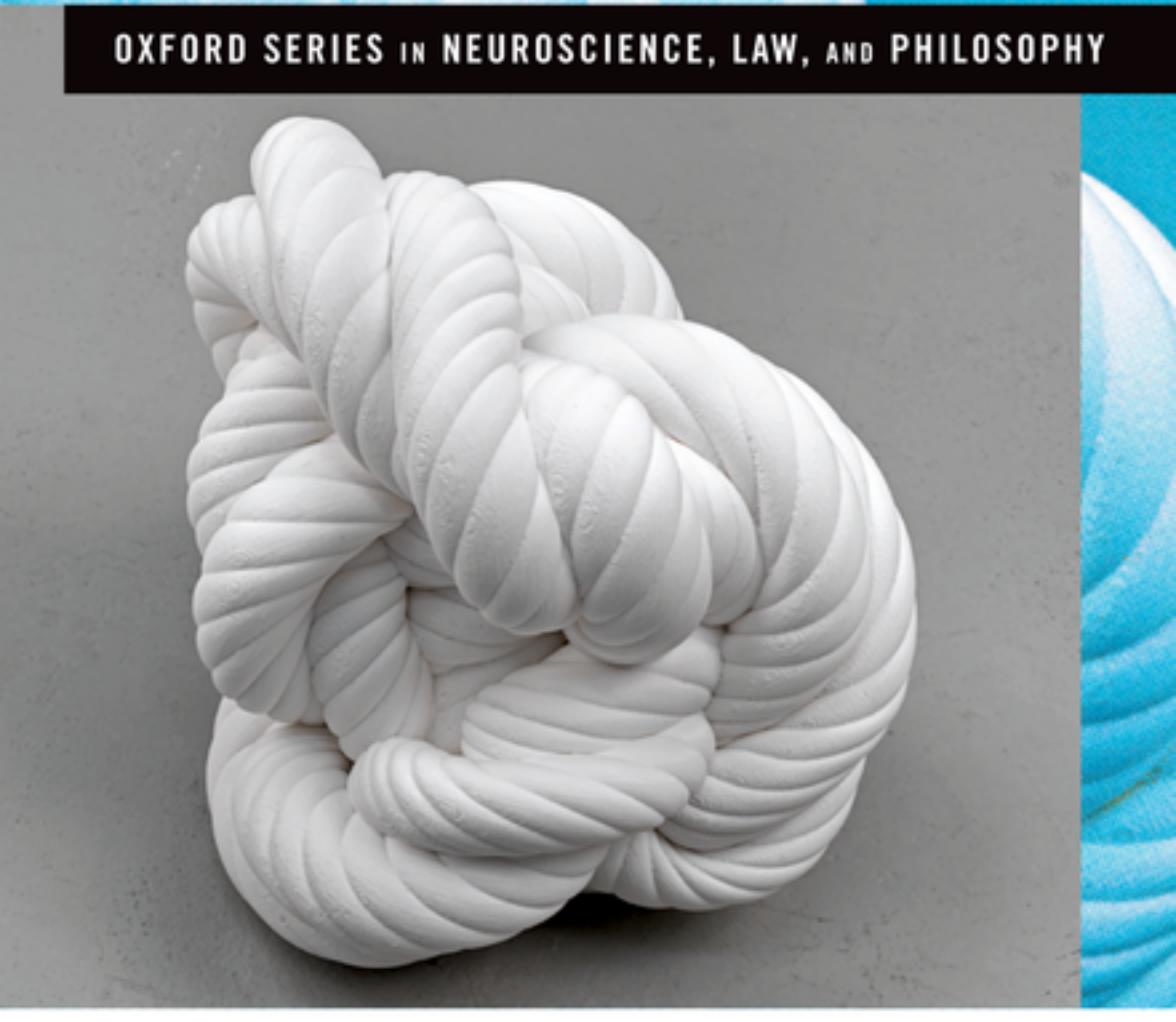
OXFORD SERIES IN NEUROSCIENCE, LAW, AND PHILOSOPHY



THE NEUROETHICS OF BIOMARKERS

What the Development of Biopredication Means for Moral Responsibility, Justice, and the Nature of Mental Disorder

