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BLACK-BOX MEDICINE

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I. INTRODUCTION

Personalized medicine, where Big Data meets Big Health, has been hailed as the next leap forward in health care, most recently in President Obama's 2015 State of the Union address.[1] It is already developing and spreading rapidly; doctors are using increasing amounts of personal information, including genetic diagnostic tests, to tailor treatments to individual patients.[2] Humans and diseases are inherently variable in many dimensions, genomic and otherwise; as a result, 38% of patients with depression, 40% with asthma, and 75% with cancer fail to respond to treatment, belying the efficacy of a one-size-fits-all model of medicine.[3] When medical science can determine what predicts *which* fraction of patients will respond to a particular treatment, that treatment can then be matched to the right patients. Personalized medicine — this tailoring of treatment — can save and extend lives by suggesting more effective treatments, and it can diminish the tremendous cost and risk of unnecessary medical interventions.[4] In addition to aiding patient care, personalized medicine can speed up and

1. *See* Francis S. Collins & Harold Varmus, *A New Initiative on Precision Medicine*, 372 N. ENGL. J. MED. 793, 793–95 (2015) (describing President Obama's "Precision Medicine Initiative"). Big Data here refers to the enterprise of using big data — that is, large datasets — to find new information and patterns in various fields. *See* VIKTOR MAYER-SCHÖNBERGER & KENNETH CUKIER, BIG DATA: A REVOLUTION THAT WILL TRANSFORM HOW WE LIVE, WORK, AND THINK (2013). For descriptions of personalized medicine in the medical literature, see Edward Abrahams & Mike Silver, *The Case for Personalized Medicine*, 3 J. DIABETES SCI. & TECH. 680 (2009); Wylie Burke & Bruce M. Psaty, *Personalized Medicine in the Era of Genomics*, 298 J. AM. MED. ASS'N 1682 (2007); Isaac S. Chan & Geoffrey S. Ginsburg, *Personalized Medicine: Progress and Promise*, 12 ANN. REV. GENOMICS & HUM. GENETICS 217 (2011); Geoffrey S. Ginsburg & Jeanette J. McCarthy, *Personalized Medicine: Revolutionizing Drug Discovery and Patient Care*, 19 TRENDS BIOTECH. 491 (2001); and Margaret A. Hamburg & Francis S. Collins, *The Path to Personalized Medicine*, 363 NEW ENG. J. MED. 301 (2010).

2. *See* Chan & Ginsburg, *supra* note 1, at 218.

3. *See* Brian B. Spear et al., *Clinical Application of Pharmacogenetics*, 7 TRENDS MOLECULAR MED. 201, 201–02 (2001).

4. *Id.* at 201.

streamline the process of drug discovery and clinical trials by identifying which patients a developing drug is most likely to help.[5]

But the version of personalized medicine being implemented today — what I dub "explicit personalized medicine" — is just an entry point into the realm of what huge amounts of data can tell us about our health and how to improve it. Current versions of personalized medicine (and of health care in general) frequently rely on what we can explicitly understand: relatively simple relationships that can be identified and validated in clinical trials that group large numbers of patients for statistical power. But biology is complicated; many important relationships are not one-to-one, two-to-one, or even several-to-one correspondences, but are instead networks among dozens of interacting variables, including those which are readily observable (e.g., age, weight, or sex) and those that are not (e.g., genomic markers or metabolite levels).[6]

This Article introduces into legal scholarship the concept of black-box medicine, which I define as the use of opaque computational models to make decisions related to health care. Black-box medicine, pursued by geneticists, personalized medicine advocates, and other health care innovators, already does and increasingly will use the combination of large-scale high-quality datasets with sophisticated predictive algorithms to identify and use implicit, complex connections between multiple patient characteristics.[7] A defining feature of black-box medicine is that those algorithms are non-transparent — that is, the relationships they capture cannot be explicitly understood, and sometimes cannot even be explicitly stated. Note that this type of medicine is "black-box" to everyone by nature of its development; it is not "black-box" because its workings are deliberately hidden from view.[8] By capturing complex underlying biological relationships —

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5. Lawrence J. Lesko et al., *Pharmacogenetics and Pharmacogenomics in Drug Development and Regulatory Decision Making: Report of the First FDA-PWG-PhRMA-DruSafe Workshop*, 43 J. CLINICAL PHARMACOLOGY 342, 349 (2003).

6. For instance, one recent technique used genetic sequence data from 5000 genes to classify two different types of lung tumor with very high accuracy; the two types of tumor respond best to different therapies. Hojin Moon et al., *Ensemble Methods for Classification of Patients for Personalized Medicine with High-Dimensional Data*, 41 ARTIFICIAL INTELLIGENCE MED. 197, 198, 203–04 (2007). The same team's efforts to predict distant metastasis of breast cancer tumors were less successful. *Id.* at 204–05.

7. Amarasingham and colleagues describe one form of black-box medicine, "predictive analytics," involving the use of real-time large datasets and predictive algorithms to help inform treatment decisions, such as who should be sent first to intensive care units. *See* Ruben Amarasingham et al., *Implementing Electronic Health Care Predictive Analytics: Considerations and Challenges*, 33 HEALTH AFF. 1148, 1148 (2014). Other forms of black-box medicine, described below, relate to the choice of which drugs to give to patients, or complex interacting constellations of disease risk factors. *See infra* Part II.A.3.

8. For an extensive treatment of algorithms that are deliberately hidden from view, see FRANK PASQUALE, THE BLACK BOX SOCIETY (2015). Such deliberately obscure algorithms are also used in personalized medicine by, for example, Assurex Health, but are not the subject of this Article.

and by potentially allowing their use with algorithmic validation rather than relying on clinical trials[9] — black-box medicine opens far more possibilities for shaping treatment and drug development. Although black-box medicine presents major challenges at conceptual, scientific, and legal levels, it also offers a faster path to medical advances that might otherwise lie many decades in the future.

Costs and hurdles exist at each phase of black-box medicine's development. First, information must be gathered and vetted, which requires financial resources and navigating legal requirements, including privacy and informed consent.[10] Second, reliable and sensitive algorithms must be developed, which requires dedicated effort by sophisticated programmers.[11] Third, since complex implicit predictions are much less amenable to the forms of validation on which we traditionally rely — scientific understanding, clinical trials, and post-market surveillance — other forms of validation must be developed by the innovating firm, regulators, and/or third parties.[12]

In addition to practical hurdles, black-box medicine raises policy concerns outside the realm of science and medicine. The first and most immediate concern is that development will require significant incentives beyond — or differently structured from — those offered by the market. Black-box medicine recapitulates the classic intellectual property story in which firms underinvest in non-excludable information goods because they cannot fully appropriate their value.[13] Black-box medicine relies principally on pure information goods: collected data, patterns discovered within that data, and validation of those patterns. Intellectual property allows firms to exclude others from the information good and therefore appropriate a higher portion — though not all — of the social welfare surplus created by innovation. However, the current intellectual property regime not only provides inadequate incentives for black-box medicine, the incentives it does provide push the field in counterproductive directions.

Patents, the primary intellectual property driver of technological innovation, are a poor fit for black-box medicine. Patents are static where black-box medicine is dynamic, are slow to issue where black-

9. Bypassing clinical trials in at least some instances is not as dramatic as it sounds. Current practices in off-label drug use (uses for a drug not currently approved by the FDA) frequently involve treatment based on correlations, connections, and hypotheses without the backstop of well-controlled clinical trials.

10. *See infra* Part III.A.

11. *See infra* Part III.B.

12. *See infra* Part III.C.

13. *See, e.g.*, Kenneth J. Arrow, *Economic Welfare and the Allocation of Resources for Invention*, *in* THE RATE AND DIRECTION OF INVENTIVE ACTIVITY: ECONOMIC & SOCIAL FACTORS 609, 619 (Univs.-Nat'l Bureau Comm. for Econ. Research ed., 1962) *available at* http://www.nber.org/chapters/c2144 ("To sum up, we expect a free enterprise economy to underinvest in invention and research (as compared with an ideal) because it is risky, because the product can be appropriated only to a limited extent, and because of increasing returns in use.").

box medicine evolves rapidly, and demand full and precise disclosure where black-box medicine is inherently incapable of being fully disclosed.[14] In addition to basic and longstanding structural concerns, which might at least be addressable, the Supreme Court has recently and sharply limited the categorical availability of patents for diagnostic methods and algorithms.[15]

Trade secrecy provides a parallel incentive for black-box medicine development, but comes with its own complications. On the one hand, exclusivity based on trade secrecy fits well with algorithms that are inherently difficult or impossible to disclose. On the other hand, trade secrecy creates problems for cumulative innovation, especially with respect to datasets, and provides little to no incentive for efforts to validate the accuracy of an algorithm. Accordingly, better-tailored incentives, set for each stage of development, are needed to drive black-box medicine forward.

A second major policy concern for black-box medicine involves privacy. The assembly of the datasets of health information needed to develop black-box medicine raises tremendous privacy concerns. Not only is inadvertent information release a possibility, but developing algorithms for black-box medicine would require that datasets be more than minimally available. Ideally, to fulfill an infrastructure role, datasets would be widely or publically available. Anonymization can address some concerns, but with increasing amounts of health data stored in a single record, even anonymized data can frequently be linked to known persons. Black-box medicine development and deployment must also comply with the detailed requirements of the Privacy Rule of the Health Insurance Portability and Accountability Act ("HIPAA").[16]

Regulation is a third key policy concern of black-box medicine. Although the U.S. Food and Drug Administration ("FDA") has long exercised enforcement discretion with respect to the type of laboratory-developed tests that could make up much of black-box medicine, the agency has recently changed its stance, and intends to regulate such complex tests fully.[17] The contours of FDA regulation — what sort of evidence will be required, how long the process will take, and crucially, whether clinical trials will be needed — will have a tremendous impact on the shape of black-box medicine. The FDA also has the ability to facilitate the development of black-box medicine, for instance, by providing a stamp of approval — whether traditional formal approval as a medical device or through a novel adaptive certi-

14. *See infra* Part IV.A.1.

15. *E.g.*, Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. ___, 132 S. Ct. 1289, 1294 (2012); *see infra* notes 116–119 and accompanying text.

16. Health Insurance Portability and Accountability Act of 1996, Pub. L. No. 104-191, 110 Stat. 1936 (codified as amended in scattered sections of the U.S.C.).

17. *See infra* Part IV.C.

fication procedure[18] — to allay concerns about new technologies or by certifying third parties to validate black-box algorithms.

Fourth and finally, at least for the purposes of this Article, policy surrounding black-box medicine must consider the challenges of commercialization. Adoption and potential insurance reimbursement of black-box medicine has implications for cost savings, treatment efficacy, and the equitable distribution of black-box medicine. Black-box medicine will likely face real difficulties in entering common medical practice, a concern closely tied with the market-entry and validation procedures adopted by the FDA. Engagement from public health care payers has the potential to help solve this problem, both by leading the way for private insurers and by helping to demonstrate the efficacy of specific algorithms.

This Article proceeds in three Parts. Part II describes personalized medicine and the differences between the current state of explicit personalized medicine and black-box medicine. Part III lays out the hurdles to the development of black-box medicine. Part IV discusses in brief the policy concerns of black-box medicine, addressing potential problems and suggesting policy interventions.

II. A NEW CONCEPTION OF PERSONALIZED MEDICINE

Personalized medicine represents a tremendous step forward for modern medicine. Doctors are already using increasing amounts of personal data, especially diagnostic genetic tests, to tailor treatments to the individual patient. These variations in treatment reflect the variation inherent among humans, and the connection between patient variability and a change in treatment is carefully examined, tested, and clinically validated. Personalized medicine has the potential to save and extend lives, to avoid unnecessary treatment, and to hasten and streamline the process of drug discovery, but can only use a limited set of relationships. With big data, we can use far more relationships than the current version of personalized medicine. This Part describes the next phase of personalized medicine, which has received significant attention among genomic researchers[19] and health technology companies,[20] but has gone largely unnoticed by legal scholars.

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18. *See infra* Part IV.C.3.

19. *See generally, e.g.*, Amarasingham et al., *supra* note 7; Jesse Davis et al., Machine Learning for Personalized Medicine: Will This Drug Give Me a Heart Attack? (2008) (unpublished manuscript) (discussing preliminary work), http://www.ualberta.ca/~szepesva/ICML2008Health/Davis.pdf; Xiaoqian Jiang et al., *Calibrating Predictive Model Estimates to Support Personalized Medicine*, 19 J. AM. MED. INFORMATICS ASS'N 263 (2012); and Moon et al., *supra* note 6.

20. Companies working in this field include Enlitic, www.enlitic.com; Englue, www.englue.com; Knome, www.knome.com; Foundation Medicine, www.foundationmedicine.com; and 23andMe, www.23andme.com; and Illumina, www.illumina.com.

A. Revolution in Personalized Medicine

Before turning to what is coming next, it is important to know the current state of the art. This Section describes the current version of personalized medicine — itself still developing and having a major impact on health care — and then addresses the changes coming in the shift to black-box medicine. It describes in turn three related ideas: (1) Personalized medicine, the most general idea, refers to the tailoring of treatment based on the differing characteristics of individual patients,[21] (2) Explicit personalized medicine, a subset of personalized medicine, refers to tailoring that is based on scientifically identified and understood relationships,[22] and (3) Black-box medicine, a newly developing subset of personalized medicine, refers to tailoring based on relationships which are *not* understood and often not identified, relying instead on opaque computational algorithms.[23]

1. What Is Personalized Medicine?

While doctor-patient relationships have historically focused on the patient, and in that sense have long been personal, new advances in medical science under the name of personalized medicine have been heralded as revolutionary.[24] Although there are many slightly varying definitions of personalized medicine, the heart of it is this: All patients are different, and treatment can and should be tailored to the individual patient to the extent possible. This Article adopts this broad definition of personalized medicine, though other definitions exist with contested and more specific meanings.[25]

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21. *See infra* Part II.A.1.

22. *See infra* Part II.A.2.

23. *See infra* Part II.A.3.

24. *See generally* A. Jamie Cuticchia, *Existing Ethical Principles and Their Application to Personal Medicine*, 2 OPEN ETHICS J. 29 (2008) (discussing the revolutionary expansion of pharmacogenomics after completion of the Human Genome Project); James P. Evans et al., *Preparing for a Consumer-Driven Genomic Age*, 363 NEW ENG. J. MED. 1099 (2010) (discussing personalized health care in the direct-to-consumer genetic testing context); Eric D. Green et al., *Charting a Course for Genomic Medicine from Base Pairs to Bedside*, 470 NATURE 204 (2011) (discussing a vision for moving toward an era of genomic medicine); Hamburg & Collins, *supra* note 1 (discussing the hurdles in moving from concept to clinical use); FEINSTEIN KEAN HEALTHCARE & MIKE SILVER, PERSONALIZED MED. COAL., THE CASE FOR PERSONALIZED MEDICINE (2009), *available at* http://cllcanada.ca/2010/pdfs/TheCaseforPersonalizedMedicine_5_5_09.pdf (discussing the benefits of personalized medicine and the necessary steps for widespread implementation).

