

# Consent recommendations for research and international data sharing involving persons with dementia

Global Alliance for Genomics and Health, Ageing and Dementia Task Team

DOI:

[10.1016/j.jalz.2018.05.011](https://doi.org/10.1016/j.jalz.2018.05.011)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Global Alliance for Genomics and Health, Ageing and Dementia Task Team 2018, 'Consent recommendations for research and international data sharing involving persons with dementia', *Alzheimer's & Dementia*, vol. 14, no. 10, pp. 1334-1343. <https://doi.org/10.1016/j.jalz.2018.05.011>

[Link to publication on Research at Birmingham portal](#)

**Publisher Rights Statement:**

Checked for eligibility: 11/10/2018

**General rights**

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

**Take down policy**

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

Perspective

## Consent recommendations for research and international data sharing involving persons with dementia

Adrian Thorogood<sup>a,\*</sup>, Anna Mäki-Petäjä-Leinonen<sup>b</sup>, Henry Brodaty<sup>c</sup>, Gratién Dalpé<sup>a</sup>, Chris Gastmans<sup>d</sup>, Serge Gauthier<sup>e</sup>, Dianne Gove<sup>f</sup>, Rosie Harding<sup>g</sup>, Bartha Maria Knoppers<sup>a</sup>, Martin Rossor<sup>h</sup>, Martin Bobrow<sup>i</sup>, on behalf of the Global Alliance for Genomics and Health, Ageing and Dementia Task Team<sup>1</sup>

<sup>a</sup>Centre of Genomics and Policy, McGill University, Montreal, Canada

<sup>b</sup>Faculty of Social Sciences and Business Studies, Law School, University of Eastern Finland, Joensuu, Finland

<sup>c</sup>Faculty of Medicine, University of New South Wales, Sydney, Australia

<sup>d</sup>Interfaculty Centre for Biomedical Ethics and Law, KU Leuven, Leuven, Belgium

<sup>e</sup>McGill Centre for Studies in Aging, McGill University, Montreal, Canada

<sup>f</sup>Alzheimer Europe, Luxembourg City, Luxembourg

<sup>g</sup>Birmingham Law School, University of Birmingham, Birmingham, United Kingdom

<sup>h</sup>UCL Institute of Neurology, University College London, London, United Kingdom

<sup>i</sup>Department of Medical Genetics, University of Cambridge, Cambridge, United Kingdom

### Abstract

Consent is generally required for research and sharing rich individual-level data but presents additional ethical and legal challenges where participants have diminished decision-making capacity. We formed a multi-disciplinary team to develop best practices for consent in data-intensive dementia research. We recommend that consent processes for research and data sharing support decision-making by persons with dementia, protect them from exploitation, and promote the common good. Broad consent designed to endure beyond a loss of capacity and combined with ongoing oversight can best achieve these goals. Persons with dementia should be supported to make decisions and enabled to express their will and preferences about participation in advance of a loss of capacity. Regulatory frameworks should clarify who can act as a representative for research decisions. By promoting harmonization of consent practices across institutions, sectors, and countries, we hope to facilitate data sharing to accelerate progress in dementia research, care, and prevention.

© 2018 The Authors. Published by Elsevier Inc. on behalf of the Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

### Keywords:

Alzheimer's disease; Dementia; Consent process; Broad consent; International data sharing; Research participation; Supported decision-making; Will and preferences; Advance directive; Representative

### 1. Introduction

Progress toward understanding and treating dementia has been painfully slow. In all biomedical research, advances in research techniques (e.g., genomic sequencing, brain imag-

ing) and information technology have led to a marked trend for gathering, linking, reusing, and sharing rich health-related data over long periods. It is now widely recognized that maximizing the societal benefit of health research almost always entails the timely release of data to the international research community. Data sharing honors the contributions of research participants, improves the transparency of research, and facilitates targeted recruitment for clinical studies. Increasingly, clinicians and health-care organizations are also expected to share data with

<sup>1</sup><https://www.ga4gh.org/ga4ghtoolkit/regulatoryandethics/>.

\*Corresponding author. Tel.: 514-398-8187; Fax: 514-398-8954.

E-mail address: [adrian.thorogood@ga4gh.org](mailto:adrian.thorogood@ga4gh.org)

**Box 1****Literature search strategy and selection criteria**

We carried out a scoping review of the literature for our research question: What consent and capacity issues impact dementia research and data sharing? We performed database searches using the terms (Dementia OR Alzheimer) AND Research AND Consent published since 2007 on Web of Science (filters: Topic), PubMed (filters: MeSH and free text; Title/abstract), Google Scholar, and SSRN, until July 21st, 2017. French language searches were carried out on SCOPUS and Google Scholar for the terms (Alzheimer OR *démence*) AND *recherche* AND (consentement OR *éthique*). We experimented with numerous spelling variations, synonyms, and additional terms (e.g., capacity, competence, and data sharing), but these did not produce additional findings. Eight hundred fourteen results were reduced to 585 after removing duplicates. References were excluded when purely scientific articles (166), sources not available in English or French (8), incomplete or inaccessible sources (13) as well as literature not addressing or only superficially addressing populations with dementia (95), health research (166), or consent issues (31). The remaining articles were grouped according to key themes established iteratively through article review and consensus deliberation of the larger task team, which included consent, decision-making authority and support, planning in advance, representation, and capacity assessment. Two researchers (A.T., G.D.) reviewed the titles and abstracts from all references. Full texts were screened, where application of exclusion criteria or key theme grouping was unclear. An additional 34 articles addressing the key themes were found in reference lists or contributed by task team members for a total of 116. The literature included systematic reviews, empirical studies of stakeholder perspectives and practices, and regulatory and ethical analyses. A complete reference list can be found in [Supplementary Materials](#). A limitation is that we did not search for literature about consent and capacity issues concerning other neurodegenerative conditions (e.g., stroke) or decision-making contexts (e.g., treatment, organ donation, and assisted dying). Such literature may provide important indirect insights but was too expansive to include, not to mention that some considerations are condition specific.

researchers to support “learning health systems” [1]. Data sharing presents opportunities for the dementia research community to pool high-quality data sets, attain larger sample sizes, maximize the value drawn from data already collected, and reduce wasteful—and sometimes harmful—duplication and delays in research.

