



Assessing the Impact of Applications of Digital Health Records on Alzheimer's Disease Research: Workshop Summary

DETAILS

46 pages | 6 x 9 | PAPERBACK

ISBN 978-0-309-37972-4 | DOI: 10.17226/21827

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**ASSESSING THE IMPACT
OF APPLICATIONS OF
DIGITAL HEALTH RECORDS
ON ALZHEIMER'S
DISEASE RESEARCH**

WORKSHOP SUMMARY

Lisa Bain and Sheena Posey Norris, *Rapporteurs*

Forum on Neuroscience and
Nervous System Disorders

Board on Health Sciences Policy

Institute of Medicine

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Washington, DC

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THE NATIONAL ACADEMIES PRESS • 500 Fifth Street, NW • Washington, DC 20001

This activity was supported by the Alzheimer's Association; Brain Canada Foundation; Contract No. HHSN26300026 [Under Master Base # DHHS-10001292] with the Department of Health and Human Services' Food and Drug Administration and National Institutes of Health through the National Center for Complementary and Integrative Health, National Eye Institute, National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, National Institute on Aging, National Institute on Alcohol Abuse and Alcoholism, National Institute on Drug Abuse, and NIH Blueprint for Neuroscience Research; Contract No. VA240-14-C-0057 with the Department of Veterans Affairs; Eli Lilly and Company; Foundation for the National Institutes of Health; the Gatsby Charitable Foundation; GlaxoSmithKline, Inc.; Johnson & Johnson Pharmaceutical Research and Development, LLC; Lundbeck Research USA; Merck Research Laboratories; The Michael J. Fox Foundation for Parkinson's Research; the National Multiple Sclerosis Society; Contract No. BCS-1064270 with the National Science Foundation; One Mind for Research; Orion Bionetworks; Pfizer, Inc.; Pharmaceutical Product Development, LLC; Sanofi; the Society for Neuroscience; Takeda Pharmaceutical Company Limited; and the Wellcome Trust. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.

International Standard Book Number-13: 978-0-309-37972-4

International Standard Book Number-10: 0-309-37972-5

Additional copies of this report are available for sale from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; <http://www.nap.edu>.

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Printed in the United States of America

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2016. *Assessing the impact of applications of digital health records on Alzheimer's disease research: Workshop summary*. Washington, DC: The National Academies Press.

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Reviewers

This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published workshop summary as sound as possible and to ensure that the workshop summary meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this workshop summary:

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SIMON LOVESTONE, University of Oxford
MATS SUNDGREN, AstraZeneca R&D
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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the workshop summary before its release. The review of this workshop summary was overseen by **ERIC B. LARSON**, Group Health Research Institute. He was responsible for making certain that an independent examination of this workshop summary was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this workshop summary rests entirely with the rapporteurs and the institution.

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1

Introduction and Overview¹

Health information technology is providing patients, clinicians, and researchers with access to data that will enable novel approaches to science and medicine. Digital health records (DHRs)—including electronic health records (EHRs) and electronic medical records (EMRs)—are capable of being shared across different health care settings for the examination of possible trends and long-term changes in a patient's disease progression or status as well as the effectiveness of the health care delivery system. While the prevalence of paper records remains high, there has been a rapid trend toward the digitalization of medical and health records in many countries (Coorevits et al., 2013). In its 2001 report, *Crossing the Quality Chasm: A New Health System for the 21st Century*, the Institute of Medicine's (IOM's) Committee on Quality of Health Care in America identified the need for increased use of information technology as central to improving the nation's health care system (IOM, 2001). Specifically, the committee recommended a “renewed national commitment to building an information infrastructure to support health care delivery, consumer health, quality measurement and improvement, public accountability, clinical and health services research, and clinical education” (IOM, 2011, p. 17). Recognizing the importance of information and communication technology for health and well-being, the

¹The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the Institute of Medicine, and they should not be construed as reflecting any group consensus.

European Commission adopted the eHealth Action Plan (2004–2011 and 2012–2020) to encourage more patient-centered services by Member States through the use of devices and technologies (European Commission, 2004, 2012). The plans included recommendations for integrated health information networks, electronic patient health cards, electronic prescriptions and referrals, among others.

DHRs are widely viewed as essential for improving health, reducing medical errors, and lowering costs (Hillestad et al., 2005). In addition, many participants noted that DHRs hold great value for the medical research enterprise. The National Institutes of Health promotes research needed to “guide design, use, and evaluation of an ever-expanding array of health information technologies,” with the Precision Medicine Initiative² being one example of an opportunity to employ DHRs to creatively use health information (Collins, 2015). Additionally, a presidential commission in 2010 advocated investment in infrastructure to enable “the robust exchange of health information” as a means of improving public health and medical research (President’s Council of Advisors on Science and Technology, 2010, p. 3). As part of the American Recovery and Reinvestment Act of 2009, the Health Information Technology for Economic and Clinical Health (HITECH) Act provided funds to promote a national health information network facilitated through the use of interoperable DHR technologies. Similarly, the European Commission released a recommendation on cross-border interoperability of EHRs by Member States to encourage the secure exchange of patient data throughout Europe (European Commission, 2008). For example, the European Patients–Smart Open Services (epSOS)³ strives to develop “a practical eHealth framework and information and communications technology (ICT) infrastructure that enables secure access to patient health information among different European healthcare systems.” In 2011, the Forum on Drug Discovery, Development, and Translation held a workshop titled “Envisioning a Transformed Clinical Trials Enterprise in the United States: Establishing an Agenda for 2020,” which called for the increased use of DHRs as a means of harnessing scientific evidence for improved medical decision making (IOM, 2012).

While the potential clinical and research opportunities using DHRs are vast, there are several challenges to consider. First, the quality of the

²See <http://www.nih.gov/precisionmedicine> (accessed September 10, 2015).

³See <http://www.epsos.eu/home/about-epsos.html> (accessed November 11, 2015).

data, with regard to their “correctness, completeness, and accuracy,” might be hindered, depending on how the data are entered into the database and by whom (Coorevits et al., 2013). This, in turn, might influence the interoperability across systems to effectively communicate with one another, which can be important for large, multisite research studies. In addition, there are a number of issues related to the privacy and confidentiality of patient data and the security of DHR databases (Coorevits et al., 2013; Ozair et al., 2015). Given that these databases have the potential to house the complete medical and health information of individuals, the potential misuse, de-identification, or breaching of these data may have serious implications.