25. The President's Council of Advisors on Science and Technology defines personalized medicine most closely to the broad version used here: "tailoring of medical treatment to the individual characteristics of each patient." PRESIDENT'S COUNCIL OF ADVISORS ON SCI. & TECH., PRIORITIES FOR PERSONALIZED MEDICINE 1 (2008) [hereinafter PRIORITIES FOR PERSONALIZED MEDICINE]. The FDA defines personalized medicine more narrowly as getting obtaining "the best medical outcomes by choosing treatments that work well with a person's genomic profile, or with certain characteristics in the person's blood proteins or cell surface proteins," Michelle Meadows, *Genomics and Personalized Medicine*, 39 FDA

Personalized medicine contrasts with a model of medicine based on traditional clinical trials. Requiring clinical trials to demonstrate drug efficacy has led to tremendous advances, identifying which drugs and treatments work, which do not, and which are better than others. However, clinical trials are typically designed to be broadly applicable across populations, so drugs are similarly approved broadly, not for subpopulations.[26] This approach develops strong scientific evidence of average treatment efficacy, but misses much of the variation among patients.[27]

Personalized medicine aims to remedy this problem by identifying scientific links between biological patient characteristics, diagnoses, and treatment options. It aims to allow physicians and patients to better choose treatment options in light of this. The analysis provides the ability to "classify individuals into subpopulations that differ in

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CONSUMER MAG., Nov.–Dec. 2005, http://permanent.access.gpo.gov/lps1609/www.fda.gov/fdac/features/2005/605_genomics.html; and the National Institutes of Health ("NIH") more narrowly still as "an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease." U.S. Nat'l Library of Med., Nat'l Inst. of Health, Glossary, *Glossary Definition of Personalized Medicine*, GENETICS HOME REFERENCE (May 4, 2015), http://ghr.nlm.nih.gov/glossary=personalizedmedicine. For a criticism of equating personalized medicine with genomic medicine, see Leigh Ann Simmons et al., *Personalized Medicine Is More than Genomic Medicine: Confusion over Terminology Impedes Progress Towards Personalized Healthcare*, 9 PERSONALIZED MED. 85, 85–86 (2012).

26. The majority of clinical trials have historically been conducted on undifferentiated patient bases, and most drugs are approved for broad use. *See* Mahvash Hussain-Gambles et al., *Why Ethnic Minority Groups Are Under-Represented in Clinical Trials: A Review of the Literature*, 12 HEALTH & SOCIAL CARE COMMUNITY 382, 382 (2004). This picture is changing; clinical trial guidelines have shifted to address these concerns and acknowledg the limitations of one-size-fits-all clinical trials. *NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*, NAT'L INSTS. HEALTH, http://grants1.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm (last updated Oct. 1, 2001) ("[W]omen and members of minority groups and their subpopulations must be included in all NIH-funded clinical research, unless a clear and compelling rationale and justification establishes . . . that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research."); *see also* National Institutes of Health Revitalization Act of 1993, Pub. L. No. 103-43, § 492 B(a)(1), 107 Stat. 122, 133–35 (1993). These efforts have met with only moderate success; a 2011 FDA study found that many clinical study populations had over 90% of patients that self-identified as white. FDA, COLLECTION, ANALYSIS, AND AVAILABILITY OF DEMOGRAPHIC SUBGROUP DATA FOR FDA-APPROVED MEDICAL PRODUCTS 20 tbl.1-3 (2013), *available at* http://www.fda.gov/downloads/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdasia/ucm365544.pdf. Population differentiation sometimes occurs; the combination drug BiDil, for instance, was approved by the FDA in 2005 to treat congestive heart failure in black patients, Press Release, Food & Drug Admin., FDA Approves BiDil Heart Failure Drug for Black Patients (June 23, 2005), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108445.htm, though that decision has generated its own controversy. *See, e.g.*, Howard Brody & Linda M. Hunt, *BiDil: Assessing a Race-Based Pharmaceutical*, 4 ANNALS FAM. MED. 556, 557–59 (2006); Susan M. Wolf, *Debating the Use of Racial and Ethnic Categories in Research*, 34 J.L. MED. & ETHICS 483, 484–86 (2006).

27. *See* P. M. Rothwell, *Can Overall Results of Clinical Trials Be Applied to All Patients?*, 345 LANCET 1616, 1617–18 (1995).

their susceptibility to a particular disease or their response to a specific treatment."[28]

Personalized medicine offers substantial benefits. It can lower costs and improve the efficiency of the healthcare system,[29] allowing doctors to provide better diagnoses and more effective treatments.[30] In addition, the pharmaceutical and biotechnology industries can focus drug development efforts on subpopulations who have the same critical genetic variants.[31] A treatment paradigm that acknowledges the variants' role in treatment and disease (although the molecular pathways need not be fully understood) should lead to better health outcomes, compared to treating all patients with the same disease in the same way.[32]

2. Explicit Personalized Medicine

The form of personalized medicine described briefly above is the standard model. However, to differentiate this current form from what is on the horizon — and what is described below — I call it "explicit personalized medicine." Explicit personalized medicine relies on scientific and clinical research to identify and explain relatively simple biological relationships between measurable characteristics of an individual patient and likely medical outcomes for that patient. "Explicit" refers to the fact that these relationships are explicitly identified and validated; that is, we know why treatment is tailored in a specific way for a specific individual.

Explicit personalized medicine uses relationships between several types of biomarkers and medical responses to determine diagnoses and treatment plans.[33] Frequently, these biomarkers are genomic variations, and genetic diagnostic tests are correspondingly the most explored version of explicit personalized medicine. However, other sets of biomarkers — different "-omics" — are also used in explicit personalized medicine, including measurements of RNA transcription levels (transcriptomics), the presence and level of various proteins (proteomics), levels of non-protein small metabolic molecules (metabolomics), and the presence of DNA modifications that affect gene expression levels (epigenomics).[34] These and other biomarkers

28. PRIORITIES FOR PERSONALIZED MEDICINE, *supra* note 25, at 1.

29. Personalized medicine offers the chance to reduce care costs by avoiding wasted treatments, avoiding adverse reactions, and improving health status more quickly. In addition, personalized medicine's stratification of patients can reduce the "size, duration, and cost" of clinical trials. *Id.*

30. *Id.*

31. *See* Ginsburg & McCarthy, *supra* note 1, at 494.

32. *Id.* at 495.

33. *See, e.g.*, Chan & Ginsburg, *supra* note 1, at 219–20.

34. *Id.* at 222–24.

can also help direct treatments of patients or improve the drug development process.

Explicit personalized medicine is already used to calibrate treatment options. One prominent example is the anticoagulant drug warfarin, which can lead to heavy bleeding if used at an improper dosage. Some patients metabolize the drug faster, and some slower; an average dose may cause overdose in a slow-metabolizer, while the same amount may be ineffective in a fast-metabolizer.[35] Earlier dosing regimens relied on trial and error combined with some easily measurable patient characteristics such as age, weight, and sex. Recently, however, researchers discovered that two proteins are particularly relevant in warfarin metabolism: the cytochrome P450 enzyme CYP2C9, which metabolizes warfarin, and the vitamin K epoxide reductase gene VKORC1.[36] These proteins come in different forms, which work less or more efficiently, and genetic tests can determine which version a particular patient has. Now, warfarin dosing can be determined after genetic testing, with more accurate results than the prior regime.[37] Warfarin is just one example; similar tests can improve drug response and reduce side effects in schizophrenia patients.[38]

Diagnostic testing can identify not only patient characteristics but also the nature of a disease itself. In oncology, genetic tests can determine the specific variant of a cancer and consequently, how best to attack it.[39] The monoclonal antibody Herceptin (trastuzumab) exemplifies this approach: Some breast cancer patients who overexpress the

35. U. I. Schwarz, *Clinical Relevance of Genetic Polymorphisms in the Human CYP2C9 Gene*, 33 EUR. J. CLINICAL INVESTIGATION 23, 28 (2003).

36. Chan & Ginsburg, *supra* note 1, at 227.

37. *Id.* at 220, 227. The information used to provide warfarin dosing information is collected at www.warfarindosing.org. According to the website, the calculator uses "clinical factors and (when available) genotypes of two genes: cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase (VKORC1)." WARFARIN DOSING, http://www.warfarindosing.org (last visited May 9, 2015) (emphasis omitted). Recommendations are based on data from a cohort of over 1000 patients, and the information used for the calculator can explain 53% of the variation in response to warfarin doses. *Id.* For clinical trials evaluating the efficacy of using genotype to guide warfarin dosing over standard protocols, see generally, for example, Jeffrey L. Anderson et al., *Randomized Trial of Genotype-Guided Versus Standard Warfarin Dosing in Patients Initiating Oral Anticoagulation*, 116 CIRCULATION 2563 (2007); Y. Caraco, S. Blotnick & M. Muszkat, CYP2C9 *Genotype-Guided Warfarin Prescribing Enhances the Efficacy and Safety of Anticoagulation: A Prospective Randomized Controlled Study*, 83 CLINICAL PHARMACOLOGY & THERAPEUTICS 460 (2008); and P. A. Lenzini et al., *Laboratory and Clinical Outcomes of Pharmacogenetic vs. Clinical Protocols for Warfarin Initiation in Orthopedic Patients*, 6 J. THROMBOSIS & HAEMOSTASIS 1655 (2008).

38. Sven Cichon et al., *Pharmacogenetics of Schizophrenia*, 97 AM. J. MED. GENETICS 98, 98–99 (2000) (describing relevant variants of genes encoding cytochrome P450 enzymes CYP2D6, CYP2C19, and CYP2C9).

39. *See* John C. Mansour & Roderich E. Schwarz, *Molecular Mechanisms for Individualized Cancer Care*, 207 J. AM. C. SURGEONS 250, 250–54 (2008).

HER2/neu receptor can usefully be treated with Herceptin,[40] while in other breast cancer patients, the side effects of the drug outweigh any benefits.[41]

Explicit personalized medicine also offers promising improvements to conducting clinical trials leading to drug approval. If only certain genetically identified participants in smaller Phase I or Phase II clinical trials respond to an investigational drug, larger and more expensive Phase III trials can focus on individuals with that genotype.[42] This approach can potentially lower the expense of the trial and generate a more focused indication and label much earlier in the process.[43]

Explicit personalized medicine offers significant potential to improve treatment and the development of new drugs. But because explicit personalized medicine relies on scientific research and clinical trials to identify and validate relationships, it is limited to the relatively simple relationships that are amenable to these approaches. Unfortunately, this leaves untapped many complex — but still important — biological relationships. Those complex relationships, however, may be exploited even without explicit identification. Black-box medicine combines large datasets and sophisticated algorithms to make predictions and improve treatments, without explaining or even identifying the underlying complex relationships.

3. Implicit Personalized Medicine: Black-Box Medicine

Black-box medicine is the next stage of personalized medicine.[44] It differs from explicit personalized medicine in three principal ways. First, the information used to develop the relationships and predictions used in treatment recommendations comes from a much larger, broader set of information.[45] Second, a large, rich dataset and machine learning techniques enable many predictions based on complex con-

40. Walter P. Carney, *HER2/neu Status Is an Important Biomarker in Guiding Personalized HER2/neu Therapy*, 9 CONNECTION 25, 27 (2006).

41. Melinda L. Telli et al., *Trastuzumab-Related Cardiotoxicity: Calling into Question the Concept of Reversibility*, 25 J. CLINICAL ONCOLOGY 3525, 3531 (2007).

42. Ginsburg & McCarthy, *supra* note 1, at 492. Phase I and II clinical trials can also potentially be targeted to identified subpopulations, though that requires knowing beforehand which populations are likely to be most responsive. *See* FDA, U.S. DEP'T HEALTH & HUM. SERVS., GUIDANCE FOR INDUSTRY: CLINICAL PHARMACOGENOMICS: PREMARKET EVALUATION IN EARLY-PHASE CLINICAL STUDIES AND RECOMMENDATIONS FOR LABELING 13–19 (Jan. 2013), *available at* http://www.fda.gov/downloads/drugs/guidancecompliance regulatoryinformation/guidances/ucm337169.pdf [hereinafter GUIDANCE FOR INDUSTRY].

43. Ginsburg & McCarthy, *supra* note 1, at 493. The FDA has issued guidance on the use of pharmacogenomic data in the context of clinical trial development, and trials increasingly include such data. GUIDANCE FOR INDUSTRY, *supra* note 42, at 13–19.

44. *See, e.g.*, Amarasingham et al., *supra* note 7, at 1153; I. Glenn Cohen et al., *The Legal and Ethical Concerns that Arise from Using Complex Predictive Analytics in Health Care*, 33 HEALTH AFF. 1139, 1140–41 (2014); Jiang et al., *supra* note 19, at 263.

45. *See infra* Part II.A.3.a.

nections between patient characteristics and expected treatment results without explicitly identifying or understanding those connections.[46] For example, as opposed to the relatively simple links described above, a black-box medicine prediction might be that patients who have a set of linked variations in a dozen different genes, smoke, and have middling-high blood pressure might predictably respond better to one medication than another — even if those factors could not be explained or even explicitly identified.[47] Third, and discussed in more detail below, the relationships used are generally not susceptible to confirmation through clinical trials. This means that different methods of validation will be needed, but also that the costly and time-consuming process of clinical trials may be avoided.[48]

a. Big Data

Far more health data is collected today than ever before, and that collection continues to increase rapidly. Data is collected for several reasons, including improving patient care, documenting care to ward off malpractice threats, increasing the efficiency of care, and keeping records to support insurance and payment claims.

The tremendous growth of recorded data has been facilitated by the gradual transition to electronic health records ("EHRs"), which store health data in electronic form rather than on paper charts.[49]

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46. *See infra* Part II.A.3.b.

47. In some sense, black-box medicine seems to be a throwback to traditional reliance on the experience and intuition of doctors: "I've tried this on patients like you before and it's worked, so that's what I'll recommend for you." Inasmuch as both this model and black-box medicine rely on implicit links, the analogy is apt. However, black-box medicine relies on far broader sets of information in making connections, and will involve quantitative validation of those models in a fashion atypical of physician experience or intuition-based treatment.

48. *See infra* Part III.C.

49. The terms electronic medical record ("EMR") and electronic patient record ("EPR") are also used, frequently interchangeably. The differences between them, such as they are, are largely not important for this Article. The growth in EHRs is attributable to several factors, a system of penalties and incentives as part of the Health Information for Economic and Clinical Health (HITECH) Act, enacted as Title XIII of Division A and Title IV of Division B of the American Recovery and Reinvestment Act of 2009, Pub. L. No. 111-5, §§ 13001–13424, 123 Stat. 115, 226–79 (codified as amended in scattered sections of the U.S. Code), and other potential cost savings. *See* Dwight C. Evans et al., *Effect of the Implementation of an Enterprise-Wide Electronic Health Record on Productivity in the Veterans Health Administration*, 1 HEALTH ECON. POL'Y & L. 163, 168–69 (2006); Richard Hillestad et al., *Can Electronic Medical Record Systems Transform Health Care? Potential Health Benefits, Savings, and Costs*, 24 HEALTH AFF. 1103, 1103–04 (2005). Improved patient care — another motivation for adopting EHRs, see Jeffrey A. Linder et al., *Electronic Health Record Use and the Quality of Ambulatory Care in the United States*, 167 ARCHIVES INTERNAL MED. 1400, 1400 (2007) — has received mixed reviews, with some finding no substantial improvement, see Ashly D. Black et al., *The Impact of eHealth on the Quality and Safety of Health Care: A Systematic Overview*, 8 PUB. LIBR. OF SCI. MED. 1, 12 (Jan. 18, 2011), http://www.plosmedicine.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pmed.1000387&representation=PDF; Max J. Romano & Randall S. Staf-

EHRs not only have capacity to record more data, they are also more readily accessible and can be combined into larger databases more easily than scattered paper patient records.

The types and volume of data collected and included in EHRs are also ballooning. Genetic testing for single-nucleotide polymorphisms, which measures some genetic variation, is now inexpensive,[50] and whole-genome sequencing continues to drop in price and to approach widespread clinical use.[51] Other "-omics" technologies, such as the testing of large panels of metabolites, gene expression levels, and protein levels, are similarly becoming more accessible.[52] Each new type of patient measurement creates large amounts of data that can be captured in EHRs and linked to patient health outcomes.

All of this data can be used to understand and improve the practice of medicine (after overcoming substantial hurdles, discussed below[53]). Indeed, providers and health care firms already use this data to improve efficiency and patient outcomes.[54] But beyond the relatively simple links that can be explicitly labeled and understood,[55] many complex relationships are impossible to observe or use without a different set of algorithmic tools.

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ford, *Electronic Health Records and Clinical Decision Support Systems: Impact on National Ambulatory Care Quality*, 171 ARCHIVES INTERNAL MED. 897, 897 (2011); and others observing some improvement, see Randall D. Cebul et al., *Electronic Health Records and Quality of Diabetes Care*, 365 NEW ENG. J. MED. 825, 830 (2011).