EDITED BY

Matthew L. Baum

OXFORD

The Neuroethics of Biomarkers

Oxford Series in Neuroscience, Law, and Philosophy

Series Editors
Lynn Nadel, Frederick Schauer, and Walter P. Sinnott-Armstrong

Conscious Will and Responsibility
Edited by Walter P. Sinnott-Armstrong and Lynn Nadel

Memory and Law
Edited by Lynn Nadel and Walter P. Sinnott-Armstrong

Neuroscience and Legal Responsibility
Edited by Nicole A. Vincent

Handbook on Psychopathy and Law
Edited by Kent A. Kiehl and Walter P. Sinnott-Armstrong

A Primer on Criminal Law and Neuroscience
Edited by Stephen J. Morse and Adina L. Roskies

Bioprediction, Biomarkers, and Bad Behavior
Edited by Ilina Singh, Walter P. Sinnott-Armstrong, and Julian Savulescu

Finding Consciousness: The Neuroscience, Ethics, and Law of Severe Brain Damage
Edited by Walter Sinnott-Armstrong

The Neuroethics of Biomarkers: What the Development of Bioprediction Means for Moral Responsibility, Justice, and the Nature of Mental Disorder
By Matthew L. Baum

The Neuroethics of Biomarkers

What the Development of Bioprediction Means for Moral Responsibility, Justice, and the Nature of Mental Disorder

Matthew L. Baum

OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS

Oxford University Press is a department of the University of Oxford. It furthers the University's objective of excellence in research, scholarship, and education by publishing worldwide.Oxford is a registered trade mark of Oxford University Press in the UK and certain other countries.

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America.

First Edition Published in 2016

Library of Congress Cataloging-in-Publication Data
Names: Baum, Matthew L., author.
Title: The neuroethics of biomarkers : what the development of bioprediction means for moral responsibility, justice, and the nature of mental disorder / by Matthew L. Baum.
Other titles: Series in neuroscience, law, and philosophy.
Description: Oxford ; New York : Oxford University Press, [2016] | Series: Oxford series in neuroscience, law, and philosophy | Includes bibliographical references and index.
Identifiers: LCCN 2015031170 | ISBN 9780190236267 (alk. paper)
Subjects: | MESH: Mental Disorders—diagnosis. | Bioethical Issues. | Biological Markers. | Risk Assessment.
Classification: LCC RC455.4.B5 | NLM WM 141 | DDC 616.89/071—dc23
LC record available at http://lccn.loc.gov/2015031170

9 8 7 6 5 4 2 3 1
Printed by Sheridan, USA

Foresight! Foresight!, which takes us ceaselessly beyond ourselves and often places us where we shall never arrive. This is the true source of all our miseries. What madness for a fleeting being like man always to look far into a future which comes so rarely and to neglect the present of which he is sure. It is a madness all the more destructive since it increases continuously with age; and old men, always distrustful, full of foresight, and miserly, prefer to deny themselves what is necessary today so as not to lack it a hundred years from now.

Rousseau (1979 [1762]), *Emile*, pp. 82–83

CONTENTS

List of Figures and Tables ix
Acknowledgments xi

Introduction

1. The Biomedical Promise of Biomarkers 3

2. Bioprediction of Brain Disorder: Definitions and Scope 13

PART I Reorientation of the Concept of Disorder

3. "There Is More Light Here": Re-illuminating the Categories of Mental Illness 37

4. The Probability Dysfunction 44

5. The Practical Ethics of Predictive Markers in Diagnosis: Can Risk Banding Address the Ethical Controversy Surrounding "Psychosis Risk Syndrome" and "Preclinical Alzheimer's Disease"? 78

