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Essay

Precision medicine: drowning in a regulatory soup?

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genetic inventions, as well as the specific regulatory issues associated with genetic, genomic, cloning and stem cell technologies, and biobanking.

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INTRODUCTION

As US President Barack Obama noted in his 2015 State of the Union address, precision medicine promises to deliver 'the right treatments, at the right time, every time to the right person' which 'gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen'.[1] These comments were a prelude to a $215 million funding commitment by the President to his Precision Medicine Initiative, the aim of which is to 'pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients'.[2] The objectives include an undertaking to modernize the current regulatory landscape.

Some six months prior to this address, a group of international scholars in the disciplines of law, biomedicine, bioethics, and the social sciences met at the other end of the world in Hobart, Australia to workshop the challenges involved in formulating a coherent regulatory framework for precision medicine. The inspiration for the workshop title, *Leading or Limping? Regulation of Personalized Medicine*, came from a famous observation by one of Australia's most eminent High Court judges, Justice Victor Windeyer in the case of *Mount Isa Mines Ltd v Pusey* (1970) 125 CLR 383 at 395, where he referred to the law as 'marching with medicine but in the rear and limping a little'. The language of personalized medicine, rather than precision medicine, was used at the workshop, because at that time it was the more common term.[3]

The terms 'precision', 'personalized', and 'medicine' already hint at some of the regulatory challenges that lie ahead. 'Precision' implies that the product or service being offered is accurate and targeted. Like any novel area, the frontier is often filled with a

health technologies, and legal aspects of health system reform. She is a recipient of the 2015–16 Australian Fellowship in Health Services Research and Policy.

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1 Jocelyn Kaiser, *Obama gives East Room Rollout to Precision Medicine Initiative*, SCIENCE DOI: 10.1126/science.aaa6436 (Jan. 30 2015).

2 The White House, *Fact Sheet: President Obama's Precision Medicine Initiative*, https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative (accessed April 23, 2016).

3 Sebastian Schleidgen et al., *What is Personalized Medicine: Sharpening a Vague Term Based on a Systematic Literature Review*, 14 BMC MED. ETHICS 55 (2013); see also US Food and Drugs Administration, *Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development*, 6 (2013).

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variety of new players some of whom will see a huge commercial opportunity and may push the boundaries of acceptability in terms of their claims. In addition, novel risks of harm to individuals may rise or be exacerbated by the new technologies. We therefore need to be assured that appropriate regulatory requirements are in place so that precision medicine can be undertaken efficiently and safely and in a manner that facilitates the translation of research into effective therapies.

Language that focuses attention on the 'person' immediately raises questions around personhood and privacy. As knowledge and understanding of personal health increases, so too do the potential threats to personal privacy. 'Medicine' implies that these new advances sit within the established medical care system, with all the regulatory checks and balances that go along with it. Yet, we will see in the discussion that follows that one of the features of precision medicine is the blurring of boundaries between the clinic, the laboratory, and the healthcare industry, creating new regulatory spaces.[4] On the one hand, this raises questions about the capacity of existing regulatory structures to respond. On the other hand, it risks regulatory overlap and confusion, a veritable 'regulatory soup' that could drown the promised advances in precision medicine.

Before we start to consider how precision medicine should be regulated, we need to be clear about what we mean by regulation. Here, the broad approach as Roger Brownsword and Morag Goodwin is adopted:

> … we can treat 'regulation' as encompassing any instrument (legal or non-legal in its character, governmental or non-governmental in its source, direct or indirect in its operation, and so on) that is designed to channel group behaviour; and we can treat as a 'regulator' any person or body who initiates regulation in this broad sense.[5]

In many ways, the regulatory challenges presented by precision medicine are reformulations of old tensions—community welfare versus individual liberty, risk versus benefit, autonomy versus paternalism. The potential for precision medicine to exacerbate existing disparities in health care, both within countries and internationally, should also be at the forefront of our concerns.[6]

Here, we provide an overview of some of the more substantive issues that are likely to arise in responding to the perceived need to modernize the current regulatory landscape for precision medicine. The issues considered are largely based on discussions at the workshop, together with some of the more notable policy and academic commentaries. In the first part of this essay, we outline some of the major technological advances in the fields of precision medicine, including genome sequencing, pharmacogenomics, genomic analysis, gene editing, and biobanking. We go on to consider the regulatory landscapes within which these technologies are positioned with particular focus on what is needed to ensure that regulation is effective in the future.

4 On the broad concept of regulatory space see Colin Scott, *Analysing Regulatory Space: Fragmented Resources and Institutional Design*, Pub. L, 329 (2001).

5 Roger Brownsword & Morag Goodwin, Law and the Technologies of the Twenty-first Century 25 (2012).

6 Kyle Brothers & Mark Rothstein, *Ethical, Legal, and Social Implications of Incorporating Personalized Medicine into Healthcare*, 11 Pers. Med. 43 (2015).

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THE PROMISE OF PRECISION MEDICINE

Claims that precision medicine will deliver more personalized healthcare, tailored to an individual's genetic characteristics, health status and family history, are supported by several recent developments, particularly targeted therapies for the treatment of cancers.[7] Some commentators, however, are skeptical about the extent to which precision medicine research will, in the near future, be translated into genuine improvements in the delivery of healthcare.[8] Recognizing the need for dispassionate evaluation of the promise of precision medicine, there is, nevertheless, little doubt that it sits within a rapidly changing milieu, as illustrated in Fig. 1.

During the past two decades, new technological developments such as massively parallel DNA sequencing have enabled high throughput analysis of DNA, RNA and proteins.[9] These developments have facilitated increased utilization of genetic and genomic information in the research context to provide valuable insights into the role of these factors in human health and wellbeing. This same genetic and genomic information is being used by clinicians in the delivery of healthcare, including assessing a person's predisposition to disease and assisting with their diagnosis and prognosis, as well as informing treatment decisions.[10] Whilst manufacture of new drugs has long been the province of pharmaceutical companies, the commercial sector is becoming increasingly involved in the delivery of healthcare, in particular diagnostic testing, once the exclusive purview of the medical profession.

Genome sequencing advances

Continuing advances in genome sequencing technology, together with massive reduction in costs, are together allowing multiple genetic variations to be assayed at the same time, often for the same cost as a single gene test.[11] Both whole exome sequencing (sequencing of the active components of human genes that code for proteins) and whole genome sequencing (WGS) are now feasible.[12] Given the possibility of extending testing well beyond the gene of interest indicated by clinical assessments, there has been

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7 Eric D. Green, Mark S. Guyer National Human Genome Research Institute, *Charting a Course for Genomic Medicine from Base Paris to Bedside,* 470 NATURE 204 (2011); see also Don Chalmers et al., *Personalised Medicine in the Genome Era,* 20 J. L. & MED. 577 (2013).

8 See eg the British Medical Journal blog post by Tim Caulfield, *Genetics and Personalized Medicine: Where's the Revolution,* http://blogs.bmj.com/ce/2015/07/23/genetics-and-personalized-medicine-wheres-the-revolution/?utm_campaign=shareaholic&utm_medium=twitter&utm_source=socialnetwork (accessed April 23, 2016) and articles in the popular press, Michael J. Joyner, *'Moonshot' Medicine Will Let Us Down,* N. Y. TIMES, 29 Jan. 2015; H Gilbert Welch & Wylie Burke, *Why Whole Genome Testing Hurts More Than It Helps,* LOS ANGELES TIMES, 27 Apr. 2015.

