PREDICTING ALZHEIMER DISEASE†

*Henry T. Greely**

Biomedical science is learning more about Alzheimer disease. As it does so, the ability to predict with substantial accuracy whether some individuals will be diagnosed with this disease is increasing rapidly. Without a useful preventive intervention, such predictions are, at best, mixed blessings. This Article surveys the science of predicting Alzheimer disease, the likely advantages and disadvantages of such prediction, and their legal status, before offering some recommendations for policy changes.

Introduction

She glided from room to room like a ghost. No longer forgetful, no longer worried, no longer talking, no longer the strong mother my wife grew up with, no longer, in most ways, human. I watched her slip into the room where my son, her four-year-old grandson, slept, touch his cheek, and slip out. And away.

Henry T. Greely is Deane F. and Kate Edelman Johnson Professor of Law; Professor, by courtesy, of Genetics; Director, Center for Law and the Biosciences, Stanford University.

† This article is dedicated to the memory of my late mother-in-law, Lucille Knoche Butcher, whose own memory was lost long ago. This article began as the Anne F. Baum Memorial Elder Law Lecture at the University of Illinois School of Law on March 7, 2016. A publishable contribution from me was part of the bargain, which I am happy to have finally fulfilled, albeit more than four years late. This piece is longer than any of us expected, which *could* be viewed as interest on the overdue debt. Somewhat to my surprise, and disappointment, the underlying science, medicine, and law have not changed nearly enough in the four years since my talk. I want to thank my (now graduated) research assistant, Brittany Cazakoff, JD '20, for her, as always, invaluable help on this paper.

I do not know–I will never know–whether my mother-in-law died of Alzheimer disease,[1] vascular dementia, or some rarer thief of the mind. But I will never forget her long decline and death, even though, living 1,600 miles away, I saw it only in glimpses. Glimpses were more than enough.

My mother-in-law died in 1995, just short of her eightieth birthday. Today, we are rounding the cusp of being able to predict whether people will be diagnosed with Alzheimer disease, people like her youngest daughter—my wife. Or like my own, now ninety-two-year-old, mother, who has had one older sister die with dementia and has another older sister living with it. Or like sixty-eight-year-old me.

Our approaching ability to predict who will, or will not, be diagnosed with Alzheimer disease is a largely unlooked-for secondary effect of basic research into the condition. There has been little visible demand for such a predictive test from consumers, or from Alzheimer disease organizations. The most relevant medical organizations have recommended against predictive testing.[2] The U.S. Food and Drug Administration ("FDA") has not approved any tests for predicting Alzheimer disease.[3] Researchers trying to predict Alzheimer disease are

1. Like many diseases, this one was named for the doctor who first described it, a German physician named Alois Alzheimer, who published an article describing a distinctive form of dementia in 1906. Alois Alzheimer, *Über einen eigenartigen schweren ErkrankungsprozeB der Hirnrinde*, 23 NEUROLOGISCHES CENTRALBLATT 1129–36 (1906). Ironically, there is now some doubt as to whether Dr. Alzheimer's first patient actually had Alzheimer dementia.

In recent years, some patient advocates have argued that diseases should not be named in a way that implies they are in some way the "possessions" of their discovering doctor. Although Alzheimer's disease, Down's syndrome, and Parkinson's disease, are still most frequently seen in the medical and scientific literature with possessive apostrophes, there is no longer a consensus on usage in major journals. I examined twenty recent articles about Alzheimer['s] disease in the New England Journal of Medicine, the Journal of the American Medical Association, and Science. I also looked at similar British journals—the Lancet, the British Medical Journal, and Nature. Although the possessive was still used more often, the results were mixed. I do not personally feel strongly about this issue—it seems to me that patients are not likely to be substantially affected by whether or not "their" disease is named in a way that implies it belongs to someone else—but, on balance, I slightly prefer the name without the "'s." That naming convention seems to me possibly a little more logical—and *clearly* a little bit shorter.

2. *See Medical Tests*, ALZHEIMER'S ASS'N, https://www.alz.org/alzheimers-dementia/diagnosis/medical_tests (last visited Dec. 5, 2020) [hereinafter *Medical Tests*].

3. *See generally The FDA Warns Against the Use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication*, U.S. FOOD & DRUG ADMIN. (Oct. 31, 2018), https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-use-many-genetic-tests-unapproved-claims-predict-patient-response-specific.

not trying to create a mass market test, but to understand the disease better, in order to better search for ways to prevent it, to treat it, to cure it—and for ways to test all of the possible interventions to those ends.[4] But, ultimately, none of these will prevent predictive tests from being made and used.

I believe a good predictive test for Alzheimer disease will be developed and used and that the tests will have consequences. Unhappily, until (unless?) those researchers succeed in discovering—and bringing to the clinic—good preventive measures, treatments, or cures, those consequences will not be primarily medical, but social, ethical, and even legal. And they will not necessarily be, on balance, beneficial. This Article sets out to predict and describe those consequences.

The Article is also one piece of a broader design. I have worked on "neuroethics" since 2002, exploring the ethical, legal, and social implications of advances in neuroscience. I have argued that most of those issues can be grouped into six categories—questions of prediction, mind-reading, responsibility, treatment, enhancement, and research methods.[5] I have written articles or book chapters focusing on five of them, but I have never published anything devoted to the issue I have always listed first—prediction.

It was prediction, though, that drew me into neuroscience from genetics in the first place. It seemed clear to me that, as with genetics, some of the major social effects of neuroscience would come from its ability to help us predict our futures—and open us to possibilities of discrimination, stigma, psychological damage, and other problems or quandaries. What would happen, I have asked, if we could predict which 0.8 percent of fifteen-year-olds will be diagnosed with schizophrenia in the next fifteen years? Or which 1 to 2 percent of young men will become psychopaths, amoral, and often criminal? Or which sixty-year-olds will, within the next ten, fifteen, or twenty years, face a diagnosis of Alzheimer disease? This Article is my first effort to flesh out the effects of neuroscientific prediction on our society and on its individual members. That it is about predicting a disease whose effects I

4. *See* Parnaz Hojjati, *Shifting from Treatment to Prevention in Alzheimer's Research*, MICH. HEALTH (July 17, 2020, 11:30 AM), https://healthblog.uofmhealth.org/wellness-prevention/shifting-from-treatment-to-prevention-alzheimers-research.

5. *See* Henry T. Greely, *Law and the Revolution in Neuroscience: An Early Look at the Field*, 42 AKRON L. REV. 687, 689 (2009) [hereinafter *Law and the Revolution*].

have seen, and a disease that personally terrifies me, may be a coincidence of how neuroscience has developed.

This Article will do five things. It will start with some short background information on Alzheimer disease. Next, it will describe some of the various ways that are being developed to predict who will get Alzheimer disease. Third, it will talk about some of the possible advantages and disadvantages of this kind of prediction. Fourth, it will analyze the regulatory constraints that currently exist (or do *not* exist) around such tests. Finally, it will end by exploring some steps we might want to take to prepare for better Alzheimer prediction.

This Article asks a lot of questions and gives very few answers. The answers, however, will have to come, and soon. Primitive versions of these tests are already here, used, for example, by uncounted thousands of 23andMe customers.[6] New developments in neuroimaging and in blood plasma biomarkers make more accurate tests seem more and more likely. "Good" predictive testing seems likely to be here soon and at least some people are going to want it.

I must confess, though, that I said almost exactly that last sentence in the March 2016 lecture that gave rise to this Article. Somewhat to my surprise, and disappointment, the underlying science, medicine, and law have not changed nearly as much as I had expected, and hoped, in the nearly five years since that lecture. In particular, fewer people than I thought are seeking out predictive testing for Alzheimer disease. The course and speed of science is hard to foresee; social and political changes can be even harder. (When I gave that talk Donald Trump seemed highly unlikely to receive the Republican presidential nomination, let alone *ever* be elected president.) More than a little humility is called for, and yet I continue to think testing to predict Alzheimer disease will become a viable option for many, and that some will choose to use it. If so, we should start deciding how to deal with them now; only a little is lost by being too early, much harm could be done by being too late.

6. *See generally Late-Onset Alzheimer's Disease*, 23ANDME, https://www.23andme.com/topics/health-predispositions/late-onset-alzheimers/ (last visited Oct. 5, 2020) [hereinafter *Late-Onset Alzheimer's Disease*].

I. Alzheimer Disease

Reader, have you seen a relative or a close friend with Alzheimer disease? Those of you who said "no" will change your answer before long—because of a grandparent, a parent, an aunt, or uncle, or, for some older readers, a friend, sibling, or spouse. It is a terrible disease.

My own closest experience with it was with my mother-in-law, who—and we are still not sure whether this was a good thing or a bad thing—lived a long time with Alzheimer disease. She survived more than twelve years after the initial diagnosis. My father-in-law refused to let her be institutionalized, replying, "I said for better or for worse." I'm not sure that was the best thing for her, but it was important to him and, for the last half of that time, she didn't know who he was—or who she was. To call a disease evil is not fair. To be "evil" should require a sort of consciousness and agency that diseases don't have. But if a disease can be evil, I'll nominate Alzheimer disease. It leaves the body working while it robs its victims of themselves…it steals the person out of the body.

Alzheimer disease is a dementia.[7] "Dementia" comes literally from the Latin *de* meaning "without," and *mens,* meaning "mind."[8] It is crucial to realize that Alzheimer disease is not the only kind of dementia.[9] This Article focuses on Alzheimer disease, but, remember, even if your Alzheimer disease prediction says you are never going to get Alzheimer disease, it doesn't mean that you won't get multi-infarct dementia, Lewy body dementia, Parkinson disease associated dementia, orbital frontal dementia, chronic traumatic encephalopathy, or any of a depressing number of other dementias.[10]

The second most common cause of dementia is called multi-infarct, or vascular dementia, caused by many small strokes.[11] In their

7. *See Alzheimer's disease*, MAYO CLINIC, https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/symptoms-causes/syc-20350447 (last updated Dec. 29, 2020).

8. *See* Kurt A Jellinger, *Should the Word 'Dementia' Be Forgotten?*, 14 J. CELLULAR & MOLECULAR MED. 2415, 2415 (2010), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3823159/pdf/jcmm0014-2415.pdf.

9. *What Is Dementia? Symptoms, Types, and Diagnosis*, NAT'L INST. ON AGING, https://www.nia.nih.gov/health/what-dementia-symptoms-types-and-diagnosis (last visited Dec. 5, 2020).

10. *See id.*

11. *Multi-Infarct Dementia Information Page*, NAT'L INST. NEUROLOGICAL DISORDERS & STROKES, https://www.ninds.nih.gov/Disorders/All-Disorders/Multi-Infarct-Dementia-Information-Page (last updated Mar. 27, 2019, 4:20 PM).

symptoms, Alzheimer disease and multi-infarct dementia are not particularly different, and they may have some causal connections.[12] For instance, cardiovascular disease is a major risk factor for each[13] and it might be more appropriate to think of some significant number of cases as "mixed" Alzheimer disease and multi-infarct dementia. But, for now, we think of Alzheimer disease as accounting for about 60 percent of dementias, micro-infarcts causing roughly 20 percent, Lewy body dementia totaling about 10–15 percent, orbito-frontal dementia another 5 percent, and many other conditions causing a few percent of dementias.[14]

These are only fairly rough estimates, largely because it is not easy to tell which dementia is which[15]—and because there is usually no good reason to determine which is which. Almost all of the dementias have the same number of effective treatments—essentially none.[16] As a result we do not spend much time, effort, discomfort, or money trying to make a definitive diagnosis.

Alzheimer disease was first described in 1906 by German physician Alois Alzheimer, at that time a research assistant to Emil Kraepelin, one of the giants in the early study of brain diseases.[17] Alzheimer described the disease based on his study of a patient in a Frankfurt asylum starting in 1901, a fifty-one-year-old woman named Auguste Deter.[18] Deter showed memory loss, disorientation, and hallucinations.[19] Alzheimer followed her for nearly five years, until her death in April 1906, when he obtained her brain for study.[20] On autopsy, Alzheimer

12. *See Risk factors for heart disease linked to dementia,* NAT'L INST. HEALTH (Aug. 15, 2017), https://www.nih.gov/news-events/nih-research-matters/risk-factors-heart-disease-linked-dementia.

13. *See id.*

14. *The Different Types of Dementia*, JOIN DEMENTIA RES., https://news.joindementiaresearch.nihr.ac.uk/different-types-dementia/ (last visited Dec. 5, 2020); *Different Types of Dementia*, ALZHEIMER'S RES. UK: DEMENTIA STAT. HUB, https://www.dementiastatistics.org/statistics/different-types-of-dementia/ (last visited Dec. 5, 2020).

15. *See Dementia*, MAYO CLINIC (Apr. 19, 2019), https://www.mayoclinic.org/diseases-conditions/dementia/diagnosis-treatment/drc-20352019.

16. *See generally* Rachel Nania, *Will We Ever Find a Cure for Dementia?*, AARP (June 25, 2020), https://www.aarp.org/health/dementia/info-2020/cure-for-dementia.html.

17. Konrad Maurer et al., *Auguste D and Alzheimer's Disease*, 349 THE LANCET 1546, 1546 (1997), https://alzheimer.neurology.ucla.edu/pubs/alzheimerLancet.pdf.

18. *Id.*

19. *Id.*

20. *Id.* at 1548.

saw that her cerebral cortex was unusually thin and that her neurons exhibited both "senile plaque" and "fibrillary tangles," visible only because of a new stain Alzheimer was able to use.[21] Alzheimer called her condition "presenile dementia."[22] Kraepelin named the disease after Alzheimer in 1910 in the eighth edition of Kraepelin's *Handbook of Psychiatry*, five years before Alzheimer's death at age fifty-one, apparently from the effects of streptococcal infection,[23] today frequently called strep throat, which could, and can if untreated, develop into the more serious scarlet fever and the much more serious rheumatic fever.[24] Ironically, in light of her age and some other aspects of her case, it is now considered doubtful whether Deter actually had what we now call Alzheimer disease, but the plaques and tangles Alzheimer saw are integral to diagnosing the disease named after him.[25]

Alzheimer disease is defined as the condition of a person who is demented, a determination based on behavior, but whose brain, when examined, shows two signs: amyloid plaque and tau tangles.[26] Amyloids are a large class of peptides (in effect, short proteins).[27] All proteins are strung together chains of shorter proteins called amino acids, which normally come in twenty different varieties.[28] The amyloids can be made up of thirty-six to forty-three amino acids.[29] One kind of amyloid, Amyloid beta 42 ("Aß42") is made of forty-two amino acids, arranged in a specific order. In Alzheimer disease patients, Aß42 is found

21. *See id.* at 1549.
22. *Id.* at 1546.
23. *Id.* at 1549.
24. *See Rheumatic fever*, MAYO CLINIC (Oct. 10, 2019), https://www.mayoclinic.org/diseases-conditions/rheumatic-fever/symptoms-causes/syc-20354588.
25. *See generally Causes of Alzheimer's Disease: What Happens to the Brain in Alzheimer's Disease*, NAT'L INST. ON AGING (May 16, 2017), https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease [hereinafter C*auses of Alzheimer's Disease*].
26. *See id.*
27. *See id.*; Rik van der Kant et al., *Amyloid-ß-independent Regulators of Tau Pathology in Alzheimer's Disease*, 21 NATURE REVS. NEUROSCIENCE 21, 21 (2020); Jun Wang et al., *A Systemic View of Alzheimer's Disease – Insights from Amyloid- ß Metabolism Beyond the Brain*, 13 NATURE REVS. NEUROLOGY 612, 612 (2017).
28. van der Kant et al., *supra* note 27, at 2; Wang et al., *supra* note 27, at 612; Karen Steward, *Amino Acids–the Building Blocks of Proteins*, TECH. NETWORKS (Sept. 26, 2019), https://www.technologynetworks.com/applied-sciences/articles/essential-amino-acids-chart-abbreviations-and-structure-324357.
29. *See* M. Paul Murphy & Harry LeVine III, *Alzheimer's Disease and β-Amyloid Peptide*, 19 J. ALZHEIMER'S DISEASE 311, 311–12 (2010), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2813509/pdf/nihms-171690.pdf.

forming plaques on the outside of the membranes of neurons that are dead or dying.[30]

There is some evidence that the Aß42 that forms plaques is misshapen, perhaps as a result of contact with another misshapen molecule of Aß42 that acts as a "seed."[31] The idea that diseases can be caused by proteins that are misfolded as a result of contact with other misshapen proteins was quite controversial when it first surfaced as an explanation for a different terrible brain disease, Creutzfeldt-Jakob disease.[32] Stanley Prusiner won the Nobel Prize in physiology or medicine in 1997 for his discovery of this disease mechanism.[33] He named the infectious proteins "prions," a concept that is generally—but not universally—accepted.[34] Aß40 is also a smaller constituent of Alzheimer-related plaques; it is the kind of Aß most commonly found circulating in the blood.[35] It remains surprisingly unclear what either of these molecules normally do in healthy people.

Tau is another protein associated with Alzheimer disease.[36] Unlike Aß42 it is found inside the cell bodies of neurons, not on the outside of their membranes.[37] It is a normal and apparently essential part of neurons; it forms part of the cells' "cytoskeletons."[38] Cytoskeletons are the tubes through which nutrients and other essential molecules

30. *See id.* (stating that an amyloid beta is a form of a common short protein [sometimes called a polypeptide] called amyloid. The beta form of this protein can be made up of thirty-seven to forty-three amino acids. In some cases, it is formed by the work of two other proteins, beta secretase and gamma secretase in carving amyloid precursor protein into amyloid beta. A version of amyloid beta with forty-two amino acids is commonly found in the plaques on neurons that are part of the definition of Alzheimer disease; another version with forty amino acids is more commonly found in the blood vessels of the brain).

31. Larry C. Walker et al., *The Prion-Like Properties of Amyloid-β Assemblies: Implications for Alzheimer's Disease*, COLD SPRING HARBOR PERSP. MED. (2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4930920/pdf/cshperspectmed-PRD-a024398.pdf.

32. *See Creutzfeldt-Jakob disease*, MAYO CLINIC, https://www.mayoclinic.org/diseases-conditions/creutzfeldt-jakob-disease/symptoms-causes/syc-20371226 (last updated Jan. 5, 2021).

33. Press Release, Nobel Media AB 2020, The Nobel Prize in Physiology or Medicine 1997, NOBELPRIZE.ORG (Jan. 21, 2020), https://www.nobelprize.org/prizes/medicine/1997/press-release/.

34. *Id.*

35. *See* Michael D. Geschwind, *Prion Diseases*, 21 CONTINUUM 1612, 1613 (2015).

36. *See* C*auses of Alzheimer's Disease*, *supra* note 25.

37. *See id.*

38. *See* Anna Mietelska-Porowska et al., *Tau Protein Modifications and Interactions*: *Their Role in Function and Dysfunction*, 15 INT'L J. MOLECULAR SCI. 4671, 4673 (2014).

move.[39] In Alzheimer disease patients, it clumps together into large tangles, like snarled fishing lines, disrupting the cytoskeleton,[40] although the exact way this kills neurons remains unknown.

If you are demented and have amyloid plaque and tau tangles, by the very definition of the disease, you have Alzheimer disease.[41] If you are demented and you have amyloid plaque but no tau tangles, you are demented, but you do not have Alzheimer disease.[42] The same is true if you are demented with tau tangles but without amyloid plaque.[43] A definitive diagnosis traditionally requires a sample of brain tissue to be used to look for amyloid plaque and tau tangles, which, given the difficulties of taking a biopsy of the brain of a living person, almost always means only at autopsy.[44] But there is rarely any reason to go through the expense and inconvenience of an autopsy in a dead dementia patient. Conversely, people can have amyloid plaque and tau tangles without being demented; they do not have Alzheimer disease, although, if they lived for many years longer they might. It has been estimated that about 10 percent of healthy adults between the ages of fifty and sixty-five are positive for amyloid plaques,[45] although a more recent study indicates that "[a]bout 30% of older adults have brains littered with enough amyloid or tau, or both, to qualify for an Alzheimer's diagnosis but without so much as a hint of dementia. . . ."[46] In fact, it is thought that plaques and tangles begin to build up in the brains of people with Alzheimer disease ten to twenty years before their diagnosis.[47]

39. *See* Eva-Maria Mandelkow & Eckhard Mandelkow, *Biochemistry and Cell Biology of Tau Protein in Neurofibrillary Degeneration*, 2 COLD SPRING HARBOR PERSPS. MED. 1 (2012).

40. *See* Mietelska-Porowska et al., *supra* note 38, at 4690.

41. *See* C*auses of Alzheimer's Disease*, *supra* note 25.

42. *See* Joel Raskin et al., *Neurobiology of Alzheimer's Disease: Integrated Molecular, Physiological, Anatomical, Biomarker, and Cognitive Dimensions*, 12 CURRENT ALZHEIMER RES. 712, 714 (2015).

43. *See id.*

44. *See Symptoms And Diagnosis Of Alzheimer's Disease: How Is Alzheimer's Disease Diagnosed?*, NAT'L INST. ON AGING, https://www.nia.nih.gov/health/how-alzheimers-disease-diagnosed#:~:text=It's%20important%20to%20note%20that, are%20used%20to%20diagnose%20Alzheimer's (last updated May 22, 2017) [hereinafter *Symptoms and Diagnosis*].

45. *See* Willemijn Jansen et al., *Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia: A Meta-analysis*, 313 J. AM. MED. ASS'N 1924, 1924 (2015).

46. *See* Sharon Begley, *They have 'Alzheimer's brains' but no symptoms.*, STAT (Feb. 27, 2020), https://www.statnews.com/2020/02/27/alzheimers-brains-but-no-symptoms/.

47. As we will see, there is a mystery about Aß42. It is clearly associated with Alzheimer disease, so much so that it is part of the disease's definition. It is also

The early symptoms for all dementias are problems with memory (especially short-term memory), problem-solving, language, and other cognitive skills.[48] These problems can occur in mild or severe forms, and can occur in people who are not demented and are not becoming demented[49]—I suspect all of us will have noticed some such issues on occasion. With dementia they become serious enough to affect the person's ability to perform the activities of daily living. For almost all dementias, this is because neurons are damaged or dying in parts of the brain important for these functions.[50] In Alzheimer disease, neuron death often starts in the hippocampus or the closely associated entorhinal cortex, regions crucial for making new memories, but it ultimately spreads to other regions of the brain.[51] Eventually, the condition destroys brain cells essential to such functions as walking and swallowing.[52] In the last stages of the disease, patients are commonly confined to their beds and require round-the-clock nursing.[53] Often they die from other immediate causes, such as pneumonia, brought on by the problems caused by Alzheimer disease. For example, pneumonia is often a result of Alzheimer disease-caused difficulties in swallowing that lead to fluid (and infections) in the lungs.[54]

Whether directly from its destruction of neurons or through a disease or condition taking advantage of it, Alzheimer disease is always

clearly affected by some of the genes that are strongly associated with Alzheimer disease, such as *APP*, *PSEN1*, and *APOE*. And yet pharmaceutical companies have lost scores of billions of dollars on drugs to block the formation of Aß42 plaques. Aß42 is clearly involved in Alzheimer disease *and* it seems increasingly, and expensively, clear that preventing it from forming plaques does not treat or prevent the disease. Why? At this point, the only answer seems to be "biology is complicated." *See id*.

48. *The differences between normal aging and dementia*, ALZHEIMER SOC'Y, https://alzheimer.ca/en/about-dementia/do-i-have-dementia/differences-between-normal-aging-dementia (last visited Dec. 5, 2020).

49. *See id*.

50. *See id*; *Causes of Alzheimer's Disease*, *supra* note 25.

51. *See* Glenda Halliday, *Pathology and Hippocampal Atrophy in Alzheimer's Disease*, 16 LANCET 862, 862 (2017) (describing reduced hippocampal volume and damage to the hippocampus are key features of Alzheimer disease); Usman A Khan et al., *Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease*, 17 NATURE NEUROSCIENCE 304, 304 (2013) (noting entorhinal cortex is implicated in early Alzheimer disease).

52. *See Symptoms and Diagnosis*, *supra* note 44.

53. *See id*.

54. *See id*.

fatal.[55] The average time from diagnosis to death is four-and-a-half years, although people first diagnosed before turning seventy live, on average, ten years after diagnosis.[56] (Note that older people are more likely to die of something else, which also reduces their total life expectancy after diagnosis.[57])

The length of time after diagnosis until death is, however, importantly influenced by the time of diagnosis.[58] The average time from patients' diagnosis to death has been increasing.[59] This may seem like a good thing—it may be a sign of better treatments prolonging life—but with this disease it is largely the result of increasingly early diagnosis.[60] Whether it is better or worse to be diagnosed earlier with an untreatable disease is unclear. A few—very few—cases of dementia are susceptible to useful treatments, notably dementia induced by a vitamin B-12 deficiency or dementia from depression.[61] Alzheimer disease is not one of them.[62]

How many people have Alzheimer disease? Good question—we do not really know.[63] There are estimates, but, in part because of the uncertainty of the diagnosis, the estimates vary widely.[64] And, with this

55. *See US Death Rates from Alzheimer's Disease Increased 55 Percent from 1999 to 2014*, CTRS. FOR DISEASE CONTROL & PREVENTION (May 25, 2017, 1:00 PM), https://www.cdc.gov/media/releases/2017/p0525-alzheimer-deaths.html.

56. *See* Salynn Boyles, *Average Dementia Survival: 4.5 Years*, WEBMD (Jan. 10, 2008), https://www.webmd.com/alzheimers/news/20080110/average-dementia-survival#.

57. *See* Alzheimer's Association, *2019 Alzheimer's Disease Facts and Figures*, 15 ALZHEIMER'S DEMENTIA 321, 336 (2019) [hereinafter *2019 Facts and Figures*].

58. *See* Henry Brodaty et al., *Dementia Time to Death: A Systematic Literature Review on Survival Time and Years of Life Lost in People with Dementia*, 24 INT'L PSYCHOGERIATRIC 1034, 1034–45 (2012).

59. *See id.*

60. *See id.*

61. *See, e.g.*, Martha Clare Morris et al., *Thoughts on B-Vitamins and Dementia*, 9 J. ALZHEIMER'S DISEASE 429 (2006); *see also* Krishna Prasad Muliyala & Matthew Varghese, *The Complex Relationship Between Depression and Dementia*, 13 ANNS. INDIAN ACAD. NEUROLOGY S69 (2010) (discussing treating dementia with antidepressants).

62. *See* Richard Mayeux & Mary Sano, *Treatment of Alzheimer's Disease*, 341 NEW ENG. J. MED. 1670 (1999).

63. *See Alzheimer's Disease Statistics*, ALZHEIMER'S NEWS TODAY, https://alzheimersnewstoday.com/alzheimers-disease-statistics/ (last visited Dec. 5, 2020).

64. *See* Richard Mayeux & Yaakov Stern, *Epidemiology of Alzheimer Disease*, 2 COLD SPRING HARBOR PERSP. MED. a006239 (2012) (In 2013, global rates were estimated to reach as high as twenty-four million while in the United States, as many as 5.5 million were affected); *2019 Facts and Figures*, *supra* note 57 (By 2019, 5.8 million Americans were estimated to have Alzheimer disease).

disease as with every disease in the U.S., there are disease organizations.[65] Disease organizations tend to use higher estimates of how many people have the disease, while other sources often have lower estimates.[66] The U.S. Alzheimer Association, however, seems to be a pretty fair and useful source of information about the disease.[67]

As noted above, one of the problems is telling Alzheimer dementia apart from other dementias, particularly vascular dementia.[68] But another part is deciding when someone is "demented." When does someone pass from mild cognitive impairment, a common precursor to dementia, to having frank dementia?

However one answers those questions, the number of people in the United States with Alzheimer disease is clearly at least five million.[69] The Alzheimer Association estimates that 5.6 million people over sixty-five have the disease along with another 200,000 under sixty-five.[70] It concludes that 10 percent of Americans over sixty-five have Alzheimer disease;[71] by the age of eighty-five it estimates that the percentage rises to about 32 percent.[72] The Alzheimer Association estimates that by 2050, the number of people living with the disease will more than double to 13.8 million.[73]

There is, however, a surprising bit of good news in terms of the number of people with Alzheimer disease. Some long-term longitudinal studies seem to show that fewer people are being diagnosed with Alzheimer disease at any given age than in the past.[74] Researchers speculate that better control of cardiovascular problems, mainly through

65. *See Organizations: A*, MEDLINE PLUS, https://medlineplus.gov/organizations/orgbytopic_a.html (last updated Oct. 5, 2020) (compiling a database of disease associations).

66. *See* Anders Ternhag et al., *Size Matters—Patient Organisations Exaggerate Prevalence Numbers*, 20 EUR. J. EPIDEMIOLOGY 653 (2005).

67. *See 2019 Facts and Figures*, *supra* note 57.

68. *See* Anna Zimny et al., *Does Perfusion CT Enable Differentiating Alzheimer's Disease from Vascular Dementia and Mixed Dementia? A Preliminary Report*, 257 J. NEUROLOGICAL SCI. 114, 114 (2007).

69. *See* Shyamal Kumar Das & Souvik Dubey, *Differentiating Mild Cognitive Impairment from Normal Cognition and Frank Dementia Utilizing Structural Changes Observed on Magnetic Resonance Imaging*, 66 NEUROLOGY INDIA 328, 328 (2018).

70. *See 2019 Facts and Figures*, *supra* note 57.

71. *Id.*

72. *Id.*

73. *Id.* at 335.

74. Claudia L. Satizabal et al., *Incidence of Dementia Over Three Decades in the Framingham Heart Study*, 374 NEW. ENG. J. MED. 523, 531 (2016) (There is another, bad, reason to think Alzheimer prevalence estimates may be too high. For the last three years, average life expectancy in the U.S. has declined, apparently largely

less smoking, but also cholesterol and blood pressure treatment, may be reducing the longer-term incidence of Alzheimer disease.[75] But, whatever the exact rate of new cases is and whether it is going up or down, the number of people with Alzheimer disease is high and, at least in the short term, it is going to get higher. Even if the rate of seventy- and eighty-year-old people with the disease is going down, the number of such people is going up sharply in America.[76] Those of us in the Baby Boom generation are now between fifty-six and seventy-five years old and moving inexorably toward, and through, being elderly.[77] As a result, some of us are moving inexorably toward Alzheimer disease.

Congress has taken note of this. The annual funding for Alzheimer disease research at the National Institutes of Health ("NIH") has gone up consistently since 2011.[78] Since then it has increased six-fold and is now, for fiscal year 2020, $2.8 billion, nearly 10 percent of the total NIH research budget of about $30 billion, which covers research for all diseases as well as basic research.[79]

And yet there has been no (or almost no) good news about preventions and treatments, let alone cures, for Alzheimer disease.[80] Quite

through drug and alcohol-related deaths, as well as suicides. Anything that lowers the number of old people lowers the number of Alzheimer patients, although, in this case, perhaps not substantially).

75. *Id.* at 527, 530.

76. *See id*; *See also Boomers, Gen X, Gen Y, and Gen Z Explained*, KASASA, https://www.kasasa.com/articles/generations/gen-x-gen-y-gen-z#:~:text=Baby%20Boomers%3A%20Baby%20boomers%20were,born%20between%201980%20and%201994 (last updated Aug. 20, 2020).

77. *See* KASASA, *supra* note 76.

78. *See Alzheimer's and Dementia Research*, ALZHEIMER'S IMPACT MOVEMENT, https://alzimpact.org/issues/research (last visited Dec. 5, 2020).