WORKSHOP OBJECTIVES

On July 20, 2015, the National Academies of Sciences, Engineering, and Medicine’s Forum on Neuroscience and Nervous System Disorders held a public session at the 2015 Alzheimer’s Association International Conference in Washington, DC, to assess the impact of DHRs on Alzheimer’s disease (AD) research. “AD is the most common cause of dementia in older adults” (NIA, 2015a). An estimated 46.8 million people worldwide are currently living with dementia, and the prevalence is expected to double every year for the next 20 years (Prince et al., 2015). Given the few therapies currently available to treat the symptoms of AD, compared to other central nervous system disorders, this session explored how DHRs may be used to help improve clinical trial design and methodology for AD research.

The session brought together an international group of experts in translational, epidemiological, and health services research along with an ethicist and representative of a big data analytics company. While there are a number of potential uses of DHRs, these speakers, along with other session participants, discussed some of the currently available DHR databases that are being mined to better understand the progression of AD and design more effective clinical trials. Session moderator Daniel Burch, vice president and global therapeutic area head for neuroscience at Pharmaceutical Product Development, charged participants to explore the future needs and challenges presented by the diversity and size of these databases, as well as ethical, societal, and legal concerns raised by the sharing of personal health data (see Box 1-1).

BOX 1-1**Statement of Task**

An ad hoc committee will plan a public session in workshop format at the 2015 Alzheimer's Association International Conference on Alzheimer's disease (AD). This workshop will explore how digital health records can be applied to support research on AD. Specifically, presentations and discussions will be designed to help participants

- examine current and future applications of digital health records and their impact on clinical trial design;
- consider scientific opportunities and challenges associated with applying digital health records to inform AD research design and methodologies;
- discuss infrastructure needs and lessons learned from other medical records-linkage systems; and
- explore what kinds of ethical, societal, and legal issues should be considered in applying digital health records on AD research.

The committee will develop the agenda for the workshop session, select and invite speakers and discussants, and moderate the discussions. A summary based on the presentations and discussions held during the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

ORGANIZATION OF REPORT

This report summarizes presentations from speakers and discussions among session participants. In Chapter 2, three case studies are presented as examples of how DHRs are being used to better understand the natural history of AD and advance therapy. This chapter also describes existing DHR infrastructure and those in development. Chapter 3 provides an overview of the ethical, legal, and societal issues related to the use of DHRs. Chapter 4 focuses on the future of DHR use in medical research, considering not only the potential value but the barriers as well.

POTENTIAL IMPACT OF DHRs ON AD RESEARCH

To date, only five medications have received Food and Drug Administration approval to treat symptoms of AD, despite substantial investment by the pharmaceutical industry (Alzheimer's Association, 2015). While additional symptomatic therapies will be necessary for all stages of disease, several participants expressed the urgent need for disease modifying and secondary prevention therapies. In light of a string of failed clinical trials for AD drugs, some companies have shifted resources from central nervous system diseases to other disease areas with a more promising return on investment. Many factors have likely contributed to the lackluster performance of AD drugs in development (Cummings et al., 2014), and one emerging consensus is that effective therapies of AD will require targeting early-stage disease (Sperling et al., 2011).

Conducting trials in the preclinical stages of disease poses unique challenges with regard to identifying and enrolling sufficient numbers of appropriate subjects and assessing treatment efficacy in the absence of symptoms. Developing the tools and resources needed to address these challenges will require a more detailed understanding of the natural history, pathobiology, and heterogeneity of the disease, which will be achieved through the analysis of large amounts of data from a broad spectrum of the population, said several participants.

DHRs offer a potentially powerful, enormous, and rich source of data for such studies. According to Simon Lovestone, professor of translational neuroscience at Oxford University, reusing data collected from existing population cohort studies and clinical databases, combined with data from a variety of other sources (discussed further in Chapter 2), can provide a means to understand the progression of disease from its earliest stages among real-world participants, rather than the more rarified group of individuals who volunteer for clinical studies.

TOPICS HIGHLIGHTED BY INDIVIDUAL SESSION PARTICIPANTS

The Value of DHRs

- One emerging consensus is that effective therapies for AD will require targeting early-stage disease, but this requires a better

understanding of the natural history, pathobiology, and heterogeneity of the disease. DHRs provide a rich source of these types of data from real-world participants, and can be married with other types of data to more fully understand disease progression (Lovestone, Rocca).

- By linking data from population observations, investigators can extract meaningful information that might be used to inform clinical and basic science research (Bynum, Rocca).

Examples of Potential Infrastructure Needs and Challenges

- DHRs include multiple types of data (including coded and uncoded or narrative or contextual data) and are stored in varied databases, presenting challenges in terms of access and use (Lovestone).
- Existing and developing infrastructure relevant to AD include, but are not limited to, large databases managed by the Rochester Epidemiology Project (REP) and the Innovative Medicines Initiative (IMI)-European Medical Information Framework (EMIF), as well as Medicare claims data (Bynum, Lovestone, Rocca).
- Regulations intended to protect the privacy of data may have the unintended consequence of stifling international collaborative medical research (Powell).
- Advances in data analytics enable researchers to move beyond correlations to better understand mechanisms and cause-and-effect relationships (Khalil).
- Researchers must respect the intentions of the persons from whom the data were derived, but at the same time ensure that data are used as widely as possible for the best possible purposes (Lovestone, Powell).

2

Building Infrastructure to Enable Data Sharing and Management

Highlights

- Many types of data are captured in digital form and are stored in diverse databases; this variability presents challenges in terms of accessing and using the digital health record (DHR) data (Lovestone).
- Fifty years of data collected by the Rochester Epidemiology Project (REP) have enabled the study of the prevalence and incidence of Alzheimer's disease (AD) and mild cognitive impairment, and the identification of subjects for clinical and biomarker studies (Rocca).
- The European Medical Information Framework (EMIF) project aims to integrate data from multiple existing cohorts in Europe, including 500,000 participants in the U.K. Biobank (Lovestone).
- The European Prevention of Alzheimer's Disease (EPAD) study will build on EMIF to establish a patient registry, identify a cohort of trial-ready individuals, and draw from that cohort for a standing proof-of-concept trial of AD therapies (Lovestone).
- Medicare claims data offer another rich source of research data on more than 50 million Americans. Linkage of Medicare claims data to other data sources provides added value and may be used for "reverse translational research" to generate hypotheses on treatment efficacy and side effects (Bynum).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among session participants.