9 Green, Guyer & National Human Genome Research Institute, *supra* note 7, at 205; Elaine S. Mardis, *A Decade's Perspective on DNA Sequencing Technology*, 470 NATURE 198 (2011); David A Wheeler et al., *The Complete Genome of an Individual by Massively Parallel DNA Sequencing*, 452 NATURE 872 (2008).

10 Francis S. Collins & Harold Varmus, *A New Initiative on Precision Medicine*, 372 NEW ENG. J. MED 793 (2015).

11 These cost reductions were already having an impact as early as 2011. See eg Eric S. Lander, *Initial Impact of the Sequencing of the Human Genome*, 470 NATURE 187 (2011).

12 For a useful overview of the key differences between whole genome and exome sequencing, see Illumina, *An Introduction to Next-generation Sequencing*, http://www.illumina.com/content/dam/illumina-marketing/documents/products/illumina_sequencing_introduction.pdf (accessed April 23, 2016).

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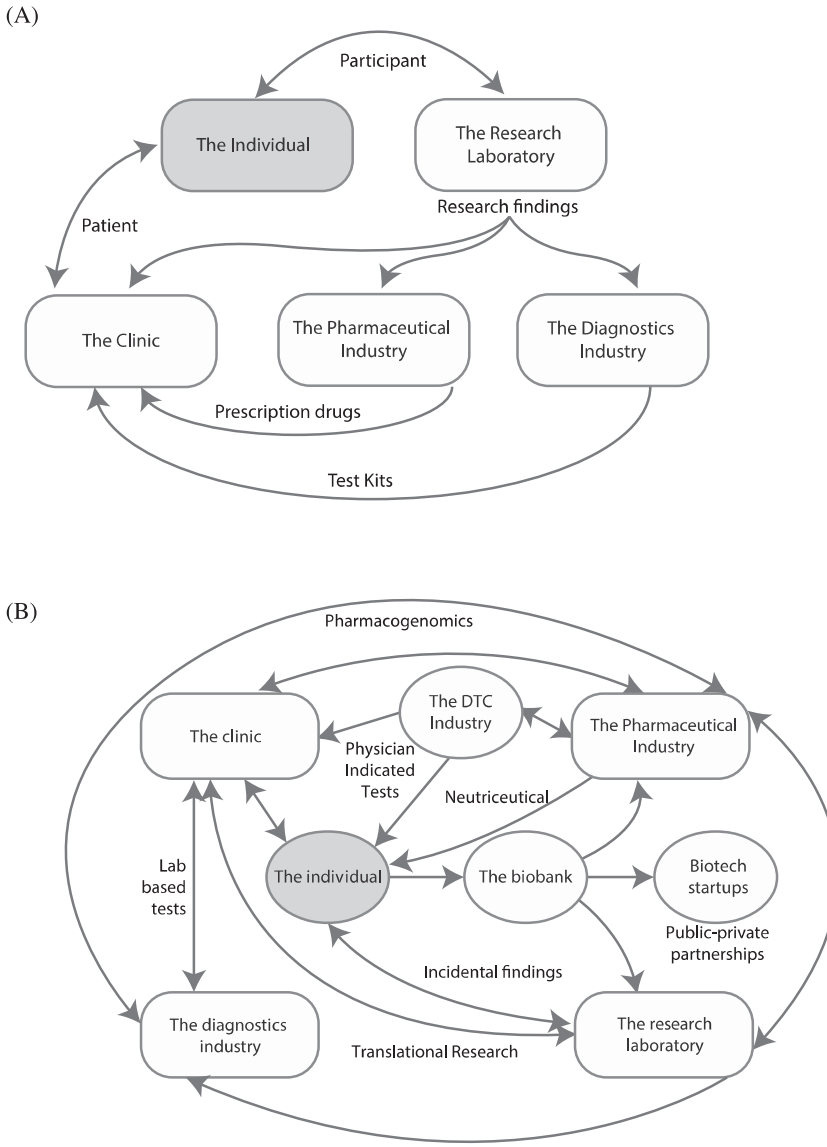


Figure 1. The changing milieu of healthcare. A. Traditional relationships between the individual and biomedical sector participants. B. Changing relationships and participants in the genomic era.

some debate as to whether there is a duty of care to assess all known genetic alterations that may be present, in both the clinical and the research context.[13]

13 Robert C. Green et al., *ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing*, 15 Genet. Med. 565 (2013); American College of Medical Genetics and Genomics, *Incidental Findings in Clinical Genomics: A Clarification*, https://www.hgsa.org.au/documents/item/582 (accessed April 23, 2016); Madhuri Hegde et al., *Reporting Incidental Findings in Genomic Scale Clinical*

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This era of more rapid genomic analysis has also witnessed the expansion of the for-profit private sector providing genomic services.[14] One of the leading sequencing companies, Illumina, is offering WGS to researchers and clinicians at rapidly reducing prices. For example, in 2011 it was offering whole tumor genome sequencing for around US$30,000.[15] By 2014, the company announced that its new sequencing technology gave it the capacity to offer WGS for US$1,000.[16] Although this figure does not factor in the significantly higher cost of bioinformatics analysis, ongoing improvements in high-performance computing and analytical algorithms will see this cost continue to decrease as well.[17]

It is timely, at this stage, to reflect on how we might utilize the benefits resulting from increased accuracy and efficiency and reduced costs of sequencing in a way that benefits society as a whole. As Tim Caulfield and colleagues point out:

Rapid, lower-cost WGS is a promising research tool with unproven clinical utility, except in a small set of very specific situations. The journey from bench to bedside is one we should travel with care. … The scale and pace of adoption of this powerful new technology should be driven by clinical need, clinical evidence, and a commitment to put patients at the centre of health care policy.[18]

These salutary words illustrate that we should not be taken in by the hype that inevitably accompanies each new technological development. Rather, we should take a purposive approach, requiring clear evidence of safety and effectiveness, and, above all, focusing on patients' needs and interests.

Precision therapeutics—pharmacogenomics

The aim of pharmacogenomics is to combine targeted therapies with companion pretreatment diagnostic tests, which identify whether a person carries a gene or other biomarker that is linked with increased sensitivity to or resistance to the particular treatment. The starting point is improved understanding of how genetic variations within a population affect responses to particular drugs.[19] The most rapid advances have been in the field of molecular pathology and development of targeted cancer therapies.[20] Francis Collins and Harold Varmus, Directors of the US National Institutes of Health of the National Cancer Institute respectively, point out that the fact that cancers have their own heterogeneous genomic signatures opens avenues to the development of many more of targeted therapies.[21] But at the same time, this illustrates that the economic

Sequencing—A Clinical Laboratory Perspective: A Report of the Association for Molecular Pathology, 17 J. Molecular Diagnostics 107 (2015).

14 A number of for-profit companies were already well established during the period when publicly funded research institutes around the world were working towards the completion of the Human Genome Project. See eg Rebecca Eisenberg, *Genomics in the Public Domain: Strategy and Policy* 1 Nat. Rev. Genet. 20 (2000).