79. *See id.* (explaining NIH funding for Alzheimer research has increased six-fold); Jocelyn Kaiser, *The Alzheimer's gamble: NIH tries to turn billions in new funding into treatment for deadly brain disease*, AM. ASS'N ADVANCEMENT SCI. (Aug. 30, 2018, 9:00 AM), https://www.sciencemag.org/news/2018/08/alzheimer-s-gamble-nih-tries-turn-billions-new-funding-treatment-deadly-brain-disease (noting Congress has tripled the budget for Alzheimer research over the past three years while recent funding proposals for more funding mean Alzheimer's research accounts for more than five percent of the NIH budget).

80. *See* Richard Harris, *10 Years After Alzheimer's Report: Any Progress?*, FORBES (Mar. 25, 2019, 3:53 PM), https://www.forbes.com/sites/nextavenue/2019/03/25/10-years-after-alzheimers-report-any-progress/#54f8789bd729.

the contrary. Before 2019, the "FDA" had approved five drugs for treating Alzheimer disease.[81] Three of the FDA-approved drugs work by inhibiting an enzyme called acetylcholinesterase.[82] The first such drug was Donepezil (trade name Aricept), which was approved in 1996.[83] These three drugs do not change the course of the disease but provide some modest improvements in cognition and behavior in some patients.[84] The last new drug approved for treating Alzheimer disease was memantine, in 2003, to treat moderate-to-severe Alzheimer disease, especially for people who cannot take acetylcholinesterase inhibitors.[85] Again, the drug is associated with some improvement for some patients but only with small effects.[86] The fifth drug is a combination of memantine and an acetylcholinesterase inhibitor, approved in 2014.[87] Basically, one drug to treat Alzheimer disease was approved in 1996, now in three variations, and another in 2003—and none of them is very good.

During much of that time, pharmaceutical and biotechnology companies have, quite literally, lost scores of billions of dollars searching for Alzheimer disease treatments.[88] The most visible failures have followed "the amyloid hypothesis." We know that amyloid plaque is found whenever a patient has Alzheimer disease—not surprisingly, as it is an essential part of the definition of the disease.[89] From that fact, as well as some success with artificial mouse models (mice do not naturally get Alzheimer disease but they can be genetically manipulated to

81. *FDA-approved treatments for Alzheimer's*, ALZHEIMER'S ASS'N, 1, 1, https://www.alz.org/media/documents/fda-approved-treatments-alzheimers-ts.pdf (last updated Aug. 2019) [hereinafter *FDA-approved treatments*].

82. *Id.*

83. *Donepezil*, ALZFORUM, https://www.alzforum.org/therapeutics/donepezil (last visited Dec. 5, 2020).

84. *See FDA-approved treatments*, *supra* note 81.

85. *Memantine*, ALZFORUM, https://www.alzforum.org/therapeutics/memantine (last visited Dec. 5, 2020).

86. *See FDA-approved treatments*, *supra* note 81.

87. *Namzaric FDA Approval History*, DRUGS.COM, https://www.drugs.com/history/namzaric.html (last visited Dec. 5, 2020).

88. Katherine E. Foley, *Why the pharmaceutical industry is giving up the search for an Alzheimer's cure*, QUARTZ (May 20, 2018), https://qz.com/1282482/why-the-pharmaceutical-industry-is-giving-up-the-search-for-an-alzheimers-cure/.

89. Kelly Servick, *Another major drug candidate targeting brain plaques of Alzheimer's disease has failed. What's left?* AM. ASS'N ADVANCEMENT SCI. (Mar. 21, 2019), https://www.sciencemag.org/news/2019/03/another-major-drug-candidate-targeting-brain-plaques-alzheimer-s-disease-has-failed.

have something somewhat like it, including amyloid plaques[90]), companies have brought medication after medication aimed at preventing, reducing, or eliminating amyloid plaque to clinical trials. Some have shown dangerous side effects but, more damningly, none has shown significant or convincing evidence of effectiveness against the disease.[91]

Given all the signs that point toward an involvement of amyloid plaque in Alzheimer disease, the failure of the amyloid hypothesis to produce any useful drugs is a mystery, and a particularly vexing one as the pipeline of other plausible approaches is nearly empty: particularly for people who already have substantial symptoms.[92] But in the last few years, company after company has announced failed clinical trials for amyloid attacking compounds—and has suspended those efforts.[93]

The whole field is in a period of painful reflection and widespread confusion. Amyloid surely *seems* to be involved, in part because genetic amyloid variations are linked to the disease (see Section II(B)(2) below). But thus far it has proven a very bad drug target. And now researchers and drug developers are advancing many non-amyloid hypotheses: that Alzheimer disease results from tau pathologies,[94] from genetic changes that occurred in some brain cells after fertilization set its "starting" genome,[95] from problems with the neuronal mitochondria,[96] from infectious agents,[97] from inflammation that might be controllable,[98] and

90. S*ee* Pei-Pei Liu et al., *History and Progress of Hypotheses of Clinical Trials for Alzheimer's Disease*, 29 SIGNAL TRANSDUCTION & TARGETED THERAPY 1, 8 (2019).

91. *See id.* at 3 (depicting a review of Alzheimer's disease hypotheses, drug treatments, and drug failures); *see also* Servick, *supra* note 89 (describing recent and historical failures of drugs targeting amyloid plaques).

92. Sharon Begley, *The maddening saga of how an Alzheimer's 'cabal' thwarted progress toward a cure for decades*, STAT (June 25, 2019), https://www.statnews.com/2019/06/25/alzheimers-cabal-thwarted-progress-toward-cure/ (describing dogmatic belief in the amyloid hypothesis may have stifled research in other treatments).

93. Gina Kolata, *An Alzheimer's Treatment Fails: 'We Don't Have Anything Now'*, N.Y TIMES (Feb. 10, 2020), https://www.nytimes.com/2020/02/10/health/alzheimers-amyloid-drug.html.

94. Liu et al., *supra* note 90, at 4–6.

95. Jun S. Park et al., *Brain Somatic Mutations Observed in Alzheimer's Disease Associated with Aging and Dysregulation of Tau Phosphorylation*, 10 NATURE COMM. 1, 1 (2019).

96. Liu et al., *supra* note 90, at 6–7.

97. *Id.* at 9.

98. Begley, *supra* note 92 (discussing Kelsey D. Biddle, et al., *Associations of Widowhood and ß-Amyloid with Cognitive Decline in Cognitively Unimpaired Older Adults*, 3 JAMA NETWORK OPEN (2020).

many other contenders. There is also interest in possible genetic variations that prevent the development of Alzheimer disease and that might—or might not—lead to direct or indirect treatments, preventive or therapeutic, for the disease.[99] It is a period of great uncertainty—and of frustration.

At least three drugs do bear watching, although not with a great deal of optimism. One is yet another amyloid hypothesis effort, Aducanumab, a human antibody that attaches to amyloid plaque and is hoped to lead to its clearance.[100] The biotech company Biogen has been running clinical trials on the compound for several years.[101] In March 2019 it announced it was halting its efforts to develop the drug and stopped two clinical trials because interim analyses showed that they could not succeed.[102] But then in October 2019, it announced that it had changed its mind. It claimed that new analyses of the "failed" trials of March showed that the drug was successful, at least at its highest doses.[103] Biogen said it would restart the FDA approval process for it.[104] In early December the company presented its interpretation of the results at the Clinical Trials in Alzheimer Disease Congress. The reactions were mixed; some (even outside the company and its consultants) greeted it with enthusiasm[105] but others showed substantial skepticism.[106]

99. Sharon Begley, *She was destined to get early Alzheimer's, but didn't. Did a rare mutation protect her?*, STAT (Nov. 4, 2019), https://www.statnews.com/2019/11/04/did-rare-mutation-protect-against-alzheimers/.

100. News Release, FDA Accepts Biogen's Aducanumab Biologics License Application For Alzheimer's Disease With Priority Review, Biogen Inc. (Aug. 7, 2020, 7:30 AM), https://investors.biogen.com/news-releases/news-release-details/fda-accepts-biogens-aducanumab-biologics-license-application.

101. *Id.*

102. Manas Mishra & Trisha Roy, *Biogen delays Alzheimer's drug filing plans, shares fall 11%*, REUTERS (Apr. 22, 2020, 6:24 AM), https://www.reuters.com/article/us-biogen-results-idUSKCN2241M7.

103. *Id.*

104. *Id.*

105. Jason Karlawish, *Aducanumab: the beginning of the end of Alzheimer's disease?*, STAT (Dec. 6, 2019), https://www.statnews.com/2019/12/06/aducanumab-the-beginning-of-the-end-of-alzheimers-disease/; *see also* Jason Karlawish, *Aducanumab isn't the simple solution to the complicated Alzheimer's crisis*, STAT (Dec. 20, 2019), https://www.statnews.com/2019/12/20/aducanumab-isnt-simple-solution-complicated-alzheimers-crisis/ (following up this [interesting] enthusiastic reaction two weeks later with a much more measured assessment of the results [along with another interesting projection of how an Aducanumab approval might play out]).

106. Kelly Servick, *Skepticism persists about revived Alzheimer's drug after conference presentation*, AM. ASS'N ADVANCEMENT SCI. (Dec. 5, 2019, 4:55 PM), https://

Aducanumab must be mentioned, though, because Biogen insists that it will seek approval for it from the FDA sometime in 2020,[107] making it the only prospective Alzheimer disease treatment I know of that is so far advanced. In the last two years, the FDA has surprised many knowledgeable observers by approving drugs with very limited evidence of efficacy, especially when the underlying diseases were serious and had no good treatments.[108] Some analysts are worried that Aducanumab will benefit from this apparent loosening of the requirements; others hope that it will. No one, however, sees it as "the cure" for Alzheimer disease. At best, it may slow the decline. At worst, its side effects may do more harm than good.

It is now thought that the FDA is quite likely to approve a different "new" drug for "treating" Alzheimer disease, probably in early 2021.[109] The scare quotes are there for good reason. The new drug, pimavanserin (Nuplazid), had been approved in 2016 to treat hallucinations and delusions in patients with Parkinson disease who developed psychosis.[110] The drug company Acadia conducted clinical trials of its use to treat psychotic symptoms in patients with dementias and those trials were very successful. Acadia submitted a "Supplemental New

www.sciencemag.org/news/2019/12/skepticism-persists-about-revived-alzheimers-drug-after-conference-presentation.

107. Mark Terry, *Biogen's Expected Filing for Alzheimer's Drug Aducanumab Delayed Until Q3,* BIOSPACE (Apr. 22, 2020), https://www.biospace.com/article/biogens-expected-filing-for-alzheimer-s-drug-aducanumab-delayed-until-q3/ (blaming the delay from BIOGEN's earlier announced Spring filing, understandably, on COVID-19); IOGEN has since filed and been FDA approved, *see* Alex Philippidis, *FDA Accepts Biogen's BLA for Alzheimer Drug Candidate Aducanumab,* GEN (Aug. 10, 2020), https://www.genengnews.com/news/fda-accepts-biogens-bla-for-alzheimers-candidate-aducanumab/.

108. *See* Caroline Chen, *FDA increasingly approves drugs without conclusive proof they work,* PBS (June 26, 2018, 11:31 AM), https://www.pbs.org/newshour/health/fda-increasingly-approves-drugs-without-conclusive-proof-they-work (explaining the FDA has recently approved more experimental treatments despite limited evidence); Zachary Brennan, *Sarepta Wins Controversial FDA Approval for First DMD Drug*, REG. FOCUS (Sept. 19, 2016), https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2016/9/sarepta-wins-controversial-fda-approval-for-first-dmd-drug (noting the FDA approved Sarepta even though outside experts said evidence of the drug's efficacy was lacking).

109. *See* Terry, *supra* note 107 (explaining Biogen will seek FDA approval for Alzheimer drug in 2020); *see also* Chen, *supra* note 108.

110. Sarah de Crescenzo, *Acadia Looks to Expand Drug Beyond Parkinson's Disease Psychosis*, XCONOMY (Dec. 6, 2019), https://xconomy.com/san-diego/2019/12/06/acadia-looks-to-expand-drug-beyond-parkinsons-disease-psychosis/.

Drug Approval" ("sNDA") application in July 2020 to add such symptoms to the indications for which the drug is approved.[111]

The treatment is not for the underlying disease but, as was the case with the Parkinson disease approval, to help alleviate the psychosis that some patients with Alzheimer disease develop.[112] It does nothing to deal with the memory problems, the neuronal destruction, or the steady progression of the condition.[113] But even for psychosis symptoms, approval of the sNDA would do less than might appear; because it has already been approved for one use. Physicians, under the off-label use doctrine, have been able to use it in Alzheimer disease patients since 2016.[114] The good clinical trial results mean that more doctors will prescribe it for those purposes even without specific FDA approval.[115] The sNDA allows Acadia to promote the drug more actively for dementia-related psychotic symptoms and may make some health insurers or payors more willing to pay for it.

Another drug was approved in September 2019 for much broader attacks of Alzheimer disease. The Chinese FDA approved Oligomannate, a seaweed-derived drug with a very different mechanism of action.[116] The drug company Green Valley Pharmaceuticals said it would sell the drug in China by the end of 2019.[117] It has not, however, sought foreign approvals from the FDA, the European Medical Agency, or the Japanese Pharmaceuticals and Medical Devices Agency.[118] In April 2020, the FDA granted an "investigational new drug ("IND") exemp-

111. *Id*. (explaining the company has been testing Nuplazid in patients with Alzheimer's and expects to meet with FDA in 2020 and then file for review "as soon after that as [they] can."); *see* Visheadha Chander, *U.S. FDA accepts Acadia's application for dementia drug*, REUTERS https://www.reuters.com/article/us-acadia-pharm-fda/u-s-fda-accepts-acadias-application-for-dementia-drug-idUSKCN2 4L2PD (last updated July 20, 2020, 4:39 PM) (explaining Acadia has since filed an application for review with the FDA).

112. *Id.*

113. *See id.*

114. *Id.*

115. *See Understanding Unapproved Use of Approved Drugs "Off Label,"* FDA, https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label (last visited Dec. 5, 2020) [hereinafter *Understanding Unapproved Use*].

116. Andrew Joseph, *A new Alzheimer's therapy is approved in China, delivering a surprise for the field but also questions*, STAT (Nov. 4, 2019), https://www.statnews.com/2019/11/04/a-new-alzheimers-therapy-is-approved-in-china-delivering-a-surprise-for-the-field-but-also-questions/.

117. *Id.*

118. *See id.*

tion" for a Chinese drug derived from seaweed, which allows the manufacturer to pursue clinical trials in the United States. If the trials go well, the company hopes to seek U.S. approval in 2025.[119] The non-Chinese response has been largely skeptical—at best, "wait and see."

What can we say? Millions of people have Alzheimer disease, many more will have it in the next few decades, and we have no good preventive measures or treatments, let alone cures. And little in the way of exciting prospects for good, new medical interventions.

II. Predicting Alzheimer Disease

Predicting is easy; being right is *hard*. Predicting Alzheimer disease is no exception, but in some cases, prediction is strong and likely to become stronger. This Section will talk first about three general issues with medical prediction and then describe five promising approaches to predicting Alzheimer disease.

A. Three General Issues of Prediction

Three general truths about prediction need to be remembered. First, predictive tests are often byproducts of other research aimed at understanding the causes of a disease and are not directly sought after as predictors.[120] Second, the line between predicting a disease and diagnosing an early case is often very fuzzy.[121] Third, the value of prediction will always depend on its accuracy and "accuracy" is *never* simple.[122]

First, we are getting enormously better at being able to predict the future of your brain, thanks to revolutions in neuroscience.[123] These revolutions are—as all scientific revolutions always are—largely revolutions in tools.[124] These can be physical tools, like telescopes, microscopes, and magnetic resonance imaging, or conceptual tools, from calculus to machine learning algorithms. Sometimes one field benefits

119. *Chinese Alzheimer's Drug Gets U.S. Approval for Stateside Trial*, BLOOMBERG (Apr. 26, 2020, 1:00 AM), https://www.bloomberg.com/news/articles/2020-04-26/chinese-alzheimer-s-drug-gets-u-s-approval-for-stateside-trial.

120. Henry T. Greely, *The Neuroscience Revolution, Ethics, and the Law*, SANTA CLARA UNIV. (Apr. 20, 2004), https://www.scu.edu/ethics/focus-areas/bioethics/resources/the-neuroscience-revolution-ethics-and-the-law/.

121. *See id.*

122. *See id.*

123. *Id.*

124. *Law and the Revolution*, *supra* note 5.

enormously from tools used in other fields.[125] The Human Genome Project and the ability to do cheap sequencing are powerful tools in neuroscience. As a result of these new tools, we know infinitely more today about how the human brain works than we did thirty years ago.[126] And thirty years from now, people will look back and say "they knew nothing, and most of what they thought they knew was wrong." We are on the vertical part of the learning curve.

Most of the time, those discoveries are not made because someone wants to find out how to predict things, but prediction is a secondary or dual use.[127] Most of the knowledge we have about brain diseases comes from efforts to prevent them, to treat them, or to cure them; but these efforts often involve trying to determine how they are caused, their etiology.[128] What is the natural history of the disease? What are the things that lead to it? Once you see the association between a trait and the subsequent development of the disease, however, you have—whether you intended it or not—discovered a "predictor." Once you learn that amyloid plaque buildup is always found in Alzheimer disease and find tools that let you see amyloid plaque buildup in living people, you have a predictor: amyloid build-up seems to be useful in predicting Alzheimer disease. And this is true whether or not it "causes" Alzheimer disease, as long as it is strongly associated with it. Falling red and yellow leaves do not *cause* winter, but, in many temperate parts of the world, they predict the coming of winter very well.

Our ability to predict Alzheimer disease is growing steadily but not because people sit down and say, "I want to come up with something to predict Alzheimer disease." Instead, they say, "I want to understand more about Alzheimer disease." Predicting Alzheimer disease, however, has different benefits and costs than understanding it, an equation rarely considered by most of the researchers involved.

Second, when are we *predicting* that someone will have a disease at some point in the future and when are we *diagnosing* a thus far asymptomatic (or only "slightly symptomatic") disease? Over thirty years ago, I wrote a paper about HIV and AIDS.[129] It seemed to me you could look at it two ways. Being HIV positive could be a predictor that

125. *See id.*
126. *See id.*
127. *See id.*
128. *See id.*
129. Henry T. Greely, *AIDS and the American Health Care Financing System*, 51 UNIV. PITT. L. REV. 73 (1989).

you would eventually get the disease called AIDS, or being HIV positive could be a disease with a series of symptoms that ultimately led to AIDS.[130] Does it matter? Maybe not. But, sometimes, maybe. The U.S. Supreme Court confronted a version of that question when it had to decide whether HIV infection without overt symptoms was a disability for the purposes of the Americans with Disabilities Act.[131]

Similarly, if we can say, "you are 99 percent certain to get Alzheimer disease," are we predicting that you *will* get Alzheimer disease, or are we diagnosing you with a pre-symptomatic case—or maybe as a very early (if we look hard enough) case of Alzheimer disease? Whether it is prediction or early diagnosis is a hard question, both philosophically and medically. We have seen diagnoses of Alzheimer disease increase in part because people are being diagnosed earlier, which in turn is partly because of greater awareness of Alzheimer disease.[132]

Third, we can predict anything. It is easy to make predictions—it is hard to be right. The accuracy of the predictions is crucial. "The Law"—meaning mainly lawyers and judges—is not good at assessing the accuracy of predictions, but few people from any background are very good at it. We all tend to think of accuracy as a number. We say something is 98 percent accurate, but accuracy is *much* more complicated than that.

A first step to better understanding is to ask about a test's specificity and sensitivity. Specificity shows you how many false positives you get—if you do 100 tests to see if someone is, let's say, infected with SARS-CoV-2, how many of them will falsely say somebody is positive (i.e. has the disease)? Ninety-nine percent specificity means only one will falsely say a person is positive (is infected). Sensitivity tells you about false negatives.[133] If a test is 99 percent sensitive, only one in 100

130. *Id.*

131. *See* Bragdon v. Abbott, 524 U.S. 624, 631–42 (1998) (holding HIV infection without overt symptoms was a disability for ADA purposes, at least for a woman of reproductive age).

132. *See U.S. burden of Alzheimer's disease, related dementias to double by 2060*, CDC (Sept. 20, 2018), https://www.cdc.gov/media/releases/2018/p0920-alzheimers-burden-double-2060.html.

133. *Understanding medical tests: sensitivity, specificity, and positive predictive value*, HEALTH NEWS REV., https://www.healthnewsreview.org/toolkit/tips-for-understanding-studies/understanding-medical-tests-sensitivity-specificity-and-positive-predictive-value/ (last visited Dec. 5, 2020).

will be a false negative (will appear uninfected while actually being infected).[134] Those things are usually inversely related. You can require a higher score on a test to call a result positive. So, for example, if you start by saying "someone with over a 160 on the LSAT will do well in the first year of law school" and then change it to "someone with over a 170 on the LSAT will do well in the first year of law school," you may get fewer false positives and hence have better specificity. But this will increase your false negatives—you will miss more people who will do well in the first year of law school—and so lower your sensitivity. Or you could drop the LSAT score target and get lower specificity but higher sensitivity. You can be very specific or very sensitive, but you can almost never be both, a good thing to remember.[135]

More valuable measurements than specificity and sensitivity are positive and negative predictive values.[136] These tell you the chance that a positive test actually is positive or that a negative test is actually negative.[137] Those results may sound the same as specificity and sensitivity, but they are not.[138] They depend crucially on how many people you expect to have the disease or trait you are looking for. If a disease is found in one person in a million people and your test is 99 percent specific, then if you test one million people, you will (on average) get one true positive, but ten thousand false positives. That positive predictive value—the chance that a positive is a true positive—is 0.01 percent, one in ten thousand. On the other hand, if we do a test for whether any random person is male, we expect roughly 50 percent to qualify. If our test has 99 percent specificity, and we test one hundred people, we'll get one false positive, but we'll get fifty true positives, and so our positive predictive value will be fifty over fifty-one—a very good result (98

134. *See id.* I find a useful way to distinguish specificity and sensitivity is similar to the way to remember the difference between stalactites and stalagmites. Stalactites hang from the ceilings of caves; stalagmites grow up from the ground. Specificity tells you about false positives; sensitivity tells you about false negatives.

135. *Id.* Another accuracy concept tries to get a combined view of this specificity/sensitivity tradeoff. It came from early radar and electrical engineering days and is called the receiver-operating characteristic. As part of this analysis, researchers plot a graph that depicts the area under the (receiver operating) curve ("AUC"). This graphs as a curve the various specificity and sensitivity results with different cutoff values; the AUC can range between 0 and 1, and a high AUC means a better test.

136. *Id.* (This is tied in with so-called Bayesian analysis, a term to remember but not something a reader needs to understand for this already too-long article).

137. Robert Trevethan, *Sensitivity, Specificity, and Predictive Values: Foundations, Pliabilities, and Pitfalls in Research and Practice*, FRONTIERS IN PUB. HEALTH (Nov. 20, 2017), https://www.frontiersin.org/articles/10.3389/fpubh.2017.00307/full.

138. *See id.*

percent). Negative predictive value does the same thing with sensitivity. It tells you how likely a negative result is to be true negative, which varies based on what percentage of your test population really is negative.

Note that this makes defining your population crucial. The true positive rate of Alzheimer disease in people under twenty years of age is tiny; in people over seventy, it is much higher.[139] A predictive test for Alzheimer disease with exactly the same "accuracy," defined as specificity, will be much better—have a much higher positive predictive value—in the over-seventies than in the under-twenties.

B. Five Approaches to Predicting Alzheimer Disease

So, keeping those three points in mind—predictive tests are usually byproducts of research aimed at other things, the line between prediction and early diagnosis is unclear, and accuracy is complicated—let's talk about ways to predict who will be diagnosed with Alzheimer disease. There are five broad approaches: behavioral tests, genetic tests, neuroimaging tests, biomarker tests, and combinations of the above. This Section will discuss all of them.

1. BEHAVIORAL TESTS

We can give people memory tests to try to see if their memory is already affected because one of the best predictors for people who are going to get Alzheimer disease is that at the relevant age they are already showing signs of memory problems.[140] Two of the common tests are the Mini-Mental State Exam ("MMSE"; also called the Folstein test) and the Mini-Cog test.[141] In addition, the FDA has also cleared several computer-based tests for clinical use that do much of the same thing as the MMSE and the Mini-Cog test.[142]

For the MMSE, a health professional asks questions that reveal the patient's ability with everyday mental skills. Thirty is a perfect score;

139. *See* Esther Heerema, *Statistics on Alzheimer's Disease: Who Gets It?*, VERYWELL HEALTH (Mar. 4, 2020), https://www.verywellhealth.com/statistics-on-alzheimers-disease-98794.

140. *See Medical Tests*, *supra* note 2.

141. *Id.*

142. Fredrick Kunkle, *FDA approves tool for diagnosing dementia in a doctor's office*, WASH. POST (Aug. 10, 2015), https://www.washingtonpost.com/local/social-issues/fda-approves-marketing-of-convenient-tool-to-diagnose-dementia/2015/08/10/fe34689e-3d47-11e5-9c2d-ed991d848c48_story.html (explaining that the FDA has approved a video-game like cognitive assessment tool).

mild dementia is indicated by scores from twenty to twenty-four, thirteen to twenty is moderate dementia, and twelve or less is frank dementia. Some of the common questions include time orientation (what year, season, month, date, and day of the week it is), knowing where you are, counting from one hundred backwards by seven, spelling "world" backwards, and drawing interlocking pentagons.[143] In one version of this test, a patient had five minutes and twenty seconds to answer twelve questions (with specific amounts of time for each question and sub-question).

The Mini-Cog test is shorter. A few minutes after hearing the names of three common objects, the patient must repeat them, then draw a clock face showing all twelve numbers in their proper places, and finally draw the clock face for a time the health care professional specifies.[144]

All of these tests can be used to diagnose dementias, including Alzheimer disease, but they can also be used to predict Alzheimer disease.[145] "Mild cognitive impairment" ("MCI") is a state short of Alzheimer disease.[146] People with this condition will forget appointments or lose things and will have trouble finding the right word.[147] So, of course, will people without any cognitive impairment (including your author and, I suspect, all of my readers, from time to time). But people with MCI will make these mistakes more often than most people of their age. They will also move on to an Alzheimer disease diagnosis at a high rate—about 80 percent of those who survive for seven years after a diagnosis of MCI will be diagnosed with Alzheimer disease.[148] By comparison, only about 1 to 3 percent of people over sixty-five with normal cognition are diagnosed with Alzheimer disease in any given year–or roughly 5 to 20 percent over seven years.[149] A diagnosis of

143. IHPA, STANDARDISED MINI-MENTAL STATE EXAMINATION: GUIDELINES FOR ADMINISTRATION AND SCORING INSTRUCTIONS (2014), https://www.ihpa.gov.au/sites/default/files/publications/smmse-guidelines-v2.pdf.

144. *Medical Tests*, *supra* note 2.

145. N. Kyle Steenland et al., *Development of a Rapid Screening Instrument for Mild Cognitive Impairment and Undiagnosed Dementia*, 15 J. ALZHEIMER'S DISEASE 419 (2008), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2679370.

146. *What Is Mild Cognitive Impairment?*, NAT'L INST. ON AGING, https://www.nia.nih.gov/health/what-mild-cognitive-impairment (last updated May 17, 2017).

147. *Id.*

148. *Id.*

149. *Id.*

"MCI" does not guarantee a subsequent Alzheimer disease diagnosis, but it does make it more likely.

These predictive tests for Alzheimer disease seem straightforward. Memory deterioration today is some evidence of likely memory deterioration tomorrow, in the form of Alzheimer disease. But there are also a wide range of not obvious (and sometimes, on their face, implausible) behavioral conditions that have been claimed as prognostic tests for Alzheimer disease.[150]

Alzheimer disease is associated with a variety of traits or conditions.[151] It is more likely to appear among women than men (1.5 to three times as likely), perhaps because of the shortage of estrogen after menopause.[152] Various issues related to vascular risks, such as high blood pressure (especially in mid-life) are also associated with increased risks of Alzheimer disease.[153] In one study, people with the highest baseline vascular risk scores had a 16 percent risk of Alzheimer disease diagnosis twenty years later while those with the lowest risk scored had only a 1 percent risk.[154] Physical activity, especially at mid-life, lowers the risk for Alzheimer disease.[155]

Some studies have shown that a decline in the sense of smell can predict Alzheimer disease (and also Parkinson disease).[156] It is claimed that, on autopsy, Alzheimer disease patients show amyloid plaques and tau tangles in the neurons of their olfactory bulbs, the parts of the brain that first process smells from the nose.[157] This is *not* a wonderful test. Colds and allergies can impair the sense of smell, as does aging in general (and COVID-19).[158] About half of people over sixty-five have problems smelling; which becomes 75 percent of those over eighty.[159]

150. B. B. Bendlin et al., *Midlife Predictors of Alzheimer's Disease*, 65 MATURITAS 131 (2010).

151. *Id.*

152. *Id.* at 133.

153. *Id.*

154. Miia Kivipelto et al., *Risk Score for the Prediction of Dementia Risk in 20 Years Among Middle Aged People: A Longitudinal, Population-Based Study*, 5 LANCET NEUROLOGY 735, 737–38 (2006).

155. Mark Hamer & Yoichi Chida, *Physical Activity and Risk of Neurodegenerative Disease: A Systematic Review of Prospective Evidence*, 39 PSYCHOL. MED. 3, 3 (2009).

156. David Noonan, *Smell Test May Sniff Out Oncoming Parkinson's and Alzheimer's*, SCI. AM. (June 12, 2017), https://www.scientificamerican.com/article/smell-test-may-sniff-out-oncoming-parkinsons-and-alzheimers1/?redirect=1.

157. *Id.*

158. *Id.*

159. *Id.*

The vast majority of those people do not have Alzheimer disease. On the other hand, the test is cheap (under thirty dollars) and easy.[160]

Other studies have singled out a variety of non-obvious predictors although how real they are, or whether they are really correlated with some other aspect of the condition, remains unclear. These include herpes infection; living in an area with high levels of air pollution; poor sleeping patterns; eating late dinners; or a history of concussions, loneliness, and financial problems.[161] Whether, and to what extent, any of these is real remains unclear but each has at least one published scientific article vouching for it.[162]

The most interesting non-obvious predictor, to me at least, comes from the Nun Study of Aging and Alzheimer Disease, which began in 1986.[163] The researchers looked at the records of 678 American nuns, members of the School Sisters of Notre Dame. Each nun had to write an autobiographical essay when joining the order, at an average age of twenty-two. The researchers measured the vivacity, fluency, and complexity of those essays (and other early writings). They found that 80 percent of the nuns whose writing was viewed as not having "linguistic density" were diagnosed with Alzheimer disease late in life.[164] This was true of only 10 percent of those whose essays were "linguistically

160. *Id.*

161. Amanda MacMillan, *8 Weird Things Linked to Memory Loss Later in Life*, HEALTH (Sept. 5, 2018), https://www.health.com/alzheimers/memory-loss-dementia-surprising-risk-factors.

162. *E.g.*, Jasmeet P. Hayes et al., *Mild Traumatic Brain Injury Is Associated with Reduced Cortical Thickness in Those at Risk for Alzheimer's Disease*, 140 BRAIN: J. NEUROLOGY 813, 814 (2017); Joanne W. Hsu & Robert Willis, *Dementia Risk and Financial Decision Making by Older Households: The Impact of Information*, 7 J. HUM. CAP. 45 (2013); Ben Readhead et al., *Multiscale Analysis of Independent Alzheimer's Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus*, 99 NEURON 64 (2018); Robert S. Wilson et al., *Loneliness and Risk of Alzheimer Disease*, 64 ARCHIVES GEN. PSYCHIATRY 234 (2007); Xin Zhang et al., *The Impact of Exposure to Air Pollution on Cognitive Performance*, 115 PNAS 9193 (Sept. 11, 2018); *Sleep Deprivation Increases Alzheimer's Protein*, NAT'L INST. HEALTH (Apr. 24, 2018), https://www.nih.gov/news-events/nih-research-matters/sleep-deprivation-increases-alzheimers-protein.