PART II Bioprediction and Moral Responsibility

6. Enhanced Responsibility: Foreseeability and New Obligations to Others 91

7. Reduced Responsibility: Distinguishing Conditions in Which Biomarkers Properly Reduce Legal Responsibility 117

PART III Bioprediction and Society

8. Bioprediction and Priority 143

Conclusion 164

Appendix I. A Brief Note on Genetic versus Non-Genetic Biomarkers 169
Appendix II. Seizure Prediction 171
Appendix III. The Case of Stefania Albertani 177
References 179
Index 191

LIST OF FIGURES AND TABLES

Figure 1.1. Discussion of the Ethics of Biomarkers Lags Far Behind the Science 8
Table 2.1. Types of Biomarker 'omics 14
Table 2.2. Bioprediction: Glossary of Terms (in Order of Appearance) 30
Table 4.1. The Three Influential Theories of Disorder 49
Table 4.2. Examples of Disorders with Increased Probability of Future Harm (But Mild or Unnoticeable Present Harm) Already in Use 58
Table 4.3. Sample Risk Calculation Scores 66
Table 4.4. Probability Dysfunction Classification Compared to Other Theories of Disorder 74
Table 8.1. Chances Of Outcomes in "Vaccination" According to The Binomial Theorum 150

ACKNOWLEDGMENTS

I am indebted to a great number of individuals without whom this book would not have been possible. I am especially grateful to my Oxford DPhil advisors, Julian Savulescu and Mark Sheehan, as well as to Tony Hope, Neil Levy, Tom Douglas, Russell Perkins, Caroline Huang, Roger Crisp, Paul Troop, my two DPhil examiners, and the anonymous reviewers at Oxford University Press for providing invaluable feedback on the arguments in this book. Andrew McCall and Tad Baum generously commented on the book nearly in its entirety, which much improved this end product. Thanks to the District I Rhodes Scholarship Committee and the Rhodes Trust for taking a chance on a molecular neurobiology student who wished to pursue a degree in neuroethics, thus enabling this work. There are many who, through careful and kind administration, helped me navigate the formal hurdles necessary for the pursuit of the ideas described in this book: Christelle Kervella-Jones, Mary Eaton, Don Markwell, Piers Nye, Susan Barrington, Andrew Cooper, Glynis Price, Nailya Nikitenko, Miriam Wood, Deborah Sheehan, and of course Joan Bossert, Louis Giulino, Lynn Luecken and the production team at Oxford University Press. To the many others who have helped me along the way who are not by name acknowledged here—among them my colleagues in the Oxford Department of Public Health, the Ethox Center, the Uehiro Centre for Practical Ethics, Rhodes House, the Oxford Centre for Neuroethics, Balliol College, Harvard Medical School, and the Petrie Flom Centre at Harvard Law School—thank you, and I apologize for not acknowledging you individually. Finally, thank you to Emmilie Aveling for supporting my pursuit of this project despite its challenges.

Any errors, mistakes, weaknesses, and omissions that remain in this book after the help of this great number of people are entirely my own; for these errors, I apologize in advance.

The Neuroethics of Biomarkers

Introduction

1

The Biomedical Promise of Biomarkers

"See, it shakes a little," he said, holding out his hand. The man's fingers circled in unison with his index finger rubbing repetitively against the soft underside of his thumb; a classic "pill-rolling tremor," he went on to say. The man's tremor was the only visible symptom of his new diagnosis of Parkinson's disease. Parkinson's disease is thought to be caused by the deterioration of a certain population of neurons that produce the neurotransmitter dopamine, and are important for the control of voluntary movement. These neurons are progressively lost from a specific area of the brain called the *substantia nigra*, which is named after the characteristically dark pigment that the high concentration of dopamine gives these neurons. Interestingly, the paradigmatic symptoms of the disorder[1]—tremor, shaking arms, bobbing head, and slowness of voluntary movement—do not appear until the person has already lost *over 80 percent of these key neurons* (Nestler et al. 2009). Therefore, once a person's symptoms can be diagnosed as Parkinson's, this neuronal population is mostly dead, and treatment difficult.