Demonstrating the effectiveness of interventions for dementia requires participation of healthy persons and persons with dementia in clinical studies and biobanks and sharing of their genomic and health-related data with many researchers. Where research involves physical, psychological, or privacy risks, researchers are generally required to seek consent [2,3]. New data types such as whole genome sequences present risks of participant re-identification, disclosure of sensitive information about disease risk or biological relationships, and misuse (discrimination in the workplace and insurance, stigmatization) [4]. It is therefore best practice for researchers to seek consent for sharing rich individual-level data (or the samples they are derived from) and also to protect these data using encryption, robust access control and ethical oversight, and network technologies that maintain secure, local storage while enabling federated analyses [5]. In general, data or sample sharing between institutions and across borders over long periods raises important consent challenges [6]. When is consent required? What form should consent take? Can adequate privacy protections be ensured between countries and institutions?

Dementia and other disorders of cognitive impairment are characterized by a progressive diminishment of cogni-

tive skills (e.g., memory, reasoning, and language) that can impact on decision-making capacity. Researchers seeking consent from persons with dementia confront ethical and legal uncertainty, such as when and how to assess capacity to consent [7]. Regulatory frameworks governing decision-making involving persons with dementia are relatively clear for treatment, but not for research. Where rules are supplied for research, they often fail to accommodate the data sharing practices and digital interconnectivity of modern research. Guidance developed for invasive clinical studies tends to be disproportionately restrictive when applied to observational research or data sharing. Most international or national research guidelines rarely delve into the consent issues for adults with diminished capacity, deferring instead to unclear or restrictive local laws. Other laws and ethical guidelines tend to lump persons with dementia together with other vulnerable populations, overlooking ethical concerns specific to adults with diminishing capacity [8].

Well-meaning safeguards to protect persons with limited capacity from abuse and exploitation, such as the requirement that researchers seek consent from a legally authorized representative (LAR), can function to exclude persons with dementia from research and data sharing activities [2,3]. Disproportionate safeguards hinder improvements in dementia research, care, and prevention and undermine the right of persons with dementia to full and effective participation and inclusion in society [9]. Legal variation across jurisdictions or sectors can

**Box 2****International comparative regulatory analysis**

We carried out a comparative analysis of international, regional and national legislative, and policy frameworks from eight countries (Australia, Canada, Finland, France, Japan, Singapore, the United Kingdom, and the United States) that govern informed consent, substitute decision-making, participation in research, and the processing of personal data. The analysis comprised both legally binding instruments and nonbinding “soft law” instruments such as declarations and policies. The jurisdictions were selected to reflect geographic diversity and legal systems diversity, with a focus on countries active in the domain of data-intensive health research. The detailed methodology of this review is available in a previous publication [17].

additionally constrain research collaborations and data sharing across borders. Such restrictive regulations contradict the views of persons with dementia and their families, many of whom have positive attitudes toward research participation [10].

This article identifies legal and ethical uncertainties, restrictions, and jurisdictional discrepancies at the intersection of consent, data sharing, and diminished capacity. The following six key themes are explored: consent standards, identifying who has authority to consent, decision-making support, planning in advance, representation, and capacity assessment. We conclude with recommendations for consent to research and data sharing involving persons with dementia, with a view to clarifying fundamental regulatory principles, and harmonizing consent processes across countries, institutions, and sectors (clinical, research, and biobanking). These recommendations are limited to consent and capacity issues, as other generic challenges for research and data sharing governance are being addressed elsewhere (e.g., anonymization, security safeguards, access processes, oversight, return of results, ethics review equivalency across sites and jurisdictions, and risk-benefit criteria for research with vulnerable persons) [11,12]. These recommendations are also founded on empirical evidence of the attitudes of persons with dementia and their families. Patient engagement is increasingly recognized as integral to effective dementia research and ethical research oversight [13]. We also sought input on the recommendations from representatives of persons with dementia and researchers.

## 2. Methodology

These recommendations were developed by the Ageing and Dementia Task Team, established by the Regulatory and Ethics Work Stream of the Global Alliance for Genomics and Health (GA4GH). The GA4GH is a consortium of over 500 research institutions, health centers, life science and IT companies, and patient advocacy groups with a mission to promote international data sharing to improve human health. Ten experts were invited to contribute to this policy, to ensure diverse expertise and geographical representation. They included clinician-researchers (M.B., H.B., S.G., M.R.), jurists (A.T., A.M., R.H., B.M.K.), ethicists

(C.G.), and patient advocates (D.G.) from across Europe, Australia, and Canada. Experts worked to achieve consensus on consent issues via teleconferences and exchange of background literature. They were asked to build on the GA4GH Framework for Responsible Sharing of Genomic and Health Related Data (2014) [14], which aims to activate the human right of everyone to benefit from the progress of science [15] and GA4GH Consent Policy (2015) [16]. Steps included are as follows: (1) preliminary policy review and teleconference to establish the mandate; (2) scoping review of the literature (Box 1) and international comparative regulatory analysis (Box 2); and (3) four drafts and rounds of comments by teleconference and email. A representative from the European Working Group of People with Dementia, patient advocates from Alzheimer Europe, and end users from the researcher-clinician network INTERDEM all provided valuable comments on drafts of these recommendations (see Acknowledgments).

