a virtuous circle that increases investment. Although this proposed approach is not new per se,[12,13,5] in this article we tried to identify concrete hurdles and resources to integrate the research and implementation fields and boost processes that bring clinical innovation for dementia.

The challenges identified in this article can be roughly grouped into two main categories, addressing how do we make progress (1) in the translational space in terms of moving new science into clinical trials and eventually into clinical practice, and (2) implementing "best practices" into clinical practice. Suggestions to improve the methodology of biomarker validation or clinical studies can be seen as belonging to #1, whereas suggestions such as translation of papers or guidance into local languages, or providing more uniform training and communication around best practices, enabling more community-based health care providers to deliver better care, can be attributed to #2. However, an effort to go beyond such dichotomous thinking may help seeing the "downstream adoption hurdles" from the very beginning of clinical research studies. This is indeed the approach taken in the field of behavioral intervention,[14] adopting experimental designs like the embedded pragmatic clinical trials, enabling the assessment of feasibility and impact from early on in validation studies. As well, involving citizens, as well as other stakeholders, from study conception in dementia research allows to achieve results that answer not just research questions, but that also address concrete needs and keep downstream constraints into account, improving the use of research resources.[48]

The gap between research and implementation is not unique to the dementia field, or to the medical sector. On the other hand, fields like technology benefit from more successful approaches. For example, research in physics provides a great return to society by turning discoveries into widely marketable products, like GPS navigation, more performant mobile communication, or computing. Considering development models from different fields and taking marketing aspects, that is, requests and constraints of health care providers, into greater account may help boost the implementation of produced knowledge. The challenge in this case is to keep the marketing drive in the proper balance with societal needs and values.

Such implementation-oriented approach is challenging, requiring a structured effort to bridge the heterogeneous aspects and stakeholders within a consistent perspective. Specific methodology is needed to

promote accessibility, empowerment, and synergies. This requires no less than a turn in culture, which is, however, timely given the increasing relevance of scientific communication to address societal skepticism, concerns of inadequate lobbyism, and mistrust of health care decisions. Hubs of scientific support and communication, like journals or funding schemes, already promote such an approach, and may more closely interact to require compliance with methodological and reporting guidelines, stakeholder involvement, effective information, and dissemination. Nonetheless, compliance requires new and specific tools, methods, and actions, yet to be developed or adapted to our field, and dedicated funding to build sustainable infrastructures.

A concrete overarching activity within the dementia research field, requiring all of the mentioned parties and affecting most of the mentioned areas, may consist of achieving a consensus definition of clinical significance, to be then operationalized into outcomes or chains of connected intermediate outcomes, measurable with existing or newly developed tools.

The main limitation of this article consists of treating such a complex field from the main perspective of biomedical dementia research. Moreover, challenges include of course more issues than we could raise here. For example, modeling was considered only relative to cost computation; different participatory method frameworks and their ability to address hurdles to and facilitators of co-development should also be compared. The greatest challenge raised here consists of identifying a mechanism that motivates concerted efforts by heterogeneous stakeholders.

Bridging research and practice in this way cannot be achieved by a single working group or initiative. Devising new methods that support such concerted efforts may boost the response of research to the increasing prevalence of dementia.

5 | GLOSSARY

Alzheimer's biomarkers in daily practice (ABIDE) is a 3-year project designed to translate knowledge on diagnostic tests (magnetic resonance imaging [MRI], cerebrospinal fluid [CSF], positron emission tomography [PET]) to daily clinical practice with a focus on mild cognitive impairment (MCI).[58] ABIDE will also develop strategies for optimal patient-clinician conversations,[58] for example, by assessing patients' and caregivers' views and experiences of decisions about diagnostic testing for Alzheimer's disease (AD) receiving test results.[59] This will provide a set of practical tools for clinicians to support the choice of diagnostic tests and facilitate the interpretation and communication of biomarker assessment[58] (www.amsterdamumc.org/en/research/highlights/abide-alzheimers-biomarkers-in-daily-practice.htm).

Co-designing Dementia Diagnosis and Post-Diagnostic Care (COGNISANCE) is a project aimed at improving the dementia diagnostic process and post-diagnostic support. This is performed by co-designing print or on-line toolkits and ultimately delivering them to people with dementia, family care partners, and health care professionals. Toolkits will provide structured information, tailored to enable health care practitioners to effectively enact national dementia guidelines around diagnostic and post-diagnostic support, and to empower people with dementia and their family care partners to seek the support they require (https://cheba.unsw.edu.au/consortia/cognisance).[60]

Decision analytic models. Decisional models can be defined as "mathematical frameworks that facilitate the estimation of the consequences of health care decisions."[61] Policy decision models attempt to estimate the impact of new health technologies in a real-world setting. Typically, they simulate a simplification of the natural disease progression, the impact of the new technology on that progression, and the consequences in terms of their change in health and change in use of care resources for a specific population. In the field of AD and related disorders, such policy-decision models often extrapolate short-term trial results to long-term impact on health and care use.