50. David B. Agus, *The Outrageous Cost of a Gene Test*, N.Y. TIMES, (May 20, 2013), http://www.nytimes.com/2013/05/21/opinion/the-outrageous-cost-of-a-gene-test.html (describing the high cost of the BRCA1/2 test as a patent-based outlier and noting the low costs of most other genetic tests).

51. Stories of imminent whole-genome sequencing for under $1000 have existed for years without fruition. *See* Simon T. Bennett et al., *Toward the $1000 Human Genome*, 6 PHARMACOGENOMICS 373, 375, 381 (2005); Erika Check Hayden, *Is the $1,000 Genome for Real?*, NATURE (Jan. 15, 2014), http://www.nature.com/news/is-the-1-000-genome-for-real-1.14530; John A. Robertson, *The $1000 Genome: Ethical and Legal Issues in Whole Genome Sequencing of Individuals*, 3 AM. J. BIOETHICS 35, 35 (2003). However, the costs have been dropping at a rapid rate. *See* Kris Wetterstrand, *DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP)*, NIH: NAT'L HUM. GENOME RES. INST., www.genome.gov/sequencingcosts (last updated Oct. 31, 2014). Quality concerns also exist; as of 2014, using whole-genome sequencing as a common clinical tool, one must cope with high false-negative rates. *See generally* Frederick E. Dewey et al., *Clinical Interpretation and Implications of Whole-Genome Sequencing*, 311 J. AM. MED. ASS'N 1035 (2014).

52. Chan & Ginsburg, *supra* note 1, at 233–34.

53. *See infra* Part III.

54. *See infra* Part II.B.

55. This is not to denigrate explicit modeling, or to understate the tremendous effort needed to develop those models, the knowledge benefit that comes from developing them, or their potential benefits for patients and the health care system. I intend rather to point to a different form of analysis, which opens many additional possibilities.

b. Black-Box Algorithms

To discover new complex relationships, black-box medicine relies on computer systems that improve their performance over time by trying a certain solution, evaluating the outcome, and then modifying that solution accordingly to improve future outcomes.[56] For familiar examples to illustrate the novel features of this approach, consider the music service Pandora and the video service Netflix, both of which make recommendations to their users.

Pandora relies on a technique called content-based filtering that is simpler and resembles the current practice of personalized medicine.[57] This technique uses discrete characteristics about an object and knowledge about the user's relationship to those characteristics to make recommendations. In the music service Pandora, experts characterize songs based on a set of explicit criteria, such as major versus minor key or the presence of vocals.[58] When a customer selects a song, Pandora identifies the traits of that song and suggests other songs that share those traits.[59] In the medical context, content-based filtering closely tracks the explicit science-based paradigm of modern medicine. If a patient presents with fever and cough and tests positive for strep throat, a doctor would likely prescribe an antibiotic to treat the likely strep infection. Content-based filtering requires a relatively small set of information — in this case, a positive test for strep might be enough — but can only make recommendations based on already known explicit links to that information.

Netflix, on the other hand, uses a technique called collaborative filtering, which is more complex and more closely resembles black-box medicine. Collaborative filtering uses information groups of similar users to construct an underlying predictive model and makes recommendations based on that model. Using this approach, Netflix predicts which movies a user might like based on a customer's ratings of watched movies and by comparing that set of data to similar data from other customers. This allows predictions without any explicit knowledge; for instance, it might be true that the vast majority of people who liked *Notting Hill*, *Casino Royale*, and the television show *Dr. Who* turn out to like the cult foodie film *Tampopo*. Someone who likes the first three would be offered *Tampopo* as a recommendation,

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56. *See generally* Davis et al., *supra* note 19. This approach is frequently referred to as "machine learning." *Id.* For a general overview of the field, see PETER FLACH, MACHINE LEARNING: THE ART AND SCIENCE OF ALGORITHMS THAT MAKE SENSE OF DATA (2012).

57. *See generally* Pasquale Lops et al., *Content-Based Recommender Systems: State of the Art and Trends*, *in* RECOMMENDER SYSTEMS HANDBOOK 73 (F. Ricci et al. eds., 2011).

58. *About the Music Genome Project*, PANDORA, http://www.pandora.com/about/mgp (last visited May 9, 2015).

59. *See* Rob Walker, *The Song Decoders*, N.Y. TIMES, (Oct. 14, 2009), http://www.nytimes.com/2009/10/18/magazine/18Pandora-t.html.

despite the lack of any clear or identified link. In the medical context, data might reveal, for example, that male patients diagnosed with schizophrenia, who have several specific genetic markers and are between the ages of twenty-two and twenty-seven, might respond significantly better to cognitive behavioral therapy when combined with low doses of caffeine. Why? The model couldn't tell us — though it might suggest that research into the mechanism might eventually be of interest — but it could suggest treatment contours in a way previously unavailable.[60] This lack of transparency is the "black-box" of black-box medicine.

The opacity of black-box medicine can come in roughly two forms: literal and practical. First, more literal opacity exists when the relationships are totally hidden, even though the machine learning process is known. A human analogy may make this clearer: Consider a radiologist with decades of experience interpreting magnetic resonance images ("MRIs"). Given an MRI, the radiologist may be able to look at an ambiguous shadow and say whether it reflects an artifact of the image, something benign, or a potentially dangerous tumor; at the same time, she may be unable to articulate the internal algorithm she uses to make that determination. Her experience has taught her to recognize a set of true underlying relationships between an image and the implicit biology, but those relationships cannot be explicitly stated.[61] Machine learning techniques can have the same sort of opacity. Artificial neural networks, for instance, involve "hidden layers" of computational facsimiles of human neurons; the network trains on a set of observations, learns to classify observations, and then is considered fully "trained."[62] Once trained, the network can take an observation

60. It is worth noting that informal versions of comparison-based recommendations are currently in use, though they are not typically well-regarded under the modern medical paradigm. Sites such as patientslikeme.com, where patients describe symptoms and successful treatments, essentially show collaborative filtering in action. These sites frequently present these treatments without any specific scientific basis for the treatment choice or its success, or quantitative or algorithmic analysis, and generally with much less data. Also note that purely retrospective data analyses come with a significant set of issues, including the possibilities of overspecification, latent variables, endogeneity problems, and other complexities. Anup Malani and colleagues, among others, have described these problems in the context of FDA approval for drugs based on post-hoc subgroup analysis. Anup Malani et al., Reforming Subgroup Analysis 6–8 (Apr. 13, 2008) (unpublished manuscript), *available at* http://papers.ssrn.com/abstract=1119970. Reliable black-box medicine would need to compensate for these issues, as does any primarily data-mining approach; Malani and colleagues suggest, as does this Article, that independent third-party validation may help counteract some problems of post-hoc analysis. *Id.* at 13–16.

61. For theoretical and empirical descriptions of implicit knowledge in medicine, see generally, David R. Kaufman et al., *Conceptual Knowledge and Decision Strategies in Relation to Hypercholesterolemia and Coronary Heart Disease*, 55 INT'L J. MED. INFORMATICS 159 (1999); Vimla L. Patel et al., *Expertise and Tacit Knowledge in Medicine*, *in* TACIT KNOWLEDGE IN PROFESSIONAL PRACTICE 75 (Robert J. Sternberg & Joseph A. Horvath eds., 1999).

62. *See* Turgay Ayer et al., *Breast Cancer Risk Estimation with Artificial Neural Networks Revisited: Discrimination and Calibration*, 116 CANCER 3310, 3316–19 (2010)

and classify it — for instance, whether an image likely shows a tumor or not — but the mechanism of that classification remains opaque to everyone, including the initial programmer.[63]

The second, more approachable opacity represents something of a midpoint between fully opaque black-box medicine and explicit personalized medicine. In this form, a machine-learning algorithm can examine data, determine a relationship, and state it, but the underlying biological relationship is too complex to be amenable to scientific understanding or clinical trials. A set of relationships between fifty different parameters, for instance, might well predict a significant medical outcome, but a complex fifty-dimensional relationship is beyond the reach of current science. Some machine learning approaches follow this pattern: A "random forest" approach can take a large number of parameters and use them to classify observations via a large set of decision trees with controlled variation.[64] At the end of the learning period, the output includes the weight and relationships of the parameters involved in the final model.[65] Under these approaches, the relationship may not be fully and formally opaque — one can list the factors and their relationships — but they are so complex as to defy understanding, and are therefore practically opaque and still "black-box."

Different forms of algorithmic medicine can be imagined to lie somewhere on a spectrum of transparency and understanding. At one end is the classical model of a well-understood, well-validated, supported-by-extensive-evidence biological relationship: transparent to doctors, scientists, and ideally patients. At the other end is a fully opaque model derived from non-transparent processes, able to make predictions but closed to explicit understanding. In the middle is some combination, perhaps where some parts of the algorithm are hidden and others are transparent, or where some aspects are understandable, but others are too complex to be understood.

B. The Benefits of Black-Box Medicine

Black-box medicine has the potential to bring tremendous benefits to the practice of medicine and to the health care system more generally. As with explicit personalized medicine, these benefits fall

(comparing performance of an artificial neural network against that of experienced radiologists in classifying the risk of breast cancer; the network outperformed the radiologists).

63. *Id.* at 3318.

64. *See, e.g.*, Katherine R. Gray et al., *Random Forest-Based Similarity Measures for Multi-Modal Classification of Alzheimer's Disease*, 65 NEUROIMAGE 167, 169, 171 (2013) (describing random forest algorithms, noting the possibility of extracting the component parameters in the resulting model, and using random forest techniques to classify Alzheimer's Disease based on parameters including clinical data, images, and genetic information).

65. *Id.* at 169–71.

into two linked main categories: improving patient care and increasing possibilities of drug discovery or drug repurposing.

1. Patient Care

Black-box personalized medicine is key to realizing the next-generation health benefits of genomics, electronic health records, and big data in the health care sector. Currently, we are amassing patient data, but are only able to use a relatively small fraction of the relationships reflected in that data because of the sheer complexity of biological systems.[66] Black-box medicine promises to make at least some of that complexity available for medical purposes, as described above.[67] New complex relationships can be used to suggest different treatment options and to fine-tune provider responses and treatments which are already in use. Black-box medicine can also potentially provide not only new treatment recommendations, but also diagnoses or preventive recommendations based on individual patient data. More specific predictions are harder to make, since black-box medicine by definition focuses on complex and implicit links. A look at aspects of current practice which are closest to black-box medicine offers some suggestions. In particular, the major benefits that have arisen from increased understanding of warfarin dosing, using individualized predictors to avoid a trial-and-error approach, are suggestive of how black-box medicine could improve other drug treatments. Black-box medicine might be especially helpful for other drugs with narrow therapeutic indices, such as warfarin.[68] In addition, black-box medicine promises to improve care indirectly through its impact on drug development and use.

2. Drug Discovery and Development

Black-box personalized medicine can help resolve a major challenge facing the drug industry: When can already-approved drugs be prescribed or used for a new purpose? It is extremely costly to develop new drugs. A significant portion of that cost goes to ensuring basic safety and administrability, and a larger fraction goes to demonstrat-

66. *See supra* Part II.B.1.

67. *See supra* Part II.A.3.

68. A drug's therapeutic index measures the range within which the drug is effective; higher doses are likely to have toxic effects, and lower doses are likely to be ineffective. In instances where the therapeutic index is relatively narrow and is also impacted by patient characteristics — like warfarin — black-box medicine is particularly likely to offer useful guidance. *See generally* Maureen Burns, *Management of Narrow Therapeutic Index Drugs*, 7 J. THROMBOSIS & THROMBOLYSIS 137 (1999). Although the number of narrow therapeutic index drugs is not large, they are used for a variety of clinical purposes. *Id.* at 137.

ing efficacy through clinical trials.[69] Therefore, there is a substantial advantage to discovering new uses for old drugs,[70] especially since most drugs have multiple uses.[71] Finding a new use avoids repeated costs in demonstrating safety but still requires costly clinical trials to demonstrate efficacy. Recouping these costs is hard because patents and regulatory exclusivity tend not to protect new uses effectively.[72]

Black-box medicine offers potentially less expensive routes to discover and confirm the efficacy of new uses. The wealth of data available in electronic health records of patients suffering from different ailments and responding to drugs they take for other purposes may be mined by big-data algorithms, which can suggest new uses. Black-box medicine would broaden the already-widespread concept of off-label use (that is, use not approved by the FDA)[73] beyond those based on practitioner experience or limited clinical trials.[74] In the black-box medicine paradigm, useful links need only be correct, not explicit or extensively validated in clinical trials; this could facilitate the off-label use of drugs which are approved as safe but not approved — and which may never be approved — for the algorithmically-suggested purpose.

Black-box medicine has other potential benefits for drug discovery and development. To the extent that black-box medicine identifies relationships between complex sets of variables that are largely implicit, black-box medicine suggests potential new research pathways

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69. Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 477 (2007) (finding average cash outlay per new biopharmaceutical of $198 million for preclinical work and $361 million for clinical trials).

70. At least in part because many drugs are relatively crudely targeted, they typically have multiple effects on the human body. The simplest example is the existence of side effects. Better-validated multiple effects enter clinical practice as off-label use; for instance, many of the drugs used in chemotherapy have not been regulator-approved for that use, and some such uses have never even been the subject of clinical trials. *See* Rena M. Conti et al., *Prevalence of Off-Label Use and Spending in 2010 Among Patent-Protected Chemotherapies in a Population-Based Cohort of Medical Oncologists*, 31 J. CLINICAL ONCOLOGY 1134, 1137 (2013) (finding a 30% rate of off-label use among ten common patent-protected intravenous chemotherapies).

71. *See* Benjamin N. Roin, *Solving the Problem of New Uses*, MICH. ST. L. REV. (forthcoming 2014) (manuscript at 19–20, 43–44), *available at* http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2337821.

72. Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717, 724–35 (2005) (finding patents and regulatory efforts ineffective at incentivizing new use clinical trials).

73. *See, e.g.*, Conti et al., *supra* note 70, at 1134.

74. The best-validated multiple effects of drugs come when pharmaceutical firms decide the limited protection available for new uses is worth the cost and effort of undertaking full clinical trials and acquiring regulatory approval for those uses. Profits available on marketing older drugs for new uses may provide an end-stage incentive that drives the creation of earlier innovations needed to get there; such incentives could potentially drive the development of black-box medicine used to discover those new uses. However, those incentives are attenuated by the difficulty in enforcing patents on new uses. *See* Eisenberg, *supra* note 72, at 725–30.

to make those implicit connections explicit. Finally, black-box medicine could also aid discovery of new drugs, or clinical validation of secondary uses for old drugs, by targeting clinical trials. Explicit personalized medicine and pharmacogenomic testing generally can already be used to streamline clinical trials.[75] Black-box medicine could further expand these possibilities by suggesting participant populations that meet a more complex set of criteria for as of yet unknown reasons. In addition, black-box medicine could more radically reduce the cost of clinical trials by avoiding more of them, especially in the context of off-label uses for already-approved drugs as described above.

III. HURDLES TO DEVELOPMENT

While black-box medicine offers large benefits, getting there will not be easy. Developing complex predictive models requires the ongoing generation and consolidation of very large datasets about individuals and their health. This requires significant costs in the collection of data — both from digital sources such as EHRs and, more expensively, from paper-filed records located in widely dispersed doctors' offices. Genetic sequence data collection will be required to complement and inform collected health records. Once the datasets are gathered, the development of accurate predictive and analytical algorithms is expensive. Finally, validating those algorithms — whether through independent testing, repeats on separate datasets, or clinical validation — will require additional funds and effort.

A. Data Collection and Coding

Black-box medicine requires large sets of high-quality health data to find the complex relationships. Notably, some firms have already amassed significant health information databases, but these are traditionally aimed either directly at immediate care or at insurance reimbursement, and lack many types of data necessary for black-box medicine development.[76] Generating large datasets suitable for black-

75. *See, e.g.*, Brian M. Alexander et al., *Biomarker-Based Adaptive Trials for Patients with Glioblastoma — Lessons from I-SPY 2*, 15 NEURO-ONCOLOGY 972, 973–75 (2013) (describing adaptive neuro-oncology clinical trials where the trials were dynamically modified based on preliminary results and biomarker associations).