Medical records have long been used for epidemiological research around the world. In the early 1960s, physicians at Oxford University began organizing and linking medical records collected by Britain's National Health Service with administrative records related to birth, death, hospitalization, etc. (Acheson, 1964). Similar efforts to link and store medical and administrative data have been implemented in Australia (Holman et al., 1999) and Canada (Doiron et al., 2013). In the United States, the use of DHRs for research has lagged, in part because of privacy concerns, including those explored in Chapter 3 (Herrick et al., 2010).

Digital health data exist in varied formats (including coded and uncoded or narrative or contextual data) and may be sourced from multiple databases, including those established for epidemiological and other research studies, Medicare administrative data, social networks, and market data. A few participants noted that integrating these data to maximize learning presents many challenges given the heterogeneity in data types, the lack of common nomenclature and ontology, the widespread distribution of data warehouses, and the enormous amount of data collected. One challenge of accessing data from preexisting datasets is that the data are housed in multiple research environments that are private and remote and cannot be moved. Several different systems have emerged to enable access and analyses of these data through trusted third parties, which enable users to query the data and receive analyses without actually having access to the raw data. A challenge not exclusive to DHRs, a recommendation in the IOM's 2015 report *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk* was that "special attention is needed to the development and adoption of common protocol data models and common data elements to ensure meaningful computation across disparate trials and databases. A federated query system of 'bringing the data to the question' may offer effective ways of achieving the benefits of sharing clinical trial data while mitigating its risks" (IOM, 2015, p. 15).

Several initiatives are under way to explore the use of DHRs on AD research. For example, OptumLabs¹ has a database of de-identified data from the American Medical Group Association, the Mayo Clinic, United-Health Group, among others, for 150 million patients. OptumLabs is working with several partners, including the Global CEO Initiative on AD,² to accelerate AD research specifically focusing on disease predic-

¹See <https://www.optum.com/optumlabs.html> (accessed November 12, 2015).

²See <http://www.ceoalzheimersinitiative.org> (accessed November 12, 2015).

tion, progression, and care delivery.³ In addition, PCORnet,⁴ the National Patient-Centered Clinical Research Network, which “integrates health data for studies and catalyzes research partnerships” from data based in health systems (clinical data research networks) and data from groups of patients (patient-powered research networks), created a network for Alzheimer’s and dementia patients and caregivers. While not an exhaustive list, several additional examples of projects currently under way internationally are discussed in this chapter.

ROCHESTER EPIDEMIOLOGY PROJECT

A number of ongoing epidemiological and natural history studies have revealed interesting correlations between a variety of exposures and the aging process. Walter A. Rocca, professor of epidemiology and neurology at the College of Medicine, Mayo Clinic, described one study that he directs—the Rochester Epidemiology Project (REP).⁵ The REP now contains nearly a half century of medical records from a single county (Olmsted) in Minnesota. The data culled from these records include demographics, medical diagnoses, surgical procedures, other medical services and procedures, drug prescriptions, laboratory tests, immunizations, and lifestyle factors. The records were collected initially on paper and have been used primarily for research purposes. Between 2000 and 2006, the paper records were progressively replaced with DHRs, a portal was created to enable searching of the records, and the catchment area was expanded beyond Olmsted County to include seven more counties in southeastern Minnesota (Rocca et al., 2012). To date, the data collected have yielded more than 2,400 publications.

Linkage of medical and administrative data allowed REP to structure the data according to time, place, and person (see Figure 2-1), providing meaningful data that enabled the study of prevalence and incidence as

³See <https://www.optum.com/news-events/news/global-ceo-initiative-on-alzheimersdisease-launches-program-harness-power-of-big-data-accelerating-pace-alzheimersresearch.html> (accessed November 12, 2015).

⁴See <http://www.pcornet.org> (accessed November 12, 2015).

⁵See <http://rochesterproject.org> (accessed September 10, 2015).

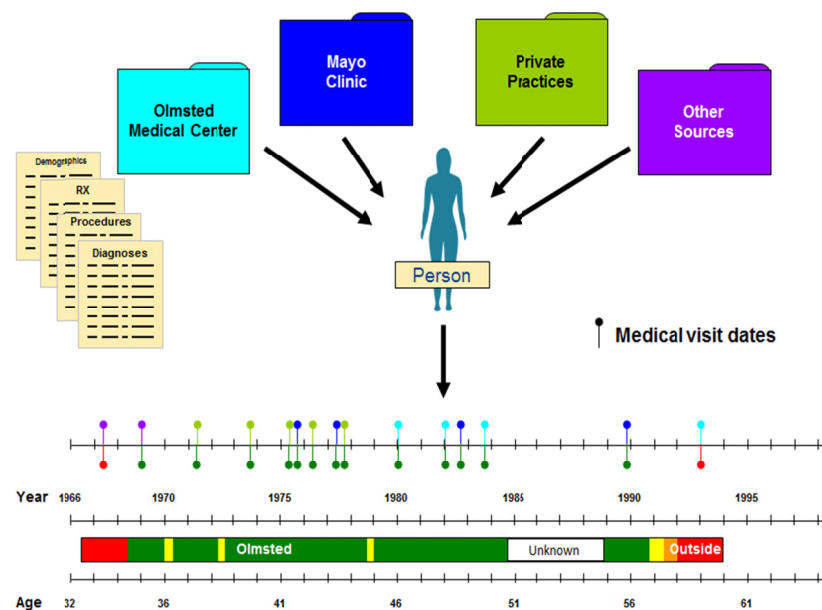


FIGURE 2-1 Linkage of records from multiple sources enables extraction of meaningful data structured into time, place, and person.

SOURCE: Presented by Walter Rocca at the Workshop on Assessing the Impact of Applications of Digital Health Records on Alzheimer's Disease Research on July 20, 2015. Modified from St. Sauver et al., 2011.

well as the identification of subjects for cohort and case-controlled studies, clinical trials, and biomarker studies. For example, this database was used to identify individuals between the ages of 70 and 89 who were invited to participate in the Mayo Clinic Study of Aging (MCSA) (Roberts et al., 2008). From this cohort, cognitively normal subjects who had undergone neuroimaging tests were selected to track the temporal progression of imaging biomarkers in the preclinical stage of AD. These data were used to support an assessment of the research criteria for preclinical AD published by a workgroup commissioned by the Alzheimer's Association and the National Institute on Aging in 2011 (Jack et al., 2012). The assessment showed that cognitively normal individuals could be classified according to their biomarker profiles into one of five groups: normal (Stage 0), one of three preclinical stages of AD (stages I–III), or a fifth group with “suspected non-AD pathophysiology” (Jack et al., 2012, p. 765).