163. David A. Snowdon et al., *Linguistic Ability in Early Life and Cognitive Function and Alzheimer's Disease in Late Life*, 275 J. AM. MED. ASS'N 528, 529–30 (1996); *see also* Pam Belluck, *Nuns Offer Clues to Alzheimer's and Aging*, N.Y. TIMES (May 7, 2001), https://www.nytimes.com/2001/05/07/us/nuns-offer-clues-to-alzheimer-s-and-aging.html.

164. Snowdon et al., *supra* note 163.

dense."[165] It is intriguing because of the early age at which the prediction can be made. I put this in the category of "fascinating, needs follow-up," but, if true, you want to write—or to have written—like Faulkner, not Hemingway.[166]

2. GENETIC TESTS

The genetics of Alzheimer disease is quite interesting and, to most people, surprising, although I suspect it will prove to be typical of the genetics of many, or most, common diseases. Alzheimer disease is completely genetic, partially genetic, and (apparently) not genetic at all, depending on the patient.

About 1 to 2 percent of people with Alzheimer disease develop what is called "early onset familial Alzheimer disease."[167] These people are diagnosed before the age of sixty and have had several family members with a similar diagnosis.[168] At least three genes are strongly involved in this disease. About one person in one thousand has a mutation in a gene called *PSEN1*, which normally makes a protein called presenilin 1.[169] This mutation may account for 50 to 70 percent of those with early onset familial Alzheimer disease.[170]

Many *PSEN1* variations exist that lead the body to make a "bad" version of presenilin 1, a version that interferes with a complicated pathway for modifying proteins, including beta amyloid.[171] People with one copy of one of the "bad" versions of this gene end up making too

165. Julien Diard, *The nun study, Alzheimer's disease and good writing*, JULIEN DIARD'S HOMEPAGE (June 25, 2010), https://diard.wordpress.com/2010/06/25/the-nun-study-alzheimers-disease-and-good-writing.

166. Although another possible explanation is that people who wrote better when they were young started with a better cognitive level. As Alzheimer disease ate into their cognitive reserve, it may have taken longer for them to get diagnosed, sometimes so long that they weren't diagnosed before dying.

167. *See* Gabrielle Strobel, *Early Onset Familial AD*, ALZFORUM, https://www.alzforum.org/early-onset-familial-ad/overview/what-early-onset-familial-alzheimer-disease-efad (last visited Dec. 5, 2020).

168. *Early Onset Alzheimer's Disease: A Resource List*, NAT'L INST. ON AGING, https://www.nia.nih.gov/health/early-onset-alzheimers-disease-resource-list (last updated June 27, 2017).

169. *PSEN1 Gene*, MEDLINEPLUS, https://ghr.nlm.nih.gov/gene/PSEN1#conditions (last updated Aug. 18, 2020).

170. Thomas D. Bird, *Alzheimer Disease Overview*, in GENEREVIEWS (Margaret P. Adam et al. ed. 1998).

171. *See* Erika N. Cline et al., *The Amyloid-β Oligomer Hypothesis: Beginning of the Third Decade*, 64 J. ALZHEIMER'S DISEASE S567, S586 (2018).

much of the Aß42 that forms amyloid plaques on dead and dying neurons.[172] They (apparently) inevitably develop early onset Alzheimer disease, with diagnoses usually in their forties and fifties.[173] Karen J. Williams, the chief judge of the Fourth Circuit Court of Appeals, took senior status in 2009 at the age of fifty-eight because of a diagnosis of early onset Alzheimer disease. She died four years later.[174]

Geneticists talk about the "penetrance" of a genetic variation (or genotype): the percentage of people with a particular DNA variation who will develop a particular disease or trait. The penetrance of dangerous *PSEN1* variations seems to be, or to be very close to, 100 percent—the only way for a person carrying the variation to avoid dying of early onset Alzheimer disease is to die first from something else.[175] These *PSEN1* mutations are found in at least 50 percent of early onset Alzheimer disease cases, but such cases only account for 1 percent or so of total Alzheimer disease cases.[176]

Variations in at least two other powerfully penetrant genes cause some of the early onset familial Alzheimer disease cases. Certain versions of the *APP* gene, which normally makes amyloid precursor protein (as it sounds, this protein is a precursor to the amyloid protein), also cause highly penetrant early onset Alzheimer disease but account for perhaps a tenth as many cases as *PSEN1* variations.[177] There is also a *PSEN2* gene. Some of its mutations also produce a high likelihood of early onset Alzheimer disease, although, unlike the other two, some people who carry those genetic variations are still healthy in old age (over eighty years).[178] It is thought that some other, as yet undiscovered, genetic variations cause or strongly contribute to early onset familiar Alzheimer disease in perhaps 20 to 40 percent of the cases.[179]

Another, and, to me, particularly cruel, version of highly genetic Alzheimer disease exists. Almost everyone with Down syndrome who

172. *Id.*
173. *Id.*
174. Charles H. Williams III, *Karen Williams Left Her Mark*, TIMES DEMOCRAT (May 16, 2019), https://thetandd.com/opinion/columnist/karen-williams-left-her-mark/article_612c9064-122a-50bb-98c0-b0bc32befe05.html.
175. Lynn M. Bekris et al., *Genetics of Alzheimer Disease*, 23 J. GERIATRIC PSYCHIATRY & NEUROLOGY 213, 217 (2010).
176. *Id.*
177. *Id.* at 216–17.
178. *Id.* at 218–19; Bird, *supra* note 170.
179. Bekris et al., *supra* note 175 at 218–19; Bird, *supra* note 170.

lives past forty develops the amyloid plaques and tau tangles characteristic of Alzheimer disease.[180] Researchers think this is because *APP* is found on chromosome 21 and Down syndrome is caused by people having three copies of that chromosome (called "trisomy 21") instead of two.[181] Thus, they would have an extra copy of the *APP* gene and, it is presumed, make more of this protein. In any event, as the life expectancy of people with Down syndrome has risen with better interventions for their non-mental medical problems and better care, parents and siblings are finding that half or more of their Down syndrome relatives are diagnosed with Alzheimer disease by their fifties or sixties.[182]

Early onset familial Alzheimer disease appears to be almost entirely genetic, caused by particular variations in *PSEN1*, *APP*, or *PSEN2*, or by trisomy 21.[183] For these people, we can predict with close to 100 percent accuracy that, if they live long enough (usually until sixty), they will be diagnosed with Alzheimer disease.[184] And we can make that accurate prediction at birth—or even before birth at the fetal or embryonic stages, through prenatal genetic testing or pre-implantation genetic diagnosis (diagnosing an IVF embryo through taking cells off of it for genetic tests, a procedure that has been in clinical use since 1990).[185]

But, from whatever cause, early onset Alzheimer disease is uncommon. It affects perhaps one or two people in one thousand and no more than 1 to 3 percent of those who are diagnosed with Alzheimer disease.[186] What about everyone else?

Another gene has a substantial effect on Alzheimer disease risk. Called *APOE*, it provides the blueprint for producing protein called

180. Bird, *supra* note 170.

181. Mary McCarron et al., *A Prospective 20-year Longitudinal Follow-up of Dementia in Persons with Down Syndrome*, 61 J. INTELL. DISABILITY RES. 843, 845 (2017); NAT'L INST. ON AGING, *Alzheimer's Disease in People with Down Syndrome*, https://www.nia.nih.gov/health/alzheimers-disease-people-down-syndrome#:~:text=Alzheimer's%20Disease%20in%20People%20with%20Down%20Syndrome,called%20amyloid%20precursor%20protein%20 (last visited Dec. 5, 2020) [hereinafter *Down Syndrome*].

182. *Down Syndrome*, *supra* note 181.

183. *Id.*

184. *Id.*

185. Bird, *supra* note 170; *Down Syndrome*, *supra* note 181; Strobel, *supra* note 167.

186. Bird, *supra* note 170; McCarron et al., *supra* note 181.

apolipoprotein E.[187] *APOE* comes in three main forms: *APOE* e2, *APOE* e3, and *APOE* e4.[188]

You should be wondering, "What happened to *APOE* e1?" The answer says something important about genetics. *APOE* e1 had very serious negative effects, which meant it was the first one discovered and identified (hence *APOE* e1), because it was easy to see.[189] It causes a bad blood disease, but evolution doesn't like extremely bad conditions—they tend to die out. So, *APOE* e1 is rare because it is strong, and it was found first because it is strong. This is a great example of ascertainment bias: you tend to first spot the things that are strong and nasty, and these are often rare. *APOE* e2, e3, and e4 make up the vast majority of the *APOE* variations found in humans.[190]

Each of us has two copies of this gene, almost always in the e2, e3, or e4 variations, one from our mother and one from our father, so almost all of us are *APOE* e2/e2, e2/e3, e2/e4, e3/e3, e3/e4, or e4/e4.[191] About half of us are e3/e3 and, not surprisingly, those people have the average risk for Alzheimer disease, about 10 to 15 percent by age seventy-five.[192] About 2 to 3 percent of us are e4/e4.[193] If you are e4/e4 and live to be seventy-five, your risk of getting Alzheimer disease appears to be in the 80 to 90 percent range.[194] On the other hand, many of those

187. HENRY T. GREELY, THE END OF SEX AND THE FUTURE OF HUMAN REPRODUCTION (2016).

188. Jose M. Ordovas et al., *Apolipoprotein E Isoform Phenotyping Methodology and Population Frequency with Identification of APOE1 and APOE5 Isoforms*, 28 J. LIPID RES. 371, 371 (1987).

189. Yu Yamazaki et al., *Apolipoprotein E and Alzheimer Disease: Pathobiology and Targeting Strategies*, 15 NAT. REV. NEUROLOGY 501, 501 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7055192/.

190. *Id.*

191. Ordovas et al., *supra* note 188 at 373–76; *Apolipoprotein E, APOE,* ON-LINE MENDELIAN INHERITANCE IN MAN, https://www.omim.org/entry/107741 (last updated Nov. 3, 2020) (There is another rare variation of *APOE* called *APOE* e5 which also seems to cause heart problems).

192. Ordovas et al., *supra* note 188 at 375–76; see BAI Beacon, *The Role of Genetics: Will I get Alzheimer's disease?*, ALZHEIMER'S PREVENTION REGISTRY (June 1, 2017), https://www.endalznow.org/news/the-role-genetics-will-i-get-alzheimers-disease.

193. *See generally Alzheimer Disease Genetics Fact Sheet*, NAT'L INST. ON AGING, https://www.nia.nih.gov/health/alzheimers-disease-genetics-fact-sheet#:~:text=APOE%20%CE%B54%20increases%20risk%20for,3%20percent%20carry%20two%20copies (last visited Dec. 5, 2020) [hereinafter *Alzheimer Fact Sheet*].

194. *See* Ordovas et al., *supra* note 188, at 371; Brandalyn C. Riedel, et al., *Age, APOE and Sex: Triad of Risk of Alzheimer's Disease*, 160 J. STEROID BIOCHEMISTRY & MOLECULAR BIOLOGY 134, 138 (2016); Penny Dacks, *What APOE Means for Your Health*, COGNITIVE VITALITY (Nov. 16, 2016), https://www.alzdiscovery.org/cognitive-vitality/blog/what-apoe-means-for-your-health.

people do not live to be seventy-five because being *APOE* e4/e4 also has coronary artery disease risks, leading them, on average, to die younger.[195] If you are e2/e2, which is about 1 percent of us, your risk of getting Alzheimer disease appears to be zero.[196] Other bad things can happen to you, including vascular dementia, but, apparently, not Alzheimer disease.[197] If you are e3/e4 or e2/e4—that's about 20 percent of all humans[198]—your risk is two or three times higher than the average person's, about 20 to 40 percent…but *not* 50 or 90 percent, and not even more than 50 percent. So, *APOE* status is a predictor for Alzheimer disease, but one that, for over 95 percent of people, is not very strong.

Even given the relative powers of these genetic variants, about half of people with Alzheimer disease do not have any of these genetic predictors.[199] For them, the genetic contribution to their Alzheimer disease risk appears to be zero, or close to it.[200] (A variety of other genetic variations have been, in different studies with different populations, weakly associated with Alzheimer disease risk,[201] though the reality and strength of these risks remain unclear.) So why do most people—the people without a known strong genetic risk—get Alzheimer disease? Perhaps because of genes we have not (yet?) identified. Perhaps

195. *Alzheimer Fact Sheet*, *supra* note 193; *see also* Jing Qian et al., *APOE-Related Risk of Mild Cognitive Impairment and Dementia for Prevention Trials: An Analysis of Four Cohorts*, 14 PUB. LIBR. SCI. MED. 1, 7–20 (Mar. 2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360223/; Stefany Montufar et al., *Association Between the APOE ε4 Allele and Late-Onset Alzheimer's Disease in an Ecuadorian Mestizo Population*, INT'L J. ALZHEIMER'S DISEASE (2019), https://www.hindawi.com/journals/ijad/2017/1059678/.

196. *People at Genetic Risk for Alzheimer's Disease to Test Prevention Drugs*, NAT'L INST. ON AGING (Aug. 23, 2016), https://www.nia.nih.gov/news/people-genetic-risk-alzheimers-disease-test-prevention-drugs [hereinafter *People at Genetic Risk*].

197. *Rare Luck: Two Copies of ApoE2 Shield Against Alzheimer's*, ALZFORUM (Aug. 8, 2019), https://www.alzforum.org/news/conference-coverage/rare-luck-two-copies-apoe2-shield-against-alzheimers [hereinafter *Rare Luck*]; *See generally* Dacks, *supra* note 194.

198. *Rare Luck*, *supra* note 197; Diego Iacono et al., *APOε2 and Education in Cognitively Normal Older Subjects with High Levels of AD Pathology at Autopsy: Findings from the Nun Study*, 6 ONCOTARGET 14082 (2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4546453/.

199. Dacks, *supra* note 194; *see also* Katrine K. Rasmussen, *Absolute 10-Year Risk of Dementia by Age, Sex and APOE Genotype: A Population-Based Cohort Study*, 190 CAN. MED. ASS'N J. 1033 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6148649/.

200. Yamazaki et al., *supra* note 189, at 507.

201. Park et al., *supra* note 95, at 2. *See generally Alzheimer's Genes: Are You at Risk?*, MAYO CLINIC, https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers-genes/art-20046552 (last visited Dec. 5, 2020) [hereinafter *Are You at Risk?*].

it is the environment. Perhaps it is from what their mothers ate when they were two months pregnant with them. Or maybe it's bad luck. We just don't know.

So, we can predict almost perfectly for one or two people in one thousand that they will be diagnosed with early onset Alzheimer disease, because they carry a disease-causing mutation in PSEN1.[202] (Note that also means for 998 or 999 out of one thousand we can also make a strong, but not perfect, prediction that they are almost certainly *not* going to get early onset Alzheimer disease.) For another 2 or 3 percent, we can predict that their risk of Alzheimer disease is somewhere above 80 percent (if they live long enough). For 95 percent of people, though, we can, thus far, say only "you are at somewhat higher than normal risk," "you are at somewhat lower than normal risk," or (most commonly) "you are at normal risk" for late onset Alzheimer disease.

3. NEUROIMAGING TESTS

The neuroimaging tests use computed tomography ("CT") scans, positron emission tomography ("PET") scans, or magnetic resonance imaging ("MRI") to "look" directly into the living brain. These are not, of course, photographs of the brain's interior or even like traditional x-rays, which capture the shadows cast on photographic plates by the brain. Instead, they are computer generated images based on either x-rays (CT scans), radiation from a particular kind of subatomic particle decay (PET scans), or radio waves modulated by a powerful magnetic field (MRIs).[203] The results can be made so realistic as to seem like "pictures," but, in many ways, they can indicate more than photographs could. And they tell us notably different things.

The most interesting and perhaps most promising neuroimaging tests are PET scans to detect the presence of amyloid plaque or tau tangles. PET works by injecting substances (the FDA calls them "PET drugs") into people that include some radioactive atoms that decay in a particular way through the production of a positron, the anti-matter equivalent of an electron.[204] The positrons almost instantly collide with electrons, annihilating both particles but producing gamma rays with

202. *Causes and Risk Factors for Alzheimer's Disease*, ALZHEIMER'S ASS'N, https://www.alz.org/alzheimers-dementia/what-is-alzheimers/causes-and-risk-factors (last visited Dec. 5, 2020).

203. *See generally Are You at Risk?*, *supra* note 201; *see also, e.g.*, Begley, *supra* note 92.

204. Bird, *supra* note 170; McCarron, *supra* note 181.

distinctive energies, causing them to depart from the collision site in exactly opposite directions.[205] These gamma rays can be detected and the location of the collision can be inferred. Those locations are then used to make computer generated images.[206]

The radioactive atoms, typically uncommon radioactive versions (or isotopes) of common, stable atoms like carbon, oxygen, and fluorine, can be attached to particular molecules that will accumulate differentially in locations with particular properties of interest.[207] For example, atoms of one of these radioactive isotopes can be attached to glucose (a simple sugar).[208] Glucose accumulates differentially in tissues that are consuming unusually high amounts of energy, such as tumors.[209] The radioactive atoms attach to the glucose decay, producing a different atom and a positron which collides with an electron and produces two gamma rays.[210] One gamma ray goes off in one (random) direction and the other goes off in exactly the opposite direction.[211] If the patient is in a PET scanner, the scanner will detect each gamma ray and based on infinitesimal differences in time the two gamma rays took to arrive at the detector, figure out where on the straight line between the two detections the decay took place.[212] Detect enough decay events and you've got a three-dimensional image of where in the body the atoms were located when they decayed.[213]

205. *People at Genetic Risk*, *supra* note 196.

206. *CT Scan*, MAYO CLINIC, https://www.mayoclinic.org/tests-procedures/ct-scan/about/pac-20393675 (last visited Dec. 5, 2020); Leah H. Portnow et al., *The History of Cerebral PET Scanning*, 80 NEUROLOGY 952 (Mar. 5, 2013), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3653214/; *MRI*, MAYO CLINIC, https://www.mayoclinic.org/tests-procedures/mri/about/pac-20384768 (last visited Dec. 5, 2020).

207. Portnow et al., *supra* note 206, at 953–54.

208. *Id.* at 945.

209. *Id.*

210. *Background: PET Scan*, N.Y.U. LANGONE HEALTH, https://med.nyu.edu/psych/research/center-brain-health/research-studies/pet-study/background-pet (last visited Dec. 5, 2020); *see also* Lisa Mosconi, *FDG-PET Changes in Brain Glucose Metabolism from Normal Cognition to Pathologically Verified Alzheimer's Disease*, 36 EUR. J. NUCLEAR MED. MOLECULAR IMAGING 811 (May 2009), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2774795/.

211. N.Y.U. LANGONE HEALTH, *supra* note 210.

212. *Id.*; *Positron Emission Tomography (PET)*, JOHNS HOPKINS MED., https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/positron-emission-tomography-pet (last accessed Oct. 5, 2020); Wenjie Li et al., *Effects of Hyperglycemia on the Progression of Tumor Diseases*, 38 J. EXPERIMENTAL & CLINICAL CANCER RES. 327 (2019); *see also* Mosconi, *supra* note 210.

213. Portnow et al., *supra* note 206; N.Y.U. LANGONE HEALTH, *supra* note 210.

Researchers from the University of Pittsburgh found an unpronounceable compound (2-(4′-methylaminophenyl)-6-hydroxybenzothiazole) that both bound to amyloid plaque *and* would host a radioactive isotope that could be used in PET scanning, in this case carbon-11.[214] (These kinds of PET drugs, which attach themselves to targets of medical interest, are called "radioligands.") The compound was first used on humans in Sweden in 2002. It was the second compound the Pittsburgh group tried and so the Swedish researchers (understandably) called it "Pittsburgh compound B," abbreviated as "PiB."[215] Carbon-11 decays through positrons, but its half-life is only about twenty minutes—that means in a little more than three hours, only one atom in a thousand will remain from the carbon-11 that existed three hours earlier.[216] This is a significant practical and commercial disadvantage. PET scanning with carbon-11 needs to be done very close to the device that creates the carbon-11 isotope.[217]

A different group found a different chemical, a molecule that could both cross the so-called "blood-brain barrier" into the brain and would then attach to amyloid plaque—but one that could be made using fluorine-18 instead of carbon-11.[218] Fluorine-18 has a much longer half-life than carbon-11.[219] This increased the lifetime of the radioactive material more than five-fold (and thus allows more time for it to accumulate in the locations of interest).[220] In 2012, the FDA approved the compound, then owned and marketed by Eli Lilly, as a drug known generically as Florbetapir F 18, with the trade name of Amyvid.[221] The drug was approved only for use in *diagnosing* Alzheimer disease, not *predicting* it,[222] although under the "off-label use" doctrine, once the FDA approves a drug (or biological product, or medical device) for one

214. William E. Klunck et al., *Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B*, 55 ANN. NEUROLOGY 306, 309 (2004).

215. William E. Klunck & Chester A. Mathis, *Whatever Happened to Pittsburgh Compound-A?*, 22 ALZHEIMER DISEASE & ASSOCIATED DISORDERS 198, 200 (2008).

216. Klunck et al., *supra* note 214.

217. Klunck & Mathis, *supra* note 215, at 200.

218. Dag Sehlin et al., *Engineered Antibodies: New Possibilities for Brain PET?*, 46 EUR. J. NUCLEAR MED. MOLECULAR IMAGING 2848, 2848 (2019).

219. *See* Erin L. Cole et al., *Radiosyntheses using Fluorine-18: the Art and Science of Late Stage Fluorination*, PMC (Jan. 1, 2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4140448/.

220. *See id.*

221. *FDA Approves Amyvid for Clinical Use*, ALZFORUM (Apr. 9, 2012), https://www.alzforum.org/news/research-news/fda-approves-amyvid-clinical-use [hereinafter *FDA Approves Amyvid*].

222. *See id.*

purpose, a doctor can generally prescribe it for any purpose.[223] At least two other similar compounds have subsequently been approved by the FDA for use in diagnosing Alzheimer disease by spotting amyloid plaque: florbetaben F 18 (Neuraceq, from Piramal Imaging) and flutemetamol F 18 (Vizamyl, from GE Healthcare).[224]

As a result, a physician can now order an FDA-approved PET scan (which is a "restricted device," equivalent to a prescription drug, and so available only on a doctor's order) to look for amyloid plaque in a person's brain. The results are not very precise—they are given as negative (few to no amyloid plaques) or positive (moderate to frequent plaques).[225] The FDA, the Alzheimer Association, and the American Association of Neurologists ("AAN") all agree that the presence of amyloid plaque does *not* mean that a person has Alzheimer disease; although, when the person has symptoms of cognitive impairment, it increases the probability that Alzheimer disease is the cause.[226] On the other hand, some people with plaque, on the PET scan or an autopsy, have no symptoms of dementia or cognitive impairment. So, the presence of plaque, even in the presence of cognitive impairment, does not necessarily mean that the patient has Alzheimer disease.

The FDA has not approved any of these amyloid PET scanning compounds for use to predict Alzheimer disease, and the Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging recommended expressly against their use for this purpose.[227]

The clinical use of amyloid PET in asymptomatic individuals is considered inappropriate at this time.[228]

> Indication 9 (Not Appropriate). The prognostic value of amyloid positivity in normal elderly individuals remains investigational . . . . There is a significant potential for patients and families to make inaccurate assumptions about risk and future outcomes on

223. *Understanding Unapproved Use*, *supra* note 115.

224. *Frequently asked questions about beta-amyloid imaging*, ALZHEIMER'S ASS'N, https://www.alz.org/media/Documents/health-care-pros-faqs-beta-amyloid-imaging.pdf (last visited Dec. 5, 2020) [hereinafter *Frequently asked questions about beta-amyloid imaging*].

225. *Id.*

226. *Medical Tests*, *supra* note 2 ("Researchers have found that more people with [mild cognitive impairment] than those without it go on to develop Alzheimer's.").

227. *FDA Approves Amyvid*, *supra* note 221; *see* K.A. Johnson et al., *Appropriate Use Criteria for Amyloid PET: A Report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association*, 54 J. NUCLEAR MED. 476, 476–90 (2013).

228. Johnson et al., *supra* note 227, at 481.

> the basis of amyloid PET results.[229] Currently, the potential harms outweigh the minimal benefits. The availability of proven preventative therapies undoubtedly would alter this judgment. [230]

Interestingly, the United States Preventive Services Task Force in early 2020 declined to recommend cognitive testing of the elderly to screen for dementia for similar reasons.[231] In fact, we still do not know how long it takes for plaque to accumulate before symptoms of Alzheimer disease appear, though the general belief seems to be that the answer is not months or years, but decades.[232]

Medicare has, thus far, refused to cover any use of PET amyloid testing except in the context of clinical trials, even though it can either rule out, or increase the likelihood, of an Alzheimer disease diagnosis.[233] At this point, knowing that a dementia is Alzheimer disease versus almost any of the other possible causes has no real medical significance because there are useful medical interventions for so few kinds of dementia.[234] (Dementia caused by depression, which is rare, is the main exception, although dementia caused by vitamin B-12 deficiency may in some cases also be reversible.)[235] Some commercial insurance will cover it for diagnostic purposes;[236] none, as far as I know, will cover it for predictive purposes.[237] If you want to pay for an amyloid PET scan yourself, the price averages $3,000 or more.[238]

Note that, although a positive result on an amyloid PET scan is weak evidence of Alzheimer disease (necessary but in no way sufficient), and based on today's knowledge, even weaker evidence of

229. *Id.* at 483.

230. *Id.*

231. *See* Douglas K. Owens, *Screening for Cognitive Impairment in Older Adults*, 328(8) JAMA 757, 757–763 (2020), available at https://jamanetwork.com/journals/jama/fullarticle/2761651; Judith Graham, *U.S. Medical Panel Thinks Twice About Pushing Cognitive Screening for Dementia*, KAISER HEALTH NEWS (Feb. 25, 2020), https://khn.org/news/u-s-medical-panel-thinks-twice-about-pushing-cognitive-screening-for-dementia/.

232. Johnson et al., *supra* note 227, at 485–86.

233. CTRS. MEDICAID & MEDICARE SERV., DECISION MEMO FOR BETA AMYLOID POSITRON EMISSION TOMOGRAPHY IN DEMENTIA AND NEURODEGENERATIVE DISEASES (CAG-00431N), (Sept. 27, 2013).

234. *How can I treat dementia?*, ALZHEIMER SOC'Y CAN., https://alzheimer.ca/en/about-dementia/how-can-i-treat-dementia (last visited Dec. 5, 2020).

235. Manjari Tripathi & Deepti Vibha, *Reversible Dementias*, 51 INDIAN J. PSYCHIATRY 52 (2009), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3038529/.

236. *See Frequently asked questions about beta-amyloid imaging*, *supra* note 224.

237. *Id.*

238. *Id.*

heightened Alzheimer disease risk; a negative result on such a scan would be good evidence that a person does not have Alzheimer disease and is highly unlikely to develop it for some time—the length of time needed for a substantial build-up of amyloid plaque.[239] That length of time is not yet known with any confidence but it is not thought to be short,[240] and with more data from people who have had amyloid PET scans that time frame should become better known.

Remember, though, that two different physical brain conditions are part of the definition of Alzheimer disease, not just amyloid plaques but also tau tangles.[241] Tau tangles can also now be imaged through PET scans. This has been done for research purposes for several years.[242] In fact, no fewer than eleven compounds have been used for tau tangle PET scanning, all but one using Fluorine-18.[243] It was not, however, until May 28, 2020, that the FDA approved the first compound used in PET scans to image tau tangles, Tauvid, or flortaucipir F18.[244] Made by Avid Radiopharmaceuticals (the same Eli Lilly & Co. subsidiary that got approval for Amyvid, the first amyloid plaque radioligand), two clinical trials showed that it was, in fact, as good as subsequent autopsies at detecting high or low levels of tau tangles in seriously demented patients.[245] Like Amyvid and the other amyloid-detecting PET radioligands, Tauvid was approved only for diagnostic use, not predictive use.[246]

Cognitively normal elderly patients have fewer tau tangles and those are found in only one area of the brain; people with Alzheimer dementia have many more tangles, in more parts of the brain.[247] Again, we do not have good information on the quantitative relationship be-

239. *See id.*
240. CTRS. MEDICAID & MEDICARE SERV., *supra* note 233.
241. *See* Antoine Leuzy et al., *Tau PET Imaging in Neurodegenerative Taupathies—Still a Challenge*, 24 MOLECULAR PSYCHIATRY 1112, 1112–34 (2019).
242. *Id*. at 1112.
243. *Id.* at 1113.
244. Press Release, Eli Lilly and Company, Lilly Receives U.S. FDA Approval of TAUVID™ (flortaucipir F 18 injection) for Use in Patients Being Evaluated for Alzheimer's Disease (May 28, 2020, 7:17 PM), available at https://www.prnewswire.com/news-releases/lilly-receives-us-fda-approval-of-tauvid-flortaucipir-f-18-injection-for-use-in-patients-being-evaluated-for-alzheimers-disease-301067441.html.
245. *Id.*
246. *See id.*
247. *Id.*

tween PET scan tau tangle findings and the diagnosis of Alzheimer disease, let alone its future incidence. Yet. But, also again, as more information accumulates, more diagnostic and predictive information should become available.

As the tau tangle PET scans have been approved for less than a month at the time I write this, they are not covered by Medicare or by any commercial insurers for any purpose—not diagnosis, let alone for prediction. But, now that they are approved, they can be used off label by physicians.

Neuroimaging also can play another role in Alzheimer disease diagnosis, and, potentially, prediction. As neurons die from Alzheimer disease, those effects can be seen by neuroimaging. Certain brain regions, especially the hippocampus, which is necessary for making new memories, will become "thinner," with fewer neurons.[248] The "thinning" of the regions can sometimes be seen on CT scans and can be more easily seen on the more precise MRI scans, scans that look at the physical shape and size of brain regions.[249]

But, not just the size, shape, and density of brain regions can be imaged but so can their levels of activity.[250] PET scans using Fluorine-18 tagged glucose can indicate the uptake of sugar in brain regions.[251] Lower than normal uptake implies lower than normal activity, which is an indicator of neuronal death.[252] A variation of MRI called "functional" MRI ("fMRI") can also indicate lower activity.[253] Brains are energy and oxygen "hogs," consuming about 18 percent of the body's energy and oxygen while only making up about 1 to 3 percent of its mass.[254] Normally, "fresh" blood floods a brain region that has just been active, giving off a signal that can be seen using fMRI. If that kind of

248. *See* Glenda Halliday, *Pathology and Hippocampal Atrophy in Alzheimer's Disease*, 16 LANCET NEOROLOGY 862, 862–64 (2017).

249. *Id*. at 862 (explaining neuronal loss and hippocampal atrophy are observed in Alzheimer patients).

250. *See* Michael Brammer, *The Role of Neuroimaging in Diagnosis and Personalized Medicine*, 11 DIALOGUES CLINICAL NEUROSCIENCE 389, 390 (2009).

251. *See* Milan M. Alauddin, *Positron Emission Tomography (PET) Imaging with 18F-based Radiotracers*, 2 AM. J. NUCLEAR MED. MOLECULAR IMAGING 55, 55 (2012).

252. *See id.*

253. *See* Reisa Sperling, *The Potential of Functional MRI as a Biomarker in Early Alzheimer's Disease*, 32 NEUROBIOLOGY AGING 37, 38 (2011).