76. *See, e.g.*, Madelyn Kearns, *Returning Patients to Data Aggregation*, MED. PRAC. INSIDER (May 10, 2013), http://www.medicalpracticeinsider.com/news/patient-care/panelists-propose-puttingpatients-back-center-data-aggregation ("The healthcare industry is still very much in the pubescent stages of data management and storage — experimenting with its new data capture proficiencies and what the general breadth of digital medical information means for care delivery."). One of the largest and best-known health data aggregators is IMS Health. The data from IMS Health is deidentified, strictly proprietary, and extremely expensive.

box medicine presents a significant practical challenge: Gathering, cleaning, and assembling high-quality health information from many different sources is an expensive endeavor. Once data is actually gathered, it must then be checked for quality and "cleaned" of unreliable observations,[77] and then put into compatible formats for a unified database. The hardware costs of actually possessing and storing large amounts of data are low, but energy, maintenance, and management software increase those costs.[78] The health data necessary to fill databases for black-box medicine will come from two different sources: EHRs and paper health records. Each raises different challenges.

Collecting electronic information should theoretically be much less expensive because it does not require encoding new data. This does not mean that collecting electronic information is cheap or free; many health records are kept in incompatible data formats, and the information tracked varies both in type and how it is recorded. The practical challenges with assembling paper health records are very high — likely higher — and of a different nature. Paper records are scattered throughout healthcare facilities, from doctors' offices to hospitals.[79] Once located, information must be encoded to electronic format, either by hand or by optical character recognition.[80] One response is to begin with electronic health information and proceed later to paper records, though this may lead to the absence of older, longer-term data and population selection effects. Either type of data may require recoding descriptive variables (e.g., "high," "overweight") into standardized variables for use in further analysis.

Practical challenges with data gathering are compounded by the complex and ideally comprehensive nature of the data being gathered. More data leads to greater capacity to tease apart complex implicit relationships. Thus, an ideal database might include not only typical physical measurements (e.g., blood pressure, heart rate, height, weight, and symptoms), but also medications being taken (both over-the-counter and prescription, including frequency and duration) and genetic information. As other new technologies such as metabolite screens, RNA expression profiles, and other biomarker sets become more readily available and are gradually adopted by practitioners,

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77. For instance, if a patient's weight in pounds is recorded over six months as 121, 119, 1200, and 119, the third observation is clearly a typographical error and should be corrected or removed.

78. Paul P. Tallon, *Corporate Governance of Big Data: Perspectives on Value, Risk, and Cost*, 46 COMPUTER 32, 34 (2013).

79. Roy Schoenberg & Charles Safran, *Internet Based Repository of Medical Records That Retains Patient Confidentiality*, 321 BMJ 1199, 1199 (2000).

80. *See* Diane Dolezel & Jackie Moczygemba, *Implementing EHRs: An Exploratory Study to Examine Current Practices in Migrating Physician Practice*, PERSP. HEALTH INFO. MGMT., Winter 2015, at 2, 13 (discussing challenges of adding paper records to EHRs, and finding in a small sample of Texas physicians that only 50% of practices imported the entire legacy paper record).

they will contribute additional data. Finally, the practical challenges of data collection are amplified by legal restrictions, discussed below.[81]

B. Developing Predictive Algorithms

The second set of challenges lies in the actual generation of predictive algorithms for black-box medicine, that is, the task of parsing the data, identifying correlations, and making sure those correlations suggest real and useful health measures. While predictive algorithms have become increasingly sophisticated, they still require extensive development and specialization to adapt them to particular contexts and specific concerns.

To take a recent example of the complexity in developing predictive algorithms, consider the Netflix Prize competition.[82] Netflix's movie recommendation algorithm is a core part of Netflix's business. Netflix developed its own predictive algorithm,[83] sought to harness outside expertise, and in 2006 offered a $1,000,000 prize for a team which could beat the performance of its in-house algorithm by 10%.[84] Over 20,000 teams registered.[85] Three years and tens of thousands of submissions later, Netflix awarded the prize to a team consisting of several researchers from different institutions — after three years of work, they had improved Netflix's performance by 10.06%.[86] The winning algorithm involved dozens of separate collaborative filtering algorithms[87] and the training of one hundred parallel predictors with results blended through eleven different computational methods. Despite the technology available, and the simplicity of the dataset, the team still ran into substantial computational limitations.[88]

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81. *See infra* Part IV.B (discussing privacy issues in data collection).

82. *See Netflix Prize*, NETFLIX, http://www.netflixprize.com (last visited May 9, 2015).

83. Netflix's original algorithm, Cinematch, used "[s]traightforward statistical linear models with a lot of data conditioning." *Frequently Asked Questions*, NETFLIX, http://www.netflixprize.com/faq (last visited May 9, 2015). This model provides only 10% better prediction of user scores than a trivial algorithm which predicted as the user score the average score the movie had received from other users. *Id.*

84. Linyuan Lü et al., *Recommender Systems*, 519 PHYSICS REP. 1, 3 (2012).

85. *Id.*

86. Prizemaster, Comment to *Grand Prize Awarded to Team BellKor's Pragmatic Chaos*, NETFLIX (Sept. 18, 2009, 9:58:04 AM), http://www.netflixprize.com/community/viewtopic.php?id=1537. Notably, the first place team submitted their results just twenty-four minutes before the conclusion of the contest. *Id.*

87. *See* YEHUDA KOREN, THE BELLKOR SOLUTION TO THE NETFLIX GRAND PRIZE, NETFLIX 1 (Aug. 2009), *available at* http://www.netflixprize.com/assets/GrandPrize2009_BPC_BellKor.pdf; ANDREAS TÖSCHER ET AL., THE BIGCHAOS SOLUTION TO THE NETFLIX GRAND PRIZE, NETFLIX 6–16 (Sept. 5, 2009), *available at* http://www.netflixprize.com/assets/GrandPrize2009_BPC_BigChaos.pdf.

88. TÖSCHER ET AL., *supra* note 87, at 3, 9, 15, 17 (some machine learning algorithms could be run only a limited number of times because of limitations in memory, processing power, and storage).

The experience of Netflix also demonstrates the extraordinary complexity of algorithm development and how it requires close and careful involvement from sophisticated programmers. The Netflix dataset was almost laughably simple compared to that necessary for personalized medicine — while it involved data from a substantial 480,189 users on 17,770 movies (for a total of 100,480,507 ratings), the ratings were simple one to five integer scores.[89] Health information databases would involve potentially thousands of relevant variables, as described above.[90] The stakes and error costs are higher, but the potential rewards are much higher as well; U.S. health care expenditures are over 17% of GDP, for a 2013 total of approximately $2.9 trillion.[91] Overall, substantial — but socially worthwhile — investment will be required to develop meaningful black-box medicine algorithms.

C. Validating Predictive Algorithms

The third challenge in developing black-box medicine is validation; that is, making sure that the algorithmic models developed by firms are accurate and useful. For typical new treatment methods — whether drugs or otherwise, validation comes in several possible forms. First, the treatment is generally scientifically understood.[92] Second, clinical trials are used to demonstrate the validity of a treatment method. Third and finally, the validity of the treatment can be confirmed by actors other than the sponsoring company, including by other clinical trials (e.g., conducted by health agencies) or by post-

89. *Id.* at 1. In fact, even with a far simpler dataset, Netflix never ended up implementing the winning solution, finding that "the additional accuracy gains . . . did not seem to justify the engineering effort needed to bring them into a production environment." Xavier Amatriain & Justin Basilico, *Netflix Recommendations: Beyond the 5 Stars (Part 1)*, NETFLIX TECH BLOG (Apr. 6, 2012, 6:30 PM), http://techblog.netflix.com/2012/04/netflix-recommendations-beyond-5-stars.html. Netflix did end up implementing some simpler solutions developed earlier in the competition. *Id.*

90. *See supra* note 70 and accompanying text.

91. U.S. CENTERS FOR MEDICARE AND MEDICAID SERVICES, NATIONAL HEALTH EXPENDITURE 2013 HIGHLIGHTS, (2013), *available at* http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/highlights.pdf.

92. Although the mechanism of action for a drug is normally understood, there are notable exceptions. For instance, lithium, used to treat mood disorders, has an unknown mechanism of action. Gin S. Malhi et al., *Potential Mechanisms of Action of Lithium in Bipolar Disorder: Current Understanding*, 27 CNS DRUGS 135, 136 (2013). Similarly, although aspirin has been commonly available since the beginning of the twentieth century, its mechanism of action was only discovered in 1971. *See generally* J.R. Vane, *Inhibition of Prostaglandin Synthesis as a Mechanism of Action for Aspirin-Like Drugs*, 231 NATURE NEW BIOLOGY 232 (1971).

marketing surveillance mechanisms and the experience of clinicians prescribing the drug.[93]

The complex and implicit models at the heart of black-box medicine face challenges at each of these stages. First, the opaque nature of the algorithms means that they cannot be well understood on a scientific level. Typical clinical trials are also likely to be challenging for two reasons: The implicit and complex relationships of black-box medicine are unlikely to be susceptible to mechanistic exploration by classic gold-standard clinical trial methodology,[94] and some of the principal benefits of black-box medicine — potentially higher speed and relatively low cost of specialized treatment recommendations — rely on avoiding a slow and costly clinical trial process.[95]

This reality increases the need for external validation of black-box medicine algorithms based on independent algorithmic validation of the same or independent data.[96] There are two principal concerns, roughly equivalent to the well-trodden concepts of analytical and clinical validity in diagnostic testing. First, a model may not predict what it says it does.[97] Second, and more specific to black-box medicine, a model may predict what it aims to, but for reasons based on idiosyncrasies of the dataset or overspecification rather than true biological phenomena.[98]

Model validation could be performed by the initial innovator or the FDA, but each has problems. The initial innovator faces strong financial incentives not to disprove its own algorithm once marketed and retains whatever biases or errors may have created problems in the first place.[99] Regulatory oversight could serve some validation

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93. Timothy Brewer & Graham A. Colditz, *Postmarketing Surveillance and Adverse Drug Reactions: Current Perspectives and Future Needs*, 281 J. AM. MED. ASS'N. 824, 828 (1999).

94. Because personalized medicine relies on very specific patient profiles, it is hard to aggregate similar patients. The expectation of different results among different patients runs counter to the average treatment effects observed in randomized clinical trials.

95. Firms could, and likely should, run broad clinical trials on black-box medicine algorithms overall; that is, does a group of patients treated according to algorithm X have significantly better clinical outcomes, in general, than patients treated according to the standard of care? But this broad form of clinical trial shows some overall validation for the full complex algorithm set, not for any particular treatment option.

96. *See, e.g.*, James D. Brenton et al., *Molecular Classification and Molecular Forecasting of Breast Cancer: Ready for Clinical Application?*, 23 J. CLINICAL ONCOLOGY 7350, 7359 (2005).

97. *See* Brian B. Spear et al., *Clinical Application of Pharmacogenetics*, 7 TRENDS MOLECULAR MED. 201, 204 (2001). Into this category fall the most basic form of errors: errors in the coding of the program ("bugs"), corrupt or flawed data, and other such challenges. These problems' mundane nature does not diminish their importance. Like in other places in the health care system, simple and mundane errors can have tremendous and costly consequences.

98. *Id.* at 202–03 (discussing clinical validity).

99. While the initial innovator has reputational incentives to ensure a high-quality product, as well as duties under tort law, prior experiences with drug company behavior shows that reputational and tort incentives cannot ensure uniform validation and disclosure of

role, but the FDA currently lacks the expertise and resources to independently replicate a company's algorithmic results; at most, it could provide procedural oversight — ensuring that the data collection, consolidation, and analysis methods are appropriate.

Validation by private third parties could better ensure the clinical relevance of an algorithm.[100] Agreement between different firms, using different computational methods, on recommended treatment options would go a long way to demonstrate that those implicit correlations are medically valid and not merely artifacts of the dataset or the specific choices of the algorithm developers.[101] Because such validation will also be expensive, policy regarding personalized medicine should also consider incentives for third-party validation.[102] Finally, post-market surveillance and provider experience can also help bolster the case for an algorithm's overall efficacy, but these rely on the wide deployment of the algorithm in the first place.

IV. POLICY CONCERNS AND CHALLENGES OF BLACK-BOX MEDICINE

Black-box medicine presents powerful possibilities for the future of medicine, including decreasing the costs and increasing the quality of medical care. It also has implications far outside the realm of medicine and science. Strong policy choices can facilitate the development, spread, and use of black-box medicine; similarly, poor policy choices can profoundly stunt its growth. A full exploration of the legal and policy aspects of black-box medicine will take substantial study. This Part briefly lays out some of the most important concerns and challenges.

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problems. In the most high-profile example, Merck failed to disclose information about risks of its blockbuster drug Vioxx for years, resulting in nearly 30,000 tort claims amid an estimated 88,000 to 140,000 excess cases of serious heart disease in the United States. David J. Graham et al., *Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with Cyclo-Oxygenase 2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs: Nested Case-Control Study*, 365 LANCET 475, 480 (2005); Harlan Krumholz et al., *What Have We Learnt from Vioxx?*, 334 BMJ 120, 120 (2007). Thus, while validation by the initial innovator is important and should be demonstrated — especially in the regulatory context — it is unlikely to suffice.

100. *See* Cohen et al., *supra* note 44, at 1143; Anup Malani et al., *supra* note 60, at 3. To some extent, noncommercial third parties — primarily foundations and academic researchers — can validate black-box medicine models in the same way that they currently check some drug trials. But that current role is quite limited; the resources necessary to conduct independent clinical trials are significant, and even performing reanalysis of clinical trial data requires time, money, and expertise.

101. *See, e.g.*, Brenton et al., *supra* note 96, at 7359 (proposing independent algorithmic validation of algorithms to predict breast cancer classifiers). Developing independent algorithms would clearly increase overall development costs, but by a substantially lower amount since the cost of developing data need not be replicated.

102. *See infra* Part IV.A.3.c.

A. Incentives

As described above, developing black-box medicine will require significant investment in assembling datasets, creating algorithms, and validating those algorithms. However, those investments all create information goods, which face an excludability problem: Once information is developed, keeping others from using that information is difficult. This non-excludability problem is a central justification for intellectual property.[103] Society benefits from innovation, but ideas and information are often expensive to produce and hard to protect. If firms cannot capture most of the value of their innovation investments, they will invest at suboptimal levels from a social-welfare standpoint.[104] Given the large spillover effects of innovation, encouraging it typically constitutes a worthy policy goal.[105] Intellectual property helps resolve this problem by allowing firms to exclude others from the use of their information goods, thereby increasing incentives to create those goods in the first place.[106] This Section briefly describes the incentive landscape for black-box medicine.

1. Problems with Patent Incentives

Incentives for biomedical innovation, including black-box medicine, arise primarily from the patent system, but such incentives are both inadequate and socially perverse. On the one hand, incentives are frequently inadequate; patents are difficult to obtain for black-box medicine, both generally and due to recent Supreme Court decisions regarding patentable subject matter.[107] On the other hand, those incen-

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103. *See generally, e.g.*, Colloquium, *Ex Ante Versus Ex Post Justifications for Intellectual Property*, 71 U. CHI. L. REV. 129 (2004).

104. *See, e.g.*, Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 507–08 (2009).

105. *Id.* at 556.

106. *Id.* at 508. This is not to argue that intellectual property does a perfect job of creating incentives, nor that these incentives come without costs; intellectual property is criticized for creating deadweight loss due to monopoly pricing, Kenneth J. Arrow, *supra* note 13, at 616–17, for distorting innovation incentives, Michael B. Abramowicz, *The Danger of Underdeveloped Patent Prospects*, 92 CORNELL L. REV. 1065, 1066–73 (2007), for creating large transaction costs, Peter S. Menell & Suzanne Scotchmer, *Intellectual Property Law*, *in* 2 HANDBOOK OF LAW AND ECONOMICS 1473, 1505 (A. Mitchell Polinksy & Steven Shavell eds., 2007), and — especially in the field of health — for sharply curtailing access to medical treatments for the poor and for those in the developing world, Aidan Hollis & Thomas Pogge, INCENTIVES FOR GLOBAL HEALTH, THE HEALTH IMPACT FUND: MAKING NEW MEDICINES ACCESSIBLE FOR ALL 1, 109 (2008). This Article does not address these concerns, taking instead as a given that biomedical innovation is an area in which intellectual property incentives are widely deployed on the policy level. Black-box medicine is an area in which the class justifications for intellectual property incentives apply, and therefore this Article will comment on the shape and magnitude of those incentives, not whether such incentives should exist at all.

