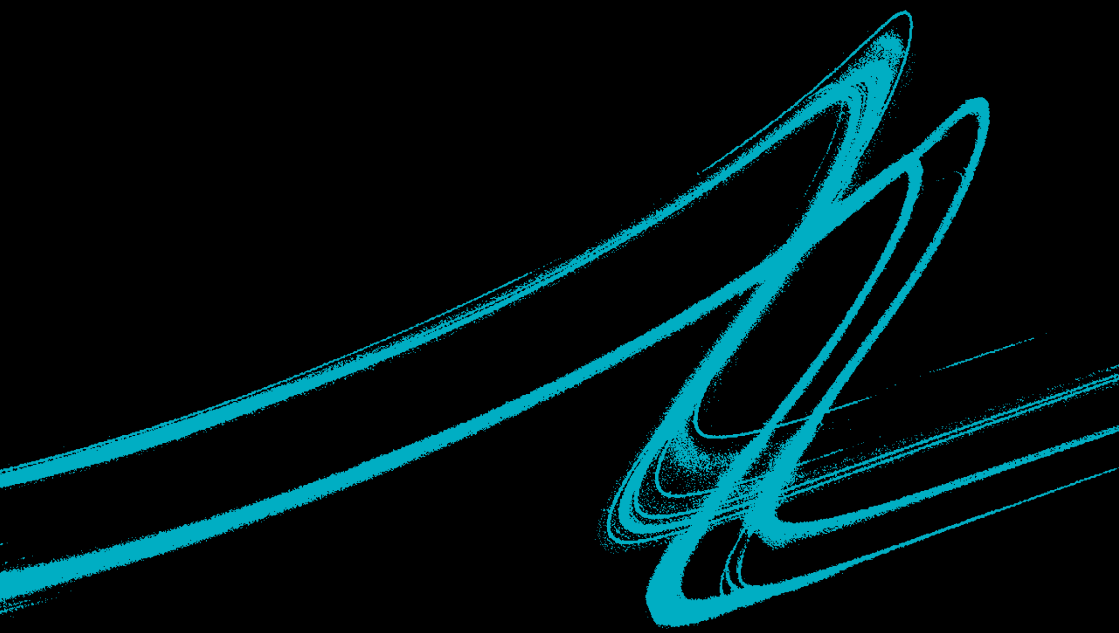
# EMERGING TECHNOLOGIES FOR DIAGNOSING ALZHEIMER'S DISEASE

## INNOVATING WITH CARE

EDITED BY MARIANNE BOENINK, HARRO VAN LENTE, ELLEN MOORS



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Medicine, health care, and the wider social meaning and management of health are undergoing major changes. In part this reflects developments in science and technology, which enable new forms of diagnosis, treatment and delivery of health care. It also reflects changes in the locus of care and the social management of health. Locating technical developments in wider socio-economic and political processes, each book in the series discusses and critiques recent developments in health technologies in specific areas, drawing on a range of analyses provided by the social sciences. Some have a more theoretical, some a more applied focus but all draw on recent research by the authors. The series also looks toward the medium term in anticipating the likely configurations of health in advanced industrial society and does so comparatively, through exploring the globalization and internationalization of health.

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# Emerging Technologies for Diagnosing Alzheimer's Disease

## Innovating with Care

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# Series Editors' Introduction

Medicine, health care, and the wider social meaning and management of health are undergoing major changes. In part this reflects developments in science and technology, which enable new forms of diagnosis, treatment, and the delivery of health care. It also reflects changes in the locus of care and burden of responsibility for health. Today, genetics, informatics, imaging, and integrative technologies, such as nanotechnology, are redefining our understanding of the body, health, and disease; at the same time, health is no longer simply the domain of conventional medicine, nor the clinic. The 'birth of the clinic' heralded the process through which health and illness became increasingly subject to the surveillance of medicine. Although such surveillance is more complex, sophisticated, and precise—as seen in the search for 'predictive medicine'—it is also more provisional, uncertain, and risk laden.

At the same time, the social management of health itself is losing its anchorage in collective social relations and shared knowledge and practice, whether at the level of the local community or through state-funded socialised medicine. This individualisation of health is both culturally driven and state sponsored, as the promotion of 'self-care' demonstrates. The very technologies that redefine health are also the means through which this individualisation can occur—through 'e-health', diagnostic tests, and the commodification of restorative tissue, such as stem cells, cloned embryos, and so on.

This series explores these processes within and beyond the conventional domain of 'the clinic', and asks whether they amount to a qualitative shift in the social ordering and value of medicine and health. Locating technical developments in wider socio-economic and political processes, each book discusses and critiques recent developments within health technologies in specific areas, drawing on a range of analyses provided by the social sciences.

The series has already published 15 books that have explored many of these issues, drawing on novel, critical, and deeply informed research undertaken by their authors. In doing so, the books have shown how the boundaries between the three core dimensions that underpin the whole series—health, technology, and society—are changing in fundamental ways. Through its focus on innovative diagnostic techniques being developed for Alzheimer's disease, this addition to the series provides new insights on these three core dimensions and their interaction, especially how innovation and care happen in many places beyond the clinic.

The editors of this collection have brought together a talented and diverse group of scholars, all concerned with the challenges posed by innovations in the diagnosis of Alzheimer's disease. The contributions highlight the instability and complexity of the challenges, as there remain controversies around the definition of Alzheimer's and certainly around its causes and diagnosis. Furthermore, there is no agreed-upon set of steps that patients or clinicians can take to prevent or treat the symptoms. Such uncertainty raises profound ethical questions about the desirability of diagnostic innovation—questions to which there are no simple answers. The editors and contributors show how values and practices underpin the meaning and use of diagnostic tools, but in doing so do not set out to judge the desirability of these tools for Alzheimer's. However, they do set out a number of conditions for conducting responsible innovation, with care and attention to the needs of patients and their loved ones, and how this should shape the work of clinicians and researchers. They also demonstrate how care for present and future concerns becomes entangled in innovation practices.

As series editors, we are confident that this collection will be of interest and value to different audiences around the world, including policymakers and researchers concerned with innovation, health, and social policies and also those involved in fostering responsible innovation in genetics, biology, informatics, and the neurosciences.

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# Notes on Contributors

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**Marianne Boenink, Ph.D.** is an assistant professor at the Department of Philosophy, University of Twente in the Netherlands. She has a background in health sciences and philosophy. Her research focuses on the conceptual, hermeneutical, and normative analysis of visions of the future of biomedicine and health care, and how these visions shape actual practices of biomedical innovation and vice versa. She is particularly interested in science and technologies pursuing 'personalized and predictive medicine'. She was project leader of the project 'Responsible early diagnostics for Alzheimer's disease', funded by the NWO programme 'Responsible Innovation', from which this volume emerged. Currently she leads a project on the early ethical and social assessment of new technologies to prognosticate patients in coma (also funded by NWO) and a Zon-MW project on the effects of involving patients and caregivers in dementia biomarkers research.

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**Harro van Lente, Ph.D.** is Professor of Science and Technology Studies and head of department at Maastricht University. He is one of the founding fathers of the Sociology of Expectations, which studies the dynamics of expectations in the development of technology. Van Lente has published widely on technology dynamics, innovation policy, and technology assessment. Since 2011, he is programme director of Technology Assessment at NanoNextNL, the Dutch nanotechnology consortium. In 2013, he was Visiting Professor at the University of California in Santa Barbara (UCSB).

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**Ellen Moors, Ph.D.** is Professor of Sustainable Innovation at Innovation Studies Group, Copernicus Institute at Utrecht University, Netherlands. Her research focuses on smart regulation, implementation, and governance of pharmaceutical innovations (biologics, biosimilars), new modes of governing pharmacovigilance, technology dynamics of life sciences innovations, understanding the role of users and institutions in emerging technologies, and designing sustainable or responsible innovation business models in the life sciences. She has received various grants on societal, regulatory, and governance aspects of life sciences research, amongst others in the field of emerging genomics developments, orphan drug development, and early diagnostics of Alzheimer's disease. She is a senior fellow at the Innogen Institute for Innovation Generation in Life Sciences in Edinburgh, and a visiting professor at the Fraunhofer Institute for Systems & Innovation Research in Karlsruhe.

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life: Anthropological sensibilities, STS interferences, and possibilities for action in care', *Science, Technology & Human Values*; 36 (5); and I. Moser and H. Thygesen (2015) 'Exploring possibilities in telecare for ageing societies' in M. Barnes et. al. (eds.) *Ethics of Care: Critical International Perspectives* (Bristol: Policy Press).

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**Julia Swallow** submitted an ESRC-funded Ph.D. at the University of Leeds in October 2015. She is now a postdoctoral research associate based in the Academic Unit of Dental Public Health in the School of Clinical Dentistry and the Department of Sociological Studies at the University of Sheffield. The project titled 'The Significance of the Mouth in Old Age' aims to discover and explain the significance of the mouth in old age by examining how the diversity of experiences of oral health and health care across the life course might impact

experiences of oral health in later life. Her scholarly interests range widely and include medicines, health and illness; age and the ageing process; (bio)medical technologies and genetics; and professional practice in healthcare.

**Peter J. Whitehouse, M.D., Ph.D.** is Professor of Neurology at Case Western Reserve University, Professor of Medicine at the University of Toronto at Baycrest Health Sciences, and President of Intergenerational Schools International. He is an internationally known expert on dementia and ageing. He completed an M.D.-Ph.D. in psychology and a Fellowship in Neuroscience and Psychiatry at Johns Hopkins University. In 1986, he moved to Case Western Reserve University to develop the University Alzheimer Center. In 1999, he founded with his wife, Catherine, The Intergenerational School, a unique public, multi-age, community school (www.tisonline.org). He is active as a geriatric neurologist, cognitive scientist, environmental ethicist, and photographer. He is also involved in visual arts, dance, and music organisations globally. He is co-author of *The Myth of Alzheimer's: What you aren't being told about today's most dreaded diagnosis* (www.themythofalzheimers.com) and hundreds of other papers and books.

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# List of Abbreviations

| | |
|---|---|
| AA | Alzheimer's Association |
| Aβ | Amyloid-beta |
| ACE-111 | Addenbrooke's Cognitive Examination Version Three |
| AD | Alzheimer's Disease |
| AD-C | Alzheimer's Disease Clinical observations |
| AD-P | Alzheimer's Disease Pathological observations |
| ADAS | Alzheimer's Disease Assessment Scale-Cognition |
| ADCS | Alzheimer's Disease Cooperative Study |
| ADI | Alzheimer's Disease International |
| AEDA | Alzheimer's Early Detection Alliance |
| ALSPAC | Avon Longitudinal Study of Parents and Children |
| AMC | Amsterdam Medical Center |
| AMTS | Abbreviated Mental Test Score |
| ANL | Alzheimer Nederland |
| APOE | Apolipoprotein E |
| CBO | Dutch Institute for Health Care Improvement |
| CFAS | Cognitive Function and Ageing Study |
| CloCKMe | Computer-Assisted Screening Tool for Dementia |
| CoEN | Cooperation between Centers of Excellence in Neurodegenerative disease research |
| CogSelfTest | Computerised Cognitive Testing for Older Adults |
| CQUIN | National Dementia Commissioning for Quality and Innovation |

| | |
|---|---|
| CSF | CerebroSpinal Fluid |
| CT | Computerised Tomography |
| CTMM | Centre for Translational Molecular Medicine |
| DAT | Dementia of the Alzheimer's Type |
| DNA | Deoxyribonucleic Acid |
| DPUK | Dementias Platform UK |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| EBM | Evidence-Based Medicine |
| ECG | Electrocardiogram |
| EDPI | European Dementia Prevention Initiative |
| ELSI | Ethical Legal and Social Issues |
| EU | European Union |
| FDA | US Food and Drug Administration |
| FFB | Food for the Brain |
| GP | General Practitioner |
| GPOCG | General Practitioner Assessment of Cognition |
| HTA | Health Technology Assessment |
| IQCODE | Informant Questionnaire on Cognitive Decline in the Elderly |
| IV | Interviewee |
| JDR | Join Dementia Research |
| JPND | Joint Programming Neurodegenerative Diseases |
| KOL | Key Opinion Leader |
| LeARN | Leiden Alzheimer Research Nederland |
| MCI | Mild Cognitive Impairment |
| MID | Multi-Infarct Dementia |
| MIS | Memory Impairment Screen |
| MMSE | Mini-Mental State Examination |
| MoCA | Montreal Cognitive Assessment Test |
| MRC | Medical Research Council |
| MRC-CFAS | MRC Cognitive Function and Ageing Study |
| MRI | Magnetic Resonance Imaging |
| NIA | National Institute on Ageing |
| NIA-AA | National Institute on Ageing Alzheimer's Association |
| NHG | Dutch College of General Practitioners |
| NHS | National Health Service |
| NIHR | National Institute for Health Research |
| NMDA | N-methyl-d-aspartate receptor |

| | |
|---|---|
| NPO | Neuropsychological examination |
| NWO | Netherlands Organisation for Scientific Research |
| PET | Positron Emission Tomography |
| POC | Point-of-Care |
| PPP-medicine | Personalised, Predictive, and Preventive medicine |
| QUALYs | Quality-Adjusted Life Years |
| R&D | Research & Development |
| RNA | Ribonucleic Acid |
| SAGE | Self-Administered Gerocognitive Exam |
| SPECT | Single Photon Emission Computed Tomography |
| STS | Science and Technology Studies |
| TIS | The Intergenerational School |
| TYM | Test Your Memory |
| WHO | World Health Organization |
| 7T | Seven Tesla |

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# 1

# Emerging Technologies for Diagnosing Alzheimer's Disease: Innovating with Care

Marianne Boenink, Harro van Lente, and Ellen Moors

Public announcements of breakthroughs in diagnosing Alzheimer's disease regularly appear in newspapers, radio and television programmes, and on the web. The types of diagnostic tests recommended range from MRI and PET scans of the brain, to spinal taps, blood tests, simple eye cell tests, and even smelling peanut butter. Most of these tests measure so-called 'biomarkers': certain molecules in the body that are linked with the pathology thought to underlie Alzheimer's disease. The usual claim is that these tests are more reliable, less burdensome, faster and/or cheaper than

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existing diagnostic procedures. But most importantly, the novel tests are thought to reveal Alzheimer's at an early stage, possibly even years before the onset of symptoms.

Early diagnosis of Alzheimer's disease (or AD) is indeed an important, worldwide goal of current research and development in the Alzheimer field (Lock 2013). However, this goal raises controversy, in society, in healthcare, even among those active in Alzheimer research themselves. Proponents argue that an early diagnosis may help to plan one's future life—for example, by deciding whether to continue living in one's own house, by making care arrangements in a timely manner, and possibly, by signing a living will guiding decision making with regard to end of life. Moreover, medication is thought to be possibly more effective when started early. An early diagnosis, followed by early medication, might then help to keep the disease at bay. However, opponents counter that this hope is futile. Current medication slows down the disease, but does not cure it. Early diagnosis and early medication, thus, probably will just extend the time spent on worrying about one's mental capacities. What is the use of an early diagnosis, critics argue, if nothing can be done about the disease? Some even suspect that the whole search for early diagnostics is largely driven by an attempt of 'big pharma' to increase the market for their AD drugs. Whatever the motives driving R&D, the response to news items or blogs announcing diagnostic breakthroughs shows that people do indeed hold different views about the desirability of early diagnosis for AD.

## The Desirability of Biomarker Diagnostics of Alzheimer's Disease

From an ethical and societal perspective, the desirability of early diagnostics for AD is, then, not self-evident. As in other cases of emerging technologies, novel tests for AD raise the question whether we should do everything we can. Should early diagnostics for AD be introduced in society? This book delves into the issues raised by the promises of early diagnostics for AD by asking *under which conditions emerging diagnostic technologies for AD could be considered a responsible innovation*. This question entails more than a reflection on the ethical and/or social acceptability

of novel tests. In our view, the question whether it is ethically and socially acceptable to introduce early diagnosis for AD is important, but not sufficient. Three additional questions need to be addressed as well. First, we need to inquire how 'Alzheimer's disease' gets defined in discussions about early diagnostics in the first place, since it refers to an equivocal, poorly delineated phenomenon. Second, it is important to critically assess the plausibility of the promises and expectations about the new diagnostic technologies to avoid speculative ethics. And last but not least, if we are interested in the ethical and social acceptability of these emerging technologies, we should not only identify and weigh social and ethical values, but we should also examine the capacity of contemporary society to productively respond to the diversity of viewpoints, concerns, and interests voiced with regard to these technologies. We will briefly discuss these three questions, and then, return to the ambition of responsible innovation.

According to historians and philosophers of medicine, the phenomenon of AD is notoriously elusive. The German psychiatrist Alois Alzheimer, in 1906, during an autopsy, identified 'plaques and tangles' in the brains of a patient who had suffered from what was then known as 'senile dementia' at a relatively young age. Whereas the plaques had been seen before, the tangles were a new phenomenon. It was actually Alzheimer's boss, Emil Kraepelin, who—in the 1910 edition of his famous classification of psychiatric diseases—coined the term 'Alzheimer's disease'. AD was defined as a specific form of dementia, diagnosed in the case of a young age of onset of the dementia symptoms *and* when, at autopsy, both plaques and tangles were found. (The presence of plaques and tangles has been part of the gold standard for diagnosing AD ever since.) The disease has been distinguished from other forms of dementia, that is, by its pathological features. Since its inception, however, the assumed relation between clinical features and pathological signs of the disease has been shifting time and again. As the historian Jesse Ballenger (2006) has shown, both the definition of the clinical picture and of the pathology of AD have evolved. Even more importantly, whatever the definitions used, the relation between clinical and pathological phenomena has never been unambiguous. Plaques and tangles can be absent in persons clinically diagnosed with AD, whereas they may be present in the brain of people who did not experience any trouble during their lifetime.

Clarifying the relationship between clinical features and pathology is complicated, for various reasons. First, usually, there is a time lag between clinical observations (during life) and pathological observations (at autopsy). During life, we can only see the *dementia* symptoms, not the *AD* pathology. Part of the promise of current research is that molecular biomarkers will help to overcome this lag, because they can show pathology *in vivo*. However, ageing is a confounding influence. Are the clinical and pathological observations characteristic of 'normal ageing' or of a disease? Moreover, the clinical symptoms of AD are various and not very specific. They may signify others types of dementia. And in particular, older patients often suffer from other diseases (they have 'co-morbidity'). To what extent current candidate biomarkers are specific for AD is as yet unclear. All this variety has brought some researchers to the conclusion that AD should not be seen as a unified disease, but as a diffuse *syndrome* of several phenomena (Richards and Brayne 2010; Richard et al. 2012). These phenomena, moreover, are not just present or absent, but can show different grades of severity. This goes both for the clinical and the pathological manifestations. In sum, suggesting that biomarker testing can *reveal AD* is a vague claim, to say the least. Without further clarification, such claims ignore the ambiguity of the label and the complexity of the associated phenomena. Since assessing the desirability of diagnosing AD is impossible if we do not know *what* is being diagnosed, this volume will pay ample attention to the different meanings of the AD label in different contexts. This is also the reason we do not limit attention to AD, but focus on emerging AD diagnostics in the broader context of diagnosing and dealing with dementia.

The second task is to critically assess the promises or expectations about how easy, convenient, early, and reliable diagnosing AD will be in the future, due to new technologies. Clearly, clarifying the meaning of AD in such claims is a first step, as well as asking what exactly is made visible by the new technology, and what this tells about the prospects of the individuals tested. The rhetoric of breakthroughs and revolutions is typical for emerging science and technology in general, but the field of AD research seems particularly prone to it. AD is perceived by many as an awful disease that they dread, and this anxiety is reinforced by predictions about rising numbers of AD patients in the near future—frequently

expressed in terms of an Alzheimer 'tsunami' or an 'epidemic'. With the awareness that decades of R&D have not resulted in an effective cure, any positive news from the R&D trenches is easily framed (by researchers, media, politics, policymakers, and public alike) as a reason for optimism and hope. For discussions about the desirability of early diagnosis, however, it is crucial to determine what these promises and expectations are actually based on. If a targeted biomarker is tested only in mice, it may be rather premature to claim that early diagnosis is near. In a similar vein, if the candidate biomarker is considered to be a predecessor of the plaques associated with AD, what does that mean for people suffering from complaints, but not displaying plaques and tangles? And will biomarker diagnostics be a 'stand-alone' test offering a yes/no verdict, as often suggested, or will it rather be an 'add on' to the existing diagnostic repertoire? Assessing the plausibility of the promises and expectations raised on behalf of emerging diagnostic technologies helps to avoid what has been called 'speculative ethics' (Nordmann 2007; Nordmann and Rip 2009; Lucivero et al. 2011). It is a prerequisite for down-to-earth reflection and debate on the ethical and societal desirability of emerging biomarker tools.

Third, asking about the ethical and social acceptability of introducing emerging technologies for diagnosing AD suggests that after weighing the pros and cons, only two answers are possible: yes or no; end of story. Moreover, the implicit assumption is that society can—and will—act on such an ethical verdict, as if there is a central gatekeeper determining whether the technology should be allowed. This seems an overestimation of both the willingness and the ability of current societies to steer innovation, or, if you prefer, an underestimation of the complexity of innovation processes. It is not very likely, for example, that contemporary governments will forbid industry from pursuing specific goals in R&D, unless there are serious concerns to health, environment, and safety. Diagnostic test providers can also easily avoid self-regulation by doctors (e.g., in the form of clinical guidelines for diagnosing AD) by offering direct-to-consumer-testing via the internet. More importantly, aiming for a yes/no verdict neglects opportunities for shaping innovation processes and their products in a more desirable direction. It may result in an unproductive sequence of emerging innovations and ethical or societal rejection of such

innovations. Asking about conditions for responsible innovation allows us to bring into focus ways of shaping emerging technologies to align with society and its values, and at the same time to identify the actors (or actor groups) responsible for doing so.

## Responsible Innovation

Our choice to reflect on the desirability of emerging biomarker diagnostics for AD in terms of responsible innovation is in line with (and a product of) a growing interest in 'responsible innovation' more generally. The notion of responsible research and innovation (for reasons of brevity, from now on, referred to as 'responsible innovation') has recently emerged as a guiding concept in discussions about the science–society relationship—in particular in Europe and to a lesser extent in the USA. It is rooted in the observation that scientific and technological advances not only produce benefits, but may have unintended and undesirable impacts, and that regulating the products of these advances (e.g., by requiring risk assessment) is insufficient, and sometimes, impossible because of the uncertainties involved. By aiming for 'responsible innovation', attention is sought not only for the potential negative impacts of innovation, but also for the positive ones. To achieve an overall positive result, both the process and the products of scientific research, technology development, and implementation should be designed in such a way that they contribute to relevant and acceptable societal goals. To make science and technology align better with society, its values should be integrated into the full innovation trajectory. Finally, the concept of responsible innovation explicitly puts on the agenda the question who, in the largely collective and complex endeavour of innovation, should take care of what to work towards relevant and acceptable benefits.

The notion of responsible innovation, thus, refers to an overarching concern and a set of partly overlapping approaches and concomitant definitions. Currently, two definitions and frameworks are widely cited. The first is by Von Schomberg:

> Responsible Research and Innovation is a transparent, interactive process by which societal actors and innovators become mutually responsive to

> each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products (in order to allow a proper embedding of scientific and technological advances in our society). (Von Schomberg 2013, p. 63)

In this definition, responsible research and innovation designates the search for the right impacts of science and technology. Von Schomberg observes that shared criteria to determine what these 'right impacts' are, are not easy to identify in current pluralistic societies. However, he argues that the values democratically agreed upon in the Treaty of the European Union might serve as normative anchor points to decide what is ethically acceptable and socially desirable. These include scientific and technological advance, sustainable development, competitive social market economy, social justice, equality, solidarity, fundamental rights, and a high level of quality of life. As the definition indicates, both the process and the products of innovation need to be assessed in terms of these anchor points to ensure responsible research and innovation.

Von Schomberg developed his take on responsible research and innovation in the context of European research funding and research policymaking, and his approach addresses this level of policymaking in the first place. Some scholars have argued that these rather abstract principles offer less guidance for specific R&D projects (Stilgoe et al. 2013, p. 1577). It is, for instance, not clear how to identify which principles are at stake in a specific setting, nor how to interpret their meaning when it comes to decisions in a specific innovation trajectory, or how to balance them. The approach of responsible innovation proposed by Stilgoe, Owen, and Macnaghten is, therefore, more concerned with particular domains in science and technology. It was developed on the basis of an inventory of concerns recurring in public debates about new domains of science and technology. These target the products, the process, and the purpose of innovation, and responsible innovation in this approach is a way to embed deliberation on these issues in the innovation process. Stilgoe and colleagues define responsible innovation as follows:

> Responsible Innovation means taking care of the future through collective stewardship of science and innovation in the present. (Stilgoe et al. 2013, p. 1570)

This definition is rather open and does not refer to specific normative ideals, but to a caring, future-oriented attitude. Stilgoe and colleagues propose a framework of four integrated dimensions that might be helpful for guiding responsible innovation on the level of innovation governance, and also within R&D projects. Responsible innovation, in their view, consists of *anticipation* (systematic thinking about future developments and the uncertainties implied), *reflexivity* (both individual and institutional), *inclusion of stakeholders* to increase the public and moral legitimacy of decisions and outcomes of innovation (later labelled as 'deliberation', see Owen et al. 2013), and finally, *responsiveness*: a 'capacity to change shape or direction in response to stakeholder and public values and changing circumstances' (Stilgoe et al. 2013, p. 1572).

## Innovating with Care

The authors in this volume explore what it would mean to innovate responsibly in the domain of emerging technologies for diagnosing AD. In doing so, we aim to contribute not only to societal and policy debates about emerging diagnostics for AD, but also to academic and policy discussions about responsible innovation more generally. Obviously, interpreting the concept of responsible innovation for a specific domain such as AD diagnostics is not a straightforward task. As outlined above, it makes sense to conceive of responsible innovation as a set of interdependent and partly overlapping activities: anticipation of the meaning and potential impacts of early diagnostics, exploring the views and values of potential stakeholders, and enhancing the reflexivity as well as the responsiveness of the actors involved. Together, these activities contribute to an innovation process that takes into account the shared values emerging in this process. However, this starting point leaves ample room for different interpretations and specifications in practice. For a start, the relative importance and the order of the activities mentioned may differ. More subtle differences result from the way the activities are performed. How exactly should one go about stimulating anticipation, reflection, deliberation, and responsiveness in a specific setting? It is hard to briefly account for the choices made in this volume, but in general our approach has been guided by the desire to avoid two pitfalls in particular.

The first pitfall is to frame an envisioned innovation and its eventual impacts exclusively as a *future* concern. The concern with emerging, uncertain developments and their even more uncertain impacts makes responsible innovation discourse prone to looking forward only. In our view, this would downplay the importance of the present situation. Innovation is not introduced into a void; it transforms the world as we know it and the values realized in that world. Nor do the changes start only after a new technology has been introduced; promises and expectations raised may have an impact already on existing practices. To assess under which conditions emerging diagnostics of AD is desirable, then, we will pay careful attention to the *present*: what is it that might be improved, shifted, or lost by this innovation? What exactly are the positives (and negatives) realized in current practices of diagnosing AD? And where and how are actors working on improving these practices? Evaluating how (promises about) an innovation might affect diagnostic practices implies that we know what is at stake in those practices, but also, which other attempts to innovate them are ongoing.

The second pitfall is to assume that current values are easily accessible. As outlined above, current approaches of responsible innovation suggest that values can be identified either by looking for principles that have been explicitly agreed upon (such as those in the EU treaty), or by asking stakeholders to voice what is important to them. Both methods imply that values are given, discursive entities, which can be made explicit when necessary. However, as research from pragmatic ethics (Dewey 1902a, b; Keulartz et al. 2004), care ethics (Tronto 1993; Pols 2012, 2014), science and technology studies (Mol et al. 2010), and empirical philosophy of technology (Verbeek 2011) has made abundantly clear, values are embedded in human practices and are realized in ways of doing good, by using specific routines, concepts, and materials. If we separate values from their practical embedding, we risk a seriously impoverished view of what is at stake. When exploring the values strived for and realized in practice, then, we will make ample use of ethnographic and analytical methods, rather than asking stakeholders right away. The results of these explorations may not only inform, but also elicit subsequent stakeholder reflection and deliberation.

Overall, then, we will tackle the question of responsible innovation of biomarker diagnostics for AD in a thoroughly *practice-based* way. We

aim to do justice to the complex and intricate relations between values, interpretative frameworks, and social and material practices, both in the present and in the future, opened up by emerging technologies. Innovating responsibly, in our view, means that the richness and complexity of both current and potential future practices are acknowledged and handled with care. If we want emerging technologies for diagnosing AD to truly improve current practices of dealing with AD, we have to explore: (1) how current practices of diagnosing and living with AD imply specific views of the world and of what is (or is not) valuable, (2) how the aimed-for innovation(s) might alter these practices, and therewith, the complex web of *de facto* values, and (3) how innovation and practice can be aligned with each other in such a way that the result can be considered an improvement. We have dubbed our approach 'innovating with care', to emphasize that to be responsible, innovation should proceed in a perceptive and careful way.

While we do not propose a full-fledged, generic methodology or framework for responsible innovation, we believe that the ideas guiding our approach of innovating with care are relevant for other cases and fields of innovation as well. Our approach guides thinking about particular innovations and R&D projects by directing the way anticipation, reflection, inclusion/deliberation, and responsiveness are handled: by paying careful attention to the present as well as the future, and to the complex interrelations between values, interpretative frameworks, and social and material practices. This may be particularly useful for settings where, as in the AD field, ample controversy exists with regard to what 'good practice' is.

## Chapter Outline

This volume provides, then, observations, analyses and reflections that may inform any attempt to innovate with care in the field of AD diagnostics. It will not pass final, overall judgement on the desirability of such diagnostics, but it will point out the conditions to innovate responsibly in this specific area. Moreover, we will reflect on what this implies for responsible innovation in diagnostics, more generally. The book is divided into four parts and a concluding chapter.

Part I (*Biomedical Research on AD Diagnostics*: *Background and Trends*) reconstructs and analyses developments in biomedical research on the diagnosis of AD and dementia. It sketches how the field has evolved into the current state of affairs and discusses important visions, concepts, and research practices on AD and dementia. This sets the stage for a broader assessment of these developments in terms of 'responsible innovation' in the subsequent parts.

Peter Whitehouse (Chap. 2) outlines the historical developments in biomedical research on AD and dementia. He presents the developments in pharmaceutical research(in which he was personally involved) and discusses how the limitations of present drugs for AD are at the background of the recent attempts to diagnose AD at an earlier stage. He then explains why such research can be labelled 'irresponsible' because it suggests that earlier diagnosis is always for the better, and because it raises false hope with regard to the possibility of a (biomedical) cure. This shot across the bows is followed by a more elaborate discussion of the current state of affairs in biomedical AD research in the following chapters.

Annette Leibing (Chap. 3) explores the recent trend towards AD prevention. She reconstructs how the emergence of a cardiovascular logic, in combination with the emerging possibility of detecting presymptomatic biomarkers, has considerably impacted the conceptual frameworks used to interpret and deal with AD. An important question now is whether preventive interventions should focus on lifestyle, drugs, or both, and who has access to such interventions. In view of the complexities involved, she argues, both biomedical researchers and social science or humanities scholars should make an effort to distinguish short cuts from valid research.

Marianne Boenink (Chap. 4) analyses how current research to identify molecular biomarkers for AD strives to link biological observations with patient needs. To this end, she analyses how the interrelation of biological and clinical phenomena related to AD is conceptualized, pursued, and shaped in: (1) discourse on the future of medicine, (2) scientific literature on AD biomarkers and new guidelines for diagnosing the disease, and (3) the design of a specific biomarker research project. Since the aimed-for connections are rather elusive, biomarker research in practice easily slides into basic molecular biology research. She suggests

that strengthening both 'epistemic' and 'translational' responsibility in AD research might help to increase its relevance and usefulness for those who suffer from AD.

In Chap. 5, Richard Milne and Shirlene Badger examine a different strand of current AD research: the emergence of 'big data' initiatives and the related trend to re-purpose existing observational cohort studies of ageing populations. Current cohort research not only studies the development of AD and dementia, but also aims to create a source of participants for intervention trials. Milne and Badger argue that to give meaning to the idea of responsible research and innovation, more attention should be paid to the research practice of cohort studies and the establishment of responsive relations between researchers and participants. In particular, the role of interviewers, study coordinators, and research nurses in such studies offers valuable opportunities to truly care for the needs of research participants.

In Part II (*Diagnosing Alzheimer's Disease*: *Current Practices*), we delve into current practices of diagnosing AD and dementia, with a particular focus on the values embedded in these practices. As argued above, a good understanding of current practices is crucial to anticipate how emerging biomarker technologies may interact with these practices, and to reflect on what this would mean for the realization of values. Most of the hopeful discourse surrounding emerging AD diagnostics presupposes that current practice of diagnosing AD is (a) uniform and (b) deficient, because it is complex, time-consuming, and produces unreliable results. AD diagnostics is thought to produce a lot of uncertainty, both for the people diagnosed, their families, and the professionals involved—uncertainties that the emerging diagnostic tools are expected to resolve. In contrast, the authors in Part II highlight the plurality and complexity of current practices of diagnosing AD. They also show how AD diagnostics is evolving anyway, partly because of innovations outside the biomedical domain. As a result of this complexity and ongoing changes, the proposed introduction of biomarker tools is likely to have different impacts in different locations. Moreover, the problems innovations of diagnostics claim to solve need not be shared by all diagnostic practices alike.

Anna Laura van der Laan (Chap. 6) observes that current medical practice of diagnosing AD and dementia in the Netherlands is very

heterogeneous. She distinguishes two general modes of diagnosing: 'pulling out all the stops' and 'holding back', and shows how these imply different sets of values. In addition, she reconstructs how the differences are distributed in practice: either on 'factual' grounds (sorting patients into specific disease subcategories), or on normative grounds (patients' preferences). Both lead to problems and uncertainties, however, because facts and values in the area of AD diagnosis are intricately related. Van der Laan concludes that emerging biomarker tools may improve this situation, provided they contribute to taxonomies that actually 'matter' to people.

Julia Swallow (Chap. 7) explores the role of low-technological cognitive screening tools in the process of diagnosing AD in everyday clinical practice in the UK. She reconstructs how the tools emerge as provisional, yet privileged devices for navigating uncertainty through the tinkering work of clinicians. However, as the tools are adopted in frameworks promoting early diagnosis, such as the National Dementia Commissioning for Quality and Innovation Framework (CQUIN), this tinkering work is constrained. Swallow concludes that when developing high-tech diagnostic tools, the adaptive and uncertainty-navigating strengths of low-tech screening tools should not be overlooked. Moreover, since such high-tech diagnostic innovation is likely to bring along further uncertainties and controversies, responsible innovation in this area should ensure possibilities for tinkering diagnostics according to the circumstances.

In Chap. 8, Claudia Egher and Sally Wyatt point out that AD diagnostics is not just taking place in the doctor's consultation room, but is available on the internet as well. This chapter starts from the assumption that the internet is an innovative diagnostic technology, and explores how digital technologies in all their multiplicity are affecting interactions and processes associated with diagnosing AD. It focuses particularly on how responsibilities in diagnosis are shifting already.

Part III (*Alzheimer's Disease*: *Multiple Realities and Concerns*) broadens the scope of discussion by focusing on the practices and meanings AD and dementia have beyond the biomedical domain. The authors contributing to this part explore the multiple meanings and 'interpretative frameworks' surrounding AD, dementia, and early diagnosis in a wide array of locations and practices. They also examine how current promises and expectations of biomarker technologies and early diagnostics relate

to those practices. As in the preceding part, the recurring question is what the multiplicity of meanings and interpretations implies for responsible innovation of AD diagnostics.

Ingunn Moser (Chap. 9) explores how Alzheimer's disease is being shaped as a 'matter of concern' in a number of locations, including: the international Alzheimer's patients' movement; medical textbook and diagnostic context; laboratory science; daily care practice; an advertisement for anti-dementia medication; general practice; and parliamentary politics. She makes visible how all these practices are implicated in politics by framing the reality of and concerns with AD in a specific way and by interfering with alternative framings. Making visible how current practices concerning AD are implicated in politics, she argues, is crucial to make these politics more open, reflexive, and collective, thus contributing to responsible innovation.

In Chap. 10, Yvonne Cuijpers discusses the worldwide emergence of national dementia strategies. Since multiple approaches to dementia coexist, strategies to address dementia as a nation are not straightforward. Cuijpers provides a reconstruction and analysis of *which* framings of dementia are articulated in the course of the development of a Dutch dementia strategy, and *how* stakeholders deal with the coexistence of multiple framings of dementia. The chapter delineates three models of coexistence: a model where different frames are considered 'fragments of a whole'; one where they are in antagonistic positions; and a model where different frames move in different directions. The process of constructing a national dementia strategy and the surrounding discussions take different shapes, depending on the assumed model of how approaches to dementia coexist.

Jeannette Pols and Amade M'charek (Chap. 11) take issue with the linear view of innovation that seems implied in discourse on responsible innovation. Focusing on the case of Alzheimer diagnostics, Pols and M'charek demonstrate that innovations do not emerge in such a linear way. Patient advocacy movements engage with scientific research, and research and clinical practices are highly intertwined. Yet, research and clinical practices may also have very different problem definitions, aims, knowledge, concerns, and pace. Pols and M'charek argue that responsible innovation, rather than privileging a particular type of labora-

tory research, should start innovations by taking notice of the different manifestations of 'Alzheimer problems' and the different science–clinic representation practices needed to address these problems.

In Part IV (*Assessing Diagnostic Innovations*), we shift focus from current practices of diagnosing and living with AD and dementia, to practices of assessing diagnostic innovations, in general. In the biomedical domain, extensive assessment and evaluation procedures have evolved since World War II. This part explores the possibilities and limitations of current procedures for Health Technology Assessment in the domain of emerging diagnostics. Moreover, it outlines several suggestions to redesign common health technology assessment procedures to better fit actual innovation practices as well as societal concerns about innovation.

Fiona Miller, Robin Hayeems, and Stuart Hogarth (Chap. 12), drawing on observations of a feasibility study of personalized cancer care, highlight the informally regulated nature of diagnostic innovation systems. Translational imperatives blur clinical and research aims, key regulatory institutions are bypassed, and other cognitive, normative, and regulative institutions encourage attention to test performance, rather than patient outcomes. In these socio-technical systems of limited accountability, intentions to help patients and act ethically are not critically assessed; instead, assumed benefits and a perceived duty to do good tend to produce diagnostic innovations of questionable value. They argue that wider patient and public engagement, together with robust, legitimate, and accountable regulatory regimes will be required to truly 'innovate with care'.

In Chap. 13, Ellen Moors and Alexander Peine observe that diagnostic innovation is increasingly perceived as an institutional interplay with many heterogeneous stakeholders, in which users are more proactively involved in diagnosis. This challenges traditional Health Technology Assessment (HTA) practices, which usually focus on efficacy, safety, quality, and costs. This chapter zooms in on the current 'logic of valuing' in HTA, and explores several examples of diagnostic innovation to point out the shortcomings of this logic. Moors and Peine conclude that to be responsible, HTA strategies and policies had better take into account the creative and transformative character of innovation. This particularly implies that HTA procedures should allow for more flexibility to respond

to changes in the actors, values, roles, or responsibilities actually at stake in diagnostic innovation.

In the Conclusion, the insights and observations from the previous chapters are brought together, asking what they mean for the case of emerging technologies for diagnosing AD. What lessons can be learned from our wide-ranging explorations? Which conditions need to be met, which pitfalls avoided, if we aim to innovate AD diagnostics? Here, we also consider the fruits of our practice-based approach for the project of responsible innovation at large: how to innovate with care.

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# Part I

## Biomedical Research on Alzheimer's Disease Diagnostics: Background and Trends

# 2

# The Diagnosis and Treatment of Alzheimer's: Are We Being (Ir)responsible?

Peter J. Whitehouse

Age-related mental decline has been described since the beginning of recorded human history—beginning with the Ebers Papyrus in ancient Egypt (Whitehouse and George 2008). Ever-evolving cultural conceptions of cognition, ageing, and health influence attempts to understand and remediate such intellectual and behavioural changes. Within a given society, who gains power to try to assist people trying to improve their memory depends on concepts of how body and brain relate to each other and what the respective roles of healers and educators (e.g. shamans, psychiatrists, neurologists, school teachers, parents etc.) are. In twenty-first-century Western culture, diet, general health, cognitive activity, education, income, and social relations have all been tied to 'brain health' and clinical conditions, such as dementia (George et al. 2013). In this chapter, I call for a radical re-examination of the factual

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and value issues surrounding this critical issue of our times—cognitive and behavioural ageing—in the context of the other complex challenges of our modern world.

Further complicating our modern attitudes towards getting old and the mind is that this human concern—even obsession—about cognitive, and especially memory, loss creates opportunities for responsible/irresponsible profit-making, and even, quackery. We live in an era of seemingly limitless scientific and technological opportunities, but also, of growing social challenges such as the increasing number of elders in the world, widening income disparities, and dangerous effects of climate change. All these problems demand careful attention to where we invest our resources to maximize the likelihood that human beings will live long and productive lives in community with as much cognitive function and quality of life as possible (George and Whitehouse 2011).

In this chapter, I set the stage for a consideration of responsible research, innovation, planning, and use of resources in addressing dementia and brain health, including discussing linguistically contested concepts, such as 'Alzheimer's disease (AD)' and 'mild cognitive impairment (MCI)'. I will examine shifts over time in perspectives about both diagnosis and therapeutics. What follows is, frankly and as requested by the editors, a personal essay reflecting 30 years of work in the field that has ranged across the full spectrum of basic and clinical research, clinical care, health organizational development, pharmaco-economics, ethics, and policy. In the 1980s, I saw the development of the cholinesterase inhibitors from the very earliest stages in laboratory research to clinical use, and then, to their arguably relative failure at the population level. I saw the field shift from efforts to treat symptoms to cure diseases. And now, I think we are in the middle of a metaparadigm shift, redressing not only an imbalance between narrow molecular 'curative' medicine and broader prevention, community and population health approaches, but a shift in the relationships between science in general and society at large (Whitehouse and George 2008).

I feel privileged to have been a leading participant in much of the last quarter century of work on so-called Alzheimer's and to be able to write this introductory chapter in this timely and important book (Whitehouse 2014). With this privilege comes the responsibility to provide an as balanced approach as one individual can, who has passionate concerns

about the current state of the field. In fact, I believe 'Alzheimer's is more important than (just) Alzheimer's'. Alzheimer's is a bellwether, a canary in the coal mine, warning of toxic elements that cloud our future as scientists, clinicians, potential patients, citizens, taxpayers, and even, as members of the human species. If we think more deeply about what science and medicine have done and are likely to be able to accomplish when addressing chronic age-related conditions, we might alter our expectations for future success and consider other pathways for investment.

I will proceed chronologically. I first review the history of diagnosis and drug development in dementia and the current state of the science and practice. I claim that the field is at a particularly confusing crossroads concerning our understanding of such conditions and that an examination through the perspective of 'Responsible Innovation' may allow us to develop future-oriented approaches that are more helpful in guiding researchers and policymakers than our current efforts. Finally, I look at areas for innovation that seem more responsible than current narrowly focused medical strategies, and point to 'irresponsibility' as more than just a personal characteristic of individual players.

## History of Diagnosis and Treatment

In Western Europe, the clinical syndrome of dementia was described and first labelled as such in the middle of the 1800s. It was characterized by loss of cognitive abilities in more than one intellectual domain in someone who had previously demonstrated normal or at least higher intellectual abilities. Originally, dementia did not imply either a progressive course or late-life onset. For example, a young person with a serious head injury could have a static dementia (Whitehouse et al. 2000).

'Alzheimer's' was first noted by German psychiatrist Dr. Alois Alzheimer and labelled as a specific disease by his boss, renowned German psychiatrist Emile Kraepelin in the 1910 edition of his influential psychiatric textbook. However, from the very beginning, differentiating so-called AD from other dementias and from normal ageing was problematic and has continued to be so (Brayne and Calloway 1988). At the turn of the twentieth century, psychiatrists had great optimism (accompanied by

great hype) that the brain secrets of mental illness would be revealed, leading to the dissipation of diagnostic confusion, and the emergence of new therapies. In this way, the state of the profession over 100 years ago mirrors the state of the field today (Whitehouse 1985).

Another 50 years were required before the ability to measure neurotransmitter markers in the brain led to advances in understanding the brain changes in disease that, in turn, eventually produced new therapies. A prominent and relevant example was the success in the early 1960s in Parkinson's disease, in which a loss of cells in the substantia nigra (a cluster of melanin-containing neurons, hence the name 'black substance' in the middle part of the brain stem) was associated with loss of dopamine (another early described neurotransmitter) (Whitehouse et al. 1982).

The identification of the cholinergic deficiency (and eventually, other neurotransmitter changes) in the brains of people with various forms of dementia led to many attempts to develop treatments (D'Amato et al. 1987). These included giving the precursor choline, which modelled the initial treatments available for Parkinson's.

In 1993, the first cholinesterase inhibitor approved in the USA—and eventually, elsewhere—was tacrine. Enthusiasm for this drug was created by what proved to be a severely flawed (some data were underreported and others did not make internal sense) study reported in the *New England Journal of Medicine,* which was accompanied by an unwise editorial celebrating the success of this approach (Summers et al. 1986). Since no drug for Alzheimer's existed at this point, no standards for approval were available, and the FDA initiated a guideline development process asking for input from the academic, lay, and industry communities about what criteria should be established for the approval of a drug to treat Alzheimer's. Parallel processes were developed in Japan and Europe.

This global but uncoordinated effort prompted us to develop the International Working Group for the Harmonization of Dementia Drug Guidelines in 1994 to try to make drug development more efficient by standardizing development and approval processes in different countries (Whitehouse 1997). Ultimately, three other cholinesterase inhibitors with much better pharmacological properties and fewer side effects than tacrine were approved (donepezil in 1996, rivastigmine in 2000, and razadyne in 2001). The race was on for the multibillion dollar market, and

the field surrounding the cholinergic story thereby shifted from science to marketing. As an identified KOL (Key Opinion Leader), I became concerned the industry was growing less interested in hearing my independent opinion about science and clinical matters and more concerned about influencing my opinion to support the sale of their drugs. Marketing departments with larger budgets than the science departments began to take over contact with outside experts. We had more meetings on trying to understand how to influence prescribing physicians and to modulate messages about likely drug benefits. Experts were paid more to speak on behalf of specific drug projects. The industry began to create expectations for benefit for off-label, and often, under-studied indications using arguably immoral, and sometimes, illegal means—which sometimes led to large fines (Whitehouse and George 2008).

It slowly became clear that the therapeutic effects of these drugs were 'modest' at best. Are these drugs worth the money to individuals and/or society, given their very limited effect sizes (Whitehouse 1997; Jonsson et al. 2000)? Particularly in the UK where the National Centre for Health and Care Excellence is charged with evaluating not just the efficacy of drugs, but their cost-effectiveness in practice, political pressure eventually caused cholinesterase inhibitors to be made more widely available than originally recommended by the centre and their experts. Rather surprisingly, because their scientific foundation was weaker than for cholinesterase inhibitors, a glutamate antagonist—namely, 'memantine'—was approved in 2003, but in general, its effects were less consistent than those of the cholinesterase inhibitors.

Pharmaceutical companies made many efforts to try to maximize profits by creating arguments that differentiated their drugs from each other. Efforts were made to get the drugs approved for different stages of the illness, including so-called mild cognitive impairment (MCI)—a supposed precursor state to AD and other dementias (Whitehouse and Moody 2006), wherein initial cognitive decline occurs without major impairments in activities of daily living. Very few head-to-head comparisons were conducted and the drugs became thought of as clinically equally effective (or ineffective).

Increasing attention was also paid to the non-cognitive or behavioural symptoms associated with dementia (Patterson et al. 1990). Cognitive

functions that related to emotions also got more attention such as Executive Dysfunction (Patterson et al. 1996). In fact, I encouraged this effort since the agitation, depression, and psychotic features impaired the quality of life, perhaps even more than the cognitive symptoms in many people.

## Current State of the Alzheimer's Field

The current state of Alzheimer's is one of quite widespread dissatisfaction with available diagnostic and therapeutic approaches from patients, families, physicians, and policymakers. A shift in emphasis from systems to molecular neuroscience occurred as genetic mutations in early-onset AD pointed to problems in amyloid-related proteins that are associated with neurotic or senile plaques. But neurofibrillary tangles, associated with the protein tau, are perhaps even more closely related to nerve cell death. The genetic revolution in medicine influenced the dementia field to raise their expectations for more powerful therapies based on understanding cause and pathogenesis.