Modern efforts in neuroscience are building an increasingly convincing case that many mental and neurological disorders, from this man's Parkinson's disease to mental retardation, schizophrenia, epilepsy, bipolar disorder, and Alzheimer's disease, *develop over time*. In what is sometimes referred to as a molecular cascade (Boenink 2009), these disorders are often preceded by increasingly aberrant molecular and circuit-level changes that develop over weeks, months, years, and even decades, *before* the appearance of the recognizable clinical symptoms of the disorders. As a student of molecular biology studying these disorders, I became increasingly fascinated by the possibility that many of the disorders as we currently diagnose them might actually be severe *end states* rather than newly onset dysfunctions. The idea is that with many disorders we are arriving very late, as if to the scene of a car accident; maybe things could be different if we could find the equivalent of sticky brakes, overinflated tires, and busted headlights that increase the likelihood of a crash.

I am not alone in that sentiment, as illustrated by the following excerpt from a paper authored by the former director of the National Institutes of Mental Health (NIMH), Tom Insel:

> Currently, mental disorders are diagnosed by symptoms that emerge at a late stage, presumably years after brain systems veer from more typical development. Diagnosing schizophrenia or bipolar disorder with the emergence of psychosis may be analogous to diagnosing coronary artery disease by myocardial infarction [heart attack]. One of the most hopeful approaches to reducing the morbidity and mortality of serious mental illness borrows a page from the cardiology playbook. By developing biomarkers [biological markers] for early diagnosis, we may be able to preempt many of the most disabling aspects of our most severe mental illnesses. (Insel 2009)

If we could identify this veering of brain systems earlier, would we have better success in treating the late stage? Could we intervene to delay or even prevent the onset of the disorder as we know it? Or could we at least prepare for the contingency, as we prepare for a possible hurricane?

The difficulty of adequately treating established disorders has prompted not only scientists, but also government, to establish as top priorities early detection and preventive medicine for brain-based disorders. In the United Kingdom (UK), the Foresight Report argued that preventive medicine in mental health is necessary to guard and maximize the nation's "mental capital" (Beddington et al. 2008). The UK Medical Research Council, in its 2010 review of mental health research, also called for greater emphasis on prevention in mental health (Sahakian et al. 2010).

For preventive medicine to be successful, however, we first need to advance methods of estimating who is at risk. In recognition of this necessity, a 2010 report from the Grand Challenges in Global Mental Health Initiative named the identification of biomarkers of increased risk of mental disorder as "Goal A" (Collins et al. 2011).

Clearly, many big players in the public sector are convinced that the development of predictive biomarkers holds vast potential for changing the health of individuals and populations, but what else might the power of bioprediction change? The following fictional, but reality-based, cases illustrate four potential domains of change.

First, the development of predictive biomarkers is poised to unsettle how we relate to the definitional categories for which the biomarkers are developed. Consider "Risky Definitions."

RISKY DEFINITIONS

Rick has been bothered by the feeling that people on the city bus he rides to school are talking about him behind his back; he knows they probably are not but he can't shake that uncomfortable feeling and he thinks this is starting to interfere with his performance in school and sports. He seeks a psychiatric consultation and after a battery of testing is told that he has a condition sometimes called "psychosis risk syndrome": in experimental settings 20–40 percent of young people who scored as he did on these tests go on to have a psychotic episode in the next two years. When Rick's primary care physician (PCP) learns of this consultation, he is displeased, explaining that since the majority of people will not go on to develop psychosis, the category needlessly causes fear and stigma.

Inclusion in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) of such a category based on risk of psychosis was hotly contested and eventually was omitted amidst concerns like those voiced by Rick's PCP: that we should not have disorders *based on risk* because many of those individuals in the category will not go on to develop the thing they are at risk for (as discussed in Chapter 5; also see Singh and Sinnott-Armstrong 2014). With the development of biomarkers, such contentious debates on risk categories are likely to multiply. What criteria can we look to in evaluating these risky disorders?

Second, the development of predictive biomarkers may change the extent of the obligations we owe to others; consider "Risky Driving."