107. *See, e.g.*, Mayo Collaborative Servs. v. Prometheus Labs., 566 U.S. ___, 132 S. Ct. 1289, 1293 (2012).

tives that do exist drive black-box medicine in socially problematic directions.

The patent system is a principal policy tool used to drive technological innovation. Inventions that are novel, nonobvious, and useful[108] are eligible for patent protection, under which the patentee has the right to exclude others from making, using, and selling[109] the patented invention for twenty years from the date of the patent application.[110] This grant of an exclusive right creates *ex ante* incentives for the investment needed to develop the invention in the first place. While they may have benefits for driving innovation generally,[111] patents function quite poorly in the context of creating incentives for black-box medicine for two key reasons: first, difficulty meeting the written description requirement, and second, issues with patent eligibility.[112]

First, patent law requires that patents include a detailed written description of the invention sufficient to enable a person having ordinary skill in the art to practice the invention.[113] Black-box medicine, by its nature, includes nontransparent elements frequently impossible to describe fully.[114]

Second, the Supreme Court has created substantial limits on what broad categories of inventions are patent-eligible under § 101, and these limitations make obtaining patents on black-box medicine even more challenging. Although the language of § 101 embraces the vast majority of inventions,[115] the Supreme Court has created three judicial exceptions: "Laws of nature, natural phenomena, and abstract ideas

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108. 35 U.S.C. §§ 101–03 (2012).

109. 35 U.S.C. § 271(a) (2012). The patentee can also exclude others from importing or offering to sell the invention. *Id.* Another set of other infringing actions can be found in 35 U.S.C. § 271(2) (2012).

110. 35 U.S.C. § 154(a)(2) (2012).

111. Substantial debate exists about the success of patents in driving innovation generally. For an excellent summary of this debate, see Lisa Larrimore Ouellette, *Patent Experimentalism*, 101 VA. L. REV. (forthcoming 2015). Nevertheless, the life sciences, and especially in pharmaceutical research and development, are generally seen as an area where patent law functions relatively well. *See, e.g.*, W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, 55 B.C. L. REV. 491, 524–25 (2014).

112. There are also potential problems with matching the timing of patent issuance and duration to the development of personalized medicine, but those interactions are complex and also depend on, among other things, yet-to-be-determined regulatory pathways. *See infra* Part IV.C; *see also* Benjamin N. Roin, *The Case for Tailoring Patent Awards Based on Time-to-Market*, 61 UCLA L. REV. 672, 693–98 (2014).

113. 35 U.S.C. § 112(a) (2012).

114. *See supra* Part II.A.3.b.

115. 35 U.S.C. § 101 (2012) (patents may be obtained on "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof"); *see also* Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980) (internal citations omitted) ("Congress intended statutory subject matter to 'include anything under the sun that is made by man.'").

are not patentable."[116] Patents on black-box medicine bump up against potentially all of these prohibitions. Under *Gottschalk v. Benson*, pure algorithms are unpatentable as abstract ideas.[117] Under *Mayo v. Prometheus*, this prohibition extends explicitly to medical diagnostic processes, which the court held to be unpatentable laws of nature.[118] Finally, though less directly, in *Association for Molecular Pathology v. Myriad Genetics*, the Supreme Court held that isolated DNA is a natural phenomenon and therefore unpatentable, casting doubt on the strategy of using patents on natural biomarkers to buttress the protection of diagnostics relying on those biomarkers.[119]

Patent incentives are not only lower for black-box medicine than for other biomedical innovations, those incentives that are available push the development of black-box medicine in unhelpful directions. After *Mayo* and *Alice*, successful patenting of algorithms requires significantly more than just the algorithm itself, which will likely be held to be either a law of nature or an abstract idea. The most straightforward way to add that "something more" is to focus on companion diagnostics and paired devices, rather than pure algorithms and data. The combination of a specific drug or treatment with a diagnostic algorithm, approved and sold as a single package, is more likely patentable than a broader-purpose algorithm standing alone. Accordingly, innovators on the margin may turn away from the implicit, complex algorithms of black-box medicine and instead focus on simpler, more explicit relationships that can be tied to a physical product or pro-

116. Mayo Collaborative Servs. v. Prometheus Labs., 566 U.S. ___, 132 S. Ct. 1289, 1293 (2012) (internal quotation marks omitted) (recognizing the long history of these judicial exceptions).

117. Gottschalk v. Benson, 409 U.S. 64, 71–74 (1972). The invention in *Gottschalk* was an algorithm for converting between different forms of binary numbers; the Supreme Court held the invention was an unpatentable abstract idea because it would preempt all uses of the algorithm. *Id.* at 71–72. Software and algorithm patents evolved after *Gottschalk* to include language requiring the addition of a computer or storage media associated with the program; the Supreme Court held in 2014 that those mere additions were insufficient to make an algorithm patentable subject matter under § 101. *See, e.g.*, Alice Corp. Pty. v. CLS Bank Int'l, 573 U.S. ___, 134 S. Ct. 2347, 2358–60 (2014).

118. The algorithm in *Mayo* disclosed a method of treatment that comprised of administering a thiopurine drug and then measuring the level of that drug's metabolite. Measurements above a certain threshold indicated that the dose was too high, while measurements below a certain threshold indicated that the dose was too low; the crux of the invention was the determination of those previously unknown levels. Mayo Collaborative v. Prometheus Labs., 566 U.S. ___, 132 S. Ct. 1289, 1295 (2012). This type of straightforward dose adjustment that is based on individual metabolism is a clear example of explicit personalized medicine. For further discussion, see generally Timo Minssen & David Nilsson, *The US Supreme Court in* Mayo v Prometheus — *Taking the Fire from or to Biotechnology and Personalized Medicine?*, 2 QUEEN MARY J. INTELL. PROP. 376 (2012).

119. Ass'n for Molecular Pathology v. Myriad, 569 U.S. ___, 133 S. Ct. 2107, 2120 (2013). Though patents on biomarkers (biological or biochemical markers with medical implications) do not themselves provide direct incentives for black-box medicine, exclusive rights to a particular set of new biomarkers, such as alleles of a gene, could restrict competition for algorithms that use those biomarkers. Such a strategy will typically be foreclosed after *Myriad.*

cess.[120] Overall, patent incentives for black-box medicine are problematic. The unavailability of many patents lowers incentives generally, and those that do exist push development away from black-box algorithms and toward simpler explicit companion diagnostics.

2. Secrecy

Secrecy is a key alternative to the patent system; if patents are unavailable, inventors can attempt to appropriate the returns from innovation by keeping the innovation secret. Secrecy has complex effects on incentives for black-box medicine. On the one hand, it matches extremely well with inherently nontransparent algorithms. On the other hand, keeping disclosable details hidden may result in challenges to trust and adoption, and secrecy about datasets and validation may sharply reduce the value of each, especially with regard to cumulative innovation. Lack of transparency may also make it more difficult or costly to obtain permission to use data.

Knowledge which is reasonably kept secret and which derives independent economic value from its secrecy is protected from misappropriation by state and federal trade secret law.[121] Trade secrecy can protect information that is unpatentable, and lasts as long as the information is secret.[122] However, secret information can legally be reverse-engineered.[123]

Secrecy seems exceptionally suitable for the algorithms driving black-box medicine. The algorithms are by definition nontransparent (otherwise they would be explicit personalized medicine, not black-box medicine). The problem created by an inability to disclose, which creates problems for patent law, fully enables and even requires secrecy.

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120. For instance, the drug Herceptin and the diagnostic test for HER2/neu gene expression were developed together and are provided together. See *supra* notes 39–41 and accompanying text; see also *Personalized Medicine and Companion Diagnostics Go Hand-in-Hand*, FDA (July 31, 2014) http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm407328.htm. If the tied product is itself protected by patent or regulatory exclusivity, the linked diagnostic can benefit from that protection, even if protection is unavailable for the diagnostic itself.

121. For a general overview of trade secrecy law, see Robert G. Bone, *A New Look at Trade Secret Law: Doctrine in Search of Justification*, CALIF. L. REV. 241, 247–51 (1998). Forty-seven states have enacted some form of the Uniform Trade Secrets Act; the exceptions are New York, North Carolina, and Massachusetts. Unif. Law Comm'n, LEGISLATIVE FACT SHEET — TRADE SECRETS ACT (last amended 1985), *available at* http://www.uniformlaws.org/LegislativeFactSheet.aspx?title=Trade%20Secrets%20Act. Under federal law, the Economic Espionage Act of 1996 makes the theft or misappropriation of a trade secret a federal crime, so long as it relates to foreign or interstate commerce. 18 U.S.C. § 1832 (2012).

122. *See* Bone, *A New Look, supra* note 121, at 248.

123. *See* RESTATEMENT (THIRD) OF UNFAIR COMPETITION § 43 cmt. b (1995) (listing reverse engineering as a proper means of acquiring a trade secret).

Secrecy, however, is a problematic incentive for the datasets underpinning the development of black-box medicine and makes method validation impossible. Datasets can certainly be kept secret, and that approach has demonstrated substantial success. A notable example is Myriad Genetics. Myriad's gene-testing process reveals combinations of alleles present in patients; the company then offers free testing to family members and analyzes family variation to determine significantly linked genetic patterns.[124] Since Myriad has a substantially greater set of data on BRCA1/2 variants, only 3% of its samples have variants of unknown significance;[125] for competitors, roughly 20% to 30% of samples have variants of unknown significance.[126] Test samples sent to Myriad are therefore much less likely to be returned to the physician as "uninterpretable" than samples sent to their competitors,[127] providing a robust competitive advantage. After its loss in the Supreme Court, the company has sought to keep other information about genetic variation secret.[128] While Myriad's data advantage could be overcome as other firms slowly assemble their own databases, the fact that Myriad currently possesses a much larger database — amassed from its period of patent protection — is self-reinforcing.[129] Myriad can provide more results and is therefore likely to continue receiving more test samples; the resulting larger database would still be kept as a trade secret.[130] Myriad's business plan includes retaining and expanding this secrecy-based advantage of mutation data and algorithms.[131]

Among other concerns,[132] keeping data secret in this area may significantly hamper the development of black-box medicine. Secrecy

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124. In a genetic test like Myriad's, the physical process first determines which alleles of a gene the patient has. That identification must then be interpreted to convey useful medical information: Are the alleles associated with a higher or a lower risk of cancer, or with no change? When the interpreting entity lacks sufficient information about a particular allele to provide a useful interpretation, it is termed a "variant of unknown significance," and that part of the test is inconclusive. *See* Douglas F. Easton et al., *A Systematic Genetic Assessment of 1,433 Sequence Variants of Unknown Clinical Significance in the BRCA1 and BRCA2 Breast Cancer-Predisposition Genes*, 81 AM. J. HUM. GENETICS 873, 873 (2007).

125. Monya Baker, *Policy Paper: Myriad Turns Cancer Genetic Data into Trade Secrets*, NATURE NEWS BLOG (Oct. 31, 2012, 11:14 PM BST), http://blogs.nature.com/news/2012/10/policy-paper-myriad-turns-cancer-genetic-data-into-trade-secrets.html.

126. *Id.*

127. *Id.*

128. Barbara J. Evans, *Economic Regulation of Next-Generation Sequencing*, 42 J.L. MED. & ETHICS (SYMPOSIUM: SPECIAL SUPPLEMENT) 51, 52–53 (2014).

129. *Id.* at 59–60.

130. *Id.* at 62.

131. MYRIAD GENETICS, INC., UNITED STATES SECURITIES AND EXCHANGE COMMISSION FORM 10-K (Fiscal Year 2013), *available at* http://files.shareholder.com/downloads/MYGN/3108552224x0xS1193125-13-334245/899923/filing.pdf.

132. Keeping data proprietary raises several potential concerns. On the ethical side, the Chairwoman of the European Society of Human Genetics' Professional and Public Policy Committee described herself as "very concerned that such important data is being withheld from those who most need it." Press Release, Eur. Soc'y of Human Genetics, Privately

slows cumulative innovation and promotes duplicative investment — though of course it also encourages *ex ante* investment.[133] For data underlying black-box medicine, predictive ability increases with dataset size and variety; this "big data" nature is what enables the discovery of complex correlations. When datasets shrink and are fragmented into firm-specific and disease-specific silos, fewer relationships are available, and those which can be found are less robust. Thus, while in other areas duplicative investment is merely wasteful, in the field of black-box medicine, keeping data fragmented prohibits the benefits of scale and has a correspondingly greater negative impact on development.

Finally, trade secrecy offers little incentive for the process of algorithm validation. Ensuring that someone else's algorithm functions as intended requires transparency; the validation must be disclosed to some combination of the original innovator, the regulator, the medical profession, and/or the public. While the value of validation is indeed difficult to appropriate, trade secrecy does not solve that problem.

3. Potential New Incentives

The incentive problem for black-box medicine — including the complex backdrop of secrecy and patent law — lacks a simple solution. This Section lays out a selection of possibilities for improvement. Rather than addressing black-box medicine as a single problem, each stage of black-box medicine development — database assembly, algorithm generation, and validation — may be most amenable to a different form of incentive.[134]

Owned Genetic Databases May Hinder Diagnosis and Bar the Way to the Arrival of Personalised Medicine: ESHG Reacts to Today's Report in the European Journal of Human Genetics (Oct. 31, 2012) *available at* https://www.eshg.org/13.0.html. She suggested that "[p]olicymakers take an urgent look at the regulatory and reimbursement issues involved in genomic testing in order for all the data that is essential to understanding the clinical significance of [mutations] to be made public, to the benefit of patients and healthcare providers alike." *Id.* Others have noted that keeping data proprietary removes them from the potential of peer review and makes us less certain of their accuracy. Baker, *supra* note 125. Other concerns arise with respect to transparency, oversight, and the blocking of future research directions.

133. *See* Bone, *A New Look*, *supra* note 121, at 266–67; Robert G. Bone, *The (Still) Shaky Foundations of Trade Secret Law*, 92 TEX. L. REV. 1803, 1807–08 (2014). For a defense of treating trade secrecy as intellectual property, see generally Mark A. Lemley, *The Surprising Virtues of Treating Trade Secrets as IP Rights*, 61 STAN. L. REV. 311 (2008).

134. Of course, there are incentive spillovers between phases of development, as with all complex projects. With drugs, for instance, separate incentives are not needed for conducting preclinical trials because the tremendous impact of incentives from patent-protected monopoly (or oligopoly) profits on the final drug product are sufficient to drive the entire enterprise. However, incentives may target specific types of information development. For example, FDA-administered market exclusivity for new drug uses provides an incentive for firms to conduct additional clinical trials for that new use even after the drug is approved and already on the market. *See* Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 359–60 (2007). Similarly, while there

a. Data

The most costly stage to developing black-box medicine is likely to be collecting, processing, and aggregating health data, as described above.[135] This stage also faces problematic incentives: patents are unavailable to mere collections of data,[136] and trade secrecy — which does allow appropriability of data — creates significant barriers to cumulative innovation.[137] In a best-case scenario, firms face incentives to engage in wasteful duplicative efforts to redevelop broad datasets.[138] In more likely but more problematic scenarios, firms face incentives to either develop their own special-purpose data in substantive silos (as Myriad Genetics[139] and others are already doing) or to avoid developing data to pursue black-box medicine at all. Data collection and processing thus demands additional incentives.

Dataset incentives could come in at least three forms. The first and simplest would be a grant model, where the government offers funding for dataset generation; grant funding might be conditioned on public access to the dataset.[140] While this fits into a traditional incentive scheme and thus might be more readily implemented, the magnitude of government involvement might be politically unpalatable.