There are, however, significant challenges to this attempt to develop molecular and genetic diagnostics and therapeutics. Alzheimer's is heterogeneous at any level at which it is examined—genetic, pathological, neurochemical, or clinical (Whitehouse and George 2008). Several hundred causative genetic mutations and a few risk-modifying genes have been described in different patient populations. The relative distribution of cell loss and pathological features can vary across different individuals. It is a truism in the field that: 'once you have seen one patient with Alzheimer's you've seen *one* patient with Alzheimer's'. Perhaps everyone's Alzheimer's condition or dementia is unique to them because different individual processes are involved throughout the life course, including factors such as head injuries, diet, alcohol consumption, and a panoply of social determinants of health, including air and water quality. Moreover, in the last several decades, increasing overlaps between ageing and dementia and among types of dementias have become more apparent (Brayne and Calloway 1988). Neuronal loss, plaques, and tangles, all can occur in individuals who do not have a clinically apparent dementia. Moreover,

these features can occur in other conditions, such as Parkinson's and frontal lobe dementia. Our ability to differentiate these overlapping conditions from each other, much less from processes associated with ageing, remains rudimentary. Even the allegedly clear-cut distinction between vascular disease and neurodegenerative disease is getting muddier, the more we look at risk factors and biological markers (Kling et al. 2013).

Attempts to improve diagnosis by developing biomarkers, especially those focusing on specific proteins such as amyloid and tau in spinal fluid, and neuroimaging using positron emission tomography (PET) scanning have intensified. Developing the ability to image amyloid using PET represented one such technological advance. However, at the same time, our neuropathological understanding of AD became more complex—particularly, in older people. For example, as mentioned above, amyloid plaques were found in people with other forms of dementia and in 'normal' ageing (Brayne and Calloway 1988). The most common dementia in older people was found to be mixed dementia, often with both neurodegenerative and vascular components (Toledo et al. 2013).

Even in the light of the pathological uncertainty at the level of the autopsy, stronger claims were made about biomarkers. The FDA approved several agents for amyloid imaging even though that approval process did not require them to demonstrate clinical utility, only that they could measure (albeit with some difficulty) what they were purporting to measure (i.e. amyloid-related proteins in the brain). Research efforts are underway to image tau in neurofibrillary tangles. Researchers talk about using multiple biomarkers associated with big data sets to lead to therapies which themselves may involve an individualized cocktail of drugs and biologics. These assertions that we need more of everything to understand the puzzle of dementia have enormous price tags associated with feeding the hungry research enterprise. Rarely are the possible harm or opportunity costs of such fantasized multifaceted diagnostic and treatment adventures considered. And the field of bioethics pays relatively little attention to this bigger picture of conflicts of interest and opportunity costs. Lip service is often paid to having a balanced approach to pharmaceutical and psychosocial (so-called non-pharmacological interventions), but drugs are held out as the definitive answer. The logo 'Care today; cure tomorrow' is used, as if cure will eradicate all needs for caring.

Moreover, attempts were made to refine the diagnostic criteria for pre-dementia states building on early attempts such as so-called Ageing Associated Memory Impairment (Crook et al. 1986). MCI became the most popular and researched (Whitehouse and Juengst 2005; Whitehouse and Moody 2006). It slowly crept from being a research term to a diagnosable condition (if not disease). Yet, several studies showed that experts use this term in highly variable, and not always reliable, ways and that the labels were confusing to people to whom they were applied. Yet, the term grew in popularity perhaps because it allowed clinicians to avoid applying the stigmatizing label of Alzheimer's or dementia. Increasingly, people began to focus on 'early' or 'timely' diagnosis, yet without the evidence that such a process was helpful to individuals affected by memory problems. When people promote early diagnosis, they rarely specify of what, of whom, where, and for what purpose. At the same time, the Alzheimer's field was worrying about underdiagnosis, a growing concern emerged in medicine about screening for, and overdiagnosis of various diseases, including memory loss.

The disappointment in current therapies also led to efforts to identify AD at even earlier stages—'preclinical' or 'asymptomatic' Alzheimer's. This effort was encouraged by the development of experimental therapies to try to address amyloid accumulation in the brain, even though we did not know the normal function of these amyloid-related proteins, or even necessarily, whether such proteins were harmful. Numerous expensive trials have been concluded and are being conducted with so far disappointing results. Several companies stopped their Alzheimer programmes after repeated failures. However, occasional encouraging signals from Lilly and Biogen allow some to say that this amyloid game is not over. Lilly bought an amyloid imaging venture so they could try to link the amyloid diagnostics to their imaging products. Despite lack of government reimbursement and the guidelines suggesting these biomarkers remain research tools, Lilly and others, including the Alzheimer's Association in the USA, support and produce programmes that encourage clinicians to think of their use clinically (George and Whitehouse 2014).

So where are we today? Some people—perhaps the majority of researchers and their advocates—think that the march to progress continues even at a slower pace. For them, the model and hope of the future is more

money, leading to more hypotheses, panels of biomarkers, bigger data sets, more efficient drug development (through less regulation and centralized, and perhaps, relaxed ethical review), and ultimately, a cocktail of therapies. Yet, many studies are not even replicated in the lab and the hope is found to be false. The recent promotion of bexarotene (Cramer et al. 2012), an already available drug for t-cell lymphoma, by my own university (Case Western Reserve University), is an example of premature claims and even drug testing, leading to backtracking. Papers from one laboratory claimed that this drug could clear amyloid rapidly from the brains of mice genetically modified to produce excess of these proteins. Multiple attempts to replicate this finding basically failed.

Alzheimer's tracks the fads in medicine, be they molecular, genetic, or as currently big integrated data sets. The AD field literally envies the cancer field with its greater visibility and budgets. It is considered a success when surveys find people fear Alzheimer's more than cancer. Just as we are culturally reinventing ageing to be viewed as a time of opportunity, not just loss, Alzheimer's remains the elephant in the room, causing fear and mental blocks. That said, an alternative, more geriatric, public health, social science, and arts/humanities-based perspective about dementia is emerging. The social sciences, such as anthropology, can provide new critical perspectives (Whitehouse et al. 2005). In this view, dysfunction and disability are more important than precise diagnosis; quality of life trumps cognitive enhancement; community engagement is key; and population health perspectives gain influence over individual health (Whitehouse 2010).

## Crafting an Innovative But Responsible Future

### Early or Timely Diagnosis

Realizing that early diagnosis may not be the right concept, the idea of 'timely' diagnosis was developed. The concept of 'timely', which emerged in England, made reference to when the time was right for an individual patient and family to receive a diagnosis, based on the patient, or perhaps, the family's own psychological and social situation. The 'timely'

concept opened the door to consideration of other factors besides the drive to earlier and earlier labelling of people with poorly understood, but possibly, life-changing diagnoses. 'Timely' implies that for different individuals in different circumstances, applying the diagnosis could occur at different points in the illness, but on what the diagnosis would depend is not entirely clear. Moreover, it's not certain whether we are talking about timely diagnosis of Alzheimer's or of MCI or of asymptomatic AD.

There are very few studies of the value of the label 'MCI', but those that have been conducted suggest that it is not necessarily helpful. Recommendations have been made against screening in general populations. Little evidence exists that screening provides value, even in the context of a general medical visit. In other words, the AD field is pushing early diagnosis without adequate scientific evidence and is neglecting the possible harm of early labels on individuals or society. It seems the only people that clearly benefit are the clinical and research communities and the politicians who can say they are doing something about the epidemic of dementia.

## Finding the Cure or Even an Effective Therapy

Much of the field has moved beyond the so-called cholinergic hypothesis to attempts to modify the disease(s), slow its (their) progression, or even, cure it (them). The major focus has been on amyloid immunotherapy which, most would agree, has largely failed to date, despite the billions of dollars being spent trying to develop such approaches and even to administer these biologics to individuals without symptoms (preclinical), such as in the NIA ADCS A4 study (Castellani and Smith 2011; D'Alton and George 2011; George and Whitehouse 2014). Experts in the field are pushing enrolment of subjects in research trials and asking whether regulations on drug companies should be relaxed. Clearly, these are once again policies that support the field and its pharmaceutical allies, but are not necessarily beneficial to patients today or even in the future.

Behind the standard view of AD and the dominant ways of presenting this perspective to the public lies much irresponsibility. The concept of Alzheimer's has changed over time, is changing now, and perhaps, even

needs elimination or significant revision. Early diagnosis is the mantra of those who want to raise the social visibility of this concept. Promises of cures abound in global planning, such as national Alzheimer's plans, as in the USA and the G7-initiated World Dementia Council. Campaigns increasing the fear of dementia suggest victims are akin to zombies. In turn, fear tends to shut off careful rational reflection about ideas and options. The only hope that is offered in response to fearful projections is drug treatments. In all these classes of human activities, inventing disease, diagnosis, and promising cure in exchange for research funding, we find plenty of behaviours that represent lack of transparency and interaction between innovators and society, inadequate attention to ethics, almost no focus on the nature and cost of to-be-marketed products, and little attention to the opportunity costs associated with the monomania of biological cures.

## A Case Study of 'Irresponsibility'

A critical look at a recent report from the Alzheimer's Association (Alzheimer's Association 2014) in the USA is a worthy case study in the responsibility of claims about innovation. *Changing the Trajectory of AD* in the USA is, I believe, an irresponsible report that attempts to demonstrate that investment in biological research to find disease-modifying or curative drugs will save hundreds of billions of dollars in our healthcare system (Gleckman 2015; Whitehouse and George 2015). Consistent with their advocacy through the National Alzheimer's Advisory Panel and through their policy efforts, the Alzheimer's Association has been asking for an additional $2 billion a year for medical research to find a more effective drug. In various places, they refer to this as a quest for a cure, a preventative, or a disease modifying drug. They imagine that, with such a level of enhanced investment, this drug could be available by the year 2025. Richard Hodes, the Director of the National Institute on Ageing at the WHO Global Dementia Summit in Geneva, referred to this as an 'aspirational' goal, but frankly, there are very few people who think that this is even remotely achievable. Because this powerful pill is rather illusory—and many think unrealistic on any timeframe, let alone

in 10 years—this concept is sometimes referred to as the discovery of a magic bullet.

The *Changing Trajectory* report was an exercise in pharmaco-economic modelling, prepared with the assistance of the Lewin Group. Various scenarios (delayed onset and slowed progression) were created, but basically, the imagined or imaginary drug would be hypothesized to prevent people from advancing as rapidly through the stages of dementia. Because people in the more severe stages require more resources, the model predicts saving hundreds of billions of dollars or even trillions, if one extrapolates beyond 2035. So, we have a hypothetical drug creating imaginary effects that essentially rescue our healthcare system from bankruptcy, not to mention, recouping any increased research investment within three years—or so, it is claimed.

However, the report is not only an exercise in imagining magic drug effects, but also, in irresponsible financial modelling. My colleague Anders Wimo, who has organized several conferences with me over the years on pharmaco-economics of dementia drugs, starting with the very first in 1998, has reported that the two major factors that affect cost savings are assumptions about the cost of the drug and about the effects of the drug on mortality (Wimo et al. 2014). The first is obvious and the second is as well, if you think for a minute that an effective drug for people with dementia might enable them to maintain their health in community and out of nursing homes, for example. But would such a powerful drug affect mortality? Nursing home placement has been shown to increase mortality under some circumstances. Patients who live longer consume more healthcare resources on average. So, take the example of the shift from severe dementia to moderate dementia. Suppose a person lives longer, yet still, eventually becomes severely demented. If this person consumes more resources at that late stage of their illness, then this person may cost more, not less, money if treated with the drug. It is, of course, very complex to figure out how a drug might affect length of life and difficult to model the implications. If a drug were wonderful enough to cure memory impairment and not delay death, then the drug that might be ideal in an economic sense.

The most obvious factor that affects projected cost savings is the cost of the drug itself. If one is not sure of how to cost the drug, then an

appropriate methodological manoeuvre is to conduct a sensitivity analysis. Using this method, one examines a range of drug prices and reports the cost savings/increases associated with each project drug price. However, the Alzheimer's Association does not use this approach; rather, as the Lewin Group is quick to point out, presumably to try to defend their own credibility, the Association chose to model the cost of the drug as *zero*. In other words, this magic drug is particularly magical because it is free. Moreover, they also assume everyone has access to the drug (easier if it is free) and gets the same magic effects. No wonder they can invent cost savings in our healthcare system with their model. No wonder they also claim that we can recoup our investments in research to develop this pill in three short years. Is this responsible? Does being irresponsible increase the costs of missed opportunities, such as investment of resources elsewhere in a non-medical way (Katz and Meller 2014; Whitehouse 2010; Portacolone et al. 2014)?

## Towards a More Responsible Future

Many have argued that ELSI (Ethical Legal and Social Issues) programmes have not been adequately critical of the medical field (Whitehouse 2003). Ironically, money and power have partially co-opted mainstream biomedical ethics. Inadequate attention has been paid to conflict of interests in medical research and practice, or to socio-environmental determinants of health. The concept of Responsible Innovation in health emerged out of Europe in the beginning of the twenty-first century as a corrective. Yet, the concept has a built-in paradox. If one of the defining features of innovation is not only creativity, but ending up with something useful, then how can irresponsible innovation actually exist, since lack of responsibility implies potential harm to someone at some point? One answer is that an irresponsible innovation can be useful to the group that promotes it, but we must, as the concept suggests, look at all the broad systemic ramifications of the 'innovation' and examine net harm and benefit to the widest group of people affected by it. It remains unclear whether Responsible Innovation offers more to society than ELSI, but this open, inclusive, reflective, system- and future-oriented process seems promising.

I have argued here that at least some behaviours in the Alzheimer's field are irresponsible. Individual scientists who self-promote, and, for example, publish studies in animals that claim dramatic implications for human disease (i.e. breakthroughs) are individually irresponsible. They raise false expectations and hope and drive resources in inappropriate directions to irresponsible actors. Universities encourage this kind of publicity seeking. Mice do not get alzheimer's and any exaggerated claim from studies of nonhuman species should be considered irresponsible. Yet, there appear to be systematic and cultural factors that create irresponsible individual and organizational behaviour.

Is the Alzheimer's field any more irresponsible (or corrupt) than others? Contentious and perhaps exaggerated projected numbers of affected individuals are promoted. Life-altering labels of unproven validity and utility are encouraged. Expectations of profound biological interventions on timescales that are unrealistic are projected. Fear and stigma are created as they portray affected individuals as zombies or 'lost selves'.

If one accepts the possibility that Alzheimer's represents various different forms of brain ageing, then one can ask whether the vast field of late-onset AD is little more than a branch of so-called antiageing medicine (Whitehouse and Juengst 2005). Advocates in antiageing medicine claim ageing is a disease that can be fixed. And yet, most would consider that ageing is not a disease and that people who promote biological products that promise to slow ageing, and hence, brain ageing are acting irresponsibly—pathologizing a 'normal' condition and building societal trepidation around it in order to create market demand for promised 'cures'. Is the Alzheimer's field any different?

## New Approaches

Efforts to improve the quality of life of people with cognitive impairment and their care partners are undergoing dramatic transformation. Although some hope is held out for molecular reductionist, genetically based therapies, more evidence is emerging that psychosocial and public health measures may be more effective. Psychosocial interventions, such as caregiver education, support groups, arts interventions, and other

community programmes have been demonstrated to improve the quality of life. No drugs have been demonstrated to do the same (George and Whitehouse 2010; Whitehouse and George 2014; Portacolone et al. 2014; D'Alton et al. 2014; Katz and Meller 2014).

Although biological innovation will continue, it is important that a comprehensive programme of social innovation be developed. Information technology can increasingly be used to support those with memory challenges. Systems of monitoring can keep people safe when they wander. Robots may be able to provide care for certain patients in certain circumstances. Communities can be resigned to promote better health.

A growing movement is also focusing on brain health and its public health implications (D'Alton et al. 2014; Whitehouse 2013a, b). Protective factors such as healthy diet, regular exercise, and mental activity are increasingly being viewed as important interventions. Ultimately, it is not neural tissue that we want to keep healthy for its own sake, but rather, because of its function (i.e. our thinking and emotional abilities). In the case of brain health, the brain may best be considered a metaphor rather than just a physical organ. In other words, when we say that somebody has a good heart, we usually do not mean that their ejection fraction (a measure of the heart pumping action) is within the normal range or superior; we mean that they are a good, emotionally balanced human being. Similarly, when we say that somebody has a good brain, we mean that they can think well and in a balanced fashion. It is frequently said what's good physically for your heart is good for your brain (and vice versa). And so too, what is good for your emotional life is also good for your cognitive life (and vice versa). Having a sense of purpose and a community network in which to manifest that purpose seems to be important for brain health. In fact, wisdom would appear to reflect a balance of thinking and emotionality in service of doing good and being appropriately constructively critical. In this spirit, it would be advisable to develop more wisdom about brain/cognitive ageing and resist fear-driven approaches that seem to turn off our critical faculties.

A deeper and broader understanding of dementia in the context of community-based brain health could lead to huge advances in the development of our human species and its ability to address the challenging

future. Education and lifelong cognitive activities have consistently shown in population studies to be protective factors against getting dementia later in life. Intergenerational education may be one social innovation relevant to community brain health and resiliency. At The Intergenerational Schools (TIS 2015) in Cleveland, local elders, including those with dementia, contribute to their own brain vitality as well as the long-term brain health of children by serving as mentors in an elementary school (George and Whitehouse 2010; Whitehouse 2013a, b). Moreover, dementia-friendly communities should be part of lifelong age-friendly communities for all of us. Attending to the cognitive harms of air and water pollution and income inequity could motivate us even further to address these global issues. Asking deeper, more critical questions about 'Alzheimer's' will expose profound challenges and dilemmas surrounding and embedded in the current role of science in society, the effects of commodification in healthcare, the nature of ageing, and, in fact, our very humanity. Addressing such more fundamental probing questions about our cultural beliefs and the distribution of power in our societies should also lead to more responsible innovations and actions.

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# 3

# On Short Cuts: The Complexity of Studying the Early Diagnosis and Prevention of Alzheimer's Disease

Annette Leibing

There have been important recent changes in the conceptualization of dementia and its most common form—Alzheimer's disease (AD)—resulting in the ideal of early detection, early diagnosis, and prevention. This important trend conceives of the pathological brain chemistry (the famous 'plaques and tangles') as being the result of genetics, in combination with a number of preventable—most notably, cardiovascular—risk factors (see Leibing 2009a, b, 2014, 2015a; Leibing and Kampf 2013). In the first part of this chapter, I will describe this newer research trend, comparing it to an earlier understanding of dementia. Part two will provide an initial discussion of something I want to call 'short cuts': the difficulty of critically analysing complex bio-social processes.

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## Two Decades, One Question

In 1993, two Swiss researchers published an article, in which they asked: 'Is prevention of dementia possible?' (Ermini-Fünfschilling and Stähelin 1993) Twenty years later, a group of North American scientists chose a similar title for their publication: 'Can we prevent Alzheimer's disease?' (Carrillo et al. 2013) Both questions appeared at historical moments when the available medications, but also, the main risk factors and biomarkers—both important considerations in the field of prevention—seemed to be almost identical.

### Around 1993

The aforementioned Swiss authors, like their contemporaries of the 1990s, were rather pessimistic in their evaluation of whether preventive measures might be possible: 'In the case of dementia of the Alzheimer type (DAT) … (risk factors) are emerging. However, they are not easily altered … ' (p. 446). Risk was, and remains to this day, linked to old age, genetic factors, head trauma, and education. These factors, which can appear in highly varied degrees and combinations, implicate different forms of dementia, of which AD is the most prevalent, or at least, has been since the mid-1970s.

Biomarkers at the beginning of the 1990s were either retrospective or confirmative entities. The microscopic examination of brains from deceased individuals with AD revealed a reduced amount of nerve cells, the presence of beta-amyloid plaques that had built up between nerve cells, and an accumulation of tau tangles that had destroyed parts of the cell transport system. Although this pattern can be found in the majority of Alzheimer patients' brains, researchers have long since known that the correlation between amounts of amyloid plaques, tau tangles, and disease manifestations is not entirely straightforward. Even in the early twentieth century, some researchers wrote of patients who displayed the typical symptoms of dementia, but without any accumulation of plaques and tangles in the brain (see Berchtold and Cotman 1998); conversely, Gellerstedt's (1933/1934) detailed early study showed that 80 % of

individuals over age 65 had the typical plaques and tangles associated with dementia, but without any manifestation of dementia symptoms. In 1940, McMenemey (quoted in Berchtold and Cotman 1998, p. 182) wrote: 'That the pathological changes in this disease are not specific is generally agreed. (…) Nevertheless, *the presence of abundant plaques and neurofibrillary alterations together with extensive atrophy of the neurons is found only in Alzheimer's disease and senile dementia*' (emphasis added).

In the 1990s, other biomarkers were investigated in vivo: brain atrophy or the shrinking of the brain, especially in the hippocampus, could be seen through modern brain imaging technologies, and proteins in the cerebral spinal fluid and blood were tested for abnormal concentrations. This procedure was generally undertaken as a means to reinforce the diagnostics—with the primary diagnostic tool being cognitive tests—rather than as a preventive measure. The only predictive biomarkers investigated prior to the onset of AD (sometimes, in combination with an analysis of the cerebral spinal fluid, and predominantly within the context of research) was the detection of certain genes—for example, the different alleles of the apolipoprotein E (APOE), of which the e4 allele increases the susceptibility to dementia (Tanzi and Parson 2000). Biomarkers in the early 1990s were, in short, primarily used for confirming diagnosis and for research. As an example, Arai wrote in 1996 about *diagnostic* markers, not about biomarkers:

> This review describes recent advances in the development of *diagnostic marker(s)* for AD. (…) In conclusion, ApoE genotyping should not be used as a sole diagnostic test for AD, and that monitoring of CSF-tau appeared to be most promising and reliable *diagnostic aid*. (p. 65; emphasis added)

The 1990s also yielded exciting advances in treatments as the first medications specifically designed for Alzheimer's arrived on the market. Beginning with Tacrine in 1993—a drug that is no longer recommended due to its serious side effects (especially liver damage)—four second-generation medications (donezepil, rivestigmine, galantamine, and memantine) were developed that continue to be prescribed worldwide to patients showing cognitive decline. By 2005, however, it had become clear—at least to those reviewing scientific publications—that

these newer medications had major side effects, and also, exhibited only a moderate effect on cognition for some (but not all) patients (see Harvard Mental Health Letter 2004; National Institute for Clinical Excellence 2001, 2005; Royall 2005; Trinh et al. 2003). The reason why these medications continue to be prescribed—despite the evidence that '[n]one of these treatment effects are large' (Birks 2005; *Consumer Reports* 2012)—rests in the fact that it remains preferable for families, patients, and doctors to take a chance on achieving slightly better functioning for the individual suffering from Alzheimer's for some time, rather than to do nothing (e.g., Smith et al. 2011): The medications' 'success appears to be borne of the significant unmet need', wrote Mount and Downton (2006, p. 784). An additional reason is the recent redefinition of what these medications are targeting—for instance, such relatively fuzzy factors such as activities of daily living—which has subsequently led to new positive results in outcome studies (see Leibing 2009a, b, for a more detailed analysis).

## Around 2013

In 2013, the list of risk factors and biomarkers for Alzheimer's disease was almost identical to those found in parallel publications from around 1993:

However, the authors of the second study mentioned in the introduction of this chapter (Carrillo et al. 2013)—the majority of whom are associated with pharmaceutical companies—were more optimistic than their Swiss colleagues had been two decades earlier: 'There is … increasing evidence suggesting that many risk factors that contribute to the development of late-life dementias are modifiable … [S]tudies have suggested that education, complexity of occupation, and an engaged lifestyle have protective effects … [U]p to half of AD cases may be attributable to *modifiable* risk factors … '. (p. 123; emphasis added)

The current excitement surrounding early detection and prevention as a new focus in dementia research is displayed through a number of recent initiatives. At the International Psychogeriatric Association's 2009 conference on 'Pathways to Prevention', for example, the organizers

noted that 'there was a sense of being at the beginning of a new era in geriatric psychiatry in which prevention is becoming an increasing focus' (Rapoport and Mulsant 2010). The Alzheimer's Early Detection Alliance (AEDA) was founded by the American Alzheimer's Association and designed to 'educate people about the signs of Alzheimer's, the importance of early detection and the resources available to help them' (Alzheimer's Association 2010). And in the European Dementia Prevention Initiative (EDPI), three large cohorts of middle-aged individuals will be followed over a longer period, in an attempt to ascertain whether cardiovascular care offers preventive or delaying measures for dementia (Dehnel 2013). Two major conceptual changes allow for this new rhetoric of prevention: The importance given to cardiovascular risk factors (see Table 3.1: '2013'), and the investigation of biomarkers even before the first onset of symptoms.

When looking more closely at the Swiss article from 1993, however, a similar argument can be found: 'The well-established *cardiovascular risk factors* such as hypertension, diabetes, and overweight are effective in the etio-pathogenesis of vascular dementia. Their treatment by diet and drugs is (…) indicated' (p. 446; emphasis added). Cardiovascular factors, therefore, played a role at that time, but only within the carefully distinguished categories of 'vascular dementia' and 'mixed dementia', both of which were far outweighed by the dominant diagnostic of 'Alzheimer's disease'. While this division is still in use, the boundaries between the different categories have become increasingly porous: many specialists now practically merge these once separated conditions under the name of 'dementia' or 'Alzheimer's disease' (e.g., Kalaria 2010).

Until the 1960s, dementia in elderly individuals was usually called 'arteriosclerotic dementia' (AD then referred only to early-onset dementia). This name, introduced by Otto Binswanger at the end of the nineteenth century, was used to define a condition of cognitive decline secondary to the atherosclerosis of cerebral vessels (Battistin and Cagnin 2010). In 1974, neurologist Vladimir Hachinski criticized this idea for being misleading, and proposed, instead, the term 'multi-infarct dementia' (MID); Hachinski thus introduced the notion that cognitive decline needed an accumulation of cerebral infarcts. Alzheimer's disease was seen as a separate disease entity that was a problem of brain chemistry

**Table 3.1** Risk factors and biomarkers for Alzheimer's Disease around 1993 and 2013 (based on Rocca 1994, and Van Dujn et al. 1994, and on Alzheimer's Association 2013, and Alzheimer's Disease International 2013)

| Alzheimer's disease | 1993 | 2013 |
|---|---|---|
| *Main risk factors* | Family history | Family history |
| | Genetics | Genetics |
| | Age | Age |
| | Education | Education |
| | Head trauma | Head trauma |
| | Down's syndrome | Down's syndrome |
| | Parkinson's disease | Parkinson's disease |
| | Late maternal age | Social isolation |
| | Depression | Depression |
| | Down syndrome | Down syndrome |
| | Aluminium | Heart–head connection (cardiovascular health—diabetes, hypertension, etc. incl. smoking) |
| | Hypothyroidism | |
| | Smoking | |
| | Others | Others |
| *Main biomarkers* | Genes | Genes |
| | Amyloid and tau proteins | Amyloid and tau proteins |
| | Brain atrophy | Brain atrophy |

(Alois Alzheimer had considered the possibility of vascular risk factors). This conceptualization became a dominant idea in dementia research, especially following the highly influential Newcastle study, which, conducted by neurologist Sir Martin Roth and colleagues (see Blessed et al. 1968), established the correlation between disease manifestation of senile dementia (what later became AD), and the amount of amyloid plaques and tau tangles in the brain (and not a stroke). This became a fundamental part of the contemporary understanding of AD and the foundation of the current research focus on amyloid plaques as central to possible pharmacological interventions.

In fact, while the link between cardiovascular risk factors and AD has been noted before, only recently have researchers given it specific attention. The APOE (apolipoprotein E) gene, and especially, its allele ϵ4 (Slooter et al. 1997; Tanzi and Parson 2000), which is understood to elevate the risk of developing dementia, are also involved in heart

disease; APOE is responsible for the transportation of fat in the body. This causal relationship was initially identified in the 1980s (Yamamura et al. 1984); however, it was widely ignored until 1993, when neurologist Allen Roses (see Roses 2006) made a significant discovery that linked APOE to the 'sporadic' form of AD (the most common form, where heredity plays less of a role than in the rare 'familial' one). Roses continues to investigate a cardiovascular link to dementia: he is now the director of his own biotech company that is currently coordinating an international clinical trial utilizing a specific predictive genetic biomarker called TOMM 40 in combination with an existing Japanese antidiabetes drug that has been reconceived for AD prevention (see Ranii 2011). The logic of cardiovascular care as prevention was reinforced by studies showing that certain groups leading a healthier lifestyle in terms of diet and exercise, and having adopted a better control of diabetes and hypertension, also seem to have a lower incidence of dementia (Ornish et al. 1998; Rocca et al. 2011; Schrijvers et al. 2012; Norton et al. 2014).

And while recommendations regarding dementia and lifestyle have been suggested in the past (e.g., Friedland 2001; Tanzi and Parson 2000, p. 201), it is only in the last few years that a cardiovascular logic has become more commonplace. The brain-based training recommendations of crossword puzzles and memory exercises are partly giving way to new preventive measures: 'Regular physical activity, in general, is believed to improve brain function, both by increasing blood flow to the brain and by stimulating the production of hormones and nerve growth factors involved in new nerve cell growth. Exercise also raises levels of "good" HDL cholesterol' (Rabin 2010).

One possible reason for the scientific community's delayed emphasis on cardiovascular risk factors can be attributed to the fact that when Roses established the link, hopes were focused on directly targeting the dysfunctional brain chemistry with the new cholinesterase inhibitors: in 1993, Tacrine arrived on the market, although from the beginning—as was the case for its successor drugs—some critical voices argued that the target of this kind of intervention was too narrow for a complex syndrome such as AD (e.g., Levy 1990).

## Even Milder Than Mild Cognitive Impairment: Prevention and Prediction

Two new sets of diagnostic criteria, both of which try to capture not only symptomatic AD (as was the standard until recently), but also, early stage asymptomatic development of supposed pre-dementia, are among the many mechanisms helping to embed a preventive logic into scientific reasoning. The 'Dubois criteria', which emerged from an international working group (Dubois et al. 2007, 2010), as well as the National Institute on Aging/the Alzheimer's Association's criteria (2011), both divide AD into three phases: (1) dementia due to Alzheimer's; (2) mild cognitive impairment (MCI); and (3) preclinical (pre-symptomatic) Alzheimer's (see Visser et al. 2012; Alzheimer's Association 2013; see Fagan and Strobel 2011, for the distinction between these two diagnostic criteria sets). The Dubois criteria establish that people who are cognitively normal, but have a positive brain amyloid PET scan or an AD-like signature in their cerebrospinal fluid (CSF) would be viewed as being 'asymptomatic' at risk for AD. Asymptomatic people who are known to get AD in the future because they carry a rare autosomal-dominant AD mutation are labelled as having 'presymptomatic AD'. Further, those who show the typical symptoms of dementia, but not the typical biomarkers, would get a diagnosis of 'prodromal AD' (Dubois et al. 2010).

For many years—at least since the 1960s (see, e.g., Kral 1962)—the concept of 'mild cognitive impairment' (MCI) was loosely attached to dementia, therefore indicating 'a transitional period between normal ageing and the diagnosis of clinically probable very early Alzheimer's disease' (Petersen 2004). In other words, a certain number of people who initially show rather unspecific and 'mild' symptoms of forgetfulness and reasoning might later develop AD. Who exactly constitutes this subgroup is not well understood, although genetic factors seem to play a certain, but not determining, role (Campbell et al. 2013). This concept, with its well-known limitations of predictive lack of specificity (certainly, not all individuals with memory problems will suffer from a dementia [see, e.g., Whitehouse and George 2008]), and the concomitant danger of a pathologization (and pharmaceuticalization) of normal forgetfulness, has now become more tightly linked to the core concept of dementia as a

second phase (although MCI is officially only used for research). A third, preclinical phase—even more preclinical than MCI—is especially relevant for the discussion of a cardiovascular logic:

> [L]arge cohort studies have implicated multiple health factors that may increase the risk for developing cognitive decline and dementia thought to be caused by AD (…) In particular, *vascular risk factors such as hypertension, hypercholesterolemia, and diabetes* have been associated with an increased risk of dementia. (Sperling et al. 2011, p. 282; emphasis added, see also Sperling and Johnson 2012)

This third stage, after Zaven Khachaturian (2011)—a pioneer in Alzheimer's research—'has (…) brought the field to the threshold of a new frontier—the struggle toward primary prevention'. The author of a *Globe and Mail* article, communicating this recent development to a general public, declared: 'It is also possible that early diagnosis may help patients make lifestyle changes that delay the onset of the disease. Studies suggest that exercise and a healthy diet may be protective. Both measures are widely advocated by doctors to prevent heart disease and stroke' (Mcilroy 2010).

The idea that a preclinical condition needs to be made concrete and detectable, simply in order to exist, is exemplified through the extent to which the new diagnostic criteria centre on biomarkers. For example, Janssen Pharmaceuticals, together with GE Healthcare, announced in December 2010 that they were developing a non-invasive assay for detecting 'biosignatures' (the beginnings of the formation of the two most important biomarkers, amyloids and tau-tangles) to facilitate early diagnosis and intervention (Johnson and Johnson 2010). Early detection in the preclinical phase was also the target of the *professorship for the prevention of dementia and Alzheimer's-related diseases*, financed by Pfizer Pharmaceuticals at Montreal's McGill University (Pfizer 2010).

These changes in understanding dementia may also influence an important ethical discussion. For a long time, a heated debate existed about whether the results of genetic testing, i.e., of being at risk, should be revealed to the affected individual and their family. While some argued that results should be made available so that necessary precautions

could be undertaken (such as the last will and testament, or other legal and emotional acts), others argued that since nothing curative could be done, and because the revelation could lead to discriminatory practices (by insurance companies, among others), social stigma, depression, or even suicide, doing so would only cause distress. This is quite apart from the fact that even for the—rare—familial form of Alzheimer's, genetics cannot predict with certainty whether dementia will occur (see Pedersen 2010). When following the logic of the cardiovascular paradigm, however, concrete preventive measures could now be undertaken. In this context, revealing the vulnerability to individuals early on would mean that they could actively engage in diet and other lifestyle changes—although the effectiveness of such measures remains an open question: While the large health organizations relativize these findings ('More research is needed … ', see NIA 2015), more popular publications, targeting the general public, communicate prevention as a *fait accompli*: 'I firmly believe that since there's no conventional cure, now or in the foreseeable future, the issue of prevention is absolutely critical if you want *to avoid* becoming an Alzheimer's statistic' (Mercola 2014; emphasis added). The crux of this debate lies in the fact that such general recommendations are not dementia-specific; they target any individual who wants to prevent decline in health and well-being regarding most chronic diseases, at least when following current dogmas in public health (e.g., Petersen and Bunton 2002). The difference to the debates conducted only some years ago is that, at that time, positive genetic testing for dementia meant impending death, while the more recent arguments seem to imply hope: of being in control and of 'taming' what is to come. However, different from the prevention of diabetes or hypertension, in the case of dementia, nothing directly curative can be done, although the risk is lowered to a certain extent. Serious studies seem to suggest that at least one-third of all Alzheimer's cases worldwide could be prevented if all people had access to preventative programmes (see Norton et al. 2014). If this is true, what is preventable in dementia is also a question of social justice and not only an individual problem.

A critical history on recent changes in dementia research has focused largely on the pharmaceuticalization of early detection and prevention of dementia. However, it seems that the older paradigm, based primarily

on cognition, would represent a frame in which medications could more easily be sold rather than the preventative measures that target lifestyle changes; modifying diets, and increasing physical activity that would cost (almost) nothing to healthcare systems and its consumers (although still raising the question of social class and access to such a lifestyle; see Tomlinson 2003). Within a North American context, however, the new paradigm of earliness—not exclusively, but more often than in Europe—means a focus on lifestyle changes through drugs (Leibing 2015b). This implies earlier (and, therefore, longer) use of the existing (and mostly ineffective) dementia drugs, such as Aricept (see AllBusiness 2007); it might also impact the development of analogous drugs, and the prescription of psychiatric drugs for cognitive, emotional, and behavioural problems associated with dementia (Leibing 2009a, b). Further, Appleby et al. (2013) provide a long list of existing medications that might become 'repurposed' for AD, some of them directly linked to the recent reconceptualization of dementia: diabetes-related agents, statins, antihypertensives, among many others.

## Simplifications and Short Cuts: On Studying Early Dementia

The aforementioned abridged history of changes consists of several simplifications on different levels. In fact, all narratives and complex practices, including the making of science, are ultimately reduced by choosing elements of coherence, by 'sorting things out' (Bowker and Star 2000; Star 1983). Simplifying arguments is a necessity within a complex world, and more specifically, within the context of limited resources (time, budget, personal and material restraints), and the need of translating complicated concepts among different disciplines and knowledge systems (Star 1983). At the same time, simplifications are highly vulnerable to manipulation, which in this case is often called 'reductionism'. One mechanism within this wider phenomenon is the skipping of one or several steps in the argument—tracing a straight line to a (desired) result that leaves out, consciously or unconsciously, other possible arguments, which might change the understanding of the achieved conclusion.

In the preceding historical reconstruction of the 'new' dementia, a number of such simplifications can be found; for instance, the message that dementia can be prevented is often communicated as a fact, especially in the media—a conclusion reached without including those steps in the argument showing that this is only true for some cases. What these simplified messages obstruct is that, as for instance, Matthews et al. (2013) show for the UK, a better control of certain risk factors has, in fact, lowered the prevalence of dementia in some areas of the country, when compared to 20 years earlier. However, there exists 'substantial variation in expected prevalence' (p. 1410), due to social inequalities.

Revealing such sidestepped details by critical scholars is an important task; in this case, an oversimplified concept of prevention medicalizes social factors, and, at the same time, generates too much optimism by suggesting that people can be in control by performing preventive acts, but confronted by a highly heterogeneous pathology. Critical accounts, however, bring their own dangers. I want to suggest an approach that could be called 'short cuts', and which is part of the described 'simplifications', but which is rarely studied more specifically: the necessity of including a 'critique of the critique' in the study of reductionisms. In other words, critical scholars, the Robin Hoods of the sciences, by accusing authors of reductionist arguments often equally rely on simplifications—short cuts—which, in some cases, impact a more balanced or nuanced understanding of a given research problem.

In the context of critically approaching dementia research, a number of scholars have questioned and condemned the role the pharmaceutical industry plays in the shaping of diagnostic criteria, clinical realities, bodies, and identities (e.g., Whitehouse and George 2008; Leibing 2009a, b; Lock 2013). These scholars have exposed the by now relatively well-known and scandalous practices of promoting ineffective or even harmful medications through a number of mechanisms (see Applbaum 2009; Healy 2012, among others). The importance of revealing such practices that are deceiving consumers, health practitioners, and health administrators is beyond any discussion. However, this kind of information would become a short cut if such an analysis results in condemning *any* research sponsored by pharmaceutical companies. Such a generalization might be countered by a theoretical framework that does not neglect the profit-oriented forces stemming from 'Big Pharma', but, rather, one

that also focuses on the multiple socio-historical factors that inform and enable pharmaceutical and non-pharmaceutical reasoning. For example, to consider the 'embeddedness of scientific knowledge' borrows from Mark Granovetter's (1985) classic article the idea that economic lives are based on complex social relations, and further, that truth claims are often, though not exclusively, linked to the ability to transmit trust. Anchoring scientific models in common knowledge implies, at least partly, a process of trust building. Doubting or debunking such theories happens in direct relation to revealing such strategies as different kinds of interests and situated knowledge. However, trust needs to be seen within a wider semantic field; it does not necessarily imply deceiving the other, but can be also linked to the notions of plausibility, tradition, and charisma, among others. Lorraine Daston (2000, p. 13; see also Latour 2000) further elaborates on the concept of 'embeddedness', and notes that 'scientific objects … grow more richly real as they become entangled in webs of cultural significance, material practices, and theoretical derivations'.

Concretely, this would mean to look at generalizations on both sides—at what needs to be critically revealed, and at critique itself. In this sense, another example of a short cut is not only the condemnation of research linked to Big Pharma, but equally of those theories and concepts the industry privileges for promoting their products. Common among scholars working on dementia is the questioning of the current approach to interventions targeting (early) biomarkers (especially, β amyloids and tau proteins). However, pointing out such strategies and critiquing their immoralities do not necessarily mean that the whole surrounding logic should be abandoned. For instance, the fact that the correlation between these biomarkers and the degree of cognitive impairment is not straightforward—some people function well despite having the typical plaques and tangles in their brains associated with AD, and vice versa—is not proof that these biomarkers are mere economic ploys of the pharmaceutical industry. Jonsson et al. (2012), for example, studying the genome of 2000 individuals, showed that some individuals have a genetic mutation that protects them from an amyloid build-up. None of the individuals with this protective mutation suffered from AD or cognitive decline in old age—a strong argument in favour of the amyloid hypothesis for some, but not all, people as they age.

George Perry, a neuroscientist at the University of Texas-San Antonio, argues that drugs are being developed based on a flawed basic idea. The example of Lilly's semagacestat, which actually worsened symptoms compared to placebo in large phase 3 trials, illustrates that amyloid may be a response to, rather than a cause of, the disease. Perry asserts, 'the amyloid theory was very appealing because it offered a therapeutic venue for intervention'. But 'if amyloid was the sole cause of the disease, removing it should have had a beneficial effect' (quoted in Moyer 2011, p. 235). It seems that a certain amount of β amyloids in the brain is needed, since it has an important neuroprotective function, which might explain the existence of β amyloids found in people who do not show significant cognitive decline (see Cárdenas-Aguayo et al. 2014; Hiltunen et al. 2009); and it is the accumulation (or loss of function) of β amyloids that causes its neuotoxicity: 'Since excessively depleting Aβ could have negative effects, limiting its trophic functions could contribute, rather than delay the process of neurodegeneration. (…) Aβ itself, might help to enhance synaptic plasticity and memory at appropriate concentration levels' (Cárdenas-Aguayo et al. 2014).

An independent research team recently defended an idea similar to the statement made by McMenemey in 1940 (cited above)—one of Aβ as a sign of trouble, but not one that can be measured in a straightforward way. They write that:

> [a]s a whole, *there are evidences for which there is absolutely no doubt on*: some cognitively normal elderly have Aβ deposition in their brain, the prevalence of amyloid-positive cases increases in at-risk populations, *the prognosis for these individuals (as a group) is worse than for those with no Aβ deposition*, and significant increase in Aβ deposition over time is detectable in cognitively normal elderly. (Chételat et al. 2013; emphasis added)

This literature indicates that cognitive decline and even a certain accumulation of β amyloids is normal when individuals age; however, there seems to exist a turning point for each individual that leads to neurotoxicity. Nevertheless, the quantity of β amyloids required for this 'turning point' is unclear, and therefore, it remains difficult to distinguish between what is natural cognitive decline associated with ageing, and what is pathology (especially, for the late-onset form of dementia).

Like β amyloids (and tau tangles), mild cognitive impairment (MCI) can be seen as a sign of future trouble. However, MCI, an ill-defined category, needs to be explained to affected individuals, giving them the chance to control certain risk factors, and not presented as a disease in itself, as some do. The short cut here is made by both researchers defending its utility without questioning its limits (and dangers), as well as critical scientists calling it useless. Another argument was made recently by Brayne (2015), who suggested that MCI might lead not only to overdiagnosis and wasted resources, but also, to something resembling a self-fulfilling prophecy: A study by Lineweaver et al. (2014) showed that when people were told they were at risk of dementia due to genetic risk factors (APOEe4), they performed worse on several scales than individuals with the same risk, but who did not know about it.

Within the context of early detection and prevention of dementia, the question whether these measures must involve lifestyle changes, drugs, or both is an essential one, as well as the issue of who has access, and at what price, to such preventive measures. Comparing the preventive doubts of 1993 with the turn towards prevention twenty years later illustrates that new logics emerge and become incorporated into scientific reasoning through multiple claims and theories. The difficult question for researchers is how to critically analyse the existing data by separating short cuts from valid explanatory pathways.

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# 4

# Biomarkers for Alzheimer's Disease: Searching for the Missing Link Between Biology and Clinic

Marianne Boenink

Biomedical research to find so-called 'molecular biomarkers' for disease is booming, and Alzheimer's disease (AD) research is definitely taking part in the trend. For more than 20 years now, all over the world researchers have been trying to identify molecular phenomena, be it on the level of DNA, RNA, proteins, metabolites, or neurotransmitters, which might be in some way or another related to AD. Is the search for AD biomarkers a form of responsible innovation? That depends, of course, on the criteria used to determine what is or is not responsible. A very basic starting point is that to be 'responsible', innovation in the AD field should at least offer a plausible way to improve the situation of people suffering from (complaints related to) AD, whether patients or relatives/caregivers.

It is actually not self-evident that AD biomarker research satisfies even this basic criterion. Some critics contest the problem definition implied in AD biomarker research, or even biomedical research on AD in general. They argue that it does not address the most urgent

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needs of patients. Patients and caregivers are concerned with how to live with the disease, how to provide high-quality care and social arrangements, not with a more precise characterization of pathology (Whitehouse and George 2008; Moser 2011 and this volume; Pols and M'charek, this volume). Others doubt the proposed means: they argue it is implausible that biomarker research will ever produce helpful clinical tools for a large group of people, because of the complex, multifactorial origins of the disease and its complex relation with ageing processes (Kitwood 1997; Richard et al. 2012; Lock 2013). And some are all the more distrustful of biomarker research because it seems to be driven by pharmaceutical, rather than patients' interests (Whitehouse, this volume). Such criticism might lead one to conclude that biomarker research can never be responsible because it is misguided, overly reductionist, and/or biased by pharmaceutical interests.

This chapter, in contrast, starts from the assumption that it would be too rash to dismiss biomarker research as fully irresponsible, because such research is more complex and ambiguous than the critics suggest. While focusing on biological processes, it is not exactly neglecting practical problems in the care for AD patients. On the contrary, it is continuously trying to link (or relink) biological findings with clinical needs and observations. The attention for such linking is reinforced, moreover, by the widely present call for 'translational research': research aiming for results that will be used in the clinic. To assess whether AD biomarker research is a responsible undertaking, the first questions to ask, then, are how it frames the clinical needs, whether these are legitimate and urgent needs, and how plausible it is that the research will succeed in connecting biology with these needs.

Accordingly, this chapter aims to analyse the way current AD biomarker research conceptualizes, pursues, and shapes the interrelation of biological and clinical phenomena related to AD. 'Clinical needs' is understood here in a broad sense, including patient needs and the needs of informal and professional caregivers involved in caring for those with complaints possibly related to AD. I will explore the construction of the interrelation between biology and clinical needs at three levels. First, I briefly analyse the crucial role the 'biomarker' concept plays in discourse on the future of medicine. Subsequently,

I reconstruct the hopes and expectations attached to biomarkers in the scientific literature on AD and in several new guidelines for diagnosing AD. Third, I investigate how the link between biology and clinical problems is shaped at the level of a specific biomarker research project. As we will see, biomarker research for AD is a dynamic business, where targets are constantly moving. In conclusion, I reflect on how the resulting shifts complicate responsible innovation and offer two suggestions to enhance responsibility in this field.

## Biomarkers: Connecting Biology and Clinic

In current discourse on the future of medicine, 'biomarkers' have a crucial role. Such discourse sketches visions of a 'personalized, predictive and preventive (or PPP) medicine' (e.g., National Academy of Sciences 2011; European Science Foundation 2012). In the future, it is suggested, it will be possible to measure an individual's bodily functioning, and the resulting information will offer clues for the diagnosis and prediction of disease, as well as for the most effective therapeutic or preventive intervention. Although interpretations of what PPP medicine would entail differ (Tutton 2014), they all start from the observation that new molecular technologies increasingly open up individuals' bodily functioning *in vivo* and *real time*. By analysing the resulting data with bioinformatic tools, it is possible to infer claims about a person's state of health or disease. Overall, PPP medicine is thought to work with a more precise characterization of a patient's bodily functioning, and with better tailored intervention strategies than current medical practice—hence 'personalized medicine', sometimes also labelled 'stratified medicine' or 'precision medicine' (Tutton 2014).

The plausibility of these visions depends first and foremost on reliable measuring and interpreting of bodily functioning at the molecular level, and this is where biomarkers come in. A biomarker is usually defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention' (Biomarkers Definition Working Group 2001). A molecular biomarker requires, first of all, technologies

to observe and measure bodily functioning at the molecular level. Such molecular observations only become 'markers', however, when they are clearly associated with relevant clinical events. Establishing such associations requires huge databases that connect molecular findings with medical files, and tools from bio-informatics to analyse the correlations between them. Biomarkers embody, then, a link between a biological observation on the one hand and a clinically relevant observation on the other. Depending on the type of clinical observation, biomarkers may predict risk of future disease or contribute to diagnosis of present disease, can offer prognostic information, help select the most fitting therapy and monitor its effects.