15 Mardis, *supra* note 9, at 199.

16 Erika C. Hayden, *Is the $1,000 Genome for Real?* Nature DOI 10.1038/nature.2014.14530 (2014).

17 Andrea Sboner et al., *The Real Cost of Sequencing: Higher Than You Think!*, 12 Genome Biol. 125 (2011).

18 Timothy Caulfield et al., *Reflections on the Cost of 'Low-Cost' Whole Genome Sequencing: Framing the Health Policy Debate*, 11 PLoS Biol. e1001699 (2013).

19 US Food and Drugs Administration, *supra* note 3, at 8; see also Mary V. Relling & William E. Evans, *Pharmacogenomics in the Clinic*, 526 Nature 343 (2015); Qiang Ma & Anthony YH Lu, *Pharmacogenetics, Pharmacogenomics, and Individualized Medicine*, 63 Pharmacological Rev. 437 (2011).

20 Collins & Varmus, *supra* note 10, at 794.

21 *Id.* at 793.

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costs of developing these bespoke treatments are likely to be enormous, requiring consideration of their value in meeting broader health system needs.[22]

Although translation into the clinic has been slow, there are a few examples of combined diagnostic-therapeutic interventions that have been shown to confer significant benefits to individual patients in the field of oncology.[23] The most obvious example is the diagnostic test for the 'HER2' receptor in breast cancer tumors. Once diagnosed, HER2 positive tumors can be provided with therapeutic intervention using the anticancer drug trastuzumab (sold as Herceptin by Genentech).[24] The US Food and Drugs Administration (FDA), the administrator of the therapeutic goods registration scheme in that country, approved supply of Herceptin for therapeutic purposes in 1998.[25] Other molecular tests paired with appropriately targeted therapeutics are available for other cancer types including malignant melanoma, colorectal cancer, and several subtypes of leukemia and lymphoma.[26]

Despite this, Collins and Varmus themselves acknowledge that many more cancer genomes will need to be analyzed and new designs of clinical trials and pre-clinical testing will need to be developed and approved to speed the adoption of precision therapies.[27] The emergence of drug resistance in cancer cells adds a further layer of complexity, perhaps requiring re-sequencing of some tumors. Whilst this experience in precision oncology is likely to expand into other spheres at some stage in the future,[28] broader adoption of precision medicine is still some way off.[29] Isaac Kohane identifies ten large challenges to be addressed for precision medicine to realize its potential.[30] Although he does acknowledge that these challenges are 'surmountable', their magnitude illustrates that we should be circumspect in our expectations about the immediacy of significant healthcare benefits arising from targeted therapies.

According to the FDA, the first challenge that must be overcome for precision medicine to advance is scientific.[31] Essentially, proof of analytic and clinical validity and clinical utility is required. However, the FDA also recognizes that regulatory policy and management challenges are posed by these technological advances.[32] Some commentators argue that current uncertainties in regulatory requirements are deterring investment in this field. This, they argue, is leading to the conclusion that there will need to be significant changes in the way that the FDA and equivalent agencies in other countries operate, along with 'unprecedented cooperation across multiple centers and

22 See Tania Bubela & Christopher McCabe, *Value-engineered Translation: Developing Biotherapeutics that Align with Health-System Needs,* 20(10) Am. J. Managed. Care (2014).

23 US Food and Drugs Administration, *supra* note 3, lists recent targeted therapy approvals at 3–4.

24 JS de Bono & Alan Ashworth, *Translating Cancer Research into Targeted Therapeutics*, 467 Nature 543 (2010).

25 US Food and Drugs Administration, *supra* note 3, at 15.

26 M Dietel et al., *A 2015 Update on Predictive Molecular Pathology and Its Role in Targeted Cancer Therapy: a Review Focusing on Clinical Relevance*, 22 Cancer Gene Therapy 417 (2015).

27 Collins & Varmus, *supra* note 10, at 794.

28 *Id.* at 794.

29 Samuel J. Aronson & Heidi L. Rehm, *Building the Foundation for Genomics in Precision Medicine*, 526 Nature 336 (2015).

30 Isaac S. Kohane, *Ten Things We Have To Do To Achieve Precision Medicine*, 349 Science 38 (2015).

31 US Food and Drugs Administration, *supra* note 3, at 14.

32 *Id.* at 14.

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departments'.[33] Such significant changes will likely require corresponding legislative reform.[34]

Direct-to-consumer genomic analysis

Whilst the requirement for an appropriate quality control framework is recognized and becoming standardized within current health care settings, the regulatory space is becoming more complicated as private entities enter into the market providing direct-to-consumer genomic analysis. Genomic analysis of particular types of biomarkers, known as single nucleotide polymorphisms (SNPs), provides an estimate of an individual's risk of developing certain diseases or conditions relative to the rest of the population.[35] Companies like 23andMe, the leading US-based provider of genomic analysis using SNP arrays, offer the entirety of their analytical services directly to consumers (DTC), including reports on health risk factors. Other companies providing health-related analyses promote their services DTC but require that the test is ordered by, or the results returned to, healthcare providers.[36] In addition to health testing, companies offering DTC testing services often offer a range of other services such as ancestry inference[37] and sports-related genetic testing.[38] A large spectrum of other providers exist in the DTC space, at least some of which offer services of dubious value to consumers, adding further layers of complexity to the ethical, legal, and social landscape.[39]

Notably, in late 2013, 23andMe ceased offering health related genomic analysis to consumers following receipt of a warning letter from the FDA requiring the company to show cause why it had not applied for marketing clearance or approval to supply this service.[40] Subsequently, in October 2015 23andMe launched a redesigned service, with authorization from the FDA, offering over sixty 'health, ancestry, wellness, and personal trait reports'.[41]

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33 Dov Greenbaum, *Policy Forum: Regulation and the Fate of Personalized Medicine*, 14 VIRTUAL MENTOR: AM. MED. ASSOC. J. ETHICS 645 (2012).

34 Margaret F. Riley, *An Unfulfilled Promise: Changes Needed to the Drug Approval Process to Make Personalized Medicine a Reality*, 70 FOOD & DRUG L. J. 289 (2015).

35 Melanie Swan, *Multigenic Condition Risk Assessment in Direct-to-Consumer Genomic Services*, 12 GENET. MED. 279 (2010).

36 Eg Color Genomics promotes its tests directly to consumers who provide DNA samples directly to the company but requires the actual ordering of the test to be done by a physician designated by the company (https://getcolor.com) (accessed April 23, 2016).

37 Jennifer K. Wagner, *Interpreting the Implications of DNA Ancestry Tests*, 53 PERSP. BIOL. & MED. 231 (2010); Jennifer K. Wagner et al., *Tilting at Windmills No Longer: a Data-driven Discussion of DTC DNA Ancestry Tests*, 14 GENET. MED. 586 (2012).

38 Jennifer K. Wagner & Charmaine D. Royal, *Field of Genes: An Investigation of Sports-Related Genetic Testing*, 2 J. PERS. MED. 119 (2012).

39 Timothy Caulfield & Amy McGuire, *Direct-to-Consumer Genetic Testing: Perceptions, Problems and Policy Responses*, 63 ANN. REV. MED. 23 (2012).

40 For an account of this and other letters sent by the FDA to DTC testing companies and their implications see: Kaye Spector-Bagdady & Elizabeth Pike, *Consuming Genomics: Regulating Direct-to-Consumer Genetic and Genomic Information*, 92 NEB. L. REV. 677, 704–17 (2015).