The second form of data incentives, borrowing from the European model, would be to implement a *sui generis* system of intellectual property protection for datasets, thus allowing appropriation of the dataset-created welfare surplus without tinkering with other intellectual property regimes.[141] Since the costs of an intellectual property

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may be spillover incentives in black-box medicine — protected exclusivity for algorithms could drive database generation — each phase nonetheless merits separate consideration due to its different function and the different identity of the relevant innovator. Databases can support a plethora of algorithms by various developers, while validation, as discussed above, should ideally come from parties independent of those developing the algorithms in the first place. *See supra* Part III.C.

135. *See supra* Part III.A (describing data collection).

136. 35 U.S.C. § 101 (2012).

137. *See supra* note 132 and accompanying text.

138. For treatment review of other trade secret problems related to big data, see generally Michael Mattioli, *Disclosing Big Data*, 99 MINN. L. REV. 535 (2014) (discussing how inadequate disclosure of big-data collection, organization, and transformation practices can limit use and reuse of that data).

139. *See supra* Part IV.A.2.

140. In a parallel situation, the NIH conditions its grant funding on free public access to the resulting publications within one year of official publication. *See* 42 U.S.C. § 282c (2012); *see also NIH Public Access Policy Details*, NAT'L INSTS. OF HEALTH, http://publicaccess.nih.gov/policy.htm (last updated Mar. 27, 2014).

141. *See* Directive 96/9/EC of the European Parliament and of the Council of 11 March 1996 on the Legal Protection of Databases, ch. 3, 1996 O.J. (L077), *available at* http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:31996L0009&from=EN (introducing specific and separate legal rights to databases). For examinations of this right and database protection, see generally Daniel J. Gervais, *The Protection of Databases*, 82 CHI.-KENT L. REV. 1109 (2007); Jane C. Ginsburg, *Copyright, Common Law, and* Sui Generis

regime function like an off-the-books tax on the consumers of the property,[142] this would avoid the political economy challenge of government expenditures, though it would impose costs on those using the dataset and ultimately for the consumers of black-box medicine.[143] On the negative side, making datasets exclusive would decrease at least some forms of follow-on innovation and would fall prey to the same anti-scale effects that make trade secrecy for datasets problematic.[144]

The third and most radical form would be to treat data for black-box medicine as something akin to public infrastructure and to commit resources to developing it accordingly.[145] Under this conception, a broad, well-developed dataset (or set of datasets) would be generated and curated by either a public or public-private partnership and made widely available for the development and validation of algorithms.[146] The nascent Precision Medicine initiative takes this approach, calling for the development of a one-million person longitudinal study linking extensive genetic and metabolomics measurements with electronic health records, creating a dataset accessible to qualified researchers.[147]

Protection of Databases in the United States and Abroad, 66 U. CIN. L. REV. 151 (1997). Such a system has been proposed and rejected in the U.S. *Id.* at 171.

142. *See* Daniel J. Hemel & Lisa Larrimore Ouellette, *Beyond the Patents-Prizes Debate*, 92 TEX. L. REV. 303, 312 (2013).

143. *Id.* at 345–52.

144. *See, e.g.*, Bone, *A New Look*, *supra* note 121, at 266; Bone, *The (Still) Shaky Foundations*, *supra* note 133, at 1808; *see also* Heidi L. Williams, *Intellectual Property Rights and Innovation: Evidence from the Human Genome* 14 (Nat'l Bureau of Econ. Research, Working Paper No. 16213, 2010), *available at* http://www.nber.org/papers/w16213 (describing the negative impact of short-term intellectual property on gene sequence data on later innovation).

145. For a discussion of public access issues with genomic data infrastructures, see generally Barbara J. Evans, *Economic Regulation of Next-Generation Sequencing*, 42 J.L. MED. & ETHICS (SYMPOSIUM: SPECIAL SUPPLEMENT) 51 (2014) (describing how some features of genomic data resemble essential facilities and outlining potential antitrust challenges); BRETT M. FRISCHMANN, INFRASTRUCTURE: THE SOCIAL VALUE OF SHARED RESOURCES (2013) (describing how infrastructure theory applies to intellectual resources and property).

146. The Human Genome Project provides clear precedent for this approach. In that case, a collaborative effort between government and private researchers sequenced the human genome with the intention of providing it freely to future researchers and innovators as a common infrastructure resource. *See generally* Francis S. Collins et al., *The Human Genome Project: Lessons from Large-Scale Biology*, 300 SCIENCE 286 (2003) (describing the organization and management of the Human Genome Project). Notably, while this public-private partnership was successful, a competing private firm, Celera Genomics, completed its parallel sequencing effort at the same time, despite a later start. *Id.* at 289. Celera makes its own version of the human genome sequence available on commercial terms — illustrating both the fact that public efforts need not crowd out private efforts and the reality that duplicative data efforts can persist even in the face of well-funded centralized public initiatives.

147. Collins & Varmus, *supra* note 1 at 794–95.

b. Algorithms

Algorithms, the heart of black-box medicine, are also costly information goods.[148] Current intellectual property incentives are both inadequate and misdirected, pointing development away from black-box medicine and complex standalone algorithms. Improved incentives could come in several forms, including changes in patent law, regulatory exclusivity, monetary incentives such as grants or prizes, and finally a quasi-status-quo reliance on trade secrecy.

The most obvious intervention, given the preceding discussion on recent changes in patent law, would be to change (or change back) patent law to provide more effective protection to algorithms. The patent system could drive innovation here as in other biomedical areas. However, the misalignment between black-box medicine and patent doctrine stretch beyond recent developments in the law and touches fundamental precepts of patents. Patents require disclosure as the *quid pro quo* for exclusivity, and black-box algorithms may be impossible to disclose fully in many circumstances.[149] And a fixed-term exclusivity matches poorly with potentially flexible and evolving algorithms. In addition, while recent cases could be overturned by, for instance, placing pure algorithms within the bounds of patentable subject matter, such a policy choice might create more problems than it solves. Black-box medicine algorithms may frequently resemble typical computer software patents and algorithms, which are criticized by academics, frequently disliked by the software industry itself, and a lasting target of reform efforts.[150] Algorithmic patents will also be difficult to enforce.[151] Overall, changes within the patent system seem

148. *See supra* Part III (describing hurdles to development, including the substantial costs involved).

149. *See supra* Part II.A.3.b.

150. For some examples of academic criticism, see Jay Dratler Jr., *Does Lord Darcy Yet Live? The Case Against Software and Business-Method Patents*, 43 SANTA CLARA L. REV. 823 (2003); Pamela Samuelson, Benson *Revisited: The Case Against Patent Protection for Algorithms and Other Computer Program-Related Inventions*, 39 EMORY L.J. 1025 (1990). For some examples of patent reform proposals and important considerations, see Colleen V. Chien, *Reforming Software Patents*, 50 HOUS. L. REV. 325, 350–90 (2012); Wendy Seltzer, *Software Patents and/or Software Development*, 78 BROOK. L. REV. 929, 985–87 (2013); Robert E. Thomas, *Debugging Software Patents: Increasing Innovation and Reducing Uncertainty in the Judicial Reform of Software Patent Law*, 25 SANTA CLARA COMPUTER & HIGH TECH. L.J. 191, 232–40 (2008). *But see* Martin Campbell-Kelly & Patrick Valduriez, *A Technical Critique of Fifty Software Patents*, 9 MARQ. INTELL. PROP. L. REV. 249, 280–81 (2005) (finding most frequently-cited software patents nonobvious and having genuine technical depth).

151. Methods patents are generally difficult to enforce, due to a combination of difficulty in observing what competitors are doing (that is, knowing that infringement is occurring) and in ensuring that all steps are being performed by individuals acting under the direction of a single actor under the Federal Circuit's rule in Muniauction, Inc. v. Thomson Corp., 532 F.3d 1318, 1330 (Fed. Cir. 2008). *See also* Rachel Sachs, Innovation Law and Policy: Preserving the Future of Personalized Medicine 19–24 (unpublished manuscript) (on file with author).

unlikely to successfully drive the development of black-box algorithms.

Regulatory exclusivity presents a more easily tailored exclusivity incentive than that provided by patent law. In regulatory exclusivity, a regulator excludes competitors from selling a product by withholding premarket approval.[152] Thus, regulatory exclusivity requires the existence of a premarket approval regime. In multiple contexts where such preapproval requirements exist, regulatory exclusivity is used as an innovation incentive;[153] in other situations, it has been proposed but not implemented.[154] The majority of extant applications of regulatory exclusivity are administered by the FDA, primarily around the marketing of small-molecule drugs and biologics.[155] If FDA approval were required for marketing black-box medicine algorithms, exclusivity could be offered; after approval, the FDA could withhold that approval from other firms offering similar algorithms for a fixed period of time as a reward to the innovator company. While regulatory exclusivity offers the advantage of flexibility, it suffers from the problems of a fixed-period exclusivity and the necessity of a preapproval regime, which brings its own problems.[156] However, in the case that the FDA proceeds with its current course and demands full regulatory approval of complex medical algorithms, exclusivity could be offered as an incentive for whatever black-box medicine algorithms remain possible.

The last exclusivity possibility is to rely not on active intervention, but rather on trade secrecy in light of other policy changes. As described above, trade secrecy matches quite well with black-box algorithms because by their very nature they cannot be fully disclosed. The method of developing the algorithm and the dataset can be disclosed, as can the results, but the underlying mechanisms of the relationships, and perhaps the relationships themselves, cannot be disclosed — or reverse-engineered or misappropriated — because they are unknown. Under this view, the major expenses of database development and validation should be the subject of active policy, but algorithm development should be protected, not by any particular policy incentive, but by advantages in quality, strength of validation, and cost-effectiveness. Algorithms impossible to disclose are difficult to

152. *See, e.g.*, Eisenberg, *supra* note 134, at 347–48; *see generally* Yaniv Heled, *Regulatory Competitive Shelters*, 76 OHIO ST. L.J. (forthcoming 2015) (on file with the author) (describing regulatory shelters, a taxonomy of types, and potential advantages and disadvantages as a public policy tool).

153. Heled proposes the more general term "regulatory competitive shelter" to describe this phenomenon. *See generally* Heled, *supra* note 152 (describing regulatory exclusivity regimes for drug, biologic, and pesticide development).

154. *See* W. Nicholson Price II, *supra* note 111, at 555.

155. Heled, *supra* note 152, at 149 (listing fourteen such regimes, of which thirteen are administered by the FDA and one by the Environmental Protection Agency).

156. *See supra* Part IV.C.2 (describing challenges with a preapproval approach).

duplicate, suggesting the effectiveness of trade secrecy for preventing appropriation.

Finally, in addition to exclusivity-oriented interventions, incentives for algorithm development could be offered through straightforward monetary rewards, in the form of grants or prizes. As an extensive literature addresses these possibilities in other contexts, they will not be discussed in detail here.[157]

c. Validation

Innovation policy should ensure that appropriate incentives exist to drive thorough validation.[158] A bounty could be implemented for external validation (with standards likely set by the FDA). Bounties could be set as a small fraction of revenues of the model overall — set as part of the initial regulatory exclusivity bargain, if one exists. The size of the reward would then roughly scale with the overall value of the model.[159] Rewards for confirmatory validation would ideally decrease asymptotically, so that initial validation would be much more valuable than further confirmation, but that any confirmation over a particular validity threshold receives at least *some* reward. This could be set to ensure that the overall fraction of originator revenue that

157. *See, e.g.*, Abramowicz, *supra* note 106, at 1121 (patent extension auctions); Michael Kremer, *Patent Buyouts: A Mechanism for Encouraging Innovation*, 113 Q.J. ECON. 1137, 1152–53 (1998) (discussing patent buyouts); Steven Shavell & Tanguy Van Ypersele, *Rewards Versus Intellectual Property Rights*, 44 J.L. & ECON. 525, 525–26 (2001) (arguing for the superiority of an optional prize system); Joseph Stiglitz, *Give Prizes Not Patents*, NEW SCIENTIST, Sept. 2006, at 21 (proposing monetary prizes); Marlynn Wei, *Should Prizes Replace Patents? A Critique of the Medical Innovation Prize Act of 2005*, 13 B.U. J. SCI. & TECH. L. 25 (2007) (examining prize systems and proposing a small-scale, optional prize system). *Contra, e.g.*, F. Scott Kieff, *Property Rights and Property Rules for Commercializing Inventions*, 85 MINN. L. REV. 697, 702–03 (2001) (arguing against prizes). For an overview of grants and prizes, which places them in a taxonomy with patents and tax incentives, and argues that all four can set economic incentives that should be at base indistinguishable to rational firms, see Hemel & Ouellette, *supra* note 142, at 310–13. For an argument that existing prize literature has exaggerated the differences between patents and prizes, see generally Benjamin N. Roin, *Intellectual Property Versus Prizes: Reframing the Debate*, 81 U. CHI. L. REV. 999 (2014). Roin also offers an extensive list of sources. *Id.* at 1001–02. This literature has typically not included regulatory exclusivity among the menu of options, perhaps because its exclusivity model parallels that of patents; to the extent that regulatory exclusivity has benefits over patents for certain fields of technological innovation, it may obviate certain criticisms that lead at least some scholars to prefer prizes.

158. *See supra* Part III.C.

159. One challenge is that focusing on monetary goals, whether revenue-based or savings-based, might focus incentives on models which deal primarily with costs rather than health improvements. If the principal goal of black-box medicine is cost-reduction, this focus would be unproblematic. However, if — as seems likely — improving health outcomes is either a primary objective of black-box medicine or at least an important ancillary objective, then an alternate path to valuing validation would be needed. An alternate possibility would be to offer rewards based on a combination of monetary savings and quality-adjusted life-years or disability-adjusted life-years.

could be siphoned to incentivize validation would remain constant.[160] On the contrary, rewards for finding problems should also exist, and should not decrease with repetition.[161] Grants or prizes could also potentially be deployed to create incentives for validation.

In sum, the substantial costs and hurdles involved in development of black-box medicine, coupled with the difficulty in appropriating returns from its information goods, suggest that significant policy incentives are needed. However, these incentives are better tailored to each phase of development, rather than trying to pursue a one-size-fits-all model by relying exclusively on patent law or trade secrecy.

B. Privacy

Black-box medicine raises significant privacy concerns as well. Large databases of detailed health information are required for the development of predictive and diagnostic algorithms. Those databases must be populated with data from individual people, and privacy is a major concern for those who might contribute data.[162] Datasets of health information, both genetic and otherwise,[163] implicate privacy concerns at the broad policy level, including discrimination, stigma, and dignitary harms.[164]

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160. For instance, for a validation cap of 2%, the first validator to pass a certain threshold could receive 1%, and each subsequent validator could receive half the amount of the previous validator; the sum of these fractions converges to 2%.

161. The incentives available for challenges to models might be expected to decrease naturally; if a model is called into question, its value presumably decreases and any fixed fraction of that value would also decrease. There are potential challenges to this approach, including falsification of the testing algorithms and eventual depletion of profits from the initial algorithm, but a fuller exploration of this mechanism must await future work.

162. *See* David J. Kaufman et al., *Public Opinion About the Importance of Privacy in Biobank Research*, 85 AM. J. HUM. GENETICS 643, 645–47 (2009) (finding that out of 4659 surveyed U.S. adults, 90% were concerned about privacy protections related to a proposed study).

163. Significant debate exists on whether genetic information raises meaningfully different privacy concerns than other health information. Genetic information has been likened to a "future diary," George J. Annas, *Privacy Rules for DNA Databanks: Protecting Coded "Future Diaries,"* 270 J. AM. MED. ASS'N 2346, 2347–48 (1993), and is subject to special protections under, among other laws, the Genetic Information Nondiscrimination Act of 2008, Pub. L. No. 110-233, 122 Stat. 881 (2008). Genetic information, in particular, can implicate the privacy not only of the individual, but also of his or her family. On the other hand, a NIH-Department of Energy Working Group concluded that genetic information is not substantially different from other health-related information, though it is undoubtedly sensitive. NIH-DEP'T OF ENERGY WORKING GRP. ON ETHICAL, LEGAL & SOCIAL IMPLICATIONS OF HUMAN GENOME RESEARCH, GENETIC INFORMATION AND HEALTH INSURANCE: REPORT OF THE TASK FORCE ON GENETIC INFORMATION AND INSURANCE (1993), *available at* http://www.genome.gov/10001750.