Our discussion is organized according to six key themes. Each section reviews important regulatory provisions, issues raised in the literature, gaps where future work is needed, and concludes with recommendations.

## 3. Discussion

### 3.1. Consent

Excluding persons with dementia from full participation in society, including research, on the basis of age or disability is discriminatory as per the United Nations Convention on the Rights of Persons with Disabilities (CRPDs) and Principles for Older Persons [9,18]. Moreover, including this population in pertinent research is essential to ensure future patients benefit from improvements in prevention and care [2,19–22]. Special attention must be paid to the vulnerabilities of persons with dementia in research [2,3,23–25]. They require specific safeguards, distinct from those in place for other vulnerable populations, to not only protect them from harm but also to respect their agency [8,26]. For the collection, linkage, reuse, and sharing of rich individual-level data, broad consent is emerging as a general best practice [2,6,16,25,27]. Broad consent as defined by

**Box 3****Summary panel of recommendations****Consent**

- Consent processes should strike a more explicit balance between supporting decision-making by persons with dementia, protecting them from exploitation, and promoting the common good. Broad consent combined with ongoing oversight can achieve this balance for the sharing of rich individual-level data.
- Persons with dementia should be presumed to have the capacity to consent unless established otherwise.

**Decision-making authority**

- Regulatory frameworks should provide clarity about who can act as an LAR for research for persons who lack capacity to consent.

**Support for decision-making**

- Persons with dementia should be supported to make their own decisions relating to research and data sharing. Even where decisions are made by an LAR, they should be included in decision-making in a manner appropriate to their level of capacity.

**Planning in advance**

- In advance of a loss of capacity, healthy persons and those with dementia should be supported to express their preferences about future participation in research and data sharing.
- Early communication should be encouraged between persons with dementia, family members, and carers about preferences relating to research and data sharing, while striving not to provoke anxiety about worsening symptoms.
- Consent forms should specify that consent to research or data sharing so provided will be respected after a loss of capacity.

**Representation**

- Researchers and LARs should respect the will and preferences of persons with dementia relating to research and data sharing, including those expressed in advance of a loss of capacity (e.g., through a broad consent), about participation, receiving results, and representation. Where preferences are unknown, the legally authorized representative should consider the person's beliefs, values, and welfare.

**Capacity assessment**

- Capacity assessment tools need to be developed and validated for persons with dementia participating in genomic research, biobanking, and data sharing. Research protocols should specify when and how capacity will be (re)assessed.
- Capacity assessment tools should be tailored to a specific decision-making context and should adduce sufficient evidence the person lacks capacity.
- The rigor and regularity of capacity assessment should be proportionate to the risks posed to person's rights and interests.

international and US research norms grants researchers the permission to use samples and associated data for a range of research studies, not specified in detail at the time of recruitment, subject to ongoing transparency and ethics oversight (Council for International Organizations of Medical Sciences/WHO Guidelines, US Common Rule) [2,27]. Broad consent does raise concerns about privacy and informational autonomy and tensions with data protection requirements in some jurisdictions [28,29]. Combining broad consent with ongoing oversight can help to ensure that privacy is protected, and uses are consistent with participant expectations. General challenges of harmonizing and implementing broad consent processes and ongoing oversight are addressed elsewhere [16]. Broad consent processes are particularly well suited for data sharing involving persons with dementia who may not be able to provide specific consent later on. Indeed, an important means of supporting decision-making is enabling per-

sons with dementia to express their will and preferences in advance (see below Section 3.2). They strike a more explicit balance between supporting decision-making by persons with dementia, protecting them from exploitation, and promoting the common good. Where possible, we recommend seeking recruitment and consent of individuals into longitudinal studies or registries before symptoms worsen, which can mitigate later challenges of capacity. Broad consents should clarify where data will continue to be used after a loss of capacity. As an additional safeguard, patient representatives can act as advisers to or be members of data access committees. Data sharing consent requirements, guidelines, language, and interpretation should also be harmonized across countries and institutions, as well as across sectors (clinical, research, and biobanking) to improve certainty about the scope of sharing, facilitate pooling and linkage, and promote the reuse of data [14,25,30].