MCSA data have also been used to study age-specific population frequencies of amyloidosis and neurodegeneration (Jack et al., 2014) as well as the effects of age, sex, and ApoE- ϵ 4—a marker known to increase the risk of AD—on memory, brain structure, and amyloid deposition in the brain (Jack et al., 2015). These data may also be used in upcoming clinical trials to identify potential trial subjects, obtain baseline and/or run-in data, study long-term outcomes and side effects after the trial phase is complete, and make comparisons to control subjects.

EUROPEAN PREVENTION OF ALZHEIMER'S DISEASE

Simon Lovestone described a multinational AD prevention program in Europe launched recently by the Innovative Medicines Initiative (IMI). Established in 2008 by the European Union and the European pharmaceutical industry, IMI is the world's largest public-private partnership, with the aim of accelerating drug development for a variety of conditions, including AD. One IMI project is the European Medical Information Framework (EMIF), which initially plans to focus on AD and obesity. In 2015, IMI launched the European Prevention of Alzheimer's Disease Consortium with nearly €26 million (more than \$28 million) from the European Commission, an additional €30 million (about \$32.5 million) from the European Federation of Pharmaceutical Industries and Associations, as well as another €8 million (\$8.7 million) from other sources. EPAD brings together partners from academia and industry in the precompetitive space to advance the development of AD therapies. To ensure a global reach for these efforts, IMI is also collaborating with the Global Alzheimer's Platform,⁶ which was established in 2014 by the Global CEO Initiative on Alzheimer's Disease and the New York Academy of Sciences.

The overall structure of EPAD is illustrated in Figure 2-2, beginning with the integration of datasets from several existing cohorts in Europe, brought together by EMIF, and ending with an innovative, self-sustaining, adaptive clinical trial. The data sources include 500,000 participants in the U.K. Biobank for Dementia Research, which was established in 2005 as a volunteer research cohort of randomly chosen

⁶See <http://www.usagainstalzheimer.org/gap> (accessed September 25, 2015).

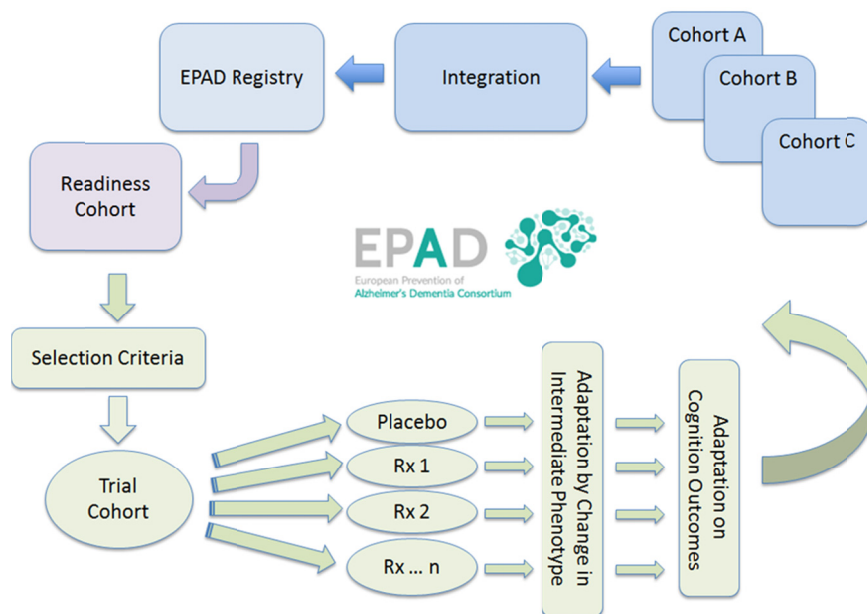


FIGURE 2-2 Overall structure of the European Prevention of Alzheimer's Dementia (EPAD) Consortium. Following integration of data from multiple cohorts into a subject registry, a trial-ready cohort will be identified, from which subjects will be drawn for participation in a standing, multi-arm clinical trial of Alzheimer's disease therapies.

SOURCE: Presented by Simon Lovestone at the Workshop on Assessing the Impact of Applications of Digital Health Records on Alzheimer's Disease Research on July 20, 2015.

participants enrolled in the U.K. National Health Service (Sudlow et al., 2015). This cohort is expected to include approximately 30,000 incident cases of AD by 2027. Baseline data collected on all participants between 2005 and 2008 include Web-based questionnaires regarding cognitive and mental health, lifestyle factors such as occupation, and exposures. Everyone in the cohort contributes DNA for genotyping of 820,000 single-nucleotide polymorphisms. It is planned to have a subset, consisting of 100,000 subjects, has multimodal imaging, including brain, cardiac, and body fat magnetic resonance imaging (MRI); bone and joint dual-energy x-ray absorptiometry (DEXA) scans; and three-dimensional carotid artery ultrasound. In addition, DHR data from mental health providers are captured, including textual data from clinical encounters.

The EPAD Consortium plans to establish a registry of subjects from whom these data have been gathered; harness that registry to identify a cohort of 6,000 individuals ready to enroll in clinical trials; and draw from that cohort to initiate a standing, multi-arm, proof-of-concept clinical trial with an adaptive design that will enable the evaluation of multiple therapies, including combination therapies. The adaptive design enables arms to be advanced or dropped based on interim results as well as the incorporation of additional arms so that the trial will operate continuously.

Follow-up data from research cohorts are collected through connectivity to DHRs as part of EMIF. One example of this is the follow-up of U.K. BioBank participants using the Case Registry Interactive Search (CRIS) system (Stewart et al., 2009), which downloads, de-identifies, and enables use of both coded data (including diagnosis for example) and uncoded narrative textual data from health care providers with a 24-hour update. CRIS has used a natural language processing system called General Architecture for Text Engineering⁷ to parse textual data and extract meaning from a combination of free text and coded data. Most information relevant to the progression of cognitive impairment is collected in the uncoded textual data, said Lovestone. Moreover, these data represent real-world conditions, rather than the highly manipulated conditions inherent in a randomized clinical trial, where stringent inclusion and exclusion criteria limit the generalizability of results.