The clinical element makes biomarker research different from molecular biology research. Biomarkers are supposed to help distinguish between 'normal' and 'abnormal' or pathological processes. They frame the difference between normal and abnormal first in quantitative terms: there is either too much or too little of a certain molecular substance. The identification and use of biomarkers, therefore, implies what the French philosopher Canguilhem, reflecting on the rise of physiology in the nineteenth century, called a 'quantitative view of disease' (Canguilhem 1991; Boenink 2013, 2016). Such a view identifies disease with abnormal functioning of the body, in terms of a lack or a surplus of certain bodily substances in comparison with the mean level of a reference population.

Canguilhem was quite critical about this quantitative view of disease. One of his concerns was that when measuring bodily functioning, one is easily tempted to suppose that biological observations *are* in themselves 'normal' or 'pathological'. The distinction between health and disease rests, however, on prior subjective and clinical decisions. Biomarkers thus do *not* offer direct access to states of disease and health. At best, they point out that a significant number of individuals with similar test results now or later experienced problems that physicians then qualified as 'disease', or responded well to a certain treatment. They embody a correlation between biological functioning on the one hand and a specific type of clinical observations on the other.

## AD Biomarker Research: Development and Clinical Drivers

If biomarker research pursues linkages between biological and clinical observations, what kinds of linkages are pursued, then, in biomarker research on AD? Research on molecular biomarkers for AD first took off in the late 1980s, with the identification of amyloid-beta (Aß) and tau (the proteins found in the plaques and tangles visible at autopsy in the brain of AD-patients) in cerebro-spinal fluid (CSF). These findings fostered the hope that measuring Aß and tau in living patients would enable a more definitive AD diagnosis during life, instead of at autopsy only. In 1998, the National Institute of Ageing organized a consensus conference about criteria to assess AD markers (Ronald and NIA 1998). Since then, AD biomarker research has broadened to other technological platforms, including several forms of brain imaging (PET, MRI, CT, or SPECT) and blood analysis (Sunderland et al. 2006; Humpel 2011). Attention has focused on three different sets of pathological activity thought to be associated with AD: biomarkers of Aß deposition, of neuronal injury, and of biochemical changes (see also Leibing, this volume). With the emergence of ever more sensitive molecular technologies, research broadened from diagnostic markers to include markers for prognosis of disease progression and prediction of disease risk.

Several authors have pointed out, however, that AD biomarker research is also strongly driven by a *pharmaceutical* logic (Whitehouse, this volume; Lock 2013). And indeed, the scientific literature on AD biomarkers is replete with references to the role biomarkers might have for administering existing drugs more effectively, or for developing novel drugs. Since it has become clear that the pathological processes leading to amyloid plaques and tau tangles in the brain may take years, researchers have hypothesized that current drugs fail because they are administered only when the pathological cascade has developed too far. If this is the case, drugs might be more effective when prescribed earlier. It has been suggested that one might even want to start with individuals who have not experienced any complaints yet, thus making drugs preventive, rather than therapeutic interventions. Biomarkers, reasoning goes, could be a

helpful tool to select to whom drugs should be prescribed. One can see the interests of industry here: moving towards AD prevention would, of course, conveniently increase the potential market for AD drugs (Lock 2013). In addition, biomarkers could serve as surrogate endpoints to evaluate the effect of novel drugs, which might considerably shorten the time span needed for (and thus the costs of) drug trials.

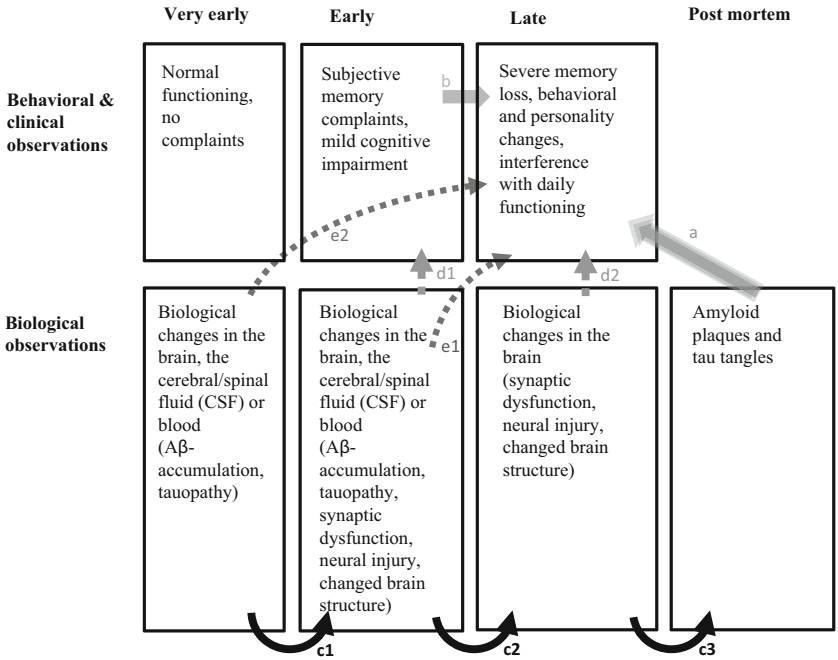
In my view the problem with this pharmaceutical logic is not so much that it is serving the interests of industry only. After all, if the expectations would come true, AD prevention might be an innovation that ameliorates the situation of at least a number of sufferers (although it could very well cause new problems too). The main problem is that the expectations are outright *speculative*. They assume not only that good biomarkers will be found, but also that drug therapies will be available and effective. However, the track record of pharmaceutical research in the AD field does not give much reason to take such speculation for granted. It seems much more plausible that biomarker tests will become available way before any drug treatment can be linked to the test results. If that is the case, what about the 'relevant and urgent need' criterion? Can biomarkers satisfy it independent from any link with pharmaceutical treatment?

Reflecting on this question, it is important to note that the search for diagnostic, prognostic, and predictive biomarkers in the AD field is *also* inspired by the hope to solve two issues vexing clinical practice. The first is the fundamental ambiguity in the label 'dementia of the AD-type', and the weak correlation between behavioural/clinical manifestations of the disease and pathological findings. The second is the difficulty to predict how an individual's complaints will develop in the future. Let me explain the pathways of hope AD biomarkers seem to offer by discussing Fig. 4.1.

The figure depicts the development in time of behavioural/clinical phenomena related to AD (upper row) and biological/pathological phenomena associated with AD (lower row), with the arrows indicating the different types of relations between these phenomena at different moments in time. AD, since its inception by Alois Alzheimer and Emil Kraepelin in the beginning of the twentieth century, has been defined as a pathological condition of the brain, which is thought to explain symptoms of dementia. The gold standard for diagnosing AD is the presence of specific pathology (now known as amyloid plaques and tau tangles)

at autopsy. Arrow A thus depicts the link underlying this gold standard for diagnosis. In clinical practice, however, diagnosis had to rely on the behavioural and clinical manifestations, since pathological phenomena could not be accessed during life. AD, therefore, always has been a diagnosis by exclusion: the symptoms should fit the clinical criteria of dementia and indicators that these are caused by other pathologies should be lacking.

However, by the end of the twentieth century it had become clear that the correlation between clinical symptoms during life and pathological findings after death is far from perfect (hence, the fuzzy contours of arrow A). Some people suffer from complaints, but their brain after death is free from plaques and tangles; others do not show any symptoms




a – gold standard for diagnosing AD; b – progression of complaints related to AD and dementia; c – possible disease pathway; d – possible correlation, maybe causal; e – prognostic (e1) and predictive (e2) relation

**Fig. 4.1** Assumed and sought for links between different types of observations associated with AD

during life, but do show plaques and tangles at autopsy (Snowdon 1997; Savva et al. 2009). This is one of the reasons that physicians, when diagnosing living patients, use the labels '*possible*' or '*probable*' dementia of the Alzheimer type. This ambiguity is, for instance, acknowledged in the recent guidelines for diagnosing AD, developed by the National Institute of Aging and the Alzheimer's Association in the USA, where the authors, for that reason, propose to make a distinction between what they call AD-C (clinical observations) and AD-P (pathological observations) (Jack et al. 2011).

The first hope associated with biomarkers is, then, that these will enable a definitive, certain diagnosis of AD *during life*, 'in vivo'. If some biological events are clearly linked with the later occurrence of plaques and tangles (constituting a biological pathway, depicted by the chain of C arrows), measuring these earlier biological changes (the 'biomarkers') can replace the latter as proof that the symptoms of dementia are indeed due to AD. As a result, link A would become irrelevant and link D2 could be the standard way to confirm a diagnosis of dementia of the AD type. This might work even if it is unclear whether D2 depicts a causal mechanism or just a correlation. Starting from the behavioural and clinical symptoms, biomarker evidence could at least provide a plausible explanation for these manifestations. In effect, then, the clinical diagnosis currently in use would be replaced by an *aetiological* diagnosis, pointing to pathological causes of the complaints. This shift is already visible in the terminology changes proposed in the NIA-AA guidelines (Jack et al. 2011) and a similar set of criteria developed by a working group of scientists in the field (Dubois et al. 2007, 2010), which speak of 'dementia *due to* AD' (my emphasis).

The second promised solution of biomarkers relates to prognosis. Until now, it has been hard to predict with sufficient certainty how the clinical symptoms of patients will evolve in time, let alone which patients with subjective complaints will proceed to full-blown dementia. Since forgetfulness is a widespread phenomenon among the elderly, it is hard to diagnose what is 'normal ageing' and who has a 'disease' to begin with. In the 1990s, the concept of mild cognitive impairment (MCI) was introduced to identify the group of people who manifest subjective memory complaints, but whose symptoms are not serious enough to satisfy the criteria

for dementia of the AD type (Petersen et al. 1999, 2009). Research in this group has shown that only a minority progresses towards dementia (depicted as arrow B), but it is hard to predict who will belong to that minority. Thus, prognosis on the basis of behavioural and clinical symptoms is almost impossible; both the person involved and the physician simply have to wait and see what happens. This is where biomarkers come in once more as a promising tool: by searching for biological characteristics, they might be able to identify those individuals in the group with subjective complaints or MCI who will develop full-blown dementia, thus enabling prognosis based on arrow E1. This presupposes, of course, that both this part of the biological pathway (indicated by the C2 arrow) and the link between the biological measurements and behavioural/clinical observations of disease (D2) are sufficiently strong.

Biomarkers thus promise to bridge two gaps at once: the diagnostic gap between clinical symptoms and pathology (where the D2 arrow would replace the ambiguous A arrow), and the prognostic gap between different stages of disease (where the E1 arrow would replace the B arrow). To top it all, it might even become possible to take a further shortcut and use biomarker test results to predict which asymptomatic individuals will develop the complaints associated with dementia of the AD type (arrow E2). Proponents of AD biomarker use argue that since the disease course from the first molecular changes to the development of clinical symptoms may take ten years, and that it make take a further ten years from the first symptoms to a full-blown dementia, there seems to exist a huge window of opportunity for biomarker measurements to fulfil a predictive function, in addition to their diagnostic and prognostic role (e.g., Dubois et al. 2007). Again, such reasoning presupposes that the associations between early biomarker test results and subsequent clinical outcomes are sufficiently strong—or, in other words, that the presupposed pathological cascade (indicated by the C arrows) is sufficiently predictable and that the link between pathology and disease manifestations (D arrows) is sufficiently unambiguous.

The catch in all three expectations is that the ultimate value of diagnostic, prognostic, and predictive markers depends to a large extent on the type and strength of the associations found. In the best case, there is a clear biological pathway that, once started, progresses in a certain

way, and this pathway is causally linked to the occurrence of behavioural and clinical manifestations. In that case, the biological pathway can be understood as a *pathological* pathway, and measuring biological functioning would indeed enable aetiological diagnosis, prognosis, and prediction of future functioning. However, if the links between biological and behavioural-clinical phenomena (the D arrows) are merely correlative, the whole picture becomes fluid again. Even if the biological pathway would inevitably lead to plaques and tangles (C1 always progresses towards C2 and C3), there is always the possibility that these biological changes are not pathological. A biomarker could then indicate an increased risk of the future emergence of plaques and tangles, but how useful is that?

Where does all this leave us when it comes to the question whether AD biomarker research addresses legitimate and relevant clinical needs—the minimal condition for 'responsible biomarker research'? First of all, one may doubt whether patients and their caregivers need an aetiological diagnosis. As van der Laan (this volume) shows, causal explanation is only one of the values pursued in diagnosis. If, instead, one is looking for a more precise description of functionality to better support patients and families in their attempts to live with AD, an aetiological diagnosis is not that relevant (see also Pols and M'charek, this volume). Van der Laan (this volume) also shows, however, that the value of prognosis is relevant to those who want to control the disease, as well as to those who try to live with it. So, the prognostic function of biomarkers may address a more widely shared need than the diagnostic function. To be sure, this applies to prognosis in the case of patients already experiencing complaints, but much less to prediction in the case of healthy individuals. The problem is that prognostication is not independent from, but presupposes diagnosis. Such a diagnosis need not necessarily be aetiological, however, and it might, in principle, be possible to pursue the identification of prognostic biomarkers without using diagnostic markers.

The crucial point of this section is that both the prognostic and the diagnostic expectations about AD biomarkers will be realized only if a sufficiently convincing connection is established between biological findings and clinical phenomena related to AD. It is far from evident that biomarker research will establish such a link, because this is quite complex

and the outcomes until now are not fully convincing. Let us take a brief look at a specific research project to further examine the difficulties.

## AD Biomarker Research in Practice: The LeARN Project

The Leiden Alzheimer Research Nederland, or LeARN-project, was funded by the Dutch Centre for Translational Molecular Medicine (CTMM) in 2007. Between 2008 and 2013, researchers at a number of universities, academic hospitals, and private companies worked on the identification and validation of biomarkers for AD. The objectives of the project were formulated as follows:

1. to develop new innovative (molecular) imaging and molecular diagnostic CSF tests for AD that exploit disturbances of amyloid metabolism and glutamate neurotransmission,
2. to translate these techniques from bench to bedside, and
3. to assess and compare the clinical and economic value of these tests, other emerging diagnostic tests, and the diagnostic tests that are currently considered the standard diagnostic work-up in a large-scale study in patients from memory clinics. (LeARN 2007, p. 1)

The relevance of these objectives is argued for with a mixture of clinic- and pharma-driven arguments. The research proposal refers both to the demand for more reliable diagnostics, and to the lack of clear selection criteria for investigating the effectiveness of, and eventually, for prescribing, drugs.

As the project leader explained in a personal conversation, biomedical research on and care for AD has long been hampered by problems along three dimensions: the underlying pathology is unclear and hard to access during life; there are no reliable diagnostic tools; and the effectiveness of drugs is limited. These uncertainties are all interrelated: diagnosis is hard because the pathology can be proven only after death, and as a result, we don't know whom to prescribe drugs; drugs show limited effectiveness because we don't know what pathology to counter and because patient

populations are not well-delineated, but delineating them is hard because diagnostics is unreliable, and so on. These interrelations lead to a complex of uncertainties perpetuating each other, which is hard to break through. Currently emerging possibilities to access the body *in vivo* might be a lever to crack this vicious circle.

It is further worth noting that the project was explicitly framed as 'translational research', claiming that it would develop biomarker tools that are useful 'at the bedside'. In practice, however, the clinical relevance of any biomarker resulting from the LeARN-project was shaped by a number of choices made in the design of the project. In the following lines, I will briefly highlight three choices that seem particularly relevant when investigating the link between biology and clinic.

## Choosing Candidate Markers and Technological Platforms

The first one concerns the choice of which potential markers to focus on in the project. As discussed above, many different biological phenomena have been proposed as potential markers for AD, and many different technologies might be used to visualize them. Given that due to time and funding constraints, any research project has to focus on a limited set of candidate markers, how does one determine which ones to go for? The LeARN-project, in general, embodied a pluralist and risk-spreading strategy. It combined different types of markers as well as different technological platforms. It looked at markers of amyloid metabolism and of glutamate neurotransmission, using PET and MRI imaging, and CSF analysis. For each of these, work on markers that had already to some extent been developed (and which was relatively low-risk) was combined with more innovative, high-risk work. The project was actually set up as an internal competition: multiple candidate markers were explored, but only the most promising would be included in the eventual clinical assessment.

Clinical considerations do not seem to have played a huge role in the choice of markers, however. Both amyloid and glutamate markers are tied up with the amyloid cascade hypothesis, and are thus grounded in the

same pathological explanation of AD. This explanation was already contested when the project was developed (e.g., Lee et al. 2004; Pimplikar 2009), but neither the controversy nor potential alternative avenues were discussed in the research proposal. The choice to focus on amyloid-related markers made it likely, however, that any biomarker resulting from the project would suffer from the uncertain correlation between amyloid plaques and clinical manifestations of AD. Moreover, individuals manifesting symptoms, but not showing amyloid pathology would not benefit from project outcomes.

Attention for the practical implications of the different technological platforms was also lacking, or at least subsumed to scientific evidence about outcomes. If the best biomarker is produced via 7T MRI or PET scans, this effectively implies that patients will have to travel to specialized centres, and in case of MRI, those with metal implants such as pacemakers cannot be tested. If CSF analysis is most reliable, patients probably can be tested nearer to home, but have to subject themselves to an invasive procedure. Such implications were not taken into account in the design of the study. The implicit suggestion is that these are minor considerations once a marker has been proven to be truly informative. Overall, then, the choice of candidate markers seems to have been driven by scientific and pragmatic motives, at the cost of considerations of clinical relevance and usability.

## Choosing Outcome Measures

A second choice concerns the way candidate markers were evaluated. As we saw above, the ambiguous relation between symptoms and AD plaques and tangles makes it crucial to establish a convincing link between amyloid and glutamate-related measurements and clinical manifestations of the disease. The question, then, is what the outcome measures of a clinical study should be: a clinical diagnosis or a pathological diagnosis at autopsy, or both? The LeARN-project, as most biomarker research, opted for clinical outcome measures. This can at least be partly explained by practical considerations. Correlating biomarker test results with post-mortem findings is unpractical and takes time. Moreover, a marker identified on

the basis of a comparison with a clinical diagnosis does have practical relevance; it will tell patients and physicians something about current or future complaints and symptoms. However, since the patient population is likely to be biologically heterogeneous, the established correlations will never be perfect, even if they are high. Any biomarker found will be at best a risk factor for the presence or future development of dementia of the AD type, but not a determining cause.

Opting for a comparison with current clinical diagnosis also poses an additional problem: what counts as a good diagnosis? Since current diagnostic practice is quite heterogeneous (van der Laan, this volume), comparing the value of biomarker information with existing diagnoses means relying on labels from heterogeneous origins. In the LeARN-project, the original diagnosis was therefore put into brackets and a new, standardized procedure was developed to establish the clinical point of reference. All patients included in the clinical study were diagnosed by a panel of three experienced clinicians with different specialties. The panel members did not meet the patient in person, but received all written material about the case. They all made their own diagnosis—first, on the basis of the material collected at inclusion, and subsequently including information collected during follow-up consultations. The three panel members convened to discuss the cases about which they disagreed. The diagnosis after the two-year follow-up was taken as the gold standard, to which the information offered by candidate biomarkers was then compared.

Such standardization, however, creates a gap between research and 'real life' diagnostic practice. If candidate biomarkers show added value, it is unclear whether this also holds in the less controlled, messier reality of everyday clinical practices. One may redesign everyday practices to mirror the procedure used in the project, but this might neglect other values implied in those practices.

In sum, opting for clinical outcome measures is not a guarantee for clinical relevance. In the case of the LeARN-project, the fundamental uncertainty regarding the pathological status of resulting biomarkers was not addressed. Moreover, such biomarkers might have added value for the streamlined diagnostic procedure set up in the research, but need not be indicative of its added value in everyday diagnostic practices.

## Choices Related to Patient Inclusion and Follow-Up

The LeARN-project investigated both the diagnostic and the prognostic value of candidate markers. The selected patients were followed for some time, to increase the certainty of the initial diagnosis and to find out whether early biomarker measurement could have predicted deterioration during the subsequent years. Again, practical considerations severely limited the prognostic part of the evaluation. The overall duration of the LeARN-project was five years, but since the first years were dedicated to identification and validation of candidate markers, the clinical study lasted two years only—which is short in view of the long time span during which AD complaints and symptoms develop. It is no surprise, then, that ultimately none of the candidate biomarkers had added value for prognosis (Handels 2014). The researchers suggest that a longer follow-up period might have led to a different result (Handels 2014, p. 167). However, if AD pathology takes a long time to develop, even five years follow-up may not produce significant differences. Moreover, the longer the time span covered by the predictive or prognostic value of biomarkers, the more one can question the actual value such predictions have for patients.

Interestingly, the researchers suggest that even though biomarkers do not show any diagnostic or prognostic value, they may prove helpful in selecting treatment when this becomes available in the future (Handels 2014, p. 165; Handels et al. 2015). This claim is based on a modelling study in which several scenarios with different assumptions about the availability of disease-modifying treatment were compared. Similar reasoning can be found in many scientific publications on AD biomarkers, but, again, it is highly speculative. It could be interpreted as *function creep*, with claims about treatment-related functions for biomarkers as cheap ways to keep the hope alive that the scientific efforts are not in vain.

Overall, the choices made in the design of the LeARN-project show the difficulty of setting up biomarker research in such a way that the results are indeed relevant and useful for patients and caregivers. Clinical considerations are easily ignored when designing a research project, even

when it is presented as translational research. When choosing markers that are related to a contested explanatory model, one can expect from the start that the outcomes might be useful for a subgroup of patients only. The same goes for the choice to use a clinical outcome measure only, without a pathological point of comparison. And limits with regard to follow-up time also limit the chance of identifying useful prognostic markers. This is not to say that there are good and easy alternatives to such a research design; with the elusive character of the AD clinical picture, AD pathology, and their correlation, it is almost impossible to come up with a research set-up that would not be compromised by this complexity.

## Conclusion

In the introduction, I argued that 'responsible' AD biomarker research should at least address legitimate and urgent needs of those suffering from AD. AD biomarker research fuels many hopes at once; biomarkers are expected to improve diagnosis and prognosis, to enable prediction of AD in healthy people, improve treatment selection, and stimulate treatment development. Since the last three aims are rather speculative, this chapter has focused on the potential diagnostic and prognostic function of biomarkers.

I first highlighted how 'biomarkers' in general link biological observations with clinical experiences. Constructing such a link in the context of AD is particularly challenging, because the biological findings that have defined the label 'AD' since its introduction do not fully match with the clinical picture associated with AD. This mismatch complicates current diagnosis and prognosis of AD, and the hope attached to biomarkers is precisely that, by establishing a clearer link between biology and clinical observations, biomarkers can improve both diagnostics and prognostics. These are at first sight indeed legitimate aims, although prognosis may actually be a more widely shared need than the aetiological diagnosis.

For both functions, AD biomarkers should establish a convincing link between biological findings and clinical observations. In practice, however, this is quite hard to pull off. This is not only because the outcomes

of biomarker research are as yet limited. As we have seen in the case of the LeARN-project, the set-up of such research also plays a role. It is quite complicated to design biomarker research in a way that cuts a clear and convincing path through the complex, multiple, and messy realities of AD and dementia. Practical considerations concerning time and budget are an important limiting factor when it comes to outcome measures and time allowed for follow-up. More importantly, scientific considerations concerning internal validity often ignore the diversity of patient populations and diagnostic practices, which limits clinical relevance of any results. Ultimately, clinical and patient-related considerations do not seem to be at the forefront during research design.

To conclude, biomarker research easily boils down to basic molecular biology research, contributing to knowledge about biological processes which may or may not be pathological, while patients' and caregivers' needs disappear from view. Is that irresponsible? Not necessarily, because one may wonder whether without such basic research, the Gordian knot of the relation between AD pathology and dementia will ever be solved. However, it is hardly what biomarker research purports to offer, thus raising questions regarding the responsibility of scientific promising. Let me end, then, with two suggestions to enhance responsibility in biomarker research.

First of all, AD biomarker research could profit from 'epistemic responsibility': the disposition to conduct one's pursuit of knowledge as well as possible (Code 1987). This means that researchers carefully tailor their research method to the aims of their project, pay attention to the concepts and theories used, how these frame the studied object, and what they do and do not make visible. An example is the proposal in the NIA-AA guidelines to clearly distinguish AD-C and AD-P. Epistemic responsibility in AD biomarker research also implies that researchers acknowledge the uncertainties, ambiguities, and limitations in and of their work, and do not overpromise. This would construe a fairer comparison between spending public funding on biomarker research, on other attempts to improve diagnostics and prognostics, or on different ways to improve the lives of people struggling with dementia altogether.

Second, researchers who do not want to give up on clinical relevance might take on an additional, 'translational responsibility'. If you truly

want to improve patients' lives and needs, it seems wise to start from the patients' situation, and then work backwards to find out how research could help solve their problems. This might impact not only the types of questions asked in science and the technologies pursued, but also the scientific methods used (see also Pols and M'charek, this volume). Instead of designing research in controlled lab settings, practice-based research may be much more helpful for the problems people are struggling with in daily life and in clinical practices.

Urging for epistemic and translational responsibility invites individual scientists and research groups to be more reflective in the design and execution of research. However, as the examples discussed in this chapter illustrate, both responsibilities ultimately point beyond the level of the individual and the scientific domain. Funding organizations, policymakers, media, and patient representatives co-shape the world in which scientific researchers make their choices. Responsible research, that is, requires careful considerations and decision-making in many places.

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# 5

# Care and Responsibility in Building Futures for Alzheimer's Disease Research

Richard Milne and Shirlene Badger

The reconceptualisation of Alzheimer's disease (AD) as a long-term process with an 'asymptomatic' stage that may precede symptoms by over a decade (Dubois et al. 2007; Sperling et al. 2011) situates it firmly within the life course, rather than as solely a disease of older people. However, the relationship between the development of pathology and the 'normal' ageing process remains unclear, the biological processes occurring at early stages of pathology poorly characterised, and the markers of these processes uncertain (see also Boenink, this volume). There is a need for new models of AD pathogenesis and progression and a search for more and better data on which to base these.

In the UK, Prime Minister David Cameron's G8 address on dementia in December 2013 laid the blame for the failure of dementia research in part on researchers who were 'frankly not really working together enough'. Rather than working together in a collegiate fashion, he

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suggested that there was, in fact, 'a lack of collaboration and openness with different scientists all over the world using different data and trying different approaches'. Data platforms such as the European Medical Informatics Framework and the Dementias Platform UK, which bring together researchers across nations and regions to offer a response to this perceived incoherence. The move to a longer-term model of AD thus draws on and fuels the hype and expectation that accumulates around the development of 'big data' initiatives (Davies et al. 2013). Moreover, as bigger research becomes the answer, traditional research structures and relationships become seen as problematic.

Two approaches are particularly prominent in the new Alzheimer's research initiatives spurred by a new wave of funding and political interest. The first is the development of new registers of the research-interested, such as the US Alzheimer's Prevention Registry or the UK's Joint Dementia Research. A second approach, considered in more detail here, draws on existing data and participation within new data platforms. In addition to bringing together data from a range of existing epidemiological studies in a standardised data sharing process, platforms potentially facilitate the recruitment of what are commonly described as 'motivated' and 'well-characterised' (in that they have known biological, social, and cognitive 'trajectories') individuals into future research. From the perspective of research funders, this contributes to 'maximising the value' (MRC 2014) of longitudinal research.

## Cohort Studies

Observational studies of population 'cohorts' fill a distinctive and little examined space in biomedical research (see Moreira and Palladino 2011, for an exception). Epidemiological textbooks and overviews highlight the classical, military etymology of the cohort as an organisational unit of the Roman army, a body of infantry of between 300 and 600 men, of which there were ten in a legion. As one introductory piece suggests, this origin continues to be relevant, providing 'a useful mnemonic: a cohort study consists of bands or groups of persons marching forward in time from an exposure to one or more outcomes' (Grimes and Schulz 2002, p. 341).

This reflects the key qualities of observational cohort studies: time—as studies which examine changes in individuals over a long period; and an imagined sociality in the identification or constitution of groups who move through time together.

The use of the 'cohort method' to describe the patterning of health and illness over the life course dates from the 1930s' work of Kermack and colleagues on death rates in the UK and Sweden, in which they showed the importance of 'the year of birth of the generation or group of individuals under consideration' in mortality (Kermack et al. 1934). The subsequent year, the term 'cohort' was used by Wade Frost in his work on the incidence of tuberculosis by sex and age in Massachusetts (Frost 1995; Doll 2001). These retrospectively identified cohorts have since been joined by prospective studies, which follow individuals over time from a shared starting point, including the regular establishment of 'birth cohorts' in the UK from the 1940s onwards (Wadsworth and Bynner 2011).

Longitudinal cohort studies have been central to the widespread reconceptualisation of disease in terms of 'risk factors' and a concomitant interest and investment in public health medicine. Large numbers of people are now enrolled in observational studies—in the UK, the MRC estimates more than two million individuals, or 3.5 % of the population, are currently participants in longitudinal cohort research. Most participants in cohort studies in the UK are currently between 45 and 74, the age group of research interest in the era of redefined AD.

As introduced above, the promise of dementia initiatives draws on the rich data provided by cohort studies. However, they also position cohorts as more than a data source, emphasising the importance of existing research infrastructure and research-motivated participants to suggest their potential value as biological and, critically, social resources for future studies including therapeutic trials. Consequently, a 2013 editorial in the *New England Journal of Medicine* suggested that the use of existing registry or cohort studies as a source of participants for therapeutic trials represents a 'disruptive technology' with the potential to 'revolutionise' clinical trials (Lauer and D'Agostino 2013) by reducing costs and increasing the speed of research. This approach is, they suggest, a pragmatic one, involving biomedical research 'making the most of what we have'. Thus, the Dementias Platform UK aims to 'create a closer synergy

between epidemiology and experimental medicine' including 'recruiting well characterised cohort participants to discovery studies and trials' (DPUK 2015).

These initiatives refocus attention on cohorts not simply as data sources, but as a social resource. Cohorts are conceptualised as 'banks' of participants about whom much is known and who have their own investment in the research process. The vision of cohort research mobilised posits a particular form of sociality—which, following Latour (2005), is never entirely 'social', involving motivated research participants and researchers but also infrastructure and data stores. In the following sections, we explore this sociality, drawing on the example of work conducted with one particular cohort.

## The Sociality of Cohorts

While the potential of cohorts to contribute to dementia research is narrated as the promise of 'big data', the construction of hopeful therapeutic futures relies on the claim that these cohorts function as social organisations. Existing research has suggested that the conduct of biomedical science has contributed to the development of new forms of sociality pivoting and organised around biology (Rabinow 1996). 'Biosociality' originally described how social identities were being formed according to genetic diagnoses (Novas and Rose 2000; Rabinow 1996) and has been used to explore how ideas and perceptions of citizenship are shaped by emerging understandings about what a disease is (Gibbon and Novas 2008). The impact of the reclassification of disease made possible by genetic knowledge, for example, catapulted sociological and anthropological investigations into the impact of a genetic predictive test or diagnosis for how people view themselves and their relationships to others. Significantly, further exploration has been concerned with how these new 'identities'—through patient organisations, charities, and other collectivities—create new relationships between affected individuals, lay people, and scientific experts (Jasanoff 2004; Rabeharisoa and Callon 2004). It is suggested that this subsequent rewriting of the intersection of the experiences and lifeworld of affected people and the science about their disease

reflects a process of democratic co-production of knowledge within the medical sciences (Nguyen 2008).

Initiatives such as Join Dementia Research (JDR) and cohort studies represent particular, if potentially very different, forms of sociality. JDR and the Alzheimer's Prevention Registry set out to capture an interested population—many subscribers are people with experience of parents, grandparents, or siblings with AD. They mobilise familial experiences of disease and draw on the strength of biological and social ties to create a constituency for the future of dementias research. In contrast, while the sociality of cohorts that we describe here is also formed through biomedical research, it is not as specifically through the biological redefinition of disease. Rather, these groupings reflect and are given sustained life by scientific definitions of the 'social' and constructed and reconstructed through innovation in the science and its changing requirements. Moreover, their form of sociality is a subtle one, in which people move in and out of identities ascribed by biomedical science and by virtue of which they are drawn into new arenas for the pursuit of technoscientific progress.

The primary consideration in thinking of cohorts as a form of sociality is the way such groupings are constituted. Although, as we expand below, existing social networks play an important role in inclusion in cohorts, the initial impetus for bringing people together is to serve a scientific purpose, and the nature of the grouping—whether a volunteer cohort such as UK Biobank, a population study, or a disease register—reflects a scientific definition of relevant characteristics or qualities. The example we focus on, a representative population study, highlights how epistemic requirements determine the bounds of the 'social' in cohort research. In a sense, people enter the research based on their insignificance. They are not expressly people with a disease, or those who are particularly interested in research—their inclusion in the social institution that is the cohort is utterly aleatory, and this is critical to the study's validity.

Once constituted, a number of heterogeneous elements can be observed that contribute to the sociality of cohorts. Based on these characteristics, longitudinal cohorts can be understood as distributed, hierarchical, and mediated social organisations that are secondary to existing social networks and which have a stable infrastructure that allows the

cohort to persist by enabling repeated interactions between researchers and participants.

Cohorts consist of associations and connections; they involve interactions between researchers and participants. The value of cohort data is based on the social organisation of research—the longer people have been involved in research, the more interactions they have had with researchers, and for those that remain involved in research, the stronger the bonds that tie them become. As cohorts evolve, they become intensified, as those who are less engaged drop out (what epidemiologists describe as 'attrition') and those who remain are those committed to the research process. Members of some cohorts may in this way develop a sense of shared identity, and researchers involved in the study become closely tied to it. This is particularly evident in the case of birth cohorts, such as the Avon Longitudinal Study of Parents and Children (ALSPAC), in which participants are part of a study from infancy, while researchers may spend a career following the same group of people.

While cohorts are themselves distinctive forms of social organisation, they are necessarily secondary to existing social networks, although the prominence and cohesion of these varies. For example, cohorts may be recruited through primary care registries as a representative or opportunistic sample (as in the case of UK Biobank), from secondary care into a patient registry, or even through kin relations—whether parents, in the case of a birth cohort, or via family members affected by a disease.

Furthermore, interaction in cohorts is materialised through the construction of networks of communication and data management and their maintenance. It is this materiality which enables cohorts to persist over time and over space, particularly in the case of studies that are geographically distributed. Such cohorts rely on the iterated but often infrequent collection of information and biological materials across a wide geographical area. The cohort infrastructure thus has to be perpetuated and maintained between interactions, requiring a core group of individuals whose role is to care for the cohort itself, as well as curating the data and facilitating access by collaborators.

In recognising the heterogeneity of the social organisation of cohorts, it is also important to point out that cohorts are hierarchical and information in the cohort is asymmetrical. Cohorts are led by individuals or

core groups of researchers, who come to act as gatekeepers to the study population. It is these individuals who determine the future direction of the cohort as an institution, and while participants and other researchers can chose to participate or not, they have traditionally had little role in determining this direction. There is also significant informational and decision-making asymmetry related to the data collected by the cohort study and its findings—despite efforts to feedback information to participants—and, most importantly, related to the future of the study. The hierarchy structures communication within the cohort, which is also asymmetric and channelled, comprising primarily information passing from participants to researchers, with little or no interaction between the former.

## The MRC Cognitive Function and Ageing Study

The promise of reusing observational data and studies and the potential of cohorts as a site for thinking through the ethics of cohort platforms can be explored through one of these studies, the MRC Cognitive Function and Ageing Study (MRC CFAS). Through the example of MRC CFAS, we hope to open up discussion of the ways in which the characteristics of cohort studies create challenges for the conduct of research that is not only ethical, but that reflects accumulated research relationships.

The MRC CFAS studies are multi-centre longitudinal research studies, first funded by the Medical Research Council in the late 1980s to investigate the ageing of the UK population, specifically focussing on cognitive decline and dementia. A representative sample of around 18,000 people, 65 or older, was recruited across the centres from the lists of GP surgeries (Brayne et al. 2006). The study involved a screening interview of the entire sample, conducted by lay interviewers, recruited and trained specifically for the study. These interviews were carried out in respondents' homes using portable computers. A randomly selected stratified sample were re-interviewed over the course of the following years, before all surviving and responding participants were re-interviewed after ten years. Over 3000 survivors from the original sample were re-interviewed when the study finished in 2003. In 2008, a 'daughter' wave of the study

began, recruiting a new cohort of 12500 respondents and conserving but expanding the original methods, with interviews again conducted by interviewers trained within the project. The aim of the second study was to provide new data that would enable comparison with the earlier study and provide baseline data on the cohort expected to be at their most frail in 2020s—when the older population peaks and therapeutic interventions 'could be expected to have an effect'.

In 2013, the governance group of the CFAS II study organised a series of workshops with core CFAS researchers and invited experts to scope the possibility of developing an intervention study using the CFAS population. This expert group identified a range of possible benefits to repurposing CFAS, including the value of accumulated data, the size and representativeness of the population, the existence of strong links with local service providers, and the well-established human and material infrastructure for conducting research. They also identified 'social' factors supporting a move to an intervention study, including the possibility of reciprocating participants' contribution to the study and the value of having a motivated, previously engaged population of people from which to recruit.

Following the expert workshops, it was suggested that it was critically important to engage the wider constituency of people involved in the study in thinking through the future of the research. This work involves two strands. The first component is a series of deliberative workshops with research participants. In addition, a day workshop was conducted with study interviewers—the individuals responsible for travelling to participants' homes, conducting a nearly 600-question research interview and thereby collecting the data on which the study's scientific value is predicated.

As described above, the nature of a cohort means repeated contact between researchers and participants. These are enabled by the infrastructure of the cohort study, but are themselves central events in the persistence of cohorts. Both CFAS studies—like much epidemiological work—were interview-intensive. CFAS I accumulated around 47000 interviews, each conducted in person in the respondents' homes. These interviews establish a long-term connection between the study researchers and respondents. This connection is mediated by a large group of

trained interviewers, drawn from a range of backgrounds, including health-related professions, such as nursing. During and between these encounters, 'good' relationships must be maintained between researchers and participants in order to facilitate future data collection and minimise the loss of individuals from the study. The repeated research encounters thus play an important role in renewing the cohort, refreshing participation, and re-familiarising participants with the study, its structure, and requirements. Attending to the encounters and interactions points to the diversity of actors involved in the production of a cohort—not only 'researchers' and 'participants', but a variety of gatekeepers, including family physicians, and research interviewers, coordinators, or research nurses.

The purpose of the interviewer workshop was twofold. First, it aimed to bring the views of interviewers on the potential development of an intervention study and different options for doing so into the decision-making process. Second, and as we focus on here, the workshop was used to explore the relationship between interviewers, participants, and the study, and to provide insights into what we suggest is a particular form of scientific sociality.

## Mediating the Cognitive Function and Ageing Study

In highlighting the social organisation of cohort research, we aim to draw attention to the relationships and encounters through which data is produced, and through which the 'social' promise of cohorts as banks of research-interested, motivated participants is maintained. However, highlighting these encounters, and their intensity, raises questions about the nature of interaction, and the implications, and potential for thinking about responsibility in research. To understand these further, we turn to work conducted with the interviewers involved in collecting data for CFAS II.

A group of trained interviewers mediates the long-term and repeatedly renewed connection between the study researchers and respondents described above. They are drawn from a range of backgrounds, including

health-related professions, often nursing, and some have been involved in the research for over a decade, conducting face-to-face interviews with CFAS participants within their particular geographic study region. The role of interviewers and other research practitioners has been an often overlooked part of the research process, but represents a potentially central one in understanding how cohorts function as social organisations, and how caring relations can be established or valorised within this.

While the work of interviewers and equivalent researchers in cohort studies has received little attention, medical sociologists have explored the role of study coordinators in clinical trials (Fisher 2006; Davis et al. 2002). Like MRC CFAS interviewers, clinical trial study coordinators are predominantly female and come from a nursing or caring background (Fisher 2006). Davis and colleagues suggest that the job of study coordinators has remained invisible in discussions of research practice because it is considered an assistant's position, with little authority or autonomy. Fisher argues that the work of study coordinators is often overlooked because it is seen as unskilled women's work. This echoes a wider bracketing of care as 'women's ethics' and its exclusion from an ethics of the male-dominated public sphere (Tronto 1993).

In clinical trials, coordinators represent the main people through whom research participants interact with the pharmaceutical industry and come to feel that they are cared for (Fisher 2006). Fisher points out that the ethical stances adopted by study coordinators relate more to interactions with the research participant than to industry ethical standards—for example, in their adoption of normative positions on whether it is appropriate for an individual to be involved in a trial, regardless of their relation to inclusion/exclusion criteria. Consequently, she suggests coordinators experience role conflicts as they try to balance their responsibilities to patient subjects with those to the pharmaceutical companies that fund their work. Davis et al. (2002) similarly capture the multiple and occasionally conflicting social positions adopted by study coordinators, who they describe as the 'invisible hand' in clinical research. They suggest these range from 'patient advocates', whose role is to 'mother' or 'take care of' participants, to 'subject advocates' focused on protecting participants' rights, to 'study advocates', who believe in the value of the study and in making it work.

## Meeting the Cohort

Unlike study coordinators, who work in a clinical trials setting, which often overlaps with the site of clinical care, interviewers work in individuals' home—often over a period of up to four hours in a structured, wide-ranging conversation. Also, unlike those involved in running clinical trials, they are not formally involved in caring for research participants. Reflecting on the interview process in the workshop, interviewers describe the extent of the information they capture about someone's life and the intensity of the interaction:

> IV4: It's amazing how much you get to know about someone, you know from the moment you arrive to the moment you leave, you get quite close to them because you've learned about their whole lives.
>
> IV6: Then they start asking you quickly about your life don't you, well I don't know anything about you, as though to make up for the conversation.
>
> IV7: Like sharing.
>
> IV6: Like where you from?
>
> IV4: Well I do share some things, I say like I've been on holiday or my daughter's at university. You just do, because it's nice, it's natural too isn't it. It helps the conversation along. I don't give them personal details but … (Source: CFAS interviewer workshop)

Interviews cover participants' 'whole lives'. Similar descriptions of the interviewer's role are found in other cohort studies. The relationships formed during the course of the interview are not those of 'everyday' interactions—they are one-sided and interaction in the interview is shaped by the requirements for the interviews to be 'data collection', rather than socialising. Nevertheless, they require everyday or 'natural' conversational elements, and as IV4 adds in the extract above, interviewers do share their own stories, to 'help the conversation along'. In their researchers' narrative 'story of the Newcastle 85+' cohort study, Morris and Kirkwood similarly describe how an interviewer's sharing of her own experiences with participants enabled her to 'enhance her relationship' (2014, p. 63) with participants.

The importance of individual interaction, and (despite its contested status in survey interviewing) 'rapport' in conducting cohort research

reflects the tension between the 'technique' of standardised interviewing and the locally accomplished interactions that constitute data collection (Maynard and Schaeffer 2000). Verbal and non-verbal interaction around the content and meaning of questions, as well as moments of arrival, departure, and breaks form unscripted moments within which the identities of 'friendly', encouraging and responsible researchers and in some circumstances, of willing and responsive research subjects are enacted.

The importance and nature of the interview process varies depending on the perceived needs of the interviewee. In particular, interviewers draw attention to the role of the interview for those who are socially isolated:

> IV4: Quite a lot of people were living on their own sort of really quite bored, sitting alone watching TV all day nothing else to do
>
> IV2: They always wanted you to stay longer didn't they, you had to be very careful how you …
>
> IV4: … I may have time to look at the family album once I've finished doing this and it was always bringing them back to the interview. They just wanted company
>
> IV2: And I think quite a few people had agreed to the interview because it was some company
>
> IV4: Yes, can you stay for your dinner or …
>
> IV2: Yeah, they do don't they? (Source: CFAS interviewer workshop)

As this extract suggests, the interviews can play an important role for both researchers and participants. Interviewers here balance the needs of the study—completing the interview without being distracted—with the perceived immediate needs of participants for company and conversation. They point to the rules of 'normal' social interaction that shape participants' understandings of the research encounter—in this case, staying for dinner after the interview. The unfamiliarity of the research encounter, its scope, and duration means that interviewers are able to make selective use of this repertoire to facilitate the conduct of an interview in a way that is as sensitive as possible to the perceived physical, emotional, and social status of the interviewee. As they continue, this may involve avoiding constituting the interview as a social interaction entirely, constituting it as much as possible as a brisk encounter to take receipt of the interviewees' 'gift' of participation:

IV1: I think for as many as who are lonely, and want to hang on to us for the interview, there's another group who have done it for sort of altruistic reasons, and they're not necessarily glad to get you out of the door, but they don't need to hang on to you. So it balances out and it's two distinct areas I think. (Source: CFAS interviewer workshop)

The perceived place and importance of the interview in the lives of participants thus varies, and interviewers attend and respond to the needs of participants by reducing the encounter to the minimum required to fulfil the requirements of the study. However, as the interviewers continue their discussion, they draw attention to a final group of participants whose experience of the interview cannot be fitted with existing forms of interaction:

IV6: Yes, and you've got the third group that it's really far too long for them and they get fed up

IV7: That was my biggest problem with the whole thing, was so much was thrown into the interview, and especially with the very older age range it felt far too long, so if we're going to go in and do something else …

IV6: Shorter

IV7: … shorter, even if it means going back more regularly (Source: CFAS interviewer workshop)

Here, interviewers draw on their experience with some participants, including the oldest in the study, to draw lessons for the conduct of future research. Again, they attempt to ensure that future research reflects the needs of the participants—in this case changing the rhythm and duration of interviews. This requirement may conflict with other factors involved in research planning, not least the cost of short, repeated interviews versus longer, one-off meetings. The attention to participants' welfare and vulnerability highlights the potential for caring relationships to form in the interview setting. However, it suggests that, like the study coordinators described by Davis and colleagues, interviewers are constantly involved in balancing their responsibilities. On the one hand, they hope to care for the people about whose lives they are learning, while on the other, they are committed to generating and collecting the data required for the research process.

## Care and Responsibility

In their work with clinical trial coordinators, Davis and colleagues point out that the pivotal role of the coordinator as 'the person with whom subjects interact the most, and the one most able to identify their needs and employ necessary procedural safeguards' (2002, p. 418). In their discussion of a care-oriented approach to the future implications of technoscience, Adam and Groves (2011) echo care theorist Held in arguing that care characterises relationships and the social contract between individuals, rather than individuals themselves. Mol's (2008) work on the clinic similarly draws attention to relationships, contrasting the role of patients in negotiating and shaping their care with nurses within a 'logic of care' with the decision-oriented, expert-driven 'logic of choice' in physician-led care. For Adam and Groves, a focus on care thus re-situates ethics within relationships between specific people in particular contexts of concern and emphasises 'social relationships of mutuality and trust'.

Adam and Groves argue that to care means to take on a nonreciprocal responsibility for performing a particular task because it falls to us to perform it. Given this nonreciprocation, they suggest that relationships viewed from this perspective are valued for their intrinsic worth, rather than what they return. As they put it, when caring, 'we act not because of a sense that the other person is of equal value to ourselves, but because they are of special and unique value to us' (2011, p. 22). As suggested in the outline of cohort sociality above, such a viewpoint captures an important motivation for care in longitudinal research—a concern with perpetuating the cohort and maintaining the quality of the relations that comprise it.

The role of care in the practice of cohort research has implications for understanding what constitutes 'responsible research' in the context of big data initiatives around dementia. 'Care' is at the centre of thinking and advocacy around dementia. The focus is understandably often on the domestic and clinical contexts in which people with dementia find themselves. However, the extension of AD into a younger, healthy population raises questions about how and where care takes place in research practice. In this chapter, we have drawn attention to local, intersubjective relationships—the embedded small things that make up 'big data',

and the sensitivity to circumstance and responsiveness that emerges within these.

In particular, our discussion of the intersubjective and contextual practice of attentiveness and responsibility points to the importance of 'opening up' the category of researchers within cohort research. It highlights the role of the research interviewer in mediating relationships between core study researchers and participants, and in practising care within the study. Interviewers, study coordinators, and research nurses connect large-scale biomedical research with its participants. Emphasising their role and the extent to which they are involved in attending and responding to the needs of individuals potentially provides a means of reintroducing care to discussions of the ethics of big data in dementia research. Further work is needed to expand the range and diversity of researcher voices involved in imagining the future directions for research, alongside deliberative activities with participants.