254. *See* Marcus E. Raichle & Debra A. Gusnard, *Appraising the Brain's Energy Budget,* 99 PROC. NAT'L ACAD. SCI. U.S. 10237, 10237 (2002) ("In the average adult human, the brain represents about 2% of the body weight. Remarkably, despite its relatively small size, the brain accounts for about 20% of the oxygen and, hence, calories consumed by the body.").

fresh blood flow is not happening when expected, it is a signal that the brain area is not being active.[255] These kinds of neuroimaging can, therefore, actually "see" either the physical deterioration of brain regions or their lessened activity. Either one is some evidence of possible existing, or future, Alzheimer disease.[256]

4. BIOMARKER TESTS

A "biomarker" is, according to the dictionary, "a measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure."[257] A wide range of things can be used as biomarkers, including PET scans, but this Section focuses on molecules in a person's blood or other fluids, notably the cerebrospinal fluid, found in the brain or around the spinal cord.[258] Cerebrospinal fluid is usually checked by drawing a sample of it from a needle stuck into the spine, known as a lumbar puncture (perhaps more familiar, especially to fans of a particular cult movie, as a "spinal tap").[259] The National Institute of Aging has prepared an excellent summary of various Alzheimer disease biomarkers, from neuroimaging through cerebrospinal fluid and blood tests.[260] Recent findings about the predictive power of biomarkers measured in blood draws reveal what may be the most promising of all the predictive tests.

Whether it is an (easy) blood draw or a (more unpleasant) lumbar puncture, doctors and researchers can examine these two fluids that bathe the brain and look for molecules that are associated with higher (or lower) risks of Alzheimer disease: Aß42 and tau. Not surprisingly, the levels of these two proteins in these fluids have been associated with the existence, or the risk, of Alzheimer disease.[261] Surprisingly, these associations are not always obvious.

---

255. *See id*.

256. *See* Sperling, *supra* note 253, at 38 (explaining that fMRI studies show people with Alzheimer's have decreased brain activity, particularly in a large part of the brain known as the medial temporal lobe).

257. *Biomarker*, LEXICO, https://www.lexico.com/en/definition/biomarker (last visited Dec. 5, 2020).

258. *See* Sean Mackey et al., *Neuroimaging-Based Pain Biomarkers: Definitions, Clinical and Research Applications, and Evaluation Frameworks to Achieve Personalized Pain Medicine*, 4 PAIN REPS. 1 (2019).

259. THIS IS SPINAL TAP (Embassy Pictures 1984).

260. *Biomarkers for Dementia Detection and Research*, NAT'L INST. ON AGING, https://www.nia.nih.gov/health/biomarkers-dementia-detection-and-research (last updated June 9, 2020).

261. *See* Sperling, *supra* note 253, at 40.

Lower, not higher, levels of Aß42 in the cerebrospinal fluid are strongly associated both with Alzheimer disease and with progression from mild cognitive impairment to Alzheimer disease.[262] Some speculate that this is because the amyloid beta has been depleted from the blood by being sequestered in plaques around the neurons.[263] Aß42 in blood plasma (the liquid part of the blood that remains after the red and white blood cells are removed) has also been associated with Alzheimer disease, though the correlation is less reliable and less consistent than that seen with cerebrospinal fluid.[264]

Tau proteins can be assessed both in their "normal" form and in a form that has a phosphate group attached to it: "phosphorylated" tau.[265] *Higher* levels of phosphorylated tau in the cerebrospinal fluid are associated with Alzheimer disease, though it does not correlate strongly with the amount of tau tangles seen in Alzheimer disease patients.[266]

Since October 2019, three studies have found strong correlations between blood plasma measures involving Aß42 or phosphorylated tau and the future likelihood of Alzheimer disease. One group found impressive predictive power in the ratio of Aß42 to Aß40 in the blood plasma. The lower the ratio (the less Aß42 to Aß40), the more likely a progression to high levels of amyloid plaque on PET scans.[267] Note—this study did not look at an Alzheimer disease diagnosis as an endpoint, just higher levels of plaque. In March 2020, two different papers (in the same issue of the same journal) correlated high levels of P-tau181 (tau protein with a phosphate group added to the protein at its 181st amino acid in the blood plasma) to higher levels of subsequently developing Alzheimer disease in people who were either cognitively normal or had mild cognitive impairment.[268]

262. *See* Tammaryn Lashley et al., *Molecular Biomarkers of Alzheimer's Disease: Progress and Projects*, 11 DISEASE MODELS & MECHANISMS 1, 3 (2018).
263. *Id.*
264. *Id.*
265. *Id.*
266. *Id.* at 3–4.
267. Suzanne E. Schindler et al., *High-precision Plasma ß-amyloid 42/40 Predicts Current and Future Brain Amyloidosis,* 93 NEUROLOGY 1647 (2019).
268. *See* Shorena Janelidze et al., *Plasma P-tau181 in Alzheimer's Disease: Relationship to Other Biomarkers, Differential Diagnosis, Neuropathology, and Longitudinal Progression to Alzheimer Dementia,* 26 NATURE MED. 379 (2020); Elizabeth Thijssen et al., *Diagnostic Value of Plasma Phosphorylated tau181 in Alzheimer's Disease and Frontotemporal Lobal Degeneration,* 26 NATURE MED. 387 (2020).

If these findings seem a bit unclear to you, join the club. *Lower* levels of Aß42 in cerebrospinal fluid and blood serum correlate with Alzheimer disease, *higher* levels of phosphorylated tau protein in the cerebrospinal fluid and in blood plasma—correlate reliably with Alzheimer disease.[269] And, a lower ratio of Aß42 to Aß40 in the blood plasma correlates with more amyloid plaque.[270]

At this point, it is not entirely clear what these fluid biomarkers mean, but because these fluids are cheap and easy (blood) or relatively cheap and not too difficult (cerebrospinal fluid) to obtain, efforts to find correlations will continue and, no doubt, at some point will have predictive findings that provide significant information at a small fraction of the cost of PET scanning—and with no radiation-induced risk to the person involved. As one of my friends who works on Alzheimer disease wrote me in mid-June 2020, "I really didn't imagine that we would have a useful plasma test anytime soon but these both seem quite legit."[271] Four months later, in October 2020, a firm called C2N, announced that it was offering a laboratory test that looks at Aß42 and *APOE* variants in the blood as a way of predicting amyloid plaque levels.[272] As far as I can tell, this test is not FDA approved but is being sold as a so-called "Laboratory Developed Test," exempt from regulation.

5. COMBINATIONS OF PREDICTORS

What do higher levels of PET scan-identified amyloid plaques mean in people with two copies of *APOE* e4? What do lower levels of Aß42 in the blood serum mean in the context of people with one copy of *APOE* e4? What do high levels of phosphorylated tau in the cerebrospinal fluid of people with two copies of *APOE* e3 and a lower level of amyloid plaques on a PET scan mean? And what do any of these mean for people with mild cognitive impairment, a poor sense of smell, or a history of concussions? We are just beginning to accumulate enough information to try to connect these different predictors into a general prediction. We are not there yet but will undoubtedly get better and better at it in the coming years.

269. *See* Janelidze et al., *supra* note 268; Thijssen et al., *supra* note 268.

270. Email from Michael D. Greicius to author (June 14, 2020) (on file with author).

271. *Id.*

272. Conor Hale, *C2N debuts Alzheimer's blood test for predicting amyloid plaque deposits in the brain*, FIERCE BIOTECH (Oct. 30. 2020, 8:35 AM), https://www.fiercebiotech.com/medtech/c2n-debuts-alzheimer-s-blood-test-for-predicting-amyloid-plaque-deposits-brain.

How good a predictor will we end up with? Optimists will say it is just an issue of more data, which is rapidly being collected, and statistical methods to analyze it, which machine learning algorithms and artificial intelligence are providing. Pessimists won't say it will not happen but will want more proof. Though I usually am a skeptic about medical advances (if one heralded medical breakthrough out of one hundred worked, we humans would be both invulnerable and immortal), I think the chances of good combination predictors for either positive results (will get Alzheimer disease) or negative results (will not get Alzheimer disease) are quite high.

6. SUMMING UP ALZHEIMER DISEASE PREDICTION

For some people, we can predict Alzheimer disease (almost) perfectly—people with a disease-causing version of *PSEN1*, in one direction, and people with two copies of *APOE* e2, in the other direction, are prime examples.[273] For others, the answers are cloudy. But we can safely predict that as long as Alzheimer disease remains a topic of research interest, these predictions will get better. Until then, we will want to know more about what causes the disease and about how to separate out high-risk people, mainly to recruit them into clinical trials.

"Big data," for better or worse, is one of the buzzwords du jour. More and more genetic analyses, PET scans, analyses of blood sera and cerebrospinal fluid *will* be undertaken, and the predictive equations will get better. Although today only a few percent of young or middle-aged people can obtain a confident prediction of what their late-in-life Alzheimer disease risk will be, as time goes on that percentage will inevitably increase—even if no one is trying to sell an Alzheimer disease prediction test to people. Of course, some people will want to sell that test—as 23andMe already does[274] in its own weak way, with its *APOE* test.

III. Potential Benefits and Costs of (Fairly) Accurate Prediction of Alzheimer Disease

I have read a great deal of science fiction. Robert A. Heinlein was one of the greatest, if not *the* greatest, science fiction writer of his era—

273. *See* Ordovas et al., *supra* note 188.
274. *See Late-Onset Alzheimer's Disease*, 23ANDME, *supra* note 6.

the 1940s through the 1960s.[275] His very first publication was a short story called "Life-Line," which appeared in the science fiction magazine *Astounding Science Fiction* in August 1939.[276] Its protagonist, a doctor named Hugo Pinero, had invented a device that would allow him to predict, down to the minute, how long someone was going to live.

Except for well-planned suicides and uncontested cases of capital punishment, right now no one has that knowledge. If it were available, would you, dear reader, want to know it about yourself?

Predicting Alzheimer disease is not (exactly) the same as predicting death and the accuracy will fall short of 100 percent even without specifying a date. But assume, for the moment, that medicine could offer you a test that would predict, with both 100 percent positive predictive value and 100 percent negative predictive value, whether or not you were going to get Alzheimer disease by the time you were seventy (or seventy-five, or eighty—pick your age). Would you want that test—and why, or why not?[277] This Section tries to provide some structure to help you (and all of us) answer that question.

Remember three things before starting that analysis. First, this Section is talking about the advantages and disadvantages of (reasonably) accurate prediction. Bad prediction has no benefits, only costs, and an overly broad early use of prediction could be of very bad prediction indeed. Second, recall that even (reasonably) accurate prediction will never be perfect prediction. If you were given a 90 percent chance of either developing or not developing Alzheimer disease and took reasonable actions based on that prediction, the reasonableness of those actions might be small comfort if you turned out to be one of the other 10 percent. And, third, the benefits and costs of prediction will in some

275. *See Robert A. Heinlein: Acclaimed Science Fiction Writer, Dies*, L.A. TIMES (May 10, 1988), https://www.latimes.com/archives/la-xpm-1988-05-10-mn-2458-story.html (explaining that Heinlein continued to write after the 1960s, publishing two novels in 1970 and 1973, then taking a seven-year break after a serious illness to publish five more novels from 1980 to 1987. The merits of these later novels are debatable, and debated, and his position as one of the leading active science fiction authors deteriorated. His last clearly successful novel was THE MOON IS A HARSH MISTRESS (G.P. Putnam Sons 1966)).

276. Robert A. Heinlein, *Life-Line*, XXIII ASTOUNDING SCIENCE-FICTION no. 6, Aug. 1939.

277. When I teach or give talks where I discuss predicting Alzheimer disease, I usually ask the audience that question. I do not count the responses, but, from a very weak form of casual empiricism, for whatever little it is worth, my impression is that around half of people want the test, about a quarter do not want it, and another quarter are unsure.

cases look very different for the small percentage of people who have a very high chance of early onset Alzheimer disease. Developing symptoms of Alzheimer disease in one's forties or fifties will often have very different consequences from developing them in one's sixties or seventies and with different consequences will come different issues for predictive testing.

A. Advantages of Prediction

Accurate prediction may well have some advantages for people predicted *not* to be diagnosed with Alzheimer disease. It could relieve anxiety and allow improved life planning. Of course, a prediction of no Alzheimer disease is not a prediction of no dementia;[278] people who would develop an untreatable non-Alzheimer dementia would receive no special benefit and might even be misled into thinking they were immune from dementia. On the other hand, a person with signs or symptoms of dementia whose predicted risk of Alzheimer disease is very low because of, say, an absence of amyloid plaque, might turn out to have one of the few kinds of dementia that can be usefully treated, which would be a great potential benefit.[279]

Even if the prediction, however, is positive, there are at least six potential benefits for some patients.

First, prediction becomes extremely attractive if it is coupled with useful interventions to prevent the disease. Unfortunately, currently there are no such interventions of proven or substantial value.[280] Mental exercise, such as doing crossword or Sudoku puzzles, makes one better at doing those puzzles, but does not appear to prevent or to even slow

278. *See generally* Alexis Moscoso et al., *Prediction of Alzheimer's Disease Dementia with MRI Beyond the Short-Term: Implications for the Design of Predictive Models*, 23 NEUROIMAGE CLINICAL 101837, 101837 (2019).

279. *See generally id.*

280. *See Care Interventions for People Living with Dementia and Their Caregivers,* AGENCY HEALTHCARE RES. & QUALITY (July 25, 2019), https://effectivehealthcare.ahrq.gov/products/care-interventions-pwd/protocol (suggesting a lack of scientific consensus concerning the effectiveness of Alzheimer's intervention techniques). *But see* Edmund Howe, *Key Psychosocial Interventions for Alzheimer's Disease*, 5 PSYCHIATRY 23 (2008) ("Psychosocial interventions may be particularly efficacious for agitation and other behavioral symptoms, because even when these patients have become cognitively impaired, they may remain remarkably responsive to interactions with other people.").

Alzheimer disease.[281] Neither does being careful about one's diet (whatever "careful" means in such a context).[282] Some evidence exists that physical exercise can help slow the progress of Alzheimer disease,[283] although not prevent it entirely.[284] Encouraging someone at high risk to exercise more could be of some help,[285] and some better methods of prevention may be uncovered at some point (soon, one hopes).

Second, perhaps knowing that a person is at high risk for Alzheimer disease would lead to earlier treatment of MCI or Alzheimer disease. Today, that offers only small benefits—although a few drugs have been approved for treating MCI or Alzheimer disease, they have very limited effects.[286] For some patients, though not a majority, these drugs can slow the mental decline from the disease a bit, pushing it back a few months.[287] Starting these drugs earlier because of the advance warning from prediction might allow a patient a few more good months that would have been lost in the confusion of a longer diagnostic process. But, again, better drugs are being sought and it is very plausible that the earlier the treatment, the better the results, perhaps through fewer neurons having died.

281. *See* Roger T. Staff et al., *Intellectual Engagement and Cognitive Ability Later in Life (The "Use It or Lose It" Conjecture): Longitudinal, Prospective Study*, 363 BMJ 1, 3–4 (2018) (finding engagement in cognitive tasks was not associated with cognitive cognitive decline [or lack thereof]).

282. *Does Diet Matter against Alzheimer's Disease?* FORT HEALTH CARE, https://www.forthealthcare.com/health-365-article/does-diet-matter-against-alzheimers-disease/ (last visited Dec. 5, 2020).

283. *Exercise Could Slow Withering Effects of Alzheimer's*, SCI. DAILY (Sept. 17, 2019), https://www.sciencedaily.com/releases/2019/09/190917124832.htm (describing a study showing exercise can slow decline in people at high risk for Alzheimer disease); *Physical Exercise and Dementia*, ALZHEIMER'S SOC'Y, https://www.alzheimers.org.uk/about-dementia/risk-factors-and-prevention/physical-exercise (last visited Dec. 5, 2020) (explaining the results of eleven studies which indicate that exercise can reduce Alzheimer disease risk) [hereinafter *Exercise Could Slow*].

284. *See Exercise Could Slow*, *supra* note 283 (noting no study has shown exercise can prevent dementia). Though, of course, if an intervention delays the decline long enough for a person to die from something else before an Alzheimer diagnosis, it will have, in effect, "prevented" a case of Alzheimer disease.

285. *See id.*

286. *See Medications for Memory*, ALZHEIMER'S ASS'N, https://www.alz.org/alzheimers-dementia/treatments/medications-for-memory#:~:text=The%20U.S.%20Food%20and%20Drug,and%20reasoning)%20of%20Alzheimer's%20disease (last visited Dec. 5, 2020).

287. *Alzheimer's: Drugs help manage symptoms*, MAYO CLINIC (Apr. 19, 2019), https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers/art-20048103.

Third, the original view of the discoverer of the relationship between *APOE* and Alzheimer disease, Dr. Allen Roses, was that its clinical value would be to increase the accuracy of an Alzheimer disease diagnosis and shorten the diagnostic process.[288] That might stem from increasing the confidence that a patient with dementia has Alzheimer disease diagnosis. The process of diagnosis is time consuming, expensive, and anxiety-producing.[289] Shortening it could be beneficial even if no preventive or treatment options were available.

A fourth possibility is financial planning. One of my friends is one of the founders of the field of elder law. He has an active legal practice counseling elderly clients. He has said he would tell all his clients, at least those with high net worth, to get such a test if it were easily available. More time to plan how to arrange their finances, if they think they may need five, ten, or fifteen years of nursing care, could make an important difference for their financial situation and that of their heirs. One version of that kind of planning is buying long-term care insurance, although, as we will see in the next Section, that could have its own problems.

Fifth, it could help people with broader life planning. Do they want to retire early? Do they want to travel a lot now? Do they want to move to be nearer to family, or be closer to good medical or long-term care? Do they want to marry, to divorce, or otherwise to change their family relationships? If the prediction comes early enough, it might even affect decisions about having children.

---

288. Katie Skeehan et al., *Impact of gene patents and licensing practices on access to genetic testing for Alzheimer disease*, 12 GENETICS MED. S71, S71–S82 (2010); Tania Bubela et al., *The mouse that trolled: the long and tortuous history of a gene mutation patent that became an expensive impediment to Alzheimer's research*, J.L. & BIOSCIENCES 213, 213–262 (2015). (Apparently, Duke, acting after spurred by Allen Roses, forced a direct-to-consumer company, Smart Genetics, to stop offering *APOE* testing for predictive purposes. Allen Roses was asked to become a consultant of Smart Genetics, refused, and notified Duke University that it was his understanding the license for the patents on which he is first inventor permitted *APOE* testing only for those with a physician's certification of a diagnosis of dementia. Smart Genetics ceased operations in October 2008. An October 2008 report in Nature corroborates the cessation of Smart Genetics risk-assessment testing, and attributes it to licensing terms between Duke and Athena, although the licensing terms between Duke and Athena are not public. [citations omitted]. I want to express huge thanks to Bob Cook-Deegan, the senior author on both of these articles, who walked me, via email, through these issues).

289. *See generally Diagnosing Alzheimer's: How Alzheimer's is diagnosed*, MAYO CLINIC (Apr. 19, 2019), https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers/art-20048075.

If a person's high risk of Alzheimer disease has a strong genetic component, he or she might want to either avoid having children or to use preimplantation or prenatal genetic testing to have children who will not have that higher genetic risk. (In an example of possible differences when the Alzheimer disease is early-onset, someone with a high risk of early-onset Alzheimer disease might also think about whether to have children who, while still in their teens or twenties, will have to live with a parent with Alzheimer disease.) All of these questions might get different answers depending on whether someone had a very high or very low chance of being diagnosed with Alzheimer disease in the near future.

And finally, some people will have psychological benefits even from an affirmative prediction of future disease. They may just be people who want to know, whether they can do anything about it or not. This seems particularly plausible among people who have long thought that they are at particularly high risk, perhaps as a result of a strong family history of the disease. Not everyone would have a good reaction to bad news—but people are deeply different in how they react to many things. Some people will find bad news better than continued uncertainty. (And, of course, more people will find good news better than continued uncertainty.)

B. Disadvantages of Prediction

I have to strain to find disadvantages to accurate predictions that people will *not* be diagnosed with Alzheimer disease. Perhaps it could lead them to ignore early symptoms of other dementias or brain problems, trusting too strongly their likely freedom from Alzheimer disease. Or perhaps it will lead them not to take actions that might have been helpful against Alzheimer disease, but would surely have been helpful against other bad health conditions. Physical exercise, for example, may be useful in slowing Alzheimer disease but it is clearly good for many other problems of aging.[290] Still, by and large, the risks of accurate predictions of *low* risk of Alzheimer disease seem minimal.

For those who receive a positive prediction, a medical announcement that they will (most likely) be diagnosed with the disease could

290. Wei-Wei Chen et al., *Role of physical exercise in Alzheimer's disease*, 4 BIOMEDICAL REP. 403, 403–07 (2016).

lead to at least five kinds of disadvantages: mistakes from misunderstanding the results, futile or even harmful attempts to prevent or treat the disease, social discrimination, strains on personal relationships, and personal psychological harm. A December 2019 article in *The New York Times* nicely describes some of these reactions from real patients to early diagnosis of Alzheimer disease.[291] One researcher summed up the responses as follows:

> Dr. Jason Karlawish, an Alzheimer's researcher at the University of Pennsylvania, did a formal study to gauge patients' responses to learning that they had elevated levels of amyloid in their brain.
>
> He did not see catastrophic reactions to the bad news. No one died by suicide.
>
> Instead, many said they were taking steps to slow Alzheimer's, putting their faith in healthy diets and exercise although no lifestyle measures have been shown to have an effect.
>
> But some were not so sure getting a diagnosis helped them. "You've now told me something about my future," Dr. Karlawish recalled one patient telling him. "I can't unlearn this."[292]

1. MISUNDERSTANDING THE RESULTS

One set of risks comes from the possibility that the recipients of the predictions will not understand them properly. As a result, they may act, or fail to act, in ways that hurt them, or, at least, are against their interests.

At the grossest level, people might even fail to understand whether their risks are high or low. It is a quirk of medical testing that "negative" is usually a *good* thing, while "positive" is a bad one. I remember when I was in first or second grade, my class all got skin tests for tuberculosis exposure. (I presume, in retrospect, that we had been exposed to someone with an active case.) The nurse told me that I should go home and tell my parents my test was "negative." I was six or seven years old, but I knew that "negative" was bad. I had no idea what tuberculosis was, but it seemed to be bad too. So, if I recall correctly (uncertain), I had an unsettling few hours before my mother reassured me. People seeking Alzheimer disease predictive testing will almost all be more sophisticated than I was, but some probably will

291. Gina Kolata, *Alzheimer's Tests Soon May Be Common. Should You Get One?*, N.Y. TIMES, https://www.nytimes.com/2019/12/20/health/alzheimers-disease-diagnosis.html (last updated July 28, 2020).

292. *Id.*

make that, or a similar mistake, especially if the results are not delivered by a trained health professional. Thinking you are high risk when you are low risk, or low risk when you are at high risk, forfeits whatever benefits prediction might have and increases the chances you will spend time, effort, and money doing the wrong thing (including needlessly worrying).

The more likely misunderstanding, though, is about certainty. We humans are poor (to be kind) at dealing with probabilities (as the popularity of state lotteries indicates). Many people may read an 80 to 90 percent chance of an Alzheimer diagnosis as "certain"; others will read a 10 to 20 percent chance as "entirely safe." At least in these cases their misunderstandings should still push them in the proper direction, but quite possibly too far, in ways that are damaging.

Finally, the test results may be misunderstood in terms of the tested person's risks for other diseases. Most clearly, people who test as having very low Alzheimer disease risks may not realize (or remember) that they still have non-trivial risks of other dementias and so may ignore, to their harm, early warnings of such problems. Or people who test positive may focus too much on their Alzheimer disease risk and ignore their continuing risks for cardiovascular disease, cancer, and even for other non-Alzheimer disease dementias.

2. USING BAD PREVENTIVE "TREATMENTS"

Some patients will react in a positive, "can do," fashion, seeking out interventions that will prevent or slow their decline in Alzheimer dementia. If their actions are only "healthy diets and exercise," they may well do nothing for their Alzheimer disease risks but, on average, they will not harm themselves, or their finances, and may do some good for other aspects of their lives, medical or otherwise.[293] But some will try other remedies that are much less benign and often much more expensive. Unproven "preventive" or "treatment" interventions for Alzheimer disease may actually harm patients who seek them out. In many cases they may also cost them dearly financially. It is a depressing reality that some people are willing to take advantage of the desperation of their fellow humans in order to profit from their fear. Alas, quacks will

293. Chen et al., *supra* note 290, at 405.

always be with us and "healers" offering unproven, unapproved, and *expensive* treatments have not been absent from Alzheimer disease.[294]

The FDA has put out a warning to patients about Alzheimer disease "cures":[295]

> These purported miracle cures are sold primarily on the Internet. They are often, though not always, falsely labeled as dietary supplements. Regardless of their form, these products fly in the face of true science. What these companies are selling is the false hope that there is an effective treatment or cure.
>
> At best, the products offered by these scam artists will have no effect on the patient; at worst they may pose a danger to a patient who takes them. Not only will they not do what they claim, the ingredients in these products may interact with, and potentially interfere with, essential medications. Furthermore, these products have not been evaluated by the FDA for safety and effectiveness. These products are a waste of money and may also delay consumers from receiving the necessary care and support for their illness.
>
> One of [the] best ways to protect yourself from fake treatments is to ask whether the claim seems too promising and if it contradicts what you've heard from reputable sources about treatments for Alzheimer disease. Companies selling unproven Alzheimer disease treatments often include a range of unsupported and expansive claims about the supposed healing powers of their products. These include statements such as:
>
> - "You can even reverse mental decline associated with dementia or even Alzheimer's in just a week;"
> - "Clinically shown to help disease of the brain such as Alzheimer's and even dementia;"
> - "Supplements are used to cure Alzheimer's disease;"
> - "can … reduce the risk of Alzheimer's by half;"
> - "May have a role in preventing the progression of Alzheimer's;" and
> - "Clinically shown to help disease of the brain such as Alzheimer's and even dementia."[296]

The products discussed in that consumer alert were largely sold as dietary supplements and were not terribly expensive. But other interventions are also available, some much more invasive and possibly risky, as well as more expensive.

294. *Unproven Alzheimer's Disease Products*, FDA, https://www.fda.gov/consumers/health-fraud-scams/unproven-alzheimers-disease-products (last updated Dec. 22, 2018).

295. *Watch Out for False Promises About So-called Alzheimer's Cures*, FDA, https://www.fda.gov/consumers/consumer-updates/watch-out-false-promises-about-so-called-alzheimers-cures-0 (last updated Mar. 28, 2019).

296. *Id.*

Some "stem cell clinics" offer, for payment, stem cell injections backed by anecdotal case reports. The rise of "stem cell clinics," offering treatments, sometimes in the guise of (patient-paid) clinical trials, has been well documented by Leigh Turner and Paul Knoepfler.[297] They found over 350 enterprises in the U.S. selling allegedly stem cell-based alleged treatments, including at least twenty-seven that made claims about treating Alzheimer disease.[298] These clinics use various types of cells, usually taken from the patient's own body, such as bone marrow cells, fat cells, or peripheral blood stem cells, and, after some manipulation, return them via intravenous infusions, intramuscular injections, or infusions into the cerebral spinal fluid.[299] "MD Stem Cells" put out a press release about a daughter's happiness with her mother's response to her first treatment from them in their new "Alzheimer's Autism Cognitive Impairment Stem Cell Treatment Study" or ACIST.[300]

> This is the first open-label, non-randomized study designed for patients with dementias, including Alzheimer's, treating them with their own bone marrow stem cells called BMSC. All enrolled patients receive active BMSC treatment—there is no placebo arm—making it different from most drug studies. The ACIST study is registered with the National Institutes of Health on their www.clinicaltrials.gov website . . . .[301]

The absence of a control group greatly limits the so-called trial's scientific value—one wants to compare the treated individuals with similar people who were not treated—but it obviously makes it more attractive to paying customers, who are less likely to pay if they may be treated with a placebo. The ballyhooed fact that the "trial" is registered with the NIH is meaningless; clinicaltrials.gov is required to list any trial that applies;[302] flaunting "NIH registration" has now, as in this case, become a way for dubious trials to appear legitimate.

Another red flag is that the firm's website claims that it has ongoing trials testing bone marrow-derived stem cells (important for making blood) to treat different eye diseases, stroke, Parkinson disease,

297. Leigh Turner & Paul Knoepfler, *Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry*, 19 CELL STEM CELL 154, 154 (2016) I am grateful to Leigh Turner for suggestions about stem cell clinics making questionable Alzheimer disease claims.

298. *Id.* at 156.

299. *See generally id.* at 155.

300. Press Release, MD Stem Cells, MD Stem Cells New Alzheimer's Treatment Shows Early Benefits (Apr. 24, 2019), https://www.pr.com/press-release/783238.

301. *Id.*

302. *Frequently Asked Questions*, U.S. NAT'L LIBR. MED., https://clinicaltrials.gov/ct2/manage-recs/faq#find (last visited Dec. 5, 2020).

multiple sclerosis, traumatic brain injury, peripheral neuropathy, spinal cord injury, autism spectrum disorders, Alzheimer disease, Lewy body dementia, multi-infarct dementia, CADASIL dementia, and aging.[303] Anything that is claimed to treat almost everything is highly likely to treat nothing, except the patient's bank account, and that negatively.[304]

Consider this example, one that looks more plausible than most. Christopher Duma, a neurosurgeon, has injected stem cells derived from patients' fatty tissues into their skulls at a price (not covered by insurance) of $10,000 per injection.[305] The doctor received approval from an institutional review board (although he did not, apparently, receive or seek an IND exemption from the FDA).[306] He thinks his first patient, who has received eight injections, is doing much better than one would expect at his stage of the disease.[307] The patient is pleased. But is the treatment working? It is not FDA approved, and it has, thus far, only been through a phase I trial, intended to show safety not efficacy (although, as is not unusual, the researchers discuss efficacy anyway).[308] The physician has published a paper describing his phase I results from thirty-one patients, ten with Alzheimer disease and twenty-one with one of six other brain conditions.[309]

Is this a genuine effort at medical research, unsupported by money from the NIH, private foundations, or pharmaceutical or biotech companies? Or is it a way to make money from vulnerable and desperate patients? Is it both? Either way, because a prediction of a high risk of future Alzheimer disease may increase a person's interest in—or desperation for—some kind of intervention, people so classified may be particularly vulnerable to ineffective, perhaps unsafe, and usually expensive "treatments."

303. *Studies & Treatments*, MD STEM CELLS, https://www.mdstemcells.com/studies/ (last visited Dec. 5, 2020).

304. *Miracle Health Claims*, FTC (Nov. 2011), https://www.consumer.ftc.gov/articles/0167-miracle-health-claims.

305. Keith Sharon, *Is Alzheimer's treatment of injecting stem cells into the brain a breakthrough or quackery?*, MED. XPRESS (Mar. 14, 2017) https://medicalxpress.com/news/2017-03-alzheimer-treatment-stem-cells-brain.html.

306. *Id.*

307. *Id.*

308. *Id.*

309. Christopher Duma et al., *Human intracerebroventricular (ICV) injection of autologous, non-engineered, adipose-derived stromal vascular fraction (ADSVF) for neurodegenerative disorders: results of a 3-year phase 1 study of 113 injections in 31 patients*, 46 MOLECULAR BIOLOGY REPS. 5257, 5257–72 (2019).

3. SOCIAL DISCRIMINATION

A second disadvantage is the possibility of social discrimination if one's (positive, which in this context mean "bad") test results are known. In predictive genetic testing, this has commonly been a fear of discrimination in employment and health insurance. In predictive Alzheimer disease testing, the issues are a little different, largely because of the disease's timing. This Section discusses the likelihood of discrimination based on Alzheimer disease risk prediction in employment, health insurance, long-term care insurance, and other areas. (The next part of this Article will discuss the legalities of such discriminations.) Note—this Section talks about whether someone may face discrimination based on such a prediction; it does not try to determine, at this point, whether such discrimination might not be appropriate, for example, for reasons of public safety or public policy.

a. Employment Discrimination

With a disease that largely strikes people over the age of sixty,[310] employment discrimination will not disappear but should become less important, particularly with respect to hiring. For people who receive their high risk information while young or middle-aged, how many employers are going to care that those employees may be at high risk for Alzheimer disease in their sixties or seventies, when they are hiring twenty-five, thirty-five or forty-five year olds?[311] The chances that any employee will stay that long in a job are quite low, whether as a result of changing jobs, being fired, or retirement.[312] Why worry about one of the many possible reasons for an employee leaving or becoming ineffective (particularly as it is not at least plausible, as well as devoutly hoped, that good preventive measures or treatments for Alzheimer disease might emerge given several decades)?

