BIOGRAPHICAL SKETCH

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NAME: Marcantonio, Edward R.

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POSITION TITLE: Professor of Medicine, Harvard Medical School

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard College, Cambridge, MA	AB	1983	Biochemical Sciences
Harvard Medical School, Boston, MA	MD	1987	Medicine
Brigham and Women's Hospital, Boston, MA	Residency	1990	Internal Medicine
Harvard School of Public Health, Boston, MA	SM	1992	Epidemiology
Harvard Medical School, Boston, MA	Fellowship	1992	General Internal Medicine
Beth Israel Hospital, Boston, MA	Fellowship	1994	Geriatric Medicine

A. Personal Statement

I am a Professor of Medicine at Harvard Medical School and serve as Section Chief for Research in the Division of General Medicine at Beth Israel Deaconess Medical Center (BIDMC). I am also an internationally recognized expert, clinical investigator, and thought leader in the field of delirium research. Over the past 25 years, I have conducted a series of observational and interventional studies to improve delirium identification, target individuals at risk, identify modifiable risk factors, and test intervention strategies to reduce the incidence, severity and duration of delirium, and its associated long-term adverse outcomes. In terms of current funding, I am PI of 3 NIA R01's, Project and Core Leader of an NIA P01, and Co-Investigator on numerous grants—see Current Funding section below for more details.

I also have a major commitment to mentoring, serving as Program Director of the HMS General Medicine Fellowship, Associate Director of both a National Institute on Aging (NIA) T32 Postdoctoral Fellowship, and the Research and Education Core of the Boston Pepper Center. I have also personally mentored over 60 students, fellows, and junior faculty researchers, have been recognized with HMS's Barger Award for Excellence in Mentoring. I was awarded a Mid-Career Investigator Award in Patient-Oriented Research (K24) by the National Institute on Aging (NIA), which has protected my time for individual mentoring of junior investigators, enabled me to leverage my ongoing projects for training, and fostered my career development to enhance my research.

I have been on the Core faculty of the Translational Research in Aging T32 training program since its inception in 2004, serving as a mentor (2004-prsent), co-director of the didactic curriculum (AARTSS: Advanced Aging Research Training Seminar Series) (2004-2019) and as Associate Program Director (2016-present). I am delighted to continue in my leadership role as Associate Program Director, fostering the strong collaboration between Hebrew SeniorLife and Beth Israel Deaconess Medical Center in the training of young investigators interested in aging. Below are representative publications of my work with junior investigators:

a. Herzig S, Howell M, Ngo LH, **Marcantonio ER**. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. JAMA 2009;301(20):2120-8.

b. Graham KL, Wilker EH, Howell MD, Davis RB, **Marcantonio ER**. Differences between early and late readmissions among medical patients. Ann Int Med. 2015;162(11):741-749. PMCID: PMC4747330.

c. Shi SM, Sung M, Afilalo J, Lipsitz LA, Kim CA, Popma JJ, Khabbaz KR, Laham RJ, Guibone K, Lee J, **Marcantonio ER*,** Kim DH* (*co-last). Delirium Incidence and Functional Outcomes After Transcatheter and Surgical Aortic Valve Replacement. J Am Geriatr Soc. Jul;67(7):1393-1401. PMCID: PMC6612597

d. Vasunilashorn SM, Ngo LH, Inouye SK, Fong TG, Jones RN, Dillon ST, Libermann TL, O'Connor M, Arnold SE, Xie Z, **Marcantonio ER**. Apolipoprotein E Genotype and the Association between C-reactive Protein and Postoperative Delirium: Importance of Gene-Protein Interactions. Alzheimers Dement. 2019 Nov 20. pii: S1552-5260(19)35476-7. doi: 10.1016/j.jalz.2019.09.080. [Epub ahead of print]

B. Positions and Honors

Positions and Employment

1994-1999	Instructor in Medicine, Harvard Medical School, Boston, MA
1999-2004	Assistant Professor of Medicine, Harvard Medical School, Boston, MA
2004-2012	Associate Professor of Medicine, Harvard Medical School, Boston, MA
2004-2012	Director of Research, Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, MA
2008-	Director, Aging Research Program, Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, MA
2012-	Professor of Medicine, Harvard Medical School, Boston, MA
2012-	Section Chief for Research, Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, MA