41 23andMe, *Press Release: 23andMe Launches New Customer Experience—Reports Include Carrier Status That Meet FDA Standards, Wellness, Traits, and Ancestry*, http://mediacenter.23andme.com/blog/new-23andme/ (accessed April 23, 2016).

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Research advances—precision gene editing

In parallel with these developments in sequencing, therapeutics and DTC genomic analysis, new trends have been emerging in the research context. Notably, there has been vast improvement in the accuracy of artificially manipulating genes,[42] particularly through Clustered Regularly Interspersed Short Tandem Repeat (CRISPR) and CRISPR associated (Cas) technology. Although still a research tool, CRISPR-Cas has been touted as having potential clinical application in the treatment of cancer and a range of other diseases.[43] For example, this technology can also be used in iPS cells (induced pluripotent stem cells), which are human cells (for example, skin fibroblasts) that are re-programmed so that they can differentiate into many different cell types.[44] This combination is opening up prospects for the development of gene therapies, particularly for blood-borne disorders but also other diseases.[45] Despite CRISPR-Cas's reported accuracy, however, there remain concerns that it could have off-target effects, potentially risking the activation of genes that trigger cancer formation.[46] Whilst advances are being made in identifying these effects, more comparative research is needed to understand how best to predict and minimize them.[47] These technological advances in gene editing have re-opened debates about the efficacy of therapeutic germline gene therapy[48] and deeper philosophical discussions around the manipulation of human embryos.[49]

Biobanking and data sharing in a commercialized research environment

Disease-specific and population biobanks have been established in many western countries to provide annotated collections of tissue, genomic data, and clinical information to researchers, through various combinations of public, charitable, and commercial funding.[50] The combined power of high throughput sequencing and electronic health records can now be harnessed to create opportunities to better understand genetic determinants of disease and health outcomes.[51] Together, they provide the essential resources and services for medical research into major diseases including cancer, cardiovascular disease, mental health disorders, and diabetes. Increasingly, we are

42 David BT Cox, Randall J. Platt & Feng Zhang, *Therapeutic Genome Editing: Prospects and Challenges*, 21 Nat. Med. 121 (2015).

43 *Genome Editing: the Age of the Red Pen*, The Economist, 22 Aug., 2015.

44 Akitsu Hotta & Shinya Yamanaka, *From Genomics to Gene Therapy: Induced Pluripotent Stem Cells Meet Genome Editing*, 49 Ann. Rev. Genet. 4.1 (2015).

45 *Id.*

46 Vivien Marx, *Gene Editing: How To Stay On-target with CRISPR*, 11 Nat. Methods 121 (2014).

47 See eg Richard Gabriel, Christof von Kalle & Manfred Schmidt, *Mapping the Precision Of Genome Editing*, 33 Nat. Biotechnology 150 (2015); Richard L. Frock et al., *Genome-wide Detection Of Dna Double-Stranded Breaks Induced By Engineered Nucleases*, 33 Nat. Biotechnology 179 (2015); Shengdar Q. Tsai et al., *GUIDE-seq Enables Genome-Wide Profiling Of Off-Target Cleavage By Crispr-Cas Nucleases*, 33 Nat. Biotechnol. 187 (2015).

48 Edward Lanphier et al., *Don't Edit the Human Germ Line*, 519 Nature 410 (2015).

49 David Cyranoski & Sara Reardon, *Chinese Scientists Genetically Modify Human Embryos*, Nature DOI:10.1038/nature.2015.17378 (2015).

50 See generally, Organisation for Economic Co-operation and Development, Creation and Governance of Human Genetic Research Databases (2006).

51 Wei-Qi Wei & Joshua C. Denny, *Extracting Research-quality Phenotypes from Electronic Health Records To Support Precision Medicine*, 7 Genome Med. 41 (2015).

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seeing harmonization of biobank collections and coordination of research efforts internationally to increase the power of these rich bioresources and related infrastructure.[52]

Whilst significant research advances have been made since the Human Genome Project commenced some 25 years ago,[53] much is still unknown about the implications of the multifaceted nature of gene and environment interactions on human health and wellbeing. We still have no clear understanding of the role of many genetic variants in human health and disease.[54] There is growing recognition of the value of data sharing in increasing our overall understanding of the human genome and facilitating the translation from early and later phases of research to clinical practice.[55] A range of organizations, including the International Cancer Genome Consortium,[56] the Global Alliance for Genomics and Health,[57] and projects like the Open Humans Network[58] have developed policies to promote the exchange of data. Data sharing does, however, become particularly complex for large-scale projects involving multiple players across jurisdictions and cultures.[59]

Aside from public collections, pharmaceutical companies have maintained their own private collections of human biospecimens from clinical trials for many years, but these have largely been unavailable to external users.[60] In addition, some DTC companies, such as 23andMe, are using their databases to engage in research programs, both independently and in collaboration with biotechnology and pharmaceutical companies and public research organizations.[61] Even more recently, there has been an indication that 23andMe is launching itself into the drug discovery environment.[62]

These developments are raising questions about how to provide appropriate oversight of research in light of the collapsing of traditional boundaries between: the research institution and the clinic; the patient, the research participant, and the consumer; the public and commercial research sectors; and the diagnostic and therapeutic sectors. Patients, research participants, and consumers are also increasingly expected to be active participants in precision medicine rather than passive subjects or recipients of its benefits (and arguably increasingly burdened with expectations of engagement).[63]

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52 See eg Gert-Jan B. van Ommen et al., *BBMRI-ERIC as a Resource for Pharmaceutical and Life Science Industries: the Development of Biobank-based Expert Centres,* 23 Eur. J. Hum. Genet. 893 (2015).

53 Eric D. Green, James D. Watson & Francis S. Collins, *Human Genome Project: Twenty-five Years of Big Biology*, 526 Nature 29 (2015).

54 Heidi L. Rehm et al., *ClinGen—the Clinical Genome Resource* (2015) 372 New Eng. J. Med. 2235 (2015).

55 Barbara R. Jasny, *Realities of Data Sharing Using the Genome Wars as a Case Study—an Historical Perspective and Commentary*, 2:1 EPJ Data Sci. DOI 10.1140/epjds13 (2013).

56 See http://icgc.org (accessed April 23, 2016).

57 See http://genomicsandhealth.org/ (accessed April 23, 2016).

58 See https://www.openhumans.org/ (accessed April 23, 2016).

59 Don Chalmers, Dianne Nicol & Margaret Otlowski, *To Share or not to Share: Is the Question,* 3 Applied & Transl. Genom. 116, 116–9 (2014).

60 Mary Anderlik, *Commercial Biobanks and Genetic Research: Ethical and Legal Issues*, 3 Am. J. Pharmacogenomics 203 (2003).

61 See eg 23andMe, *23andMe Launches the Lupus Research Study in Collaboration with Pfizer Inc, Press Release*, http://mediacenter.23andme.com/blog/23andme-launches-the-lupus-research-study-in-collaboration-with-pfizer-inc/ (accessed April 23, 2016).