For people closer in age to the likely onset of Alzheimer disease, many, perhaps most, will be at an age where they are no longer looking for employment. And for those who are, employers are likely to expect

310. *Facts and Figures*, ALZHEIMER'S ASS'N, https://www.alz.org/alzheimers-dementia/facts-figures (last visited Dec. 5, 2020).

311. *Genetic Information and the Workplace*, NAT'L HUM. GENOME RES. INST., https://www.genome.gov/10001732/genetic-information-and-the-workplace-report (last updated Oct. 25, 2012) [hereinafter *Genetic Information and the Workplace*].

312. U.S. BUREAU LAB. STAT., USDL-20-1791, EMPLOYEE TENURE SUMMARY (2020) [hereinafter EMPLOYEE TENURE SUMMARY].

their period of employment to be short.[313] If an employer contemplates hiring a sixty year old, it is most likely not with the expectation of twenty or thirty years of service. With all the other health-related employment risks that come with advancing age, the high likelihood of Alzheimer disease at some, as yet unknown, time in the future should not be a huge issue.

There are a few predictable exceptions at the hiring stage. Consider a Supreme Court justice or federal court judge.[314] Presidents increasingly seek to appoint justices who will provide the maximum number of (ideologically safe) years on the bench.[315] Only seven justices have left the U.S. Supreme Court in the twenty years since 2000 through retirement or death, and they did so at an average age of just under eighty-one: eighty-one, seventy-six, seventy, ninety, eighty, eighty-two, and eighty-seven.[316] Of the current nine, three are between seventy and eighty-two.[317] Two more are sixty-five.[318] The ten to twenty years that an Alzheimer disease diagnosis could take off of a justice's effective working life might be worth worrying about. (A farsighted and public-spirited president might also consider the consequences of life tenure and the difficulty, a few decades later, of removing a justice with early

313. *See Genetic Information and the Workplace*, *supra* note 311; EMPLOYEE TENURE SUMMARY, *supra* note 312.

314. David J. Garrow, *Mental Decrepitude on the U.S. Supreme Court: The Historical Case for a 28th Amendment*, 67 U. CHI. L. REV. 995 (2000); John S. Goff, *Old Age and the Supreme Court*, 4 AM. J. LEGAL HIST. 95 (1960); *Life Tenure for Federal Judges Raises Issues of Senility, Dementia*, PROPUBLICA (Jan. 18, 2011, 7:30 AM), https://www.propublica.org/article/life-tenure-for-federal-judges-raises-issues-of-senility-dementia; *cf.* Teneille R. Brown, *Double Helix, Double Standards: Private Matters and Public People*, 11 J. HEALTH CARE L. & POL'Y 295 (2008) (arguing for genetic testing of political candidates).

315. AUTHOR REDACTED, CONG. RES. SERV., R44235, SUPREME COURT APPOINTMENT PROCESS: PRESIDENT'S SELECTION OF A NOMINEE 1 (2018).

316. Marco della Cava, *Death in office a rarity for modern justices*, USA TODAY, https://www.usatoday.com/story/news/2016/02/13/death-office-rarity-modern-justices/80352230/ (last updated Feb. 13, 2016, 11:04 PM); Nina Totenberg, *Justice Ruth Bader Ginsburg, Champion Of Gender Equality, Dies at 87*, NPR (Sept. 18, 2020, 7:28 PM), https://www.npr.org/2020/09/18/100306972/justice-ruth-bader-ginsburg-champion-of-gender-equality-dies-at-87 (updating these figures through November 24, 2020, and, sadly, including the death of Justice Ginsburg).

317. Richard E. Berg-Andersson, *United States Supreme Court Justices*, GREEN PAPERS, https://www.thegreenpapers.com/Hx/SupremeCourt.html (last updated Sept. 18, 2020).

318. *Id.*

or late dementia.)[319] A similar example might arise if an employer considers employing a person who is sixty or older for an important job with a hoped-for ten-year term; for example, a university president. In that kind of situation, knowing that a candidate is at high risk for Alzheimer disease could be important to a hiring decision. Otherwise, it probably is not.

Employment discrimination, however, can take place not just in hiring but also in compensation, promotion, and firing; but again, mainly for older employees. Few employers are going to avoid promoting or giving raises to otherwise qualified employees because in twenty-five years they are likely to have Alzheimer disease. When those employees are fifty-five or sixty, however, an employer's calculation may change. For promotions, that might be as a result of the perception that the employee may well have less effective time in the higher position than someone not at risk (although, of course, Alzheimer disease is only one of many possible causes for shortened tenure). For raises, the employer may feel less need to encourage an employee to stay through raises, when again, the employee's total future

319. CLARE CUSHMAN, COURTWATCHERS: EYEWITNESS ACCOUNTS IN SUPREME COURT HISTORY 239 (Supreme Court Historical Society & Rowman & Littlefield Publishers, Inc. 2011); *see* Charles Alan Wright, *Authenticity of 'A Dirtier Day's Work' Quote in Question,* 8 SUP. CT. HIST. SOC'Y Q. 6, 6–7 (1990) There is a wonderful Supreme Court anecdote about this. Chief Justice Charles Evans Hughes wrote:

> I heard Justice Harlan tell of the anxiety which the Court had felt because of the condition of Justice Field. It occurred to the other members of the Court that Justice Field had served on a committee which waited upon Justice Grier to suggest his retirement, and it was thought that recalling that to his memory might aid him to decide to retire. Justice Harlan was deputed to make the suggestion. He went over to Justice Field, who was sitting alone on a settee in the robing room apparently oblivious of his surroundings, and after arousing him gradually approached the question, asking if he did not recall how anxious the Court had become with respect to Justice Grier's condition and the feeling of the other Justices that in his own interest and in that of the Court he should give up his work. Justice Harlan asked if Field did not remember what had been said to Justice Grier on that occasion. The old man listened, gradually became alert and finally, with his eyes blazing with the old fire of youth, he burst "Yes! And a dirtier day's work I never did in my life!"

That was the end of the effort of the brethren of the Court to induce Justice Field's retirement; he did resign not long after.

Alas, the complete accuracy of Hughes's retelling of Harlan's statement to me is somewhat questionable. It appears Justice Field may not have been in the group that talked to Justice Grier.

time on the job is expected to be fairly short. (And their options for moving to a better, higher-paying job may appear lower.)

Firings, and the scrutiny associated with possible firings, may be the biggest issue. An employer may fire someone who can no longer do the job because of Alzheimer disease or any other condition (subject to some limitations from the ADA, discussed in the next Part).[320] Firing people just because they are at higher risk for eventually being diagnosed with Alzheimer disease and becoming unable to do the job at some time in the future is less rational (especially as the onset of the disease is usually slow enough as to be likely to provide time for an easy transition). But it may be rational for employers to monitor employees more closelywho are at high risk for Alzheimer disease, looking harder to detect the first symptoms, and the first losses of efficiency. And, when people look hard enough, they may see things even if they are not there.[321] It certainly seems rational for people at high risk for Alzheimer disease to worry that, if their supervisors know about this risk, their work will be watched especially closely and perhaps, consciously or not, ungenerously.

Matthew Lawrence and Jalayne Arias have laid out a detailed assessment of one such situation in an article about possible use of predictive biomarkers for Alzheimer disease in commercial airline pilots.[322] The Federal Aviation Administration ("FAA") requires "first class" "fitness to fly" medical certification for pilots for commercial common carrier airlines, termed "airline transit pilots."[323] Every six months (for pilots over forty years old) or twelve months (for pilots under forty), depending on the pilot's age, an FAA-certified medical examiner does a medical examination of the pilot and reviews his or her medical history.[324] The medical examiner makes a recommendation to certify the

320. *See Genetic Information and the Workplace*, *supra* note 311.

321. Carole Fleck, *Coping with Cognitive Declines at Work*, SOC'Y HUM. RES. MGMT. (Sept. 3, 2015), https://www.shrm.org/hr-today/news/hr-magazine/pages/coping-with-cognitive-declines-at-work.aspx.

322. Matthew W. Lawrence & Jalayne J. Arias, *Alzheimer's Disease Biomarkers: Another Tool for FAA Pilot Screening?* 6 J.L. BIOSCIENCE 85, 85–110 (2019) (building on earlier work by Arias and others surveying both physicians and human resource managers about the use of biomarkers to predict Alzheimer disease in different kinds of employees); Jalayne J. Arias et al., *To Test Or Not To Test: Physician Perspectives On Biomarker Testing, Law, And Ethics*, 12 ALZHEIMER'S & DEMENTIA 817 (2016); Jalayne J. Arias et al., *Employment Discrimination Risks Based on Preclinical Alzheimer's Disease Biomarkers,* 14 ALZHEIMER'S & DEMENTIA 888 (2018).

323. Lawrence & Arias, *supra* note 322, at 86–87.

324. *Id.* at 97.

pilot, to deny the certification, or to defer to decision to the FAA.[325] The process is detailed in the *Guide for Aviation Medical Examiners*; the examiner can only deny certification for a reason listed in the Guide.[326] Any other fitness concerns are deferred to the FAA.[327] The approval or denial recommendations do not bind the FAA; they are, however, strongly influential. Administrative and ultimately judicial review is available to pilots unhappy with the decision.[328]

Pilots must apply for certification or re-certification.[329] The pilot and the medical examiner jointly complete the application but the pilot has a duty to disclose any pertinent medical information. Pilots can be permanently denied certification for failing to disclose even medical conditions that would not have barred their certification.[330] (The FAA wants *full* disclosure.) Some conditions expressly lead to denials, such as substance abuse or epilepsy.[331] Dementia is not listed on the application but is discussed in the Guide, thus highlighting it to the medical examiners.[332]

Lawrence and Arias conclude that pilots who know that their biomarkers show a heightened risk of Alzheimer disease (something unlikely today given the absence of clinical use of such testing in people without symptoms) must disclose this to the medical examiner.[333] They further conclude that the FAA could use biomarker status in making certification decisions, based on FAA precedents based on HIV infection, on the presence of the genetic variation responsible for Huntington disease, and on age (no airline transit pilot over age sixty-five can be medically certified, a limit moved up from sixty by statute in 2009).[334] They recommend against a blanket disqualification based on

325. *Id*. at 89.
326. U.S FED. AVIATION ADMIN., GUIDE FOR AVIATION MEDICAL EXAMINERS 15 (2020), https://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/media/guide.pdf.
327. *See id*. at 10.
328. *Pilot Medical Certification Questions and Answers*, FED. AVIATION ADMIN., https://www.faa.gov/licenses_certificates/medical_certification/faq/response14 (last updated Apr. 16, 2013, 7:52 AM).
329. Lawrence & Arias, *supra* note 322, at 90.
330. *See* 14 C.F.R. § 67.403 (1996).
331. Lawrence & Arias, *supra* note 322, at 89.
332. *Id*.
333. *Id*. at 109.
334. *Id*.

biomarkers but suggest increased scrutiny through neuropsychological and neurocognitive testing.[335]

Commercial airline pilots are only one example of employees who may be subject to this kind of increased scrutiny. Lawrence and Arias note that police officers, military personnel, and commercial truck drivers all must pass occupation-specific medical examinations.[336] Aging physicians may have special reason to worry that a known higher risk for Alzheimer disease might lead to them being fired or, in the context of a hospital, deprived of their staff privileges while they are still competent. Or that they might be required to undergo different competency testing than other physicians. (Some hospitals already require regular mental competency testing for staff physicians over a certain age, without regard to the nature of their practice.)[337]

b. Health Insurance Discrimination

The employment discrimination picture is complicated, but that is only one area of possible discrimination. Health insurance is another. But, again, the age of onset makes a difference. Many people at near-term risk for Alzheimer disease will be sixty-five and (almost always) eligible for Medicare.[338] If they are not yet old enough for Medicare, they may well be covered by an employer, their own insurance, or a partner's. And if not that, then under the Affordable Care Act they should be able to purchase relatively reasonably priced health insurance coverage without regard to their health risks (without so called "medical underwriting")[339]—although predicting the future of the Affordable Care Act, and any of its provisions, has often seemed much harder than predicting Alzheimer disease.

335. *Id*.

336. *Id.* at 105.

337. Lucette Lagnado, *When Are Doctors Too Old to Practice?* WALL ST. J., https://www.wsj.com/articles/when-are-doctors-too-old-to-practice-1498311380 (last updated June 24, 2017, 1:46 PM).

338. *See Who is eligible for Medicare?*, U.S. DEP'T HEALTH & HUM. SERV., https://www.hhs.gov/answers/medicare-and-medicaid/who-is-elibible-for-medicare/index.html#:~:text=Generally%2C%20Medicare%20is%20available%20for,failure%20requiring%20dialysis%20or%20transplant (last updated Sept. 11, 2014).

339. Gary Claxton et al., *Pre-existing Conditions and Medical Underwriting in the Individual Insurance Market Prior to the ACA*, KAISER FAM. FOUND. (Dec. 12, 2016), https://www.kff.org/health-reform/issue-brief/pre-existing-conditions-and-medical-underwriting-in-the-individual-insurance-market-prior-to-the-aca.

It is also the case that, for better and for worse, currently Alzheimer disease is not terribly expensive for health insurers,[340] decreasing their incentive to discriminate against people at high risk. In an ironic benefit to the absence of treatments, Alzheimer disease has a relative absence of expenses covered by health insurance.[341] This is particularly true as *health* insurance provides effectively little to no coverage for long-term care.[342] Nursing facilities are typically only covered for short periods, usually during recovery from injury or a hospitalization.[343] The same is true of Medicare.[344]

c. Long-Term Care Insurance Discrimination

Long-term care, though, fills a need not just for recovery from acute injuries or hospitalizations, but for help to people who need assistance with "activities of daily living."[345] Various lists exist of these activities, but six seem commonly invoked: (1) bathing; (2) dressing; (3) eating; (4) transferring (in and out of bed, a chair, or a wheelchair); (5) toileting; and (6) bowel and bladder continence.[346] In addition, there are varying lists of functions called "instrumental activities of daily living," which are not necessarily things that someone would need to do every day but would need to be taken care of in order to live independently.[347] These include shopping, traveling, managing money, doing housework, preparing food, using the phone, or taking medicine.[348] People with Alzheimer disease (or other dementias) will, sooner or

340. *See* Kimberly Lankford, *Does Insurance Cover Alzheimer's Care?*, KIPLINGER (Jan. 18, 2013), https://www.kiplinger.com/article/insurance/t066-c000-s001-does-insurance-cover-alzheimer-s-care.html.

341. *See* Barbara Marquand, *Long-Term Care Insurance Explained*, NERDWALLET (May 28, 2019), https://www.nerdwallet.com/blog/insurance/long-term-care-insurance.

342. *What is Covered by Health & Disability Insurance?*, U.S. DEP'T HEALTH & HUM. SERV., https://longtermcare.acl.gov/costs-how-to-pay/what-is-covered-by-health-disability-insurance/index.html (last updated July 23, 2020).

343. *Insurance*, ALZHEIMER'S ASS'N, https://www.alz.org/help-support/caregiving/financial-legal-planning/insurance (last visited Dec. 5, 2020).

344. *Id*.

345. *What does "activities of daily living" (ADLs) mean in a long-term care insurance policy?*, EXTENSION (May 30, 2019), https://personal-finance.extension.org/what-does-activities-of-daily-living-adls-mean-in-a-long-term-care-insurance-policy.

346. *Id*.

347. *Learning About Instrumental Activities of Daily Living (IADLs)*, KAISER PERMANENTE, https://healthy.kaiserpermanente.org/northern-california/health-wellness/health-encyclopedia/he.learning-about-instrumental-activities-of-daily-living-iadls.abk6308 (last updated Mar. 2, 2020).

348. *Id*.

later, need help with both the activities of daily living, instrumental and otherwise. And, as a result, many Alzheimer disease patients eventually end up needing some kind of long-term care, residential or otherwise.[349]

Modern private long-term care is actually a product of the New Deal.[350] Social Security would pay for some long-term care but refused to pay anything for publicly provided care, which was commonly available in so-called "poor houses"—places of ill-repute for over a century even then.[351] In 1843, when Dickens published the immortal "A Christmas Carol,"[352] he had a philanthropic character say of the English equivalent, the workhouses, "Many can't go there; and many would rather die."[353]

So, the private long-term care industry grew.[354] What exactly should be counted within that term is uncertain. The range goes (at least) from skilled nursing facilities to less intensive assisted living facilities where the residents live largely independent lives but in a facility that provides some aid with household chores, cooking, shopping, and so on.[355] (Some new facilities combine independent adult living, assisted living, and nursing home care in one place.) As of 2016, about 1.17 million Americans were in the country's roughly 15,600 nursing homes with another 760,000 in assisted living facilities.[356] Other kinds

349. *Medicaid*, ALZHEIMER'S ASS'N, https://www.alz.org/help-support/caregiving/financial-legal-planning/medicaid#:~:text=Medicaid%20and%20long%2Dterm%20care,portion%20of%20nursing%20home%20costs (last visited Dec. 5, 2020).

350. *See* Edward Berkowitz, *Medicare and Medicaid: The Past as Prologue*, 29 HEALTH CARE FIN. REV. 81 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4195036/pdf/hcfr-29-03-081.pdf.

351. *Long-Term Care in the United States: A Timeline*, KAISER FAM. FOUND. (Aug. 31, 2015), https://www.kff.org/medicaid/timeline/long-term-care-in-the-united-states-a-timeline [hereinafter *Long-Term Care*].

352. It is one of my favorite pieces of fiction and the source of the title of the other piece I've published in a law review published by the University of Illinois: Henry Greely, *Richard Epstein's Moral Peril: Ebenezer Scrooge Meets the American Health Care System,* 1998 U. ILL. L. REV. 727 (1998).

353. CHARLES DICKENS, A CHRISTMAS CAROL 14 (Lippincott Company 1915) (1843).

354. *Long-Term Care*, *supra* note 351.

355. *Id.*

356. CTRS. FOR DISEASE CONTROL AND PREVENTION, FIGURE 17 (2018), available at https://www.cdc.gov/nchs/data/hus/2018/fig17.pdf (last visited Dec. 5, 2020).

of arrangements include home health agencies, adult day services centers, and hospice services, which can be provided to the terminally ill at home or in a residential facility.[357]

Each of these can be expensive. In 2018 the median price of nursing home care was $100,400 per year for a private room.[358] Assisted living facilities cost a median $48,000 per year.[359] A home health aide, present in the home for 30 hours a week, costs an average of over $34,000 a year.[360] Adult day care costs $18,700 per year.[361] The AARP estimates that slightly more than half of people turning sixty-five will need a version of residential long-term care at some point in their lives.[362] About 27 percent of those people will need long-term care for less than two years, but about 12 percent will need it for two to five years, and 14 percent (18 percent of women because of their longer life spans) will need long-term care for more than five years.[363] Certainly not all of those who need long-term care will have Alzheimer disease nor will everyone with Alzheimer disease need long-term care, but the overlap will be substantial.

These numbers quickly become staggering. In 2017, for society as a whole, direct spending on long-term care and support services was $235 billion.[364] But it is even more staggering for individuals and their families. Median annual household income in the United States is about $60,000;[365] very few households can afford to spend $100,000, $48,000, or even $34,000 a year for long-term care.[366]

So how does long-term care get provided? Four main sources exist: out-of-pocket payments, Medicaid, unpaid care, and "other" (long-

357. Edem Hado & Harriet Komisar, *Long-Term Services and Supports*, AARP PUB. POL'Y INST. (Aug. 2019), https://www.aarp.org/content/dam/aarp/ppi/2019/08/long-term-services-and-supports.doi.10.26419-2Fppi.00079.001.pdf.

358. *Id.* at 2.

359. *Id.*

360. *Id.*

361. *Id.*

362. Donald Redfoot & Wendy Fox-Grage, *Medicaid: A Program of Last Resort for People Who Need Long-Term Services and Supports*, AARP PUB. POL'Y INST. (May 2013), https://www.aarp.org/content/dam/aarp/research/public_policy_institute/health/2013/medicaid-last-resort-insight-AARP-ppi-health.pdf.

363. Vivian Nguyen, *Long-Term Support and Services*, AARP PUB. POL'Y INST. (Mar. 2017), https://www.aarp.org/content/dam/aarp/ppi/2017-01/Fact%20Sheet%20Long-Term%20Support%20and%20Services.pdf.

364. Hado & Komisar, *supra* note 357, at 3.

365. *See* Jessica Semega et al., *Income and Poverty in the United States: 2019*, U.S. CENSUS BUREAU (Sept. 15, 2020), https://www.census.gov/library/publications/2020/demo/p60-270.html.

366. *See* Hado & Komisar, *supra* note 357, at 2.

term care insurance, the Department of Veterans Affairs, and charitable institutions, for example).[367]

Many pay, or have their families pay, for their long-term care from earnings and savings.[368] Few can afford to do this for long. Nonetheless, in 2017 out-of-pocket payments accounted for more than 23 percent of the money expenditures for long-term care, or about $54 billion.[369]

For the many who cannot pay, or who have run out of money to pay for such care, their main recourse is Medicaid, the federal/state program that provides health coverage for (many of) the poor.[370] Unlike Medicare, Medicaid does cover long-term care,[371] but Medicaid is very complicated. States have some choice over who they will or will not cover, more since the Affordable Care Act allowed states to expand Medicaid coverage with huge federal subsidies.[372] States must provide some kinds of services in their Medicaid plans but can choose to cover other services, sometimes with federal subsidies and sometimes with only their own funds.[373] States have substantial discretion over the ways they will use resources to provide for the health needs of the covered poor.[374] But, one way or another, 57 percent of all paid long-term care, about $134 billion in 2017, is paid by Medicaid, typically at much lower rates than what a nursing home will receive from a private payer.[375]

Much of the care Alzheimer disease patients need comes from another source—family, usually women, wives, or daughters.[376] More than half of the people receiving such care have no paid care at all; of those who used paid help, three-quarters also received unpaid help.[377] In 2017, an estimated 41 million Americans provided about 34 billion

367. *Id.*; Redfoot & Fox-Grage, *supra* note 362, at 2.
368. *See* Redfoot & Fox-Grage, *supra* note 362, at 2–3.
369. Hado & Komisar, *supra* note 357, at 3. This is a minimum estimate. For home health care assistance, it only includes people hired through home health care agencies, not aides hired individually by the patients or their families. The number and qualifications of those directly-hired helpers, as well as the extent to which their income or payroll taxes are paid, are unknown.
370. Redfoot & Fox-Grage, *supra* note 362, at 3–4.
371. *Id.*
372. *See State and federal spending under the ACA*, MACPAC, https://www.macpac.gov/subtopic/state-and-federal-spending-under-the-aca/ (last visited Oct. 10, 2020).
373. *See id.*
374. *See generally id.*
375. *See* Hado & Komisar, *supra* note 357, at 3.
376. *2019 Facts and Figures*, *supra* note 57.
377. Nguyen, *supra* note 363, at 2 (These numbers are from 2004).

hours of such unpaid care worth approximately $470 billion.[378] This care is not only uncompensated but brings high costs to the caregivers in their own careers, their own physical and mental health, and in every other part of their lives, including some direct financial costs: in 2016 family caregivers spent an average of $7,000 out of pocket in providing care.[379]

It is, and has been for many years, easily predictable that the costs of long-term care are going to be an enormous public policy problem, especially as the very large Baby Boomer generation—those born between 1946 and 1964, who are now between fifty-six and seventy-five years old—continues to age.[380] Medicare does not cover it, Medicaid covers it poorly, and family-provided care varies widely in its quality,[381] but always imposes great stress and costs on the patients' families.

Long-term care financing is a slow-motion train wreck. Everyone who has bothered to look at it has seen the disaster coming for decades but no one seems to be able to do anything to stop it. A major government effort, the Pepper Commission, issued recommendations in 1990 calling for more government support for long-term care.[382] The Clinton Administration health plan, as proposed in 1993, included improved Medicaid coverage for long-term care plus minimum standards for long-term care insurance coupled with tax incentives to encourage its purchase.[383] Those proposals died with the plan in 1994.[384] The Affordable Care Act made some tweaks to the system, both for Medicaid support for long-term care and for private long-term care insurance, but

378. Susan Reinhard et al., *Valuing the Invaluable 2019 Update: Charting a Path Forward*, AARP PUB. POL'Y INST. (Nov. 14, 2019), https://www.aarp.org/ppi/info-2015/valuing-the-invaluable-2015-update.html.

379. Hado & Komisar, *supra* note 357, at 4.

380. *See generally The Baby Boomer Effect and Controlling Health Care Costs*, USCPRICE, https://healthadministrationdegree.usc.edu/blog/the-baby-boomer-effect-and-controlling-health-care-costs/#:~:text=As%20the%20baby%20boomer%20generation%2C%20born%20between%201946,rise%2C%20taking%20health%20care%20expenses%20upwards%20with%20them (last visited Dec. 20, 2020).

381. *See* Hado & Komisar, *supra* note 357, at 3–4.

382. John D. Rockefeller IV, *The Pepper Commission Report on Comprehensive Health Care*, 323 NEW ENG. J. MED. 1005, 1005–07 (1990), https://www.nejm.org/doi/pdf/10.1056/NEJM199010043231429?articleTools=true.

383. *See* Walter A. Zelman, *The Rationale Behind the Clinton Health Care Reform Plan*, HEALTHAFFAIRS (1994), https://www.healthaffairs.org/doi/full/10.1377/hlthaff.13.1.9.

384. *See* Adam Clymer et al., *THE HEALTH CARE DEBATE: What Went Wrong?*, N.Y. TIMES (Aug. 29, 1994), https://www.nytimes.com/1994/08/29/us/health-care-debate-what-went-wrong-health-care-campaign-collapsed-special-report.html.

nothing major.[385] In 2013 another long-term care commission reported to Congress on issues in long-term care, with recommendations on service delivery and the long-term care workforce.[386] It was unable to reach any conclusions on financing and so presented no agreed-upon recommendations, instead setting out only the ideas of its various members.[387]

At one point, private long-term care insurance emerged as the great hope, an equivalent to private health insurance provided by employers or purchased by individuals that would allay, if not entirely cover, the costs of long-term care. As early as 1987, the Robert J. Wood Foundation, a major health care foundation, began supporting public/private partnerships in four states as pilots to encourage people to purchase long-term care insurance. The idea is that people would invest early in long-term care insurance, paying (or having their employer pay) premiums through their young and healthy years to defray the costs decades later, when they need them.[388]

That vision has not come true. Today, long-term care insurance pays for about 4 percent of paid long-term care and only 7.2 million Americans have this kind of insurance.[389] Fewer young and healthy people want to pay substantial premiums for long-term care that they may, or may not, need in three to five decades.[390] More than three-quarters of new purchasers are fifty or older; over 35 percent are over sixty.[391]

385. Edward Alan Miller, *The Affordable Care Act and Long-Term Care: Comprehensive Reform or Just Tinkering Around the Edges?*, 24 J. AGING & SOC. POL'Y 101 (2012).

386. REPORT TO CONGRESS, COMM'N ON LONG-TERM CARE 14 (Sept. 18, 2013), https://www.medicareadvocacy.org/wp-content/uploads/2014/01/Commission-on-Long-Term-Care-Final-Report-9-18-13-00042470.pdf.

387. *See id.* at 16.

388. Carolyn NewBergh, *The Robert Wood Johnson Foundation's Commitment to Nursing*, ROBERT WOOD JOHNSON FOUND. (Nov. 2005), https://healthforward.org/wp-content/uploads/2015/11/hcf-rwjf-commitment-to-nursing.pdf.

389. *See* Benjamin T. Allaire et al., *Who Wants Long-Term Care Insurance? A Stated Preference Survey of Attitudes, Beliefs, and Characteristics*, 53 INQUIRY: J. HEALTH CARE ORG., PROVISION, & FIN. 1, 1 (2016) ("[L]ong-term care insurance (LTCI) market is depressed, with only 7.4 million people owning policies."); *see* Jeffrey R. Brown & Amy Finkelstein, *Insuring Long-Term Care in the United States*, 25 J. ECON. PERSP. 119 (2011) (finding that only four percent of long-term care is paid for by private insurance and majority is paid for by the public sector).

390. *See* Howard Gleckman, *Why People Don't Buy Long-Term Care Insurance*, FORBES (Sept. 12, 2011), https://www.forbes.com/sites/howardgleckman/2011/09/12/why-people-dont-buy-long-term-care-insurance/#43b3595a3817 (reporting that the most important reason people do not buy long-term care insurance is price).

391. *Long-Term Care Insurance Facts–Data–Statistics 2019 Report*, AM. ASS'N FOR LONG-TERM CARE INS., https://www.aaltci.org/long-term-care-insurance/learning-center/ltcfacts-2019.php#2019buyerages (last visited Dec. 5, 2020).

"Traditional" long-term care insurance will typically pay about $160 per day toward nursing home coverage, with a three-month waiting period for any benefits and a three-year maximum.[392] Premiums average about $2,700 per year and increase sharply with the insured's age.[393] (Premiums increase 8 to 10 percent between age sixty-four and age sixty-five, for example.)[394] The degree of inflation protection in the benefits varies.[395]

And the industry itself has gone through hard times. More than one hundred insurers sold long-term care policies in the 1990s; today fewer than fifteen do.[396] A newer "hybrid" long-term care insurance mixes long-term care insurance and life insurance—if insureds don't "use up" their long-term care benefits, their beneficiaries receive a life insurance payment.[397] This can be attractive to people worried that they will never receive any benefit from their long-term care coverage, but the hybrid policies have premiums that are two to three times higher than those of the traditional plans.[398] Nonetheless, they account for about five-sixths of all new long-term care insurance policies.[399]

This has been a very long dive into long-term care insurance for a section about disadvantages of Alzheimer disease prediction, but for good reason. Long-term care insurance is an area where discrimination against people at high risk is most likely to be real. Long-term care insurers, unlike employer-provided health coverage or health insurers

392. Ellen Stark, *5 Things You SHOULD Know About Long-Term Care Insurance*, AARP (Mar. 1, 2018), https://www.aarp.org/caregiving/financial-legal/info-2018/long-term-care-insurance-fd.html ("Typical terms today include a daily benefit of $160 for nursing home coverage, a waiting period of about three months before insurance kicks in and a maximum of three years' worth of coverage.").

393. *See id.*

394. *Id.*

395. *See Long Term Care Insurance Inflation Protection*, LONG TERM CARE INS. PARTNER, https://www.longtermcareinsurancepartner.com/long-term-care-insurance/long-term-care-insurance-inflation-protection (last visited Dec. 5, 2020).

396. Eric C. Nordman, *The State of Long-Term Care Insurance: The Market, Challenges and Future Innovations*, NAT'L ASS'N INS. COMM'RS 1, 12 (May 2016), https://www.naic.org/documents/cipr_current_study_160519_ltc_insurance.pdf.

397. *See* Stark, *supra* note 392.

398. *See id.*

399. *See generally* John Hilton, *Analysts: LTC Hybrid Policies Will Keep Driving Life Insurance Sales*, INSURANCENEWSNET (Aug. 14, 2019), https://insurancenewsnet.com/innarticle/analysts-ltc-hybrid-policies-will-keep-driving-life-insurance-sales# ("Eighty-five percent of long-term care sales last year were on the hybrid product shelf, either chronic illness or acceleration of benefits.").

under the Affordable Care Act, are allowed to do "medical underwriting."[400] They can, and do, base their decisions on whether to issue a policy, or at what price, or with conditions, on the applicant's health status.