For example, in a post-marketing (phase IV) study of acetylcholinesterase inhibitors—the most widely used drugs prescribed for AD—keyword searching was used to identify cases (patients receiving these drugs) in the South London and Maudsley National Health Service Foundation Trust Biomedical Research Center Case Register (Perera et al., 2014). This approach enabled the analysis of Mini-Mental State Examination⁸ scores from more than 2,500 patient records collected in routine practice, a far larger number than would be practical to enroll in a randomized clinical trial. The rate of improvement among these real-world subjects mirrored that seen in clinical trials, supporting the validity of this approach (Perera et al., 2014). Importantly, the heterogeneity of subjects in the case register and the collection of extensive data on socio-demographic factors, comorbidities, and other variables provided a rich

⁷See <https://gate.ac.uk> (accessed September 30, 2015).

⁸See <http://www4.parinc.com/Products/Product.aspx?ProductID=MMSE-2> (accessed September 10, 2015).

source of data to study the effects of the drug in the presence of these covariates.

The EMIF catalogue contains data from multiple types of cohorts on AD or aging, including population-based and clinical cohorts, as well as European and national multicenter studies. Combined, these cohorts provide access to a total of more than 15,000 subjects with subjective or mild cognitive impairment as well as more than 30,000 controls. For example, cerebrospinal fluid-associated data are available from more than 5,000 subjects. The DHR data sources available through the EMIF platform are even larger, with a cumulative total of about 48 million subjects.

MEDICARE ADMINISTRATIVE DATA

Medicare billing data offer another rich source of data for research, according to Julie Bynum, associate director at the Center for Health Policy Research, Geisel School of Medicine at Dartmouth College. Medicare provides health insurance to Americans age 65 or older as well as younger people with disabilities or certain illnesses. Medicare claims data capture all services delivered (except for medications), with each service attached to a diagnosis, thus providing a central and uniformly collected source of data on more than 50 million people (CMS, 2015). As a health services research tool, these data provide long-term outcome information from a large, diverse population.

Bynum described a study she led in 2002 to examine the independent effect and association of dementia with the risk of hospitalization. At the time, there was a debate about whether patients with AD have more comorbid conditions than patients without dementia. Her team examined claims data from a 5 percent random sample of Medicare beneficiaries in 1999. Of the 1.2 million cases in this study, about 100,000 had a diagnosis of dementia. These data showed that the average number of chronic conditions among dementia patients was twice as high as in those with no dementia. Dementia patients were also older and had more than twice the mortality rate. Using regression techniques that adjusted for age, sex, race, and comorbidity, the team showed that dementia was associated with an average threefold increased risk of hospitalization at all levels of comorbidity (Bynum et al., 2004).

Although these data have been used by others to inform policy, Bynum highlighted an important caveat: a 20 percent mortality rate among dementia patients indicates that these were people in relatively

late stages of the disease, suggesting a failure to diagnose patients in early stages. The reasons are multifold, she said. First, an individual needs to seek care from a physician; then the clinician must accurately diagnose the condition and code it correctly on the claims form. At the time of this study, Bynum said there were financial disincentives to code patients with a diagnosis of AD. Since then, multiple studies have shown a decline in mortality among those with a dementia diagnosis, suggesting that people are being diagnosed at earlier stages of disease. Other weaknesses of using Medicare claims data, according to Bynum, include the cost of start-up and the fact that some populations are missing, for example, individuals with insurance plans that pay a fixed amount of money per patient, regardless of services used, such as Medicare Advantage.

One way to boost the value of these datasets, according to a few participants, is to link them to other data sources. Bynum described two studies where she linked data from relatively large cohort studies with outcomes measurable from billing data: The Health and Retirement Study (HRS) and the Nurses' Health Study. HRS is a longitudinal study begun in 1992 with approximately 20,000 individuals over the age of 50, from whom data were captured every 2 years about their physical and mental health, financial status, employment, insurance coverage, and family support (NIA, 2015b). By linking survey data from HRS respondents who died between 1998 and 2007 with Medicare claims data at their last interview before dying, Bynum's team, led by Lauren Hersch Nicholas, showed that approximately two-thirds had cognitive impairment prior to death (Nicholas et al., 2014). Participants in the Nurses' Health Study have been followed for more than 30 years with serially collected cognitive measures in a subset of women over 70; this study is still under way but will investigate the role of early-stage cognitive impairment on risk of hospitalization.

Bynum is also using pharmaceutical billing data from Medicare (Part D) as a research tool to learn more about patients with a dementia diagnosis. Among more than 400,000 patients with more than 1 year of medication use in 2009, more than half had a low income, and more than 40 percent were newly diagnosed.

Beyond its use in health services research, Bynum suggested that Medicare claims data could provide population observations to inform clinical and basic science research, what she called "reverse translational research" (see Figure 2-3). For example, in research lead by Dr. Nancy Morden at Dartmouth, medication exposure information gleaned from pharmaceutical billing data, combined with clinical claims data, is being

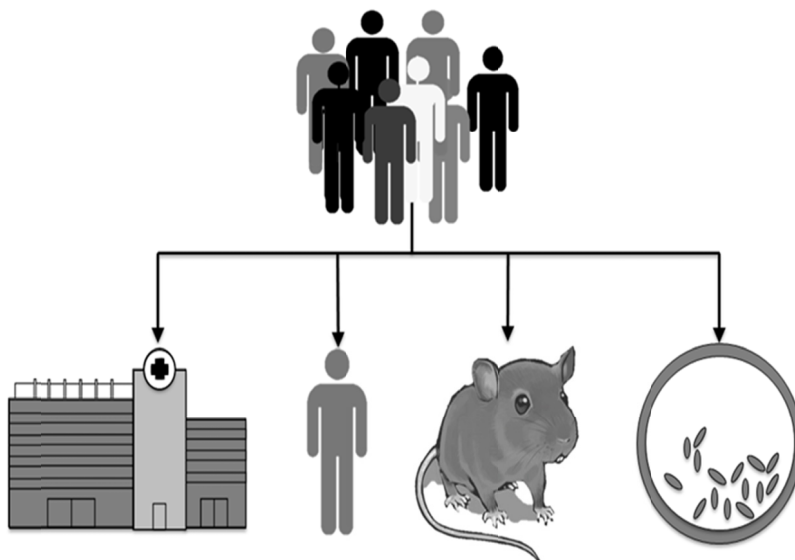


FIGURE 2-3 Reverse translational research: Using population observations from Medicare claims data to inform clinical and basic science research.