62 Kelly Servick, *Can 23andMe Have It All?* 349 Science 1472 (2015).

63 Yann Joly et al., *The Ethical Framing of Personalized Medicine,* 14 Curr. Op. Allergy & Clin. Immunology 404 (2014).

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Precision medicine heightens many of the concerns about ethical, legal, and social implications (ELSI) raised during the course of the Human Genome Project and beyond.[64] The linkage of genotype and phenotype, past medical history, lifestyle, and other personal information, raises particular concerns around consent, privacy, and confidentiality, together with obvious practical questions about the accuracy, safety, and clinical validity of the therapeutic products. These and other ELSI come into sharp focus as precision medicine advances, with the proliferation in the amount of information potentially available, the scale of linkage, and the untested nature of many of the claimed therapeutic outcomes.[65]

DROWNING IN THE REGULATORY SOUP?

Regulating across areas of emerging or rapidly developing technologies with evolving industry structures will always present unique challenges.[66] Regulation must be responsive to technological developments and as future-proofed as possible, if it is to have a chance of 'leading'. In a world of increasingly porous borders and increased participation in the borderless online world, regulation must be accommodating of differing cultural norms, not just within, but amongst individual countries or regions.[67] This is a tall order for any regulator when the landscape and the key participants keep changing.

These regulatory challenges need not—and probably should not—result in new, highly targeted laws, which are liable to be outpaced by scientific change. Instead, and to the greatest extent possible, precision medicine should be regulated by the large body of existing laws and other regulatory instruments that apply to other aspects of clinical care and medical research. Nor should it be used as a justification for recalibration of high-level ethical principles such as those contained within the Declaration of Helsinki, with the potential of undermining the current authority of those principles.[68] Whilst precision medicine might be scientifically new, it exists within these well-established regulatory and oversight systems.

Some of the most relevant broadly-based regulatory and legal requirements include: consumer protection legislation designed to ensure product safety and prevent false or misleading marketing; privacy legislation that protects personal medical information; and established duties of care and consent requirements with remedies for breaches (for example, the torts of trespass and negligence). There are also a number of specifically designed regulatory regimes relating to drug approvals, diagnostic testing, and research. Their adequacy and appropriateness with regard to some of the key features of precision medicine is discussed further below.

Specific regulatory challenges for pharmacogenomics

Pharmacogenomics is positioned within the regulatory and oversight system for market approval of therapeutic goods. The current model for regulating drug approvals clearly has inadequacies in this space because the evidence upon which decisions are made

64 Chalmers et al., *supra* note 7, at 578; Brothers and Rothstein, *supra* note 6, at 43.

65 For a recent perspective on ELSI of precision medicine see: Ian V McGonigle, *The Collective Nature of Personalized Medicine*, 98 GENET RES, CAMB e3 (2016).

66 See eg Editorial, *Direct-to-consumer Genetic Testing*, 380 THE LANCET 76 (2012).

67 See Brownsword & Goodwin, *supra* note 5, at 47.

68 Joseph Millum, David Wendler & Ezekiel J. Emanuel, *The 50th Anniversary of the Declaration of Helsinki: Progress but Many Remaining Challenges*, 310 JAMA 2143 (2013).

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comes from large randomized clinical trials.[69] The system is simply not designed with personalized treatments in mind.[70] In response to these and other pressures, governments in a number of jurisdictions are examining reform options from both the regulatory perspective (for example, through adaptive licensing) and the funding perspective (including performance-based risk sharing agreements).[71] Concerns have been raised as to whether these proposed reforms can be implemented successfully, with commentators urging that they should be 'approached with a healthy degree of skepticism'.[72]

Other commentators posit that what is needed is a new approach of hypothesis-testing clinical trials, arguing that analytical validation of biomarker assays will be a key component.[73] In this regard, note should be taken of the work of the International Conference on Harmonization, which is attempting to formulate mutually agreed biomarker qualification standards between the European Union, USA, and Japan.[74] The FDA itself has recognized that one of the significant challenges in approvals for targeted therapies and companion diagnostics is that the products are regulated by different FDA Centers and often sponsored by different companies.[75] The FDA has taken some modest steps in response, but recognizes that more will need to be done.[76]

Regulating direct-to-consumer genomic analysis

Genetic diagnostic testing is subject to a range of specific regulatory instruments. For instance, the US-based genetic diagnostic testing sector is subject to laboratory accreditation at the state level and through the Centers of Medicare and Medicaid Services, as well as market clearance and approval for in vitro devices (IVDs) through the FDA. Other jurisdictions have similar regulatory requirements.[77]

As precision medicine moves further into a world of DTC delivery, consumers can increasingly bypass traditional healthcare systems and healthcare providers in favor of these commercial offerings.[78] While existing consumer protection regulatory frameworks may already adequately cover products made directly available to consumers, they do not necessarily provide the same level of protection in relation to DTC services.[79] Concerns have long been expressed about the accuracy of the predictions made

69 de Bono & Ashworth, *supra* note 24, at 543; Shannon G. Gibson & Trudo Lemmens, *Niche Markets and Evidence Assessment in Transition: a Critical Review of Proposed Drug Reforms*, 22 MED. L. REV. 200 (2014).

70 Riley, *supra* note 34, at 290; see also W Nicholson Price III, *Black-box Medicine*, 28 HARV. J. L. & TECH. 419, 426 (2015).

71 Gibson & Lemmens, *supra* note 69, at 209–211.

72 *Id.* at 219.

73 de Bono & Ashworth, *supra* note 24, at 545–547.

74 Stuart Hogarth, *Regulatory Experiments and Transnational Networks: the Governance of Pharmacogenomics in Europe and the United States*, 25(4) INNOVATION—EUR. J. SOC. SCI. RES. 1 (2012).

75 US Food and Drugs Administration, *supra* note 3, at 56, 57, at 32, 35.

76 For example, in 2012 the FDA established the Office of Combination Products in 2012, *Id.* at 16.

77 US Food and Drugs Administration, *supra* note 3, at 56, 57; Dianne Nicol & Meredith Hagger, *Direct To Consumer Genetic Testing—A Regulatory Nightmare?* 198 MED. J. AUSTL. 501 (2013); Stuart Hogarth, David E. Barton & David Melzer, *The European IVD Directive and Genetic Testing*' in QUALITY ISSUES IN CLINICAL GENETIC SERVICES 49, 62 (Ulf Kristoffersson, Jörg Schmidtke & JJ Casiman eds., 2010).

78 Heidi C. Howard & Pascal Borry, *Direct-to-consumer Genetic Testing: More Questions Than Benefits?* 5 PERS. MED. 317 (2008).

79 Caroline F. Wright, Alison Hall & Ron L. Zimmern, *Regulating Direct-to-consumer Genetic Tests: What is all the Fuss About?*, 13 GENET. MED. 295 (2011).

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by DTC testing companies,[80] and consumer ability to understand and interpret test results, particularly in an environment where there is typically no genetic counseling.[81] It should be noted, however, that a robust evidence base of documented harms is still lacking.[82] Moreover, the nature of some of these harms is contestable, with some commentators arguing that adults, as healthcare consumers, should have the freedom to choose whether or not to access these services, and indeed that they have the right to access and possess their health data.[83]

One recent extension of regulatory oversight has been to include laboratory-developed tests (LDTs) within the IVD regulatory framework.[84] In the USA, the FDA is still in the process of developing this framework for oversight of LDTs, and once further developed may face legal challenge.[85]

Regulating the evolving research space

Publicly funded researchers and public research institutions are bound by national codes of research ethics; and in the clinic, health care practitioners are bound by professional and ethical codes of conduct. These 'soft' laws can provide more nuanced assistance in guiding ethical conduct than blunt legislative intervention. But it is perhaps in these areas that the regulatory puzzle is most perplexing. In the era of precision medicine, where the traditional boundaries around public research and professional care are being transcended,[86] can these soft laws be adapted to suit this new environment? There is a risk that these soft laws could actually create more layers of regulatory complexity and confusion in this multidisciplinary area, given that different professions have different codes of conduct, and that a substantial body of hard laws is already in existence. Thus, achieving regulatory consistency in this cross-disciplinary, cross-jurisdictional space, positioned between the public and private sectors, will be challenging.