Other Experience and Professional Memberships

1989-	Member, American College of Physicians
1990-	Board Certification, Internal Medicine (renewed 2000, 2010)
1991-	Member, Society of General Internal Medicine
1992-	Member, American Geriatrics Society
1994-	Board Certification, Geriatric Medicine (renewed 2004, 2014)
1995-	Member, Gerontological Society of America
2000-	Editorial Board, Journal of the American Geriatrics Society
2001-2004	Research Committee, American Geriatrics Society
2003-2008	Aging Systems and Geriatrics Study Section, Center for Scientific Review, National Institutes of Health, Ad hoc member 2003-2004, Empaneled Member 2004-2006, Chair, 2006-2008
2010-19	Council of Mentors, Harvard Medical School
2011-	NIA Beeson Career Development Award Review Committee, member
2012-	Editorial Board, Journal of Gerontology: Medical Sciences
2014	Co-Chair, AGS/NIA U13 Conference on Delirium Research
2014-	Member, International Society to Advance Alzheimer's Research and Treatment (ISTAART)
2014-	Associate Director, Harvard Translational Research in Aging Fellowship Program (NIA T32)
2015-	Member, Alzheimer's Association Medical and Scientific Committee, Massachusetts Chapter
2019-	Program Director, Harvard Medical School Fellowship in General Medicine

Honors:

1983	A.B., Summa cum laude, Harvard College
1997	New Investigator Award, American Geriatrics Society
1999	Paul Beeson Physician Faculty Scholarship for Aging Research
2003	Outstanding Scientific Achievement for Clinical Investigation Award, American Geriatrics Society
2005,15	Best Doctors in America
2007	Excellence in Mentoring Award, Beth Israel Deaconess Medical Center
2009	A. Clifford Barger Excellence in Mentoring Award, Harvard Medical School
2012	Lumlean Lectureship, Royal College of Physicians, London, United Kingdom
2014	Association of American Physicians, elected member
2016	Program Award for Culture of Excellence in Mentoring, Section for Research, Division of General Medicine and Primary Care (Chief: Marcantonio), awarded by Harvard Medical School
2020	John Morley Award for the Best Paper Published in the Journal of the American Medical Director's Association, 2019

C. Contribution to Science

1. Epidemiology of Postoperative Delirium: When I began my career in aging research in the early 1990's, the epidemiology of delirium was not well described. In the series of studies below, I defined the incidence and risk factors for delirium after elective non-cardiac surgery (a) and cardiac surgery (c). It was also believed that delirium was short-lived and had no impact on long term outcomes. Instead, we found that delirium was an independent risk factor for poor functional recovery after hip fracture (b) and was associated with an acute decline, prolonged recovery, and persistent decline in cognitive function after cardiac surgery (d). I conceived and executed all of these studies, and served as first author or senior author on the resulting manuscripts.

a. **Marcantonio ER**, Goldman L, Mangione CM, Ludwig L, Muraca B, Haslauer CM, Donaldson MC, Whittemore AD, Sugarbaker DJ, Poss R, Haas S, Cook EF, Orav EJ, Lee TH. A clinical prediction rule for delirium after elective non-cardiac surgery. JAMA 1994; 271(2):134-9.

b. **Marcantonio ER**, Flacker JM, Michaels M, Resnick NM. Delirium is independently associated with poor functional recovery after hip fracture. J Am Geriatr Soc 2000;48(6):618-24.
c. Rudolph JL, Jones RN, Levkoff SE, Rockett C, Inouye SK, Sellke FW, Khuri SF, Lipsitz LA, Ramlawi B, Levitsky S, **Marcantonio ER**. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. Circulation 2009;119(2):229-36. PMCID: PMC2735244
d. Saczynski JS*, **Marcantonio ER*** (co-first), Quach L, Fong TG, Gross A, Inouye SK†, Jones RN† (co-last). Cognitive trajectories after postoperative delirium. New Eng J Med. 2012; 367: 30-9. PMCID: PMC3343229.

2. Interventions for Delirium: A second major emphasis of my career has been the development and testing of interventions for the prevention or abatement of delirium. I first developed a model of proactive geriatrics consultation for hip fracture patients, and tested it in a randomized trial that demonstrated a significant 36% reduction in postoperative delirium and a greater than 50% reduction in the incidence of severe delirium (a). I also developed a program for management of persistent delirium in post-acute skilled nursing facilities, and tested it in cluster randomized trial (b). The program led to a greater than 3-fold improvement in recognition of delirium, but did not result in a shortening of its course. I have also tested novel pharmacological interventions for delirium, including performing a randomized trial of donepezil, a cholinesterase inhibitor commonly used for treatment of dementia (c). While this did not show a benefit, the trial was a valuable contribution to the field in that it led to reduced unnecessary exposure to these drugs in patients at risk for delirium. More recently, I conducted a factorial design randomized trial studying the impact of perioperative sedation and analgesic practices on the incidence of delirium. We found that intravenous acetaminophen administered for the first two days after cardiac surgery reduced the incidence of postoperative delirium by over 50% (d).