The reasons seem clear—if they had to offer long-term care insurance at the same price and on the same terms to everyone, people who knew they were very likely to need long-term care would be eager to buy. But their expected costs would be extremely high, requiring the insurer to set rates that no one else would be willing to pay. This is what the insurance industry calls the problem of "adverse selection"—the people who select themselves as customers have a risk profile "adverse" to the insurer's interests.[401]

Buying long-term care insurance could be a very rational response by people who have just learned of their high risk for Alzheimer disease. (In fact, it is one of the responses that empirical work on people at high risk for the disease has shown.)[402] The problem for the long-term care insurance firms is that the customers' rational decisions could destroy their business. The problem is not just that one year's customers will cost more than expected, causing a loss, but that the loss will require the insurer to raise rates in the future to match its customers now-revealed risk profile. This will make its offering even less attractive to lower risk people so only even higher risk people will find insurance worthwhile. Each year the costs get higher and so do the next year's premiums, so that ultimately premium costs are so high that (almost) no one will buy the insurance. That insurance product has gone through the adverse selection "death spiral."[403]

So, although *health* insurance discrimination, even if legal, should not be a common problem for people diagnosed as at high risk for Alzheimer disease, efforts to discriminate by *long-term care* insurers should be expected: the insurers will need to protect themselves from this

400. *See* Portia Y. Cornell et al., *Medical Underwriting in Long-Term Care Insurance: Market Conditions Limit Options for Higher-Risk Consumers*, 35 HEALTH AFF. 1494, 1494 (2016) ("A key feature of private long-term care insurance is that medical underwriters screen out would-be buyers who have health conditions that portend near-term physical or cognitive disability.").

401. *See generally id*. at 1495 (explaining the implications of adverse selection on market conditions).

402. Donald H. Taylor Jr. et al., *Genetic Testing for Alzheimer's and Long-Term Care Insurance*, 29 HEALTH AFF. 102, 104–05 (2010) (explaining people who find they are at higher risk for Alzheimer are 2.3 times more likely to increase their long-term care insurance).

403. David M. Cutler & Richard J. Zeckhauser, *Adverse Selection in Health Insurance*, 1 FRONTIERS HEALTH POL'Y RES. 1, 8 (1998).

source of adverse selection. Insurers *will* ask applicants whether they have ever been tested for Alzheimer disease risk and, if so, with what result. They may ask to examine their medical records for evidence of such a test. And if the insurers do issue policies but later conclude that the applicants misled them about their knowledge of their Alzheimer disease risk, the insurers can seek to void the policy.

This analysis, though long, is not novel. At least as early as 2010, a group of scholars published an important paper in the journal *Health Affairs* on the likely (negative) effects of *APOE* testing on long-term care insurance.[404] Subsequent work published in 2018 showed that that kind of discrimination, if done on the basis of biomarkers, would be legal under state laws.[405]

How important a disadvantage of Alzheimer disease predictive testing is discrimination by long-term care insurance? Given the relatively small number of people who buy long-term care insurance, perhaps not very big. But it is an example of how the circumstances of Alzheimer disease prediction will make a difference in the likelihood of discrimination.

d. Other Discrimination

Would people at high risk face other kinds of discrimination? It depends on both the effects of Alzheimer disease and the kinds of activities people at high and fairly near-term risk would likely engage in. Incentives for employment and health insurance discrimination are not very strong; long-term care insurance discrimination is extremely likely. Life insurers probably would not have a strong motive to discriminate; they try to avoid covering people who are likely to die soon, but the course of Alzheimer disease is relatively slow.[406] Would automobile insurance companies, either for collision or for liability insurance, want to discriminate? That probably depends on their experience—do people with Alzheimer disease lead to more claims because of, say, bad driving, or do they lead to fewer claims because family, the state, or their own unease stops them from driving?

404. Taylor Jr. et al., *supra* note 402.

405. Jalayne Arias et al., *The Proactive Patient: Long-Term Care Insurance Discrimination Risks of Alzheimer's Disease Biomarkers*, 46 J. L. MED. & ETHICS 485 (2018).

406. *See* Craig J. Thalhauser & Natalia L. Komarova, *Alzheimer's Disease: Rapid and Slow Progression*, 9 J. ROYAL SOC'Y INTERFACE 119, 119 (2011) (explaining Alzheimer's disease can last for a few years to decades).

4. REACTIONS OF INTIMATES

If you received a prediction that you had a very high risk of Alzheimer disease and you were married or had a long-term partner, would you tell him or her? If so, when? What do you think the reaction would be? As The New York Times article about early diagnosis asked, "Will your friends stay with you? How about your spouse?"[407]

Perhaps the spouse or partner would leave. After all, the prospect of spending possibly more than a decade taking care of an Alzheimer disease patient, even (especially?) one you love, could be daunting. But other, less dramatic, reactions may also be important. Imagine you now see pity in your partner's eyes. How would it affect your relationship?

The *Times* story continues, quoting two patients:

> Wallace Rueckel, 75, of St. James, N.C., worries about what will happen as his disease progresses. He has been reluctant to let people other than relatives know he has early Alzheimer's disease.
>
> "I don't want people to feel sorry for me," he said.
>
> Jay Reinstein of Raleigh, N.C., 58, learned he had early-stage Alzheimer's disease in March of 2018. He stepped down from his job as an assistant city manager in Fayetteville, N.C., later that year.
>
> "I was numb," Mr. Reinstein said. "I loved working. Work was my life. That was my identity."
>
> And he was not the only one left reeling by the diagnosis.
>
> "My wife is not doing well with this," Mr. Reinstein said. "It has really taken a major toll on our family. I have become depressed."
>
> He worries what his life will be like in a few years. He worries that friends will fall away.[408]

It may be that friends and family will grow even closer and provide crucial support for someone coping with a high risk of Alzheimer disease. Or it may not. How can one know, in advance, how other people will react?

This is, of course, not a problem unique to prediction of Alzheimer disease. People who have recently received a diagnosis of any bad disease face the same issues. After all, a diagnosis of an almost always incurable disease—metastatic pancreatic cancer, glioblastoma multiforme, amyotrophic lateral sclerosis—is not just a diagnosis but also a prediction, a prediction of almost certain death, and often fairly soon. In those cases, though, people have symptoms that they want explained, symptoms that might be more benign or more treatable. There the prediction is a secondary effect of another, valuable inquiry.

407. Kolata, *supra* note 291.
408. *Id.*

Predictions in asymptomatic people do not have that same value in explaining symptoms. In that respect Alzheimer disease prediction (as opposed to Alzheimer disease diagnosis) is more like a prediction for people at high risk for a terrible genetic condition. Huntington disease is the classic example. It is an untreatable and inevitably fatal neurodegenerative disease that is perfectly predictable through genetic testing and that typically strikes people in their mid-thirties to their mid-fifties.[409] They face the same kinds of questions around whether or not they want to know those future risks, and then want others to know.

Prediction could also affect other aspects of your life where your family may have substantial power. Consider this question (crucial at least in California)[410]—when does your partner, or one of your children, take your car keys away? Californians without cars are, in some ways, disabled—their day-in, day-out lives become much harder and their independence is greatly limited.[411] If their families know that they have been predicted to be at high risk for getting Alzheimer disease, they probably will lose the car keys sooner, at an earlier stage of the symptoms, or perhaps before any symptoms. They may also lose their checkbooks, credit cards, and other rights, powers, privileges, and duties they are accustomed to. Those kinds of family issues are important but not often discussed.

5. PERSONAL PSYCHOLOGICAL EFFECTS

For some people, the biggest concern may be their own psychological reaction. Specifically, will a positive test result make life less bearable, either through the increased likelihood of Alzheimer disease sometime in the future or in the day to day worries—will there be heightened anxiety any time something is forgotten? We all forget things; we all have always forgotten things. But as we age, we may well notice this forgetting more frequently, and more acutely.

409. Henry T. Greely, *Genotype Discrimination: The Complex Case for Some Legislative Protection*, 149 U. PENN. L. REV. 1483, 1485 n.4 (2001).

410. *See generally* UCLA HEALTH, *For Patients with Dementia, It May Be Time to Give Up the Car Keys*, VITAL SIGNS ISSUES, https://www.uclahealth.org/vitalsigns/for-patients-with-dementia-it-may-be-time-to-give-up-the-car-keys (last visited Dec. 5, 2020) (explaining mandatory reporting laws in California require health professionals to report a diagnosis of dementia to the Department of Public Health who in turn reports to the Department of Motor Vehicles).

411. *See generally* Kristine Dwyer, *Driving Dilemmas: Risk vs. Independence*, CAREGIVER (May 16, 2017, 12:04 PM), https://caregiver.com/articles/driving-dilemmas-risk-vs-independence/.

Our memories typically do get worse as we age but that does not stop us from worrying about it more. I remember the names of students from my first property class, in 1986, better than I remember my students from some recent courses. That didn't used to be true. I sometimes talk of "age appropriate memory impairment," which I have defined, only partly in jest, as: "when your memory isn't as good as you remember your memory having been." It may well be one thing to deal with forgetfulness but an entirely different, and more difficult, thing to deal with it when you know you are at high risk for Alzheimer disease. If I knew I were at high risk for Alzheimer disease, would every student's name I forgot trigger fear of what was about to happen to me? "Is this the beginning?"

The good news is that researchers have studied this topic in the context of Alzheimer disease and have concluded that serious adverse reactions are uncommon. As Karlawish noted, they've seen no suicides in his group which received predictions based on their brain amyloid levels.[412] Another Alzheimer disease researcher quoted in *The New York Times* story, Gil Rabinovici, said of his patients (who received first diagnoses rather than risk predictions), "'Most who receive positive diagnoses have told him that after the initial shock, they did not regret being tested. It ends the diagnostic odyssey,' he said. 'It ends the uncertainty.'"[413] Robert Green's group, which has done the most work on this question, and with the most patients, sees some effects on patients' moods.[414] Those who test positive are less happy; those who test negative are happier.[415] But these differences, in his studies, are, on average, fairly small and they dissipate quickly, at least over the time of the study.[416]

This is consistent with a long string of more general psychological studies of happiness. Most people will be less happy after bad changes in their lives, such as paralysis from a car accident, and more happy after good changes, such as winning the lottery. But after a short time,

412. Kolata, *supra* note 291.
413. *Id.*
414. Robert C. Green et al., *Disclosure of APOE Genotype for Risk of Alzheimer's Disease*, 361 NEW ENG. J. MED. 245 (2009).
415. *See id.* at 245 ("Test-related distress was reduced among those who learned that they were APOE ε4–negative.").
416. *See generally id.*

most of them return to their earlier level of happiness, either high or low.[417]

One can quibble about some aspects of Green's work—the research participants had been screened several times in ways that should have excluded those at high risk for a negative effect and that very few people in those studies were at truly high risk—in the case of his studies, which were based on revealing *APOE* status to willing research participants, *APOE* e4 homozygous.[418] And the participants had only been followed for several months or a few years.[419]

Still, I am willing to accept as likely true the findings by Green and others that the effects of this bad news are usually generally small and dissipate quickly. But human behavior makes many bell curves. Even if most people's reactions to a positive Alzheimer disease prediction are ultimately neutral, some will have negative reactions—and, odd as it may seem, some will even have positive reactions. Similarly, of those who get good news—a negative test result—most will feel somewhat better and some will, oddly, feel worse.

One interesting question that, as far as I can tell, has not been studied, is how well can people predict how they will react to a prediction that they are at high risk for Alzheimer disease? That seems to me a hard question to answer with any certainty—I really don't know how I would react. Having read the literature I would expect that, most likely, I would not react very negatively, and any reaction would not last long, but would I be an exception? That uncertainty about one's own reaction should factor into a person's decision whether to undergo predictive testing for Alzheimer disease.

IV. Regulating Prediction of Alzheimer Disease…and its Consequences

Alzheimer disease prediction is not entirely unregulated—but close. This Section will first look at the regulation of the predictive

417. *Id.* (finding no significant differences in time-averaged measures of anxiety, depression, or distress between patients who test positive for Alzheimer risk gene and those who test negative); JS Roberts et al., *Using Alzheimer's Disease as a Model for Genetic Risk Disclosure: Implications for Personal Genomics*, 80 CLINICAL GENETICS 407, 411 (2011) (finding no increased psychological harm when disclosing risk information in a controlled setting).

418. *See* Green et al., *supra* note 414, at 248.

419. *Id.*

methods themselves and then at three approaches to regulating the possible consequences to patients from Alzheimer disease prediction.

A. Regulating the Predictive Tests

Some of the methods for predicting Alzheimer disease are, in different ways and to a greater or lesser extent, regulated. Some are regulated as drugs, others as tests, others are regulated through accreditation requirements for testing bodies, still others have required gatekeepers with their own licensure mandates.[420] Some are "quasi-regulated," limited not by government laws and rules but by professional standards or, in effect, by the reimbursement decisions of healthcare payors. Others are not regulated at all.[421]

Of the prediction methods discussed above, only the PET scans for amyloid plaque or glucose metabolism are fully and directly regulated in the United States because only they are regulated as "drugs."[422] As PET scanning began to move from solely research to clinical uses in the 1990s, the FDA took the position that the molecules containing positron-decaying radioactive isotopes, whether used to bind to amyloid plaque or tau tangles or to be metabolized as sugar, were drugs—"PET drugs."[423] This position was confirmed by Congressional action in 1997's Food and Drug Administration Modernization Act. Section 121 of that statute directed the FDA to create approval procedures and manufacturing requirements for these PET drugs.[424]

420. *See generally* Qi Tang et al., *The Government's Role in Regulating, Coordinating, and Standardizing the Response to Alzheimer's Disease: Anticipated International Cooperation in the Area of Intractable and Rare Diseases*, 5 INTRACTABLE & RARE DISEASES RES. 238 (2016).

421. *See generally id.* This Section discusses only American regulation, not because the roughly 4 percent of the world's population living in the United States is uniquely important or its regulatory systems are uniquely good, but because it is the only regulatory system with which I am somewhat deeply familiar. The European Union, Japan, and many other jurisdictions have their own regulatory systems that will treat some of these predictive tests similarly to their U.S. treatment, and some of them differently.

422. *See Positron Emission Tomography (PET)*, FDA, https://www.fda.gov/drugs/pharmaceutical-quality-resources/positron-emission-tomography-pet (last updated July 22, 2020).

423. *See generally id.* Despite the occasional frustration with Google searches, PET drugs should not be confused with drugs for pets, which FDA regulates as animal drugs.

424. FDA Modernization Act of 1997, Pub. L. No. 105-115, § 121(c), 111 Stat. 2296 (codified as amended 21 U.S.C. § 301 (2018)).

These drugs must be approved in the same way as other human drugs—a sponsor must provide evidence convincing the FDA that the drug is safe and effective for a particular use.[425] The FDA generally requires that effectiveness be proven by "at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness."[426] Sponsors for new PET drugs must show that they are safe and effective. FDA approval of Amyvid, the first approved amyloid plaque PET drug, was held up because FDA wanted more studies showing consistency in the way readers interpret scans.[427]

FDA regulation does not stop with the PET drug's approval. The FDA also must approve the labeling of the drug, information intended to let physicians decide when to use, not use, and stop using the drug (in this case, when to rely on this PET drug).[428] It also regulates the manufacturers who make the PET drug, requiring that they register, undergo inspections, and conform to the FDA's "current Good Manufacturing Practices" rules.[429]

Only in May 2020 did the FDA approve the PET drugs (in this case, radioligands) that bind to tau tangles.[430] Until then, that "drug," Tauvid, could not be used clinically, doing so would have been a violation of the Food, Drug, and Cosmetic Act (distributing a misbranded or adulterated drug) and subject to both criminal and civil sanctions.[431] But they could have been, and were, used in humans for research if the investigator has received an "Investigational New Drug exemption," from the FDA.[432] These require some proof of safety and efficacy but the requirements are far short of those required for drug approval;[433] INDs

425. *See* 21 U.S.C. § 355(b)(5)(B) (2018).

426. FDA, GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS (1998).

427. *See FDA Approves Amyvid*, *supra* note 221 (explaining that the FDA "temporarily rejected [Amyvid] pending better inter-reader reliability of the scans.").

428. *See* 21 U.S.C. § 355(d) (2018).

429. *See Current Good Manufacturing Practices (CGMPs) for Food and Dietary Supplements*, FDA, https://www.fda.gov/food/guidance-regulation-food-and-dietary-supplements/current-good-manufacturing-practices-cgmps-food-and-dietary-supplements (last updated Jan. 30, 2020).

430. *See* Yearn Seong Choe & Kyung-Han Lee, *PET Radioligands for Imaging of Tau Pathology: Current Status*, 49 NUCLEAR MED. MOLECULAR IMAGING 251 (2015).

431. *See* 21 U.S.C. §§ 331(a), 333 (2018).

432. *See* 21 C.F.R. § 312 (2020).

433. *See* 21 C.F.R. § 312.20 (2020).

for the tau tangle PET drugs have been widely available for researchers.[434] With the May 2020 approval of Tauvid, clinical uses are allowed, although in its press release announcing the drug's approval, Lilly said, "[a]vailability of TAUVID will initially be limited and will expand in response to commercial demand and payor reimbursement."[435] It is much too soon to see how often it will be used clinically.

The FDA regulates several of the other methods as medical "devices." In relevant part, the definition of a "device" for purposes of FDA regulation is:

> an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—
> ***
> (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals….[436]

All of the imaging machines involved—CT scanners, PET scanners, and MRI scanners—have to be approved or cleared by the FDA.[437] Their use will be permitted based on evidence for particular uses, but once they are clinically available for one use, physicians can order their use for any purpose. The FDA, at the constant urging of the American Medical Association, says it does not "regulate the practice of medicine."[438] As a result, once a CT scanner has been approved, it does not need any additional approvals to be trained on different human organs.

434. *Alzheimer 'tau' protein far surpasses amyloid in predicting toll on brain tissue,* SCIENCEDAILY (Jan. 1, 2020), https://www.sciencedaily.com/releases/2020/01/200101144012.htm.

435. Press Release, Eli Lilly and Company, Lilly Receives U.S. FDA Approval of TAUVID™ (flortaucipir F 18 injection) for Use in Patients Being Evaluated for Alzheimer's Disease (May 28, 2020, 7:17 P.M.), https://www.prnewswire.com/news-releases/lilly-receives-us-fda-approval-of-tauvid-flortaucipir-f-18-injection-for-use-in-patients-being-evaluated-for-alzheimers-disease-301067441.html.

436. 21 U.S.C § 321(h) (2018).

437. *See* 21 C.F.R. § 814.20 (2020). The first time a new and potentially dangerous device comes before the FDA, it is normally the subject of a "Premarket Approval Application," which typically requires clinical trial and substantial evidence of its safety and effectiveness, akin to that required for new drugs. Once one such device is approved, however, FDA will allow the marketing and clinical use of "substantially similar" devices through a less arduous process, called Section 510(k). The FDA insists that devices that have gone through a PMA have been approved, while those that have only gone through Section 510(k) are merely "cleared."

438. *FDA's Role in Regulating Medical Devices*, FDA, https://www.fda.gov/medical-devices/home-use-devices/fdas-role-regulating-medical-devices (last updated Aug. 31, 2018) (explaining that the FDA lacks authority to regulate physicians' practices, make doctor recommendations, and rate medical devices).

Once a PET scanner and a PET drug, such as a radioactively tagged glucose, have been approved, no additional approval is required to use that combination to look for different conditions.[439] Unless someone intends to use a completely new imaging device for the purpose of predicting Alzheimer disease, regulation of the scanning machines as devices will not be important.

On the other hand, laboratory tests are also medical devices under this definition.[440] A test that looks for a particular genetic variation of medical interest, such as a pathogenic *PSEN1* mutation, or the level of a particular biomarker in a particular location, such as Aß42 in cerebrospinal fluid, is usually "[a]n instrument. . . or other similar or related article. . . intended for use in the diagnosis of disease. . . or in the cure, mitigation, treatment, or prevention of disease. . . ."[441]

The FDA, however, has taken an interesting position with respect to clinical laboratory tests. If the test is performed by a licensed clinical laboratory, accredited under the requirements of the federal Clinical Laboratory Improvements Amendments Act ("CLIA"),[442] *and* if the test is not performed through a test kit or other testing system purchased from a third party, the FDA calls the test a "Laboratory Developed Test," or "LDT."[443] (Note that this is true whether or not the laboratory actually has any role in "developing" the test; it is more a question of its role in performing the test. Just wetting a purchased strip with a patient's urine would not be an LDT; running a patient's blood sample through a machine that would calculate a hemoglobin level would be.)[444] The FDA has taken the position that LDTs are medical devices within the coverage of its statute, and hence within its jurisdiction, but

439. *See Premarket Notification 510(k)*, FDA, https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k (last updated Mar. 13, 2020).

440. *How to Determine if Your Product is a Medical Device*, FDA, https://www.fda.gov/medical-devices/classify-your-medical-device/how-determine-if-your-product-medical-device (last updated Dec. 16, 2019).

441. *Id.*

442. 42 U.S.C. § 263a (2018); *see also* 42 C.F.R. § 493 (2020).

443. *Laboratory Developed Tests*, FDA, https://www.fda.gov/medical-devices/vitro-diagnostics/laboratory-developed-tests (last updated Sept. 27, 2018).

444. *See generally* FDA, FDA-2011-D-0360, DRAFT GUIDANCE FOR INDUSTRY, FOOD AND DRUG ADMIN. STAFF, & CLINICAL LABS. (Oct. 23, 2014) (defining Laboratory Developed Tests to include tests where the accredited laboratory outsourced design or manufacture of the test).

has announced that it will use its "enforcement discretion" not to regulate such tests as medical devices.[445] These tests, therefore, need not be approved by the FDA as a result of a PMA or cleared by the FDA under Section 510(k). Clinical laboratories can offer them without any proof offered to the FDA that they are either safe or effective.[446]

On the other hand, the clinical laboratories that offer them are licensed by states.[447] They are also (almost) always accredited by the College of American Pathologists ("CAP"), which inspects each accredited laboratory every few years to see that it meets the CAP requirements (one of which is that each lab must have a medical director who is a pathologist, certified as such by CAP).[448] Furthermore, CLIA, a federal statute jointly enforced by the FDA, the Centers for Disease Prevention and Control, and the Center for Medicare and Medicaid Services, also makes demands on these laboratories.[449] They must meet its many requirements, ranging from the right font size on sample labels to passing regular proficiency tests.[450]

These requirements arguably do a decent job in ensuring that the laboratory performs its tests well—that it is accurately measuring what it says it is measuring. This is known as "analytic validity."[451] States' laws (with one big exception)[452] and CLIA do not require that the laboratories show that their test actually has any medical meaning, so-called "clinical validity."[453] It is reminiscent of the line Professor Henry Higgins sang in *My Fair Lady*: "The French never care what they do, actually, as long as they pronounce it properly."[454] If a test accurately says

445. *See* Jonathan R. Genzen, *Regulation of Laboratory-Developed Tests: A Clinical Laboratory Perspective*, 152 AM. J. CLINICAL PATHOLOGY 122, 122 (2019) (noting FDA has a practice of not exercising regulatory oversight over LDTs).

446. *See id.*

447. *See Standards for Laboratory Accreditation: 2017 Edition*, C. AM. PATHOLOGISTS 2 (2017), https://elss.cap.org/elss/ShowProperty?nodePath=/UCMCON/Contribution%20Folders/WebApplications/shared-assets/lap-standards.pdf [hereinafter *Standards for Laboratory Accreditations*].

448. *Id.* at 2.

449. *See* 42 U.S.C. § 263a (2018).

450. *Id.*

451. Wylie Burke, *Genetics Tests: Clinical Validity and Clinical Utility*, CURRENT PROTOCOLS HUM. GENETICS (Apr. 24, 2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4084965/.

452. *See How can consumers be sure a genetic test is valid and useful?*, U.S. NAT'L LIB. MED., https://medlineplus.gov/genetics/understanding/testing/validtest/ (last visited Dec. 5, 2020).

453. *Cf. id.* (stating that "[c]onsumers, health providers, and health insurance companies are often the ones who determine the clinical utility of a genetic test.").

454. MY FAIR LADY (Warner Bros. 1964).

that a person has a substantially higher than normal level of homocysteine in his or her blood serum, it is analytically valid. If it is used to say that the person has a much higher chance than average of being killed in an asteroid strike, it is *not* clinically valid. Almost all states and CLIA do not care about clinical validity, even though, ultimately, this is crucial to a test's value.[455] No regulator cares whether the test results lead to information that has "clinical utility"—that is medically useful, through guiding an intervention, for example.

In 2010 the FDA announced its increasing concern that the tests it had historically called LDTs, and had avoided regulating, were becoming more complex and more important and called a public meeting on the subject.[456] It said that it would be exploring ways to improve the safety and efficacy of such tests.[457] In October 2014, the FDA released a draft guidance, putting forward its thoughts on what a good regulatory system for LDTs would look like.[458] Reactions from within the testing industry varied from a lack of enthusiasm to outrage. In December 2016, after the results of the 2016 presidential election, the FDA announced that it was withdrawing the draft guidance and would be looking at the issue anew.[459] It published a document in January 2017 giving some of its thoughts on how to proceed;[460] meanwhile, a coalition of clinical laboratories and other interested parties began to craft its own possible legislative solution to the problem of regulating LDTs, an effort that led to a bill being introduced in Congress.[461] Its prospects

455. *See* U.S. NAT'L LIB. MED., *supra* note 452 (the state of New York is the one exception. It will not allow a lab in New York to offer a clinical test unless that test has been shown to have clinical validity. As a result, 23andMe's tests are not available to New York residents [at least in theory—enforcing such a rule is difficult]).

456. *See* Oversight of Laboratory Developed Tests, 75 Fed. Reg. 34, 463 (June 17, 2010) (providing notice that because LDTs are more complex and increasingly present public health concerns, the agency believes it time to reconsider its policy of non-enforcement concerning LDTs) [hereinafter Oversight of Laboratory Developed Tests]; Genzen, *supra* note 445.

457. *See* Oversight of Laboratory Developed Tests, *supra* note 456.

458. *See* U.S. FOOD & DRUG ADMIN., FRAMEWORK FOR REGULATORY OVERSIGHT OF LABORATORY DEVELOPED TESTS (LDTS) (2014).

459. Zachary Brennan, *FDA Delays Finalization of Lab-Developed Test Draft Guidance*, REGUL. AFFS. PROS. SOC'Y (Nov. 18, 2016), https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2016/11/fda-delays-finalization-of-lab-developed-test-draft-guidance (explaining the FDA halted finalization of guidance on LDTs pending the change in administration).

460. *See Discussion Paper on Laboratory Developed Tests (LDTs)*, U.S. FOOD & DRUG ADMIN. (Jan. 13, 2017), https://www.fda.gov/media/102367/download.

461. *See* Verifying Accurate, Leading-edge IVCT Development Act of 2020, H.R. 6102, 116th Cong. (2020); Verifying Accurate, Leading-edge IVCT Development Act

during the lame duck Congressional session of a thus far chaotic 2020 and into the next Congress, are unclear.

At this point, the FDA has taken no action and the discussed legislation has not been passed.[462] LDTs, including genetic tests for *PSEN1*, *APP*, and *APOE*, as well as biomarker tests for varying levels of Aß42 or of tau (phosphorylated or otherwise) are basically only regulated for analytic validity (whether a lab is doing the test well) and not clinical validity (whether the test results have any medical meaning), at least as long as they are ordered by a doctor and returned through a doctor.[463]

The vast majority of behavioral tests to predict Alzheimer disease are not limited by federal regulation.[464] In the only exceptions, the FDA has regulated several computer-based memory tests, but the mini-mental status or mini-cog test administered in person is not regulated.[465] Neither is asking about a patient's sense of smell (or even testing it unless, perhaps, there is a special "smell test" kit marketed for Alzheimer disease prediction).[466] MRI and PET scanners are regulated but their use in looking for signs of grey matter thinning in the hippocampus or other indicative areas is not federally regulated.[467] Biomarkers are not typically regulated, at least when they are tests performed by clinical laboratories that fall within the LDT category.

But the FDA is not the only way to regulate Alzheimer disease prediction methods. Guidelines from professional organizations do not have the force of law but they can be quite persuasive for physicians deciding whether or not to offer or order a test.[468] Recommendations from respected disease organizations can also affect both patients and,

---

of 2020, S. 3404, 116th Cong. (2020); *see also* Aaron L. Josephson, *The VALID Act, Aiming to Reform the Regulation of Diagnostic Products, Is Finally Introduced in Congress*, 10 NAT'L L. REV. 72 (Mar. 12, 2020), https://www.natlawreview.com/article/valid-act-aiming-to-reform-regulation-diagnostic-products-finally-introduced (providing useful background and descriptions of the bill).

462. *See* VALID Act of 2020, S. 3404, 116th Cong. (2020), https://www.govtrack.us/congress/bills/116/s3404.

463. *See* Josephson, *supra* note 461.

464. *See* Joshua Preston et al., *The Legal Implications of Detecting Alzheimer's Disease Earlier*, 18 AMA J. ETHICS 1207, 1210–11 (2016), https://journalofethics.ama-assn.org/sites/journalofethics.ama-assn.org/files/2018-05/hlaw1-1612.pdf.

465. *See* Computerized Cognitive Assessment Aid, 21 C.F.R. § 882.1470 (2019).

466. *See generally id.*

467. *See generally* Electronic Product Radiation Control, 21 C.F.R. § 1020.30 (2006); *Radiography*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/radiation-emitting-products/medical-x-ray-imaging/radiography (last updated Sept. 28, 2020).

468. *See, e.g.*, Johnson et al., *supra* note 227, at 476.

sometimes, physicians. In 2012, the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging convened an Amyloid Imaging Taskforce ("AIT").[469] Its 2013 report discusses in detail the evidence for and against the use of Amyloid PET scanning in Alzheimer disease.[470] It supported its use in three situations:

1. patients with persistent or progressive unexplained mild cognitive impairment;
2. patients satisfying core clinical criteria for possible Alzheimer's disease because of unclear clinical presentation, either atypical clinical course or etiologically mixed presentation; and
3. patients with progressive dementia and atypically early age of onset (usually defined as sixty-five years or less in age).[471]

It rejected as inappropriate its use in all other situations, including:

1. patients with core clinical criteria for probable Alzheimer's disease with typical age of onset;
2. to determine dementia severity;
3. solely based on a positive family history of dementia or presence of *APOE* e4;
4. patients with a cognitive complaint that is unconfirmed on clinical examination;
5. in lieu of genotyping for suspected autosomal mutation carriers;
6. in asymptomatic individuals; and
7. non-medical usage (e.g. legal, insurance coverage, or employment screening).[472]

I have found no evidence, either in publications or from discussions with people active in Alzheimer disease's scientific community, that any substantial number of people have been making use of amyloid PET testing to predict whether they will get the disease. Some of this may be due directly to this and other guidelines. But the guidelines also have secondary effects. They can strongly influence decisions of

469. *See id.; Amyloid Imaging Task Force,* ALZHEIMER'S ASS'N, https://www.alz.org/research/for_researchers/partnerships/amyloid-imaging-task-force (last visited Dec. 5, 2020).

470. *See* Johnson et al., *supra* note 227, at 477.

471. *See id.* at 481.

472. *See id.*

insurers and other payors on whether to cover a test.[473] At several thousand dollars for a PET scan,[474] lack of insurance coverage could be a strong deterrent for most patients. The guidelines can also affect a doctor's possible malpractice liability,[475] although it is hard to imagine much litigation over referral for an amyloid PET scan—the potential damages seem too low to interest a plaintiff's medical malpractice lawyer.