National ethical research codes, which put the responsibilities associated with approval and compliance on institutions, are not a good fit for collaborative research that crosses institutional and disciplinary boundaries because research teams inevitably face review by a multitude of institutional research ethics committees (referred to as Institutional Review Boards in the US). This problem has already been recognized by the US Department of Human and Health Services (DHHS) in its review of the Federal

80 See eg Gregory Kutz (United States Government Accountability Office), *Direct-to-consumer Genetic Tests: Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices*, July 2010; Rachel Kalf et al., *Variations in Predicted Risks in Personal Genome Testing for Common Complex Diseases*, 16 Genet. Med. 85 (2014).

81 Alice K. Hawkins & Anita Ho, *Genetic Counseling and the Ethical Issues Around Direct to Consumer Genetic Testing*, 21 J. Genet. Counseling 367 (2012).

82 Timothy Caulfield, *Direct-to-consumer Testing: If Consumers Aren't Anxious, Why Are Policymakers?* 130 Hum. Genet. 23 (2011).

83 See eg Robert Green & Nita Farahany, *The FDA Is Overcautious on Consumer Genomics*, 505 Nature 286 (2014).

84 Barbara J. Evans, *The Limits of FDA's Authority to Regulate Clinical Research involving High-throughput DNA Sequencing*, 70 Food & Drug L. J. 259 (2015); Nicol & Hagger, *supra* note 77, at 502.

85 US Food and Drugs Administration, *supra* note 3, at 32.

86 See eg Joe Alper & Claudia Grossmann, Rapporteurs; IOM Roundtable on Value & Science-Driven Care; Institute of Medicine, Integrating Research and Practice: Health System Leaders Working Toward High-Value Care: Workshop Summary (2015).

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Policy for the Protection of Human Subjects (also known as the Common Rule).[87] The situation becomes even more complex for multinational data sharing projects.[88]

The US FDA is starting to discuss oversight of genome sequencing techniques, because of concerns about how to measure their analytical and clinical validity in this context.[89] This is raising concerns about the consequences of the FDA moving into the research space, and the constitutional authority for it to do so.[90] Barbara Evans notes that despite the FDA's good intentions, this move into the research space has the potential to slow the progress of genomic discovery, interfere with scientific inquiry and freedom of speech, and upset the primacy of the states to regulate medical practice.[91]

In the context of gene editing, there is a developing body of bioethics literature.[92] Discussions are also beginning about the need for model regulatory frameworks that balance research and practice, with particular focus on research involving human embryos.[93] This is an area where there is consensus that the law must keep pace with the technology, but also recognition that rushing to regulate is not always the best approach.[94] A recent review of the international regulatory landscape revealed a patchwork of approaches, ranging from absolute prohibition of clinical germline gene therapy applications to non-enforceable guidelines.[95] The need for clarity and consistency is prompting policy makers to reevaluate the adequacy of their regulatory responses.[96]

This is an area of genetic technology where self-regulation has, in the past, played a significant role. In the early 1970s, recombinant DNA technology was beginning to be adopted as a viable research tool. The scientific community took the lead in imposing their own moratorium on certain research uses of this technology.[97] Subsequently, in 1975, leading scientists in the field met at the International Conference on Recombinant DNA Molecules (the Asilomar Conference). They agreed that some aspects of research using recombinant DNA technology should be allowed to proceed, on the proviso that stringent safeguards were in place, but there remain 'certain experiments in

87 US Department of Health and Human Services, *NPRM 2015—Summary*, 2015, http://www.hhs.gov/ohrp/humansubjects/regulations/nprm2015summary.html (accessed April 23, 2016); see also Ann-Margret Ervin et al., *Evidence Gaps and Ethical Review of Multicenter Studies*, 350 SCIENCE 632 (2015).

88 This is an area of activity for the Global Alliance for Genomics and Health (G4GH) Ethics Working Group Ethics Review Equivalency Task Team, which is developing models that allow for mutual recognition of ethics review, https://genomicsandhealth.org/working-groups/our-work/ethics-review-equivalency (accessed April 23, 2016).

89 US Food and Drugs Administration, *supra* note 3, at 31; Evans, *supra* note 84, at 259, 260.

90 Evans, *supra* note 84, at 260, 261.

91 *Id.* at 260, 261.

92 Eg the American Journal of Bioethics dedicated a whole issue in its 2015 volume to this topic: http://www.tandfonline.com/toc/uajb20/15/12 (accessed April 23, 2016).

93 The Hinxton Group, *Statement on Genome Editing Technologies and Human Germline Genetic Modification* (2015); Debra JH Mathews, et al., *A Path through the Thicket*, 527 NATURE 159 (2015).

94 Eli Y. Adashi & I Glenn Cohen, *Editing the genome of the human germline: may cool heads prevail*, 15 AM. J. BIOETHICS 40 (2015).

95 Motoko Araki & Tetsuya Ishii, *International Regulatory Landscape and Integration of Corrective Genome Editing into In Vitro Fertilization*, 12 REPROD. BIOL. & ENDOCRINOLOGY 108 (2014). See also Heidi Ledford, *The Landscape for Human Genome Editing*, 526 NATURE 310 (2015).

96 Ledford, *supra* note 95, at 310.

97 Paul Berg et al., *Summary Statement of the Asilomar Conference on Recombinant DNA Technology*, 72 PROC. NATL. ACAD. SCI. USA 1981 (1975).

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which the potential risks are of such a serious nature that they ought not to be done with presently available containment facilities'.[98]

Moving to 2015, a group of scientists, including some of the participants at the Asilomar Conference, came together early in the year to discuss the same types of issues with regard to the latest technological developments in gene editing, with particular focus on CRISPR-Cas.[99] As with Asilomar participants, this group urged cautious adoption of gene editing technology, with particular focus on transparency and open discussion of the merits and risks, and strongly discouraged the use of this technology in germline genome modification.[100] Quite how well the self-regulatory approach that was so successful in the 1970s can work in the modern research environment is open to question. It is notable that the participants at the 2015 meeting were all US-based scientists. The research world was a more uniform place back in the time of Asilomar—now new research powerhouses like China will make self-regulation and international harmonization more difficult.

More recently, the US National Academy of Sciences and the National Academy of Medicine hosted an international summit as part of their Human Gene-Editing Initiative. The application of somatic gene editing was endorsed in a statement released following the conclusion of the summit, but the same could not be said for germline editing.[101] The statement highlighted that it would be irresponsible to proceed with clinical use of germline editing without resolution of safety and efficacy issues, societal consensus, and appropriate regulatory oversight.[102]

Regulating biobanking and data sharing

Biobanking and data sharing are heightening ongoing concerns about the nature of the consent process for future unspecified research uses of tissue and genetic data. The establishment of large-scale population-wide biobanks led to a rush of policy statements[103] and practical guidelines.[104] Some biobanks have also developed their own ethics and governance frameworks.[105] Yet, by their nature, biobanks are not able to fully inform participants at the time when they are asked to consent to participate about matters such as future research opportunities, tissue and data sharing partners, return of research results and incidental findings,[106] and commercial

98 *Id.* at 1981.