SOURCE: Presented by Julie Bynum at the Workshop on Assessing the Impact of Applications of Digital Health Records on Alzheimer's Disease Research on July 20, 2015. Image courtesy of Nancy Morden, Geisel School of Medicine at Dartmouth College.

used to assess the influence of individual drugs or combinations of drugs on disease progression or incidence of adverse effects. The value of this approach is that clinical testing of exposure pairs is expensive and time intensive; thus, little is known about combined use.

3

Ethical, Legal, and Societal Considerations

Highlights

- Cyberattacks and other types of data breaches have exposed the vulnerability of databases, including those holding sensitive personal health information, to misuse (Powell).
- Laws and regulations have been developed to protect the privacy of personal health information, yet may have unintended consequences for medical research (Powell).
- Patients are often willing to share their data for research purposes, but they want some privacy protections and the ability to give consent (Powell).

NOTE: These points were made by the individual speaker identified above; they are not intended to reflect a consensus among session participants.

In 1854, John Snow used geographical grids to chart deaths from the cholera epidemic that was ravaging London. The map showed that cases clustered around a water pump on Broad Street, identifying the pump as the source of the epidemic. By combining individual health information with a map, Snow quietly began a revolution in public health, by creating exceptionally powerful data that revealed new patterns and risk factors, said Tia Powell, director of the Montefiore Einstein Center for Bioethics at the Albert Einstein College of Medicine.

Fast forward to 2015, where massive amounts of personal data are stored in databases all over the world, and a single data breach at the Office of Personnel Management led to the theft of personal information from some 21.5 million federal government employees and applicants for federal jobs, as well as some of their spouses and friends, who had been subjected to background checks. The data included names, Social Security numbers, addresses, and financial and health history (Davis, 2015). This cyberattack and others like it highlight a growing problem, said Powell: How can we devise policies to facilitate the harvest of knowledge from big data while protecting individual privacy and respecting individual preferences?

Big data, including medical data, can be used in what some consider ethically troubling ways, noted several participants. For example, Powell said that FICO, the company that created the FICO score as a measure of consumer credit risk, has developed a medication adherence score based on publicly available data, and is free to sell that information to insurance companies or anyone else who has an interest in patient compliance with doctor recommendations (Parker-Pope, 2011). Mining big data is also widely used by retailers to enable targeted marketing. Although the public may object to some of these uses of personal data and clamor for more privacy protection, Powell cautioned that regulation is a blunt instrument and that legitimate uses of data, such as for medical research, may be inadvertently swept up in regulations intended to protect privacy.

POLICIES AND LEGISLATION TO PROTECT PATIENT DATA

The sources of data relevant to medical research are diverse and broad, as outlined in Chapter 2. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 was designed to protect the privacy of personal health information by removing 18 specific items from health records. But the anonymization of data proved more complicated than originally thought. Powell recalled the work of Latanya Sweeney, then a graduate student at the Massachusetts Institute of Technology, who in 1996 cross-referenced “de-identified” data from Massachusetts state employees that had been released by the Group Insurance Commission, and reidentified many of the individuals using publicly available voter rolls, which included name, address, zip code, birth date, and gender of

every voter. She then presented Massachusetts Governor William Weld at the time with his personal health records (Ohm, 2010). This incident led to changes in the HIPAA Privacy Rules; for example, HIPAA now precludes the use of name, date of birth, full zip code, and address. A recent study suggests that reidentification is now more difficult, but that some data sources are still vulnerable (Benitez and Malin, 2010). According to a recent IOM report, “de-identification and data security alone may not provide adequate protection; additional privacy and security techniques are being developed for these cases” (IOM, 2015, p. 13).

When HIPAA was updated in 2009 with passage of the HITECH Act,¹ provisions were incorporated that were intended to strengthen privacy protection by establishing civil and criminal enforcement rules regarding the electronic transmission of health information. A recent study of reported data breaches affecting 500 individuals or more between 2010 and 2013 identified 949 breaches affecting 29.1 million records (Liu et al., 2015). Breaches frequently involved laptop computers and portable electronic devices, and most resulted from criminal activity. The authors of this study concluded that because it only included reported breaches, it “likely underestimated the true number of health care data breaches,” and predicted that these numbers are likely to increase with the rapid expansion of DHR use.

According to Powell, participant preferences for data use vary by region and nation. Many people are willing to share data for medical research, but they want to be asked, give consent, and have some privacy protection (Kim et al., 2015). Willingness to give consent also varies by who holds the data (hospital, corporation, government) and its planned use, for example, to cure or diagnose a disease or for marketing or government surveillance purposes.

In 1995, the European Commission established the Data Protection Directive (95/46/EC) as an effort to regulate the processing (which should be transparent, for legitimate purposes, and not in excess for the purposes in which they were obtained) and movement (within or outside the European Union) of personal data to protect individuals (European Commission, 1995). In 2012, the European Commission proposed a General Data Protection Regulation (De Hert and Papakonstantinou, 2012). Powell said this legislation, which would add restrictions for big

¹See <http://www.hhs.gov/ocr/privacy/hipaa/administrative/enforcementrule/hitech/enforcement.html> (accessed September 10, 2015).

data collection and require re-consent for use of data in many legacy repositories, has been widely debated. Critics view the regulations as an impediment to international research collaborations, with significant implications for genetic and other types of medical research. In response to concerns about the responsible use of genomic and other data, the Global Alliance for Genomics and Health² was established in 2013. It brought together an international group of researchers, patient advocates, bioethicists, and privacy experts to develop best practices for sharing and protecting research data.

²See <http://www.genomicsandhealth.org> (accessed September 10, 2015).

4

Potential Next Steps

Highlights

- Advances in data analytics offer great potential for researchers to move beyond correlations to mechanisms and cause-and-effect relationships (Khalil).
- Incorporating patient-reported outcomes, clinical care records, and data from personal devices such as smartphones will further enrich the data available for mining (Lovestone).
- Patient consent to access and use data remains a thorny issue for citizens, researchers, and legislators (Bynum, Lovestone, Powell, Rocca).
- Researchers must respect the intentions of the persons from whom the data were derived, but at the same time ensure that data are used as widely as possible for the best possible purposes (Lovestone).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among session participants.