Similarly, with biomarkers, although clinical laboratories are not regulated by FDA as to what LDTs they use, they almost all face accreditation by the College of American Pathologists.[476] Performance of unusual or unsupported tests might come back to haunt the laboratories, although how this would happen is not clear. The laboratory, as opposed to the physician who ordered the test, does not necessarily know what the test results are to be used for.[477] Alzheimer disease biomarkers do have accepted clinical uses for diagnosis in some cases[478]—if the doctor has ordered it for prediction, an unsupported use, would the laboratory even know?

As noted above, payors can play an important role in *de facto* regulation of a technology's use.[479] If insurers won't reimburse it, many patients will not want it, especially if it is expensive. In 2013, the Centers for Medicare and Medicaid Service issued a national coverage decision for Medicare on the coverage of Amyloid PET.[480] It determined that nowhere in the country would Medicare cover PET scans for Aß42, with

473. *See Brain Scans Prevent Alzheimer's Misdiagnosis and Lead to Better Treatment—But They're Not Covered By Medicare*, BEING PATIENT (Apr. 2, 2019), https://www.beingpatient.com/amyloid-pet-scan/; Timothy K. Mackey & Bryan A. Liang, *The Role of Practice Guidelines in Medical Malpractice Litigation*, 13 AMA J. ETHICS 36 (2011). [hereinafter *Practice Guidelines*].

474. *See* Catherine Poslusny, *How much does a PET scan cost?*, NEW CHOICE HEALTH, https://www.newchoicehealth.com/pet-scan/cost (last visited Oct. 12, 2020).

475. *See Practice Guidelines*, *supra* note 473; *see also PET Scan Use in Diagnosing Alzheimer's Disease*, MED. MALPRACTICE LAWYERS (Apr. 26, 2012), https://www.medicalmalpracticelawyers.com/blog/pet-scan-use-in-diagnosing-alzheimers-disease/.

476. *See Standards for Laboratory Accreditation*, *supra* note 447, at 2 (discussing accreditation standards).

477. *But see id.* at 3 (explaining how a directing pathologist should effectively communicate with the medical and laboratory staff).

478. *See* Mackey et al., *supra* note 258 (discussing biomarkers).

479. *See Standards for Laboratory Accreditation*, *supra* note 447.

480. *See generally Amyloid PET*, CMS.GOV, https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/Amyloid-PET (last updated June 23, 2020).

two exceptions: (1) to rule out Alzheimer disease in some narrowly defined cases of diagnostic uncertainty, giving the example of Alzheimer disease versus frontotemporal dementia; or (2) as part of clinical trials for prevention or treatment of Alzheimer disease.[481]

Medicare covers the vast majority of Americans who are over sixty-five and thus are at the highest near-term risk for developing Alzheimer disease.[482] Had it decided to cover predictive uses, even if "only" for people with family histories or genetic risks, predictive testing would have exploded. Even if Medicare had approved it for diagnosis in apparently routine cases, the vast increase in its use by neurologists might well have led to a spillover increase in its use for predictive purposes. In the absence of Medicare coverage, PET scanning Aß42, although legal, is uncommonly used, for prediction or for diagnosis.[483]

In summary, there is legal regulation of methods for Alzheimer disease prediction, although not much. Methods other than legal regulation, such as guidelines or reimbursement standards do seem to have had some effects on their use.

B. Regulating the Consequences of Prediction

Regulation can affect not only whether predictive testing is used but, at least to some extent, what consequences, if any, will follow from

481. CTRS. FOR MEDICARE & MEDICAID SERVS., CAG-00431N, DECISION MEMO FOR BETA AMYLOID POSITRON EMISSION TOMOGRAPHY IN DEMENTIA AND NEURODEGENERATIVE DISEASE (2013) ("A.…determined that the evidence is insufficient to conclude that the use of positron emission (PET) amyloid-beta (Aβ) imaging is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member for Medicare beneficiaries with dementia or neurodegenerative disease, and thus PET Aβ imaging is not covered under §1862(a)(1)(A) of the Social Security Act ("the Act"). B. However, there is sufficient evidence that the use of PET Aβ imaging is promising in two scenarios: (1) to exclude Alzheimer's disease (AD) in narrowly defined and clinically difficult differential diagnoses, such as AD versus frontotemporal dementia (FTD); and (2) to enrich clinical trials seeking better treatments or prevention strategies for AD, by allowing for selection of patients on the basis of biological as well as clinical and epidemiological factors. Therefore, we will cover one PET Aβ scan per patient through coverage with evidence development (CED), under §1862(a)(1)(e) of the Act, in clinical studies that meet the criteria in each of the paragraphs below.").

482. *See* Olivia Dean et al., *Who Relies on Medicare? A Profile of the Medicare Population*, AARP (Nov. 2017), https://www.aarp.org/content/dam/aarp/ppi/2017/11/who-relies-on-medicare-a-profile-of-the-medicare-population.pdf (noting many relevant facts concerning the Medicare population).

483. *See* Kolata, *supra* note 291 (concerning a physician who got himself tested by an Aß42 PET scan, although, in his case it was for diagnosis of an early case, not for a prediction. He tested positive.).

its use. It could try to ensure people are given good explanations of the testing and its risks and benefits in advance of their decision to test, as well as good explanations of the results. Or it could use two different strategies to try to regulate how test results showing a high risk for Alzheimer disease can be used against the tested person. It could limit access to information about their test results or it could forbid their use against the tested person. This Section discusses both the current legal protections and some of the possible new interventions that might protect people from (some of) the disadvantages of Alzheimer disease prediction.

1. REQUIRE GOOD, ADVANCE INFORMATION

This approach does not so much limit risks as it tries to match them to the risk preferences of the person considering testing. It does that by trying to make sure the person understands the risks of predictive testing and makes a considered decision to accept them.

This seems a lot like standard medical informed consent. A physician needs to tell a patient about the risks (and benefits) of a procedure seeking the patient's consent—and that consent is normally essential for proceeding. Three problems, though, arise with the standard doctrine of medical informed consent in the context of Alzheimer disease prediction.

First, whether predictive testing for Alzheimer disease would, under existing law, require informed consent may be unclear. Many states apply a "professional standard of practice" test: a physician must provide information and seek consent to the extent that other reasonable physicians would do so in the same circumstances.[484] But physicians may not see an Alzheimer disease predictive test as risky enough to require such consent. Assessing, or perceiving, risk can be particularly tricky for predictive tests.[485] Back surgery has concrete and obvious risks, like paralysis.[486] The risks of predictive tests are less tangible. They include the possibilities of discrimination, the effects of test results on family members, the psychological effects on the patient, and

484. *See* Richard Weinmeyer, *Lack of Standardized Informed Consent Practices and Medical Malpractice*, 16 AM. MED. ASS'N J. ETHICS 120, 121 (2016) (noting that approximately half the states use the "reasonable physician standard.").

485. *See generally id.*; Moscoso et al., *supra* note 278, at 101838.

486. *See* Gabriela Pichardo, *Back Surgery: Pros and Cons*, WEBMD (June 27, 2020), https://www.webmd.com/back-pain/back-surgery-types#1.

more.[487] Even for predictive tests that require a physical intervention, like a lumbar puncture for biomarkers or a PET or MRI scan, physicians may well focus on the (small but not trivial) physical risks of those tests and ignore the less obvious ones. If physicians in a "professional standard" state do not consider things like predictive tests for Alzheimer disease as risky and, as a result, most physicians do not perform informed consent for such testing, or think they should do so, the law in those states won't require it.[488]

Other states apply a "reasonable patient" standard.[489] A physician should inform patients of the risks in a course of action if it would be material to—or make a difference to—a reasonable patient.[490] How do you know what a reasonable patient would want to know? You can ask a jury, but this is unlikely to lead to very clear or helpful standards (especially before many, or any, cases have been tried).

In some contexts, states have required specific consent language or consent forms for some procedures. In California, for example, any procedure aimed at reproductive sterilization (usually a vasectomy or a salpingectomy) can only go forward after obtaining the patient's informed consent based on specific criteria set out in the statute.[491] No state has done anything similar with Alzheimer disease prediction risk or even with the related but broader risks of genetic testing.[492]

The second problem is that not all Alzheimer disease risk tests go through physicians or other licensed health care providers who face informed consent requirements. 23andMe, which offers an *APOE* allele test, has no pre-test role for health professionals and no required post-test role, though it will make a list of genetic counselors available for the customer to contact (and to pay) directly.[493]

487. *See* Moscoso et al., *supra* note 278, at 101841. *See generally* Weinmeyer, *supra* note 484.

488. *See* Moscoso et al., *supra* note 278, at 101845. *See generally* Weinmeyer, *supra* note 484.

489. *See* Weinmeyer, *supra* note 484.

490. *Id.*; *see also* K. H. Satyanarayana Rao, *Informed Consent: An Ethical Obligation or Legal Compulsion?*, 1 J. CUTANEOUS & AESTHETIC SURGERY 33, 33–35 (2008).

491. CAL. CODE REGS. tit. 22 § 70707.3 (2020).

492. Edmund Howe, *Informed Consent, Participation in Research, and the Alzheimer's Patient*, 9 INNOVATION CLINIC NEUROSCIENCE 47, 48 (2012).

493. *Frequently Asked Questions by Healthcare Providers*, 23ANDME, https://medical.23andme.com/faq/ (last visited Dec. 5, 2020) (explaining 23andMe does not offer pre- or post-genetic counseling services but offers links to help consumers find a counselor).

The company's web site provides links to fairly detailed information about each of its "genetic health predisposition" tests.[494] To its credit, it does provide special warnings about its tests for four kinds of genetic disease risks, including *APOE* as well as two breast and ovarian cancer risk genes, a Parkinson disease risk gene, and a gene that in some variants increases the risks for a certain kind of colon cancer.[495]

> Some of our reports are about serious diseases that may not have an effective treatment or cure. Others may have effective treatment or prevention options, but these actions may carry their own health risks. You may be upset by learning about genetic risks for these diseases, and about genetic risks for family members who share DNA. If you tend to feel anxious or have a personal history of depression or anxiety, this information may be more likely to be upsetting. Knowing about genetic risks could also affect your ability to get some kinds of insurance.
>
> You can choose to exclude the following reports individually from your account before your results are returned to you:
>
> BRCA1/BRCA2 (Selected Variants)
>
> MUTYH-Associated Polyposis
>
> Late-Onset Alzheimer's Disease
>
> Parkinson's Disease
>
> If you are interested in receiving these reports, we recommend that you consult with a genetic counselor before purchasing. Additional relevant information about these reports will be provided when you go through the process of setting your report preferences, after registering your kit.[496]

But, although one can make sure that a potential customer or patient is provided with good information and perhaps even that that information is provided well, one cannot make that person understand it or consider it seriously. Consider how many times a week you "accept" terms and conditions for access to a website or a software update without ever opening them, let alone reading them, understanding them, or seriously weighing their positive and negative consequences.[497] Perhaps people click through and read the fine print more seriously for

494. *23andMe Genetic Health Risk Reports: What You Should Know*, 23ANDME, https://www.23andme.com/test-info/ (last visited Dec. 5, 2020).

495. *Id.*

496. *Id.*

497. Caroline Cakebread, *You're not alone, no one reads terms of service agreements*, BUS. INSIDER (Nov. 15, 2017, 6:30 AM), https://www.businessinsider.com/deloitte-study-91-percent-agree-terms-of-service-without-reading-2017-11 (citing a Deloitte survey of 2,000 U.S. consumers finding that ninety-one percent of people consent to legal terms and services conditions without reading them).

health information. I doubt it, but it might be a good empirical research project.

One might try to mitigate this problem by requiring a "good" consent process that is delivered, face to face (or perhaps via video screens) from health professionals trained to convey these risks and to counsel patients. A model for such professionals exists: genetic counselors. Genetic counselors typically have an undergraduate degree and a master's degree in genetic counseling.[498] They are trained to understand genetics but they are also trained to counsel people, to try to direct their attention to the kinds of risks and benefits that they may care about.[499] Genetics counselors can provide services both in advance, as part of the process through which a patient decides to be tested, or after the test, to help the patient understand and react to the information that has been gained.[500] Predictive testing for Alzheimer disease could use both roles, helping the patient decide whether to be tested and helping the tested patient understand and deal with the test results. (This, of course, is not surprising as genetic testing regularly will deal with not just predicting testing for Alzheimer disease but predictive testing for things not that different, such as whether a person carries genetic variations that will lead to Huntington disease or that greatly increase the risks of some cancers.)

One could imagine taking three steps to improve the consent process. First, one could ban Alzheimer disease predictive testing services that are not offered through licensed health professionals. Second, one might set out a well-defined informed consent standard for those professionals before the testing decision is made. And, third, one could require (good) counseling as part of receiving test results. That could help substantially—although its political feasibility might be questionable. But how can anyone stop people from giving ill-informed customers Alzheimer disease risk information based on a smell test or a mini-mental status test?

498. *Who Are Genetic Counselors?*, NAT'L SOC'Y GENETIC COUNS., https://www.aboutgeneticcounselors.org/who-are-genetic-counselors (last visited Dec. 5, 2020).

499. *Id.*

500. *Id.*

2. REGULATE ACCESS TO INFORMATION ABOUT PREDICTION RESULTS

Instead of, or in addition to, making sure customers are well informed, governments could try to limit the negative effects on customers of getting a predictive Alzheimer disease test. This would not work for personal psychological distress, but it might help with issues like discrimination in employment, insurance, and other contexts. One approach is to limit access to that information. Many, though not all, of the risks of predictive testing come not from the reaction of the tested person but from the reactions of others—employers, insurers, friends, and family—to those results.[501] One big concern may be that the institutions or people who did the testing, or have the test results, might reveal the test results to others against the wishes of, or without the knowledge of, the person tested. Guaranteeing that secrets will be kept has always been hard. As Benjamin Franklin said (perhaps optimistically) "Three may keep a secret, if two of them are dead."[502]

But in many health-related contexts, we do try to keep some information secret, or, at least, limited to appropriate users (who, unfortunately, always seem to number more than three).[503] If the testing is done by a physician in a medical context, the good news is that test results should be as protected as all other personal health information, through the privacy regulations adopted under the Health Insurance Portability and Accountability Act ("HIPAA") and various state confidentiality protections.[504] The bad news is that test results would (for the most part) only be as protected as all other health information, which is not nearly as protected as most patients expect.[505]

When HIPAA regulations apply, they limit the distribution of what is defined as "personal health information" but they contain many exceptions. Particularly relevant are exceptions having to do with payment (for example, to tell an insurer what it is being asked to pay

501. *See* K.G. Fulda & K. Lykens, *Ethical Issues in Predictive Genetic Testing: A Public Health Perspective*, 32 J. MED. ETHICS 143, 145 (2006); *Human Genomics in Global Health*, WHO, https://www.who.int/genomics/elsi/gentesting/en/#:~:text=Stigmatisation%20and%20discrimination,and%20discrimination%20within%20the%20community (last visited Dec. 5, 2020).

502. BENJAMIN FRANKLIN, POOR RICHARD'S ALMANACK (1735).

503. *Summary of HIPAA Privacy Rule*, HHS.GOV, https://www.hhs.gov/hipaa/for-professionals/privacy/laws-regulations/index.html (last visited Dec. 5, 2020) [hereinafter *HIPAA Summary*].

504. *Id.*

505. *Id.*

for or why it should pay for something); public health; or in emergencies affecting life or safety; judicial and administrative proceedings; law enforcement, workers compensation; or other situations where disclosure is required by other laws.[506]

HIPAA-protected information can also be released after it is "de-identified." De-identification makes it no longer personal health information and hence no longer protected.[507] HIPAA regulations set out two paths to de-identification; the more straightforward one is the "safe harbor," which is available if eighteen specific kinds of identifying information are removed.[508] These include things like names, telephone numbers, social security numbers, email addresses, and full-face photographs.[509] In addition the institution must "not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is a subject of the information."[510] The problem is that re-identification may often be quite possible, and the more detailed the medical information provided the more possible it becomes—and being "quite possible" is not the same as the institution having "actual knowledge" that it could be used for identification.[511]

HIPAA provides no private cause of action for someone whose privacy rights have been violated, but the federal government, acting through the Office of Civil Rights of the Department of Health and Human Services, can enforce them through requiring corrective action or

506. HIPAA, 45 C.F.R. § 164.512 (2016); *HIPAA Summary*, *supra* note 503.

507. *HIPAA Summary*, *supra* note 503; *see also Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule*, DEP'T HEALTH & HUM. SERVS. 9, http://privacyruleandresearch.nih.gov/pdf/HIPAA_Privacy_Rule_Booklet.pdf (last visited Oct. 12, 2020) [hereinafter *Understanding HIPAA*]; *see also Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule*, HHS.GOV, https://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html#:~:text=Regardless%20of%20the%20method%20by,longer%20considered%20protected%20health%20information (last updated Nov. 6, 2015) [hereinafter *Guidance Regarding Methods for De-identification*].

508. *HIPAA Summary*, *supra* note 503; *Guidance Regarding Methods for De-identification*, *supra* note 507.

509. *HIPAA Summary*, *supra* note 503; *Understanding HIPAA*, *supra* note 507; *Guidance Regarding Methods for De-identification*, *supra* note 507.

510. Health Insurance Portability and Accountability Act of 1996 (HIPAA), 45 C.F.R. § 164.514(a)(b) (2013); *De-identification of Protected Health Information: How to Anonymize PHI*, HIPAA J. (Oct. 18, 2017), https://www.hipaajournal.com/de-identification-protected-health-information/.

511. *HIPAA Summary*, *supra* note 503; *Guidance Regarding Methods for De-identification*, *supra* note 507.

through fines.[512] Since the 2009 legislation, state attorneys general have also been authorized to sue over violations of HIPAA's privacy rules that have affected their states' citizens, but are again limited to requiring corrective action and levying fines.[513] States may also have their own privacy laws, sometimes limited to health and sometimes more general, that can be enforced, largely through fines.[514]

State laws also provide some other protections against disclosure by health care providers. One famous example is the doctor-patient evidentiary privilege.[515] What is often overlooked is that this is only an evidentiary privilege—it allows and sometimes requires physicians and other health care personnel to refuse to answer questions in a judicial proceeding but it does not, in itself, require them to keep secrets in other contexts.[516] State common law and statutory law, however, often do make such requirements, with varying enforcement mechanisms.[517]

But then, of course, not all the predictive testing will be done by physicians in a medical context. 23andMe and similar firms, for example, are not health care providers.[518] They generally are subject neither to the rules of HIPAA nor of doctor-patient confidentiality.[519] They are bound mainly by the terms of service they contractually agreed to with

512. *Can A Patient Sue for A HIPAA Violation?*, HIPAA J. (Nov. 7, 2017), https://www.hipaajournal.com/sue-for-hipaa-violation/; *see also Enforcement Highlights*, HHS.GOV, https://www.hhs.gov/hipaa/for-professionals/compliance-enforcement/data/enforcement-highlights/index.html (last updated Sept. 11, 2020).

513. Health Information Technology for Clinical and Economic Health Act of 2009, Pub. L. No. 111-5, 123 Stat. 115, § 13410(e) (codified as amended at 42 U.S.C § 1320d-5).

514. *See, e.g.*, Cal. Civ. Code § 56.36 (2016) (imposing civil penalties for unauthorized access to or use or disclosure of medical information).

515. *See generally* Kristen Johnson, *What Is a Doctor-Patient Privilege?*, LEGALMATCH, https://www.legalmatch.com/law-library/article/doctor-patient-privilege.html (last updated Apr. 19, 2018) [hereinafter *What is a Doctor-Patient Privilege?*]; *see, e.g.*, WIS. STAT. § 905.04 (2018).

516. *What is a Doctor-Patient Privilege?*, *supra* note 515; *see also Confidentiality, Patient/Physician*, AM. ACAD. FAM. PHYSICIANS, https://www.aafp.org/about/policies/all/confidentiality-patient-physician.html (last visited Oct. 12, 2020).

517. *See, e.g.*, Cal. Civ. Code § 56.36 (2016). *See generally Examples of Federal and State Laws Affecting Confidentiality*, CTR. FOR ETHICAL PRAC., https://centerforethicalpractice.org/ethical-legal-resources/legal-information-other-states/examples-oflaws-affecting-confidentiality-2/ (last visited Dec. 5, 2020).

518. *See, e.g.*, *Company*, 23ANDME, https://medical.23andme.com/company/ (last visited Dec. 5, 2020).

519. *See* Peter Pitts, *The Privacy Delusions Of Genetic Testing*, FORBES (Feb. 15, 2017 1:26 PM), https://www.forbes.com/sites/realspin/2017/02/15/the-privacy-delusions-of-genetic-testing/#37f3bf151bba; Mason Marks & Tiffany Li, *DNA donors must demand stronger protection for genetic privacy*, STAT NEWS (May 30, 2018), https://www.statnews.com/2018/05/30/dna-donors-genetic-privacy-nih/.

(or more realistically, imposed on) their customers.[520] These terms may be difficult for customers to understand and may be, by the contract's own terms, alterable by the companies.[521] If such a company violated those terms of service by disclosing a customer's information—*and* if the customer realized the disclosure had happened—the only remedy, as a general matter, would be for the customer to sue the company.[522] And, under the terms of many contemporary consumer contracts, that dispute would end up being resolved by arbitration, with serious limitations on the customer's recovery.[523]

Thus far we have been looking only at voluntary disclosures by health care providers or testing firms. Not all disclosures are voluntary. Some can be the result of legal action—search warrants, subpoenas, or discovery requests.[524] It will not often be the case that a person's Alzheimer disease prediction will be relevant to a criminal trial or in civil litigation, but it is not impossible. Consider a case where the person's mental state is important, and their predictive Alzheimer disease information is allegedly of some value as evidence of that state. That a person with very high levels of Aß42 plaque or tau tangles at the time of testing might, then or at a subsequent time, have been experiencing some memory or other cognitive problems might well be relevant to, for example, assessing that person's competency at relevant times. These kinds of legally required disclosures are not protected by HIPAA, doctor-patient privilege, or any other privacy laws.

But the unintended and even unknown disclosures through hackers may be far more important than these kinds of legally compelled disclosures. Anyone who guarantees that your personal information in their database will stay securely protected is either a liar or a fool. (And anyone who believes such a statement is, these days, a good candidate for a fool.) Every week seems to bring more news of unauthorized individuals (or in some cases governments) obtaining confidential data.[525]

520. *See, e.g.*, *Terms of Service*, 23ANDME, https://www.23andme.com/about/tos/ (last visited Dec. 5, 2020).

521. *See id.*

522. *See id.*

523. *Id.*

524. *See generally When does the Privacy Rule allow covered entities to disclose protected health information to law enforcement officials?*, HHS, https://www.hhs.gov/hipaa/for-professionals/faq/505/what-does-the-privacy-rule-allow-covered-entities-to-disclose-to-law-enforcement-officials/index.html (last updated July 26, 2013).

525. COMM. ON REG'L HEALTH DATA NETWORKS, HEALTH DATA IN THE INFORMATION AGE USE, DISCLOSURE, AND PRIVACY 17 (Molla S. Donaldson & Kathleen N. Lohr eds., 1994).

If someone truly wants to guarantee that information will be kept secret, then they should not allow their data to be kept in a database. This is likely impossible—it is hard these days to imagine any testing system that does not involve someone keeping electronic records.[526] It is not clear why any hacker would want to make people's Alzheimer disease prediction status public, but it does not mean that such information might not be included in a major data breach in a way that makes it widely available. And it would not require (much?) paranoia for a person contemplating predictive testing to worry that someone interested in her results might be able to obtain that information through hacking.

Of course, the discussion thus far has ignored one very easy way for someone—an insurer, an employer, a friend—to seek information about a person's predicted risk of Alzheimer disease: ask. The strategy of protecting someone from (some of the) adverse consequences of predictive testing through limited access to the information only works if the person does not have to disclose it themself.

Legal protection against questions from family and friends is inconceivable. Social conventions may discourage some kinds of questions—few people in ordinary circumstances would ask strangers about their sexual orientation, for example—but the closer the friendship or the family relationship, the less powerful such conventions are likely to be. After all, intimacy in friends or family or romance is in part, a function of being able to talk about hidden things.

But what if an application for long-term care insurance requires, as a condition for the application being considered, that applicants disclose whether they ever have had any kind of predictive testing for Alzheimer disease? And, if the answer is "yes," asks what the testing revealed (or, more likely, for a copy of the test report)?

Society, acting through the law, can limit what questions some institutions can ask. In fact, in ways potentially relevant to Alzheimer disease predictive testing, society already has through the Genetic Information Nondiscrimination Act ("GINA")[527] and the Americans with Disabilities Act ("ADA").[528] These statutes have prohibitions against some actions, which we will discuss in the next Section, but they also contain bans on seeking some kinds of information. GINA largely for-

526. *Id.* at 15.

527. Genetic Information Nondiscrimination Act of 2008, Pub. L. No. 110-233, 122 Stat. 881 (codified as amended in scattered sections of 29 U.S.C.).

528. 42 U.S.C § 12101 et seq. (2009).

bids employers and health insurers from asking for genetic information, defined very broadly to include not just DNA tests or other molecular (RNA or protein) tests, but also family history.[529] The exceptions are limited.[530]

The ADA is much broader than GINA, and its employment discrimination provisions have been in effect since 1992, seventeen years longer than GINA.[531] It has had the time and scope to generate a complex set of rules about what can and cannot be asked. In brief, it forbids employers from asking potential employees about the existence, nature, or severity of a disability or to require or conduct a medical examination of the applicant until after the employer has made an initial assessment and made a conditional job offer—conditioned on the applicant being able to perform the job's essential functions.[532] Once such a conditional job offer has been made, an employer may ask about disabilities and require or conduct medical examinations, but only if it does so for all applicants for that position.[533] It can therefore ask about conditions that could affect the applicant's ability to perform essential job functions or that might require the employer to provide accommodations (such as, for example, sign language interpreters for the deaf) to allow the (provisionally accepted) applicant to do the job.[534]

529. 29 U.S.C. § 1191b(d)(6)(A)—(C) ("(A) In general. The term 'genetic information' means, with respect to any individual, information about—(i) such individual's genetic tests, (ii) the genetic tests of family members of such individual, and (iii) the manifestation of a disease or disorder in family members of such individual. (B) Inclusion of genetic services and participation in genetic research. Such term includes, with respect to any individual, any request for, or receipt of, genetic services, or participation in clinical research which includes genetic services, by such individual or any family member of such individual. (C) Exclusions. The term 'genetic information' shall not include information about the sex or age of any individual.").

530. *Id.*

531. Vocational Rehabilitation Act of 1973, Pub. L. No. 93-112, 87 Stat. 355 (showing that the ADA had a precursor that applied to the federal government and to some federally-funded activities or federal contractors); *see also* 38 U.S.C. § 4212 (2012) (showing that it still applies to some employers, in addition to the ADA, and has some of its own intricacies concerning asking about disabilities, as does the Vietnam Era Veterans' Readjustment Assistance Act) [hereinafter V.R.A.].

532. *Job Applicants and the ADA*, EEOC (Oct. 7, 2003), https://www.eeoc.gov/laws/guidance/job-applicants-and-ada#:~:text=The%20ADA%20prohibits%20employers%20from,as%20well%20as%20medical%20examinations.

533. *Id.*

534. *Id.*

These provisions of GINA and the ADA just prohibit employers (and, for GINA, health insurers) from asking about particular characteristics.[535] They do not prohibit them from noticing such characteristics, which is unlikely with regard to Alzheimer disease prediction, given the nature of those characteristics (brain scans, biomarkers, mental status tests). They also, however, do not prohibit applicants from volunteering that information.[536] In a world where one side could not ask about an important trait, but the other side could get a benefit from revealing a good result, one might reasonably expect any prohibition on asking to be meaningless. Those who had a low predicted risk of Alzheimer disease, in this case, would (legally) volunteer that information and have it acted on. Those who were at high risk would either say nothing or would lie, both risky. A protective strategy that focuses solely on blocking someone from getting information about a person's Alzheimer disease risk status has many problems which is why such statutes are usually complemented by limitations on actions, not just information gathering.[537]

3. DIRECTLY REGULATE (SOME OF) THE NEGATIVE CONSEQUENCES

In some areas of life, we directly prohibit others from using information about persons' characteristics in ways that harm them. The Constitution itself protects people from government actions based on some characteristics, particularly race.[538] Title VII of the Civil Rights Act of 1964 goes farther and regulates non-government actors, banning discrimination in employment (among other things) based on race, gender, national origin, or religion.[539] Some of these characteristics, like race or gender, would often (although not always) be obvious to an observer, making information protection strategies ineffective. Others, such as religion, would often (though not always) be less clear merely from observation so that one might try to prevent a prospective employer from asking about an applicant's religion. But the Act does not focus on preventing access to information, it bans discrimination.[540] GINA and the ADA may provide some substantive protection against discrimination on the basis of Alzheimer disease prediction status,

535. *Id.*
536. *Id.*
537. *Id.*
538. *See, e.g.*, U.S. CONST. amend. XIV, § 1.
539. 42 U.S.C. § 2000e-2.
540. *Id.*

though as already noted, their coverage is, in one case, partial and, in the other, unclear.[541] (Mark Rothstein has an insightful new article pointing out the overlapping "non-coverage" of the ADA and GINA; one deals (mainly) with existing disabilities and the other with only future (genetic) predictions; he urges that new legislation cover those gaps.)[542]

As discussed in the previous Section, GINA greatly limits employers and health insurers from asking about genetic information, broadly defined. It also prohibits them from acting on such information.[543] This applies to some Alzheimer disease prediction, but only for some methods of prediction.[544]

Remember that, for *some* people, Alzheimer disease can be very strongly predicted through the genetic variants they carry.[545] For early-onset Alzheimer disease, known versions of the genes *PSEN1*, *PSEN2*, and *APP*, as well as the presence of a third copy of chromosome 21 (on which *APP* sits), mean, with very high probability, that a person (or a fetus, or an IVF generated embryo) will, barring currently unknown powerful medical interventions, develop early-onset Alzheimer disease.[546] Similarly, possessing two copies of the *APOE* e4 variant creates a very high risk of being diagnosed with Alzheimer disease, although in one's sixties or seventies, not forties or fifties.[547] Possessing one copy of the *APOE* e4 variant doubles or triples a person's risk, although it does not bring it to 50 percent.[548] A wide variant of other DNA variations have been associated with higher (and lower) risks of Alzheimer disease, though with effects so small that employers or health insurers are unlikely to care about them.[549]

541. Jalayne J. Arias & Jason Karlawish, *Confidentiality in Preclinical Alzheimer disease studies*, 82 AM. ACAD. NEUROLOGY 725, 727–28 (2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3945659/pdf/NEUROLOGY2013546689.pdf.

542. Mark A. Rothstein, *Predictive Health Information and Employment Discrimination under the ADA and GINA*, 48 J. L. MED. & ETHICS 1, 4 (2020).

543. *Id.* at 6–7.

544. *Id.*

545. Bekris et al., *supra* note 175, at 8.

546. Bekris et al., *supra* note 175, at 223.

547. *See id*.

548. *Id.* at 223–24.