Following Tronto (1993), our aim is not to replace the macro-political emphasis of the responsible innovation programme, nor the rules-based approach of mainstream research ethics. Instead, a focus on the micro, the local, and the relational aims to complement existing work, to open up the range of perspectives in a manner that engages with the contexts from which research futures emerge. This has implications for thinking about what constitutes responsible innovation in the context of big data 'dementia platforms', which draw together researchers, participants, and data from a range of local research settings. In particular, it points to tensions between the numerical and geographical scale of platforms and between the practices of building bigger data, and those of carrying out cohort research. Bringing data and participants together risks distancing cohorts from the sociotechnical networks that establish and sustain them and through which the practice of care in research can occur.

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# Part II

## Diagnosing Alzheimer's Disease: Current Practices

# 6

# Grey Matters: Emergent Biomarkers and Good Alzheimer's Diagnostics

Anna Laura van der Laan

In the Netherlands, a large research consortium is working on the development of biomarker instruments for diagnosing Alzheimer's disease (AD) (CTMM 2015). According to the project description:

> The main question for patients with memory complaints is whether they will develop dementia or whether memory loss will continue to be an isolated finding. Consequently, for physicians dealing with these patients, an important challenge is to differentiate those who will not develop dementia (and who can thus be comforted) from those who will develop full-blown AD with dementia (and for whom healthcare should be provided). Currently, reliable tests for a definite diagnosis of AD in living patients are not available. […]
>
> [Biomarker instruments for AD] have potential as (a) sensitive and conclusive, noninvasive, in vivo molecular diagnostic tests for patients in whom the diagnosis AD is considered, (b) reliable biomarkers for developing new

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generations of AD drugs, and (c) molecular markers indicative of disease heterogeneity that will help stratifying patients for personalized treatment.

This text has rhetorical strength: when reading it, the 'goodness' (cf. Willems and Pols 2010) of what is being developed seems to be self-evident. But is it? In promises such as these, hardly any attention is paid to the practices in which the emergent biomarker tools are to be used. That these tools, by providing an early and conclusive diagnosis, whether or not combined with medical treatment, would *improve* these practices is more or less taken for granted. The particularities of these practices get black boxed and this hinders a proper evaluation of the merits of biomarker instruments. In this chapter, therefore, I will explore how biomarkers could affect diagnostic practices. Let me now present four exemplary case descriptions constructed on the basis of an ethnographic case study (see next section) of current Dutch practices of diagnosing people with cognitive problems.

*Case 1—Mrs Overbeek:*

Mrs Overbeek is a 71-year-old woman in good health. She is referred to the memory clinic in a general hospital because of mild cognitive problems. She is accompanied by her husband. The diagnostic programme takes a whole day and consists of: blood lab; weighing; ECG; anamnesis; heteroanamnesis (with husband); physical, psychiatric and neurological examination; neuropsychological examination (NPO, Dutch acronym); and magnetic resonance imaging (MRI). At the multidisciplinary meeting, the professionals involved conclude that she has 'mild cognitive impairment' (MCI). The findings are argued to be 'suggestive for AD' because of some 'red flags', that is, a typical presentation of progressive memory loss, a typical pattern of cognitive problems found with NPO, and hippocampus atrophy found during MRI. It is decided to do a follow-up in six months in order to see how the symptoms progress and to be able to provide Mrs Overbeek with anticholinergic drugs as soon as the MCI turns into a dementia.

*Case 2—Mrs Soekhai:*

Mrs Soekhai (75) visits, together with her husband, her general practitioner (GP) because of progressive cognitive problems. Despite her history with some vascular problems, she still is in good shape. After a short examination with a few cognitive tests, the GP diagnoses her with a dementia. The GP suggests that she comes back when the problems get worse and

care is needed. Ten months later, the husband passes away. This seems to worsen strongly her cognitive problems and troubles in daily functioning. The GP refers her to a nursing home for further diagnostics, which consists of a blood lab, anamnesis, heteroanamnesis (with her daughter) and an extended NPO. Here, Mrs Soekhai is diagnosed with mediate stage AD. She gets an indication for admission in a nursing home, which is applied for right away.

*Case 3—Mr Willemsen:*

Mr Willemsen is a 72-year-old, healthy and independent man. He has been a widow for more than two decades and has been preoccupied with signs of cognitive impairment for many years, having witnessed both his parents dementing. Each media item addressing scientific progress in Alzheimer research catches his attention. From a close friend in the bridge club he heard about a clinical trial for a possible medicine. He visits the GP for further diagnostics and asks whether he would be entitled to participate in the trial.

*Case 4—Mrs Van de Pol:*

Mrs Van de Pol is a 75-year-old woman, living together with her husband in a pleasant neighbourhood, with two of their children around the corner. Together, they are enjoying to the full their old age, although they do notice her slowly progressing memory problems. However, this doesn't worry them too much: they manage quite well and have always had an attitude of 'what comes, comes'. Their exposure to the television items by Alzheimer Nederland, with the message 'Memory complaints? Don't walk around with it', made them decide to visit their GP, just to see what his suggestion would be.

As the first two cases show, diagnostic procedures can be quite different. Moreover, patients may have different motivations for seeking help, as in the cases of Mr Willemsen and Mrs Van de Pol. Indeed, in the Netherlands, the field of AD-diagnostics is rather diverse. What would emergent AD-biomarker tools do in this diversity? Project descriptions such as that of LeARN assume a uniform, desirable, future diagnostic practice, though they neglect the fact that clinical practices are always heterogeneous and that medical innovations may have various different effects. In this chapter, I open up the heterogeneity of current diagnostic practices for AD so as to consider the different ways in which they may

play out in future practices of AD-diagnostics. Such a practice-based reflection enriches deliberation on the conditions under which biomarker diagnostics for AD could be an innovation with care.

## Background and Methods

Scholars in the field of Science and Technology Studies (STS) have argued that in (health care) practices, 'norms, values and strivings for the good cannot be separated from activities and ways of knowing practices' (Pols 2014, p. 176). Accordingly, what is considered as 'good' or as 'improvement' in these practices depends on many things and may differ from practice to practice (Mol 2006; Pols 2012). It is by ethnographic research methods (Pols 2014) that the various, interrelated ways by which goodness appears—or rather gets 'enacted' (Mol 2002; Pols 2004)—may be opened up.

The case study on which this chapter is based was set up to do such an ethnographic study of AD-diagnostics. It draws upon the works of Mol and Pols by studying and analysing reality and normativity as enacted in diagnostic practices. As such, my contribution to this volume should be seen as an empirical, philosophical, rather than a sociological, study of AD-diagnostics. It does not look at people or meanings from the outside, but at practicalities and 'materialities' from the inside (Mol 2002).

I conducted interviews with 20 professionals, five patients and six informal caregivers that are or have been involved in various settings for AD-diagnostics. I made observations of three of those settings: at a nursing home, a memory clinic in a general hospital and a memory clinic in an academic hospital. In the interviews and observations, I looked for the enactment of 'good AD-diagnostics'. Since emergent biomarker diagnostics for AD first and foremost bring in a whole new knowledge source, I zoomed in on goods related to the knowledge aspects of diagnostics. In doing so, I left out the goods concerning cost aspects, logistics, the physical and practical burdens on patients and families, and the relationship between professionals and patients. This is not to suggest that these aspects will be left untouched by AD-biomarkers tools, but just that they are beyond the scope of my study.

In the following, I first highlight the heterogeneity of current practices of AD-diagnostics. Then I present the different ways in which 'good

AD-diagnostics' play out there. The second part of my analysis is an exploration of the distributional mechanisms that support these differences. I conclude my analysis with a reflection on my findings and discuss how practices of AD-diagnostics may be improved and what this implies for emergent biomarker tools.

## Current Practices of AD-Diagnostics in the Netherlands: A Heterogeneous Field

In the Netherlands, the GP has a leading role in health care. It is the GP who is the first to see a patient who seeks medical help because of cognitive problems. The GP decides to refer, or not to refer, a patient to a specialised diagnostic setting for further investigation. GPs in the Netherlands have a clinical standard for diagnosing 'dementia'—one of the key characteristics of AD. The category of 'dementia' is also called a 'syndromal' disease category, for it is based on a particular combination of symptoms of cognitive decline. In contrast, disease categories such as 'AD' are called 'aetiological' categories, because they refer to the underlying *cause* of the symptoms.

The GP standard advice is to refer patients for aetiological diagnostics in certain specific cases (Moll van Charante et al. 2012). However, the referral habits of GPs in the case of dementia are far from uniform. While some routinely refer patients with cognitive problems for further diagnostics, others adopt a 'wait and see' attitude. In the case where a GP decides to refer a patient, there are several options, which are, again, quite different. Additional diagnostics take place in various settings, from nursing homes to academic hospitals. Moreover, there are various (medical) professionals involved, such as specialists in elderly care, geriatricians, neurologists, social workers, occupational therapists and many more. Who exactly is involved differs from setting to setting and from case to case. Also the diagnostic procedure itself—the way it is organised, its elaborateness and the tests and tools used—varies.

Despite this heterogeneity, there is a Dutch guideline for dementia in specialised settings: the Centraal Begeleidings Orgaan, Dutch acronym (CBO) guideline for 'diagnostics and medical treatment of dementia' (CBO, NVKG 2005). This guideline offers criteria for providing aetiological diagnoses in the context of dementia, among which is AD. In these

criteria, distinctions are made between 'possible', 'probable' and 'definite' AD, which are based on the level of diagnostic certainty that is achieved. According to this guideline, 'definite' AD cannot be diagnosed in living patients, for it relies on the post-mortem identification of so-called 'plaques' and 'tangles' in the brain. So, in practices of AD-diagnostics, only 'possible AD' and 'probable AD' can be diagnosed.

Besides the labels 'dementia' and (probable, possible) 'AD', new labels turn up in the context of AD-diagnostics, which are differently employed in current practices. Both new syndromal labels, such as 'mild cognitive impairment (MCI)' and 'subjective memory complaints', and new aetiological labels, such as 'Alzheimer pathology' and 'asymptomatic AD' are employed. Also, new labels combining syndrome and aetiology are increasingly used, such as 'MCI, due to AD'. The rise of these new labels is related to the move to earlier diagnoses. Whereas the classical category of AD incorporates the presence of dementia, the new categories are meant to incorporate people who experience cognitive problems that are not (yet?) severe enough to be labelled a 'dementia'. This is the group of people that emergent biomarker tools developed by LeARN are aimed at, as can be seen in the excerpt from their project description presented above.

Lastly, differences in AD-diagnostics can be seen at the level of individual patients and their informal caregivers. Firstly, the manifestations of the cognitive problems greatly vary, from very mild to quite severe, and from very clear-cut to extremely subtle or intertwined with all kinds of other physical, behavioural, or psychiatric symptoms. Moreover, patients and their informal caregivers behave in different ways. Some turn to the doctor with only vague complaints, others wait a long time before they seek medical help. In addition, they have different requests, different wishes and different needs; some are very outspoken, others more implicit.

## Good AD-Diagnostics: Differences

Within this heterogeneous field of AD-diagnostics, 'the good' plays out in various ways as well. In this section, I analytically discern five diagnostic values and I argue how these are enacted in different modes of diagnosing (see Table 6.1).

**Table 6.1** Modes of diagnosing and diagnostic values in current practices of AD-diagnostics

| Mode of diagnosing | Epistemic value | Predictive value | Directive value |
|---|---|---|---|
| 'Pulling out all the stops' | Causal explanation | Prognosis | Control |
| 'Holding back' | Describing functionality | Prognosis | Living with |

## The Good Diagnosis: Five Diagnostic Values

From my field materials, I distinguish five diagnostic values: 'causal explanation', 'describing functionality', 'prognosis', 'control' and 'living with'. The first two values concern the epistemic question: 'what is the matter?'. By definition, diagnoses incorporate an epistemic claim: they are supposed to correspond to some reality to which they refer. In the context of AD-diagnostics, this epistemic claim is twofold. On the one hand, a causal explanation for the complaints is given, which is done by providing an aetiological label. On the other hand, the current state of cognitive and daily functioning is articulated. This is done by use of syndromal labels, eventually complemented by some functionality grading scales. The values of 'causal explanation' and 'describing functionality' respectively refer to these two epistemic claims.

The value of 'prognosis' is about knowing what the future will look like. A good diagnosis provides a clue about what to expect, so it is often argued. The last two values, 'control' and 'living with', concern the 'directives' (cf. Pols 2012) of diagnoses. They concern the ways in which diagnoses invite, lead or even urge to certain actions or consequences. Directive values of diagnoses primarily relate to the question: 'what to do?'. The value of 'control' is about fighting AD. It concerns the way in which a diagnosis directs the means to prevent, cure or slow down the disease process. The value of 'living with' in contrast refers to diagnoses that direct the means to improve living *with* the symptoms of AD. For example, by entitling patients and their informal caregivers to care services, by empowering them to make certain individual choices based on a diagnosis—quitting their job, making a world trip, writing a will—or by helping them to give meaning to the symptoms.

## Modes of Diagnosing: 'Pulling Out All the Stops' or 'Holding Back'

The five values regarding the diagnosis are closely connected. After all, in diagnostics, knowledge about reality is never pursued for the sake of knowing alone, but always for the sake of the goods this knowing is supposed to bring. As a consequence, the goodness of epistemic values that turn up in AD-diagnostics relies on their relation with predictive and directive values. In practices of AD-diagnostics, I discerned two 'modes of diagnosing' (cf. Pols 2004) in which diagnostic values are typically enacted together. These modes of diagnosing should be seen as two extremes on an axis that refers to the degree of diagnostic and therapeutic efforts taken.

On the one hand, a 'pulling out all the stops' mode of diagnosing can be recognised, as in the case of Mrs Overbeek. This mode brings together the values of 'causal explanation', 'prognosis' and 'control'. The diagnostic process is oriented towards reaching a high level of aetiological certainty. This entails the deployment of a variety of diagnostic tools, among which are elaborate cognitive test batteries and brain imaging techniques. In particular MRI and the analysis of cerebrospinal fluid (CSF) are increasingly embraced as a means to find additional evidence of 'Alzheimer pathology'. They may reveal atrophy of specific areas in the brain which is considered to be a pathological hallmark of AD and, as such, to contribute positively to a causal explanation.

In the case where AD is diagnosed, the prescription of anticholinergic drugs are more or less common practice in a 'pulling out all the stops' mode of diagnosing, thereby enacting the value of 'control'. Anticholinergic drugs are thought to have some positive effects on the symptoms of AD, although the scientific evidence for those effects is controversial and the actual effects found are quite modest. They are specifically indicated in the case of dementia 'due to AD'. Thus, to prescribe them, a 'causal explanation' is needed. Moreover, the *timing* of providing an aetiological diagnosis becomes relevant as well for the prescription of anticholinergic drugs. Current guidelines for treating AD say that they can best be given at the moment an MCI turns into a dementia—that is

when they have the greatest effect. The guidelines strongly advise against prescribing anticholinergic drugs in absence of a dementia. As a result, within the 'pulling out all the stops' mode of diagnosing, diagnosticians tend to follow up closely on patients who are diagnosed with MCI, in order to intervene with anticholinergic drugs as soon as their cognitive problems turn into a dementia.

It is by the linking of causal explanation and control that the diagnostic value of 'prognosis' also turns up. In 'pulling out all the stops' modes of diagnosing, 'prognosis' appears as a process of cognitive decline that is to be slowed down by interfering in the supposed underlying pathogenesis.

The second mode of diagnosing could be dubbed a 'holding back' way of working and can be recognised in the case of Mrs Soekhai. In 'holding back' modes of diagnosing, the enactment of the values 'describing functionality', 'prognosis' and 'living with' prevails. The diagnostic process typically follows a 'wait and see' strategy in the case of cognitive troubles. This goes together with accepting a low level of aetiological certainty about the diagnosis. In 'holding back' modes of diagnosing, GPs tend to refer only patients for further diagnostics when real problems in daily functioning show up and further examination is needed in order to cope better with these. However, these further diagnostics are far less extensive than in 'pulling out all the stops' procedures. Usually, no imaging techniques are used, and anticholinergic drugs are hardly ever prescribed. Instead, more attention is given to the level of functioning of the patient and his or her living environment. In doing so, the focus is on articulating 'care needs' by differentiating between different levels of functionality, for example by using a grading scale to determine the severity of the dementia, or by explicitly articulating the kind of health care service that is needed. The diagnostic value of 'prognosis' mostly appears here in the anticipation of decreasing functionality. However, in holding back procedures, the prognosis tends to be communicated in a very cautious way, by stressing its uncertainty. Clinicians often tell patients that it is hard to predict how the course of the cognitive deterioration will go. Some even stress that the situation may remain stable for a long time. This is then received as a comforting message by patients and their informal caregivers—in their case, it may not go that fast, or not become that bad.

## Distributing Differences

In the above, I have brought some order to the heterogeneous field of AD-diagnostics by discerning two different modes of diagnosing that foreground different diagnostic values. Differences are inherent in clinical practices and are not per se a bad thing (Mol and Berg 1998). However, in view of the aim of scientists to *improve* current diagnostic practices of AD, it is relevant to understand these differences. Biomarker tools may support certain diagnostic values, but they may discard others. They may contribute to certain modes of diagnosing, but discourage others. In this section, I further explore the differences I have found. I show how differences are 'distributed' (cf. Mol 2002), that is, how they are made to co-exist in the current diagnostic field of AD. I argue that there are two different distributional rationales at work here.

### Distribution by Taxonomic Considerations

First of all, distribution takes place by linking different patient groups—in which 'age' and 'physical conditions' are the differentiating factors—to different diagnostic procedures. This linking mechanism is deeply embedded in the socio-material structures of AD-diagnostics. For example, in the general hospital of my study, patients are scheduled for one out of a number of different diagnostic programmes. In people of 65 and younger, in whom the cognitive troubles are often an isolated finding, a 'pulling out all the stops' mode of diagnosing is common practice. This procedure is primarily focussed on providing patients with an—as certain as possible—aetiological diagnosis, and, in the case of AD, prescribing them anti-AD drugs. In contrast, older people are enrolled in 'holding back' modes of diagnosing, in which more attention is given to 'describing functionality' and to improving daily life with the cognitive problems at hand. Similarly, in the nursing home of my case study, the vast majority of people who are diagnostically examined are (much) older than 70 and often have other age-related conditions. Here, the usual mode of diagnosing is one of 'holding back'.

This suggests that good AD-diagnostics in the 'young and healthy' corresponds with the 'pulling out all the stops' way of working, whereas

in the 'old and fragile' it rather entails a diagnostic process of 'holding back'. An important rationale that underlies this distinction is that, in these groups, different 'diseases' are attended to. It is often argued that the category of 'AD' actually refers to—at least—two different entities, which could be dubbed as 'pure AD', which usually is found in the young and healthy, and AD mixed with other causes of dementia, which usually is found in older patients with additional diseases (Richard et al. 2012).

The taxonomic distinction between 'pure AD' and 'mixed AD' is based on differences in the assumed straightforwardness of the relations between pathogenesis, early and late clinical symptoms. In 'pure AD', these relations are rather straightforward: accumulating, irreversible pathological changes in the brain are considered to lead to slowly progressive cognitive and behavioural problems in daily life. This explains why 'pulling out all the stops' is more or less common practice in the case where the diagnostic hypothesis is a 'pure AD'—that is, in younger, healthy patients with isolated cognitive problems. It makes sense to strive for a causal explanation—that is 'AD-pathology'—because it gives reliable clues about the course of events, as well as clues about the kind of drugs that may improve the condition—even though the working of current anti-AD drugs is still quite modest. It also makes sense to strive for an *early* aetiological diagnosis. This is because of the irreversibility of the pathological process.

In contrast, in 'mixed AD', the aetiological and temporal relations between pathology and clinical symptoms are much more uncertain. The cognitive and behavioural problems are considered to be caused by a complex interaction of pathological, ageing and environmental processes. As a result, their course is harder to predict. This explains why in elderly patients, in whom the diagnostic hypothesis is 'mixed AD', less efforts are made to provide certainty about the aetiology, and more attention is given to 'describing functionality' and improving life with the symptoms. After all, in 'mixed AD', the goodness of providing a patient with an (early) causal explanation becomes questionable. Given the uncertain relations, a causal explanation is not believed to provide a reliable prognosis, nor are drugs intervening in AD-pathology expected to have much effect. It thus becomes more important to find ways to improve life with the symptoms, to which 'describing functionality' is a better means.

The taxonomic distinction between 'pure' and 'mixed' AD, however, lacks sharp boundaries. Whereas it is possible to discern some autosomal-dominant inheritable 'pure ADs', affecting people at a very young age and having an evident pathogenesis and predictable course of cognitive deterioration, these only concern a very small minority of all patients that enter AD-diagnostics. For the large remainder of ADs, there rather seems to be a broad, age-related continuum of increasing aetiological complexity and decreasing levels of certainty about the expected course of clinical symptoms. Moreover, most people that enrol in AD-diagnostics are neither 'young and healthy' nor 'old and fragile'. They often are somewhere in-between: not *that* young and not *that* healthy, but not *that* old and not *that* fragile as well. This leaves practices of AD-diagnostics in a large grey area in which taxonomic uncertainties hinder the choice between diagnostic procedures. This may explain why Mrs Overbeek, who is not 'below 65', still receives an elaborate diagnostic examination and gets monitored in order to prescribe anticholinergic drugs as soon as this is indicated, while the diagnostic procedure in Mrs Soekhai, who is only a few years older and not convincingly 'fragile', is clearly one of 'holding back'. But there is more to say about this, because taxonomic considerations are not the only distributional rationale behind different practices of AD-diagnostics.

## Distribution by Patients' Preferences

The second distribution mechanism regards the linking of preferences of patients and their informal caregivers to different kinds of diagnostic procedures. (For the sake of readability I will further speak of 'patients' preferences', but these also include the preferences of informal caregivers.) As argued before, patients act upon their cognitive problems in different ways and have different requests. For example, Mr Willemsen knows very well what he wants. He turns to the GP with a specific request: he wants to 'pull out all the stops': he wants to know what causes his complaints, and he wants to fight it. In contrast, Mrs Van de Pol and her husband do not have a specific quest for help, nor do they express an explicit wish to fight the problems they encounter. They rather want to get advice on how best to deal with them. Based on these kinds of differences, physicians

make different decisions, and as far as it does not conflict with their own professional standards, they are inclined to follow up on the patient's wishes. As one of my interviewees—a GP—argued:

> yes, the Alzheimer centres of course have even much more opportunities, but there are also forms of diagnostics that I would not always wish for my patients, I have to say. If people want it, that is fine, but …

This respondent clearly has his doubts about extensive diagnostics, but 'if people want it, its fine'. With that last remark, he stresses the primacy of patients' own preferences. The distributional rationale of following up on patients' preferences and wishes is also called the 'logic of choice' (Mol 2008). The logic of choice, as distributional rationale in health care, frames different diagnostic and treatment options as different offers, among which patients—as consumers—should be able to choose freely (ibid.).

As for AD-diagnostics, I found in particular a link between patients' *views* on AD and their behaviour or preferences. I roughly discerned two groups of patients. First of all, there are people like Mr Willemsen, people who have a rather outspoken view on AD. That is, AD as a *dreadful* disease; as a violation of the 'self', of the very 'essence' of what it is to be human. In the words of one of my interviewees—a diagnostician—who reflects upon his own wish for euthanasia in case he were diagnosed with AD:

> I don't want that process of decay. I *really* think it's … of course; I work a lot with it … I really think, in general … I think it's horrible. Just being robbed of your own, you know, your identity, your own memories, your own I, that is just horrible, isn't it?

Persons with such explicit dramatic views on AD, tend to seek medical help in the case of only mild symptoms, and do so with the specific wish to fight against cognitive impairment by all means. Stated differently, these patients want their doctor to 'pull out all the stops'.

Besides this group of patients with a dreadful-disease view of AD, I found another entering AD-diagnostics who were more like Mrs and

Mr van de Pol. Their views on AD are not that outspoken, nor that dramatic, though they have often been facing cognitive decline for longer periods. In contrast to the previous group of patients, they rather appear to view AD as a more or less bearable condition. This view can be illustrated with the words of one of the interviewed diagnosticians:

> I think … you know … what you read, and hear, and see, or hear from Alzheimer Nederland [the Dutch Alzheimer's Society], that it is all so problematic, and doom and gloom, while I really do have loving couples that stay stable for years. Without anyone needing to intervene. They just manage. With their family around them. And then I think 'yes, that is also possible … yes'.

These people tend to act upon their cognitive problems in a more expectant way, only seeking medical help when they feel they get stuck in daily life. As a consequence, they are more often enrolled in 'holding back' procedures which are primarily directed at improving their lives with the cognitive problems they encounter.

However, I observed situations where the preference-centred distributional rationale was not that evident. For example, a demented patient and her family enrolled in extensive diagnostics, while they just wanted to know how to live better with the troubles they were facing. And a patient and his wife who greatly feared AD were diagnosed in the nursing home without being aware of the possibilities of further diagnostics and treatment. These people rather appeared to be at the mercy of the—taxonomically organised—'system' rather than as autonomous human beings treated in accordance with their personal views. Also in my interviews with patients and informal caregivers, it became clear to me that they often do not really know what the options are, nor did they really feel like they actually had a choice.

These apparent 'misfits' (cf. Pols 2012) between taxonomic considerations and patients' preferences could be explained by a lack of well-articulated preferences by patients, which, in turn, may be explained by ignorance about the actual choices. In these cases, taxonomic distribution mechanisms seem to dominate. But there could also be an actual clash between the two distributional rationales, since evidently the preferences

of patients do not necessarily align with taxonomic considerations. This may lead to situations where, from a taxonomic point of view, following up on a patient's well-articulated wish may be considered a 'taxonomically irresponsible' thing to do.

## Revisiting Current Practices of AD-Diagnostics: From Good to Better?

I have shown that the field of AD-diagnostics in the Netherlands is heterogeneous. I have discerned two modes of diagnosing—'pulling out all the stops' and 'holding back'—that bring together different diagnostic values. Furthermore, I have argued that two distributional rationales are at play to allow for these different modes of diagnosing: distribution by taxonomy and distribution by patients' preferences. The taxonomic distributional rationale, however, has fuzzy boundaries due to scientific uncertainties, and the preference-centred distributional rationale often gets blurred due to a lack of explicit patients' preferences or by patients' ignorance about the options. Moreover, the two distributional rationales may clash because patients' preferences and taxonomic considerations point in different directions. This leaves current practices with a grey area in which it is not clear what to do for the best.

So there is room for improvement. My analysis invites us to seek improvement by strengthening and aligning the two distributional mechanisms. In this last concluding section, I explore these issues. I start by pointing to the interrelatedness of the distribution mechanisms. Then, I discuss how current practices of AD-diagnostics may be improved and how emergent biomarker tools may contribute to that.

### Value-Laden Taxonomies and Taxonomy-Laden Preferences

It may be tempting to see the taxonomic distribution mechanism as being based on facts, and the preference-centred distribution mechanism as being based on values. This is in line with the tendency to conceive of

clinical practices as encounters where clinicians just deliver the options and available evidence—based on taxonomic considerations—and patients make a choice based on their values (Mol 2008). The underlying assumed fact-value distinction, however, is problematic. Firstly, the options—and concomitant uncertainties—presented by the clinician are value-laden. This is because, in STS language, there is not just one way to represent the world, but many. And the greater the scientific uncertainties, as in the case of AD, the more possible ways there are. It makes a difference which way is taken, whether a new taxonomy is primarily based on, for example, aetiological or prognostic facts, or on facts related to selecting the most effective therapy. Stated differently, taxonomies provide different 'versions of reality' (Mol 2002, 2013), and in doing so, they support different diagnostic values.

The preferences of patients who turn to AD-diagnostics, in their turn, are not free from taxonomic considerations. As I have argued, patients' preferences are linked to their views on AD, which affect the mode of diagnosing they enrol in. Their views on AD, however, are not just based on some personal, good-life values. They are fed by the ways in which AD, 'taxonomically', appears to them. This is particularly the case for the views of AD as a dreadful disease. Here, public discourse on AD plays an important role, where the most dominant taxonomic conception of AD more or less corresponds with the pure variants on the broad spectrum of ADs, thus AD is conceived as an aetiologically distinct pathogenic process with a devastating prospect of—if untreated—inevitable cognitive decline. This conception evidently feeds the view of AD as a dreadful disease. Media items about scientific developments in the field of AD also tend to go together with a taxonomic image of pure AD, thereby further feeding patients' preferences to 'pull out all the stops'. But, as argued in the previous section, pure variants of AD only concern a small portion of AD-patients. In public discourse, the other variants and concomitant uncertainties are fairly absent. As a consequence, the very term 'AD' tends to be predominantly associated with what actually only concerns a minority of all ADs while the remainder are hidden behind this overarching label. This implies that particular people's views of AD as a dreadful disease may be based on false beliefs and expectations.

## Improving Practices of AD-Diagnostics

The interrelatedness of facts and values in the distributional rationales in AD-diagnostics should be taken into account when considering how to strengthen the two mechanisms of distribution. Currently, the strengthening of taxonomic distribution mechanisms is first and foremost taken up in practices of science and technology development. In these practices, a lot of work is done to reduce scientific uncertainties in AD. This is what AD-biomarker research is aimed at. Scientists are trying to produce new, more certain, facts about aetiology, prognosis and the effectiveness of therapy. In doing so, they make new differentiations between patient groups. This could improve the current taxonomy, and as such serve a more robust taxonomic distribution mechanism for AD-diagnostics. This would decrease the taxonomic fluid space in which AD-diagnostics currently take place.

Given the normativity of taxonomies, however, the question as to what would be a 'better' taxonomy is not to be answered by seeking better representations of reality, but rather for representations—or better 're-scriptions' (Pols 2014)—of reality that actually 'matter' (cf. Moser 2008) to people. This then is a crucial criterion for improving practices of AD-diagnostics: developing taxonomies that actually *matter* to people. This turns the question of what would be a good taxonomy into a political concern, which has to do 'with how to value contrasting versions of reality. Which version might be better to live with? Which worse? How, and for whom?' (Mol 2013, p. 381).

The strengthening of the preference-centred distribution mechanism is taken up by clinical medicine in general, not just in the context of AD-diagnostics. It goes under headings such as 'shared decision making' and particularly focuses at improving clinicians' skills to communicate clinical uncertainties in such a way that patients can make a well informed choice (Epstein et al. 2004). These kinds of interventions are motivated by the argument that patients should have a greater say in the treatment they get.

Developing taxonomies that matter, implementing them in practices of AD-diagnostics and having diagnosticians communicating them to patients may improve this mechanism. But as I have argued, patients'

views on AD often go together with taxonomic conceptions of AD and conform to its relatively uncommon pure variants, which they derive from public discourse. Strengthening preference-centred distribution mechanisms should thus go beyond diagnostic practices and doctor–patient encounters. It should be taken up in public discourse as well. This asks for public awareness about taxonomic uncertainties and normativities in AD. For example, AD-variants at the mixed side of the spectrum deserve more attention. This may support views of AD as a bearable condition. However, creating more public awareness is not expected to be an easy task. Cultural values, financial interests and professional power struggles may hinder getting rid of the negative connotations surrounding the term AD. As a result, even if a better taxonomy is available, it may remain hidden behind this very term.

## To Conclude: Emergent Biomarker Tools for AD

As argued above, emergent biomarker tools may support the making of new taxonomic distinctions. To really improve current practices of AD-diagnostics, however, they should contribute to taxonomies that actually matter to people. This should go together with public awareness about the interrelatedness of taxonomic uncertainties and normativities. The goodness of emergent biomarker tools for AD thus not only lies in the hands of scientists and innovators, but also with patients and their informal caregivers, with health care professionals, policy makers and all actors that contribute to the public discourse on AD. This calls for alignment of the development of emergent biomarker tools with practices and the concerns of all parties involved.

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# 7

# Understanding Cognitive Screening Tools: Navigating Uncertainty in Everyday Clinical Practice

Julia Swallow

The 'ageing population' in the UK, pertaining to an increase in the number of individuals living above the age of 65 in the general population (see Rajah et al. 2009), has firmly cemented Alzheimer's disease (AD) as a site for concern across medical and scientific research, and healthcare policy. In an attempt to manage the number of individuals set to develop AD, given that age is the greatest risk factor for the disease, efforts to increase early diagnosis rates drive both medical and scientific research and healthcare policy. In research globally, biomarker technologies are being developed, which aim to provide earlier, more accurate diagnoses to prevent and treat the disease in its earliest stages (see Dubois et al. 2007; Zetterberg 2011). In healthcare policy in the UK, initiatives such as the National Dementia Commissioning for Quality and Innovation Framework (CQUIN) aims to increase referral

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and subsequent diagnosis rates by introducing a standardized framework for assessment. All individuals over the age of 75 admitted to an Acute Medical Unit are assessed for cognitive decline. Aside from innovation in research, however, the CQUIN adopts the use of an existing low-technological cognitive screening tool for detecting decline in its earliest stages: the Abbreviated Mental Test Score (AMTS). An interesting development is the increasing detection of AD through low-technological means, despite innovation in research.

It is anticipated that diagnostic innovation in research will more reliably and accurately detect AD in its earliest stages than technologies currently used in practice. Diagnosing AD overall is, however, a complex endeavour. A definitive diagnosis of AD can only be confirmed at post-mortem examination (see Hardy 2006), and symptoms associated with cognitive decline are difficult to separate from those of normal ageing processes (Gubrium 1986). In particular, detecting normal from pathological ageing processes in the *earliest* stages of the disease is difficult, as symptoms tend to manifest themselves in the later stages of the disease (see Meyer et al. 2010). As a result, diagnosing AD is uncertain, as there is no one technique or technology that can definitively determine the boundaries of the disease. The desirability of early diagnosis is also a contested issue as it raises questions around exactly what is being made known at earlier stages and for whom it is better to know. Advocates of an early diagnosis of AD argue that it enables individuals to plan and prepare for their future and yet at the same time, those who oppose it contend that it simply extends the time individuals worry or anticipate further cognitive decline.

Aside from innovation in research, what has been easily overlooked within the promotion of early diagnosis is the role of *existing* low-technological cognitive screening tools in clinical practice. Clinical practice relies on the use of low-technological cognitive screening tools for detecting initial cognitive decline. These tools, which are pervasive across healthcare practice, are used to assess initial cognitive decline, and also, review levels of cognitive function for individuals with an established diagnosis (Ismail et al. 2010). A number of cognitive screening tools are used across UK clinical practice and the tools of pertinence to this chapter are the Abbreviated Mental Test Score (AMTS), Addenbrooke's

Cognitive Examination Version Three (ACE 111), and the Montreal Cognitive Examination (MoCA). They are used alongside magnetic resonance imaging (MRI) and computerised tomography (CT) scans in the diagnosis process. Blood tests are also used to *rule out* the presence of pathologies associated with diseases other than AD.

Prior to exploring the role of these cognitive screening tools in initiatives promoting early diagnosis, the first part of this chapter captures their role in everyday clinical practice for navigating uncertainty associated with measures of cognitive decline. In the clinician–patient interaction, three significant dimensions of uncertainty manifest. First, there is uncertainty associated with the difficulty in categorizing AD in the clinic through any one technique or technology. Second, the tools are at times ambiguous, and third, there is uncertainty around the meaning of a diagnosis for patients. In order to navigate uncertainty, I demonstrate the ways in which clinicians are able to approach and perform these tools as provisional devices in the clinician–patient interaction. In the second part of this chapter, I go on to discuss the role of the tools as adopted in the National Dementia CQUIN and the ways in which clinicians approach the framework and early diagnosis overall. I explore how the CQUIN and promotion of early diagnosis might shift how the tools are used for navigating uncertainty, and the process of classification overall. In the final section of the chapter, I conclude by anticipating (see also Stilgoe et al. 2013) what might shift, be improved, or lost with the emergence of diagnostic innovation for early diagnosis by reflecting on what is currently valued in *existing* practice for diagnosing AD.

## Methods

In order to explore the role of cognitive screening tools, a technology-in-practice approach was adopted (see Berg 1996; Mol 1998, 2002; Timmermans and Berg 2003). Science and Technology Studies scholars who adopt a technology-in-practice approach encourage an understanding of what technologies do and how, foregrounding practice to understand how reality is constituted (Berg 1996; Mol 1998, 2002). Therefore, in line with this approach, I argue that the realities of disease do not

exist outside of the practices in which they are 'done'; rather, they are constituted across socio-material practices and socio-technical arenas. As a result, the realities of cognitive decline associated with AD are multiple and 'brought into being' (Woolgar and Lezaun 2013, p. 323); handled through the everyday work of clinicians (Garfinkel 1967) across a particular set of healthcare practices. Overall, I adopted a qualitative approach, drawing on ethnographic methods where I developed the notion that 'technologies are embedded in relation of other tools, practices, groups, professionals, and patients and it is through their location in these heterogeneous networks that treatment, or any other action, is possible in health care' (Timmermans and Berg 2003, p. 104). Fieldwork was carried out across a memory service and an elderly medicine department in a NHS teaching hospital in the UK. I adopted ethnographic methods, including observation of consultations and team meetings, to explore what was embedded or 'taken for granted' in relation to how clinicians approached the tools in practice. I also carried out semi-structured interviews with 21 clinicians. Overall, the research design responded to and emerged from empirical work, and data were analysed thematically.

## Clinician–Patient Interaction: Making of Provisionality

As the following analysis will demonstrate, cognitive screening tools as technologies are fluid and adaptable across different sets of practice (see also Mol et al. 2010). Tracing interview transcripts and observation notes, I demonstrate how cognitive screening tools are used, adapted, and made provisional in the everyday clinician–patient interaction. This is not to suggest, however, that the observations I make reflect what happens in other secondary healthcare memory services across the UK. First, I will show how the process of detecting initial cognitive decline involves navigating uncertainty. Uncertainty is associated with the difficulty in categorizing AD overall, the ambiguities associated with the tools, and the meaning of a diagnosis for patients. Drawing on Mol et al. (2010), I describe how, through the tinkering practices of clinicians, the tools are performed as provisional devices during initial consultations for

navigating these uncertainties. I therefore argue that their value(s) are not 'stable and predefined', but 'grappled with, articulated, and made in concrete practices' (Dussauge et al. 2015, p. 1). The articulation of the tools in the clinic and their subsequent value(s) are constituted through their ability to navigate uncertainty. Despite demonstrating the tools as provisional devices, I am not suggesting that these tools are downgraded since this suggests that they hold intrinsic value in terms of their successes and failures. In fact, they do not fail or succeed in their role as detectors of initial cognitive decline. Rather, as I will demonstrate, they depend on clinicians accounting for individual particularities (Dodier 1998) and situated exigencies (Berg 1996). In this sense, I argue that the tools 'depend on care work. On people willing to adapt their tools to a specific situation whilst adapting the situation to the tools, on and on, endlessly tinkering' (Mol et al. 2010, p. 15).

Observed across the memory service, part of this tinkering work involves clinicians performing mediation and manipulation practices to ensure cognitive decline becomes a 'manageable problem' for both practitioner and patient (Berg 1996, p. 504). To 'manage the problem', clinicians across the memory service recognize that there is no one technique or technology with which to confirm AD dementia.

> There's always a danger that if you attach too much importance to one aspect of the diagnostic process, that you might have missed something and it is often a process of exclusion rather than confirmation in terms of the diagnostic process of dementia. (Interview Clinical Psychologist Three)

For Clinical Psychologist Three, the tools are treated as partial devices because of the extent to which categorizing AD is an uncertain process, overall. For clinicians to make sense of diagnosis, no one technique or technology is privileged. This was a point made by a number of clinicians during interview. Clinicians across the professional hierarchy continually recounted that the tools are *'not the be all and end all',* thus making up only one aspect of what Memory Nurse Two described as *'a little piece of the picture'*. The role of the tools in the clinical encounter in terms of their ability to organize AD and navigate uncertainty, however, emerges from the *interactions* observable in the clinician–patient encounter.

The space of the clinic also produces particular uncertainties and anxieties around the meaning of testing and diagnosis overall—*'there's a huge psychological dimension to a potential diagnosis … it can have all kinds of different responses' (Interview Memory Nurse Six).* Anticipating the *'psychological dimension'* of a possible diagnosis relates, in part, to the negative discursive constructs around AD and mental health, which exist in the general population—a frequent note of observation across clinic appointments. During an observation with Specialty Doctor One, the clinician asks the patient about family mental health history, at which point, both the patient and the family member claim that the patient's mother had memory loss, saying she'd *'lost it—she didn't even know her own husband in her own house!'* This was also illustrated during an observation with Trainee Psychiatrist Two, when the family member asks the clinician whether the patient has *'lost the plot',* following questions about the patient's memory. During an observation with Consultant Psychiatrist Four, the family member also describes the case of their mother-in-law, who had been diagnosed with AD, suggesting that, '*she was saying all sorts of silly things*'. Anticipating how patients might respond to the possibility of AD was also performed during the clinician–patient interaction. I observed in practice a 'culture of testing' emergent in the clinic, shaping how clinicians use and approach the tools. In order to navigate this uncertainty frontstage (Goffman 1969), clinicians mediate the tools in the clinic.

> The clinician starts by explaining to the patient that the test is only *'part of the assessment and it does not matter if you got 0 or 100' and* this is *'not an intelligence test and they see lots of intelligent people who can't read or write very well'* clarifying to the patient that he can tell he *'is an intelligent man'* from the history taken; at which point the test begins. (Observation Consultation Memory Nurse Six)

Recognizing that the tools have the ability to be perceived as markers of intelligence, Memory Nurse Six claims that *'it doesn't matter if you get 0 or 100'.* When asked during de-brief to explain why they approached the tool in this way, *'I suppose it's also a generation thing about the idea of exams and things like that—a cognitive test isn't an exam*'. For Memory Nurse Six,

there is a discursive culture of testing that emerges in the clinic, enacted by the tools. Concurrently, this shapes how clinicians narrate the tools, *'not an intelligence test',* and this mediation work becomes necessary for navigating how patients conceive the nature of testing in the clinic. The uncertainties associated with measures of cognitive decline, however, extend beyond this culture of testing to the ambiguities inherent to the tools and clinicians as users of the tools. Tracing observation field notes, clinicians respond to this ambiguity by actively manipulating the tools. This was evidenced during an observation with Trainee Psychiatrist One.

> The test begins and Trainee Psychiatrist One asks the patient to repeat three words 'lemon, key, ball'. The patient repeats the words 'lemon' and 'key' but is struggling to repeat the word 'ball'. Trainee Psychiatrist One interrupts at this points and explains that *'I will give that point to you because of my accent. It could either be bull or ball with my accent'.* The patient laughs and the trainee psychiatrist writes a scribbled note in the margin of the test. Trainee Psychiatrist One gets back to the test and asks the patient to *'subtract seven from 100'*. The patient repeats the question a number of times but does not understand what the clinician is asking them. At this point the family member interjects to tell the clinician that the patient does not know what the word 'subtract' means asking the trainee psychiatrist to, *'say take away instead of subtract'*.

The ambiguities associated with both the tools and clinicians as users of the tools shifts the way in which they are performed in the clinic. In order to navigate ambiguity and uncertainty, Trainee Psychiatrist One gave points for unanswered questions. This manipulation work with respect to omitting some of the questions was also observed during a consultation with Trainee Psychiatrist Three, *'when asked by the clinician to point to the "marsupial", the patient asks the clinician directly what a marsupial is. Instead of answering, the clinician exclaims that 'a lot of people don't know what that is so we'll leave it'.* In essence, the tool produces or 'boxes' a specific type of patient for classification, regardless of specificity of the situation. Responding to this, both clinicians adapt the tools to the situation, which was a frequent note of observation across the professional hierarchy. My observation notes were replete with examples of

clinicians changing the format of the tools, omitting sections, and giving points when patients had not answered the question. The mediation and manipulation work observed thus far, I describe as specific elements of what Mol et al. (2010) argue is 'tinkering work' performed in response to the uncertainty that has the potential to disrupt the classification process.

Despite the tools emerging as provisional devices, I do not suggest, however, that these tools are redundant in the classification process. In fact, drawing on the work of Berg (1996), who describes the constitutive role of the medical record, I argue that the practices of the clinic 'bring [the tools] to life' (p. 501), shaping how cognitive decline and AD are approached and measured. Developing this point further, it could be argued that as clinicians are able to approach and perform these tools as provisional devices, the technologies have failed to reach a level of *certainty* in the clinic. Therefore, as scholars such as Atkinson (1984) have previously addressed, this lack of certainty leads at times to the privileging of clinical judgement. As a result, with the active manipulation of cognitive screening tools to account for ambiguities *in situ* or 'situational exigencies' (Berg 1996, p. 515), clinical judgement plays a key role in configuring how the tools perform. Consultant Psychiatrist One describes during interview, *'the ACE 111 and MoCA are tools to support our clinical history and clinical acumen',* while for Consultant Psychiatrist Two, '*clinical judgement is important, setting things in context is very important as well*.' In the interpretive repertoire of the clinic, an additional aspect of provisionality is witnessed as clinicians (particularly consultants) exercise clinical judgement.

So far, I have sketched a number of ways in which clinicians grapple with the tools in the clinician–patient interaction in order to navigate the uncertainties associated with detecting initial cognitive decline. Thus far, the 'goods' of the tools enacted in practice have much to do with their ability to be mediated and manipulated and treated as provisional devices. Adapting the tools in practice is crucial to navigating uncertainty and yet, current practice for detecting initial cognitive decline is undergoing significant change. In what follows, I argue that through initiatives such as the National Dementia CQUIN, this is leading to less room for 'care work' (Mol et al. 2010, p. 15). I investigate the National Dementia CQUIN as a device for increasing diagnosis rates at earlier stages, which shifts how clinicians approach cognitive assessment, and produces particular anxieties for both patients and clinicians.

## National Dementia CQUIN and Early Diagnosis: Constraining 'Care Work'

With a view to managing the 'ageing population', increased efforts to detect AD at earlier stages dominates both research around AD diagnostics, and also healthcare policy initiatives in the UK. In terms of healthcare policy, efforts to increase referral and early diagnosis rates, as laid out in initiatives such as the National Dementia CQUIN, impact the everyday practices of assessing cognitive function, producing further uncertainties around the diagnosis process. In what follows, I capture how the framework is dealt with by clinicians, both in the hospital setting and memory service, and demonstrate the ways in which clinicians respond to early diagnosis more broadly. Tracing interview accounts with geriatricians, the CQUIN has the potential to constrain clinical autonomy, where it is 'de-emphasised' in favour of transparency and order in healthcare (Rose 1998, p. 189). However, it also has the potential to formalize current working practice, or as Berg (1998) describes, strengthen 'good clinical reasoning' (p. 227). This is highlighted by Consultant Geriatrician One, who claims that the CQUIN *'provides some momentum and gives us a bit of a structure to doing something about it once they've left hospital'*. The framework, therefore, steers how clinical practice should *already* be performing and grounds current practice in a formalized framework. However, according to Registrar Geriatrician One, the adoption of the *technology* within the framework (the AMTS) shifts the ways in which clinicians approach cognitive decline, confirming that the framework has the potential to constrain professional autonomy. As Registrar Geriatrician One explains,

> I think it's [AMTS] a really blunt screening tool I preferred it when I could use my discretion. I think it's really obvious when you are talking to a patient who's got cognitive impairment that may not have been picked up recently, and I think that these things are better done if they're more targeted and that you just pick this stuff up. I think also the other side of that is just by screening everybody, there are some people who find it really offensive that you're asking them these questions.

For Registrar Geriatrician One, the CQUIN shifts and interferes with the ways in which clinicians use the AMTS in clinical practice. Unable

to exercise discretion makes it difficult for clinicians to adapt the tools to the specificity of situation. In this sense, the technology produces further uncertainties for the patient around what it means to be tested, since some patients may find the process *'offensive'*. The tools as provisional devices are somewhat constrained by the implementation of the CQUIN, and for Registrar Geriatrician One, a more 'targeted' approach to healthcare would be more productive. Constraining the provisionality of the tools not only affects the practice of assessment in the hospital setting, it also impacts the memory service, as the following field notes recount:

> The memory nurse explains that during a home visit they tried to administer the ACE 111 but the patient had fallen asleep (scored 32/84). The memory nurse suggests that although she wants to carry out a scan she does not think it would be beneficial for the patient as he is *'near end of life'*. The nurse exclaims that the patient's memory decline is *'almost the least of the patient's worries; it's a wonder why people get referrals'*. A memory nurse interjects at this point, *'it's because of the CQUIN'*. (Observation Team Meeting Ridge NHS Centre)

The memory nurse in the team meeting questions why some individuals are referred to the memory service. In doing so, she highlights a concern, which resonated across the memory service: initiatives such as the CQUIN limit the extent to which clinicians are able to account for individual particularities (Dodier 1998, p. 55), *'near end of life'*. Furthermore, the tensions and pitfalls of the testing process overall are well recognized by clinicians which as I have demonstrated are effectively navigated in the clinic. Yet, the CQUIN constrains the anticipation work performed in the clinic, in terms of being able to navigate how patients might conceive the nature of diagnosis. As I will go on to elaborate, this produces further and different uncertainties particularly around patient *futures* in relation to early diagnosis since the CQUIN reflects a broader commitment in healthcare policy and practice towards detecting AD in its earliest stages.