a. **Marcantonio ER**, Flacker JM, Wright JR, Resnick NM. Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc 2001;49(5):516-22.
b. **Marcantonio ER**, Bergmann MA, Kiely DK, Orav EJ, Jones RN. Randomized trial of a delirium abatement program for post-acute skilled nursing facilities. J Am Geriatr Soc 2010; 58(6): 1019-26. PMCID: PMC2924954
c. **Marcantonio ER**, Palihnich KA, Appleton P, Davis RB. Pilot randomized trial of donepezil hydrochloride for delirium after hip fracture. J Am Geriatr Soc; 2011; 59 Suppl 2: S282-88. PMCID: PMC3233977
d. Subramaniam B, Shankar P, Shaefi S, Mueller A, O'Gara B, Banner-Goodspeed V, Gallagher J, Gasangwa D, Patxot M, Packiasabapathy S, Mathur P, Eikermann M, Talmor D, **Marcantonio ER**. Effect of Intravenous Acetaminophen versus Placebo Combined with Dexmedetomidine versus Propofol on Postoperative Delirium in Older Patients Following Cardiac Surgery: A Randomized Clinical Trial. JAMA. 2019 Feb 19;321(7):686-696. PMCID: PMC6439609.

3. Improved Assessment Methods for Delirium: Delirium can be challenging to assess, both in research and clinical settings. Another major focus of my career has been to develop better measurement tools for delirium. We used a database of 4744 detailed delirium assessments with cognitive testing and advanced measurement methods to develop both an improved severity instrument for delirium (the CAM-S) (a), and a brief structured diagnostic interview for delirium that can be completed in 3 minutes or less (the 3D-CAM) (b). The latter 2 tools are already being widely adopted in research. We are now pursuing new work to develop strategies for clinical implementation, including development of an ultra-brief 2-item bedside screening test of delirium (c), which effectively rules out delirium in less than 1 minute. Finally, we derived and validated a method using items from the 3D-CAM to replicate the CAM-S measure for delirium severity (d).

a. Inouye SK, Kosar CM, Tommet D, Schmitt EM; Puelle MR; Saczynski JS, **Marcantonio ER*,** Jones RN* (co-last). The CAM-S, a new scoring system for delirium severity in 2 cohorts. Ann Int Med. 2014; 160: 526-33. PMCID: PMC4038434.
b. **Marcantonio ER**, Ngo L, O'Connor MA, Jones RN, Crane PK, Metzger ED, Inouye SK. 3D-CAM: Validation of a 3-Minute Diagnostic Interview for CAM-defined Delirium. Ann Int Med. 2014;161(8):554-61. PMCID: PMC4319978.
c. Fick DM, Inouye SK, Guess J, Ngo LH, Jones RN, Saczynski JS, **Marcantonio ER**. Preliminary development of an ultra-brief 2-item bedside test for delirium. Journal of Hospital Medicine. J Hosp Med. 2015 Oct;10(10):645-50. PMCID: PMC4665114.
d. Vasunilashorn SM*, Guess J* (co-first), Ngo L, Fick DM, Jones RN, Schmitt E, Kosar CM, Saczynski JS, Travison TG, Inouye SK**, **Marcantonio ER**** (co-last). Derivation and validation of a severity scoring method for the 3-Minute diagnostic interview for CAM-defined delirium. J Am Geriatr Soc. 2016; Aug 64(8):1684-9. PMCID: PMC4988867.

4. Biomarkers and Mechanisms of Delirium: Despite its prevalence, morbidity, and cost, delirium remains a wholly clinical diagnosis and very little is known about its underlying mechanisms. Moreover, there are no

biomarkers to guide its diagnosis or management. After conducting a systematic review on this topic (a), I conceived and led a project entitled Biomarker Discovery for Delirium as part of the Successful Aging after Elective Surgery (SAGES) study. This project used state-of-the-art biomarker discovery technologies, including quantitative proteomics, to identify a "biomarker signature" for delirium. This project has resulted in several high impact publications (see b-d below). Most notably, we found strong evidence for the involvement of systemic inflammation in delirium, with higher concentrations of plasma interleukin-6 and C-reactive protein, and other proteins among patients who developed delirium vs. matched controls (b-d).