RISKY DRIVING

Sally, a 33-year-old female, was brought into the emergency room after being hit by a bicycle as she crossed the street. Sally had a few scrapes and bruises, but was otherwise unharmed. Having had an uncle pass away unexpectedly from a heart attack, and feeling pain in her chest, Sally was quite distressed about her heart. An echocardiogram (an ultrasound on the heart) was performed. The echo-technician was surprised to find that the walls of Sally's heart were profoundly thickened. When Sally learned that the presence of this biomarker, increased heart wall thickness, corresponds to an increased risk of sudden cardiac death, the first thing she did was to make arrangements to stop driving the van for her children's playgroup. When asked about that decision, Sally explained that she felt "it would have been irresponsible to do otherwise."

Sally felt that the knowledge of her biological risk required her to take special precautions to minimize the likelihood that the risk would translate to harming those she cared for. Under what conditions should knowledge of biological risks, as estimated by biomarkers, enhance moral responsibility in this way? Might there be some cases in which one could be blameworthy for continuing to drive in ignorance of the risks one might pose to others?

Third, the development of predictive biomarkers may change those whom we punish, and how much we punish them; consider "Risky Punishment."

RISKY PUNISHMENT

> *In Brad's murder trial, his lawyer argued for a reduction in sentence on account of Brad's genetic, environmental, behavioral, and neuroimaging markers, which research has shown are enriched in groups of individuals that, on the whole, are more likely to commit reactive violence. The opposing legal team objects on the grounds that data gathered on groups do not validly apply to Brad as an individual, that these biomarkers are problematically probabilistic, and that a proneness to violence is no grounds for a reduction in legal responsibility.*

As biomarkers risk flooding the courts, there are split opinions about whether and under what conditions biomarkers should rightly reduce legal responsibility. While the courts have structures for determining the relevance of a given mental disorder, it is unclear where to fit biological risks.

Fourth, biomarkers may change the obligations of society to individuals in terms of the way it chooses to distribute resources or opportunities; consider "Risky Allocation."

RISKY ALLOCATION

> *The social service of Hynkley is reviewing the way it currently allocates its resources for at-risk children. Among the proposals being considered is one that controversially suggests that resource allocation should be prioritized through violence risk estimation, incorporating biomarkers. It is argued that children at higher risk of future violence are more likely to have life opportunities curtailed by the justice system, and that the social service should prioritize these worst-off children in the distribution of the service's limited resources.*

Are those with higher risk of something bad in the future actually worse off? After all, most of the children in the hypothetical village of Hynkley will not

end up in trouble with the justice system, just like most of the young people with "psychosis risk syndrome" will not develop psychosis. Are such risky assessments plausible grounds to change how we should distribute resources? Just as public health is expanding to consider social influences on health, should institutions of distributive justice also expand to consider these biological influences on social outcomes?

Though this science is young, the rapidly expanding development of biomarkers in neuroscience will increasingly enable the estimation of the likelihood (bioprediction) of future adverse psychological events, from the emergence of full psychotic episodes and the onset of dementia to impulsive violent reaction.[2] The medical potential of biomarker discovery is immense and worthy of the excitement that surrounds it, but the discussion needs to extend to the ethical implications of bioprediction (the use of those biomarkers), some of which are illustrated by "Risky Definitions," "Risky Driving," "Risky Punishment," and "Risky Allocation" and will be discussed as this monograph unfolds. As shown in Figure 1.1, discussions on what we *ought to do* with the biomarker explosion lag far behind discussions of what we *can or might do.* Though discussion of the neuroethics of biomarkers is just beginning, it is not contained solely within the vials of the medical clinic, but spills into courts and statehouses, drawing the interest of a uniquely interdisciplinary group of scientists, lawyers, doctors, and philosophers.

It is the preliminary examination of several ethical issues of bioprediction, and the construction of a philosophical groundwork with which to assess others, that are the goals of this book. What makes bioprediction interesting is that it not only raises moral challenges, but also challenges our moral frameworks. I argue that much of the current ethical controversy about biomarkers stems from disagreements about how (or whether) to integrate bioprediction's explicitly probabilistic predictive information into existing medical, legal, and political structures.