While a number of clinicians across the memory service recognize the value of early diagnosis for allowing patients to prepare for their future—*'early diagnosis is so important so that you can allow people to make decisions about their future themselves'* (Interview Consultant Psychiatrist Two)—

there are two distinctive, yet interrelated, sets of concerns about early diagnosis evident from interview accounts. First, there is a concern among clinicians that early diagnosis creates unintended anxieties for patients about a future with AD. Second, clinicians are concerned that promoting early diagnosis reflects the biomedical model for managing AD: care as a viable alternative for managing the disease is relatively neglected in terms of material resources. To address this first concern, for Trainee Psychiatrist One, early diagnosis is not necessarily of value to *all* patients because it produces further uncertainties about what the future might hold.

The following extract from an interview with Trainee Psychiatrist One highlights this well:

> I also think there's a real danger with early diagnosis … so not everybody wants a diagnosis. I had a case recently, a still on-going case that I'm seeing next week, of a gentleman in his early 70's used to be very, very high functioning, ran his own law firm and he came in; he had really good cognitive decline. I've given them a diagnosis of dementia and him [sic] and his wife are just devastated.

What is interesting about Trainee Psychiatrist One's claim is that early diagnosis presupposes that individuals always exercise the agency to *seek* a diagnostic label. In fact, as she explains during interview, for some patients and their family members, the label itself creates further uncertainties, particularly around what it means to live with an AD diagnosis. For Trainee Psychiatrist One, what early diagnosis has the potential to do is shift what is currently valued in the clinic—the ability to account for patient particularities and adapt the tools to the situation in recognition of the fact that *'not everyone wants a diagnosis'*. Furthermore, early diagnosis perhaps constrains the extent to which clinicians are able to navigate the uncertainties associated with a meaning of diagnosis; *'patients are wary about the language of dementia so we've got to be careful'* (Observation Team Meeting Nunmill Hospital). Paradoxically, the conditions of uncertainty in which early diagnosis is promoted *produces,* rather than sorts, a number of uncertainties, particularly around patient futures.

Promoting early diagnosis also reflects the broader commitment in healthcare to a biomedical model for managing AD. In accordance with

the prevailing biomedical model, the 'triumph of "cure" over "care"' (Chaufan et al. 2012, p. 792) privileges early diagnosis over care as an alternative option for managing AD. During an interview with Clinical Psychologist Three, she argues that the biomedical approach promoting early diagnosis has the potential to produce uncertainty for patients. As she explains:

> It's a really difficult balance to strike here isn't it because early diagnosis absolutely is very important … but the other side, the flip side of that coin, is that you can potentially create huge anxiety in the worried well … because there's a great danger with pathologising it because with pathology comes great anxiety. With pathology also comes a whole biomedical kind of culture and system of something that perhaps isn't best addressed in a biomedical environment but more in a community kind of environment.

Clinical Psychologist Three attests that by promoting early diagnosis, patients are subjected to longer periods of anxiety about what the future might hold. However, she also recognizes that early diagnosis is important. Therefore, a balancing act ensues between recognizing the importance of early diagnosis and navigating the anxiety it causes for patients since diagnosis reflects a *'biomedical'*—as opposed to a *'community'*—model approach to managing the disease. With this in mind, in terms of care as material resource, a number of clinicians are also concerned that care is being under-resourced.

> I worry about the resources being invested into that [early diagnosis] verses resources for people after they've had a diagnosis … I wonder about the balance. What happens to all those people who have a diagnosis, and if there is such a value placed on them having a diagnosis, do we then lose sight of the individual at the centre of it; what it means for them to have that diagnosis, how they want that to be? (Interview Clinical Psychologist Two)

For Clinical Psychologist Two, there is an imbalance between promoting diagnosis and resourcing care as an appropriate and viable alternative to managing AD. As she highlights, this may impact the *experiences* of individuals living with AD. Arguably, this relates to the idea that the

biomedical model of dementia, overall, not only impacts allocation of resources, but also negatively impacts the experiences—*'how they want to be'*—of individuals with a diagnosis (see also Lyman 1989). This also relates to the point I made earlier about navigating the meaning of a diagnosis for patients and family members. The meaning of a diagnosis of AD *already* produces particular anxieties for patients in the clinic about how they conceive AD overall.

The CQUIN and promotion of early diagnosis shifts how cognitive decline is approached, assessed, and made sense of in the clinician–patient interaction. Not only has it the potential to constrain the ways in which clinicians are able to engage in tinkering work, but also how uncertainty is navigated and managed for clinicians, patients, and family members. The CQUIN and early diagnosis overall produce particular uncertainties around patient futures. This is a point which should be developed further, particularly since the hopeful discourse around emerging diagnostic innovation for AD is based on the idea that these technologies are able to *navigate and manage* the uncertainties produced by existing practice.

## Discussion

In this chapter, I have explored the role of existing, low-technological cognitive screening tools in the clinic. I have demonstrated the ways in which clinicians are able to engage with mediation and manipulation practices framed around what Mol et al. (2010, p. 15) describe as 'persistent tinkering in a world full of complex ambivalence and shifting tensions', in order to account for uncertainty. Overall, I did not explore whether cognitive screening tools were succeeding or failing to sort uncertainty and produce knowledge about AD. Rather, the purpose of this chapter was to reflect on the articulation of the tools in practice, and the ways in which clinicians grappled with and adapted them to make sense of the classification process. I have adopted the concept of tinkering work to encompass the often ad hoc and informal ways in which clinicians are able to approach and use the tools as provisional devices. Despite the making of the tools as provisional devices, however, they emerge as central mediators for navigating the uncertainties that have the

potential to disrupt the classification process. As I mentioned at the start of this chapter, the values associated with cognitive screening tools are enacted and constituted in practice, shaped by the conditions in which they operate. With respect to the emergence of biomarker technologies, exploring their role within these conditions would be fruitful since they are assumed to sort the uncertainties existing in current practice.

The contribution of this chapter to responsible innovation of diagnostics, therefore, is to elucidate the myriad ways in which clinicians are already anticipating and affected by frameworks promoting early diagnosis such as the CQUIN, since everyday clinical practice relies heavily on tinkering work to navigate uncertainty. When discussing responsible innovation, it is important to take these 'low-tech' technologies into account, particularly when they are governed in frameworks promoting early diagnosis, which, as demonstrated in my analysis of the CQUIN, has the potential to shift and constrain the interrelated tinkering practices observed in the clinic. Analysing the CQUIN, I captured the ways in which the framework constrained the anticipation work of clinicians, constrained discretion, and therefore, mediation and manipulation practices, and produced anxieties around patient futures in terms of what AD might bring, and the availability of resources post-diagnosis. These concerns are interrelated since the ways in which professionals approach assessment rely on anticipating the anxieties it causes for patients, as observed in practice, and recognizing that care is an under-resourced material practice. In this sense, it is perhaps only possible to explore the values associated with more innovative diagnostic technologies in *existing* practice. Diagnostic innovations are likely to produce further and different uncertainties; their promissory claims for sorting uncertainty associated with current practice may only be realized through extensive use in practice (see also Ulucanlar et al. 2013).

The question remains then as to what might shift, be improved, or lost by the emergence of diagnostic innovation overall, which aims to more accurately detect AD in its earliest stages. To innovate diagnostics responsibly requires logical thought about future technological development and its anticipated uncertainties (see Stilgoe et al. 2013). It is *anticipated* and expected that biomarker technologies, which are the focus of this book as a whole, will 'reveal' AD at earlier stages, be more accurate

at revealing AD, and thus, sort the uncertainties and inefficiencies associated with the technologies currently in use. However, the constitutive values of the *low-technological* tools explored in this chapter is that they can be adapted and made provisional for the purpose of navigating uncertainty since they are *not* upheld as the panacea for producing knowledge about AD. Furthermore, the case of the CQUIN highlights the fact that despite the hopeful discourse around early diagnosis, clinicians remain concerned about the effect that this may have for clinical practice and for patients, in particular. Categorizing AD is not simply a task of being able to 'reveal' AD, (this is of course a contested issue in itself related to how AD is defined overall) and determine the normal from the pathological; it is also about navigating the meaning of a diagnostic label. As a number of clinicians suggest, some patients do not always seek a diagnosis and clinicians, patients, and family members do not necessarily *always* value early diagnosis. It is not necessarily the case that earlier *is* better.

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# 8

# Testing Memory, Shifting Responsibility: Internet-Based (Self-) Diagnostics of Alzheimer's Disease

Claudia Egher and Sally Wyatt

More and more ageing people, worried about their health, have started to engage in online self-diagnosing practices. Using a search engine such as Google immediately identifies a great number of diagnostic tests, of varying degrees of complexity and duration. We start from the assumption that the Internet is an innovative diagnostic technology, with the potential to change how risks and benefits of disease categories and treatments are presented and interpreted, and how diagnostic expertise is constructed and demarcated. A diagnosis 'bind[s] the biological, the technological, the social, the political and the lived' (Jutel 2009, p. 294). It takes time, and involves complex procedures, experts, devices, and places. It is a dialogic process, and the medium through which the required information exchanges take place is of crucial importance. In this chapter, we explore how the Internet, a highly complex and heterogeneous medium, transforms responsibility

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regarding diagnostic (self-) tests for Alzheimer's disease (AD), and discuss these developments in relation to their meaning for conceptualizing responsible research and innovation.

In our analysis of the Internet as an innovative diagnostic tool, we take up the perspective on responsible innovation developed by Stilgoe et al. (2013), and discussed more extensively in the introduction to this volume. In studying online (self-) tests for AD, we therefore consider the possibilities they afford for anticipation, reflexivity, inclusion, and responsiveness. We first provide a brief overview of the ways in which the Internet has been perceived in relation to medical practices and then, continue with a description of online (self-) tests available for AD. We draw on insights from science and technology studies (STS) in order to study how the users of these tests are imagined—their identity, the responsibilities ascribed to them, and the options at their disposal. We combine this analysis with insights from the sociology of health and medicine to make several critical points on the changes in responsibility ascription they bring about, and the normative implications thereof.

## Internet Use and Healthcare Practices

The Internet has been used in various ways in healthcare, sometimes raising high hopes, but also leading to disappointment. In its early days, many scholars assumed it would have a democratizing effect, providing people all over the world with access to information, and redressing the power imbalance between medical professionals and lay people (Korp 2006). Studies on the distribution of Internet users for health-related purposes in the population have provided more sobering views, identifying the existence of a digital divide, with the majority of users being young, highly educated, and often women (Korp 2006; Wyatt et al. 2005). The diffusion of the Internet in advanced industrialized societies has resulted in more people having access. The number of e-health information-seekers over the age of 65 has increased significantly, and people with low incomes have been able to access online information using mobile phones or the computers located at various public institutions. These developments have led

to the Internet being credited for bringing about 'e-scaped medicine' (Nettleton and Burrows 2003), the diversification of the sources of medical knowledge away from the hospital and the laboratory, and closer to people via various online platforms.

The quality of online information remains difficult to control. Sources and information have varying degrees of reliability and trustworthiness, and also, depend on the context of their transmission and use. Thus, the type of online platform, the surrounding text and images, the mental and physical state of Internet users, their skills and ability to interpret correctly relevance, validity, and applicability play an important role in how information is understood (Nettleton et al. 2004; Nettleton and Burrows 2003). People derive important cues regarding the quality of information from the environment, and the type of interactions through which they receive it. The Internet affects diagnostic practices in multiple ways. People can type their symptoms in search engines in order to distinguish between serious and minor symptoms; find out what condition(s) they might have; and gather information about a disease before seeing a physician. In these ways, the Internet can help people become somatic experts, managing particular aspects of somatic experience (Rose 2007). It also makes it possible for users to get in touch with medical professionals, to select them (depending on the healthcare system) based on their online professional profiles, and to receive test results outside the walls of medical institutions. As such, the space where tests are taken is separated from where results are provided, and there may be changes in the temporal distance between the moment when the results are received, and when they are discussed with a professional. The Internet alters the means through which the results are communicated, and the shape this communication takes. Thus, by transforming how people relate to their medical state and interact with medical professionals, the Internet has contributed to 'the socialization of clinical diagnosis' (Webster 2002a, p. 448).

Apart from the constellation of actors involved, any online diagnostic practice depends on the specific character of a condition, on the design of the e-health technology, and on the dominant social, economic, and normative landscape. The appearance and development of online (self-) tests needs, therefore, to be placed in the broader context of the re-conceptualization of health and illness that has been underway over

the last decades. As technologies have enabled medical professionals to penetrate with their gaze into the deepest recesses of the human body, and to become more successful in the treatment of numerous conditions, the overall character of disease has shifted from acute to chronic (Armstrong 1995). Medical conditions are increasingly managed rather than treated, and the emphasis has moved from the moment when a disease becomes manifest to the period preceding its onset. Thus, online (self-) tests for AD inscribe themselves in a set of complex practices, which mark the turn towards prevention and early diagnosis. Apart from the heightened emphasis on risk factors, disease susceptibility (Rose 2007; Webster 2002b), and screening (Ashford et al. 2007), the spread and popularity of online (self-) tests has been further promoted by pharmaceutical companies, seeking to raise awareness of diseases as new treatments become available.

## Methodology

In this chapter, we focus on (self-) diagnostics of AD, identified using the search engine Google during the period December 2013–February 2014. The Google query using the keywords 'online (self-) tests for Alzheimer's Disease' generated 7,220,000 hits. We aimed to mimic the approach of regular users, and, using the Google index as an indicator of relevance, we confined our analysis to the results provided on the first 30 pages. By subsequently filtering the data for tests, and excluding multiple pointers to the same item, we identified 15 online tests in English, provided on platforms specifically dedicated to AD as well as on sites addressing broader memory and health-related issues. (See Appendix A for a full list of the tests examined.) In order to acquire a better understanding of how these tests may be perceived by users, one of the authors (Egher) completed each test.

In developing innovations, a popular implicit method designers use to represent potential users is the 'I-methodology' (Oudshoorn et al. 2004; Akrich 1995), defined as '[r]eliance on personal experience, whereby the designer replaces his professional hat by that of the layman' (Akrich 1995, p. 173). To understand how test users are imagined in the tests

we study, we use Akrich's notion of 'de-scription', which denotes 'the inventory and analysis of the mechanisms that allow the relation between a form and a meaning constituted by and constitutive of the technical object to come into being' (Akrich 1992, p. 209). While designers may ascribe to users their own competencies and preferences in interacting with technology, users can subscribe, by accepting the scripts embedded in a certain technology, they can de-inscribe, by resisting or seeking to transform the expected forms of interaction, or they can engage in anti-programme practices, through which users follow their own goals, disregarding the perspective put forward by designers (Oudshoorn and Pinch 2003). We compare the tests, not only by focusing on the characteristics of each, but by considering them as elements of discourse, the meaning of which is constituted through complex interactions between individual elements, the medium in which they are situated, and their users. We subsequently build upon findings regarding the importance of the personal, social, and cultural context for diagnostic practices to provide counter-interpretations to these tests. Autonomy and privacy are crucial values against which innovative healthcare practices are assessed in order to understand their consequences at a personal and social level. While aware of the dangers of combining rich descriptions with a prescriptive approach, we find it necessary to deepen our analysis by considering the impact of online (self-) tests for AD on the autonomy and privacy of their (potential) users, and make several evaluative claims. We identify important differences in the types and levels of agency and reflexivity of the various stakeholders approaching online (self-) tests for AD—aspects which are at the heart of any discussion on responsible innovation.

## Characteristics of Online (Self-) Tests for AD

There are (self-) tests available for people to download, print, and fill in by hand, whereas other tests can be completed online (e.g., see Appendix A). In terms of content, all (self-) tests analysed aimed to assess a person's level of memory and cognitive impairment, and required a minimum of motoric functions. They were designed with a variety of users in mind: medical professionals, people worried about the decline of their own

cognitive functions, and concerned relatives or friends. While the downloadable (self-) tests are free, others need to be paid for, and yet others require medical data in exchange. For the latter, the data collected may help users to observe the potential decline of their cognitive abilities over time, and enable the site owners to donate or sell the data for various (research) purposes. The tests are of varying duration: Mini-Cog (FAQ) consists of two main tasks and requires 3–4 minutes to complete whereas others may last 15–30 minutes. Most downloadable tests do not have a time limit, but may be expedited if someone else administers them, and provides help and instructions. Few online tests provide immediate feedback to respondents, and even such assistance is limited to the introductory examples, and is not available during the actual tasks. Some (self-) tests have varying time limits for different tasks. In some cases (Food for the Brain test), the time allowed is so brief that respondents are warned that nobody succeeds in fully completing it. Regrettably, no information is made available to explain this particular design choice. While there are four different versions of the SAGE test, meant to account for cultural-geographic differences, the tasks are the same, and the distinctions are restricted to the images used for object-recognition, and to the categories of concepts—countries, animals, vegetables—that respondents are asked to enumerate. The other downloadable tests do not take cultural differences into account, and we encountered a similar approach online, where only Food for the Brain (FFB) warned people that it 'makes no representation that materials in the site are appropriate or available for use in other locations, and access to them from territories where their contents are illegal is prohibited'. Unlike the other tests, FFB also inquired extensively into respondents' dietary habits, and provided not only the test results, but also personalized lifestyle advice.

Important differences exist regarding the ways in which the tests are designed. Most consisted of various tasks to be completed, yet there were also online (self-) tests where respondents were asked to evaluate themselves, with the expectation that they had already engaged in self-monitoring activities, and could recall accurately their behaviour. Such self-tests resemble those for informants, although the latter often consist of yes/no questions. Figure 8.1 provides two examples:

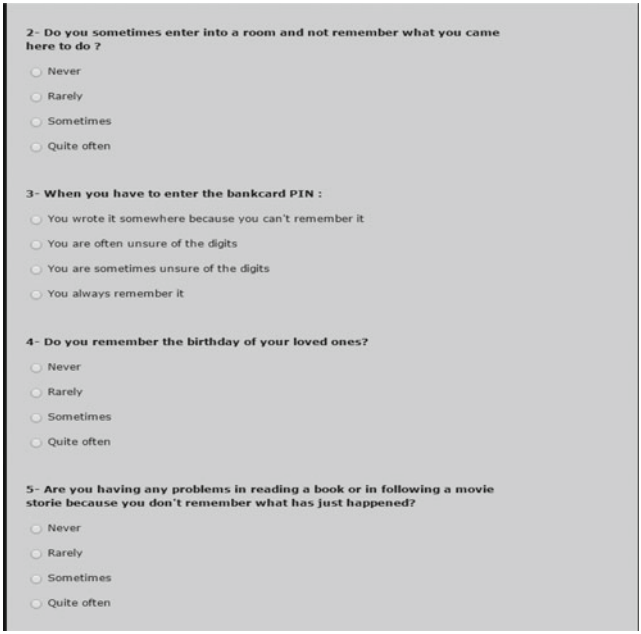


**Fig. 8.1** Excerpts from online tests (**a**) excerpt from online self-test MiniCog, (**b**) excerpt from downloadable test GPCOG for informants

In the case of self-tests, participants are required to assess their recent performance, whereas tests for informants ask family members to compare the current behaviour and abilities of their relatives to those of five–ten years earlier, making the assessment largely dependent upon the quality of the informants' memories. While the downloadable tests sought to measure also the respondents' language and literacy capabilities, online, these aspects were neglected. Even though they differ in terms of number of tasks and their level of difficulty, downloadable tests better assess the abstract-thinking abilities of respondents, whereas online tests focus on visual recognition and memory. Depending on the colour scheme and font style, the tests vary in readability, which may also influence the results. Both downloadable and online tests contained instructions that were, at times, unclear.

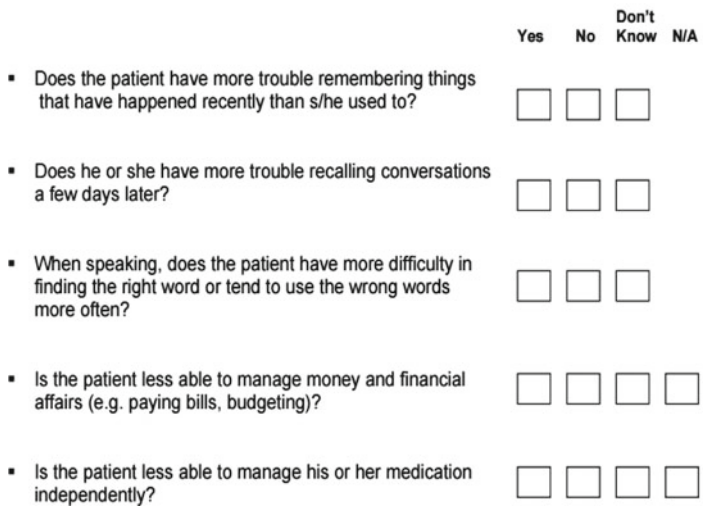


**Fig. 8.1** (Continued)

## (Self-)Diagnostics of AD and the Role(s) of the Internet

In order to interpret online (self-) tests for AD in the broader context of diagnostic practices shaped by the Internet, we assessed which of the many roles ascribed to the Internet were important, in light of the content and character of each test. Based on the literature discussed earlier, we identified three main roles the Internet plays: medium of distribution, of education, and of data collection. Each is discussed below, focusing on the changes brought about in the relations between stakeholders, and on possible counter-interpretations.

By making such tests available worldwide, the Internet is *a medium of distribution*. This may be considered democratizing, as it provides

(pre-)patients and their families with access to tools and practices previously available only to medical professionals, and/or to people living in healthcare systems with open access to such tests. It also enables people to choose the tests they take, and to compare the results from different tests before deciding what to do. Since the use and interpretation of online (self-) tests is mediated by the social, cultural, and medical tradition in which the participant is acculturated, this feature of the Internet may lead to new problems. Worldwide distribution might affect the validity of results, leading to false positives, because the content of tests may be culturally biased, and bear traces of power relations from their places of origin. Thus, people may be more or less at ease identifying oil tankers, daffodils, or harmonicas, all examples to be found in online tests. Uprooting online (self-) tests from clinical settings might lead to unreliable results, since some questions may elicit multiple interpretations, and by not having anyone to ask for advice, it may be difficult for the participant to decide. Since many tasks require a high degree of concentration, the mood of the participants may influence the test results and their reactions to them. This is acknowledged on some platforms (e.g., Memozor), which indicate that the results may also be due to depressive syndromes, among others. The user scripts embedded in such tests indicate that in the absence of clinical supervision, the participant is called upon to behave appropriately, and becomes responsible for the accuracy of the data provided, a guarantor of their quality. Yet, how people take and react to such tests also depends on their intentions and attitudes towards the Internet. For instance, people may discard worrying results if they do not consider the Internet a reliable diagnostic tool. Or they might attempt to re-inscribe their meaning, by using the tests to assess their vision or motor skills. People might even attempt to displace such tests from a medical context, by completing them in order to train their memory or simply out of curiosity. The tests might even be a form of entertainment (Harris et al. 2014), with playfulness and irony rather than seriousness and gravity characterizing the attitude of some participants. Thus, by physically removing the test from the clinic, the Internet contributes to a blurring of categories, and enables users to try out various roles, some of which were previously prohibited.

Second, the Internet is a *medium of education* for (pre-)patients, family members, care givers, and medical professionals. Online (self-) tests can thus be seen as anticipations and forms of preparation for the face-to-face encounters between medical professionals and lay people. Medical professionals may learn how to better administer tests and deal with their patients' anxieties, but their reliance upon online tests to initiate a diagnosis may bring hierarchies of knowledge and responsibility into question. Furthermore, medical professionals may be rigorous in their selection of tests, but simply by using them, they legitimize the whole category of online tests in the eyes of other stakeholders. Any (self-) test consists of three parts: solving the tasks, acquiring the results, and interpreting them. The relations between these components can be rather complex, and the way the results will be interpreted depends significantly upon the interpreter's level and types of knowledge. Thus, even when people take online tests identical to those used by medical professionals, they might fail to interpret the results correctly. This is partly the case because medical evaluations are more complex, and take into account education level and language proficiency (Hort et al. 2010). While recommendations on how to interpret cut-off scores are available in scientific journals, they do not accompany online printable tests.

Third, and most relevant in connection to its potential as a responsible innovation, the Internet is a *medium of data collection*, a process which sometimes occurs without the knowledge or informed consent of the person taking the test. While certain tests had the archiving and reuse of data as an additional option, others required participants to agree in advance for their data to be collected before gaining access to the test. Even when formal agreement is required, participants appear to lose any agency regarding subsequent uses of the provided data, as no further details are given beyond that they will be used for research purposes. No distinction is apparently made between research into causes and research for treatment (and what kinds of treatment). Furthermore, the acceptance of a diagnosis and (particular forms of) treatment depends upon personal values and cultural perspectives, so results obtained from studies based on data collected this way, even when reliable, would not benefit

all respondents. Yet, the concept of 'research' appears imbued with normative and political values reminiscent of conceptualizations of science as an engine for progress, meant to benefit everyone. It seems that simply mentioning that the data will be used for scientific purposes is sufficient for respondents to trust that data will be used responsibly, and according to values they also share. We also identified instances where test providers sought not only to collect data regarding the test participants, but also to increase their profit (or that of other companies), by encouraging people to purchase additional medical tests to determine the value of certain amino acids thought to have predictive value in the diagnosis of AD, such as homocysteine.

Matters become more complicated when considering that some online tests enrol medical professionals as data collectors by giving them the option to fill in a patient's answers directly online with the advantage of having the results automatically calculated. We do not know whether medical professionals know more about the purposes for which the data will be used, whether they inform the patients that data will be collected, and what will happen with them. Tests available online for medical professionals might also represent a means for them to retain authority in the context of competing forms of knowledge. More recent online tests, such as ClockMe or FFB, seek to engage both test takers and their general practitioners, either by sending the test results only to the latter or automatically sending the participant not only the results, but also a letter addressed to the GP. This shows that depending on the role it fulfils in relation to (self-)diagnosing practices, the Internet significantly influences the type and number of stakeholders who are enrolled as well as the practices in which they are afforded to engage. It is important to note that on the sites we examined, no information was provided about data storage, nor about the fate of such data in the eventuality of the dissolution of the organizations owning the sites.

The reliability of the data collected through such tests depends on the honesty of the data providers and on the absence of technical problems. Yet none of the online tests we studied contained mechanisms to prevent one from completing multiple tests under different names, nor was there any way to ensure that the personal data provided, such as age or level

of education, were correct. Since dementia can affect people's abilities in different ways, it may be difficult to know when the test was completed in a playful manner, and remove it from the data, even upon assessing the results. Furthermore, technical difficulties, such as a slow Internet connection or a server malfunction, may also negatively influence the results. Thus, findings based on data collected this way may be erroneous and inaccurate.

How new technologies are adopted depends also on the moral landscape in which they are implemented, and their use may, in turn, have important consequences on the norms and values of that society. We, therefore, turn our attention to the ways in which the online availability of (self-) tests for AD affects the level and form of responsibility of (pre-) patients and informants, and of test developers and researchers.

## (Pre-)Patients and Informants

By making diagnostic tests publicly available, the Internet contributes to an increase in people's level of responsibility regarding their health, but may endanger their level of personal autonomy by turning particular behaviours from personal choices into social obligations. As some (self-) tests target users aged 50, and recommend annual repeats (e.g., FFB), individuals are transformed into pre-patients. They are asked to constantly monitor their brains, and the future is brought into the present, with lifestyle restrictions, which were generally the consequence of a diagnosis, now used preventively. This blurs the boundaries between people with an actual AD diagnosis, people thought to be at risk, and people who fear they might develop it at some unspecified future point. Individuals come, therefore, to inhabit a sort of 'therapeutic limbo' (Webster 2002a, p. 445), and are relegated to a perpetual state of concern. Pushing the argument to its extreme, this may also mean that through the life choices made, individuals become personally, albeit still partially, responsible for their trajectory towards the development of AD. While previously medical practices required people to tell the truth about themselves, online self-diagnostic practices suggest that people are increasingly expected to find out the truth about themselves (Foucault 1961/2010), that personal

medical knowledge may become more of an obligation rather than an empowering option. This move is aggravated by the fact that no controls are in place to prevent people who are already diagnosed with a form of dementia from taking such online tests and from consenting to the data provided being collected and reused. Such data may be in fact valued, as some online tests inquire whether respondents have been diagnosed with a form of AD. Even though their brain functions may be impaired, people are addressed as fully responsible individuals, and are required to provide additional information about their medical history and that of their families. We may therefore conclude that while the level of personal responsibility for one's health is increasing, the degree of autonomy that one can exercise is simultaneously decreasing, as individual choices are weighed against social interests.

Personal autonomy is further affected by the provision of AD online tests for the caregivers of severely impaired people. The ascription of health-related responsibility becomes a bottom-up approach nuanced by the state of one's cognitive abilities: as soon as suspicion arises that they may have severely deteriorated, the next-of-kin are called upon to engage in diagnostic practices. The availability of such tests is built upon certain normative expectations regarding family and friendship, as relatives or friends are assumed to respect the autonomy of the person and act in his/her best interest. Yet, such assessments can be arbitrary and online tests could be used in an abusive manner. Their availability brings one under double surveillance, both self-achieved and enacted by those with whom one shares one's life, while one's level of cognitive functioning becomes an unusual form of common property. Suspicions that one's brain may no longer function properly curtail one's right to make decisions, and to choose the health practices one wants to engage in. We noted this tendency also in the content of tests. The objects that people are asked to identify are not realistic depictions or photos, but drawings reminiscent of children's books. Since books for children represent means of acculturation, this infantilizing approach suggests that taking such a test threatens to weaken one's position in society, to initiate a process of alienation that may lead eventually to no longer feeling at home in the world.

Online (self-) tests may also lead to a reduction in important aspects of personal privacy, as respondents are not only required to find out the

truth about themselves, but also to make it available to others, to share information about the inner workings of their brains as a form of civic duty. Data are gathered online in search for cures which may become available in the future, when the data providers are no longer able to benefit. Personal information, the cognitive capacities of individuals, and how people age are turned into a novel form of currency, and (self-) tests become a method to enrol individuals in 'clinical labour', and to thereby extract 'biovalue' (Mitchell and Waldby 2010). In so doing, online tests may contribute to enlarging what counts as biovalue, including not only physical samples, but also cognitive ones. As the projected care costs often lead to people older than 80 being envisioned as burdens to society (Fukuyama 2002), such extraction of biovalue may be seen as a preemptive tax individuals are required to pay in order to enjoy their old age without experiencing severe pangs of conscience.

Nevertheless, benefits may also be identified in relation to online (self-) tests for AD. Their availability enables individuals to take matters into their own hands at an early stage, to retain a higher degree of privacy, and to make decisions when their right to do so is not contested. Studies (Fisk et al. 2007) have shown that self-reports of subtle cognitive decline represent a reliable indicator of future cognitive decline in older individuals, even when no objective indicators can be found. So, people may start taking such tests long before their impairment becomes noticeable to others. Since in Western societies the ability to reason is paramount in defining human nature, people may be ashamed and reluctant to share such concerns with others, and might prefer, instead, for their data to be used anonymously in studies they know nothing about. Moreover, an online evaluation may enable the person to decide if and when to contact a medical professional. Nonetheless, this form of empowerment represents a double-edged sword: the ability to make informed decisions regarding one's course of treatment may open cognitive decay to normative evaluations, with the progression towards AD achieved more or less graciously, depending on the person's choices.

Disclosing diagnoses directly to the person tested is culturally dependent, and significant variations in treatment and care choices are recorded, depending on the family member making the decision (Pucci et al. 2003). (Self-) tests may thus represent a means of empowering the potential patient

and a way of fighting the benign or malign control of relatives. While (self-) tests may provide a certain kind of privacy, they render participants wholly responsible for their subsequent behaviour, raising important ethical issues. Upon finding out they have AD, people often experience depression, suicidal tendencies, mental shock (Draper et al. 2010). Online (self-) tests are even more problematic, as they are available to people all over the world, who have different levels of access to care, and for whom AD may mean distinct things, denote different levels of personal responsibility, and thereby affect self-worth and social standing in different ways.

## Test Developers and Researchers

The online availability of (self-) tests seems to minimize the level of responsibility of their developers, who are either briefly mentioned in terms of name and occupation—often simply as 'researcher'—or who are completely absent. This may be partly because numerous (self-) tests were transferred online from medical contexts, and their developers may refuse liability for their use in a different environment or may distrust the ways in which cognitive screening is provided online. Part of the responsibility may instead be ascribed to the platform owners, as the level of trustworthiness users ascribe to the platform may influence their attitude towards the (self-) tests. If we shift responsibility from shadowy developers to computer algorithms, then the trust previously bestowed upon a human being, even if only in the quality of overseer, is now placed in machines. Even though automata have become increasingly capable of learning from experience, they determine a responsibility gap (Waelbers 2009; Matthias 2004), as there are too many people involved in their development, and there are still too few ways of making machines accountable.

The epistemic dimension of responsibility for online (self-) tests may also be lacking, since little is known about the modification processes they undergo before being placed online, nor is information provided about their validity. For instance, in 2011, the U.S. National Institute of Neurological Disorders and Stroke, and the Alzheimer's Association, which issue the most used diagnostic criteria for AD, modified the classification of symptoms (Jack et al. 2011) and enlarged the diagnostic focus beyond

memory impairment. Nevertheless, online (self-) tests continue to focus on memory and to neglect changes in attitudes and behaviours. While this may imply that online information is not always as up-to-date as many users assume, or are led to assume, the same flaws are present in tests developed more recently. Such obduracy might suggest a preference for test items that are quantifiable, indicative of the pervasive tendency to trust numbers, to bestow upon them the quality of indubitable facts. The Internet creates distance between those providing data and those collecting/using them, and symptoms, which, despite their cognitive character, used to be embodied are reduced to a few answers on basic arithmetic and recall exercises. Little is known about the ethics by which researchers conduct their trials, nor about to whom they are professionally responsible. The lack of detail about the use(s) of the collected data raises more ethical issues if such information were to be made available to insurance companies and/or employers. Knowing to what extent the data provided can be traced back to the individual participant becomes highly important and the necessity to protect the privacy of online test users all the more urgent.

## Concluding Reflections

In this chapter, we have discussed how, through online (self-) tests for AD, the Internet redistributes responsibility between different actors, across national borders, and through different means. The shift in authority towards (pre-)patients occurs as their responsibilities increase compared to other stakeholders. To the extent that (self-) diagnostics rely upon objective results provided by computers, their authors largely escape responsibility as they can rarely be confronted directly. Their involvement is lost in a dense network, including researchers, medical professionals, technicians, IT experts. We present below some suggestions to improve its character as a responsible innovation, by focusing on anticipation, reflexivity, inclusion, and responsiveness.

Anticipation may be extremely hard to achieve, since the Internet as a diagnostic tool may be adopted and shaped differently around the globe. Studies on how people have engaged with other communication and diagnostic technologies may provide relevant insights, since previous experiences shape how people relate to innovations (Suopajärvi 2015). It

might be more productive, however, to focus on surprise, and to develop strategies that would enable quicker and more effective responses. In the context of such a dynamic and heterogeneous medium, reflexivity also risks being severely compromised. It might be helpful to provide participants with information regarding the development of the test they are about to take, or ask them to describe how they experienced the test upon its completion. Ensuring that developers and researchers know how their tests are provided online, and organizing periodic encounters between them and a wide variety of online (self-) tests users may enhance reflexivity, as the former will be better able to understand how the meaning and use of the tests evolve over time and across cultures. Opportunities for test developers, medical professionals, (potential) users, and other stakeholders to engage in collective experiments would also help to ensure that online (self-) tests better respond to the varied needs of different stakeholders. They would also increase developers' awareness that users, whether as patients or consumers, often have rather different skills and cognitive abilities from those they may have imagined. This is particularly important because in the near future, downloadable tests will most likely be replaced by ones that must be completed online, as the target group starts to consist of people with longer familiarity with digital technologies. Such encounters would also provide insights about the different moral theories through which developers, medical professionals, and users evaluate online (self-) tests and ascribe responsibility (Doorn 2010).

One way to increase the level of responsibility may be through enrolling the general practitioners of those who openly engage in self-diagnosing practices, to develop feedback channels through which information regarding the validity and predictability of the test results could be transmitted. Even if the results of online (self-) tests may not be harmful for participants, our analysis shows that the benefits may be rather limited, and often of a transitory nature. Equally important is to consider whether such benefits are intended for individuals or communities. Deeply embedded in the (self-) tests we studied was an absolute valuation of rationality, which did not allow room for conceiving of a decline in cognitive abilities as anything other than negative. The use of other sources which illustrate the selfhood of a person affected by AD, such as novels or artworks, may be helpful in imagining and designing technologies that represent the condition in a more nuanced manner.

## Appendix A: Overview of online tests studied

| Name | Type[a] | Association | Participant | Date accessed | Link |
|---|---|---|---|---|---|
| Alzheimer's Disease Assessment Scale-Cognition (ADAS) | D | *Dementia Collaborative Research Centres* | Medical Professional | 3.1.2014 | http://www.dementia-assessment.com.au/cognitive/ADAS_Packet.pdf |
| ClockMe. Home-Based Assessment Tool for Dementia Screening | O | *Georgia Tech* | (Potential) Patient & Medical professional | 3.1.2014 | https://www.youtube.com/watch?v=MEbWeiKxd0c |
| CogSelfTest (payment required) | O | *COGSelfTest* | (Potential Patient) | 3.1.2014 | http://cogselftest.com/ |
| Food for the Brain Cognitive Function Test | O | *Food for the Brain* | (Potential) Patient | 3.1.2014 | http://cft.foodforthebrain.org/ |
| GPCOG Screening Test | D | *Alzheimer's Association* | Medical Professional (GP) | 4.1.2014 | http://www.alz.org/documents_custom/gpcog(english).pdf |
| Memory Impairment Screen (MIS) | D | *Alzheimer's Association* | Medical Professional | 4.1.2014 | http://www.alz.org/documents_custom/mis.pdf |
| Mini-Cog | D | *Alzheimer's Association* | Medical Professional | 4.1.2014 | http://www.alz.org/documents_custom/minicog.pdf |
| AD8 Dementia Screening Interview | D | *Alzheimer's Association* | Medical Professional | 5.1.2014 | http://www.alz.org/documents_custom/ad8.pdf |
| Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[b] | D | *Alzheimer's Association* | Informant & Medical Professional | 3.1.2014 | http://www.alz.org/documents_custom/shortiqcode_english.pdf |

| | | | | | |
|---|---|---|---|---|---|
| Mini-Mental State Examination (MMSE) | D | *Alzheimer's Society* | Medical Professional | 21.1.2014 | http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=121 |
| Montreal Cognitive Assessment Test (MOCA) | D | *MyBrainTest* | Medical Professional | 3.1.2014 | http://www.mybraintest.org/dl/moca-test-english-7-1.pdf |
| Self-Administered Gerocognitive Exam (SAGE) | D | *The Ohio State University. Wexner Medical Center* | (Potential) Patient | 23.12.2013 | http://medicalcenter.osu.edu/patientcare/healthcare_services/alzheimers/sage-test/Pages/index.aspx |
| Test Your Memory (TYM) | D | *Test Your Memory* | Medical Professionals & (Potential) Patient | 3.1.2014 | http://www.tymtest.com/tym-test-download.php |
| The Mini-Cog Test for Alzheimer's and Dementia | O | *Alzheimer's Reading Room* | (Potential) Patient | 3.1.2014 | http://www.alzheimersreadingroom.com/2009/03/mini-cog-test-for-alzheimers-and.html |
| Do the test for Alzheimer online | O | *Memozor. Games and Tests for Memory Online* | (Potential) Patient | 3.1.2014 | http://www.memozor.com/memory-tests/test-for-alzheimer-online |

[a]Downloadable tests are marked with D. Tests to be completed online are marked with O
[b]This test is available on numerous other sites

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# Part III

## Alzheimer's Disease: Multiple Realities and Concerns

# 9

# Making Alzheimer's Disease Matter: The Politics and Interferences of Different Practices Concerning AD

Ingunn Moser

Bodies with Alzheimer's disease (AD) are appearing in public in new ways. Patient associations have been set up in many countries. Alzheimer's now turns up in public discourse, media, film, and fiction. Dementia is high on the agenda in policy documents on the future of welfare services. Priorities in science and technology have started to change too. Recent research in neuroscience is moving AD into the centre of attention, and in biomarker diagnostics for AD, the issue is how innovation can be made more responsible and caring. All of this shows that AD *matters* both in the sense that it is of concern or importance, and that it materialises and becomes 'matter-real'. But *how* it matters, *what* is made of it, and what this *implies*, varies. Different versions and practices of AD therefore entail implicit, yet varying, politics. It is therefore vital to have a good understanding of how and where these current politics are occurring, what their implications are, and what the alternatives are or might be. The aim of this chapter is to make visible how current practices

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concerning AD are implicated in politics, and by so doing, to contribute to Responsible Innovation by helping make these politics more open, reflexive and collective.

In order to open up the unfolding politics of AD, I draw on a body of work in science and technology studies (STS). Scholars in STS have argued forcefully that science, technology, and medicine are ordering and materially productive practices (Haraway 1997; Mol 2002; Law 2004). They do not simply discover, define, interpret, or account for these. Realities including health, bodies, and disease are brought into being in material practices and relations, in a process that brings together and aligns actors and elements in particular ways, and so, shape both matters of concern and the collectives they come with. 'Matters of fact' are also 'matters of concern' because facts are value-loaded and charged matters (Latour 2004b). 'Matters of fact' are in this view products of such processes that have been made indisputable and erased.

A new generation of STS focuses in particular on differences within medicine, and between medicine and other locations (Berg and Mol 1998; Heath 2006; Martin 1994, Mol et al. 2010; Lock 2013). The challenge of difference is related to the fact that if objects of knowledge emerge in particular relations and practices, then different objects get enacted in different sets of relations and contexts. This also implies that practices are neither innocent nor isolated. They co-exist, relate and also interfere with one another. This has implications for the shaping of matters of concern and their politics. But how? And what implications?

The concern driving this contribution is that it is important to explore the character and the politics of the prevailing realities, including the differences and patterns of interference that they make. It is further important to raise questions about and consider which realities we want to live with and contribute to. In this way, the technoscientific fabrication of disease and daily life realities might be made more reflexive, open, collective and possibly also democratic (Barry 2006; Latour 2004a).

In line with this, the chapter investigates how AD is being shaped as a 'matter of concern' in a range of locations and practices, and in the relations and interferences between them. They include an international Alzheimer's disease movement; a medical textbook and diagnostic context; the laboratory; care practice; an advertisement for anti-dementia

medication; general practice; and parliamentary politics. I show that each of these locations presents a different version of what Alzheimer's is and how the problem should be dealt with. I then explore how these locations, knowledges, and matters interfere with one another, and how they co-exist in various forms of relation, tension, and disjunction. I argue that to open up the politics of AD, we need: first, to trace the multiplicity of realities-in-progress, the alternatives they present and the politics they imply; and, second, to appreciate the complex relations and interferences in which they are produced, and which shape positions, influences, possibilities and inequalities.

The chapter draws on empirical material from Norway, but the relations in which the disease reality comes into being extend beyond the boundaries of a single nation state. The chapter further revises an article first published in 2007. The material presented reveals how a condition that used to be understood as part of a normal ageing process has been reconceived and turned into a public matter of concern.

## The Alzheimer's Disease Movement: Building Networks That Transform Facts of Life into Global Matters of Concern

So AD matters today. But how did it turn into a matter of concern?

One obvious reason might be that the number of people afflicted is growing. Populations are growing older, and living longer increases the risk of suffering from dementia diseases. According to the organisation Alzheimer's Disease International (ADI), the estimate is that by 2030, 75 million people will be suffering from AD and other dementias. ADI suggests that this is especially so in the rapidly developing and heavily populated regions of China, India, and Latin America. Public health and patient associations argue that most will become heavily dependent upon care and assistance, and that this will become a major global social and political challenge.

But these numbers and facts don't make themselves and don't work by themselves. It takes effort and hard work. Numbers are, however, important: they are mobilised to help make a case. Population-based studies and

statistics are pivotal. The persistent efforts by patient associations to raise awareness, map the prevalence and impacts of Alzheimer's and dementia, build networks, and mobilise an international Alzheimer's movement have been vital. These figures and arguments form a first example of a practice in which AD is actively being turned into a matter of concern. This is being done by building transnational networks between patient associations, health policy agencies, and, epidemiological and biomedical research.

According to Fox (2000) and Whitehouse et al. (2000), a highly productive association between patient associations and biomedicine, with biomedicine taking an active role in the shaping of strategies and priorities of an emerging Alzheimer's movement, has benefited both parties in their efforts to make their voices heard in public. In this way, biomedicine has become integral to the Alzheimer's movement and its making of a global matter of concern. Biomedicine has been crucial in establishing Alzheimer's as something to be treated, and dealt with actively in the first place (Fox 2000; Moreira 2009). The progressive differentiation, definition, and diagnostics of dementias have been achieved through the instruments, networks, and circulations of international biomedical research. In this way, a 'universal' notion and disease object has been made possible. At the same time, the Alzheimer's movement has built on and circulated this notion of Alzheimer's (and dementia), and supported epidemiological mapping in member countries based on it. The two have become mutually dependent and supportive.

## Laboratory Science: Enacting Facts and Objects Through Microbiological Puzzle-Solving

The next location shows another instance of this mutual dependence and support. Jannike is a young scientist whose PhD is on the relationships between beta amyloid, impaired glutamatergic neurotransmission, and reduced memory in AD. Her research reached the news in the context of the image of Alzheimer's as an epidemic, where it was presented as helping to lay the foundations for the development of future therapies and treatment (Forskning 2003; Uniforum 2003). But what, more

precisely, is the foundation, the universal disease object that is carried by the networks and practices of science and movement? What does it make of Alzheimer's and what is its politics?

Jannike introduces her work by emphasising the complexity of this disease: there are many different systems and mechanisms involved and there also seem to be numerous causes to the development of the disease. She explains that one theory is that the glutamatergic signal system in the brain is damaged. And she continues: 'With Alzheimer's patients we see, among other things, that the cells using glutamate as transmitter substance are damaged. We don't know for sure what causes it, but one theory is that it is overstimulation of the glutamatergic system that leads to this damage to the neuronal cells' (Uniforum 2003).

To investigate the reality and mechanisms of these relations, she did a series of in vitro and in vivo experiments. In one, she used rats to model and test the relationship between glutamatergic transmission of neuronal signals and memory in vivo. First, she destroyed the neuronal transmission of signals using glutamate in the brains of rats by injection or surgery. Then, she exposed the rats to behavioural tasks and memory tests to see if this led to impaired memory. This, she argues, proved to be the case. Next, she administered further agents intended to compensate for the injuries. These were agents that stimulate the glutamate receptors and glutamatergic transmission of signals. And then, the last step—a new set of behavioural tasks and tests—showed that the rats treated with these agents remembered just as well as healthy rats. Jannike also worked on the ways in which the aggregation of beta amyloid leads to neuronal damage via production of reactive oxygen species—and how this, again, may lead to altered neurotransmission, and so, result in impaired ability to form new memories.

Now, this is obviously a smooth story about how a disease such as Alzheimer's comes into being in laboratory practices. But it also shows that Jannike and her colleagues together with the rats are involved in a form of *micro*-biological puzzle-solving. She repeatedly stresses that there are many mechanisms and systems involved that result in different consequences and forms of damage. The puzzle is what these are and how they work, individually and in interaction. This means that questions about the causes and mechanisms of the disease are split into a

myriad of smaller 'sub-disciplinary' issues, which are again broken down and specified into questions and hypotheses that can be treated, modelled, manipulated, and tested in experimental set-ups—and inscribed, observed, and demonstrated through different imaging technologies. It is through these models and experimental set-ups that parts or representatives of the realities to be explored are made, or allowed to act and interact. Then the outcomes are interpreted as supporting a hypothesis or not, and as opening or closing paths of research. In this way, relations are defined and redefined, objects are stabilised or transformed, and small bits of the puzzle to be solved are created.

The puzzle is defined and delimited as the human brain, its cognitive functions and capacities, their mechanisms, and the mechanisms of disease or degeneration. The focus is predominantly on factors internal to the brain or organism that might explain why things go wrong in the first instance.