a. **Marcantonio ER**, Rudolph JL, Culley D, Crosby G, Alsop D, Inouye SK. Serum biomarkers for delirium. J Gerontol A Biol Sci Med Sci 2006;61(12):1281-86.
b. Vasunilashorn SM*, Ngo L* (*co-first), Inouye SK, Libermann TA, Jones RN, Alsop DC, Guess J, Jastrzebski S, McElhaney JE, Kuchel GA**, **Marcantonio ER**** (**co-last). Cytokines and postoperative delirium in older patients undergoing major elective surgery. J Gerontol Med Sci. 2015;70(10):1289-95. PMCID: PMC4817082.
c. Dillon ST*, Vasunilashorn SM* (co-first), Ngo L, Otu HH, Inouye SK, Jones RN, Alsop DC, Kuchel GA, Metzger ED, Arnold SE, **Marcantonio ER****, Libermann TA** (co-last). Higher C-reactive Protein Levels Predict Postoperative Delirium in Older Patients Undergoing Major Elective Surgery: A Longitudinal Nested Case-Control Study. Biological Psychiatry. 2017;81(2):145-53. PMCID: PMC5035711.
d. Vasunilashorn SM, Ngo LH, Chan NY, Zhou W, Dillon ST, Otu HH, Inouye SK, Wyrobnik I, Kuchel GA, McElhaney JE, Xie, Z, Alsop DC, Jones RN, Libermann TA*, **Marcantonio ER*** (co-last). Development of a Dynamic Multi-Protein Signature of Postoperative Delirium. Journal of Gerontology: Medical Sciences. 2019 Jan 16;74(2):261-268. PMCID: PMC6333936.

5. The Relationship of Delirium and Alzheimer's Disease and Related Dementias: Another focus of my research has been both the epidemiological associations between delirium and Alzheimer's Disease and Related Dementias (ADRD), and potential shared mechanisms between the two syndromes. We first demonstrated that patients with AD were at increased risk of delirium during hospitalization, and had an increased risk of new nursing home placement and functional decline (a). In a separate study, we found that cerebrospinal β-Amyloid/Tau ratio (the "CSF signature" of AD) measured preoperatively is associated with postoperative delirium (b). On the other hand, we found that the apolipoprotein E ε4 genotype did not increase risk for postoperative delirium (c). Finally, we found that in a large cohort of patients without AD, the occurrence of delirium was associated with a cognitive trajectory characterized by a punctuated decline and accelerated cognitive decline over the subsequent 36 months (d).

a. Fong TG, Jones RN, **Marcantonio ER**, Tommet D, Gross AL, Habtemariam D, Schmitt E, Yap K, Inouye SK. Adverse Outcomes Following Hospitalization and Delirium in Persons with Alzheimer's Disease. Ann Int Med; 2012; 156: 848-56. PMCID: PMC3556489.
b. Xie Z, Swain CA, Ward SAP, Zheng H, Dong Y, Sunder N, Burke DW, Zhang Y, **Marcantonio ER**. Preoperative cerebrospinal fluid β-Amyloid/Tau ratio and postoperative delirium. Ann Clin Trans Neurol. 2014 May;1(5):319-328. PMCID: PMC4029597.
c. Vasunilashorn S, Ngo L, Kosar CM, Fong TG, Jones RN, Inouye SK,* **Marcantonio ER**.* (co-last) Does apolipoprotein E genotype increase risk for postoperative delirium? Am J Geriatr Psychiatry. 2015 Oct;23(10):1029-37. PMCID: PMC4591079.
d. Inouye SK, **Marcantonio ER**, Kosar C, Tommet D, Schmitt EM, Travison TG, Saczynski JS, Ngo L, Alsop D, Jones RN. The Short- and Long-Term Relationship between Delirium and Cognitive Trajectory in Older Surgical Patients. Alzheimers Dement. 2016.12: 766-75. PMCID: PMC4947419.

Complete List of Published Work in MyBibliography: http://www.ncbi.nlm.nih.gov/sites/myncbi/edward r.marcantonio.1/bibliography/40762113/public/?sort=date&direction=ascending

D. Research Support.

Ongoing Research Support (selected)

R01AG051658 (Marcantonio, Libermann) 1/15/2016 - 12/31/2020 (NCE)
NIH/National Institute on Aging (NIA)
Advancing the Understanding of Postoperative Delirium Mechanisms via Multi-Omics
This project aims to leverage specimens from two recently completed NIA-funded studies, SAGES (**S**uccessful **Ag**ing after **E**lective **S**urgery), and an independent orthopedic cohort, HiPOR (**H**ealth**i**er **Po**stoperative **R**ecovery) that collected and stored both plasma and preoperative cerebrospinal fluid (CSF). We will apply cutting-edge systems level "Omics" methods to define delirium signatures that integrate proteins, lipids, and metabolites from both plasma and CSF. We will seek to confirm and further elucidate the dysfunctional inflammation model for delirium identified in our previous work, and discover new mechanisms for delirium.
Role: Principal Investigator (contact)