### 3.2. Who can make decisions?

To respect the dignity and autonomy of participants, researchers should first try to seek consent from the person with dementia. The influential United Nations CRPD is critical of proxy consent processes and instead emphasizes limiting intrusion on legal capacity by supporting decision-making by persons with mental disability [31,32]. In research contexts, consent processes should ensure that researchers, family members, and carers all provide support to persons with dementia to assist participation in decision-making [9,22,31,33]. There will still be situations where despite decision-making support, a person with dementia is ultimately found to lack the capacity to consent to research or data sharing after a formal capacity assessment. In such situations, researchers are generally required to seek consent from an LAR. In many countries, however, researchers face difficulties identifying the LAR for research [10,34–38]. Different categories of LARs apply in different circumstances, including court-appointed guardians, agents designated by an advance directive, or one-time surrogate decision makers designated by statute (e.g., family members, carers, or other concerned persons) [17,20,21,39,40]. Research norms do not typically specify who may consent, but instead defer to local consent and capacity laws. Unfortunately, local laws may limit or restrict LAR authority to consent to research participation or impose prohibitive requirements such as court approval [21,41]. Acceptable risk/benefit thresholds determining when an LAR can consent to research vary confusingly across jurisdictions and research sectors. Traditional requirements are that research directly benefits the individual or be limited to minimal risk research that benefits individuals of the same age or disease group [3,42]. But, risk thresholds are not coordinated across regulatory frameworks, making it unclear who can act as LAR to research participation. In addition, researchers and family members may have false assumptions about regulatory requirements [43]. In any case, persons without supportive family or carers may be excluded from research (and its benefits) because they lack representation [44]. Regulatory divergence between countries adopting or not adopting the CRPD may threaten international collaboration. Researchers from CRPD countries may not be allowed to use data collected under LAR consent in noncompliant ones. Following the lead of the Council for International Organizations of Medical Sciences/WHO Guidelines and US Common Rule revisions, regulatory frameworks should provide more clarity about who can act as LAR for research [2,27]. Recognizing the importance of including vulnerable populations in research, a proportionate approach to risk-benefit is increasingly adopted, especially for data sharing [2,14]. We recommend that persons with dementia be supported to make their own decisions about research participation and data sharing (see Section 3.3). They should be presumed to have the capacity to do so, un-

less established otherwise (see Section 3.6). In advance of a loss of capacity, both healthy persons and those with dementia should be supported to designate representatives and to express their preferences about participation in research and data sharing (see Section 3.4).

### 3.3. Support for decision-making

Given the nature and complexity of research, and the related risks and benefits, it may be difficult for persons with diminished capacity to satisfy high informed consent standards. Decision-making can be supported by simplifying consent forms, providing visual or memory aids, taking interactive or educational approaches (where persons with dementia are asked to explain their understanding of consent elements), re-explaining misunderstood information, or involving familiar carers to facilitate explanation and communication of a decision [45–49]. In a process consent approach, researchers come to know the participant and to tailor consents to his or her preferred means of communication [50]. More work is needed to determine how consent supports can be effectively adapted for persons with dementia. In practice, decision-making with persons with dementia is often a collaborative process [51]. Research ethics guidelines generally promote supported or shared decision-making and may require researchers to seek an affirmation from persons with dementia of their willingness to participate (assent) and to respect objections to continued participation (dissent) [2,3,48,51]. A remaining controversy is whether researchers or LARs should be obliged to respect an “uninformed” objection to participate by a person or simply take it into account [20]. To safeguard respect for human dignity, we recommend that researchers, family members, carers, and LARs take all reasonable efforts to support persons with dementia to make their own decisions, relating to research and data sharing. Even where decisions are made by an LAR, efforts should be made to include persons with dementia in decision-making in a manner appropriate to their level of capacity. Consent processes involving persons with dementia may therefore require additional steps, expertise, and resources. Policy makers, funders, and researchers should be sensitive to the social and psychological pressures facing persons with dementia, family members, and carers and the environments from which persons with dementia are recruited [52].

### 3.4. Planning in advance

One means of supporting decision-making is to allow persons to appoint a representative and/or to specify their will and preferences in advance [9,38,53]. Empirical studies show that most older adults with dementia are willing to provide consent to some forms of research in advance or to allow a representative to do so [10,54]. Some guidelines highlight the importance of respecting or taking into account expressed wishes [23]. A few recognize the

possibility of advance research consent [2,19]. Regulatory frameworks do not, however, consistently authorize individuals to provide binding instructions in advance or to designate an agent in advance to make decisions relating to research or data sharing [17,21,55,56]. There is also significant regulatory variation over the formalities of advance directives and the extent to which they may be overridden by a health professional or family member. The effectiveness of advance directives for research, especially “positive” ones (“I wish to be included”), is limited by the high standard of informed consent in research; the unknown, complex nature of future research; a lack of awareness and uptake by the public; and difficulties persons with dementia face participating in research without the practical support of family and carers [57]. Philosophers debate whether advance directives remain legitimate if preferences, and even identity, fundamentally change over time or as symptoms evolve [57,58]. Especially in longitudinal research, the question arises whether consent can be presumed to “endure” after a loss of capacity [59]. This issue will remain controversial for experimental research, where clear protocols are needed to determine when capacity will be reassessed. For sample and data sharing, however, broad consent processes already explicitly encode “precedent autonomy”. They can be designed to capture the will and preferences of persons with dementia expressed in advance of a loss of capacity (e.g., through a broad consent), such as preferences about participation, receiving results, or who represents them. To alleviate uncertainty, we recommend that consent forms should specify that consent to research or data sharing so provided will be respected after a loss of capacity, unless the person dissents or the LAR withdraws (following the appropriate decision-making standard) [21]. Jurisdictions recognizing advance directives may be more accepting of durable broad consent. More generally, policy makers and researchers should encourage early communication between persons with dementia, family members, and carers about preferences relating to research and data sharing, while striving not to provoke anxiety about worsening of symptoms [41]. Current societal efforts to encourage individuals to express instructions or wishes about personal care—in living wills, health records, or even government registries—could be expanded to address research and data sharing. This would reduce the need for repeated advance planning discussions. The uptake, effectiveness, and empathy of advance planning can also be improved by structured, educational discussions held over time that include trained facilitators and representatives [60].