The lesson to be drawn is that AD is still very much a puzzle, rather than a matter-of-fact and a fully-fledged object. Few elements and relations are made indisputable here. But a regime of hope (Moreira and Palladino 2005) based on trust in the progressive character of biomedical research and its promise of cure means that it can still work in a more pragmatic manner. It works as a fact, but also as a framing of what kind of problem we are dealing with and how it might be dealt with.

## A Diagnostic Context: Making Difference and Establishing Alzheimer's Disease for Clinical Purposes

So the Alzheimer's movement, teamed up with biomedical or neuroscience, presents us with a global matter of concern and contributes to enacting and stabilising a universal disease object. The next example is from a setting where this is challenged.

The mandate of the National Advisory Unit on Ageing and Health is to secure national competency building on dementia and old-age psychiatry. It operates a number of research projects, develops diagnostic tools and educational materials, offers advice to local and central government,

and acts as an advocate for the dementia issue. In one of its publications, *Dementia. Facts and challenges* (Engedal and Haugen 2009), AD is defined as one of a series of different diseases that lead to dementia, or have dementia as their symptom. Dementia, for its part, is a 'generic term for a condition (syndrome) that can be caused by different organic diseases, and which are characterized by chronic and irreversible cognitive failure; failing ability to carry out activities in daily life in a satisfactory manner compared with earlier abilities; and changed social behaviour' (p. 17).

According to Engedal and Haugen, with the exception of a few hereditary cases, there is no known, isolated, specific cause that leads to dementia of Alzheimer's type. Instead, there are probably multiple causes that lead individually or in interaction to the development of AD. At present, we don't know whether the pathological changes characteristic of AD (including aggregation of beta-amyloid protein fragments; neurofibrillary 'tangles'; reduction of synapses and signal substances …) *are* the disease, the causes of disease, or whether they are expressions or consequences of it.

The primary concern of this book is not however to describe the condition and our state of knowledge of it. It is intended for clinical practice. It therefore goes on to elaborate upon the symptoms, diagnostic tools, the possibilities and limits of new imaging technologies and other diagnostics, and forms of intervention. On the latter, the text book says that at present we know of no treatment that can prevent, stop, reverse, or cure the development of AD. It is only possible to alleviate symptoms, either by medication or environmental measures.

So here, a difference is made in medicine—and this difference is irreducible. The text book builds on biomedical research, but draws on other sources too. It is not obvious what the use-value of biomedical research is in the clinical situation. Some patients have symptoms of AD with few or no pathological changes. The same is true the other way round. Finally, the differentiation of the sub-species of dementia is neither neat nor clear in practice. Many people have hybrid or multiple forms of dementia.

Further, there are tensions between the different enactments of AD in lab research and in clinical practice. Where lab science focused strictly on biomedical therapies and interventions in individual brains, the textbook

notes that 'there is a long way to go' and that 'treatment on this level is far removed from our clinical everyday'. But it adds that even if we do not have any treatment for stopping or curing dementia, 'we think it is important for the quality of life of the patient that he or she is met with understanding by relatives and health personnel' (p. 91).

The medical intervention suggested here, thus, takes a different form to that imagined within biomedical research. As a part of this, Alzheimer's has become reconfigured and relocated from pathological changes in brain tissues. It becomes a matter of the attachments, interactions, and the living together of a collective that encompasses not simply the patient, but care persons, relatives, health personnel, and the organisation of the home.

## Caring with Marte Meo: Enacting Alternatives in Nursing Practice

Once we situate (bio)medicine in lived reality, it becomes apparent that there are many ways of relating to and enacting disease. It also becomes clear that many locations may be invisible if we simply follow scientists or trace developments and networks in scientific fields. The following example comes from the quite different circuits of care practice, and it rests on and interferes with another underlying set of enactments that appear, for instance, in the media.

The Marte Meo Method was developed in clinical psychology as a tool for improving communication between parents and infants, but has increasingly been taken up and used in care for people with dementia. In a conference introducing Marte Meo to dementia care, one of its advocates argued that: 'The disease is chronic, there is today no cure for it and it progressively gets worse. The most important treatment measure we have today is therefore human relations'. And she continued:

> One of the biggest challenges carers face, is difficulties in interpreting the expressions of the patient as meaningful. (…) By video-filming everyday situations, for instance like meals, and then analysing and discussing these afterwards, it becomes easier for the carers to recognise the initiative of the

> patient. The result is that the staff become more aware of the competences of patients with dementia. (…) They are often much more capable than we think.

According to further presentations, patients who are restless and 'difficult' have calmed down and eat better since they introduced this method. The carers work by relating to the patient and the situation 'here and now'. If too many things are introduced at once, patients become scared and nervous and try to take control. This may lead them to act in ways that are easily characterised as difficult or problematic. 'We have verbal language as our tool to take control of incomprehensible matters. People with dementia don't. But even if a person has dementia this doesn't mean that it is empty in there. You just have to find her language'. And: 'They haven't sailed off and totally disappeared into the darkness. Their emotional life is still there even if their brain is impaired'.

This is not like biomedicine. It is a different way of working on and enacting AD. According to its advocates, the Marte Meo Method cares primarily about the nature and quality of the human relations with people with AD. But this does not mean that it is opposed to and inconsistent with object(ive)-knowledge, expertise, and technology, or that biomedicine is simply about objects while caring is about relations. As we have seen, here too, the reality of AD is both objective and relational. It is something you are confronted with and something that can, within limits, be shaped. When the nurses work on the relations of Alzheimer's, they also transform the object. For instance, if they slow down verbal communications and interaction, the person with dementia may be able to act and participate competently. But if the nurses don't take the time to wait for a response and move on to new themes and questions or to new patients before the person with dementia has time to respond, this leads to misunderstanding, frustration, and aggression.

Further, as with the earlier versions, the Marte Meo version is also worked upon in specific material practices and arrangements. These include videotaping, analysis, experimenting with objects and relations, and manipulating these in typically problematic situations. But the objects and relations targeted here are not like those of biomedicine. Neither, too, are the framing assumptions about what makes a person,

or the character of subjectivity. Ideas about where those capacities reside, how they are expressed or done, and how this is affected by the introduction of AD are also different. The result is that the challenges and solutions that emerge and become imaginable in this practice are also quite unlike those of biomedical research.

But this Marte Meo version is not just different. It is enacted explicitly as an *alternative* to the reality of biomedicine, and perhaps, especially that of the pharmaceutical industry. It says that there is no simple answer or solution, no easy pills to be taken, but there are still things that can be done.

This means that the Marte Meo Method is also articulating a critique of—and offering an alternative to—yet another set of enactments of Alzheimer's that circulates widely in and beyond the media. This is the idea that people with Alzheimer's disappear into the 'mist of oblivion' and that they get lost to us before they have actually left us. Thus, it is widely argued that people lose or are deprived of their mind, their rationality, and, by implication, their subjectivity and dignity.

These enacted realities are also at work here in their absence. The nurses training as Marte Meo therapists contest these tropes. They argue that though people with dementia may not have verbal language, this does not mean it is 'empty in there'. They haven't 'sailed off'. They still have an emotional life, communicative capacities, initiative, and competencies.

What these nurses are involved in, then, is the fabrication of an alternative version of AD—together with an alternative form of subjectivity. By manipulating and working on the relations and practices of care, they reconfigure subjectivity and redistribute it—with the effect that people with AD also come out as active, rational, conscious, communicative, and emotional. They emerge as full of life rather than its opposite.

The reality in the nursing home also shows that when Alzheimer's is made to matter, it is not simply that *a* single new version of Alzheimer's replaces one that is older. Instead, it shows that there are different and changing versions of AD, that there are *gradients* of definiteness and realness, and that these realities co-exist and interfere with one another.

## The Promise of the Drug: The Solution That Excludes, Disarticulates, and Makes Care Alternatives Invisible

Having brought out some of the ways in which AD is practised, disputed, and experimented with in different locations, the question of their co-existence and relations becomes pressing. *How* do these different versions of Alzheimer's, all at work at the same time, co-exist and interfere with one another? Do they support or undermine each other? Are they kept apart or brought together? What is kept apart, and what is brought together and made present *where*, and with what effects? What becomes more present, visible, real, and powerful—and how? What spaces are there for contestation and intervention? In the examples that follow, I explore these questions, and I start with an advertisement for anti-dementia medication.

'Look her into her eyes', it says in bold type, 'and tell her that she has to move from her home'. This message heads a double-page advertisement in the programme of the Dementia Days, an annual conference directed at healthcare professionals. On the left-hand page, the reader is drawn to and confronted by the insistent eyes and image of an old woman. There is no doubt that she is there, and you are forced to meet her and look her into her eyes—even though her picture is cut in half, perhaps indicating that she is already starting to disappear. The other half of the page immodestly claims that 'continued treatment with Aricept makes it possible for patients with Alzheimer's disease to stay home for more than five years'.

Aricept is a so-called acetylcholinesterase inhibitor. It targets the cholinergic signal system in the brain by blocking the breakdown and reduction of cholinergic transmitter substances and signal transmission. Cholinergic signal transmission is deemed crucial to memory and language, and so, by introducing agents that promote it instead of reducing it, the promise of the pill is that it will postpone the symptoms, if not the progression, of the disease.

We have already indirectly met this enactment of Alzheimer's in talking of the Marte Meo Method. And now, it is present in this conference

programme. It also appears in thematic sessions on the experiences and evaluations of anti-dementia drugs. And by allying themselves with doctors, patients, relatives, and public figures, the pharmaceutical companies also appear in the mass media and in parliamentary politics.

The pharmaceutical industry's strategies for building networks and tapping into existing ones, for circulating its version of the disease within them, are worthy of study themselves. Here, I can only hint at how this is achieved. But this enactment of AD is done in other ways too. It is made present and real by interfering with other enactments, by going along with these and drawing on them, by supporting them, or by weakening, silencing, or making them absent. For instance, it both builds and depends upon biomedical laboratory science and the trajectory of research invested in the cholinergic hypothesis. Active association with biomedical science in the advert strengthens this relation and the idea that Alzheimer's is an object(ive) reality in the brain and mind of the patient. This again draws upon and runs along with the set of popular representations that constitute people with dementia as 'sailing into darkness'—as being on a track where, in the end, there is no mind, no self, no dignity left. Further, in promising to prevent or postpone dependency, it plays on and is supported by common conceptions of dependency, loss of mind and self as failure. And, crucially, in promising to postpone institutionalisation by five years, it sets up the pill-version of the disease as opposed to (or as an alternative to) care, and especially, institutional care. Indeed, it sets up care, and institutional care, in particular, as an admission of failure too. This is seen as a bad thing, partly because care becomes equated with passive acceptance rather than active intervention, and partly because the pill is seen as a way of cutting costs (because it is assumed to reduce the need for healthcare services). All of this means that there is no alternative to biomedical or pharmaceutical treatment.

What we learn here is that enacting AD as a matter of manipulating neurochemical transmission in the brain simultaneously enacts and denies other realities. The latter include experimental and inventive practices in care, but also, the differences and tensions in medicine that were brought out in the medical textbook. They are made absent and invisible, excluded, and disarticulated.

## A Gathering Around the Doctor's Desk: The Pill Meets Lived Reality in Clinical Practice

The pharmaceutical enactment of Alzheimer's works by keeping certain versions of the disease together, while others are carefully kept apart. However, the next example comes from a location where these things are actively brought together: that of clinical practice.

Whenever there is a suspicion of dementia, the general practitioner has to collect and bring together a broad variety of information from different sources. On and around her desk, most—if not all—versions of AD are brought together. There are those of the patient herself, her relatives, worried neighbours, the community nurse, the medical literature, information from the pharmaceutical industry, and test results from the lab. If the general practitioner concludes that the diagnosis is 'probable AD', she must consider what can be done, and add further information from clinical trials, evaluations from the Medicines Agency, directives from the National Insurance, and her knowledge of local care arrangements.

Mari is a general practitioner who is concerned with how these versions of Alzheimer's disease relate, and what their implications are. Having attended the yearly Dementia Days, she wrote a review and a commentary in a journal of general practice:

> There were no critical commentaries on the eagerness to treat with AC-blockers and other anti-dementia medications. The message was that as soon as the diagnosis is set, medication should start. But what is it that we are offering? A medicine that has proved effective in only ten percent of cases, and then delays the cognitive impairment by only six months on average. An increase in dose from five to ten mg gives no extra effect, only more adverse effects. There are no documented guidelines for the duration of the treatment. At the same time one in sixteen will experience such serious side effects during treatment that it has to be stopped. What other medicine would be accepted by the Medicines Agency on the basis such figures? (Johansen 2004)

She goes on calculating: Three months of treatment with five mg Aricept costs €300. If we give donepezil five mg daily to 12 people over a year,

more than €13,437 have been used, to no effect. During the last three years, national insurance has spent €23,500,000 on Aricept alone. How many more people with dementia and their families would benefit from support groups for relatives, home-based ambulant services, a short-term bed in a nursing home, or a place in a day care centre (Johansen 2004)?

This shows that realities that were carefully kept apart and even made invisible and absent by the pharmaceutical industry are brought together in the clinical consultation. On Mari's table, the location of the disease in care realities (institutions, homes, and family relations) and these relations' constitutive role for subjectivity are no less real than relations between donepezilhydroclorid, blocked breakdown of acetylcholine, and memory and language. The differences and tensions in medicine brought out in the textbook are also being made manifest here.

Second, the gathering of all these different enactments around the doctor's desk extends and multiplies the webs of relations. As it reshuffles and reconfigures them, the relations built in by the advert—the presences, absences, and denials to which it contributes—are disturbed. For instance, the support that the pharmaceutical version drew from association with science, that also worked by homogenising science, is weakened when the differences in medicine enter the arena. And while the pharmaceutical and biomedical enactments get weaker, the other versions get stronger.

But alongside this pluralisation and levelling, other things are happening too. As Mari also points out in her report, some of these versions are in conflict. For instance, Marte Meo caring clashes with local healthcare services, which want to set limits to staff and budgets. At the same time, money spent on support groups, education, and day care centres may postpone and reduce the need for places in nursing homes. But if you opt for the pill and the biomedical version, and hope, at the same time, to cut care budgets, you end up with exhausted relatives, worried neighbours, police complaints, the possibility of tragic accidents and deaths, and a whole new group of patients with dementia in the hospital's accident and emergency unit. The implication is that you cannot have the one without the other(s). And, further, you do not really have an option in the sense that the advertisement seems to suggest, because the different

practices and realities they enact are so complexly related and implied in each other.

Mari has to work out how to handle these competing and at least partially conflicting versions of AD in each individual case. In working for and towards particular versions of AD, rather than others, she necessarily enacts one and not others, which means that she takes a practical and political position in a controversy. In her commentary in the journal of general practice, *Utposten*, she also takes it further by transporting the conflicts she experiences in her daily clinical work to new sites. In this, she works to disturb both the prescription practices of other general practitioners and the debate about anti-dementia medication.

## The Performativity of Parliamentary Politics: Regulating Medication, Containing Dissent, and Disarticulating Alternatives

As we have seen, clinical practice and the journal of general practice are examples of locations where different versions of Alzheimer's—including those of the pharmaceutical industry and or biomedical research—both come to matter, and to be gathered, contested, and politicised. The final example takes us to another, in some sense *the*, site where matters are assumed to get collected, acquire voice or representation, be confronted and opened up—namely, parliamentary politics. In practice, however, it is almost the opposite that happens. This is because the site of parliamentary politics also works to contain dissent and disarticulate alternatives, rather than fostering them. Notwithstanding intentions to the contrary, the effect is that pharmaceutical and biomedical enactments are strengthened.

In 1997, Pfizer requested that Aricept as the first medical therapy available against AD be admitted onto the Norwegian health market and included in the list of medications paid for by National Insurance. In 1998, the Medicines Agency approved Aricept for prescription, but reimbursement was refused. Since then, there has been a recurring controversy about this. Do these drugs have the expected effect? And are

they cost-effective? Who should pay, and who should decide? After repeated proposals and rounds of negotiation in parliament, the standard administrative procedures for evaluation were overturned. Since 2002, anti-dementia medications have been reimbursed. In 2004, the case was reopened when a new study questioned the efficiency of the drug (AD2000 Collaborative Group 2004) and suggested that it had no effect on rates of institutionalisation. These findings were taken up by the media and returned the issue to the political agenda. The ministry asked an expert panel in collaboration with the Medicines Agency to evaluate the data and the conclusions of the study, to compare them with other studies, and to advise whether existing policy and therapy guidelines should be changed. The answer was no.

The first point to be made here is that the institutional apparatus of parliamentary politics is an important site in relation to the politics of science, medicine, and disease. This is where healthcare services and medical treatments, including pharmacotherapies, get approved or not, and where directives and guidelines are developed. The pharmaceutical definition of what kind of matter of concern AD is and what kind of intervention it calls for would not become an alternative if it did not get through this process.

So, parliamentary politics is an important site. It is a location that is supposed to collect, but also, to evaluate and regulate what versions of the matter at hand should be included and excluded. The story above shows that the pharmaceutical enactment of Alzheimer's disease is indeed circulated into parliamentary politics. But it is not simply present; it is also quite dominant. Searches through the last ten years of parliamentary debates and ministerial documents for dementia- and Alzheimer's-related issues show that these always led to discussion about medication and reimbursement. So, debate has been recurrent, but this has not shifted from the limited frame of clinical trials and their technicalities. It has never turned into a discussion of alternative ways of working with the disease, or the relations between such different practices and enactments. So, why is this? What follows are some tentative suggestions.

First, it is much easier for parliamentary politics to handle, approve of, and promise access to medications than it is to promise competent,

adapted, long-term care services. It is also difficult for parliamentary politics—'from the centre'—to define the ambitions, standards, methods, and ideals for care. Further, since pharmaceutical actors need to go through official administrative procedures to get the stamp of approval for every new product they want to release into the market, this also means that they have an apparatus for handling these processes and are present in the administration in a way that healthcare services are not and do not. Dementia care services seldom have research and communication departments that help translate and transport results from care practice into parliamentary politics. This favours pharmaceutical enactments, and it also means that there is an asymmetry about what has to pass through and be made present in parliamentary politics. Finally, it also reveals the performativity of this political apparatus.

In addition, there has been a long and persistent process of network-building and lobbying by the pharmaceutical industry. The interaction between industry and politics has generated a concern with how to contain discussion within expert committees, advisory boards, and agencies, and prevent them from being brought into the parliament. As Barry (2006) also argues, politics is often more geared towards regulating and containing dissent and debate than towards promoting and fostering it. Notwithstanding all the intentions to the contrary, here the result is that pharmaceutical and biomedical enactments are strengthened.

But why don't the experts in the field who are called upon to evaluate existing evidence and offer advice, articulate the alternatives and contribute to shift the debate?

It deserves mention that more recently alternative ways in care and in so-called environmental or non-medical therapies get increasingly acknowledged. It is argued for the need for public funding for clinical trial or studies that document their effect or results. But one final suggestion as to why medical experts may be reluctant to confront and shift the debate: clinical medicine and care practice include the pharmaceutical enactment of the disease, but the same is not true the other way around. Experts with backgrounds in clinical medicine may not want to set pills and care against each other. As the advertisement showed, however, this is not necessarily mutual. The pill-version of Alzheimer's is built on a disconnection from care-versions.

The implication, then, is that in this case, at least the apparatus of parliamentary politics does not really work to collect, present, confront, and evaluate different concerns. Instead, it works to make particular pharmaceutical and biomedical versions of the disease present, visible, and dominant, while others are made absent, invisible, and so, also less real.

## Conclusion

Drawing together the analyses offered, the argument comes in several parts. First, I have argued that AD is experimented with and enacted into being in different ways in a variety of locations and practices. These locations, practices, and enactments are however neither tied together by a single nature, nor by a single process of progressive definition and stabilisation. Science is not the centre of reality-production. Second, I have shown that the different versions of AD do not simply co-exist, but also, interfere with one another in complex ways that contribute to make certain enactments present or absent, visible or invisible, more real or less real. Third, I have argued that the politics of disease is a decentred, complex, contingent, and ongoing *process*, reducible neither to biomedical science, industry, nor to the institutional apparatus of parliamentary politics. The roles of science, medicine, politics, and other locations and practices are not given. In this case, politics contributed to closing down, rather than to opening up. Locations and practices where things were opened up and gathered were medical. If we are to contribute to opening up the politics of disease, we need to appreciate the multiplicity of realities-in-progress and the alternatives that they present; the complex relations in which they are produced; and the ongoing political inventiveness that disturbs the webs of relations in which matters matter.

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# 10

# Dikes and Dementia: How Multiple Framings of Dementia Coexist During the Development of a National Dementia Strategy

Yvonne Cuijpers

With the rise of dementia as a public health challenge, national dementia strategies are being developed worldwide (World Health Organization 2012; G8 2013; Alzheimer-Europe 2015). Since multiple approaches to dementia coexist (Downs et al. 2006; Innes and Manthorpe 2012; Moser 2008), it is safe to assume that the development of national dementia strategies is not a straightforward activity. There is a politics involved because every approach will reflect a particular view on what the problem is and every solution will favor a particular view, at the expense of others (Innes and Manthorpe 2012). Every national dementia strategy somehow has to deal with this multitude of approaches. However, while the aim of national strategies to collectively address dementia is clear, it is less clear how and why certain directions for action become part of national dementia strategies. In this chapter, I address the prevalence of particular views on dementia as a matter of 'framing' and I investigate how the multiplicity of framings coexist in one, Dutch, case of a national strategy.

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The Netherlands has had several national dementia programs running since 2005. Building upon these earlier activities, in 2013, a new national action plan (the Deltaplan Dementie) was launched (Ministry of VWS 2013). The development of this plan and its launch were accompanied by struggles on how the problem should be defined and which strategies would be most appropriate to collectively deal with dementia. These struggles will likely have their counterparts in other countries in which national dementia strategies are being developed.

This study provides a reconstruction and analysis of *which* framings of dementia are articulated in the course of the development of a Dutch dementia strategy, and *how* stakeholders deal with the coexistence of multiple framings of dementia. First, I will elaborate on the theory on collective action framing, which I have used to analyze the data and to structure this chapter. Second, I will show the framings used to draw public and political attention, followed by the framings in the research program that are part of the Deltaplan Dementie, and finish with an analysis of framings in the media and interviews with the participants of the public debate. I show not only how dementia is framed in a national dementia strategy, but also how different frames are assumed to coexist. Finally, I present three models of how frames are assumed to coexist. In the conclusion, I will reflect on the consequences of these three models and point out the importance of acknowledging the power differences between frames and how to deal with them.

## Theory and Methods

The launch in 2013 and the implementation of the Dutch Deltaplan Dementie is an occasion in which articulations of, interactions between, and contestations about multiple framings of dementia as a public health concern are made explicit. In this way, the Deltaplan can be seen as a crystallization point in which what is fluid is temporarily joined together and solidified. This process shows the dynamics of the construction of dementia by actors responding to each other.

I can fruitfully draw on framing analysis (e.g., Entman 1993; Schon and Rein 1995; Gamson 1992; Van Gorp and Vercruysse 2012) and, in

particular, on theories of collective action framing (Benford and Snow 2000) to analyze the way in which dementia gains meaning in the development of and the discussions surrounding the Deltaplan Dementie.

Frames can be defined as sense-making devices that operate through two processes: first, by making some parts of reality more visible than other parts (referred to as 'selection' and 'salience' in framing literature), and second, by proposing a particular view on social reality by defining what is problematic, what the causes of these problems are, how to evaluate a situation, and what to do about it (Gamson 1992). Framing generally involves the telling of stories to make sense of a situation. These stories are called frames when they are strong, generic narratives. In the case of collective action framing, these narratives typically also include a story that urges for action. The characteristic *content* of collective action frames consists of three parts: (1) diagnostic framing of defining the problem, (2) prognostic framing of what should be done to deal with the problem, and (3) motivational framing to mobilize action (Benford and Snow 2000).

The content of frames is shaped by a number of *processes*: first of all through the telling of stories to make sense of a situation (discursive processes). But next to this, frames are often strategically aligned with the interests of possible constituents and resource providers to increase the chances of mobilizing support and resources. Furthermore, since the aim of collective action frames is to change something, they are often confronted with disputes within the movement (framing disputes) and contestations from opponents, bystanders, and media (framing contests), which in their turn, shape the collective action frame.

The data used for this chapter are: (1) newspaper articles that appeared on the Deltaplan Dementie in the large national newspapers from 2010 to 2015 ($n$ = 57) collected through the newspaper database LexisNexis, including calls for the need of a deltaplan dementia, news articles announcing the launch of the plan, opinion articles and letters to the editor, as well as editorial articles reflecting on the public debate, (2) the official documents on the Deltaplan Dementie, and (3) interviews with ten stakeholders who were involved with either the development of the plan, or public debate on the plan (the initiator, a director of the Alzheimer Association, the director of the Deltaplan Dementie, a policymaker from

the ministry of health, an employee from the governmental funding agency, two scientists that provided input during the development of the plan, and three dementia professionals who contested parts of the plan in the media). The interviews were semi-structured and the topics included a reconstruction of the development of the Deltaplan, the involvement of the actor in the plan or in contesting (parts of) it, and the motivational, diagnostic, and prognostic framing of dementia by the actor.

## Together, We Build the Dike

So, how is dementia framed in the drawing of the Deltaplan Dementie and subsequent discussions? I will first analyze the development of the plan from the perspective of the initiators. What was the motivational framing of the plan and the general direction of its diagnostic and prognostic framing?

'*If no measures are taken now, this disease will become the epidemic of the future*' (De Telegraaf 2012). The neurologist pleading for the Deltaplan starts 'beating the drum more loudly' to warn that in our ageing society, more and more people will develop dementia and society is utterly unprepared for the upcoming 'dementia wave'. In line with the metaphor of a wave, the term Deltaplan Dementie is launched. The term 'Deltaplan' itself is a powerful metaphor within Dutch society. It refers to the gigantic project to protect the Netherlands against floods (initiated after a disastrous flood in 1953) and makes the Netherlands what it is today. '*In 1953 in the Netherlands we were flooded totally unexpected: the delta works were the answer. Now we build a dam in advance, because we can see the flood, the increasing number of persons with dementia, coming. It is five to twelve*' (ibid.). The original Deltaplan is seen as a victory of mankind over the forces of nature. The Deltaplan Dementie should battle dementia in the same successful way as the Dutch delta works have beaten the water. The main message, thus, is that as a nation, we need to join forces in the battle against dementia. 'We are working on a battle plan in which government, business, banks, health insurers and scientists all at the table'. The Deltaplan aims to unite the forces of government, health care organizations, and companies. '*Together we build the dike!*' (Ministry of VWS

2013) Although the metaphor used has a clear national ring, the underlying type of argumentation is hardly unique. The motivational framing of a disaster to be averted has been a generic and successful strategy to draw public and political attention and mobilize resources to address the problems of AD since the 1980s (see also Chaufan et al. 2012; Diesfeldt 2014; Johnstone 2013). It has been referred to as 'apocalyptic demography' (Robertson 1990; Robertson 1997), or 'health politics of anguish' (Fox 2000).

In the case of the Deltaplan Dementie, however, a second generic strategy was applied to urge government and business to collaborate. One driver to beat the drum for Deltaplan Dementie was that investments in dementia research were needed to secure the position of the Netherlands in European research programs. To urge public investments in Alzheimer research, the Deltaplan Dementia is strategically aligned to the Dutch innovation policy. This is done by emphasizing the societal challenges posed by dementia and stressing the need for investments in science and innovation to face these challenges. Investing in science and innovation, it is argued, will lead to a triple-win situation because innovation will solve the societal problems posed by dementia, help the elderly, and boost the economy at the same time. This is a strong, widespread, and appealing discourse to argue for the need of innovations to face societal challenges related to ageing, formerly defined as an 'ageing and innovation discourse' (Neven 2011). This strategic frame alignment (and its success) is particularly visible in a Letter to the Parliament, written by the Minister of Health, when he announced an investment of €32.5 million in the Deltaplan:

> Following the effort to improve dementia care in the Netherlands and to anchor international programs in our country, Dutch scientists and Alzheimer Nederland have taken the initiative to develop the Deltaplan Dementie. (…) We expect the Deltaplan to contribute to increasing awareness on dementia, controlling of costs, maintaining of labor productivity of informal caregivers and provide economic chances for different industries. With the collaboration between government, science and business the Deltaplan fits perfectly with innovations aimed for by the cabinet through the top sector policy. (…) We trust the plan will be a success (…) firstly for

> persons with dementia and their relatives, secondly for care professionals who can improve the quality of care provision, and finally that the Deltaplan will be an impulse for scientific research in this field and for related business sectors. (Ministry of Health 2013)

Thus, the motivational framing is shaped, in large part, by strategic processes common in the field of dementia and ageing to mobilize resources. Furthermore, the initiators and developers of the Deltaplan Dementie stress unity: ultimately, there is one goal and one plan, and everybody benefits. A multitude of stakeholders should unite forces to jointly battle dementia.

To be sure, in the starting phase of drawing attention and resources for a Deltaplan Dementie, there are already some distinct indications as to what the Deltaplan should target, and which remained to structure the plan throughout its development. The terms 'the patient of today' and 'the patient of tomorrow' structure the Deltaplan and are often repeated in the report of the plan, in the media, and in interviews conducted for this study. Research for 'the patient of today' aims to improve the quality of life and care for current patients. Research for 'the patient of tomorrow' aims for long-term outcomes that will be helpful for future patients. This mainly includes biomedical research to understand the underlying disease mechanisms that are expected to improve prevention, diagnosis, and enable the development of disease-modifying treatment. Again, this distinction is not typically Dutch. The phrase '*care today, cure tomorrow*' was, for example, also used during the recent WHO summit on dementia (World Health Organization 2015).

## Keeping All Frogs in the Wheelbarrow

The decision of the government to invest €32.5 million in the Deltaplan Dementie to be exclusively spent on scientific research (the whole plan also covered other areas), led to the creation of a research program called Memorabel.

The process of creating a research program involved a further elaboration of the content. This process included alignment with EU programs

(JPND—Joint Programming Neurodegenerative Diseases, and CoEN—Cooperation between Centers of Excellence in Neurodegenerative disease research) attuned to building upon the strength of the Netherlands. It included the research agenda of Alzheimer Nederland, based upon the input of a panel of informal caregivers and persons with dementia. And because the Deltaplan promised to unite forces, it also involved enrolment of the relevant scientists. An invitational conference was organized with researchers from the dementia field. Additional extensive conversations were conducted with stakeholders in the field who were hesitant to enroll in the program. What problems should the research program address and which directions should be pursued?

While the Deltaplan suggested a general consensus that action was needed to battle dementia, as soon as problems and directions for research had to be specified, a fragmentation occurred. This is clearly visible in the research program Memorabel. It starts by acknowledging that multiple approaches to dementia coexist: 'The Deltaplan aims to cope with the societal challenges of dementia, a *heterogeneous* condition that affects people worldwide' (ZonMW 2013, emphasis added). In its aims, it states that:

> Views on the approach of dementia differ, though they are essentially complementary. Dementia touches upon many sectors and policy terrains (care, cure, prevention, living, welfare) and the number of organizations and professionals involved in care and support for people with dementia is extensive and their involvement and expertize divergent. This demands careful programming. (ZonMW-Memorabel 2013)

This formulation followed a long and laborious process to draw out the research program. An employee of the funding agency explained the following:

> We need to service all aspects (…) of the disease, everything that is involved. (…) So we need to service researchers who say (…) we need to know more about the genetic aspects because that is where advances can be made (…) But also people who say that we need to work on medical treatments now, because there is a short term benefit to gain. But also people who say that

> all that is not going to work with dementia, because it is too complex, we have been trying to find medication for twenty years and it is not working, so please lets invest the little money there is in good care, and a movement that says (…) we should work on prevention. (…) All these elements are in the program. All approaches can apply for research funding. (Interview funding agency)

In other words, while preparing the research program, definitions of 'the' societal problem of dementia multiplied. This multiplication enters the research program through the input of different professional sectors and policy terrains in the research program that have diverging approaches to dementia, yet should collaboratively contribute to facing up to the challenges dementia raises for society. In principle, all Dutch dementia research in the Netherlands is united in the research program, '*but you cannot keep all the frogs in the wheelbarrow*' (Interview of policy-maker, Ministry of Health).

The final research program consists of a list of topics for research, organized around four themes: (1) causes and mechanisms of disease, (2) diagnosis, (3) treatment and prevention, and (4) effective care and support. It started with the dissemination of a 'building blocks' document in the form of a bullet list of research topics for each theme. This list was based on the European research programs, JPND (Joint Programming Neurodegenerative Diseases) and CoEN (Cooperation between Centers of Excellence in Neurodegenerative disease research), adjusted to the research strengths of the Netherlands and supplemented with the research agenda of Alzheimer Nederland (the Dutch Alzheimer Association). An invitational conference was organized in The Hague in September 2012. Attendants of the invitational conference could provide input and comments on the 'building blocks' document during working groups sessions. Among the many comments made in the reports made by these working groups, I would like to highlight one repetitive comment: '*the connection between different themes is missing*', '*a synthesis is missing*', '*it is not clear how the cohesion between different outcomes of different parts of the program will be established*' (quotes taken from the reports of the working groups of the invitational conference). While surely this was improved in later versions, the fragmented character is still present in the eventual research program.

During the development of the research program, we see the assumption that different framings of dementia are essentially complementary. The effort to join forces to defeat dementia led to a fragmentation of diagnostic and prognostic frames. The problem of dementia is redefined into a large number of particular problems that specific scientific disciplines address. They are considered to be fragments of a whole that can be synthesized into or added up to a complete whole. The main idea seems to be that if all professionals get funding, it will add up to be an encompassing program in which everybody works on a part of the puzzle.

These multiplications make it difficult to understand how the separate research activities add up to a full-fledged research plan on how to deal with dementia in Dutch society. With the assumption that different approaches to dementia are essentially complementary, the question arises if the different parts really add up to a whole, and how a synthesis can be achieved.

## Framing Contests Becoming Public

Now, we move to the public arena, where a different dynamic is played out. During the development of the plan and after its launch, a stream of letters to the editors and critical opinion articles emerged in the national newspapers, written mainly by scientists and medical professionals. In these opinion pieces, framing contests became publicly visible. Journalists writing about the plan also started to position different stakeholders in terms of proponents and opponents of the plan. In the media, framing contests thus played out in an antagonistic fashion. The different framings of dementia and the problems it poses for society did not seem complementary, but in tension with each other. They might even exclude each other.

In these opinion articles, all parts of the collective action framing in the Deltaplan Dementie were contested: the motivational, the diagnostic, and the prognostic framing. The quote '*Big numbers in combination with the fear for a tsunami of patients are maintained by scientists and pharmaceutical industry*' nicely captures the contests of the motivational framing (NRC 2012). The use of a disaster rhetoric was contested for

exaggerating the problem and playing on the fear and instigating anxiety for a condition that is already one of the most feared conditions in Dutch society. The use of the ageing-and-innovation discourse was contested by questioning the integrity of the Deltaplan and its initiator, wondering in whose interest the Deltaplan Dementie has been developed. The diagnostic framing of dementia as a disease of which research will, in the future, unravel the causes and develop a treatment is deemed misleading. Too much emphasis on medical interventions is considered to be out of place and misguiding. The articles show a long list of issues that the Deltaplan seemingly overlooks or that deserve more attention.

In the arena of public media, different framings of dementia created tension. On the one hand, the struggles appear in the media in terms of actors being 'for' or 'against' and questions on 'who is right'. On the other hand, journalists speak of ideological struggles, illustrated by headlines such as: 'reader does not know which expert to believe anymore', 'ideological struggles between researchers on Deltaplan Dementie', and 'is dementia really such a big problem?' Several articles start distinguishing different 'schools of thought' to make some sense of the discussions going on.

Which diagnostic and prognostic framings are behind the critiques? To better understand where these critiques stem from, interviews were conducted with a number of persons who raised their voice in the media. From these interviews, not one unified picture arose. The main reason is that in every interview, a particular diagnostic and prognostic frame was articulated, which partly overlapped with other interviews, but not completely. Some of the interviewed persons explicitly said they were still searching for the right way to frame what they were after. One said s/he felt part of a paradigm shift that is setting in, but which has a hard time in gaining a foothold.

Interviewees used two diagnostic frames to explain the problem of dementia. The first framing focuses on dementia as a disease, and argues that dementia should be seen as a heterogeneous, complex condition, overlapping with normal ageing processes, and finally, leading to a dementia syndrome. Even though the research program Memorabel also refers to dementia as a heterogeneous condition, this framing was explicitly articulated as a 'counterframe', opposing the framing of dementia as

a neurodegenerative disease. A second diagnostic framing centers not on the nature of the condition, but stresses that dementia is first of all a condition of a person and that the person should be central. '*I think medicine is a humane discipline and it should be about people. Many branches of medicine have become so super-specialist that it is only about cells and organs*'. This is not so much a counterframing, opposing a framing of dementia as a disease as it is a shift in emphasis in what problems should be addressed. These discussions have been roaming the dementia field for decades e.g., Lock 2013; Kitwood 1997; Dillmann 2000; Downs et al. 2006).

These diagnostic framings also lead to particular strategies to deal with dementia (and thus, to specific prognostic framings). Some interviewees consider a 'cure' impossible, while others keep open the possibility that perhaps, in the long run, a kind of disease-modifying treatment will be possible. Putting the hope for a cure between brackets, learning to live with the condition, as a person, as informal caregivers, and as society becomes most prominent. Rather than 'battling dementia', 'living with dementia' becomes the aim to strive for. From this line of reasoning, two lines of action emerge. The first is that while dementia cannot be cured in the stages that it manifests itself, there may be possibilities to delay its onset through preventative measures and a healthy lifestyle. The second is that society needs to become prepared to live with dementia. This means that when adhering to this framing of dementia, the distinction made in the Deltaplan Dementie between research for 'the patient of today' and for 'the patient of tomorrow' collapses. Following this framing, the structure of a national dementia strategy would not be 'care today, cure tomorrow', but would be more in line with Peter Whitehouse's rephrasing: 'care today, care tomorrow, cure good luck and prevention yes' (Myth 2015). A national dementia strategy should be geared toward facing the reality of a society including persons with dementia. From this position, medical research is still valuable, but is positioned next to other kinds of research on dementia. Similar pleas to re-invent the science of dementia in which medical research has a more humble position have been made by, for example, Portacolone et al. (2014). Box 10.1 summarizes the issues mentioned in newspaper articles and interviews that deserve more attention in the alternative framings of dementia and in a research program on dementia.

**Box 10.1 Examples of issues foregrounded in alternative framings**

**Patients**

- Understand the needs and wants of patients and informal caregivers

**Human life**

- Approach elderly with dementia as persons in their final stretch of life
- Focus on what makes life worthwhile and enjoyable

**Prevention**

- Preventative strategies
- Lifestyle approaches

**Cultural**

- Tackle societal discomfort with dementia
- Change cultural perception of dementia

**Societal**

- Enable a dementia-friendly society
- Social inclusion of persons with dementia
- Raise awareness on dementia and how to deal with persons with dementia

**Health care system**

- Support for informal caregivers
- More attention for long-term care
- Integration of professional approaches
- A demand driven health care system

## How Frames Coexist

This chapter started from the assumption that since multiple framings of dementia coexist, the development of a national dementia strategy is not a straightforward activity. This chapter has reconstructed

which framings of dementia surfaced during the development of a Dutch dementia strategy and how these coexist. This reconstruction confirmed the starting assumption: the efforts to collectively tackle the challenges dementia poses to society has indeed unleashed a multitude of framings of dementia.

Surrounding the Deltaplan Dementie, we see a struggle for who gets to define what a dementia strategy should constitute. As I hope to have made clear in part three, it does matter who gets to define strategies. Framing struggles surrounding a national dementia strategy is 'politics of signification' in action. While Peter Whitehouse and Danny George wrote their book *The Myth of Alzheimer's. What You Aren't Being Told About Today's Most Dreaded Diagnosis* in 2008, we can say that in 2015, framing struggles have become public, and we are being told a lot about today's most dreaded diagnosis. Furthermore, all stakeholders are aware of the existence of multiple framings of dementia and the scientific controversies raging in the field. The question now has become how to deal with this multiplicity. This reconstruction shows different models on how framings are considered to coexist.

In the initial phase of the Deltaplan, the main aim was to draw public and political attention and resources. This was done drawing upon proven strategies such as a disaster rhetoric and an ageing-and-innovation discourse. Dementia is framed rather homogeneously as a societal challenge that should be addressed. During the further explication of the plan, a multiplication of frames occurs. During the development of the research program, the different approaches to dementia are considered to be essentially complementary. The main difficulty is how these different parts can be synthesized again, whereas in the public arena of newspapers, a less peaceful picture arises. Contestations arise and discussions play out in an antagonistic fashion in terms of care versus cure, for or against. Journalists start wondering who is right and delineate different 'schools of thought' or even paradigms in the dementia field. Personal interviews with participants of the public debate show a multitude of frames moving in different directions and revealing a rather different type of preferred research agenda.

This reconstruction shows not only different framings for dementia but also three models of how these are assumed to coexist.

One model in which different framings co-exist is as parts of a whole. To raise public and political awareness and resources for dementia, professionals working on dementia were presented as willing to join forces to jointly face the societal challenge dementia poses to society. This endeavor needed to be specified in the research program Memorabel. Also, in the research program, the different framings are considered to be essentially complementary. They are seen as parts of a whole. Dementia as a large societal issue is fragmented or specified into a multitude of approaches, which are supposed to add up. This model assumes an essential harmony and possible peaceful coexistence (Fig 10.1).

A second model in which framings co-exist is as antagonistic positions. In the public debate following the launch of the Deltaplan Dementie, different framings were positioned as being in active opposition. Criteria are sought to settle who is right and who is wrong. And discussions start to focus on who is most powerful and whose interests are served by a particular framing (Fig. 10.2).

A third model in which framings co-exist is as framings moving in different directions. During the public debate and the interviews with participants of the public debate, the different framings appear as different directions that can be pursued. Rather than wondering who is right, the question becomes which directions to pursue with how much effort and resources. Emphasis on one direction or another is a political and normative choice of how we, as a society, want to deal with dementia in society. These different directions do not coexist in peaceful harmony, nor are they perpendicular to each other. There are coalitions, as well as disagreement, frictions, and tensions on particular issues between different framings (Fig 10.3).

While all models may apply at times, I would like to argue here that it is important to reflect on which model is most appropriate when. To deal with dementia in society, the problems dementia poses are specified. This is very useful. The grand societal challenge dementia poses cannot be dealt with without specifying what it is we are talking about. At the same time, with, for example, the controversy between the two medical approaches of dementia, it may be argued that one is right and the other is wrong. Yet, specific research may be interesting, whatever theory is adhered to. Furthermore, the model of multiple framings moving in

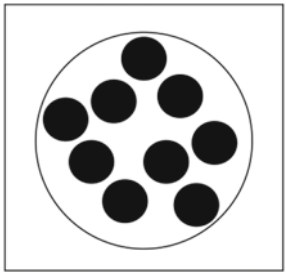

**Fig. 10.1** Parts of a whole

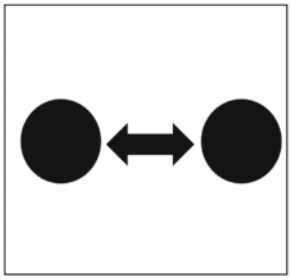

**Fig. 10.2** Antagonistic positions

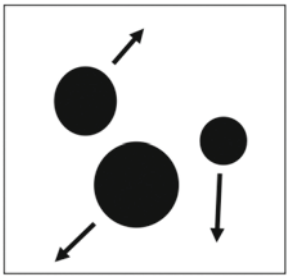

**Fig. 10.3** Moving in different directions

different directions can reveal the tensions between different schools of thoughts, and shows that even if you put all expert scientists together in one room, the choice of which directions to pursue will remain a political one.

I would like to end this chapter with a brief reflection on what should be a minimum requirement for responsibly dealing with a multiplicity of frames. I have shown how different framings of dementia are made to coexist. Yet, an issue that remains on the table and is highly relevant is how to deal with power differences. I will use the example of the drawing of the research program to illustrate my point. The funding agency used the first model (different framings as essentially complementary) to service all aspects and all approaches to dementia. Yet, they did not clearly acknowledge that there may be a misbalance between different approaches to dementia. One of the main critiques on the Deltaplan Dementie was that it appeared to be a rather medically oriented plan. The medical approach to dementia has had a strong foothold for the last decennia and has a well-articulated, fine-grained, and specific research agenda. My interviews with professionals who approach dementia as a condition of a person, or as a societal phenomenon (the 'living with' approaches), showed that they had a much more sketchy research agenda. Some of them stated they were still searching for the best way to frame what they were after. Moreover, these researchers are not as well-organized (institutionally) as medical research(ers) on AD. The framing contests in the media particularly addressed this misbalance, and thus, showed an antagonistic model. This created a discussion in terms of cure versus care (Cuijpers and van Lente 2014). The democratic way of gathering input for the research program by the funding agency aimed at servicing all researchers and all approaches to dementia did not take into account the difference in power and voice between different approaches. If the funding agency had adhered to the second model of antagonistic positions, or to the third model of frames moving in different directions, they might have realized that approaches favoring 'living with' dementia may need more time and space to further develop their position, strengthen their vision, and articulate research directions.

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# 11

# Responsible Innovation: The Case of Alzheimer Diagnostics

Jeannette Pols and Amade M'charek

Biomedical innovations are often envisioned as a linear process that translates results from laboratory research to the social world of professionals, patients, carers, and values. Both the directionality of innovation and the assumed separateness of social and scientific spheres foster the hope that scientific work will actually be helpful to the society we live in (Brown 2003; Brown and Michael 2003; Borup et al. 2006). The sciences promise to add something new to what is already there and will help solve problems that were impossible to solve so far. Because an innovation is new to the actors concerned, the idea of *responsible* innovation is often

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sought in democratic models to engage different social actors to whom the scientific results will have to be relevant. These may be patients, professionals, informal carers, citizens, and so on (see the introduction to this volume).

In this chapter, we question the directionality of innovation as well as the idea that scientific and social practices are separated, with the social practices waiting, as it were, for science to innovate them. Our aim is to think through the idea of 'responsible innovation', here, in the case of innovations of Alzheimer's diagnostics. We will show that scientific practices and the (care) practices in which the results would have to become relevant are not neatly separated entities. To do this, we build on ethnographic work in Science & Technology Studies (Harbers 2005; Mol 2002; Moser 2011 and this volume; M'charek 2014).

We will argue that there are many different practices already involved in negotiating the meaning of 'good diagnosis', and will analyse how research relates to that. Patient organizations, for example, are engaged with research practices and funding in different ways. Apart from these entanglements, we will also show some impressive gaps, when different practices incorporate very different ideas on what Alzheimer's is, and to what concerns this amounts. Moreover, each practice also incorporates its own ideas about what the other practices might need or may do for them. We conclude that these complexities call for new alignments of laboratory research, clinical practice, and patient representation.

In the chapter, we will analyse the entanglement of laboratory science, patient advocacy and representation, and clinical practices in the case of scientific attempts to improve Alzheimer diagnostics. We will analyse how respective practices understand improved 'Alzheimer diagnosis'—and even Alzheimer's disease (AD) itself—and how they embed particular understandings of one another. What concerns are addressed in each practice relating to AD and its diagnostics? What kind of 'clinic', 'research', or 'representation' practice are inscribed and how are they inscribed? In the conclusion, we will suggest an approach to responsible innovation that takes these different concerns and values into account.

## Methods

Ethnographic techniques are the appropriate means to elucidate what happens in different practices. The very multisitedness of places where Alzheimer's diagnosis plays a role makes an ethnographic study a huge task that many science and technology students could devote extensive careers to—granted that they would receive the funding to do so. Because the argument of this chapter is a theoretical one, aimed to better understand what innovation might entail in this particular context, we can only open up a vista towards what such research may deliver. We do this by analysing documents and by bringing together analytical work done by colleagues. We will first analyse the position of advocacy organizations (Alzheimer Societies) and their entanglements with research practices. Second, we will have a look at clinic–laboratory entanglements through analysing a research proposal that got funded to improve early Alzheimer diagnostics. Third, we will analyse a paper on diagnostic work on what is here called *dementia* in Dutch General Practice, and trace the built-in assumptions about how the laboratory (which is also a clinic) functions. Here, the problem of dementia or AD manifests itself in quite different ways than in the research practice of the protocol we analysed.