164. *See, e.g.*, Berrie Rebecca Goldman, *Pharmacogenomics: Privacy in the Era of Personalized Medicine*, 4 NW. J. TECH. & INTELL. PROP. 83, 84 (2005); Joseph Phelps et al., *Privacy Concerns and Consumer Willingness to Provide Personal Information*, 19 J. PUB. POL'Y & MARKETING 27, 28 (2000); Laszlo T. Vaszar et al., *Privacy Issues in Personalized Medicine*, 4 PHARMACOGENOMICS 107, 110 (2003).

Disclosure of personal health information raises the potential for discrimination in multiple contexts.[165] Discrimination by health insurers, where insurance would be refused to individuals with known health risks or genetic predispositions, is largely prohibited by the Affordable Care Act ("ACA") and other statutes.[166] In addition, genetic employment discrimination — based on worries about job performance or enhanced occupational risks — is a lasting concern, though it, too, has been largely addressed by the Genetic Information Nondiscrimination Act ("GINA")[167] and the Americans with Disabilities Act ("ADA").[168] However, discrimination in the market for life insurance against actuarially expensive patients remains unaddressed.[169]

In addition to discrimination in insurance and employment contexts, stigma based on the disclosure of personal health information is a major privacy concern. Individuals may face stigma based on existing disease states, such as HIV/AIDS,[170] or on a predisposition, such as that for Alzheimer's disease.[171]

Finally, there are dignitary harms from the disclosure of personal health information without consent. Control of personal health information, genetic or otherwise, is an important autonomy right for individuals.[172] Disclosure without consent impinges this autonomy right and harms the dignity of the individual whose data is disclosed.

In some respects, privacy and scientific development concerns seem to be directly opposed. Broader sets of available information in a dataset increase the power and number of relationships that can be identified, but also increase the likelihood that anonymous data can be reassociated with an individual.[173] Broader access to datasets increas-

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165. Fears about discrimination seem to be greater than the actual incidence of discrimination, though evidence is limited. *See* 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, 744 (2012).

166. *Id.*

167. Genetic Information Nondiscrimination Act §§ 201–208.

168. *See* Mark A. Rothstein, *GINA, the ADA, and Genetic Discrimination in Employment*, 36 J.L. MED. & ETHICS 837, 838 (2008).

169. *See* Yann Joly et al., *Genetic Discrimination and Life Insurance: A Systematic Review of the Evidence*, 11 BMC MED. 25, 25 (2013); Cathleen D. Zick et al., *Genetic Testing, Adverse Selection, and the Demand for Life Insurance*, 93 AM. J. MED. GENETICS 29, 29 (2000).

170. Angelo A. Alonzo & Nancy R. Reynolds, *Stigma, HIV and AIDS: An Exploration and Elaboration of a Stigma Trajectory*, 41 SOC. SCI. MED. 303, 305 (1995).

171. Peter J. Neumann et al., *Public Attitudes About Genetic Testing for Alzheimer's Disease*, 20 HEALTH AFF. 252, 259–60 (2001).

172. Lawrence O. Gostin, *Health Information Privacy*, 80 CORNELL L. REV. 451, 524 (1995).

173. *See generally, e.g.*, Bradley Malin & Latanya Sweeney, *How (Not) To Protect Genomic Data Privacy in a Distributed Network: Using Trail Re-Identification To Evaluate and Design Anonymity Protection Systems*, 37 J. BIOMED. INFO. 179 (2004); Paul Ohm, *Broken Promises of Privacy: Responding to the Surprising Failure of Anonymization*, 57 UCLA L. REV. 1701 (2010); Felix T. Wu, *Defining Privacy and Utility in Data Sets*, 84 U.

es the likelihood that a greater variety of actors can develop black-box algorithms, but decreases control over the information.[174] To the extent that privacy concerns decrease the number of individuals whose information can be included in datasets, these privacy issues also matter for algorithm robustness and ease of development.

Data collection must also meet the specific legal requirements of the Health Insurance Portability and Accountability Act, widely known as "HIPAA."[175] In relevant part, HIPAA limits the disclosure of patients' protected health information by "covered entities" and their "business associates": Covered entities include providers, health insurance plans, and healthcare clearinghouses.[176] Business associates include anyone who assists or performs any HIPAA-regulated activity on behalf of a covered entity, or provides services to the entity that involve individually identifiable health information.[177] The protected information includes medical records and billing records.[178] Generally, protected health information may only be disclosed by a covered entity with the patient's permission[179] or for certain narrowly defined permitted purposes.[180]

Consent for the sharing of health information for research purposes may be given without incentives or in exchange for monetary compensation,[181] though consent is challenging to obtain for past health records.[182] HIPAA also contains a broad exception, which allows

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COLO. L. REV. 1117 (2013); Jane Yakowitz, *Tragedy of the Data Commons*, 25 HARV. J.L. & TECH. 1 (2011).

174. *See supra* Part IV.A.3.a (describing datasets as infrastructure for future innovation). On the other hand, a substantial fraction of individuals have little concern over wide access to such data. *See* Kaufman et al., *supra* note 162, at 647 (noting that 49% of respondents were willing to have deidentified health information and research results "made available on the internet to anyone").

175. Health Insurance Portability and Accountability Act of 1996, Pub. L. No. 104-191, 110 Stat. 1936 (1996); *see* Cohen et al., *supra* note 44, at 1141 (describing HIPAA interactions with predictive analytics — a version of black-box medicine — and recommending collection of deidentified data while providing notice and possibly added privacy safeguards).

176. 45 C.F.R. § 160.102 (2014). Only providers who transmit health information in electronic form in connection with certain transactions are "covered entities." *Id.* Healthcare clearinghouses process information between different formats. 45 C.F.R. §§ 160.103, 164.500(b) (2014).

177. 45 C.F.R. § 160.103 (2014).

178. 45 C.F.R. § 164.501 (2014).

179. 45 C.F.R. § 164.510 (2014).

180. 45 C.F.R. § 164.502 (2014).

181. *See* Kaufman et al., *supra* note 162, at 645 (noting that 73% of respondents would probably or definitely "sign a consent to provide past medical records" as part of a proposed study).

182. *Cf.* Gert Helgesson et al., Letter to the Editor, *Ethical Framework for Previously Collected Biobank Samples*, 25 NATURE BIOTECH. 973, 974 (2007) (discussing the related issue of consent for samples in biobanks). Recontacting individuals whose records have previously been generated, but who are not currently in contact with the record-holder, can be an expensive proposition.

nonconsensual data use:[183] Patient-level data can be used without the patient's consent as long as that data is deidentified, either by removing eighteen named identifiers including city, name, and e-mail address; or by the declaration of an individual with appropriate expertise that "the risk [that data can be reidentified] is very small."[184] This exemption for deidentified data allows significant possibilities for assembling data,[185] but faces two problems. First, deidentification makes updating datasets much more challenging, especially when the updates derive from multiple sources.[186] Second, as more data are added to a particular person's record, even if standard identifiers are removed, the possibility of reidentification increases.[187] The first problem potentially increases the cost of developing black-box medicine, and the second reduces the practical effect of anonymization, though it does not compromise technical HIPAA compliance.

C. Regulation

The regulation of black-box medicine will also be central to its development and spread. Although regulation arises from different sources, including through the mechanism of tort law,[188] the FDA exercises the most prominent regulation authority of black-box medicine.[189] This Section will briefly describe the current regulatory regime governing the technology involved in black-box medicine, including the FDA's recently proposed changes to that regime, and will then discuss regulatory challenges of black-box medicine.

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183. *See* Barbara J. Evans, *Much Ado About Data Ownership*, 25 HARV. J.L. & TECH. 69, 82–86 (2011) (discussing nonconsensual use of data).

184. 45 C.F.R. § 164.514(b) (2014).

185. Cohen et al., *supra* note 44, at 1141; Vaszar et al., *supra* note 164, at 107.

186. The challenge arises because data are anonymized by removing a patient's name or identifying information and instead associating the data with a unique identifier. For an example of irrevocable identification stripping, see Jill Pulley et al., *Principles of Human Subjects Protections Applied in an Opt-Out, De-Identified Biobank*, 3 CLINICAL TRANSLATIONAL SCI. 42, 43–46 (2010), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3075971/. As long as future data from that patient can be associated with the same unique identifier, that data can be added to the anonymous record. However, if data about the patient is anonymized in different ways from different data sources (e.g., if John Smith becomes XB17562 in one database, but 15064324C in a different database), it is difficult if not impossible to combine those records. Other databases and biobanks allow the possibility of reidentification.

187. *Id.* at 45.

188. Black-box medicine raises significant tort law questions: If an algorithm is unknown or impossible to disclose, under what context can physicians be liable for decisions relying on that algorithm? Is knowledge of the reliability of the algorithm sufficient to immunize against such liability? These questions, and other issues of tort law, are outside the scope of this Article but are important for the development of black-box medicine.

189. In addition — and in tension with — the FDA's regulation of black-box medicine as a medical device, black-box medicine can be considered a form of practicing medicine, which is typically not under the FDA's jurisdiction. Rather, this is governed by state law. Exploring the scope of this juxtaposition is outside the scope of this Article.

1. Existing Regulatory Structures

Although the FDA has long left diagnostic tests relatively unregulated, that situation has recently begun to change, so that black-box medicine will likely be subjected to more stringent requirements. As a baseline, the FDA exercises regulatory authority over medical devices, which are subject to premarket approval under the Federal Food, Drug, and Cosmetic Act ("FDCA").[190] "Medical device" is defined very broadly to include any "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article . . . which is . . . 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."[191] *In vitro* devices are a subset of devices used in diagnosis.[192] As apparatuses "intended for use in the diagnosis of disease or other conditions," the computer systems used in black-box medicine likely fall under this broad definition of "medical device."[193]

Medical devices are subject to a premarket-approval regime based on risk classification from low-risk (Class I) to high-risk (Class III).[194] Class I devices are subject only to general controls.[195] Class II devices require premarket approval, but that approval can be based on a determination that the product is substantially equivalent to an already-approved product.[196] Class III devices require a full premarket approval process, which is substantially more expensive and time-consuming than either simple notification or demonstration of equivalence under Class II regulations.[197]

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190. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended in scattered sections of 21 U.S.C.); 21 U.S.C. § 360c(a)(1) (2012).

191. FDCA § 321(h). Devices also include instruments, etc., which either are recognized as such in the National Formulary or the United States Pharmacopeia or are "intended to affect the structure or any function of the body of man or other animals." *Id.* Devices must not primarily operate through chemical action within or on the body. *Id.*

192. The FDA defines "*in vitro* diagnostic devices" as "those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae." 21 C.F.R. 809.3(a) (2014).

193. The FDA has taken an expansive interpretation that computer systems dealing with health information are properly classified as medical devices. *See* 21 C.F.R. § 880.6310 (2014) (defining medical device data systems as devices which transfer, store, convert, or display electronic data from medical devices). On the other hand, at least some forms of black-box medicine could be characterized as pure data, that is, datasets, algorithms, predictions, and recommendations with no affiliated apparatus at all. Under such a view, black-box medicine would appear much closer to the pure practice of medicine rather than as a regulable device. A full analysis of this question is outside the scope of this Article, but the FDA's treatment of diagnostic laboratory-developed tests will undoubtedly be the subject of scholarly attention and, potentially, litigation.

194. 21 U.S.C. § 360c(a)(1).

195. *Id.*

196. *Id.* at §§ 360c(a)(1), 360c(i).

197. *Id.* at §§ 360c(a)(1), 360e.

Until quite recently, a large fraction of black-box medicine developers could expect shelter from this regulatory structure under the FDA's exercise of enforcement discretion with respect to laboratory-developed tests ("LDTs") — but no longer. Since the creation of this regime in 1976 in the Medical Device Amendments, the FDA has not enforced premarket approval requirements for *in vitro* devices that are "designed, manufactured, and used within a single laboratory."[198] While such LDTs were initially relatively simple tests using FDA-approved clinical materials, the category has expanded dramatically to include complex diagnostics run through a central facility.[199] The FDA, reacting to this change, is reconsidering its policy of enforcement discretion, and in July 2014, informed Congress that it intended to regulate LDTs comprehensively under the risk-based framework applied to all *in vitro* devices.[200] Adding to the likelihood that the FDA will regulate the technologies involved in black-box medicine, the FDA specifically described potential risk factors in modern LDTs, including that many LDTs are "used to direct critical treatment decisions (e.g., prediction of drug response)" and/or are "highly complex (e.g., automated interpretation, multi-signal devices, use of non-transparent algorithms and/or complex software to generate device results)."[201] These characteristics are central to the concept of black-box medicine, and thus significantly increased FDA regulation appears likely.[202]

The eventual classification of black-box medicine implementations will await FDA action.[203] However, the FDA has identified as a

198. FOOD AND DRUG ADMIN., U.S. DEP'T OF HEALTH & HUM. SERVS., DRAFT GUIDANCE FOR INDUSTRY, FOOD AND DRUG ADMINISTRATION STAFF, AND CLINICAL LABORATORIES: FRAMEWORK FOR REGULATORY OVERSIGHT OF LABORATORY DEVELOPED TESTS (LDTS) 6 (2014).

199. *Id.* at 7–8. Arguably, the FDA's exercise of enforcement discretion with respect to LDTs created incentives for innovators developing new tests to keep them centralized to a laboratory instead of selling diagnostic kits or otherwise distributing the technology. This could be viewed negatively, as firms exploiting the agency's policy choice, or positively, as the agency deliberately allowing space for innovation or attempting to avoid controversial limitations on the development of new medicine. *See* Sharon Jacobs, *The Administrative State's Passive Virtues*, 66 ADMIN. L. REV. 565, 623 (2014) (arguing the benefits of agency decisions not-to-decide or to decide issues piecemeal).

200. Letter from Sally Howard, Deputy Comm'r, FDA, to Tom Harkin, Chairman of the Comm. on Health, Educ., Labor and Pensions, United States Senate (Jul. 31, 2014), *available at* http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf.

201. FOOD AND DRUG ADMIN., *supra* note 198, at 8.

202. This discussion elides the question of the extent to which regulation of black-box medicine is desirable, rather than merely expected. Instead, it focuses briefly on the regulatory challenges that might arise, given the likelihood of regulation.

203. In determining the risk classification of an LDT, the FDA will consider, among other factors, the risk level of the disease/patient population, use in screening versus diagnosis, what clinical decision will be based on the test, the availability of other information in making that decision, alternatives for diagnosis and treatment, the cost of error, and the existence of adverse events. FOOD AND ADMIN., *supra* note 198, at 12.

generally higher-risk class those devices "that act like companion diagnostics," including those "that claim to enhance the use of a specific therapeutic product, through selection of therapy, patient population, or dose, but which are not included in the therapeutic product labeling (e.g., devices . . . that claim to predict who will respond to a therapy approved for use in a larger population)."[204] The FDA will likely find that this definition applies to most of black-box medicine, and thus, implementation of black-box medicine will often be subject to greater approval hurdles.

2. Regulatory Challenges

Black-box medicine is an awkward fit for the FDA's typical regulatory paradigm.[205] The FDA approval process focuses on explicit knowledge, typically derived from systematic experimentation and clinical trials; in fact, the premarket approval process in particular almost always requires clinical trials.[206] Black-box medicine, on the other hand, by definition relies on implicit processes and relationships that are not amenable to explication and straightforward validation through clinical trials.[207] To the extent that FDA preapproval relies on clinical trials to demonstrate safety and efficacy — as the premarket approval process does — black-box medicine will face major challenges meeting those goals. As mentioned briefly earlier, validation of black-box medicine requires rechecking algorithms, ideally with parallel development models.[208]

A second key challenge of applying FDA regulatory approaches to black-box medicine — particularly a preapproval approach — is the inherent plasticity of at least some forms of black-box medicine. Some black-box medicine models can be static, that is, developed based on a static set of data, validated, and then stabilized after initial development. Others can be dynamic, with an algorithm that considers additions to the dataset and updates the predictive model in response. This latter type fits extremely poorly into a preapproval regime, which approves one product at a time with the expectation that such a product will remain constant for enough time to recoup the cost and effort of regulatory approval.