### 3.5. Representation

The public and persons with dementia support LAR consent to research, particularly for low-risk research [10,34–38]. But, what decision-making standard should an LAR follow? Standards vary across countries and research

sectors, and research ethics committees may interpret these standards differently [17,20,21,61]. Traditional guardianship approaches emphasize that LARs should focus on the person’s “best interests” or welfare [33]. Substituted judgment standards focus more on the person’s expressed wishes, values, and beliefs and ask the LAR to substitute the judgment of the person with dementia for their own [62]. Emerging agency models emphasize respect for the “will and preferences” of the person [31,63]. In the research context, best interests approaches protect against exploitation, but they can be exclusionary, especially for nontherapeutic research [62,64]. For research and data sharing decisions, the will and preferences of persons with dementia are often unknown, and it may be difficult to render substitute judgments based on vague values and beliefs [17,61,65]. There are also concerns about the accuracy of decisions by LARs because of the potential for therapeutic misconception and conflicts of interest [66,67]. Future work is needed on how best to hear the preferences of people with more complex support needs and how to establish oversight of LARs proportionate to the risks posed to the person’s rights and interests [68]. We recommend that LARs involved in decision-making relating to research or data sharing should respect the known will and preferences of the person with dementia. Ascertaining the will and preferences may require the LAR to consult persons with dementia, advance planning documents, as well as family members and carers. Researchers should inform LARs exercising rights on behalf of persons with dementia (e.g., to withdraw consent) of known wishes expressed by the persons with dementia (e.g., a broad consent) and should encourage LARs to respect such wishes. Where the will and preferences of persons with dementia cannot be ascertained, LARs should make decisions on behalf of persons with dementia that take into account the person’s beliefs, values, and welfare. Transparent processes should be in place for reporting failures of researchers or LARs to respect proxy decision-making standards, and for adjudicating disputes. For minimal risk research and data sharing, it may be practical to extend more deference to LARs. Readers should respect locally applicable standards that differ from these recommendations.

### 3.6. Capacity assessment

Researchers have an ethical and legal obligation to ensure that persons with dementia have the capacity to consent or refuse to participate in research or data sharing. Simply assuming lack of appropriate capacity because of a diagnosis of dementia, or because a person makes a decision that seems eccentric or unwise, may be discriminatory [31]. Functional capacity assessments are typically used in a biomedical context, in which a health-care provider evaluates a person’s ability to understand relevant information, to appreciate consequences, to reason, and to express a

decision [69]. For research, this includes understanding and appreciation of the purpose, procedures, risks, and benefits of a specific project or data sharing initiative [69]. Assessment is especially challenging for longitudinal research, however, because capacity may fluctuate in the short and long term [22,69–72]. Decision-making may need to be delayed to see if capacity returns. Capacity assessment is a time- and context-specific process. Generic tests and test thresholds cannot be established. Instead, they should be proportionate to the risks to the individual's rights and interests, to balance risks of exploitation against risks of discrimination. Persons with dementia who lack the capacity to consent to one type of treatment or research participation may retain the capacity to consent to less risky or complex research or to data sharing (if relevant). Those lacking the capacity to make certain decisions may still have the capacity to appoint an LAR to make decisions on their behalf [73]. A number of assessment tools have been adapted from the treatment to the research domain [46,74–76]. There remains no gold standard, and most tools rely on the professional (and potentially biased) judgment of a member of the research team [21,77]. Tools still need to be developed and validated for persons with dementia participating in genomic research, biobanking, and data sharing [26]. Notions of capacity likely differ significantly across cultures, complicating harmonization of regulation and research data governance. This could result in barriers to international research collaborations, where relying on data from other countries might be considered exploitative (for countries with less rigorous assessment or lower thresholds) or discriminatory (for countries with more rigorous assessments or higher thresholds). Fortunately, more widespread adoption of supported decision-making and inclusion of persons with dementia in decision-making will diminish the consequences of variation in this area.

We recommend that researchers presume that persons with dementia have capacity, until demonstrated otherwise. Capacity assessment tools should be tailored to a specific decision-making context and should adduce sufficient evidence the person lacks capacity (and not vice versa). They should also be standardized and validated with respect to the research protocol and associated risks. Capacity may need to be reassessed over time, for example, at different research stages or on recontact. The research protocol should specify when and how participants' capacity will be reassessed. Routine, formal capacity assessment can be difficult for both persons with dementia and researchers, so the rigor and regularity of assessment should be proportionate to the risks posed to person's rights and interests. For minimal risk research or data sharing, capacity assessment may be integrated with an interactive consent process including a questionnaire [78], potentially facilitated by a family member or carer. For riskier studies, a staged approach is advisable, moving on in cases of uncertainty from brief screening tools to formal, rigorous assessments [76]. Similarly, test thresholds should be proportionate to risks, to limit incursion on the individual's auton-

omy. Capacity of persons with dementia to form an advance directive and capacity of representatives (e.g., ageing caregivers) should also be considered.

#### 4. Conclusion

The last decade has seen a substantial increase in genomic and health-related data generated about patients with dementia. The systematic collection, storage, and sharing of large sets of research data are increasingly central to understanding aging and dementia. Collaboration between governments, researchers, health-care institutions, and industries is essential but is hindered by legal uncertainty and restrictiveness, especially with regards to persons with diminishing capacity to consent. Researchers still struggle to determine if persons with dementia can be included in research or if their data can be shared. They lack tools and know-how for supporting persons with dementia to make their own decisions or for determining when they are unable to do so. Regulatory frameworks remain unclear about who, if anyone, can provide consent on behalf of a person with dementia to research participation. Moreover, when LARs are asked to provide consent, they face uncertainty over how to balance previous instructions and wishes with current wishes and welfare considerations. Divergence in how countries resolve these questions may come to undermine international collaboration.