Evidence-based decisions are decisions that leverage evidence based on evidence-to-decision procedures (EtD). EtD are algorithms assessing whether scientific advancements, for example, a new diagnostic test or treatment, can be used in practice based on published evidence on its validity and usefulness, including the assessment of the quality of evidence relative to risk of bias and of the size and consistency of effects. Such procedures include the Grading of Recommendations Assessment, Development and Evaluation –GRADE,[62] the Cochrane reviews,[63] or Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH) OMAR (Office of Management Analysis and Reporting) in US contexts.[64]

^{18}FDG-PET: ^{18}fluorodeoxyglucose positron emission tomography. ^{18}FDG-PET, which measures cerebral glucose metabolism, is a biomarker for the identification of clinical and prodromal Alzheimer's disease (AD). 18F-FDG works as a proxy for neuronal activity in the resting state.[65] Impaired activity in AD is evident as reduced 18F-FDG uptake predominantly in temporo-parietal association areas, including the precuneus and posterior cingulate is detected. 18F-FDG PET is more sensitive in detecting neuronal dysfunction in neocortical association areas and, since the function of these areas is primarily related to cognitive deficits in non-memory domains such as language and orientation, this technique appears to be particularly well suited for monitoring AD progression.[65]

National Institute on Aging (NIA) IMbedded Pragmatic Alzheimer's disease (AD) and AD-Related Dementias (AD/ADRD) Clinical Trials (IMPACT). The IMPACT project aims at building the capacity to conduct pragmatic clinical trials of interventions embedded within health care systems for people living with dementia and their care partners. In addition to disseminating implementation methods specifically adapted to dementia and providing training, the project aims at catalyzing collaboration among stakeholders, health care providers, and investigators and ensuring that research include culturally tailored interventions and people from diverse and under-represented backgrounds (https://impactcollaboratory.org/overview/).[66,67]

Models of Patient Engagement for Alzheimer's Disease (MOPEAD) is an IMI (Innovative Medicine Initiative) project assessing different Patient Engagement models across Europe, to identify efficient approaches of earlier identification of mild AD dementia and prodromal AD. The project compares the efficiency in improving early

detection of different tools, mechanisms, and processes for community engagement, patient identification, and resource utilization. These entail a citizen-science page, an open house initiative, and two different clinical contexts providing screening for cognitive impairment (https://www.mopead.eu/about-mopead).[68]

Strategic Biomarker Roadmap (SBR). The AD Biomarker Roadmap[69,70] (Figure 2) is a methodological framework describing the kind and sequence of the investigation steps necessary for the proper validation of diagnostic biomarkers. This sequence entails the demonstration of analytical validity (ie, the assay can measure the target anomaly), clinical validity (the test does detect the target clinical disease), and clinical utility (the test improves the health of the target patients). These steps must be followed in the described order to avoid propagating variability that cannot be amended post hoc, affecting the eligibility of results to evidence-to-decision procedures. This methodology was adapted from oncology,[71] which imported it from drug development and adapted to the validation of oncological diagnostic biomarkers in 2001.

Strengthening responses to dementia in developing countries (STRiDE). STRiDE is a 4-year project led by the led by the Care Policy and Evaluation Centre at the LSE. It aims to build capacity in dementia research in seven developing countries, in order to support development, financing, planning, implementation, and evaluation of national dementia plans (https://www.alzint.org/what-we-do/research/stride/).

Technology readiness level (TRL). Methodology used to assess the level of maturity of a technology and explain it to collaborators and stakeholders. The TRL method was developed originally by NASA in 1974 and is currently adopted in research and development contexts. Assessment based on TRL ranges from 1 (idea development) to 9 (fully developed system, already deployed in the marketplace and used operatively). For a detailed and reader-friendly explanation, see www.nasa.gov/topics/aeronautics/features/trl_demystified.html. The concept has been adapted to different contexts (governmental, technological, industrial).

Translational research. Translational research refers to a wide range of concepts. These range from basic research investigating analytical validity of newly developed compounds with translational potential (eg, https://www.scripps.edu/research/tri/index_sav.html), to clinical studies expected to have a concrete clinical impact in the short term. Although the latter is most frequent in Europe than in the United States, this is increasingly embraced in the United States too (eg, https://ncats.nih.gov/). To try to overcome discrepancies, the European Society for Translational Medicine (ESTM) proposed to consider translational research as a continuum entailing all such studies from the levels of analytical validity, clinical validity, and clinical utility.[12,72]

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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