The Century Cures Act, which, among other goals, aims to advance interoperability in health information technology as a pathway to improved biomarkers and therapies for AD and other diseases.

Beyond the potential of exploiting these clinical data, researchers now measure things with greater granularity, marry data across types, and combine these data with computational and machine learning

techniques to move beyond correlations to mechanisms and cause/effect relationships, said Iya Khalil, executive vice president and co-founder of GNS Healthcare. For example, computer algorithms combining anthropometric and laboratory measures are now capable of predicting risk of developing metabolic syndrome and model response to various interventions, providing the capability for personalized medicine. Similarly, companies such as GNS Healthcare are working to integrate multiple layers of data from AD patients to develop an algorithm that can predict who is at risk for AD as well as the optimal treatment protocols. These data go beyond simple clinical and laboratory measures to include linkage of genetic and molecular markers and imaging readouts to longitudinal clinical outcomes, providing insight into how things work from the biological level to the health care system level. Big data may also be useful as a means of providing real-world data about areas of unmet need, noted Khalil.

Simon Lovestone added that the ability to incorporate patient-reported outcomes, clinical care records, and measures from personal devices such as smartphones will further enrich the data available for mining. The key, he said, is to enable patients to have some control over their data. Tia Powell noted that much less research is done on low-income and minority groups, so working to build trust among these populations will be especially important.

However, a few participants noted that consent to access and use data from DHRs remains a challenge for citizens, researchers, and legislators alike. For example, Minnesota law requires patients to provide general consent before their medical records can be used for Institutional Review Board–approved research, said Walter Rocca. Regulatory decisions may also be open to reinterpretation over time. Julie Bynum said that an older regulation about access to information on substance abusers and substance abuse was recently reinterpreted to require removal of all substance abuse claims from claims data. The result of that change is that if a researcher tries to examine claims data to assess longitudinal change in risk of substance abuse, claims for a segment of high-risk individuals will be missing, compromising the results of the analysis.

Multinational studies may be especially impacted by regulations limiting the sharing and reuse of data, said Lovestone. As a research community, he said, we have a responsibility to respect the researcher's intentions for data utilization, but ensure in tandem that data are used as widely as possible for optimal purposes.

A

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B

Workshop Agenda

ASSESSING THE IMPACT OF APPLICATIONS OF DIGITAL HEALTH RECORDS ON ALZHEIMER'S DISEASE RESEARCH

Presented at the Alzheimer's Association
International Conference on Alzheimer's Disease
Washington, DC | July 20, 2015

- 8:00 a.m. **Session Overview**
- DANIEL BURCH
Vice President, Global Therapeutic Head for
Neuroscience
Pharmaceutical Product Development
- 8:05 a.m. **Clinical Trial Design: Digital Health Record (DHR)
Collaborative Efforts in Europe**
- Examine how electronic medical records (EMRs), research, and epidemiology cohorts have been used in the United Kingdom and Europe to identify biomarkers, recruit study participants, and model future clinical trials.

- Discuss the European Medical Information Framework progress toward an integrated platform for data aggregation.

SIMON LOVESTONE
Professor of Translational Neuroscience
Oxford University

8:20 a.m.

Infrastructure Needs

Half a Century of Medical Records Linkage in the Rochester Epidemiology Project

- Explore how passive record-linkage systems can be combined with active contacts to strengthen research to discover risk and protective factors for Alzheimer's disease.
- Review lessons learned, limits and gaps of EMR linkage systems, and how these can be used as practical tools.

WALTER A. ROCCA
Director, Rochester Epidemiology Project
Professor of Epidemiology and Neurology
College of Medicine, Mayo Clinic

Lessons Learned from Medicare Claims–Based Methods of Studying DHRs

- Review the current state of research and diagnostic methodologies based on administrative data and DHRs.
- Examine reverse translations and limitations of DHRs and identify other necessary data sources.

JULIE BYNUM
Associate Professor of Medicine
Dartmouth Institute for Health Policy & Clinical Practice
Geisel School of Medicine at Dartmouth College

8:45 a.m. **Ethical, Societal, and Legal Considerations**

- Examine what kinds of ethical, societal, and legal issues must be considered in applying DHRs on Alzheimer's disease research.

TIA POWELL

Director, Montefiore Einstein Center for Bioethics
Professor of Clinical Epidemiology and Clinical
Psychiatry
Albert Einstein College of Medicine

9:00 a.m. **Opportunities for Alzheimer's Disease Research:
Facilitated Panel Discussion**

- Identify a set of core principles that can be used to support innovative clinical trial design as well as infrastructure and cloud computing needs for Alzheimer's disease.
- Discuss how information contained within DHRs holds the potential to identify novel surrogate markers and modify clinical trial design.
- Identify the data-sharing and management strategies and infrastructure necessary to identify potential surrogate outcomes.
- Discuss next steps and strategies for moving forward.

SIMON LOVESTONE

Professor of Translational Neuroscience
Oxford University

WALTER A. ROCCA

Director, Rochester Epidemiology Project
Professor of Epidemiology and Neurology
College of Medicine, Mayo Clinic

JULIE BYNUM

Associate Professor of Medicine

Dartmouth Institute for Health Policy & Clinical
Practice

Geisel School of Medicine at Dartmouth College

IYA KHALIL

Executive Vice President and Co-Founder

GNS Healthcare

TIA POWELL

Director, Montefiore Einstein Center for Bioethics

Professor of Clinical Epidemiology and Clinical
Psychiatry

Albert Einstein College of Medicine

9:30 a.m.

ADJOURN

C

Participant Biographies

Daniel Burch, M.D., M.B.A., is global therapeutic area head and vice president for Neuroscience at Pharmaceutical Product Development (PPDi). Dr. Burch holds an M.D. from Vanderbilt University and an M.B.A. from the Wharton School, University of Pennsylvania. He completed a residency in Internal Medicine at Vanderbilt University School of Medicine and a Fellowship in Infectious Diseases at Washington University School of Medicine. Dr. Burch has worked in the pharmaceutical/biotech industry for a total of 20 years at Abbott Laboratories, SmithKline Beecham, GlaxoSmithKline (GSK), and CeNeRx BioPharma. His most recent posts were senior vice president, Neurosciences Medicines Development Centre at GSK and executive vice president of research and development and chief medical officer of CeNeRx BioPharma. He was appointed to his current position in 2012.