Our recommendations aim to facilitate researcher compliance with applicable laws and guidelines and encourage the harmonization of regulatory frameworks and research governance. Central recommendations are summarized in [Box 3](#). Though these recommendations focus on persons with dementia, they may well serve as a model for consent to research and data sharing involving adults with other conditions affecting decision-making capacity (e.g., stroke and traumatic brain injury), with appropriate modifications and patient engagement. Future guidance is needed for related decision-making contexts, such as when to provide family members with access to the genomic- and health-related data of persons with dementia and how to handle the return of individual results from dementia research.

#### Acknowledgments

The authors would like to thank Vasiliki Rahimzadeh for her invaluable assistance with background research and coordination. They would also like to thank Fritze Kristensen, Ann Kolanowski, Manuel Menendez, Jean Georges and Helen Rochford Brennan for their thoughtful input on these recommendations. We also gratefully acknowledge the financial support of Genome Quebec, Genome Canada, the Government of Canada, the Ministère de l'Économie, Innovation et Exportation du Québec (Can-SHARE grant 141210), and the Canada Research Chair in Law and Medicine. Serge Gauthier is a member of the ELSI committee of Canadian Consortium on Neurodegeneration in Aging, which is funded by the Canadian Institute of Health Research.

## Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jalz.2018.05.011>.

### RESEARCH IN CONTEXT

1. **Systematic review:** This manuscript is based on a scoping literature review covering previous systematic reviews, empirical studies of stakeholder perspectives, and regulatory and ethical analyses, as well as a comparative analysis of international, regional and national (eight countries) law and policy frameworks.
2. **Interpretation:** This manuscript, drawing on human rights developments, integrates analysis and recommendations across a range of consent issues in dementia research: legal authority, decision-making support, planning in advance, ethical representation, and capacity assessment.
3. **Future directions:** This manuscript identifies areas for future exploration: (a) clarifying who can act as the legally authorized representative for research across jurisdictions; (b) adapting consent supports for persons with dementia; (c) improving the uptake and accuracy of advance planning tools; (d) developing principles for research related decision-making by representatives; and (e) developing and validating capacity assessment tools for persons with dementia participating in data-intensive health research.

## References

- [1] Organisation for Economic Co-operation and Development (OECD). Recommendation of the OECD Council on Health Data 2017. Paris: Governance; 2017.
- [2] Council for International Organizations of Medical Sciences (CIOMS), with the World Health Organization (WHO). International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva: CIOMS; 2016.
- [3] World Medical Association (WMA). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects; 2013.
- [4] Joly Y, Feze IN, Song L, Knoppers BM. Comparative approaches to genetic discrimination: chasing shadows? *Trends Genet* 2017; 35:299–302.
- [5] Global Alliance for Genomics and Health. A federated ecosystem for sharing genomic, clinical data. *Science* 2016;352:1278–80.
- [6] ParisAddressing Dementia: the OECD Response Organisation for Economic Co-operation and Development (OECD). Paris: OECD Publishing; 2015.
- [7] Grady C. Enduring and emerging challenges of informed consent. *N Engl J Med* 2015;372:855–62.
- [8] Jongsma K, Bos W, Van de Vathorst S. Morally relevant similarities and differences between children and dementia patients as research subjects: representation in legal documents and ethical guidelines. *Bioethics* 2015;29:662–70.
- [9] United Nations General Assembly. Convention on the Rights of Persons with Disabilities. New York; 2006.
- [10] Karlawish J, Rubright J, Casarett D, Cary M, Ten Have T, Sankar P. Older adults' attitudes toward enrollment of non-competent subjects participating in Alzheimer's research. *Am J Psychiatry* 2009; 166:182–8.
- [11] Global Alliance for Genomics and Health. Regulatory and Ethics Toolkit. Available at: <https://www.ga4gh.org/ga4gh toolkit/regulatoryandethics/>. Accessed July 4, 2018.
- [12] Knopman D, Alford E, Tate K, Long M, Khachaturian AS. Patients come from populations and populations contain patients. A two-stage scientific and ethics review: the next adaptation for single institutional review boards. *Alzheimers Dement* 2017;13:940–6.
- [13] Robillard JM, Feng TL. When patient engagement and research ethics collide: lessons from a dementia forum. *J Alzheimers Dis* 2017; 59:1–10.
- [14] Global Alliance for Genomics and Health. Framework for Responsible Sharing of Genomic and Health Related Data 2014. Available at: <https://www.ga4gh.org/ga4gh toolkit/regulatoryandethics/>. Accessed May 11, 2017.
- [15] United Nations General Assembly. Universal Declaration of Human Rights. Paris; 1948.
- [16] Global Alliance for Genomics and Health. Consent Policy 2015. Available at: <https://www.ga4gh.org/ga4gh toolkit/regulatoryandethics/>. Accessed May 11, 2017.
- [17] Thorogood A, Deschênes St-Pierre C, Knoppers BM. Substitute consent to data sharing: a way forward for international dementia research? *J Law Biosci* 2017;4:133–58.
- [18] United Nations. Principles for Older Persons (Resolution 46/91). New York; 1991.
- [19] Council of the European Union. Regulation 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. 2014.
- [20] Shepherd V. Research involving adults lacking capacity to consent: the impact of research regulation on “evidence biased” medicine. *BMC Med Ethics* 2016;17:55.
- [21] Ries NM, Thompson KA, Lowe M. Including people with dementia in research: an analysis of Australian ethical and legal rules and recommendations for reform. *J Bioeth Inq* 2017;14:359–74.
- [22] Murphy K, Jordan F, Hunter A, Cooney A, Casey D. Articulating the strategies for maximising the inclusion of people with dementia in qualitative research studies. *Dementia (London)* 2015;14:800–24.
- [23] United Nations Educational, Scientific, and Cultural Organization (UNESCO). Universal Declaration on Bioethics and Human Rights. Paris; 2005.
- [24] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Guideline for Good Clinical Practice E6(R1). 1996.
- [25] International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). Guideline on Genomic Sampling and Management of Genomic Data - E18. 2017.
- [26] Togni E, Dierickx K, Porteri C. Participation in biobanks for research by incapacitated adults: review and discussion of current guidelines. *Int J Geriatr Psychiatry* 2014;29:670–81.
- [27] United States Department of Health & Human Services. Federal policy for the protection of human subjects. Final rule. *Fed Regist* 2017; 82:7149–274.
- [28] Council of the European Union. Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on