99 See David Baltimore et al., *A Prudent Path Forward for Genomic Engineering and Germline Gene Modification*, 348 SCIENCE 36 (2015).

100 *Id.* at 37.

101 Organizing Committee for the International Summit on Human Gene Editing, *International Summit Statement*, 3 Dec. 2015, http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a (accessed April 23, 2016).

102 *Id.*

103 Eg HUMAN GENOME ORGANISATION ETHICS COMMITTEE, STATEMENT ON HUMAN GENOMIC DATABASES (2003); OECD, GUIDELINES FOR HUMAN BIOBANKS AND GENETIC RESEARCH DATABASES (2009).

104 ISBER, *Best Practices for Repositories I: Collection, Storage, and Retrieval of Human Biological Materials for Research*, 3 CELL PRESERV. TECH. 5 (2005); NATIONAL CANCER INSTITUTE, FIRST-GENERATION GUIDELINES FOR NCI-SUPPORTED BIOREPOSITORIES (2006).

105 UK BIOBANK, ETHICS AND GOVERNANCE FRAMEWORK, VERSION 2.0 (2006).

106 The issue of return of research results becomes even more complex from the perspective of relatives of research participants. See Susan M. Wolf et al., *Returning a Research Participant's Genomic Results to Relatives: Analysis and Recommendations*, 43 J. L. MED. & ETHICS 440 (2015).

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relationships.[107] A new model of 'broad' consent was developed especially for biobanking to deal with these practical difficulties.[108] Some commentators, particularly Tim Caulfield and Jane Kaye, remain unconvinced that the justifications for this move away from traditional notions of consent are adequate.[109] In response, new consent models are being developed, such as dynamic consent,[110] which uses online digital technologies to communicate and engage with participants and to provide them with the information needed to give an informed consent in a changing research environment. Others have suggested discarding the consent model altogether in favor of a property approach, which employs the gift relationship as the basis of biobanking.[111] It is noteworthy that in the USA the DHHS review of the Common Rule favors a broad consent model with regard to the collection of biospecimens,[112] although that seismic shift in policy remains highly controversial. The regulatory challenges in data sharing extend beyond the issue of consent to privacy and data protection, particularly when data is released into the public domain.[113] A key challenge is to ensure risk management minimizes the risk of harm from sharing of genomic data for participants and for their relatives. These dual risks arise because of the features genomic data that implicate distinct individual and collective interests.[114]

Another emerging governance issue is the question of who should have access to biobank resources and on what terms. One key issue is whether differential fees should be charged for access by for-profit and non-profit entities. In Genomics England's current industry trial of access to data in its '100,000 Genomes Project', companies have to pay a fee to join a consortium before they can access any data.[115] This access regime contrasts quite dramatically to those of other biobanks. UK Biobank, for example, operates on a cost-recovery basis regardless of research purpose.[116] Whilst the types of data and tissue that are available for access at different biobanks vary considerably and will inevitably be of different value, governing bodies should be careful to ensure that any access policy they put in place does not unduly compromise access to these invaluable resources. Indeed, this type of 'regulation' has the ability to slow the genomic discovery process just as much as any other formalized regulatory requirement.

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107 Timothy Caulfield et al., *A Review of the Key Issues associated with the Commercialization of Biobanks,* 1 J. L. & Biosci. 94 (2014).

108 Christine Grady et al., *Broad Consent for Research with Biological Samples: Workshop Conclusions*, 15 Am. J. Bioethics 34 (2015).

109 Timothy Caulfield & Jane Kaye, *Broad Consent in Biobanking: Reflections on Seemingly Insurmountable Dilemmas*, 10 Med. L. Int'l 85 (2009).

110 Jane Kaye et al., *Dynamic Consent: a Patient Interface for Twenty-First Century Research Networks*, 23 Eur. J. Hum. Genet. 1 (2014); Hawys Williams et al., *Dynamic Consent: A Possible Solution to Improve Patient Confidence and Trust in How Electronic Patient Records Are Used in Medical Research*, JMIR Med. Informatics DOI 10.2196/medinform.3525 (2015).

111 Cameron Stewart et al., *The Problems of Biobanking and the Law of Gifts,* in Persons, Parts and Property: How Should we Regulate Human Tissue in the 21st Century? 25, 38 (Imogen Goold et al. eds., 2014).

112 US Department of Health and Human Services, *supra* note 87.

113 See for example, Wolf et al., *supra* note 106, at 445; Alondra Nelson, The Social Life of DNA: Race, Reparations, and Reconciliation After the Genome (2016).

114 Chalmers, Nicol & Otlowski, *supra* note 59, at 116, 119.

115 Genomics England, *A Framework for Industry Engagement*, Mar. 2015, at 5 and 6.

116 UK Biobank, *Principles of Access*, http://www.ukbiobank.ac.uk/principles-of-access/ (accessed April 23, 2016).

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Other regulatory tools

Research funding, health care reimbursement schedules, and insurance coverage must be recognized as key components of the regulatory framework. Although perhaps not traditionally thought of as regulatory instruments as such, each of these is relevant because it has the capacity to channel group behavior, thereby coming within Brownsword and Goodwin's definition of regulation. Regulatory theorists have long accepted that there is more to regulation than laws and other regulatory instruments.[117] For instance, reimbursement will only be provided for new genetic tests if there is clear evidence of analytical validity, clinical validity, and clinical utility.[118] Essentially, in such circumstances, reimbursers become de facto regulators, fulfilling like functions.[119]

Other legal regimes, including the patent system, also have a regulatory function in this space, particularly with respect to diagnostic testing. Perhaps inadvertently, recent decisions of the US Supreme Court and the Australian High Court redefining the legal requirements for patentable subject matter[120] may have the effect of increasing the regulatory burden on the FDA and others. The reason for this suggestion is that removal of the threat of patent infringement will likely open up the diagnostic testing market to new entrants. In the past, the grant of patents claiming rights to nucleotide sequences and associated diagnostic methods created de facto barriers to entry into the genetic diagnostic testing market, either through actual instances of patent enforcement, or fears from diagnostic testing laboratories that they at any time could face patent infringement lawsuits. As noted in the recent *Report on Confirmatory Genetic Diagnostic Test Activity* by the US Patent and Trademarks Office, these cases have 'dramatically affect[ed] the landscape of diagnostic testing'.[121] Although the Report focuses specifically on confirmatory (or second opinion) tests, it illustrates the point that the gatekeeping role of gene-based patents has been largely extinguished. The Report concludes that this changing landscape will result in many smaller providers entering the market.[122] This will be beneficial to consumers, if it increases choice and decreases cost, but may increase the burden on regulators in ensuring regulatory compliance as the number of providers expands. Moreover, the gatekeeper role could shift to the insurer to make choices around such questions as which tests from which laboratories should be eligible for reimbursement. However, to date only the US and Australian courts have ruled on the ineligibility of nucleotide sequence patents based on the subject matter ground. In Europe, provisions in the European Biotechnology Directive (particularly Article 5)[123] make it difficult for legal actions seeking to invalidate nucleotide sequence claims on the

117 See eg John Braithwaite, *The Essence of Responsive Regulation* 44 UBC L. Rev. 475 (2011).

118 Patricia A Deverka & Jennifer C. Dreyfus, *Clinical Integration of Next Generation Sequencing: Coverage and Reimbursement Challenges*, 42 J. L., Med. & Ethics 22, 23 (2014).