Julie Bynum, M.D., M.P.H., is associate professor of medicine at the Geisel School of Medicine at Dartmouth and the Dartmouth Institute for Health Policy and Clinical Practice, where she is also the co-director of the Data Analytic Core. Dr. Bynum's work is focused on assessment of health system performance for the elderly using national U.S. Medicare administrative data. Dr. Bynum has foundation and National Institutes of Health (NIH) funding to study quality and efficiency of health care delivery to high-risk elderly, particularly those with multiple chronic conditions or cognitive impairment. Dr. Bynum has received funding from the American Geriatric Society Foundation for Health in Aging Program for Research on Health Outcomes and has been a Robert Wood Johnson Physician Faculty Scholar. She was a National Institute on Aging Beeson Scholar (K23), studying quality and efficiency of health care delivery to

high-risk elderly. One of Dr. Bynum's contributions to the field has been to develop a method of creating "virtual" physician-hospital networks that allow the measurement of care delivered and its outcomes for a population served by a specific group of providers. These networks were used in the conceptual development of the accountable care organization legislation. She has continued her policy-relevant efforts as a 2011–2013 Health & Aging Policy Fellow funded by the Atlantic Philanthropies and was a member of the Institute of Medicine committee that created the report *Vital Signs: Core Metrics for Health and Health Care Progress*. Currently she leads three NIH-funded studies: Efficiency of Care for High-Cost, High-Need Beneficiaries; Optimizing Fracture Care Outcomes: A Comparative Effectiveness Approach; and a study that links the Nurses' Health Study to Medicare claims titled Relationship of Cognitive Decline with Healthcare Costs and Hospitalization Risk. She also leads a Hartford Foundation-funded study of primary care, hospitalization, and costs in older adults with multiple chronic conditions.

Iya Khalil, Ph.D., is a technology entrepreneur and physicist with a vision of transforming medicine into a discipline that is quantitative, predictive, and patient-centric via big data analytic approaches. She co-founded two big data companies, Via Science and GNS Healthcare, and is the co-inventor of the proprietary computational engine that underpins both entities. She trained in theoretical physics at Cornell University, and has more than 11 years of experience in big data analytics for health care, medicine, and the life sciences. She has led several key foundational collaborations with providers, pharmaceutical companies, foundations, and government agencies. Dr. Khalil's expertise spans applications in drug discovery, drug development, and all the way to treatment algorithms that can be applied at the point of care. She is a frequent speaker at industry events and conferences, has appeared in several industry journals, has published several articles in the field, and was recognized by President Obama at a White House dinner as a leading entrepreneur in genomic medicine. More recently, she was named to the PharmaVOICE 100 list of the most inspiring people in the life sciences industry. She was recognized for her ability to build bridges across the life science and health care industries, bringing people together to harness the power of predictive modeling to change the lives of patients.

Simon Lovestone, Ph.D., MRC Psych, is professor of translational neuroscience at Oxford University and also lead for the National Institute for

Health Research Translational Research Collaboration in Dementia (a network of six Biomedical Research Units and Centres in England focused on dementia), lead for informatics in the Dementias Platform U.K., and co-coordinator of the European Medical Information Framework. He has research interests in the regulation of tau phosphorylation, dementia therapeutics, and in the search for genetic and other biomarkers of Alzheimer's disease. Underpinning all these studies is the use of informatics—clinical informatics, bioinformatics, and the challenges of extracting value from very large variable datasets.

Tia Powell, M.D., founded and directs the bioethics master's program and directs the Center for Bioethics at Montefiore Health System and Albert Einstein College of Medicine, where she is professor of clinical epidemiology and clinical psychiatry. Her bioethics expertise is in the domains of public policy; dementia; decision-making capacity; lesbian, gay, bisexual, transgender issues; mediation and consultation; and public health disasters. She served 4 years as executive director of the New York State Task Force on Life and the Law, the state's bioethics commission. She has served the Institute of Medicine (IOM) on multiple workgroups and was a co-author of IOM's recent report *Cognitive Aging*. Dr. Powell was a 2013–2014 Health and Aging Policy Fellow; based on her work during that fellowship, she continues as a senior advisor for the U.S. Department of Health and Human Services to assess and develop federal health initiatives related to dementia and ethics. She is a board-certified psychiatrist and fellow of the New York Academy of Medicine, the American Psychiatric Association, and the Hastings Center.

Walter A. Rocca, M.D., M.P.H., is professor of epidemiology and neurology and the Ralph S. and Beverley E. Caulkins Professor of Neurodegenerative Diseases Research at the Mayo Clinic. He is also the director of the Rochester Epidemiology Project medical records-linkage system and co-director of the Mayo Clinic Specialized Center of Research on Sex Differences. Finally, he chairs the Clinical Research Subcommittee and is a member of the Science Committee of the American Academy of Neurology. Dr. Rocca previously worked for the National Institute of Neurological Disorders and Stroke (NINDS); for the Italian Research Council; and for other European institutions. Dr. Rocca's research focuses on brain aging and on the etiology of common neurodegenerative diseases, such as parkinsonism and dementia. The fundamental idea is that these diseases are heterogeneous at the population level, multi-

factorial at the individual level, and dimorphic (vary in men and women). These diseases are the result of complex genetic, environmental, social, and cultural risk and protective factors interacting in different phases of life (intrauterine, perinatal, early development, childhood, adolescence, adult life, and late life). He has recently focused his work on the effects of surgical menopause and estrogen on brain aging in women. He is also contributing to the emerging fields of dimorphic neurology and dimorphic medicine (impact of sex and gender on health and diseases). Dr. Rocca received his M.D. from the University of Padua, Italy; his Diploma of Specialty in Neurology from the University of Verona, Italy; and his M.P.H. from the Johns Hopkins University School of Hygiene and Public Health. He completed postdoctoral fellowships at Johns Hopkins University and at NINDS. Dr. Rocca served on several expert panels for the National Institutes of Health and for other institutions nationally (National Academies of Sciences, Engineering, and Medicine; Centers for Disease Control and Prevention; U.S. Department of Veterans Affairs; and U.S. Department of Defense) and internationally (national research agencies of Canada, France, Italy, Saudi Arabia, Spain, and the United Kingdom).