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204. *Id.* at 26–27.

205. *See* PRIORITIES FOR PERSONALIZED MEDICINE, *supra* note 25, at 40 (noting the potential for heavy-handed or uncertain FDA regulation to stifle the development and adoption of personalized medicine).

206. *See PMA Clinical Studies*, FDA, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050419.htm (last updated Sept. 5, 2014).

207. However, some form of overarching clinical trial is possible, as mentioned *supra* note 95.

208. *See supra* Part III.C.

3. Potential Regulatory Solutions

The status quo/business-as-usual approach is unlikely to allow the innovative development of algorithmic medicine, with its attendant benefits. Three potential oversight mechanisms might ameliorate the situation. First, the FDA could shift to an adaptive certification role, drawing from the extensive efforts — both policy and scholarly — on adaptive governance and regulation. Under this approach, rather than requiring one-shot premarket approval of black-box medicine implementations, the FDA could more dynamically allow market access subject to increased validation, historical success, and monitoring of benefits and adverse events.

Second, the FDA could rely more heavily on third-party validation of black-box medicine techniques, either as a precondition of marketing or as a continuing evaluation after early limited market approval. As described above, expert third parties can rigorously evaluate algorithms by completing parallel testing on the same datasets, checking new test datasets, and also completing quality-control checks on development methods.[209] Third-party validation has the potential to be more nimble and flexible than oversight through the FDA's regulatory structure; rather than trying to increase the agency's agility, that role can be outsourced to private parties.[210] Third parties could be compensated either directly by the FDA or through a bounty-based system as described previously, which would create strong incentives for critical evaluation.[211]

Third and finally, the FDA could implement a less centralized oversight regime based on as much transparency as possible. In each of the prior two possibilities, confidentiality could be maintained for the data on which the initial black-box medicine developer based its algorithms, for the algorithmic development, and for the algorithms themselves. Some aspects, such as the precise structures of the algorithms and the relationships underlying them, could not be disclosed in any case; such is the nature of black-box medicine. A transparency model would mandate disclosure of much if not all of the information capable of being disclosed, which would open the algorithms up to examination by a larger range of parties, including the agency — which would likely retain some role — and both commercial and non-commercial third parties. The clearest role here would be for academics demonstrating problems with black-box medicine implementations. Since transparency would sharply curtail the availa-

209. *Id.*

210. The FDA already allows some such outsourcing; for instance, the definition of medical device includes those items categorized as such in the privately run U.S. Pharmacopeia and the National Formulary. FDCA, 21 U.S.C. § 321(h) (2012).

211. *See supra* Part IV.A.3.c.

bility of trade secrecy, it would need to be coupled with other innovation incentives.[212]

None of these regulatory mechanisms is a panacea. However, each possibility seems better suited to the new phenomenon of black-box medicine than attempting to shoehorn nontransparent and potentially plastic algorithms into a clinical-trial-based model ill-suited for their evaluation and approval.

D. Commercialization

A fourth and final challenge for black-box medicine lies in its commercialization, and especially in insurance reimbursement. While commercialization does not always raise policy concerns, the public health and social justice aspects of black-box medicine suggest that the issue is worth attention. If black-box medicine does indeed create significant improvements in medical care,[213] such improvements have the potential to improve health and lower health care costs, but only if the technology is actually adopted into medical practice. With respect to social justice, black-box medicine could also easily become an expensive technology, the province of only wealthy patients. To combat this possibility, adoption should be widespread and should interface with programs designed to provide health care access to disadvantaged populations.[214]

1. Reimbursement

Payment is the dominant concern for adoption of a newly available medical technology. Doctors must be paid for using the new technology, and in the world of health care, that largely means that insurers, whether public or private, must make or reimburse that payment.[215] Accordingly, reimbursement decisions by insurance providers, whether public or private, are a key concern for black-box medicine. Although the standard reimbursement rubric is likely to be problematic for black-box medicine, public policy could drive overall

212. *See supra* Part IV.A.

213. This assumption is difficult to verify or falsify, as black-box medicine is still in early development. Personalized medicine, moreover, has made less of a difference to medical practice than its early proponents promised, suggesting that some skepticism may be in order. However, the magnitude of the problem — variable drug response and languishing second uses for approved medicines, in particular — and the enormous trove of data creates grounds for at least cautious optimism about black-box medicine's potential impact.

214. *See* Cohen et al., *supra* note 44, at 1146.

215. Without insurance, doctors can still be paid for treatment, of course. However, if treatments not covered by insurance are expensive, they may be beyond the reach of non-wealthy patients, raising concerns about both the breadth of patient adoption and about the equitable use of new technology.

adoption by encouraging reimbursement by public insurers, especially Medicare and Medicaid.

Reimbursement decisions are made both publicly and privately, and at both national and local levels. For public payers, the Centers for Medicare and Medicaid Services ("CMS") make national decisions about reimbursement; these decisions are typically the bellwether for private reimbursement decisions.[216] Medicare only reimburses genetic tests where they are "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."[217] National coverage decisions apply to all Medicare contractors and administrative law judges.[218] In the absence of FDA approval for laboratory-developed tests,[219] which make up the majority of explicit personalized medicine diagnostic tests, the Medicare Evidence Development and Coverage Advisory Committee has advised CMS to consider Medicare reimbursement for genetic testing only where there is strong evidence that it improves health outcomes.[220] However, outside the national decision structure, local Medicare Administrative Contractors can approve personalized medicine tests for reimbursement, sometimes with national effect.[221] Medicare does not reimburse for asymptomatic screening tests.[222]

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216. Michael D. Graf et al., *Genetic Testing Insurance Coverage Trends: A Review of Publicly Available Policies from the Largest US Payers*, 10 PERSONALIZED MED. 235, 235 (2013).

217. 42 U.S.C. § 1395y(a)(1)(A) (2012); *see also* SECRETARY'S ADVISORY COMMITTEE ON GENETICS, HEALTH, AND SOCIETY, FINAL REPORT: COVERAGE AND REIMBURSEMENT OF GENETIC TESTS AND SERVICES (2006), *available at* http://oba.od.nih.gov/oba/sacghs/reports/CR_report.pdf.

218. *See, e.g.*, 42 C.F.R. § 405.1060(a)(4) (2014).

219. *See supra* Part IV.C.

220. Meeting Notice, 74 Fed. Reg. 10918 (Mar. 13, 2009); Meeting Notice, 73 Fed. Reg. 77717 (Dec. 19, 2008).

221. 42 U.S.C. § 1395ff(f)(2)(b) (2012). Although Medicare Administrative Contractors only approve local reimbursement, as long as at least 14 days elapse between a physician's request for a test and the laboratory's conducting that test, reimbursement is determined on the basis of the laboratory's location instead of the patient's location. CMS, MEDICARE CLAIMS PROCESSING MANUAL, ch. 1, § 10.1.5.4, *available at* http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS018912.html. Accordingly, many laboratory-developed tests have national reimbursement scope based on local decisions of the jurisdiction encompassing the location of the laboratory. For instance, a local coverage decision that covered several Western states nationalized reimbursement for BRCA1 and BRCA2 genetic testing, as the only laboratory doing such testing — Myriad Genetics — lay within that decision's jurisdiction. CMS, LOCAL COVERAGE DECISION: GENETIC TESTING (2014), *available at* http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=24308&ContrId=356&ver=73&ContrVer=1&Date=04%2f23%2f2009&DocID=L24308&bc=iAAAAAgACAAAAA%3d%3d&.

222. CMS, MEDICARE CLAIMS PROCESSING MANUAL, ch. 16, § 120.1, *available at* http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS018912.html ("Tests that are performed in the absence of signs, symptoms, complaints, personal history of disease, or injury are not covered except when there is a statutory provision that explicitly covers tests for screening as described.").

Private insurers must make similar coverage decisions and, in the absence of FDA approval, look to Medicare and Medicaid reimbursement decisions — both national and local — and professional guidelines.[223] Reimbursement for the explicit personalized medicine diagnostic tests available today is "limited and variable" between different tests and different insurers.[224] Reimbursement is generally driven by the strength of the available clinical evidence; tests with better clinical evidence are more likely to be covered by more insurers.[225] About a third of private insurers reimburse at least one genetic test as of October 2013.[226] The genetic tests most commonly reimbursed by private payers are related to cancer.[227] Roughly half of all insurance policies explicitly exclude coverage of a particular genetic test.[228]

The current reimbursement landscape for explicit personalized medicine does not suggest an easy road for reimbursement of black-box medicine. Full FDA approval would facilitate reimbursement,[229] but as described above, such an approval requirement is likely to stunt its development.[230] Absent such approval, public and private programs typically require strong clinical evidence of improved medical outcomes; the evidence for pharmacogenomics testing to determine the optimal dose for the drug warfarin, for instance, was deemed insufficient in 2009 to justify Medicare reimbursement.[231] This type of explicit clinical evidence is unlikely, by design, to be present for the vast majority of black-box medicine; if black-box medicine is subject to the same reimbursement rubric, it will almost certainly not be reimbursed. In addition, because Medicare reimburses only tests to aid in diagnosis and treatment — that is, not asymptomatic or prophylactic screening — predictive black-box medicine aimed at catching problems before they become serious are unlikely to be reimbursed.

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223. Marc S. Williams, *Genetics and Managed Care: Policy Statement of the American College of Medical Genetics*, 3 GENETICS MED. 430, 433–34 (2001).

224. Joshua P. Cohen & Abigail E. Felix, *Personalized Medicine's Bottleneck: Diagnostic Test Evidence and Reimbursement*, 4 J. PERSONALIZED MED. 163, 171 (2014).

225. Lisa M. Meckley & Peter J. Neumann, *Personalized Medicine: Factors Influencing Reimbursement*, 94 HEALTH POL'Y 91, 92–94 (2010).

226. Graf et al., *supra* note 216, at 235.

227. *Id.* at 239.

228. *Id.* at 238.

229. Under 42 C.F.R. § 411.15(o) (2014), experimental or investigational devices are generally not eligible for reimbursement.

230. *See supra* Part IV.C.2.

231. *See, e.g.*, CMS, CAG-00400N, DECISION MEMO FOR PHARMACOGENOMIC TESTING FOR WARFARIN RESPONSE (Aug. 3, 2009), *available at* http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=224&NcaName=Pharmacogenomic+Testing+for+Warfarin+Response&DocID=CAG-00400N&id=224; BLUECROSS BLUESHIELD OF ALABAMA, GENE-BASED TESTS FOR SCREENING, DETECTION, AND/OR MANAGEMENT OF PROSTATE CANCER (2014), *available at* https://www.bcbsal.org/providers/policies/final/534.pdf; *see also supra* notes 35–37 and accompanying text.

Black-box medicine promises better care, more individualized care, with lower overall costs;[232] theoretically, then, this is something that both profit-motivated private insurers and health-and-funding-motivated public payers should prefer. However, adoption of new medical technologies for reimbursement inevitably faces the challenges described above, and the key differences of black-box medicine (complex implicit relationships and the absence of explanatory clinical trials) make those challenges greater.

Nevertheless, CMS can play a clear and leading role in facilitating reimbursement of black-box medicine and adoption generally. CMS could broaden its requirement for significant evidence of medical improvement to include not only clinical evidence, but also validation of the type discussed above.[233] Similarly, CMS could recognize that complex algorithmic medicine may blur the line between diagnostic testing, once symptoms exist, and asymptomatic screening: Holistic algorithms which take into account a large set of biomarkers and other data may perform both functions and could realistically be reimbursed even if not purely diagnostic or treatment-oriented.

At least in the current setting, where CMS leads, private insurers often follow, suggesting that CMS adoption could drive reimbursement for black-box medicine generally.[234] Even if private insurers did not follow the policy choice for its own merits, widespread adoption by CMS would drastically increase the data available if implementation studies followed. This increase in data would allow other payers to follow suit even without deviating from their own standard evidentiary requirements. Finally, CMS decisions to allow the reimbursement of black-box medicine implementations would counter some concerns about equity, as CMS pays for medical care for many of the relatively disadvantaged.

2. Adoption

An additional related concern is the adoption of black-box medicine by patients and doctors in practice. In particular, the implicit nature of black-box medicine creates at least potential problems for trust: If doctors do not know the biological relationships underlying a validated black-box medicine recommendation and cannot explain it to patients, will they be less likely to adopt that recommendation as their own? Will patients be less likely to accept advice if they cannot

232. Even if black-box medicine is costly in itself, avoiding more costly complications and disease progression should offset that cost.

233. In an integrated policy structure, CMS approval of certain types of validation could be used as a lever to drive that type of validation and to ensure the quality of black-box medicine as an unconventional innovation incentive. This possibility, while promising, is outside the scope of this Article.

234. Graf et al., *supra* note 216, at 235.

understand its genesis because no one does?[235] And, if so, how can law and policy choices facilitate acceptance by patients and providers?[236]

Law could help address this adoption concern in at least two different ways, either by directly enhancing trust or by altering the incentives to offset the trust deficit. Under the first possibility, approved or well-validated black-box medicine implementations could be given a formal imprimatur. The formal FDA approval process would certainly be such an assurance of efficacy, though as discussed above, the standard FDA process has problematic effects on the development of black-box medicine in the first place.[237] Third-party certification could provide a similar effect, provided that the third party is itself either officially certified or acquires trustworthiness of its own.

The second possibility requires adjusting treatment incentives to offset the problem of trust in implicit mechanisms, at least long enough to drive initial adoption. For instance, to allay fears of malpractice suits arising from the use of a new and inherently nontransparent form of medicine, specialist associations (or state lawmakers) could make clear that some set of implementations — presumably, those well-validated as described above — would be accepted as within the standard of care.[238] Such measures would ideally have only temporary effects; once a particular black-box implementation reached widespread use, it would presumably be acceptable as the standard of care on its own merits (or similarly, fail on its own merits).[239] Along these lines, no policy action in this respect might actually be needed; the potential benefits of black-box medicine could themselves provide enough of an incentive to drive initial adoption.

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235. Black-box medicine also raises potential issues of informed consent, though those are outside the scope of this Article.

236. One potential response, admittedly somewhat cynical, is recognition that doctors and patients already accept treatments even though they have relatively little knowledge of the evidence for those treatments. *See, e.g.*, Donna T. Chen et al., *U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey*, 18 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 1094, 1097–99 (2009) (finding physicians could only correctly identify whether a drug was FDA-approved for a particular indication 55% of the time on average); Editorial, *Mechanism Matters*, 16 NATURE MED. 347, 347 (2010) (noting that mechanism of action is unknown for many drugs). However, even given that possibility, it seems likely that at least some knowledge is better than none.

237. *See supra* Part IV.C.2.

238. This approach, at least in its private form, is challenged by the resistance courts have shown to giving conclusive effect to clinical practice guidelines. *See generally, e.g.*, Conn v. United States, 880 F. Supp. 2d 741, 745–47 (S.D. Miss. 2012) (discussing judicial differences on the utility of clinical practice guidelines in establishing the standard of care); Michelle M. Mello, *Of Swords and Shields: The Role of Clinical Practice Guidelines in Medical Malpractice Litigation*, 149 U. PA. L. REV. 645 (2001).

239. Indeed, interventions to classify a particular implementation as acceptable care *should* be temporary, so as to avoid ossifying treatment options.

V. CONCLUSION

Overall, black-box medicine offers immense promise for changing the way medicine is practiced and the way medical technologies are created and deployed. Instead of waiting for the painstaking development of explicit knowledge through the clinical trial pathway, limited by coordination, the number of available subjects, and the identification of intersecting biological pathways, the continually growing trove of health data allows underlying relationships to be leveraged to improve health, lower the cost of developing treatments, and better tailor medical recommendations and treatments. However, the path forward is neither smooth nor straightforward. Careful attention is needed to the legal and policy areas implicated by black-box medicine, including innovation incentives, privacy, regulation, and commercialization. The infrastructure for innovation is not just in datasets and computers; it also encompasses the policies surrounding emerging technology. This Article seeks to lay the initial groundwork for law and policy surrounding black-box medicine and to begin a conversation about how best to shape the legal infrastructure for the future of medicine.