549. *Id.*

Information about all these genetic variations is clearly covered by GINA, as is information about a family history of Alzheimer disease.[550] That means employers and insurers cannot ask for such information. It also means that, should they somehow obtain that information, they may not act on it by, say, denying a job or refusing to issue health insurance.[551] This also avoids the problem of volunteering "good" information—just as employers and health insurers cannot act negatively on information about high risks, they cannot act positively on information about low risks.[552]

Of course, laws are mainly useful if they are followed. Race and sex discrimination in employment has been illegal for over fifty-six years but few think it has completely vanished.[553] (Murder has been illegal even longer but every year about fifteen thousand Americans are murdered.[554]) GINA was passed in 2008; laws with similar goals had already been passed in more than forty-five states.[555] There have been enforcement actions, especially at the federal level, but not very many.[556] In fact, there was, for various reasons, substantial doubt about whether genetic discrimination was occurring at anything above tiny rates;[557] arguments for banning it often rested more on reassuring the

550. Taylor Jr. et al., *supra* note 402.

551. Carolyn Riley Chapman et al., *Genetic Discrimination: Emerging Ethical Challenges in the Context of Advancing Technology*, J.L. & BIOSCIENCES 1 (2019), https://academic.oup.com/jlb/advance-article/doi/10.1093/jlb/lsz016/5651192.

552. U.S. DEP'T OF LABOR, *The Genetic Information Nondiscrimination Act of 2008: "GINA"*, https://www.dol.gov/agencies/oasam/centers-offices/civil-rights-center/statutes/genetic-information-nondiscrimination-act-of-2008/guidance (last visited Oct. 12, 2020).

553. *Id.*

554. 42 U.S.C. § 2000e-2.; *Number of reported murder and nonnegligent manslaughter cases in the United States from 1990 to 2019*, STATISTA RES. DEP'T (Sept. 28, 2020), https://www.statista.com/statistics/191134/reported-murder-and-nonnegligent-manslaughter-cases-in-the-us-since-1990/.

555. Genetic Information Nondiscrimination Act of 2008, Pub. L. No. 110-233, 122 Stat. 881; Eric A. Feldman, *The Genetic Information Nondiscrimination Act (GINA): Public Policy and Medical Practice in the Age of Personalized Medicine*, 27 J. GEN. INTERNAL MED. 743 (2012).

556. Sonia M. Suter, *GINA at 10 years: the battle over 'genetic information' continues in court*, 5 J. L. & BIOSCIENCES 495 (2018).

557. Timothy Caulfield et al., *Harm, Hype, and Evidence: ELSI Research and Policy Guidance*, 5 GENOME MED. 21, 23 (2013) (explaining there is "little evidence suggesting that genetic discrimination is a significant or common social phenomenon.").

public from a perceived threat than on protecting it from an actual one.[558]

GINA applies only to discrimination in employment and in health insurance.[559] As noted above, Alzheimer disease prediction is unlikely to have a substantial impact in those areas. But, in the context of Alzheimer disease, GINA's bigger limitation is that it applies only to *genetic* information.[560] True, it defines genetic information broadly but not so broadly as to include mini-mental status tests, olfactory tests, biomarker tests (unless the particular protein or its abundance or absence was strongly linked to particular genetic variations), or, most notably, brain scans.[561] Although the many state laws on genetic discrimination have many provisions different from GINA, including some that arguably include some non-health forms of insurance, they share with GINA the reality that they are about *genetic* discrimination.[562]

One interesting question, to which I do not know the answer, is how GINA would treat actions that are based in part on genetic information but in part on non-genetic information. Let's say that researchers develop a predictive algorithm that looks at both *APOE* status from genetic testing and Aß42 and tau buildup from brain scans, along with results of a mini-mental status test. Would the result, in which genetic information played only one part, be something whose use against the person should be held to violate GINA? I suspect, but do not know, that it would as long as genetic information played a non-trivial role in the prediction. As (good) predictions of Alzheimer disease risk seem likely to try to incorporate as much relevant information as possible, that may bring more people within the scope of GINA—unless employers, insurers, or testing groups decide to develop a "gene free" predictive testing algorithm for the purpose of avoiding GINA. Such an algorithm might not be as good as one incorporating genetic information, but it might well be "good enough."

558. Henry T. Greely, *Banning Genetic Discrimination*, 353 NEW ENG. J. MED. 865 (2005); Henry T. Greely, *"Genotype Discrimination": The Complex Case for Some Legislative Protection*, 149 PENN. L. REV. 1483 (2001).

559. Genetic Information Nondiscrimination Act of 2008, Pub. L. No. 110-233, 122 Stat. 881.

560. *Id.*

561. *Id.*

562. Suter, *supra* note 556, at 496.

The ADA might provide another safety net.[563] The relevant part protects people with disabilities from (mostly) employment discrimination, and not from insurance discrimination. The Act defines a disability as:

> (a) a physical or mental impairment that substantially limits one or more major life activities of such individual;
> (b) a record of such an impairment; or
> (c) being regarded as having such an impairment….[564]

Is being at higher than normal risk for Alzheimer disease a disability? Maybe, but we do not know. We might have gotten an answer through efforts to apply the ADA to genetic risk predictions but GINA (and, probably more importantly, state versions of what was eventually GINA) took that away as an ADA question before it was resolved.[565] The issue might depend on whether being at high risk is, in itself, a "physical or mental impairment."[566]

There is some case law—from the U.S. Supreme Court itself—relevant to this issue. In the late 1980s a dental patient sued her dentist for refusing to perform oral surgery on her because she was HIV positive, even though she did not have AIDS (which was, in that era, viewed as the inevitable result of her infection).[567] When the case reached the Supreme Court as *Bragdon v. Abbott*, the Court held that being HIV positive could be a disability even without symptoms.[568] It started by asking

563. V.R.A., *supra* note 531. Another, earlier federal law—the Vocational Rehabilitation Act—applies to the federal government, state and local governments in programs with federal grants, and federal government contractors. It uses a very similar definition of disability and is unlikely to add much to a person's protections. As with GINA, many states have their own laws against disability discrimination and, again as with GINA, these have terms that vary substantially, with the ADA and with each other. There may be some exceptions but, again, for the most part these are unlikely to add to the protections of someone who is predicted to be at high risk for Alzheimer's disease.

564. 42 U.S.C. § 12102(1).

565. *See* Genetic Information Nondiscrimination Act of 2008, Pub. L. No. 110-233, 122 Stat. 881.

566. *See Questions and Answers on the Final Rule Implementing the ADA Amendments Act of 2008*, U.S. EQUAL EMP. OPPORTUNITY COMM'N, https://www.eeoc.gov/laws/guidance/questions-and-answers-final-rule-implementing-ada-amendments-act-2008#:~:text=The%20regulations%20define%20%22physical%20or,%2C%20cardiovascular%2C%20reproductive%2C%20digestive%2C (last visited Dec. 20, 2020).

567. Bragdon v. Abbott, 524 U.S. 624, 628 (1998).

568. *Id.* at 632–39.

if there was an impairment.[569] It held that HIV infection was an impairment because from the moment of infection the virus was attacking the patient's cells, including quickly their immune system, long before symptoms were apparent.[570] The Court then had to answer the second question: did her infection substantially affect a major life activity?[571] The Court ruled that it affected the patient's ability to engage in the major life activity of bearing a child.[572] It affected that activity by creating a high risk (true at that time, less so today) that the HIV infection would be passed on to any child.[573] (The ADA Amendments Act of 2008 expressly made "disability status" easier for people with HIV to claim, limiting the direct importance of *Bragdon v. Abbott* for HIV patients but not in other situations.)[574]

Could that work for Alzheimer disease prediction? Maybe. The impairment showing should work if brain scanning, for example, showed that neurons were dying, or gray matter was becoming less dense. Perhaps a court would be willing to accept high amyloid plaque or tau tangle levels as sufficient evidence of an impairment. The second part, the interference with a major life activity, is trickier. The best argument may be a somewhat circular one. Employment is a major life activity; if your impairment is used to discriminate against you in employment, you are covered.

On balance, then, people who are predicted to be at high risk for Alzheimer disease have some protection under GINA and state laws from employment and health insurance discrimination—if the prediction is based on genetic information—and might, or might not, have any protection under the various disability rights acts. This reality, and

569. *Id.* at 631.
570. *Id.* at 637.
571. *Id.*
572. *Id.* at 638–39.
573. *Id.* at 639, 647 (finding that HIV infection, even if a person is asymptomatic, substantially limits the ability to reproduce).
574. Pub. L. 110-325, Section 4(a), codified as 42 U.S.C. §12102(4)(D) (which would cover the plaintiff's asymptomatic HIV infection as a disability as if it were active, because it was "episodic" or "in remission."); see Lisa M. Keels, *Substantially Limited: The Reproductive Rights of Women Living with HIV/AIDS*, 39 U. BALT. L. REV. 389, 414 (2010) (Alzheimer's prediction does not seem to fit the statutory model, but may still fall within Bragdon's holding).

the other limitations on protections discussed in this Section, lead to the question "what is to be done?" [575]…and the last Section of this Article.

V. What Is To Be Done?

Right now Alzheimer disease prediction is uncommon but not unknown, especially thanks to 23andMe and its direct-to-consumer *APOE* testing.[576] But other methods are either already available (such as mini-mental status examinations or Aß42 or tau PET scans) or might be available soon (some of the new blood plasma biomarker tests).[577] So what should we, as a society, do about prediction of Alzheimer disease? This last Section starts with one important observation about the (non-existent) line between early diagnosis and prediction and its importance to regulating Alzheimer disease prediction. It then makes three recommendations. We should (1) regulate the quality of tests; (2) require that people receive good and well-provided information before and after predictive testing; and (3) create some thoughtful and nuanced protections for some people against some, but not all, kinds of discrimination based on their Alzheimer disease risk status.

575. I have used this as the title for sections of papers several times. Given that I generally approach most questions from the perspective of suggesting better policies, it substantively makes sense. But I like it for another reason as well. It was the title of an 1863 novel by Nikolay Chernyshevsky, a nineteenth century Russian writer, editor, populist, and democratic socialist. The novel argued in part for the creation of small socialist communes, for industrial production as well as agriculture, but, more importantly, for the crucial role of dedicated and ascetic intellectuals in leading the workers to a benign socialism. NIKOLAY G. CHERNYSHEVSKY, *CHTO DÈLAT'*? [WHAT IS TO BE DONE?] (1886). But it was also the title used in 1902 when Vladimir Lenin (an admirer of the novel) gave it to one of his pamphlets in which he argued that a strong Marxist political party, with a solid theoretical foundation, was needed to lead the working classes from solely "trade union" concerns to a pursuit of true socialism. VLADIMIR LENIN, CHTO DELAT'? NABOLEVSHIYE VOPROSY NASHEVO DVIZHENIYA [WHAT IS TO BE DONE? BURNING QUESTIONS OF OUR MOVEMENT] (Russ.), translated in LENIN'S COLLECTED WORKS (Foreign Language Pub. House: Moscow 1961). One title, two answers.
Chernyshevsky wrote his novel (in prison) as a critical response to Ivan Turgenev's 1862 novel, FATHERS AND SONS; Chernyshevsky's novel then prompted not one but two critical responses from Fyodor Dostoyevsky, in his 1864 novella, NOTES FROM THE UNDERGROUND, and his 1872 novel, DEMONS. I like this history because I love nineteenth century Russian literature, but also as a reminder to humility: what is to be done is not always clear and even when, to some people, it is clear, to others it will be clearly different. IVAN TURGENEV, *OTTSY I DETI* [FATHERS AND SONS] (1862); FYODOR DOSTOYEVSKY, NOTES FROM THE UNDERGROUND (1864); Fyodor Dostoyevsky, DEMONS (1872).

576. *See Late-Onset Alzheimer's Disease, supra* note 6.

577. *See Medical Tests*, *supra* note 2; Lashley et al., *supra* note 262.

A. The Continuum Between Early Diagnosis and Prediction

Let's start with the observation: early diagnosis of Alzheimer disease and prediction of Alzheimer disease exist on a continuum, with no clear lines between them.[578] People seeking early diagnosis may end up without a diagnosis but with a strong prediction; people seeking a prediction may end up with a diagnosis.[579] Everything we know about this evil disease seems consistent with a series of slow changes: in memory, in Aß42 and tau protein, in sense of smell, in gray matter density. And some of the more distinctive indications, like the presence or absence of a genomic variation associated with Alzheimer disease, may not only be predictions but may also be important in making a diagnosis.[580] For example, a forty-five-year-old with a pathogenic *PSEN1* variation who is unhappy about memory lapses is much more likely to have, and to be diagnosed with, early-onset Alzheimer disease than one without a *PSEN1* mutation.[581]

Why is this important? Because if diagnostic tests and predictive tests are, in practice, the *same* tests, one cannot regulate one meaningfully without regulating the other. One might want to limit predictive testing but not diagnostic testing, but their huge overlap may make that difficult, if not impossible. One line might be the extent to which people are already showing significant memory problems of the sort associated with Alzheimer disease, but also other conditions. At that point the problems the test results cause will shift from those of predicting what will likely happen in the future to dealing with what is happening in the present. But will such a line work? What would count as "significant" memory problems? And wouldn't looking for the significant memory problems required as a prerequisite to testing also be a kind of test with its own "predictive" value, whether done by patient self-report or through, say, a mini-mental status test? At the very least, handling the (relevant) differences between predictive and diagnostic testing will require careful thought.

578. *See generally* Michael W. Weiner et al., *The Alzheimer's Disease Neuroimaging Initiative: Progress report and future plans*, 6 ALZHEIMER'S DEMENTIA 202, 202–11 (2010).

579. *See generally id.*

580. *See* Park et al., *supra* note 95.

581. *See* Bruno Dubois et al., *Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria*, 12 ALZHEIMER'S DEMENTIA 292, 292–323 (2019).

B. Regulating the Quality of Alzheimer Disease Predictive Tests

First, the quality of tests used to predict (or to diagnose) Alzheimer disease should be regulated. They should be shown to be both effective and safe before they are allowed to be performed, and they should be performed only by trained and qualified professionals. Most people do not have any trouble thinking about whether a test is "effective." If the purpose of testing is creating information, "effective" becomes the same as "accurate."[582] And accuracy will be important, probably more in terms of positive and negative predictive values than sensitivity, specificity, or the area under the curve ("AUC"). An inaccurate test helps no one (except, perhaps, those getting paid to administer or analyze it).

But what does "safe" mean? In this context, it means that the benefits of the test, when applied appropriately, outweigh its risks and harms.[583] Those risks and harms may be from inaccurate results, but they also may be from inappropriate responses to test results from patients who misunderstand them. I would insist not just on studies that show a sufficient level of accuracy (however one might define "good enough" in a context where one knows the accuracy of any test will inevitably be less than perfect), but studies that show that those who received the tests results experienced, on average, more benefits (broadly defined) than costs (also broadly defined). In addition, even if the average (either mean or median) results were positive, I would want a close look at the negative outliers. A few people bearing extremely serious costs might outweigh a large number of people with minimal benefits—or, more usefully, that kind of analysis might help distinguish between different classes of patients who should get more or fewer precautions in testing.

"Regulation" might be through the FDA, but there are additional paths. If the FDA continues not to regulate LDTs done by licensed clinical laboratories, the state regulators may be able impose constraints

582. In some circumstances it may be better to equate "effectiveness" with "clinical utility": does the result make any useful difference in the medical outcome? Some argue that even the most accurate genetic tests (predictive or diagnostic) for diseases will have no clinical utility if the disease is basically untreatable (as Alzheimer disease currently is). Clinical utility is not a crucial criterion in a context where patients are seeking predictive information for a disease they know is not treatable.

583. J. Scott Roberts & Sarah M. Tersegno, *Estimating and disclosing the risk of developing Alzheimer's disease: challenges, controversies and future directions*, 5 FUTURE NEUROLOGY 501, 501–17 (2010).

with coercive legal force, and the College of American Pathologists, as the accrediting agency, may be able to impose requirements that, although without coercive legal force, are effective in determining how the tests are provided.[584] Similarly, some effective "regulation" can be imposed through what insurers will and won't pay for, led by (especially in older people) Medicare.[585] Medical professional organizations could also play important roles, such as the American Academy of Neurology or the American College of Radiology as well as, among primary care providers (who might, for example, administer mini-mental status tests), the American College of Physicians (for internal medicine specialists) or the American Academy of Family Physicians (for family practitioners). At some point state medical boards might become involved, deeming some kinds of testing as unprofessional and subjecting physicians to professional discipline.

But would that be enough? Guidelines from professional organizations are persuasive but not binding.[586] Reimbursement limits will affect some patients but not those who are willing to pay out of pocket.[587] And some of these tests—olfactory abilities or mini-mental status tests—could be performed by people who are not licensed professionals at all.[588] It may be that direct legal regulation of these tests, whoever performs them, would be important. Some of the tests could be FDA-regulated but others would not be, either because they do not require medical devices, drugs, or biological products or because, even if they did, as a practical matter, they might escape FDA regulation.[589] Thus, one could imagine a way of testing someone's sense of smell that would be a complicated device, requiring careful manufacture by an entity the FDA could regulate. But one could also imagine a non-professional setting out bowls with rosemary, garlic, mint, and other scents before a customer paying for a prediction about Alzheimer disease. As a practical matter, how could the FDA regulate that?

Perfection in regulation, as in anything, is unobtainable. It should not be held up as a complete barrier to some regulation, if useful.

584. *Cf. Standards for Laboratory Accredidation*, *supra* note 447, at 2.
585. *See generally id.* at 6.
586. *See generally id.* at 2.
587. *Cf.* BRIAN BRUEN ET AL., THE IMPACT OF REIMBURSEMENT POLICIES AND PRACTICES ON HEALTHCARE TECHNOLOGY INNOVATION 4 (2016).
588. *See generally Medical Tests*, *supra* note 2.
589. *Id.*

C. Requiring the Receipt of Good Information, Well Provided

Of course, just saying that a test is accurate does not mean that the testing *process* will be a good one. Test results must not just be meaningful but those tested must understand the results—and for this kind of testing must understand enough before being tested to make a good decision about whether to be tested. As discussed in Part III, Section (B)(1), misunderstandings of the meaning, and implications, of test results can be harmful.[590] The FDA's approval of 23andMe's *APOE* tests convinces me that the test is analytically sound—that it measures what it says it measures, the presence or absence of *APOE* e2, e3, and e4 alleles.[591] Although the FDA says 23andMe showed through survey evidence that customers could understand what the test would do and its results,[592] I think we should demand, for this and for other Alzheimer disease predictive testing, a higher standard for informing users, both before and after they are tested.

Good informed consent is very important here. Purely predictive testing for Alzheimer disease offers fewer benefits and more risks than diagnostic testing.[593] For some people, with certain kinds of personalities, families, jobs, and other things, testing will make sense. For others, it will not. Something akin to good pretest genetic counseling should be required. The existence of a paragraph, or of a disclaimer, on an internet site provides very little evidence that a person has understood or even read a discussion of the pluses and minuses of getting tested, let alone thought hard about it.[594] Face-to-face counseling (including face-to-face over a computer screen through a video link, something the COVID-19 pandemic has accustomed more and more people to)[595] will

590. *Id.*

591. Press Release, U.S. Food & Drug Admin., FDA Allows Marketing of First Direct-to-Consumer Tests that Provide Genetic Risk Information for Certain Conditions (Apr. 6, 2017), https://www.fda.gov/news-events/press-announcements/fda-allows-marketing-first-direct-consumer-tests-provide-genetic-risk-information-certain-conditions (explaining a FDA approved 23andMe direct-to-consumer testing premised in part on a user study that showed users could easily understand the reports). [hereinafter FDA Allows Marketing].

592. *Id.*

593. *Alzheimer's Disease Fact Sheet*, NAT'L INST. ON AGING (May 22, 2019), https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet. [hereinafter *Fact Sheet*].

594. *How Effective Are Disclaimers?* RODRIGUEZ & ASSOCS. (Sep. 27, 2018), https://www.rodriguezlaw.net/how-effective-are-disclaimers/.

595. *Using Telehealth Services*, CTRS. FOR DISEASE CONTROL & PREVENTION (June 10, 2020), https://www.cdc.gov/coronavirus/2019-ncov/hcp/telehealth.html.

not be perfect. It will, however, make sure that a trained professional has provided the relevant information in ways that cannot be skipped; has sought out and answered questions; has had a chance to spot signs of misunderstanding, confusion, or concern; and, perhaps most important, has brought home to someone considering testing what kinds of issues that person may want to think about.

Even more important would be counseling after the test. People with a negative test result, who test at low risk, should be reminded that "low risk" for Alzheimer disease is, unfortunately, not the same as *no* risk.[596] And, perhaps more importantly, that Alzheimer disease is not the only kind of dementia and that tests that predict it will often not predict other forms of dementia.[597] But the value of a trained explainer is likely to be even higher in the case of a positive test result. Those people will often need to be reminded, or reassured, that "high risk" is not the same as "certain."[598] They need to be counseled about the kind of reactions they might have to the news, as well as to the reactions that others—from friends and family to insurers and employers—might have. And perhaps referrals to some good resources, from health care providers to organizations, like the Alzheimer Association.[599]

Notice, though, that both the need for this kind of information and what information should be provided depends on many things. If, as is devoutly hoped, a good treatment to prevent, or even substantially slow, Alzheimer disease is developed, predictive testing becomes much more useful (especially if the intervention works best when it is used early). The question whether to test or not to test therefore becomes, for most people at least, a lot less difficult, which would mitigate the need for truly good informed consent procedures. At the same time, the post-test counseling would focus much more on the medical interventions and how to get them. What is important, both to convey and to understand, depends on the context, and the context may well change. This makes efforts to regulate the information process more complicated; the rules need to be easy to adjust in light of changes. And those changes might not just be in medicine but might also be in society, through changes in protections for people at high risk for Alzheimer disease.

596. *Cf. Fact Sheet*, *supra* note 593.
597. *See generally id.*
598. *See generally id.*
599. *See generally id.*

D. Nuanced Protections for People at High Risk for Alzheimer Disease

GINA protects people from genetic discrimination in employment and health insurance decisions.[600] Do we need a "NINA"—a "Neuroscience Information Non-Discrimination Act"? Some have begun to argue for that, or, at least, some form of it.[601] But the devil is in the details, and these details are devilish, indeed.

The basic problem is that there are some good reasons to discriminate, in various ways, "against" people who have dementia or, at least, against their immediate wishes. Some of those reasons involve protecting them, some involve protecting other people directly, and some involve protecting broader issues of social policy. Weighing this balance is much more difficult than weighing the balance in race, national origin, religion, or sex discrimination.[602]

The key issue is generally one of enhanced monitoring rather than of direct discrimination. Actually having significant symptoms of dementia can lead to harms for the person involved, ranging from financial victimization to driving accidents, as well as to third parties, such the patients or clients of doctors or lawyers with dementia, let alone airline passengers.[603] The danger comes from symptoms, not from risks, but symptoms can be difficult to spot.[604]

I suggest a two-step approach. First, we should adopt a general prohibition on discrimination by governments, employers, or businesses against people who are demonstrated to be at significantly higher risk than most people of Alzheimer disease. (I would not try to

600. Stephanie A. Kostiuk, *After GINA, NINA? Neuroscience-Based Discrimination in the Workplace*, 65 VAND. L. REV. 933, 970–71 (2012) (calling her proposal a "Neuro Information Nondiscrimination Act." Professor Nita Farahany, a leading law and neuroscience scholar [and acknowledged as the mentor to the author of the paper above], suggested in her February 2012 article, Nita A. Farahany, *Incriminating Thoughts*, 64 STAN. L. REV. 351, 406 (2012), that Congress adopt such legislation. She preferred the name "Neuroscience Information Technology Act," although she did not spell out its acronym).

601. *Id.*

602. *Id.* (explaining one might be able to make a somewhat plausible argument in favor of sex discrimination based largely on the empirical reality [though a reality without a compelling normative basis] of a bigger maternal role in the vital task of childrearing. I don't find that argument persuasive, but it seems to me more plausible than any argument, in a liberal democracy, for race, national origin, or religion discrimination—but not nearly as plausible as the argument for discrimination, in some circumstances, with regard to Alzheimer disease risks).

603. Kostiuk, *supra* note 600, at 976.

604. *Id.*

regulate private actors' actions; attempting to intervene in family decisions about who can write checks or can have the car keys seems to me a step much too far.) *But*, second, to allow (generally) higher levels of monitoring of those people for symptoms of Alzheimer disease. Thus, governments (in their roles as, say, grantors of drivers licenses, professional licenses, security clearances, and so forth) and employers and (most) insurers could not discriminate against people solely because the people were at higher risk of getting Alzheimer disease. That's a class that, considering *APOE* e4 carriers, makes up more than 20 percent of the world's population.[605] But I would allow them to discriminate against high risk people by subjecting them to more serious or more frequent cognitive testing.

This is not an entirely benign resolution. People who are subjected to regular cognitive testing are going to have to spend time doing something that produces anxiety and, in many cases, wastes their time. And they will feel themselves singled out for special negative treatment and potentially stigmatized by those who know they are getting this testing, and hence are at higher risk. One might well want to require that the liability for more frequent testing be kept confidential, though, in a work environment, keeping that kind of thing secret may be difficult. But even if, against the odds, the identities of those subject to this more frequent testing were kept secret, just being required to undergo testing that their fellows were not required to take could be perceived as humiliating, much as cognitive testing requirements for staff privileges for older physicians have caused unhappiness.[606] The response will likely be, as it has been from at least some of those older staff physicians, "Why not test everyone? Those of us who have tested as at higher risk for Alzheimer disease are not the only people who are at higher risk for cognitive or other problems." I know that I, at least, would be deeply angry if singled out for cognitive testing.

There is no deeply satisfying answer to that question. Cognitive or other mental problems can strike anyone, at any age, and with any genotype or set of biomarkers.[607] But the unsatisfying answer is pragmatic. Testing people at higher risk is cheaper—and evokes less resentment—than testing everyone. That answer will not satisfy everyone, and I can well imagine that some cognitively normal people might quit

605. FDA Allows Marketing, *supra* note 591.
606. *Medical Tests*, *supra* note 2.
607. *Id.*

in disgust, thinking that they do not need to deal with this insulting requirement. That would make them unhappy (perhaps) and would deprive the world of their still useful services. But it could also prevent harms to third parties from people who are already suffering from dementia, although usually without knowing it.[608]

Allowing discriminatory testing does raise the issue of acting on the test results.[609] This might be something of a protection for people predicted to be at higher risk for Alzheimer disease. Legislation providing general protection from discrimination along with permission for increased monitoring or testing could set a minimum standard for negative actions against tested people, perhaps expressed in their scores on tests for actual, frank (not just predicted) dementia. And it could also seat minimum standards for the quality of the test being used, good evidence that they had, in fact, been proven to be good tests for potentially dangerous symptoms of dementia. There are no perfect answers to real, human problems, but this compromise—a general ban on discrimination with an allowance of discriminatory testing but with a set requirement in the test results for negative actions—might be a useful approach. It would be, at least, for Alzheimer disease, a somewhat limited NINA.

Such a resolution does require exceptions to some privacy approaches to this kind of information. To be able to implement enhanced testing, employers, licensors, or other relevant authorities would receive information about positive test results, in a way similar to the way the FAA compels the disclosure of pilots' medical conditions. This kind of resolution would have to let the relevant authorities ask for, or demand, information about whether someone had been given a prediction of being at high risk of Alzheimer disease.

This approach—no discrimination except in increased monitoring and testing, where (defined) negative results could lead to negative consequences—might work in most contexts, but not in all. The biggest exception is in long-term care insurance. These insurers, already struggling, do not care whether someone already has symptoms of dementia. They are harmed by the differential purchase of their policies by people who are at undisclosed high risk for Alzheimer disease. So are people who rely on, or hope to rely on, the long-term care insurers as

608. Francis X. Shen, *Aging Judges*, 81 OHIO ST. L. J. 235, 238 (2019), https://ssrn.com/abstract=3490832 (suggesting judges should be provided with confidential cognitive assessments at regular intervals throughout their careers).

609. *Medical Tests*, *supra* note 2.

(partial) solutions to the problems of long-term care, individually or as a society-wide matter. Adverse selection seems likely to be a real problem for them.

It is deeply unclear whether private long-term care insurance will provide any useful help in the coming problem of long-term care financing, but allowing people who know they are at high risk for Alzheimer disease to apply for such insurance without disclosing their high risks will certainly lower the chances that it will be helpful. If we care about maintaining a viable private long-term care insurance industry (to me, a genuinely open question), we probably need to allow that industry to discriminate openly based on Alzheimer disease risk, including rescinding the policies of people who knew but did not disclose that they were at high risk for the disease.

Conclusion

So, after many, many words, where are we left? Alzheimer disease is an enormous problem—for patients, for their families, and for societies—and, barring a medical solution, one that will get larger. Our ability to predict who will get, or not get, Alzheimer disease is also expanding, not so much because people are looking for predictors, but more so because the research on underlying causes or correlates of the disease often lead, as secondary or dual uses, to ways to predict individual fates.

Predictive tests are not entirely benign procedures;[610] they have consequences and some of those are negative, certainly when the tests are inaccurate but also when they are accurate. Predictive tests for Alzheimer disease are not exceptions; they raise many difficult issues for those who might take the tests, for those who might offer them, and for society more broadly. This Article has been an effort to set out some of the facts, their likely consequences, and what we might do about them. I cannot delude myself into thinking that I've identified all the issues with Alzheimer disease predictive testing or analyzed correctly all the issues I have spotted. Neither can I believe that I am the first to think and write on these questions, having benefited from work by Jalayne Arias, Jason Karlawish, Bob Cook-Deegan, and many others. But I do hope this Article is helpful.

610. PERRY KLASS, A NOT ENTIRELY BENIGN PROCEDURE (Putnam: New York 1987). I am stealing that description from the title of a book about being a medical student.

This piece is part of my longer-term plan, to look at prediction in neuroscience more generally. What does it tell us there? I think the answer is, as is almost always the case, that "it depends." Predicting Alzheimer disease, which usually strikes in old age, is going to have different consequences than predicting schizophrenia, which is usually diagnosed in the patient's late teens or twenties. And predicting psychopathy, in adolescents or children, raises still other questions. The world is complicated, and facts are stubborn things;[611] no one answer or set of answers will fit all neuroscience predictions.

But does it even make sense to talk about "neuroscience-based predictions"? SAT scores make predictions, driver's license tests make predictions, diagnostic tests for various diseases make predictions, law school grades (among other things) make predictions. Is neuroscience special?

With full recognition of the likelihood that I am biased by my long involvement in neuroethics, I think the answer is a qualified yes. Neuroscience-based prediction is, somewhat, different for two reasons. First, it is complicated and usually involves methods that are hard to understand and to implement—and hence easy to get wrong. But, second, neuroscience predictions seem (to me at least) different because they involve our brains, our minds, our selves in a deep and special way. Predicting that I am at higher than average risk of being diagnosed with type 2 diabetes (I am, both from my age and from my weight) says something that may have good and bad consequences, but it says something less meaningful, less powerful, less basic than predicting that I am at high risk for Alzheimer disease.

As a matter of science, the Cartesian dualism of mind versus body has been appropriately discarded. As a matter of identity, though, it is hard not to see the mind, and the brain, the organ that immediately creates it, as special, as me in a way my heart, liver, or kidneys are not. That resonance with personal identity does make neuroscience-based predictions different, whether they are about Alzheimer disease, schizophrenia, psychopathy, or any other "mind-linked" condition. The appropriate medical, legal, and social responses will vary from situation to situation, but they will all have some special aspects because of their connection to our brains, our minds, our selves.

611. *Facts Are Stubborn Things*, QUOTE INVESTIGATOR (Jun. 18, 2010), https://quoteinvestigator.com/2010/06/18/facts-stubborn/. Variously attributed to John Adams, Tobias Smollett, Alain René Lesage, and "proverb."

One last point, as a coda. Remember my discussion above of the Robert Heinlein story, *Lifeline*, about Doctor Hugo Pinero, who invented the "how long will you live" device? At the end of the story he is killed by thugs hired by life insurance companies because the companies had seen the adverse selection threat his invention posed. When his body was found, the investigators found, in his coat pocket, a slip of paper with the date and time of his own death on it. Prediction did not help him. Let us hope that we can make the almost certainly coming surge of Alzheimer disease prediction work better for us all.