- the free movement of such data, and repealing Directive 95/46/EC. 2016.
- [29] Rothstein MA, Knoppers BM, Harrell HL. Comparative approaches to biobanks and privacy. *J Law Med Ethics* 2016;44:161–72.
- [30] Deetjen U, Meyer ET, Schroeder R. *Big Data for Advancing Dementia Research*. Paris: OECD Publishing; 2015.
- [31] Committee on the Rights of Persons with Disabilities, General Comment No. 1 on the right to equal recognition before the law. 2014.
- [32] Stainton T. Supported decision-making in Canada: principles, policy, and practice. *Res Pract Intellect Dev Disabil* 2016;3:1–11.
- [33] Council of Europe, Committee of Ministers, Recommendation No. R (99) 4 of the Committee of Ministers to member states on principles concerning the legal protection of incapable adults. 1999.
- [34] Derse AR, Spelley R. Ethical and regulatory considerations regarding enrollment of incompetent adults in more than minimal risk research as compared with children. *Am J Bioeth* 2015;15:68–9.
- [35] Dunn LB, Fisher SR, Hantke M, Appelbaum PS, Dohan D, Young JP, et al. “Thinking about it for somebody else”: Alzheimer’s disease research and proxy decision makers’ translation of ethical principles into practice. *Am J Geriatr Psychiatry* 2013;21:337–45.
- [36] Bravo G, Kim SY, Dubois MF, Cohen CA, Wildeman SM, Graham JE. Surrogate consent for dementia research: factors influencing five stakeholder groups from the SCORES study. *IRB* 2013;35:1–11.
- [37] De Vries R, Ryan KA, Stanczyk A, Appelbaum PS, Damschroder L, Knopman DS, et al. Public’s approach to surrogate consent for dementia research: cautious pragmatism. *Am J Geriatr Psychiatry* 2013; 21:364–72.
- [38] Alzheimer Europe. *Informed Consent to Dementia Research 2012*. Luxembourg: Alzheimer’s Society, 2012. Available at: <http://www.alzheimer-europe.org/Ethics/Ethical-issues-in-practice/Ethics-of-dementia-research/Informed-consent-to-dementia-research>. Accessed May 11, 2017.
- [39] Bioethics Commission. *Gray Matters (volume 2): Topics at the Intersection of Neuroscience, Ethics, and Society*; 2015.
- [40] Porter C, Petrini C. Research involving subjects with Alzheimer’s disease in Italy: the possible role of family members. *BMC Med Ethics* 2015;16:12.
- [41] Galeotti F, Vanacore N, Gainotti S, Izzicupo F, Menniti-Ippolito F, Petrini C, et al. How legislation on decisional capacity can negatively affect the feasibility of clinical trials in patients with dementia. *Drugs Aging* 2012;29:607–14.
- [42] United Nations Economic, Social and Cultural Organisation (UNESCO). *Universal Declaration on the Human Genome and Human Rights*; 1997.
- [43] Onyemelukwe C. Neuroscience research involving older persons in Canada: some legal and neuroethical concerns. *Med law* 2013; 32:389–422.
- [44] Pachana NA, Liddle J, Peel NM, Beattie E, Juang C, Knight BG. Can we do better? Researchers’ experiences with ethical review boards on projects with later life as a focus. *J Alzheimers Dis* 2015; 43:701–7.
- [45] Prusaczyk B, Cherney SM, Carpenter CR, DuBois JM. Informed consent to research with cognitively impaired adults: transdisciplinary challenges and opportunities. *Clin Gerontol* 2017;40:63–73.
- [46] Simpson AR. Barriers and facilitators to the consent process in a study of complex genetic factors. *Am J Bioeth* 2015;15:89–90.
- [47] Sweet L, Adamis D, Meagher DJ, Davis D, Currow DC, Bush SH, et al. Ethical challenges and solutions regarding delirium studies in palliative care. *J Pain Symptom Manage* 2014;48:259–71.
- [48] Diener L, Hugonot-Diener L, Alvino S, Baeyens JP, Bone MF, Chirita D, et al. Guidance synthesis. Medical research for and with older people in Europe: proposed ethical guidance for good clinical practice: ethical considerations. *J Nutr Health Aging* 2013;17:625–7.
- [49] Nishimura A, Carey J, Erwin PJ, Tilburt JC, Murad MH, McCormick JB. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. *BMC Med Ethics* 2013;14:28.
- [50] Dewing J. Process consent and research with older persons living with dementia. *Res Ethics Rev* 2008;4:59–64.
- [51] Black BS, Wechsler M, Fogarty L. Decision Making for participation in dementia research. *Am J Geriatr Psychiatry* 2013;21:355–63.
- [52] Kolanowski A, Mulhall P, Yevchak A, Hill N, Fick D. The triple challenge of recruiting older adults with dementia and high medical acuity in skilled nursing facilities. *J Nurs Scholarsh* 2013;45:397–404.
- [53] Heesters AM, Buchman DZ, Anstey KW, Bell JA, Russell BJ, Wright L. Power of attorney for research: the need for a clear legal mechanism. *Public Health Ethics* 2016;10:100–4.
- [54] Wood F, Prout H, Bayer A, Duncan D, Nuttall J, Hood K, et al. Consent, including advanced consent, of older adults to research in care homes: a qualitative study of stakeholders’ views in South Wales. *Trials* 2013;14:247.
- [55] Gennet É, Kressig RW. Chapitre 7. Les personnes âgées vulnérables dans les recherches biomédicales: quelles réponses du droit européen? [Vulnerable older people in biomedical research: how does European law respond?]. *J Int Bioethique* 2016;27:115–44.
- [56] Andorno R, Gennet E, Jongsma K, Elger B. Integrating advance research directives into the European legal framework. *Eur J Health Law* 2016;23:158–73.
- [57] Jongsma K, van de Vathorst S. Advance directives in dementia research: the opinions and arguments of clinical researchers— an empirical study. *Res Ethics* 2015;11:4–14.
- [58] Buller T. Advance consent, critical interests and dementia research. *J Med Ethics* 2015;41:701–7.
- [59] Warner J, Nomani E. Giving consent in dementia research. *Lancet* 2008;372:183–5.
- [60] Bravo G, Arcand M, Blanchette D, Boire-Lavigne AM, Dubois MF, Guay M, et al. Promoting advance planning for health care and research among older adults: a randomized controlled trial. *BMC Med Ethics* 2012;13:1.
- [61] Wildeman S, Dunn LB, Onyemelukwe C. Incapacity in Canada: review of laws and policies on research involving decisionally impaired adults. *Am J Geriatr Psychiatry* 2013;21:314–25.
- [62] Yarborough M. Inconsistent approaches to research involving cognitively impaired adults: why the broad view of substituted judgment is our best guide. *Am J Bioeth* 2015;15:66–7.
- [63] Carney T. Supported decision-making for people with cognitive impairments: an Australian perspective? *Laws* 2015;4:37–59.
- [64] Harding R. The rise of statutory wills and the limits of best interests decision-making in inheritance. *Mod Law Rev* 2015;78:945–70.
- [65] Bravo G, Wildeman S, Dubois MF, Kim SY, Cohen C, Graham J, et al. Substitute consent practices in the face of uncertainty: a survey of Canadian researchers in aging. *Int Psychogeriatr* 2013;25:1821–30.
- [66] Dunn LB, Palmer BW. When does therapeutic misconception affect surrogates’ or subjects’ decision making about whether to participate in dementia research? *AMA J Ethics* 2017;19:678.
- [67] Kim SYH, Kim HM, Ryan KA, Appelbaum PS, Knopman DS, Damschroder L, et al. How important is “accuracy” of surrogate decision-making for research participation? *PLoS One* 2013; 8:e54790.
- [68] Arstein-Kerslake A, Flynn E. The general comment on Article 12 of the convention on the Rights of Persons with Disabilities: a roadmap for equality before the law. *Int J Human Rights* 2016;20:471–90.
- [69] Palmer BW, Harmell AL, Pinto LL, Dunn LB, Kim SY, Golshan S, et al. Determinants of capacity to consent to research on Alzheimer’s disease. *Clin Gerontol* 2017;40:24–34.
- [70] Trachsel M, Hermann H, Biller-Andorno N. Cognitive fluctuations as a challenge for the assessment of decision-making capacity in patients with dementia. *Am J Alzheimers Dis Other Dement* 2015;30:360–3.
- [71] Palmer BW, Savla GN, Roesch SC, Jeste DV. Changes in capacity to consent over time in patients involved in psychiatric research. *Br J Psychiatry* 2013;202:454–8.
- [72] Palmer BW, Ryan KA, Kim HM, Karlawish JH, Appelbaum PS, Kim SY. Neuropsychological correlates of capacity determinations