R01 AG030618 (Marcantonio, Fick) 4/11/2016 – 3/31/2021(NCE)
NIH/National Institute on Aging
READI: Researching Efficient Approaches to Delirium Identification
This is a competing continuation of my previous 3D-CAM R01, which derived and validated the 3D-CAM, a 3-minute Diagnostic assessment for Delirium using the Confusion Assessment Method algorithm and also identified a highly sensitive two-item screener that can effectively rule out delirium. We now propose to 1) validate this two-item delirium screener in two independent cohorts; 2) combine the screener and 3D-CAM into a two-step delirium identification protocol; 3) measure the effectiveness and cost-efficiency of having clinicians administer this protocol to a new cohort of 400 hospitalized older patients enrolled in two diverse hospital settings; 4) employ qualitative methods to determine barriers and facilitators to implementing the protocol.
Role: Principal Investigator (contact)

R24 AG054259 (Inouye) 9/1/2016 – 8/31/2021
NIH/National Institute on Aging
NIDUS: Network for Investigation of Delirium: Unifying Scientists
We propose to create a collaborative research network for delirium across the United States and internationally designed to unify scientists in this field. NIDUS consists of two Cores: Research Resources, which is creating a database of all delirium research, and Measurement and Harmonization, which is identifying the best delirium measures and creating crosswalks between them. There are also three task forces: Career Development, which coordinates an annual bootcamp and mentoring activities, Pilot grants, which awards two grants per year and Dissemination, which focuses on communication and social media. Together, the two Cores and three Task Forces will help to stimulate new research and collaboration to move this field forward.
Role: Director, Research Resources and Database Core

K24 AG035075 (Marcantonio) 9/1/2017 – 5/31/2022
NIH/National Institute on Aging
Mid-Career Mentoring Award for Patient-Oriented Research (POR) in Aging
The Specific Aims are: 1) To continue to build my research program around improving the quality and outcomes of care for hospitalized older adults with delirium. 2) To build a mentorship program that expands patient oriented research (POR) in aging at BIDMC and HMS, with a focus on delirium and related conditions. 3) To expand my mentorship program to include a focus on implementation science, with the goal of bringing the ever-accelerating scientific advances in delirium research to the bedside.
Role: Principal Investigator

P01 AG031720 (Inouye) 9/15/2018 – 5/31/2023
NIH/National Institute on Aging
Delirium, Dementia and the Vulnerable Brain: An Integrative Approach.
This program project seeks to define the complex relationship of delirium, dementia, and brain vulnerability through a series of five, interrelated projects, each of which examines a unique aspect of vulnerability. I serve as overall Co-Principal Investigator, as well as Leader of Project 2, The Role of Inflammation in the Pathophysiology of Delirium and its Associated Long Term Cognitive Decline, and Leader of Core B, the Field Core. Project 2 builds on our findings from the first cycle of funding and will give us a more complete picture of how the inflammatory response differs in patients who do and do not develop delirium and long term cognitive decline. In addition to my scientific roles, I will continue to serve on the P01 Executive Committee, Operations Committee, and Co-Chair of the Biorepository/Database Committee.
Role: Project Leader, Core Leader

R01 AG065554 (Marcantonio, Subramaniam, Talmor) 9/30/2019 – 5/31/2024
NIH/National Institute on Aging
PANDORA: Scheduled Prophylactic 6-Hourly IV Acetaminophen to Prevent Postoperativfe Delirium in Older Cardiac Surgical Patients
We will conduct a randomized, triple blind clinical trial that enrolls 900 patients 60 years of age or older undergoing cardiac surgery. Through this trial, we will determine the effect of IV acetaminophen on; 1) the incidence, duration, and severity of postoperative delirium, 2) the use of opioids and other rescue analgesics in the first 48 postoperative hours, daily pain scores at rest and exertion, and length of stay in the Intensive Care Unit and overall hospital length of stay 3) longer-term (one, six, 12 months) cognitive, physical, and self-care functional recovery after surgery. We will pursue these aims using an innovative method of administering a routine drug intravenously in scheduled, six hourly intervals for 48 hours, which is the period of maximum secondary injury, inflammation, and pain postoperatively.
Role: Principal Investigator