The backdrop to these documents and discussions is that, so far, there is no clear relation between Alzheimer's clinical signs and anatomical changes witnessed in post-mortem studies (see also Boenink, this volume). The hypothesis has always been that AD is caused by amyloid plaques and neurofibrillary tangles. However, heavily plaqued and tangled brains were taken out of the bodies of symptom-free persons, whereas clinically severe cases showed 'clean' nerve tissue post-mortem. The lack of a clear cause and effect structure that points to a disease entity or process has led to the labelling of dementia as a *syndrome* to be established when four criteria from DSM IV for 'Dementia Not Otherwise Specified' are present. This makes the distinction between a normal ageing process and dementia less clear-cut. The debate about this relation is still unsolved, yet crucial to understand the gaps between the sites of our study.

## Advocacy Through Scientific Research

One type of associations that may count as an advocacy group for Alzheimer patients is the Alzheimer societies that exist in various forms in Europe and the USA. The Dutch Alzheimer society, Alzheimer Nederland (ANL) states its aim as follows:

> Preventing or curing dementia. That is our mission. And until that time we work on a better life for patients and their direct environment. […] Alzheimer Nederland supports and informs people with dementia and their environment for 30 years now. By representing interests and financing scientific research, we work on a better future, eventually without dementia. (ANL 2015)

Contrary to the Alzheimer societies in other countries, ANL is directly involved in financing and supporting of biomedical research that is aimed at prevention and cure, as the web text states. The website text also states another goal, which is to contribute to a 'better life for patients and their direct environment' through information and representation.

These aims already form a strange mix. The organization represents people with Alzheimer's, while at the same time attempting to make them disappear. Hence, the organization represents two groups: the people who do not yet suffer from Alzheimer's, but run the risk of becoming a patient in the future (the majority of the population), and those who already live with the disease, together with the people that care for them. These target groups are very different, and they have different interests that may be difficult to reconcile in a world of austerity. One could say that 'the patients' do not speak in one voice. The two types of patients have very different concerns.

ANL is also involved in research. In contrast to Irish and UK Alzheimer's societies, the Dutch organization does not conduct its own research, but lobbies for the funding of research and helps in allocating research money. This means that when representatives of ANL would be invited to the group of concerned people who have to reflect on the consequences of particular innovations, they are not an 'independent group' or a mere voice that articulates 'social' concerns. ANL is entangled with

the research they help to get the funding for and that aims to serve the different interests of those they represent. Rabeharisoa et al. (2014) call this entanglement of (in their cases mostly social) science and advocacy 'Evidence Based Activism'. With this concept, they highlight that patient organizations engage with scientific research to support their political causes (see also Epstein 1996).

In their detailed studies of Alzheimer's societies in the UK and Ireland, Moreira et al. (2014) show that the respective organizations have research goals that evolved over time. Different from their Dutch sister, these organizations represent *actual* rather than future sufferers—which makes their position less ambiguous than that of ANL. The UK Alzheimer Society emerged in the 1970s, when the welfare state withdrew and 'self management' and community care became more important. By employing social scientific methods and interviews, the UK Alzheimer Society produced reports to put Alzheimer's on the social policy agenda as an urgent matter that needed a response by organizing care services. The Irish Society struggled with reconciling a Catholic tradition of volunteer services with the expansion of professional care organizations.

In both contexts, not only political struggles for recognition and better care were being debated. Discussions about social scientific methods emerged and were directly related to the difficulty of giving people with AD a voice in research. Moreira and colleagues mention the UK Alzheimer Society's critiques on the 'positivist bias' of common research methods and their failure to make the voices of people suffering from dementia audible (Moreira et al. 2014). The critique on the 'medicocentric model of dementia' (Bond 1992; Moreira et al. 2014, p. 9) and the development of 'person-centered care' (Kitwood 1993) became famous export products that directly criticized biomedical research for the particular values it embeds (however, see Leibing 2008, for a critical discussion of opposing biomedicine and personhood).

The careful and detailed historical reconstruction of the evolvement of both the Irish and the British Alzheimer societies offered by Moreira and colleagues does not only show national differences in concerns, but also documents shifts in focus within the same organization over time. The organizations worked in evolving policy contexts to which they adapted. For instance, after having put AD on the agenda as an urgent political

and social issue, reports on the specificities of organizing care followed in the UK. More recently, the matter of 'voice' for Alzheimer sufferers emerged. Beard (2004) relates this to AD being diagnosed earlier, allowing a more eloquent group of AD patients to emerge.

An important lesson is that advocacy, doing research, or finding funding for it, and shaping the concerns for which Alzheimer societies stand are deeply intertwined. There is no singular, one-directional move of innovations from the laboratory to the society 'out there'. The patient organizations are already 'in the lab', or they create alternative versions of relevant scientific practice. What is being shipped out of a laboratory is already highly politically structured. Or, to put it differently, what patient representatives come to represent is highly entangled with what kind of research they use or advocate. The patient organizations are not mere recipients for whom laboratory innovations are of importance: they are already fully engaged in designing them. ANL is implicated in the quest for better Alzheimer diagnostics, as well as in representing patients-who-are-not-patients-yet. This is different in Ireland and the UK, where Alzheimer societies represent sufferers. For this reason, they use social scientific research, rather than medical research.

## The Laboratory Observed Through the Research Proposal

Our second case is a Dutch research proposal. Doing research does not only mean 'collecting data', but also entails the bringing in of research funds, either through helpful funding agencies, or through competing for money with colleagues by submitting research grants. These proposals are interesting documents because they have to convince colleagues and financing agencies (and through them, 'the public') that the research is worth financing. To this end, the promises of the research must be spelled out. We will now analyse a research proposal that got funded in 2008 by the Dutch Centre for Translational Molecular Medicine. Financing was sought by a consortium of different university hospitals and industry, to conduct a project working towards novel forms of diagnostics of

AD. Although this proposal will be used here as an exemplar of laboratory research, it is important to notice that 'the laboratory' itself, that is, the medical sciences, do not speak in one voice. Medical research is driven by different logics of understanding of and dealing with AD (see also Leibing, this volume, and Boenink, this volume). These logics are not compatible. The cardiovascular hypothesis, for instance, provides very different explanations and demands very different activities than the amyloid hypothesis.

Back to our protocol. What does the protocol promise its reviewers and funding agency? The project wants to develop new diagnostic tests for AD that are based on disturbances of the amyloid metabolism, glutamate neurotransmission, and/or their interaction. Imaging techniques (PET and MRI scans) to visualize the brain, and the detection of aggregates of amyloid B in cerebrospinal fluid are used to visualize these processes. The reason for targeting these processes is the hypothesis that neurofibrillary plaques are not the *cause* of AD, but an anatomical *result*. The proposal refers to this when it contrasts the new approach to the post-mortem diagnostics of AD by identifying plaques. The reason why correlations between clinical symptoms and anatomical changes is weak is that the processes that are actually relevant occur on a molecular rather than an anatomical level. These processes are not visible to the bare eye. The proposal states:

> The evidence for AD that can be obtained with conventional MRI techniques is limited to the presence of focal atrophy, which is an *indirect, non-specific and late* sign of AD. Earlier detection of the disease requires detection of the molecular and metabolic changes, instead of detection of macroscopic changes in brain structure. And more specific detection than is currently possible requires detection of primary microscopic changes that are specific for AD, such as the amyloid plaques and fibrillary tangles that serve as the basis for the final diagnosis at autopsy. (p. 3)

Hence, the problem that neurofibrillary plaques and clinical signs of dementia have never corresponded in a consistent way can be explained. We simply did not look closely enough! It is not anatomy, but physiology the scientists should look at. Medical scientists thus far have started looking when AD was already too far developed. Through what one could call a *molecularization of AD,* the project promises to make visible what is

hidden before clinical signs become apparent. In this way, it aims to find biomarkers that predict the development of clinically relevant AD. This should allow for early intervention, even if the intervention is as yet to be developed.

The second goal of the project is to translate these techniques from 'bench to bedside', and compare the clinical and economic value of these tests. Here, the link between laboratory and society is made explicit. We will now analyse the ways in which this link takes shape in the proposal by looking for the clinical practices that are implicitly or explicitly referred to in the proposal: the hidden clinic. We identify three versions of the hidden clinic. There is the hidden clinic of the people that are addressed by the proposal as research participants. This clinic is part of the research practices. Then, there is the clinical practice 'as usual', which is presupposed, but hardly referred to in the proposal. And there is the 'hidden clinic' in the projected future practice of AD diagnosis and care for future patients.

## From the Public to Research Practices

The proposal starts with stating the general trend of increasing numbers of Alzheimer patients, and firmly grounds its relevance in concerns from 'patients with memory complaints' (p. 1). What these patients want to know, according to the proposal, is 'whether they will develop dementia, or whether memory loss will continue to be an isolated finding' (p. 1). Clinicians would want to know how 'to differentiate those who will not develop dementia (and who can thus be comforted) from those who will develop full-blown AD with dementia (and for whom healthcare should be provided)' (p. 1)—the nature of this care is not specified. This is the clinic in the guise of the public (who are implicitly judging the proposal through the reviewers' and funders' eyes). Good diagnostics would tell 'them' if 'they' have AD or not.

Then, this metaphorical bedside quickly moves out of sight. The proposal now moves on to relate the clinic and patients' daily life to research: 'Therapeutic challenges in AD are related to diagnostic challenges', the text reads. New drugs are coming up, and 'These drugs have shown

significant clinical effects in AD patients, although predicting these effects in individual patients is impossible' (p. 1). Why could these new drugs not be developed further? This is because of a lack of possibilities (here: biomarkers not witnessed before) to build a proper diagnosis. Why are diagnostics necessary? The proposal lists three reasons:

> (a) the absence of reliable diagnostic criteria to define patient populations for drug studies, (b) the absence of reliable disease-specific markers to monitor drug efficacy on the primary AD-specific histological changes, and (c) the absence of tests that permit assessing in vivo the effect of candidate drugs at the level of NMDA receptors. (p. 1)

These are much more specific reasons for the need for reliable diagnostics than the concern for the worried patient with memory problems and the GP finding out what to do. In a couple of sentences, we moved away from the bedside and find ourselves deeply involved in the concerns of the research lab. Diagnostics, we find out, are at this stage not needed to support *clinical* practice. The aim of improving diagnosis is to support the practice of *drug research.* To do research, the researcher needs a disease-specific population. The identification of a population of people with possible AD is needed to identify biomarkers that prove AD's existence in an individual. After that, it can be analysed how medication interacts with these markers. In other words: early diagnostics of AD is needed in order to be able *to do drug research*. Before even the *feasibility* of the innovation of clinical work comes into view, a laboratory needs to be put in place.

## Constructing New Patients

The proposal continues by delineating its target group of test persons for research, and it is at this point that we find the hidden clinic created by the effects of the research practice: 'Due to the lack of symptoms during the early phase of the disease, early treatment will depend completely on diagnostic tests that permit early diagnosis. Such tests are currently lacking' (p. 1). So, early diagnoses are needed in order to establish the

effect of drugs. To this end, people who have AD, but do not have clear symptoms yet, are needed. Within one or two years, it will be clear if clinical signs have developed or not, and the predictive capacity of the biomarkers may be tested. The effects of being recruited for a possible diagnosis on people who are healthy, or who think of themselves as such, are not addressed. Getting an early diagnosis for a terrible disease without there being any treatment is a clinical and ethical question that is not contemplated. 'Early' is an unquestioned value, and this relates to the research practices' quest to find out how to detect the disease. The 'bedside' here is to metaphorically put people to bed at a much earlier stage, by diagnosing them as diseased much earlier than before, and before they notice something is wrong.

Interestingly, the *prospect* of early detection of AD through the identification of biomarkers in symptom-free subjects collided with the *actual* clinical practice in which the research took place. This practice is aimed at diagnosing and treating people with complaints about their memory. It is here that the ethnographer studying the project, Anna Laura van der Laan, could witness a clash between the ideals of the research and the proposal and the clinical world. In practice, the research project did not recruit or include people without symptoms. The clinics participating in the project got referrals only from people who worried about symptoms, so these were the subjects to work with (van der Laan, personal communication). *No new 'possible patients' were created through the practice of research*.

In a different way than with the Alzheimer societies, the laboratory can also be seen to influence the social world of patients and carers. The laboratory and the clinic are the same place, and are deeply entangled. By organizing research in different ways, the treatment of patients will also change. It is here that tensions may become visible.

## The Research Practice as a Clinic

The medical research practice is a clinical practice at the same time. The clinical practice that comes with the research is not described in the proposal as a clinical practice. It is referred to in the technical terms of 'making biomarkers visible in cerebrospinal fluid'. Yet, it is also a practice in

which worried people are tested, and spinal cord fluid is taken by inserting a needle between their third and fourth vertebra. Other tests are done as well, such as making PET scans to visualize the brain. This involves putting patients with their head in the scanning machine. Next to that, patients are asked to answer batteries of specific questionnaires to determine the nature and severity of the decline of their cognitive functions. This may be very confronting to people who are aware they should be able to answer simple questions.

These are examples of the clinic built in that supports the research practice. It is about medical interventions in bodies and lives. Yet, as we saw, the aim of this clinic is not to *treat* these people better, or improve their daily lives, but to perform a search for biomarkers that is needed to equip *medical research*. Again, particular patients are being created through the research practices. The idea of transporting improved diagnostics to peripheral and GP clinics is far beyond the horizon. Medication might eventually be developed for future patients, but this is uncertain, medical grounds are as yet to be built (Are the targeted biomarkers really markers of AD? And do these predict the development of AD well, or are they as erratic as their anatomical counterparts?) and effects need yet to be demonstrated. Deep in the lab, we are far away from the promise of curing or preventing the dementia that Alzheimer Nederland presented us with. Simultaneously, this research *is* impacting people, and aims to turn them into patients by administering tests. Care and research practices are entangled here in different ways.

There is yet another interesting interference of research and clinical work in the proposal. At the bedside in the specialist clinic, diagnostic tests are already routinely performed. Translations from the new diagnostic techniques to this bedside of routine tests means: to find out which of the tests—PET, MRI, or CSF analysis—has a better diagnostic, prognostic, or predictive value to establish the presence of AD (see also Boenink, this volume). How could this be verified? According to the protocol, this may be established after 12 months 'of natural cognitive decline' (there are no therapies anyway, so the decline will be there if it *was* AD after all). This is taken as the gold standard of comparison, ultimately together with 'post mortem verification' to determine if the new tests are better predictors. The protocol:

> The diagnosis after 12 months of observing the natural course of cognitive decline is considered to be the 'gold standard'. After these 12 months clinical assessment and part of the neuropsychological testing may be repeated. In principle, the gold standard diagnosis will be made by a panel of clinicians consisting of at least one experienced clinician from all three sites, using well accepted standard criteria (CBO 2005). The panel will use all data available at that time, including the initial diagnosis at the patients' inclusion, the initial diagnostic findings, and the changes in neuropsychological test scores over time. In patients with an unclear diagnosis at 12 months, this clinical assessment process will be repeated at 24 months. To prevent bias, CSF, PET, and (f)MRI data that has to be assessed will not be available for the panel. Furthermore, informed consent to obtain post-mortem verification will be strived for in as many patients as possible. By this approach, the complete gold standard will be clinical diagnosis with verification of the disease in time, in some patients confirmed with post-mortem diagnosis, all WITHOUT using the results of the methods/biomarkers under study. To this end, all results will be kept blinded to the treating physicians in the centres and stored at the central database in M. (p. 7, emphasis in original)

The 'hidden bedside' here is the care for the patients and test subjects, for the duration of the study, but also later. Even before they are officially turned into patients, the test subjects are asked to donate their brains for post-mortem research. One might wonder about the implications this has for the relation between researcher and participant, as well as the feasibility of this request. How to obtain those brains?! Anderson (2013, 2008) shows the intense relationships medical researchers needed to establish with the families of patients whose brains they wanted to collect for study. Actually, the ethnographer studying the AD research project did not witness any use of post-mortem research for the validation of biomarkers (van der Laan, personal communication).

This is, however, yet another example of how research practices may 'innovate' clinical care without any innovative diagnostics having been invented yet. The research practice that prepares these innovations could certainly be scrutinized as well, rather than leaving it to the vulnerable visitors of the clinic to consent to or not. Once more, we see that the clinic and society are *inside* the lab that simultaneously shapes them.

## The GP Clinic

The entanglements between the lab, the clinic, and patient representation are already complicated, yet we want to add one extra layer to focus more specifically on the ideas and practices of Alzheimer *diagnostics* in a completely different way. The question in the research proposal concerning Alzheimer diagnostics was: does this person have AD or not? This is different in the GP's clinic. We show this through a study (research again, but of a very different nature) at the department of General Practice of the AMC into the practices of Alzheimer diagnosis (Prins et al. 2016). This is our third research site. The question was when the GPs performed diagnoses of dementia themselves, and when they would refer patients to the memory clinic (which we discussed above), and for what reasons. The broad aim of the study was to gain insight into the workings of clinical practice with the question if it could be improved. The study addressed an audience of GPs interested in the developments in their profession.

The study shows that diagnosis in the GP clinic did not serve to decide between the presence and absence of Alzheimer's, as the research protocol suggested by evoking the worried patient. One of the situations in which the GPs wanted a diagnosis was when it concerned young persons, less than 65 years of age. In such cases, the GPs did not want to provide someone with a serious diagnosis without being really certain about it. Young dementia patients, however, usually suffer from fronto-temporal dementia, not from AD. Typically, for the very old, slowly declining patients, the GPs carefully weighed whether diagnosis would add something good to the situation.

> The GPs indicated that they viewed dementia in elderly patients as a gradual process, continuous with the ageing process. Therefore with increasing age, it becomes less important to have a formal diagnosis. '*If it is a very old patient and it all happened very gradually … then I don't take immediate action' (GP12).* (Prins et al. 2016)

The question is not: 'is it Alzheimer's or not?' Alzheimer isn't quite the bounded entity that figures in the lab. The GPs related it to a more gradual

ageing processes, rather than to a pathological state. The GP guideline (NHG 2012) describes 'dementia' as a syndrome, based on DSM IV criteria. Importantly, there is also the possibility to make a 'care diagnosis' to establish what care is needed. 'Diagnosis', then, is of no particular use if nobody is asking for it and if it does not have consequences for organizing care. Some care services, such as case management, demand a diagnosis; a situation that favours particular administrative practices rather than patients' well-being.

In contrast to the research proposal where undergoing tests such as retrieving cerebrospinal fluid are not discussed as possibly inconvenient for patients, in the GP's office, 'inconvenience' is an important factor. It is related to the generalized frailty in these patients. Costs and benefits are weighed: would a hospital visit be too demanding, considering the value it may add?

> It was frequently mentioned that patients of very old age were not referred to the hospital due to the impact of the hospital visit itself. In addition, GPs stated that referral to the hospital often had no additional value. '*For the very old people I do not see much value of a referral, because we can also do a lot for them ourselves' (GP3).* (Prins et al. 2016)

Indeed, it is not only a matter of inconvenience to travel to the hospital and wait in the corridor of a buzzing hospital when one is old, frail, and confused. There is the promise of a set of invasive, disturbing, and sometimes, risky tests to be done that should be taken into account. But the GPs interviewed were caregivers and pragmatists. They envisioned that if there is no therapeutic gain, whereas diagnostic tests cause more trouble than the result would warrant, they would rather let it be. There is no pill to cure Alzheimer's, after all, they reasoned. Note that the Dutch guideline for GPs favours early diagnosis for reasons of anticipation and care planning. What is 'early' remains, however, vague. 'Early' should be read as 'timely', and relates to the possibility for the patient to make end-of-life decisions, surveillance of their driving capacities, support of the relatives, and preparation for a future with dementia (NHG 2012; Dhedhi et al. 2014). It is clear that the Dutch GPs foreground patient care.

> Another reason GPs gave for not pursuing a specific diagnosis was when patients' cognitive limitations did not yet cause major problems in their overall functioning. '*The other day there was a lady who said: "I'm a bit forgetful". But I won't do anything with that, because I think it will be all right, she is still functioning well, she still has a clear mind' (GP2).* '*When I think: this might give problems with medication and all that, I'll do something' (GP2).* If elderly patients already had home care GPs would not refer them to a specialist. *'If people already have a lot of care and they are deteriorating, then I do a lab test and a MMSE. And if indeed it has deteriorated, but there is already appropriate care, I wouldn't refer them to the memory clinic' (GP2).* (Prins et al. 2016)

The MMSE is a screening instrument consisting of nine questions that are easy to answer for most adults (such as: what is today's date?), but difficult or impossible to answer for people with dementia. The screener focuses on clinical signs, rather than on biological ones. The reason for GPs to refer patients for further diagnosis to a memory clinic, such as the one discussed above, is often related to the demands from patients and their families, or when the GPs feel that the diagnosis would have consequences for care. The question then may be: is it Alzheimer's or some benign memory loss, but also, is it Alzheimer's or some *other* form of dementia? The idea is that for different dementias—say, those with an important vascular component or Lewy Body disease—particular treatments may be useful. This concern shows that a causal 'disease-model' is also present in GP practice, next to the model of the syndrome (see also van der Laan, this volume). Ironically, however, the new lab tests discussed above cannot make this distinction. The protocol:

> However, to distinguish AD from other dementias is a more challenging task, since the specificity of the currently available CSF biomarkers is < 85 %. (p. 5)

All in all, the idea of curing AD, but also of diagnosing it, is far removed from the practices where GPs support the elderly, and care rather than cure is the central concern.

So, the question 'AD or not?' that formed the rationale for the research into biomarkers for AD is but one of the possible questions in General Practice and is a marginally relevant one. It is not of much meaning to the

slowly declining elderly seen by the GP, who are most probably the people with AD, whereas the diagnosis of other forms of dementia may be relevant. For the GPs dealing with dementia patients, there is not much value in pinpointing a discrete disease entity, as long as it does not have consequences for care or treatment. The diagnosis has a large impact on patients receiving it and the GPs do not treat this as a trivial matter. This prevents GPs from referring those who are not (yet) worried about forgetfulness—a group the researchers so eagerly want to include. Their aim to get patients 'as early as possible' clashes with the GP's virtue to interfere with and disturb people as little as possible. Note that in the international literature, GPs' reticence is being challenged. Mild cognitive impairment is said to be 'missed' by GPs (Mitchell et al. 2011; Van den Dungen et al. 2012). The findings of Prins and colleagues suggest, however, that this may result from a felt lack of urgency to make a diagnosis at this stage. In light of these findings, it is striking that in the scientific GP literature, early diagnosis of dementia is increasingly being promoted.

If AD is regarded as a syndrome combining different symptoms of slow decline, and stipulating its presence has no effect on care, the quest for tests that mark the causal pathological processes becomes dubious. Critics have also pointed out that if medication is to have any effect at all, dementia will not be *prevented*, but, as a syndrome, it may be stretched out (Whitehouse and George 2008; Whitehouse, this volume). This means care will have to be arranged anyway, particularly when considering the high caregiver burden related to care for a family member with dementia. A better diagnosis of Alzheimer's, merely in the sense of predicting or establishing its existence, has no meaning to GPs. It is their job to organize care. Added to the increased burden of new diagnostic tests, it is not likely that GPs will become keen on referring their frail elderly, let alone their symptom-free patients, to the clinic. The GP thus implicitly influences research practices, too.

## To Conclude

We had a look into three sites: Alzheimer societies, a funded research proposal, and General Practice. These sites represent practices that are nodes in the complex network around AD diagnostics, research, and innovation.

These practices showed different entanglements between the meaning of AD and its early diagnosis, the concerns that were deemed worthy of scientific attention, as well as the policy that is hence implied, and the people who should be represented. The different practices did not only contain specific ideas about the other practices, they also directly interfered with them by supporting the lobby for funding, by mixing clinical practice and research practice, or by making care prevail over diagnosis. Who is represented by what practices is already shaped in the practices that provide and support particular innovations. In other words, society and its values already exist in the lab, and are being co-produced with science and technology. These practices 'innovate' one another, even before the targeted innovation sees the light of day. There is no one-directional chain that sequentially moves from bench to bedside. The chain loops between different configurations of science-care-and-representation that are heavily intertwined from the start and interfere with each other in discontinuous ways.

What does this entanglement imply for responsible innovation? First, we suggest a further exploration of alternative science-clinic-representation entanglements, not only in places marked as 'laboratory'. One may then look how innovation might take place at different sites, or what innovations are already being made. This also suggests that innovations may take place elsewhere, and may deserve dissemination or development. This is both a matter of political priorities *and* epistemological choices about what kind of scientific knowledge would fit what kind of concerns. For instance, AD as a problem of 'early diagnostics' is but one particular way of framing what the problem with AD is. It is related to concerns of the practice of research. Foregrounding this definition and set of concerns is a political move. It might trivialize the concerns of other sites or make them inaccessible for research, such as the GP practices that are concerned with patient care.

Innovation does not start when a lab delivers a tool. Innovation starts with the framing of concerns, the financing or prioritizing of (research into) some concerns and not others, the ways in which patients can be made to participate, and so on. All ways in which research, clinical practice, and social concerns interfere deserve ethical scrutiny, particularly in the absence of a clear and predictable end point. The ethical questions, then, are not about (slight) re-shapings of technologies and innovations

from the lab that leaves their goals and problem definitions intact. Rather, these are questions about what are proper ways for improvement. This discussion includes research methods to assess and bring about this improvement (see also Moser 2010; Mol 2006; Moreira et al. 2014; Rabeharisoa et al. 2014). Care research demands different scientific practices and expertise than biomarker research. The incompatibility of the different entanglements demands particular ethical caution as to which practices to support.

Our suggestion for responsible innovation is to turn the sequence of translational medicine and innovation around, and *start* with the question of what kind of knowledge clinicians, patients, and carers need to support their practices (Moser 2010; Pols 2014)? How—and what type of—research can support these practices? Again, this is a question that involves different locations. It would need innovative research supported by methods from different disciplines. It needs responsive research practices that can deal with complexity and may venture into the wild, rather than new technologies that are designed from the molecular disease logic in the lab only. It asks for responsible entanglements between science clinic and representational practices that starts from problems that are urgently felt, but not yet addressed well in research. It would mean taking responsibility for practices, rather than for particular scientific problem definitions.

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# Part IV

## Assessing Diagnostic Innovations

# 12

# Informally Regulated Innovation Systems: Challenges for Responsible Innovation in Diagnostics

Fiona A. Miller, Robin Z. Hayeems, and Stuart Hogarth

Expectations for diagnostic innovation are high, with hope for significantly expanded capacity to detect disease early or before it takes hold, and to identify patients most likely to suffer disease recurrence or respond to specific drugs (Graber 2014). Scientific and technological discoveries appear to be driving these developments, with expanded knowledge and capacity in genomics and related 'omics' initiatives (proteomics, metabolomics) heralding an era of what is variably characterized as 'personalized', 'precision', or 'stratified' medicine (Hamburg and Collins 2010). Though often seen as technical—even inevitable—advances (Miller et al. 2006) these developments are actively shaped within socio-technical systems. Materials and artifacts are manipulated

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in these systems by actors, whose beliefs and behavior are molded by institutions, including regulative rules that monitor, incent, or sanction normative expectations about what is right and good, and culturally stabilized cognitive rules, or 'shared conceptions that constitute the nature of social reality and the frames through which meaning is made' (Scott 2013; Geels 2004).

The call for responsible innovation, like other work before it (Schot and Rip 1997), contests the inevitability of scientific and technological advance, and seeks more responsive and anticipatory governance of the products, processes, and purposes of innovation (Stilgoe et al. 2013). Proponents aim to go beyond the minimal requirements of existing post hoc, state-led, statutory regulation of harm to human health and the environment, to also address socio-economic and ethical concerns and attend to social needs (Owen et al. 2009). Yet, despite the plethora of governance mechanisms in the health sector, and growing commitment to patient and public engagement (Boote et al. 2002), the socio-technical systems of diagnostic innovation appear to limit our ability to 'innovate with care' (Boenink et al., this volume).

A first challenge arises from the weakness of the most visible of the regulatory institutions that govern the development and adoption of novel diagnostics. The result is that diagnostics enter practice with limited evidence of their benefits and harms. Diagnostic innovation in genomics has historically proceeded within environments that are practice-based and 'informally regulated', drawing heavily on the efforts of clinical practitioners and only secondarily on the involvement of for-profit firms (Hopkins 2006). These practice-based innovation systems sidestep statutory regulations governing market access (e.g., US Food and Drug Administration), which might otherwise impose requirements related to safety, efficacy, and good manufacturing practice. In addition, current emphasis on translational science encourages 'novel forms of clinical research designed to extend genomics into the clinic' (Kohli-Laven et al. 2011)—developments that blur clinical and research practices, and bypass the soft law regulatory constraints of collective buyers (e.g., through Health Technology Assessment), which might otherwise seek evidence of comparative clinical or cost effectiveness.

The growing role of industry in diagnostic innovation may alter these dynamics, increasing the scope for formal regulatory review (Hogarth et al. 2012). But the weakness of key regulatory institutions governing diagnostics remains a challenge. Statutory regulation governing market access is much reduced relative to drugs for technologies regulated as devices, as are diagnostics (Sorenson and Drummond 2014). Similarly, Health Technology Assessment is better developed to evaluate drug than non-drug technologies, and its mechanisms are often bypassed where technological change assists rather than anticipates service change or expansion (Banta 2003). As well, even robust regulatory mechanisms are challenged where not supported by other regulative, as well as normative and cognitive, institutions.

Diagnostics are a substantial contributor to poor quality in healthcare, with error frequent, expensive, and harmful (Graber 2013). Yet, diagnostics practitioners are latecomers to the quality movement and comparatively inattentive to the problems of overuse, misuse, and underuse (Newman-Toker and Pronovost 2009). Galvanizing attention to quality in diagnostics is challenging, as diagnostics are not themselves the direct source of any health benefit, or harm. Rather, these accrue as a result of other actions that tests guide (Epner et al. 2013). Laboratory practitioners do not have full control over—or visibility into—the patient pathway and the outcomes that ultimately arise, so the cognitive and normative institutions guiding practitioners, as well as the formal regulatory institutions governing laboratories, stress the immediate technical indicators of performance, such as test sensitivity or specificity (Hilden 2004; Sciaocovelli et al. 2006). This tendency toward technical and short term endpoints is compounded by the complex experiential value of diagnostics.

Diagnostics are often experienced as having value independently of their effect on ultimate health outcomes. Medical diagnostics have social roles that extend beyond the allocation of health benefits. A diagnosis may be key to gaining access to social benefits such as educational assistance, or workplace and disability entitlements, and thus may be welcomed irrespective of its accuracy (Miller et al. 2005). In addition, diagnoses may have metaphysical significance beyond any instrumental impact. Thus, the identification of genetic variants as plausible (though unproven) causes of

a disorder may be valued by patients for reducing uncertainty and feelings of guilt, and welcomed for enabling providers to give *something* to patients (Miller et al. 2010). Further, and ironically, patients and providers may experience the errors that diagnostics routinely produce as positive events (Welch et al. 2011). A false positive result regarding disease may be experienced as a 'near miss'. If a second test confirms that the first was incorrect, patients are as likely to be jubilant that they are not sick as angered that they have been misled. Similarly, patients who are, in truth, overdiagnosed—receiving unnecessary surveillance or treatment for a disease that was never destined to cause harm—may sincerely believe they are the beneficiaries of life-saving interventions (Welch et al. 2011). These experiential factors, and the institutions that support them, help to explain the persistence of excess public and provider enthusiasm for medical screening initiatives (Schwartz et al. 2004), and diagnostic innovations more generally.

We draw on an ethnographic study of diagnostic innovation in personalized cancer care to illustrate key challenges of this socio-technical system. Specifically, we present data from our observation of a clinical feasibility study that introduced new diagnostic technologies into the care of patients with advanced, typically end-stage, cancer. The team was not trying to assess whether the intervention had the potential to work as in a typical clinical trial. They were not asking whether the intervention improved diagnostic accuracy, reduced clinical symptoms, or resulted in few adverse effects. Instead, the study assessed endpoints such as completion rate: could tissue in sufficient quantity and quality be collected to enable genomic analysis, across testing platforms? It also assessed timeliness: could patient recruitment, tissue retrieval, laboratory testing, result adjudication, and report to physician be completed within three weeks? Researchers were not simply *testing* diagnostic platforms, bioinformatics technology, sample management protocols, or clinical pathways. Instead, working largely beyond the purview of formal regulatory institutions, they were trying to design a socio-technical system that coordinated and stabilized these elements to translate genomics into clinical care. Moreover, they were doing so in the context of end-stage cancer care, where 'hype and hope' and the anticipated needs of desperate patients are often seen to justify harmful patterns of care (Davis 2015).

## Methods

Two of us (FM, RH) served as observers of a clinical feasibility study of genome-based diagnostics in cancer. Participants were patients at five hospital sites in Ontario, Canada in 2011–12, who were running out of options for standard-of-care therapies and eligible for phase one and two clinical trials. Participants underwent a biopsy to collect tumor cells from the site of their metastatic disease; where possible, an archived specimen from their original tumor site was also retrieved. These tissues were analyzed using genotyping in a clinical lab as well as high-throughput targeted gene sequencing in a research lab to identify somatic variants in tumor tissue that might be associated with disease. The study was supported by an expert panel of medical oncologists, genome scientists, and laboratory practitioners who assessed the functional and clinical relevance of the genetic variants that were identified, to assess which should be reported to physicians, and patients. Expert panel meetings provided the opportunity for discussion of operational and design issues.

Elsewhere, we reported on the qualitative experiences of participating patients and physicians (Miller et al. 2014); here, we report on our non-participant observation of expert panel meetings. Specifically, we observed near-weekly meetings for more than a year ($n$ = 44) and conducted brief ethnographic interviews with panel members. We took detailed field notes, and also had access to formal meeting agendas and minutes. We analyzed field notes and minutes, drawing on an interpretive descriptive approach—a low-inference analytic strategy in the tradition of naturalistic inquiry (Thorne 2008). We searched for information-rich stories where emerging challenges or issues were discussed in depth or across multiple meetings, and used techniques of constant comparison to identify themes related to the organization of the research or reasoning about research results.

Conceiving of the capacity for 'personalized' cancer care as sociotechnical in nature, we differentiate two components of the system that team members were attempting to put in place. First, team members sought to enroll and produce material and organizational capacity—that is, to generate routines and standardize stages and processes, from sample

collection and analysis through data interpretation and reporting. Team members also sought to standardize the normative core of this diagnostic capacity—that is, the judgments of what, in the sea of data produced by these material and organizational routines, constituted clinical information *worth knowing*. We review these two components below.

## Material and Organizational Socio-Technical Capacity: Building the Capacity to Know

Operational discussions at weekly meetings centered on efforts to coordinate socio-technical resources across the many staff and sites in this complex study. Though interconnected, we distinguish three sets of resources that team members worked to consolidate.

### Stabilizing Knowledge

In the context of a rapidly evolving scientific field, the team worked to stabilize a platform of clinically-relevant information that expertly accommodated relevant global standards (Timmermans 2015). This involved initiatives to, for example, produce and maintain mutation reports that consolidated scientific knowledge about genetic variants and their role in various cancers. Here, one challenge was to produce rules of thumb for searching and synthesizing existing genomic sequencing data: what databases to use, how much to search, how to interpret results? Our field notes of a pilot review of 27 mutations identified team efforts to build consensus, centering on the 'need for use of common sense about what [variants] are ridiculous and of no relevance; the need for standardization of common sense judgments' (March 9, Field Notes).

Information of all sorts had to be stored and made appropriately available to serve local needs and comply with international norms. Bioinformatics capacity was needed to track study endpoints related to completion and timeliness, to enable clinicians to monitor patients, and to enable laboratory scientists and clinicians to manage reports. It was also needed to trigger actions, such as facilitating handoffs (e.g., of patients,

tissues, results), issuing reminders when key milestones were not met, or flagging errors when nonsensical data were entered. Dedicated bioinformatics staff used technical software and much discussion to generate and refine data architecture, attending to the 'specific elements that would be relevant to the interest of individuals currently using them' (June 29, Minutes). These staff also navigated technological limitations and evolving international standards. Seeking to redesign off-the-shelf report architecture, bioinformatics personnel asked, 'what is the best long term representation for a mutation?' (June 1, Minutes) and were reminded 'to conform with international rules' (June 15, Field Notes).

## Stabilizing Technology

Scientific knowledge was not the only domain facing rapid change. Technological capacity to detect genetic changes was also in flux. Thus, a second set of socio-technical resources to be stabilized pertained to laboratory-based diagnosis, specifically related to the *detection* of the gene variants of interest.

Importantly, the clinical study was designed to test, refine, and extend diagnostic capacity across clinical and research domains. The laboratory protocol was complex and continuously evolving. The clinical lab used version 1 of the Oncocarta panel of 238 mutations in 19 genes, run on a next-generation sequencing platform from Sequenom. Though run in a clinical lab, this product had not been approved by statutory regulators for clinical use and was thus sold 'for research use only'—'not for use in diagnostic procedures' (Sequenom Inc. 2011). Since the lab's use of this technology was new, it also used the time-consuming gold standard of Sanger sequencing to confirm mutations identified on the Oncocarta panel. Alongside this, the research lab used some of the latest technology, specifically a next-generation sequencing platform from Pacific Biosciences, which was also 'research only' (Pacific Biosciences of California Inc. 2014). Set up originally to assess the same 238 mutations in 19 genes, the research lab slowly ramped up its investigation of additional mutations and genes. Further, as the team wished to report findings to physicians to guide experimental treatment selection, results

had to be validated in the clinical lab, which was licensed and accredited to conduct molecular pathology testing for patients in Ontario.

At many meetings, this complex diagnostic capacity was taken as given. All of the diagnostic technologies were seen to align, to produce findings that were accepted as real, and adjudicated as either reportable or not. But some discussions exposed more active efforts to refine or rework diagnostic tools. The team came to realize that some mutations identified on the Oncocarta panel—which, *a priori* were deemed relevant to cancer—were spurious, included on the panel as 'an accident of the development process' (June 1, Field Notes). The clinical lab was 'developing its own home brew' platform that would exclude these spurious mutations while including others that were considered relevant (June 1, Field Notes). In addition to spurious findings, the team sometimes had to manage the problem of spurious non-findings—to marshal efforts to find something they were sure was *there*. When the clinical lab found 'a known, well documented, recurrent mutation that is associated with treatment response', there was no debate over its clinical significance (May 5, Field Notes). But it took another month for the research lab to adjust its process and primers and confirm 'that there were concordant results and no technical issues' (June 1, Field Notes).

In addition to negotiating technological capacity and scientific knowledge, the team had to navigate different social standards governing the quality and veracity of laboratory results. As the research lab expanded its capacity to detect more mutations, tension emerged over what kind of verification requirements in the clinical lab might be 'good enough' (Miller 2006). The clinical lab asserted its independence, arguing for experience and repetition in the identification and verification of variants—not simply the technical capacity to find them. Also, the clinical lab preferred to independently source needed reagents when a new-to-them variant had to be validated, not receive the reagent from the research lab. However, those eager to see new variants reported quickly mobilized a different standard—one that anticipated that formal processes of verification in the clinical lab would be sufficient, using research reagents where feasible, and the clinical lab was encouraged to make concessions (June 8, Field Notes).

## Stabilizing Clinical Practice

As debates about verification of diagnostic results make clear, the team's navigation efforts extended beyond technological capacity and scientific knowledge to clinical standards. Material and organizational efforts to interface with clinical practice were particularly evident in work conducted to manage human tissue for laboratory analysis, and to support medical oncologists in accommodating genomic information within clinical routines (Kohli-Laven et al. 2011).

In part, this involved modifying lab protocols to conform with clinical practice. The team had, for example, intended to prepare tissue samples in two different ways—fresh and frozen—to align with the technical requirements of the research lab's new diagnostic technology, and to assess whether both methods of tissue preparation produced comparable results. The two methods were not, however, comparable clinically. One method—fixing fresh tissue in paraffin—was consistent with clinical practice, as tissue retrieved from the clinic was prepared in the lab. The other—flash freezing fresh tissue—was inconsistent, as it required that tissue be frozen *in the clinic*. The team proved able to manage these complexities for patients recruited from the main clinical site. But as the study spread across the province, the incompatibility of flash freezing with clinical practice became unmanageable. Recognizing this, the team moved quickly to reconcile their lab practice with clinical needs—requiring that the new diagnostic technology adapt to 'where the world is going' and foregoing scientific certainty about the comparability of these protocols 'because frozen is really not possible for the other sites and, it appears, would cost more' (June 15, Field Notes).

The study's interaction with the clinic was not solely reactive to its norms. It also involved interventions to modify them (Kohli-Laven et al. 2011). This was especially apparent in work to build information capacity for physicians who were not closely connected to the study. On several occasions, the team discussed what was necessary to convey complex research information to the clinic. One such discussion was relatively brief, and 'fairly quickly led to the conclusion that in cases where some mutations were definitely actionable as a "standard of care", there should

be—possibly by type of cancer—some way of reporting that there were (1) standard of care mutations that would typically be assessed in these cases to guide practice, and (2) that such mutations had or had not been found' (May 18, Field Notes). Another such discussion was more protracted, as it centered on 'how much homework the Expert Panel should do with respect to interpreting mutations, compiling evidence, and relevant trial details for the treating physicians'. Concerns about the timeliness of the study's processes implied that the responsibility for interpreting clinical meaning and identifying experimental options should lie beyond the study, in the hands of treating physicians. But this logic was overruled by concerns about ensuring access to relevant up-to-date information among clinicians who were not tapped-in to the academic physician's knowledge base, and desire to emulate capacity in exemplary US centers (July 20, Field Notes).

## Normative Socio-Technical Capacity: Constituting Knowledge Worth Having

In addition to operational discussions, the expert panel made decisions about which results to report to physicians. This function was sometimes readily discharged: discussion was limited, consensus seemed clear. Some cases, however, were much more difficult, involving rich, serial, debate. In these cases, the parameters of reasoning and judgment came into focus.

### Clinical Obligations

Early on, a case of discordant clinical findings arose—between what was known about the case originally, and what came to be known through testing completed by the team. This case highlighted a potential new role for the team: that of reporting to physicians the results of archived samples from the patient's original tumor.

There had always been an expectation that the team would analyze archival samples—to answer scientific questions about the stability of cancer mutations, and practical questions about whether archived

samples could reliably be retrieved and tested. However, this case was challenging for the team because it suggested that archived results might also be *clinically* relevant. The case involved a patient whose tumor's genetic status, according to a fresh biopsy of a metastatic site, precluded standard-of-care treatment. However, the archival tissue from the original disease contradicted this finding, suggesting that the patient *had* been eligible for a treatment she had never received. This case led the team to question whether archival results might be clinically relevant in future cases, and what should be done.

There was agreement about many issues in the discussions that ensued. It was agreed that the initial protocol had *not* anticipated that results from the archived sample might be reported. It was agreed that archival samples were typically time-consuming to collect, and could not be analyzed on the study timeline. Further, it came to be agreed that clinical testing of archived samples (as distinct from research lab testing) was not in the original study budget, and would add to total costs. Finally, it was agreed that the clinical significance of discordant findings between archival and current tissue was very uncertain. Nonetheless, such scientific uncertainty did not obviate what were characterized as clinical obligations.

Physician members of the expert panel wondered how they would manage a patient with discordant results, but asserted their right to decide. When one of the more reticent physicians highlighted the uncertainty of the situation, another agreed 'but stated that he would want to know' (June 1, Field Notes). A week later, another physician on the team was even more assertive, 'As a physician—and this is a decision for physicians—I would want to know this' (June 8, Field Notes). As the minutes of that meeting recorded, 'The consensus was that clinicians would likely wish to have any information on mutations that might influence treatment decisions and that the process questions can be addressed' (June 8, Minutes).

Team members were explicit that a normative sensibility about clinical *obligations* and *ethics* motivated—and should motivate—their decisions. Minutes from one meeting noted the need for consideration of felt obligations, noting that 'input from [the head of the clinical laboratory] and clinicians is sought as the key issue may be what they feel they would like to know and what is our obligation to report (and how)' (June 1,

Minutes). One physician argued that ethics was not solely on the side of reporting these results—'one can ethically and reasonably either report or not report' (June 8, Field Notes). But this was a minority opinion. So strong was the sense that clinicians had reporting obligations that the team considered ways of 'insulating the clinician investigators on the team from this type of information—depending on their comfort level with respect to their responsibilities' (June 1, Field Notes). Though considered, the dominant view favored reporting—that 'we have to do this as an obligation' (June 8, Field Notes).

## Ensuring Options

In addition to illustrating the central importance of felt clinical obligations in governing the conduct of the team, this early case illustrated the presumption of beneficence built into this clinical obligation and the determination to facilitate choice. In the face of uncertainty and complexity, team members believed that it was better to do more—to err on the side of giving a patient the choice of access to a drug (albeit, an experimental one), rather than excluding them from it. This was made explicit during the debate about disclosing archival results, as one physician 'made a point of highlighting what she thinks is a characteristic of clinicians—part of their judgment—that as a clinician, you always want to try to maximize the treatment you can offer to patients, and that this disposition would factor into how to deal with discordant results.' Another physician agreed, noting that in the context of uncertainty, 'you don't want to deny patients a potentially useful therapy' (June 8, Field Notes).

Several months later, another case illustrated this disposition just as clearly. This case arose as the research lab expanded its search capacity with the more experimental Pacific Biosciences platform, and identified a first mutation in a patient's tumor that was not on the clinical Sequenom panel. This case was also unusual because the team was unable to find any information in existing mutation databases about the specific genetic variant. The genome scientists acknowledged that 'because [the variant] had not been reported before, it would have to be seen as uncertain' (August 3, Field Notes).

Because the team has previously decided that 'actionable' mutations were to be reported, discussion ensued about what it was to be actionable. For one physician, 'since there is no information about it, it is not actionable'. For other physicians, however, the result was actionable because the patient is 'out of options' and the variant could be used to guide access to phase-one trials. As one physician put it, 'What is there to lose?' From this perspective, the burden of proof was to be reversed, so that 'if they knew it was *not* actionable, then would *not* report'. As reiterated by the chair, the variant could 'be seen as actionable because we have no information to the contrary and the patient has incurable disease', though a more reticent physician suggested that this was, 'stretching to the limits of actionable' (August 3, Field Notes). The meeting minutes recorded some discomfort with the decision to validate the variant in the clinical lab and report it to the physician, noting that 'Although this was the consensus there were opinions expressed that in the absence of knowledge, the mutation should not be reported' (August 3, Minutes).

## Discussion

The study of 'personalized' cancer care that we observed was designed to assess feasibility, not safety or efficacy. As such, it was one among a host of similar translational research initiatives around the world that intend to bring genomics to the clinic (Kohli-Laven et al. 2011). For members of the team, the desirability of this technological trajectory was not in dispute. Instead, the problem was how to marshal sometimes-recalcitrant artifacts, actors, and institutions into a stable system. Their efforts illuminate several truths about the dynamics of diagnostic innovation, and prospects for doing so more responsibly.

First, this study makes clear the active and contingent nature of diagnostic innovation—the construction of a socio-technical system involving material artifacts that impose restraints, but do not fully determine outcomes, and actors who negotiate among alternatives, in accordance with institutional rules (Geels 2004). Technologies came with capacities to detect certain variants, but these capacities could be accommodated or changed in accordance with judgments about what was 'actionable'. Such judgments were informed by global standards for mutation identification

whose expert use and modification is, as Timmermans has shown, key to transitioning genome-based diagnostics from the laboratory to the clinic (Timmermans 2015). Further, these expert judgments were guided by beliefs about the value of pursuing highly unlikely benefits (Davis 2015), as well as belief in the right of physicians to decide in the face of uncertainty. Similarly, biological material required some form of fixing to be interrogated by extant diagnostic platforms, and recalcitrant organizational routines—together with tacit agreement that such routines should be accommodated—prescribed which form of fixing would be stabilized. Indeed, as Kohli-Laven and colleagues (2011) have shown, whether extant organizational routines are accommodated or challenged as new genomic technologies are deployed is a key element of their sociotechnical script.

Second, this study highlights the implications of the 'informally regulated' nature of this innovation system (Hopkins 2006), where clinical and research aims were blurred by translational imperatives, and key regulatory institutions had limited purchase. The platform technologies and laboratory-developed tests reviewed here were not subject to the requirements of statutory regulation governing market access. These technologies were 'not for use in diagnostic procedures', though this prohibition was ignored, as is common in molecular genetics. Regulation through the licensing and accreditation of clinical labs imposed quality expectations, but quality was narrowly defined, involving technical definitions of performance alongside cognitive and normative commitments that valued diagnostic information independently of its impact on patient outcomes (Hilden 2004; Sciaocovelli et al. 2006; Miller et al. 2005; Miller et al. 2010; Welch et al. 2011). Further, in the context of translational research, these quality standards were further challenged in aid of timeliness in coordinating across clinical and research laboratories. Finally, in the context of translational research and practice-based innovation, soft regulatory constraints on technology adoption were also muted. In the absence of a decisively new product or service to be covered, decisions regarding collective payment—as exemplified by Health Technology Assessment—were not invoked. Research funds supported many translational expenses, while subtle shifts in practice were enabled by the clinical autonomy of physicians.