Much existing debate centers on a perceived categorical division between disorders and biological risks. The difficulty is in part that our institutions have gotten on well *enough* by cleaving the world into the healthy and the sick. Consequently, medicine, law, and society have special protocols for disorders, but not *risk of disorders.* A disorder changes how we allocate resources, like health care or social services. A disorder changes the moral attitudes we hold, like whether we excuse or blame—and how much. Or a disorder creates new responsibilities for the person who has it—for example, driving restrictions if one has epilepsy or visual impairment.

But what do we do if someone does not have a named disorder, but has a biological risk?

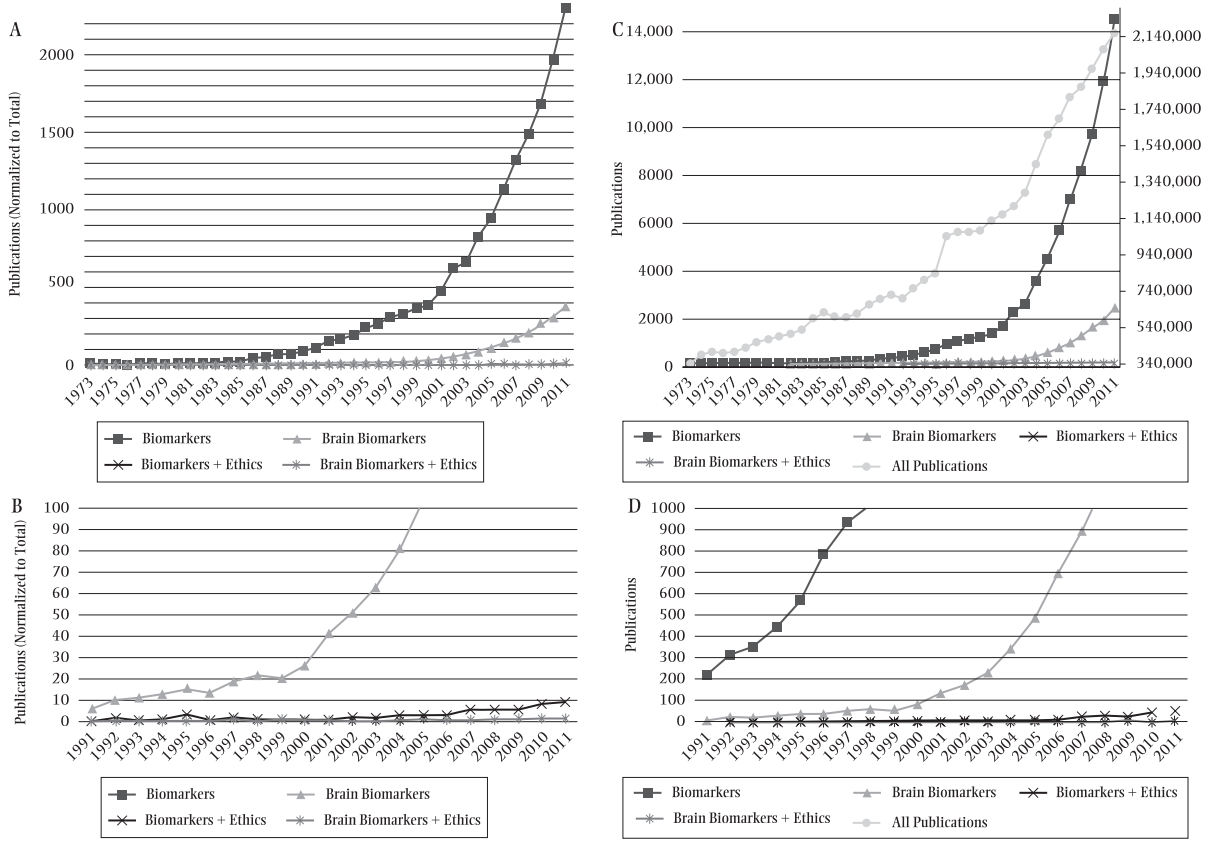


Figure 1.1 Continued