- in Alzheimer disease: implications for assessment. *Am J Geriatr Psychiatry* 2013;21:373–81.
- [73] Kim SYH, Karlawish JH, Kim HM, Wall IF, Bozoki AC, Appelbaum PS. Preservation of the capacity to appoint a proxy decision maker implications for dementia research. *Arch Gen Psychiatry* 2011;68:214–20.
- [74] Seaman JB, Terhorst L, Gentry A, Hunsaker A, Parker LS, Lingler JH. Psychometric properties of a decisional capacity screening tool for individuals contemplating participation in Alzheimer's disease research. *J Alzheimers Dis* 2015;46:1–9.
- [75] Duron E, Boulay M, Vidal JS, El Bchiri J, Fraisse ML, Rigaud AS, et al. Capacity to consent to biomedical research's evaluation among older cognitively impaired patients. A study to validate the University of California Brief Assessment of Capacity to Consent questionnaire in French among older cognitively impaired patients. *J Nutr Health Aging* 2013;17:385–9.
- [76] Appelbaum PS, Grisso T. *MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR)* 2001. Sarasota, Florida: Professional Resource Press/Professional Resource Exchange; 2001.
- [77] Lingler JH, Seaman JB, Parker LS. False positives, outliers, and other considerations in decisional capacity screening for research consent. *J Alzheimers Dis* 2015;46:15–6.
- [78] Jeste DV, Palmer BW, Appelbaum PS, Golshan S, Glorioso D, Dunn LB, et al. A new brief instrument for assessing decisional capacity for clinical research. *Arch Gen Psychiatry* 2007; 64:966–74.