As Hopkins has noted in his analysis of the 'informally regulated' innovation system that produced clinical cytogenetics over the course of

the twentieth century, informality limited the system's accountability to 'impartial parties', resulting in tangible harm to patients (Hopkins 2006). In the case reviewed here, limited accountability implied limited responsiveness to regulatory institutions, which embody expectations related to safety, effectiveness, and quality. Limited accountability extended to cognitive and normative institutions, which embody expectations related to the meaning of benefit, the significance of hope or harm, and the role of professionalism and patient autonomy. As Kohli-Laven and colleagues have shown, genome-based diagnostics are made to be 'congruous with physician conceptions of both clinical utility and adequate care' (Kohli-Laven et al. 2011). In their case and ours, these beliefs about utility and adequacy prioritized not 'depriving' patients of options (Kohli-Laven et al. 2011). Moreover, as in the contexts of end-stage cancer care studied by Davis, these systems emphasized faint hope, exaggerated the possible benefits of therapeutic options and seemed to ignore the possibility of harm (Davis 2015). Yet, as systems with limited accountability, these contestable beliefs and expectations were protected from critique (Miller et al. 2008).

Third, this study highlights the perverse ways in which practice-based and informally regulated innovation systems—which orient toward users and use (Morlacchi and Nelson 2011; Oudshoorn and Pinch 2003)—often appear to be especially responsible. Notably, physicians as users were lead designers of this socio-technical system and sought actively to serve the needs of patients as end users. This arises also from the secondary (though not null) role played by private for-profit firms and marketed health products relative to clinicians and scientists. As Hopkins has noted of these 'bottom-up processes', those involved appear to be 'working to achieve objectives that seem less related to personal financial incentives and more about serving the "greater good"' (Hopkins 2006). And yet, despite appearances and sincere belief, this conception of 'the good' requires unpacking. While some physicians were actively involved in design processes, those with less research-intensive practices, from less urban centers, or with less sub-specialist concerns were not, while patients were implicated but entirely absent in these processes (Clarke and Montini 1993). The socio-technical system that was produced reflects these power discrepancies and partial engagements. Prioritized were commitments to empowered sub-specialist users with a right and

responsibility to manage uncertain test results and the logic of managing the differential capacity of physicians to understand and act upon such results through strategies of education and communication. Also prioritized was a characterization of the patient as needing faint hope, willing and able to choose and gain access to experimental therapies (despite known challenges (Miller et al. 2014)), and uninterested in a good death.

Many proponents of responsible innovation would recommend broader and deeper engagement as a remedy to these failings (Macnaghten and Chilvers 2013; Stilgoe et al. 2013). Invoking the potential of deliberative democracy, they would enjoin engagement with a diverse array of users, including patients, clinicians, and publics. We would endorse that remedy, but caution that the partial responsibility that does exist in these socio-technical systems may dampen the power of engagement to unpack extant challenges. Moreover, the responsibility to 'innovate with care' transcends these particular actors within their local, practice-based innovation system (Boenink et al., this volume). Thus, there is also need to elaborate and enforce robust, legitimate, and accountable regulatory regimes (Black 2008), and particular potential to do so in the health sector. The light touch of regulatory mechanisms in the innovation system we reviewed should not deter us from this goal, but rather, embolden efforts to strengthen and apply these fundamentally democratic structures.

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# 13

# Valuing Diagnostic Innovations: Towards Responsible Health Technology Assessment

Ellen Moors and Alexander Peine

This chapter deals with valuing diagnostic innovations. Until now, this valuing has been dominated by traditional Health Technology Assessment (HTA) practices, measuring efficacy, safety, quality, and cost parameters of a new health innovation. As we are living today in an increasingly 'individualized society of consumers' (Bauman 2001), who are undertaking action to self-actualization and co-creating their own lives, a more comprehensive view on valuing is needed. Also, users and citizens want more proactive involvement in co-developing innovation. User communities are collectively engaging and creating innovation platforms for cooperation, for co-creation of shared values (Prahalad and Ramaswamy 2004), or for convergence of ideas and expertise, such as in online patient platforms. Further, innovation and institutional practices, such as regulation, norms, and informal values, are becoming increasingly

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intertwined nowadays (Lounsbury and Crumley 2007). These current trends demonstrate the increasing role of users and institutional practices in valuing innovation processes.

Nowadays, diagnostic innovation is not bound anymore to specialists and laboratories, where traditional HTA takes place. It is increasingly perceived as an institutional interplay with many heterogeneous stakeholders, in which users are more proactively involved in diagnosis. The current 'e-revolution', for example, is causing a shift in information distribution between medical professional and patient, in which digital self-management of diseases and prevention is becoming more important. Furthermore, diagnostic innovation increasingly moves from professional medical practices, in which the patient is often regarded as passive receiver of healthcare, into domestic, informal care spaces, in which patients are actively involved in self-diagnosing and managing their disease or health by monitoring a diverse range of health parameters, and by maintaining contact and sharing health data with medical specialists and caregivers (see also Peine et al. 2014).

These novel diagnostic innovations, however, also lead to problematic issues, such as privacy-related threats, more awareness raising, user acceptance, and treatment compliance problems. So, besides the traditional HTA parameters of efficacy, safety, quality, and costs, other values which take into account the social and ethical norms and expectations, positions, and distributed roles of various stakeholders, become more important in diagnostic technology assessment as well.

This constitutes a challenge for traditional HTA approaches, which need to take these other values into account. In other words, it requires us to reconsider the current logic of HTA that does not fit the practices of designing, evaluating, and using contemporary diagnostic innovations. To capture, characterize, and analyse the processes of valuing, we focus in this chapter on the 'logic of valuing', which we define as the set of implicit or explicit justifications and practices that render a value valid and relevant. We assume that different practices may have different logics of valuing. We also assume that while the logics of valuing have some durability, they may also change in due course. Accordingly, this chapter critically reflects on the question *which set of values, which logic of valuing, could be leading in new practices of HTA for diagnostic innovations?*

We carry out this reflection in three steps. As a first step, the next part zooms in on how the 'logic of valuing' is currently organized in HTA. Then, as a second step, illustrative empirical cases on diagnostic innovations are presented that report on the 'logic of valuing' in actual diagnostic innovations. Third, the last part discusses how these steps are related and what this implies for HTA strategies, policies, practitioners, and the role of users in diagnostic innovations, in order to become more flexible and responsible.

## The 'Logic of Valuing' in Current HTA Practices

For decades, healthcare systems in the Western world have been adjusting to different kinds of new health technologies (Lehoux 2006; Faulkner 2009). Like pharmaceutical innovation, diagnostic innovations take place in highly regulated markets and sectors, and for health policy, it is thus important to assess the value of diagnostic technologies. The increasing importance of health innovation, therefore, has been accompanied by various ideas about how to assess more rationally its value. By and large, these ideas have resulted in what is known as Health Technology Assessment (HTA)—the conviction that health policy decisions should be based on 'the "best available evidence" on the costs, efficacy, and safety of health technology' (Lehoux and Blume 2000, p. 1083). Focusing on the logic of valuing in current HTA practices, we are interested in two particular aspects that seem to be characteristic of ongoing HTA discussions:

First, HTA revolves around the idea that health policy decisions should be based on 'facts' (Banta and Perry 1997) to evaluate the value of a particular health innovation. According to Lehoux, HTA is as a scientific and policy movement operating in the manner of 'regulatory science' (Jasanoff 1990) and seeking to foster the institutionalization of knowledge-based changes in healthcare systems, and the relevance of adopting and using technologies proven to be effective, safe, and economical (Lehoux 2006, p. 1). Although HTA approaches should be broad *in principle*, most *actual* approaches are grounded in epidemiology and health economics, thus focusing on the treatment value for patients and the often

substantial costs of adopting new health technologies (Lehoux 2006). Standard HTA procedures can be seen as a cost-benefit analysis that tries to assess the value of a new technology in terms of costs per health benefit. However, the wider ethical and social values, although considerably sidelined, have been part of the HTA literature since its inception as well (Banta 2003; Draborg et al. 2005). Only recently, discussions have more decidedly focused on the value of technology beyond the logic of cost-benefit analyses. Such discussions have tried to unravel how social and ethical values can be addressed in HTA procedures (Bombard et al. 2011; Lehoux and Williams-Jones 2007; Busse et al. 2002), and how they are addressed by different stakeholders (May 2006; Lehoux et al. 2010, 2011, 2012). The scope of values to be included and addressed in HTA exercises is principally infinite, and a prolific body of literature has proposed a variety of procedures to deal with this issue worldwide (see also Banta and Johnsson 2012), thus widening the knowledge base of HTA (Battista 2006). Less attention, however, has been given to the *position* of these values in relation to emerging technologies.

Second, in this latter regard, the emergence of HTA has been closely connected with the evidence-based medicine (EBM) movement in healthcare (Moreira 2007). Although EBM is much narrower in focus—it deals with assessing the clinical effectiveness of medical interventions—its basic tenet that interventions should be based on sound evidence has been central in defining the HTA field (Giacomini 1999). EBM carried a specific idea about what constitutes sound evidence in HTA procedures. Indeed, randomized controlled trials as well as systematic reviews of existing evidence are seen as the gold standard for proving the value of an intervention in EBM, whereas anecdotal evidence from case studies and practice are regarded as less reliable (Williams et al. 2003; Lambert et al. 2006). In this sense, EBM is strongly associated with an empiricist and positivist epistemological position (Goldenberg 2006; Hjørland 2011), and the art of compiling systematic reviews and meta-analyses has become the stronghold of procedural and methodological debates (Moreira 2012). This position is subject to ongoing disputes within both the medical profession itself and critical analyses from science studies (see also Drummond et al. 2013; Moreira 2007). Nevertheless, the basic ideas of EBM have quickly gained attention among health policymakers due to

their putative ability to provide an unambiguous basis for decisions about health interventions (Goldenberg 2006; Gordon 2006). HTA has been quick in borrowing from EBM the basic logic that decisions about health technology should be based on a sound understanding of the costs per quality-adjusted life years (QALYs) (Drummond et al. 2013). This has two effects that permeate established HTA practice: it describes a rigid scheme of what counts as evidence (i.e. ideally insights about a clear-cut medical effect and its costs based on the results of randomized controlled trials compiled in a systematic review), and it describes how this evidence should be included in policy decisions (i.e. as 'facts' established before the technology is adopted or rejected). It is this logic of assessing the value of health technology that interests us most in this chapter, because it implicitly ascribes certain roles to patients and users, policy makers, and technology developers in defining and assessing value.

What transpires from this discussion is not so much that the value of health or diagnostic innovation is too narrowly defined in the practices of HTA. Rather, it becomes apparent that HTA both describes a range of knowledge, in terms of values, to inform decision makers, and a relation of this knowledge to decisions about emerging health technologies. The latter narrowly frames knowledge about the value of a specific health or diagnostic technology as an *input* that can be assessed before this technology is put to use, as a one-time decision, instead of a continuous assessment as a result. In this way, traditional HTA is not so flexible with regard to changing values and creative or unexpected use of new innovations. The HTA field inherited this stance from its origins in medical practices (Perleth and Lühmann 2010), where health innovations meet their users as patients. The question is whether this basic position, this logic of valuing can fruitfully inform the assessment of current diagnostic innovations that increasingly meet their patients as consumers or citizens in their informal care and domestic environments. In domestic life, even more than in other care spaces, health technology not only meets a medical need, but also needs to address emotional values, to contribute to an evolving sense of self and place, and to function as both a functional and symbolic object in the everyday practices of people (Peine 2009). As the boundaries between medical professionals and patients and citizens are blurring, it leads to possibilities for co-creation of health and care

innovation, defining the needs and wishes, creating values and co-creating solutions in healthcare practices, in which various types of stakeholders are involved. Innovation is then not just geared towards efficacy, safety, quality, and low costs, but also implies specific social expectations, values, and norms. From an STS perspective, this question translates into the problem of agency: how current HTA practices impute roles and responsibilities on different stakeholders in emerging diagnostic innovation systems, and on patients and their formal and informal caregivers as end users in particular (Akrich 1995).

The next part illustrates, by means of some empirical examples, various practices of diagnostic innovations in order to better understand their set of values.

## Empirical Findings on Valuing Diagnostic Innovations

Building on empirical examples of practices of Alzheimer's disease (AD) diagnostic innovations in Cuijpers and van Lente (2015), of various diagnostic innovations in this volume (Van der Laan, this volume; Egher and Wyatt, this volume; Miller et al., this volume) and of Point-of-Care (POC) diagnostic innovations in primary and secondary care practices (Ten Kate 2011), we extend the logic of valuing in current HTA practices to the analysis of how values evolve in the entire diagnostic innovation process.

Cuijpers and van Lente (2015) argue that in the HTA practice of the Dutch Leiden Alzheimer Research Nederland (LeARN) project, various meanings of early diagnostics exist: as value for money, as changing healthcare practices, as innovation trajectory, as changing disease definitions, as a step towards medication, and as early management. A diagnostic test for AD, or combination of tests, would change the AD practice a lot and would have far-reaching consequences for AD care. Early AD diagnostics could be part of disease management in early phases, providing better information at an earlier stage of the condition, when patients can still understand the diagnosis. In this way, it provides possibilities for patients, and for professional and informal caregivers to better

manage the AD condition, that is, timely making plans, arranging care and support. So, values might shift from the need for an accurate AD diagnosis towards also delivering value in terms of patients better dealing with the diagnosis when they are better informed. Traditional HTA fails in this as it focuses only on costs and limited type of evidence as treatment outcome, but not on new values, such as recognizing the roles and responsibilities of the various stakeholders involved in AD diagnostic innovation (Cuijpers and van Lente 2015).

Van der Laan (this volume) highlights the heterogeneity of Dutch AD diagnostic practices and the distributional mechanisms underlying these different practices, based on observations in different AD diagnostic settings: a nursing home, a memory clinic in a general hospital, and a memory clinic in an academic hospital. She discerns five diagnostic values, including the epistemic values *causal explanation* and *describing functionality*, about what is the matter. The value of *prognosis* is a predictive one, about knowing what the future will look like, what to expect. The values of *control* and *living with*, concern the 'directives' of diagnoses (see also Pols 2012), about 'what to do?' These two latter values concern ways in which diagnoses lead to certain actions, for example, fighting or eliminating AD, or diagnoses that direct to improving life with AD, for example, enabling 'patients and informal caregivers for care services, and empowering them to make particular individual choices, such as quitting their jobs, writing a will or helping them to give meaning to the symptoms' (Van der Laan, this volume). She argues that these five diagnostic values are connected, while enacted in different modes of diagnosing. She discerns two modes of diagnosing AD: pulling out all the stops, and holding back way of working, in which various diagnostic values are enacted and aligned. These modes are not only based on traditional HTA approaches of scientists and AD specialists, but also on preferences, concerns, and practices of patients, caregivers, on healthcare professionals, policymakers, and stakeholders contributing to the public discourse on AD.

Miller et al. (this volume) highlight the challenges of informally regulated diagnostic innovations in the care of patients with advanced, end-stage cancer, in which clinical and research aims are blurred by various translational imperatives. They argue (Miller et al., this volume): 'Team

members were not trying to assess whether intervention had the potential to work as in a typical clinical trial, they were not asking whether the intervention improved diagnostic accuracy, reduced clinical symptoms, or resulted in few adverse effects. Instead, the study assesses endpoints like completion rate: could tissue in sufficient quantity and quality be collected to enable genomic analysis, across testing platforms? As well, it assessed timeliness, could patient recruitment, tissue retrieval, laboratory testing, result adjudication and report to physician be completed within three weeks?' In their case, the researchers were not just testing diagnostics or clinical pathways, but designing a socio-technical system for translation of genomics in clinical care in the context of end-stage cancer care, in which 'hype and hope' and the expected needs of the patients are often justifying risky care patterns. In other words, physicians as users of these informally regulated genomic innovations actively tried to serve the needs of patients as end users. They sought to improve patient care and to assess feasibility. The case of Miller et al. (this volume) showed that limited accountability implied limited responsiveness to regulatory institutions, which embody traditional HTA expectations related to safety, effectiveness, and quality. This limited accountability is extended in their case to cognitive and normative values, representing expectations related to the meaning of benefit, the significance of hope or harm, and the role of professionalism and patient autonomy.

Egher and Wyatt (this volume) assume that innovative Internet-based (self-)diagnostic technology could change the way how risks and benefits of disease categories and treatments are interpreted and how diagnostic expertise is constructed and demarcated. They explored how the Internet transformed responsibility with regard to diagnostic (self-)tests for AD, and identified three main roles of the Internet regarding online (self-)tests—namely, as medium of distribution, as medium of education (anticipating and preparing for the face-to-face encounters between medical professionals and lay people), and as medium of data collection. The role of the Internet as a *medium of distribution* by making tests available worldwide is especially interesting when studying the logic of valuing in distributed practices of diagnostic innovations. Democratizing values might be considered, as the Internet provides everyone who wants (including (pre-)patients, families, people in particular countries, or

healthcare systems) with access to diagnostic tools, formerly available only to medical professionals. Egher and Wyatt (this volume) indicate that the validity of test results might be affected by worldwide distribution, due to the fact that the content of diagnostic tests may be culturally biased and 'bear traces of power relations from their place of origin'. So, cultural habits and personal interests may play a role in valuing diagnostics. Online diagnostic tests call upon the participant himself or herself to become responsible for the accuracy of the data provided, of the quality of the data. This shows that user compliance is needed to bring about these diagnostic processes. 'How they take or administer such tests, and how they react to the results depends on their intentions, on their attitude towards the Internet, and their digital skills' (Egher and Wyatt, this volume). It is the question whether they consider the Internet as a reliable diagnostic tool. 'People might even attempt to displace such tests from a medical context, by completing them in order to train their memory or simply out of curiosity'. Then, playfulness and entertaining elements comes into play. Egher and Wyatt clearly showed that the Internet as distributed practice leads to confusing categories, enabling users to experiment with various roles in valuing diagnostics.

We also revisit a case study conducted on the set of values medical professionals in primary and secondary care discuss in relation with Point-of-Care (POC) diagnostics (Ten Kate 2011). POC diagnostics are those analytical testing activities that take place near or at the site of patient care, outside clinical laboratories. These new diagnostic devices are often based on biosensors and deliver fast results, are small, handheld, enabling data management and communication with a larger ICT infrastructure, also sometimes referred to as 'labs-on-a-chip', because they make the laboratory step in the diagnostic process unnecessary. We found that values such as analytical accuracy (validity and reliability proven by means of medical scientific results), diagnostic accuracy (value of diagnostic test is the difference in health outcome resulting from the test), clinical utility (health-related outcome of test-plus-treatment strategy), cost effectiveness (total costs test-plus-treatment -strategy), and indirect utility, such as non-health-related (efficiency) impact on procedures, routines, social behavioural impacts, and lifestyle are important for POC technology. The key POC implementation path would initiate in secondary care,

where important evidence could be collected in a relatively confined organizational setting. The more distributed primary care setting, with its comparably high distribution of actors and activities, was perceived to be too messy to collect the necessary evidence in a clinically meaningful way. This focus on secondary care indicates the importance of collecting best available evidence from valid and practically relevant scientific research before a decision is made by clinical guideline developers to take up a new diagnostic tool and thus make it accessible to larger patient groups. This logic fits well the models of traditional HTA procedures, as it highlights costs and effects as the most relevant values of POC diagnostics. What emerges from this focus on the secondary care setting is a logic of addressing value that revolves around compiling high-quality evidence according to the established hierarchy of EBM. The values to be addressed, therefore, are regarded to be more or less pre-given, while the collection of evidence is delegated to experts and specialists. Although some of these specialists, most importantly general practitioners (GPs), are also users of the technology, their role is largely confined to probing into the value of the POC device along pre-figured dimensions. Other, less specialized users such as nurses or patients are not perceived to be central actors in this process. This POC diagnostics case demonstrates how in professional medical settings the performance of a new diagnostic technology has to prove its effects on established values, before its wider impact can be explored and become manifest.

## Discussion

The illustrative empirical examples in the previous section demonstrated the process of valuing in various diagnostic innovation practices. This section discusses how these practices are related to current HTA practices and what this means for (improvement of) HTA strategies and policies of practitioners and users of diagnostic innovation.

The empirical cases revealed that emerging diagnostic technologies impact a broad range of values, such as epistemic, predictive, and directive values (Van der Laan, this volume) that are complex and interrelated. Egher and Wyatt (this volume) demonstrated that the Internet as

distributed self-testing diagnostic has contributed to changing the ways people value and relate to their medical state and interact with medical professionals. The cases also showed that these values are difficult to predict and to anticipate, as diagnostic innovation becomes more distributed between formal, specialist care practices and more informal, home care practices, and clinical diagnosis becomes more socialized (see also Webster 2002). In other words, the examples showed that there is a need for flexibility and experimenting to cover the broad range of often emergent values in the early development of novel diagnostic innovations.

As argued in the previous section (e.g. in POC-diagnostics case), standard procedures of HTA are likely to carry the image of passive diagnostic technology users. This is potentially problematic, as these HTA interventions impute only limited agency on both the emerging diagnostic device and most of its technology users. Against this background, we argue that current HTA practices are not suitable to guide health policy decisions about more spread diagnostic innovations and that an alternative approach is needed, incorporating another logic of valuing diagnostic technology in order to fully take into account the potential of novel diagnostic innovation processes. To rethink current HTA practices and to indicate in which direction current HTA could be transformed, we connect the discussion of our cases to Callon's recent distinction between *prosthetic* and *habilitating* social policies (Callon 2008). In this distinction, Callon highlights that a key task for social policy making is to compensate 'for maladjustments encountered by individuals in their professional and private lives "to" the mold of the Western neo-liberal subject' (Callon 2008, p. 46). He defines *prosthetic* social policies as measures that produce disciplined agency where individuals are empowered to follow preconfigured scripts for individual action. *Habilitating* social policies, by contrast, are those measures that include individuals in the creation and exploration of scripts for individual action, and thus, empower them to contribute to the evolving mould of the neo-liberal subject itself. It deals with *interactive individual agency,* where individuals are empowered to explore and develop their needs and preferences.

There are striking similarities between Callon's discussion of social policy and the policy debates about the value of and meaning of diagnostic innovations in healthcare (see also Peine and Moors 2015). In other

words, traditional HTA works as a *prosthetic device* that evaluates diagnostic practice according to values defined in the traditional medical, institutional domain. At the same time, it downplays values associated with experimentation, learning, playfulness, and everyday care practices. Established HTA procedures highlight costs and effects as the most relevant values of diagnostics. What emerges from such a focus on the professionalized specialist care setting is a logic of addressing value that revolves around compiling high-quality evidence according to the established hierarchy of Evidence-Based Medicine (EBM). The values to be addressed, therefore, are regarded to be more or less pre-given, while the collection of evidence is delegated to experts and specialists. Although some of these specialists, most importantly doctors, are also users of the technology, their role is largely confined to probing into the value of the device along preconfigured dimensions. Other, less specialized users such as nurses or patients are not perceived to be central actors in this process. The valuing practice that emerges from these analyses resembles a prosthetic logic: novel diagnostic devices should be optimized in such a way as to deliver the best value within the pre-defined mould of existing clinical standards. The exploration of new values is considered to be ancillary to cost effectiveness and clinical impact. This demonstrates how in professional clinical settings the performance of a new technology has to prove its effects on established values, before its wider impact can be explored. As a side effect, this logic imputes only limited agency on both the emerging devices and most of its users in defining new values that might be more suitable to assess new, emergent networks in distributed care settings. It shows the practices and pitfalls of mainstream HTA practices and the underlying logic of evidence-based medicine.

We are certainly not the first to highlight the problematic aspects of established HTA procedures (Faulkner 1997, 2009; Lehoux 2006 are excellent entries into the prolific body of literature in this regard), nor are we the first to show that HTA practices are often messier and more fractious than their textbook versions suggest (e.g. May 2006). Instead, our interest in HTA has been triggered by our own involvement with diagnostic innovation, where in particular the notion of evidence in the strict sense suggested by EBM seems to permeate policy debates.

In Callon's terms, health technology decisions based on the traditional HTA logic are likely to produce technology that focuses on changing sociotechnical assemblages in diagnostic care along pre-set dimensions. Individual agency in the sphere of users and use is framed to be disciplined and passive, as erratic usership would disturb the precious relationship between costs and health effects so carefully established before. Accordingly, health policy decisions based on established HTA practices will work to discipline individual agency; they are not equipped to deal with the constant experimentation and learning in the absence of evidence that is so typical for emerging diagnostic innovation processes. The case of Miller et al illustrated this experimental dynamics for new diagnostic innovations targeting the clinic. The researchers in these cases gradually learned to perceive the users of the new diagnostic technology—for example, clinicians, nurses, or patients—as agents that are essential for the process of valuing the diagnostic technology. This way of recognizing value as something open and fluid suggests implementation strategies that ascribe the ability to experiment and explore new practices on users of diagnostic innovations. Such implementation strategies understand that users are active agents in innovation processes, and give them space to experiment and to learn about the value of a technology. It demonstrates that for diagnostic innovation, it would be crucial to broaden HTA practices in such a way that they are able to deal with this experimental co-evolution of values and evidence. Otherwise, HTA runs the risk of prematurely cutting short diagnostic innovation with promising prospects but limited available evidence, missing out on important values in various healthcare practices, which take into account the various roles of involved stakeholders.

To conclude, we use these insights to outline advice for HTA practices that might better fit the conditions of emerging diagnostic practices, give rise to habilitation interventions, and contribute to configuring users of diagnostic innovations as proactive consumers or citizens able to fully participate in policy decisions about health innovation. This suggests that the range of values itself, however broadly defined, should not be the main concern of adapting HTA exercises to the realities of emerging diagnostic innovations. Rather, the logic of valuing in diagnostic innovation processes should be broadened and be more flexible,

to embrace uncertainties, elusiveness, controversies, and diversity, to include experimentation and the use and diffusion of new biomedical technologies (see also, Boenink 2012). For emerging diagnostic innovations, the health value they will ultimately be able to deliver depends on learning processes that stretch well into the diffusion and use phase of the technology. Prosthetic values explored independently of technology are not able to deliver this. What we need, instead, are values that incorporate a habilitation logic—that is niches for experimentation and joint probing into the value of diagnostic innovations. Many heterogeneous actors should have a voice in which values are important in a HTA, not defining beforehand what a good technology should do, but together, articulating what is necessary for different involved actor groups. Dealing with early diagnostics and coping strategies, patients, and formal and informal caregivers as end users of diagnostic technologies seem, to us, especially important. Taking their values on board, and allowing them a voice in HTA practices and outcomes strikes us as crucial. So, agency and specific positions and roles of actors responsible need to be taken into account, to move towards more *responsible* forms of HTA. Current discussions in HTA fall short of delivering such broader notions of logic of valuing, although some claims for constructive forms of HTA point to the right direction (see also Douma et al. 2007). Further research is needed on how habilitation plays out across different distributed diagnostics settings.

Summarizing the above, this chapter emphasized paying careful attention to the complex interrelation between practice, values, and technology and focused on how to redesign common HTA procedures under the label 'responsible innovation', to better fit actual innovation practices as well as societal concerns about innovation. As shown, innovations in the field of diagnostics are not just geared towards efficacy, safety, quality, and low costs, but also imply specific social expectations, values, and norms. It is an emerging key challenge of responsible diagnostic innovation to be simultaneously prosthetic and habilitating, that is, it should enable individuals to follow preconfigured scripts as well as empower them to explore their needs and preferences, in order to provide stakeholders with the necessary agency to negotiate health and illness.

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# 14

# Diagnosing Alzheimer's Disease: How to Innovate with Care

Marianne Boenink, Harro van Lente, and Ellen Moors

This volume has explored the global attempts to innovate the diagnostics of Alzheimer's disease (AD), by means of biomarkers or otherwise. This exploration exceeded the confines of memory clinics and research centres, but also included sites such as newspapers, policy documents, patient groups, general practitioners, and online diagnostics tools. The diversity of sites reflects the many faces and manifestations of AD: it is not just one thing but many. This diversity brings along that the very notion of the disease and how it should be addressed are elusive. Diagnosis can take many

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forms and play different roles, and is not equally important for everyone. Moreover, exploring the different sites where AD manifests itself shows that ideas of what AD is and how its diagnostics should be improved often are contested. Innovation of AD diagnostics, so much is clear, takes place in an elusive and controversial field. How to answer, then, the question about the desirability of emerging diagnostic technologies?

Concerning the desirability of AD diagnostics innovation, new technological tools, and their use practice, the first point to make is that several innovations are aimed for at the same time. In the biomedical domain, molecular biomarker tools raise high hopes, but as Boenink shows, such tools can still have multiple functions. Outside biomedical R&D, we see governments introducing national screening policies using low-tech cognitive tests (Swallow). And Egher and Wyatt discuss how outside the traditional medical domain, a myriad of (self-) diagnostic tools has become available on the Internet. Interestingly, all these (aimed for) innovations focus on *earlier* diagnosis. This fits, as Leibing and Whitehouse show, with the trend towards Alzheimer prevention, whether by pharmaceutical, lifestyle, or environmental interventions. A recurrent theme throughout the preceding chapters is, nonetheless, that earlier diagnosis is not necessarily better—partly because the possibilities to act on diagnosis are rather limited, but also because a diagnosis is often not necessary to take action, and because not all people feel the need for early diagnosis and taking preventive action.

The preceding chapters also show, however, that when discussing the desirability of early diagnosis, it is crucial to ask *what* exactly is being diagnosed. All these tests diagnose different phenomena, and may serve different purposes. Before passing judgement on the desirability of any diagnostic innovation, them, we had better determine first *what* precisely is being diagnosed, how *reliable* the resulting information is, but also how *relevant* and how *useful*. As the authors discussing them made clear, each of these innovations has its own advantages and limitations. This also implies that in each case, different conditions for responsible innovation are required, which have been discussed in the separate chapters. Together, these chapters point out that the question 'is it desirable?' cannot be answered in the same way for all innovations and all practices involved. Formulating the question about desirability in such a general way brings

confusion in both what 'it' is and what 'desirable' is—as both depend on the practices in which they gain meaning, salience, and relevance.

What does this observation imply for the ambition to make Alzheimer diagnostics innovation more 'responsible'? Should we give up on the attempt altogether? Not at all, but it does show that stimulating responsible innovation is more complicated and harder than is sometimes suggested. Let us reiterate first how we already modified some basic tenets of responsible innovation literature in our introductory chapter, before harvesting the insights gained from the set of chapters. Responsible innovation, we said in our introduction, means innovation contributing to acceptable societal goals and values. We referred to Stilgoe and colleagues, who pointed out that such innovation requires *anticipation*, *reflection*, *stakeholder inclusion and deliberation,* and *responsiveness*. We also indicated, however, that responsible innovation in our view should be approached in *a practice-based* way. Both values and innovations are not simply there, but are expressed and sustained in practices. One of the implications is that to stimulate responsible innovation, one should not focus only on potential future impacts of a promised (but uncertain) innovation. In this volume, we therefore investigated how emerging innovations already impact the present. For instance, R&D practices are based on ideas about what existing diagnostic practices look like, what problems they encounter, and how to improve diagnostics. While these ideas may hold or not in the future, they already have consequences for diagnostics practices now. At the same time, actors involved in existing practices of diagnosing, caring for, and living with AD are often also working on innovation themselves, actively trying to improve that practice.

Our practice-based approach of responsible innovation stresses, moreover, that the values at stake in innovation do not exist as abstract entities, apart from and prior to practices. Nor are they just 'there', easily accessible to stakeholders. Instead, values are enacted in ways of doing within existing practices as well as within attempts to innovate these practices. To make the values implied in diagnosing AD accessible for reflection and deliberation, we investigated which values are made to matter in both current practices dealing with AD and dementia and in R&D practices dedicated to innovate diagnosis. This is the epistemic and normative starting point of all chapters in this volume.

The overall idea behind our practice-based approach of responsible innovation is that an analysis of the values, concepts, and potential conflicts implied in the myriad of practices dealing with AD and dementia brings to the fore what is, and could be at stake when innovating diagnostics. Such an analysis could then inform and facilitate further reflection and deliberation among those involved, and should ultimately enhance responsiveness to such values. The preceding chapters explored and analysed a wide variety of practices concerned with AD, and/or with diagnosis. We deliberately included practices dealing with AD and with dementia more broadly conceived, since the notions and practices of AD are not neatly delineated from those of dementia at large. Our exploration ranged from different scientific research practices in Part I, diagnostic practices (both in and outside the medical domain) in Part II, a variety of societal and policy practices in Part III, to practices of diagnostics innovation in general and its assessment in Part IV. As stated above, our exploration of this variety of practices clearly showed that it does not make sense to formulate conditions for responsible innovation of AD diagnostics on a general level. What other insights came to the fore in the preceding chapters, and what did we learn about responsible innovation in the AD field and more generally?

## Elusive Concepts, Elusive Values

First of all, this volume testifies to the elusiveness of the very core notions at play in innovating AD diagnostics. The terms 'Alzheimer's disease', 'dementia', 'disease', 'biomarker', but also 'diagnosis', and 'diagnostic practice' are all used in a variety of ways. As a result, discussions on what constitutes good diagnostics and care for people with AD or dementia are often very slippery. The chapters by Whitehouse, Leibing, and Boenink discuss how the concept of AD has been ambiguous from its conception and how the meaning ascribed to the term has evolved over the years. Technological developments (both in diagnostics and in therapy) have co-shaped this evolution. It need not come as a surprise, then, that recent developments in diagnostics tend once more to shift the meaning of AD and related concepts. These chapters also show, however, that the hope

that molecular research will finally put an end to the confusion might be vain. As yet, such research adds to, rather than decreases ambiguity. This is partly because the concept of a 'biomarker', while keeping its generic promise of being a stepping stone to understanding and solutions, also appears to be elusive. What part of 'bio' does it 'mark'? And how is this related to pathologies and patient complaints?

Current attempts to standardise and discipline the use of terminology, for example, in the different proposals for new diagnostic guidelines, at least acknowledge that the term AD should be used with more care. Such proposals wrongly suggest, however, that defining concepts is just a matter of reviewing the scientific evidence and updating the vocabulary to match with the most recent facts. An important finding in several chapters in this volume is that *concepts and interpretive frameworks are usually closely bound up with both the practices in which they are used and the values pursued in those practices*. This is evident in diagnostic practices, but also in practices of caring for or about those suffering from AD and dementia.

As for diagnostic practices, several chapters illustrate how the organisation of screening and diagnosis builds on a specific view of the phenomena AD and dementia, and prioritises specific problems and values. The chapter by van der Laan, for example, shows how different views of 'diagnosis' co-exist, albeit often uneasily, leading to different types of 'AD' being diagnosed. She shows how these views not only ascribe different aims to diagnosis (building on different values), but also how they may lead to a different organisation of diagnostic practice. Egher and Wyatt, focusing on online diagnostic tools, highlight how these tests frame AD as a memory problem, and thus, prioritise cognitive functioning. Swallow in her analysis of the use of cognitive screening tests shows how diagnosis in a memory clinic is shaped by particular ways of using these tools, and how such use realises specific values that tend to get lost when the same tests are used as systematic, standardised screening tools.

Looking beyond diagnostic practices to other sites and practices dealing with AD and dementia, similar connections are visible. Both Moser and Pols and M'charek show how AD and dementia are made to matter in many different social practices, and how the framing of AD and the problems it poses differ widely among these practices. They also make clear how these practices often sit uneasily with one another. Cuijpers discusses

how the heterogeneity of framings of AD, dementia, and diagnosis may lead to explicit controversy at the public and political levels, when decisions are made about the best direction of a national dementia policy. Controversies about what AD actually is, which problems it poses, and how it should be dealt with at this point became public and outright political. The elusiveness and heterogeneity of both the concepts and interpretative frameworks at play, and the values at stake pose a major challenge when aiming for 'responsible innovation'.

The least one can say is that any dedicated attempt to innovate AD diagnostics is an intervention in a very complex and shifting field of only partly overlapping practices. Ideas of what counts as 'good diagnosis' vary among these practices. These ideas are, moreover, associated with different conceptualisations of the phenomenon to be diagnosed, the technologies available, and the way these are used. Concepts, interpretative frameworks, routines, organisation, and technological tools are all so intertwined that changing one piece of the conglomerate tends to directly influence the others. Innovation is like starting to pull at or replace one thread in a tight-woven fabric, thus affecting all the other threads as well. Innovating with care means, then, that one tries to become aware of the fabric *beforehand*, instead of realising it is tight-woven only after one started pulling.

In terms of the four dimensions distinguished by Stilgoe and colleagues, then, our practice-based approach of responsible innovation shows that anticipation requires reflection, not only on the future, but first and foremost, on the present. Only by carefully exploring present practices, it is possible to anticipate the potential impact of emerging science and technologies and to respond to the most urgent and relevant needs in current society.

## Controversies Are Here to Stay

A second conclusion to be drawn from the chapters in this volume is that the controversies about biomedical research and diagnostic innovation are here to stay. As observed above, the different outlooks and perspectives that come with the rich set of practices dealing with AD and

dementia often sit uneasily with each other. In some cases, this results in explicit controversies; in other cases, the perspectives conflict without causing uproar. As noted above, it is unlikely that the developments in biomedical research and innovation described in Part I of this book will be able to settle these disputes. Both Leibing and Boenink point out how hard it is to establish a convincing connection between biological and clinical observations in the complex and shifting AD field. Other authors, such as Swallow, Moser, and Pols and M'charek, argue that biomedical research tends to cater for needs that may not be shared (or similarly prioritised) by patients, caregivers, and others dealing with AD and dementia. Both arguments explain why even (hypothetical) success of biomedical researchers in 'improving' diagnostics is not a guarantee for general acceptance, and thus, for smooth innovation.

Moser, Cuijpers, and Pols and M'charek all point out that the coexistence of different conglomerates of interpretative frameworks, needs, and values is not necessarily peaceful. They interfere with each other, so that the activities of one may reduce the opportunities of the other to flourish and improve. This means that adjudicating the 'facts' of what AD pathology actually consists of, the aim often ascribed to scientific research into AD, is not a neutral endeavour. Rather, as suggested above, the attempt to establish biomedical 'facts' should be regarded as an intervention in a highly contested field, which will provoke the presentation of 'counterfacts' from clinical or other social practices—and the outcome of the ongoing struggles is uncertain.

This is another reason why the exhortation to 'innovate with care' seems particularly apt in the context of innovating AD diagnostics. If there are so many different practices, frameworks, and values at stake, if these are not easy to combine, and if reinforcing one (e.g. improving the accuracy of identifying AD pathology) may actually diminish others e.g. the social acceptance and possibilities to live with dementia), we had better develop non-naïve ways to deal with heterogeneity and controversy. This requires, again, a reflective awareness of the differences at stake, both on the level of diagnostic practices, and on the level of innovation policy. In addition, we need carefully crafted strategies to deal with the differences in a way that acknowledges the interlinkages of interpretative frameworks, practices, and values, and acknowledges the normative and

political implications of any proposal for innovation. Pleas for responsible innovation often suggest that it is crucial to give all stakeholders a voice in decision making on what and how to innovate. The assumption that this will automatically result in a harmonious innovation process seems rather naïve, however, in particular in the complex setting of AD diagnostics. Two examples from chapters in this volume illustrate why.

Van der Laan discusses how in Dutch AD diagnostic practice, different modes of diagnosing co-exist. In which practice a specific patient ends up depends on rather contingent factors, such as geographical distance, the willingness of professionals to refer to colleagues, and how articulate patients and informal caregivers are in developing and communicating their preferences. Against this background, strengthening the right of patients and caregivers to decide about their own diagnostic trajectory might be considered an improvement. However, as van der Laan argues, well-considered choices by patients presuppose that they know what the options are. Since the options and values perceived by patients and caregivers depend on the interpretative frameworks used, equal public visibility of all different views on what AD is and what diagnosis means is crucial. In a similar vein, Cuijpers, in her chapter, argues that composing a research agenda by simply combining the many different frameworks and approaches of AD and dementia in one programme is a rather naïve way to deal with the differences. To start with, the different perspectives do not automatically and without further support add up to a coherent whole. Moreover, this approach ignores that different approaches and frameworks may actively counteract each other. And it does not acknowledge the power differences between frameworks: some may be further articulated and have many more resources than others.

Again, responsible innovation requires carefulness. Where Stilgoe and colleagues stress the importance of stakeholder involvement and deliberation, our practice-based approach suggests that this is definitely not a panacea to solve conflicts. *The effectiveness of such involvement hugely depends on a careful crafting of the conditions for deliberation.* Paying attention to the worlds different stakeholders live in, to the intricate fabric of interpretative frameworks, values, and practices, and to the power relations between practices, is crucial to ensure that the voice of

all stakeholders is sufficiently audible and taken seriously. Ethnographic research may help stakeholders to articulate their concerns or to explain why it can be quite hard to arrive at shared viewpoints.

## Care and Responsibility in Practice

The third and last issue to address is what responsible innovation in such an elusive and controversial domain might mean. First of all, several chapters in this volume point to irresponsibilities in the field of biomarker development for AD. Whitehouse, for instance, points to the apparent agenda-setting power of pharmaceutical interests in AD research. He argues that the whole field of AD and biomarker research suffers from structural flaws, and his appeal is to give attention to systematic and cultural factors that create irresponsible individual and organisational behaviour. Leibing, partly in contrast, points to the predominance of 'shortcuts', both in biomedical research and in social science. Such shortcuts may engender irresponsible reasoning and outcomes, at the expense of patients and caregivers. Another source of irresponsibility is related to the endemic uncertainties of the field, in combination with the despair and hopes of patients. Boenink argues that epistemic responsibility is at stake here, a responsibility to account for the concepts and terms that researchers and others use.

Our practice-based approach of responsible innovation also brings out very clearly, however, that the search for responsibility does not have to start from scratch. Many chapters make clear that by looking closely at existing practices, responsibility and care can be found, sometimes in unexpected corners. Remember how the interviewers in the cohort studies discussed by Milne and Badger, whose primordial task is to collect data, care for the needs of participants and are willing to make extra efforts. Van der Laan, Swallow, and Pols and M'charek all show how clinicians adjust diagnostics to the needs of patients—provided the organisational conditions are right. Egher and Wyatt illustrate that the Internet as online self-testing diagnostic tool can also lead to more socialised, playful ways of care. Such instances of caring activities could actually be used to strengthen possibilities to take responsibility for improving the practice

one is part of. This might take the form, as Pols and M'charek suggest, of initiating improvement within a practice. One could also think of facilitating these actors to bring their concerns to the attention of other actors involved in innovation of AD diagnostics.

Here, another observation recurring throughout the book is relevant. Many chapters show how practices of research and care actually (maybe increasingly) overlap. Pols and M'charek point out, for example, how research is not just an activity that is exclusively located in laboratories, but is entangled with and actually *needs* patients. Miller and colleagues also show how due to the translational imperative, the sharp distinction between research and clinical care is blurring. For example, requirements for informed consent are more extensive and complex when patients are involved in research compared to clinical practice. Although Miller et al. rightly point out that basic norms to protect patients should not be discarded, this increasing entanglement of research and care also offers opportunities to stimulate exchange and deliberation on what counts as good diagnostic practice and what improvements to strive for (and how). Along this line of reasoning, Egher and Wyatt suggest that it might be a good idea to create feedback channels from patients and informal care givers to medical professionals about the validity and predictability of tests. Boenink proposes that biomedical researchers might be stimulated to reason backwards from patients' and caregivers' needs to determine research priorities.

The practice-based approach of responsible innovation brings out, then, that responsible innovation does not necessarily require completely new structures and activities. *By looking at practices, we become more aware where and how actors already care for the worlds they are engaged in and where existing responsiveness could be further strengthened, facilitated, or aligned.* Careful attention to existing practices may also lead to ideas for novel activities that help to align ongoing attempts to innovate, within and among practices. In contrast with the approach outlined by Stilgoe and colleagues, we would like to argue that responsiveness is not only at stake when the stakeholder deliberations are completed. Responsiveness, in the sense of a sincere attempt to understand and care for the concerns and needs of those suffering from AD and dementia, is a precondition for productive exchange and deliberation about diagnostic innovation. This is

particularly relevant because of the elusive character of the phenomena and experiences at stake.

This does not imply, however, that existing practices dealing with AD are hardly problematic. As we observed above, there definitely are irresponsible tendencies in current biomedical research. Many of the preceding chapters show all too clearly that any practice dealing with AD is unavoidably political and controversial. Moreover, there are huge power differences among these practices when it comes to bringing their concerns to the fore and making themselves heard. When bringing stakeholders together to deliberate innovations, then, it is crucial to create conditions for a fair and balanced deliberation about innovations. Maybe even more important, however, as Pols and M'charek point out, is to be aware that practices themselves already shape who is represented. Critical attention needs to be paid to the political character of any problem formulated.

In addition to strengthening *de facto*, existing opportunities to innovate with care, we do need *dedicated* ways to shape innovation. As Miller and colleagues point out, a certain degree of robust, legitimate, and accountable regulation of diagnostic practices is indeed desirable for 'innovating with care', Our evaluation of the merits of practices and their innovations, does challenge the traditional HTA-based evaluation of new diagnostic devices, however. Swallow discusses how standardisation of diagnostic practices may lead to a loss of values. Moors and Peine argue that we need to develop more flexible forms of assessing emerging technologies, which respond to emerging changes in the actors, values, roles, and responsibilities at stake. Ultimately, such assessment would reflect the creative character of innovation.

## Innovating with Care

To summarise, what does our exploration of care and responsiveness in practice offer for the *specific* question about the desirability of emerging technologies for the diagnosis of AD, and for the *general* ambition of responsible innovation at large? About the specific concern—the desirability of early diagnosis of AD—four conclusions stand out. First, given the elusiveness of concepts and the feeble bridges between biology and

clinic, it is unlikely that novel techniques for early diagnosis of AD will bring clarity and certainty for all. Second, given this lack of certainty and the lack of medical cure, but also given alternative, non-biomedical approaches of AD, the very idea of early diagnosis is not uniformly welcomed as an improvement. Third, the wide variety of alternative, non-biomedical ways to deal with AD in (daily) practice often tastes defeat in the competition with the dominant biomedical routes of framing and solving 'the' problem of AD—conceptually, morally, financially, and politically. Fourth, any meaningful attempt to do justice to the many stakeholders in the case of AD has to account for this fundamental disparity between biomedical and non-biomedical approaches of AD. Just inviting patients and informal caregivers to stakeholder deliberations about any biomedical innovation will not do. The interpretative frameworks and values implied in non-biomedical practices need to be supported and strengthened for these stakeholders to acquire an equal say in the deliberations.

The practice-based approach of responsible innovation, then, also offers valuable insights for the *general* quest of responsible innovation. In the introduction, we argued that the current frameworks or responsible innovation are, in particular, concerned with the process, with a focus on the involvement of stakeholders. While this is a sensible concern, this volume stresses that such a focus abstracts from—and hence neglects—the diversity of practices. After all, stakeholders do not speak for themselves; they speak about, through and of behalf of practices. And the multiplicity of practices, as we argued above, brings along the elusiveness of concepts and the contestations of framings and values. One implication is that the aim of consensus often cannot be reached and need not be reached. What should be reached is an alignment of practices, starting from the awareness that power differences may favour particular values and interpretative frameworks (including concepts and taxonomies) at the expense of others. What is needed—from researchers, patients, caregivers, and policymakers—is reflection on one's own and other perspectives, responsiveness to the needs and concerns these perspectives care for, and the willingness both to deal with basic epistemic and moral uncertainties, and to redress power differences. Anticipation and deliberation can only flourish on the basis of such reflection and responsiveness.

In a field as elusive and controversial as AD diagnostics, it would be both naïve and rash to suggest that there is one procedure that guarantees responsible innovation. In view of the basic epistemic and moral uncertainties at play, it seems wise to 'innovate with care'. We can now conclude that this entails a dual direction: first, understanding how values and concepts are manifested in practices and what activities of care already follow from this, and second, considering how practices relate to each other, how this may favour some values and interests and undermine others, and how resulting imbalances may be addressed—a political matter indeed. Armed with such understanding and awareness, stakeholders need to collectively deliberate which innovations are worth pursuing, in both dedicated and de facto, informal ways. Innovating with care, after all, is a joint responsibility.

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