119 *Id.* at 25; J Larry Jameson & Dan L. Longo, *Precision Medicine—Personalized, Problematic and Promising* 372 New Eng. J. Med. 2229, 2233 (2015).

120 In the USA, see particularly Mayo Collaborative Services v. Prometheus Laboratories, Inc., *132 S. Ct. 1289* (2012) and Association for Molecular Pathology v. Myriad Genetics, Inc., *132 S.Ct. 1794* (2012); in Australia, see d'Arcy v Myriad Genetics, Inc [2015] HCA 35.

121 US Patent and Trademarks Office, Report on Confirmatory Genetic Diagnostic Test Activity, 12 (2015).

122 *Id.* at 32.

123 European Parliament and Council Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions [1998] OJ L 213/13.

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subject matter ground to be brought in countries that have implemented the Directive into their domestic patent legislation.

It is also pertinent that other intellectual property regimes are already taking the place of patents in regulating entry of alternative providers into the diagnostic testing market. Companies that have been offering diagnostic tests exclusively for a number of years in reliance on their patent rights, now have extensive databases of population-wide genetic data, which are used to compare genetic variations of otherwise unknown significance with particular disease manifestations.[124] Trade secrecy laws allow them to keep their data confidential. Circumventing this proprietary database dilemma will require creation of an equivalent public access dataset.[125] This will take time, and in the interim private companies will still exert a powerful influence in regulating market entry of other providers.

The regulatory soup

Figure 1 illustrated how the traditional boundaries between the clinic, the research lab and the different industry sectors are breaking down. One consequence is that the defined regulatory spaces within which each of these sectors operate become a diffuse regulatory soup, as illustrated in Fig. 2.

The first task in responding to President Obama's call to modernize the current regulatory landscape is not so much about adding further ingredients to this regulatory soup, but working out how to engage with, interpret and, where necessary, expand existing ingredients in new areas of technology. Equally important, this task will require us to work out how to avoid overlap and duplication. Relevant questions to consider when assessing the reach of regulation include (but are not limited to): what are the regulatory requirements for approval of targeted therapies that provide an appropriate balance between incentivizing innovation and ensuring that clinical validity and patient safety requirements are satisfied;[126] should DTC companies that provide risk reports based on SNP analysis be regulated in the same way as more conventional providers of genetic diagnostic services; and how should genomic research be regulated, in light of these collapsing boundaries?

THE REGULATORY FUTURE— CAN REGULATION BE EFFECTIVE?

As noted by Collins and Varmus, the regulatory challenge is to find a way of supporting innovation and ensuring that the technology is safe and effective, and also cost effective.[127] While there is a tendency to criticize the law for 'limping behind' technology, best practice regulation can only be achieved if it is informed by an appropriate evidence base, with adequate opportunities for reflection and debate. The sector needs to remain adaptive, flexible and responsive to change and new research and clinical opportunities.

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124 Robert Cook-Deegan et al., *The Next Controversy In Genetic Testing: Clinical Data As Trade Secrets* 21 EUR. J. HUM. GENET. 585 (2013); John M. Conley, Robert Cook-Deegan & Gabriel Luzaro-Munoz, *Myriad after Myriad: The Proprietary Data Dilemma,* 15 N. C. J. L. & TECH. 597, 613 (2014).

125 *Id.*

126 See Reza Mirnezami & Jeremy Nicholson, *Preparing for Precision Medicine*, 366 NEW ENG. J. MED. 489 (2012); Eric S. Lander, *Cutting the Gordian Helix—Regulating Genome Testing in the Era of Precision Medicine*, 372 NEW ENG. J. MED. 1185 (2015).

127 Collins & Varmus, *supra* note 10, at 795.

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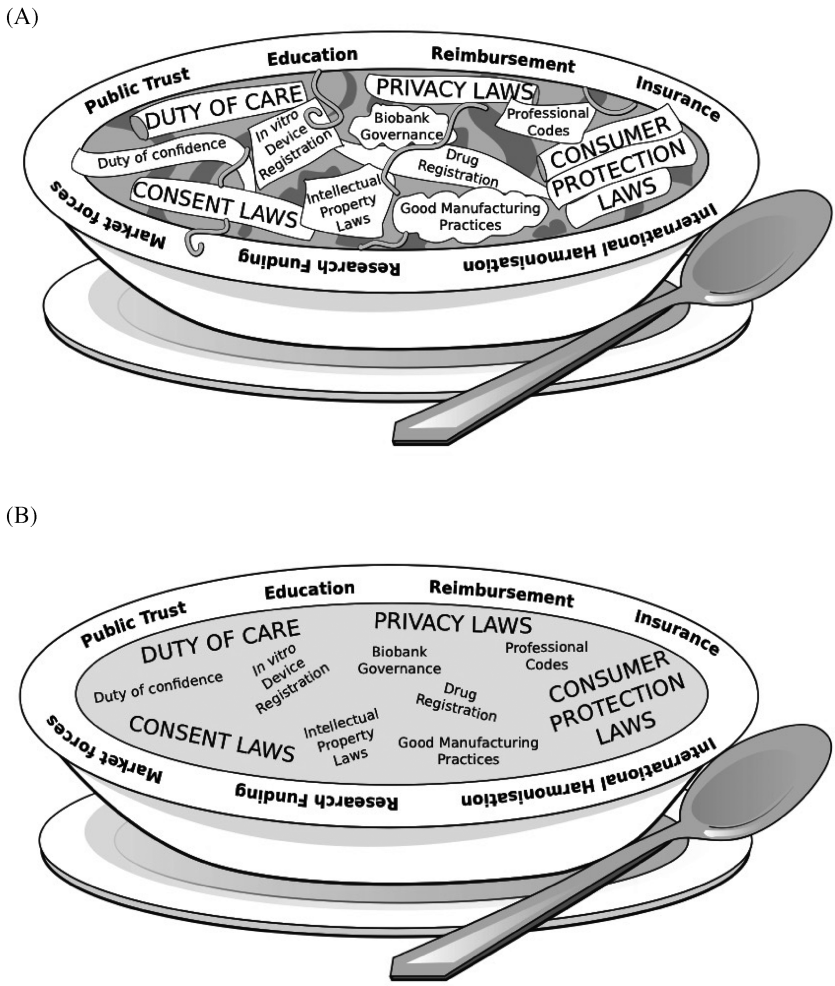


Figure 2. The changing regulatory soup engulfing precision medicine. A. Traditional circumscribed regulatory instruments. B. Breaking down of the boundaries of traditional regulatory instruments.

Caution is required in law reform relating to precision medicine, lest we fall victim to genetic exceptionalism, which might introduce more problems than it resolves.[128]

Scope and context

It is not yet clear, whether effective implementation of precision medicine will require a different approach to how we apply and use regulation than what is currently the case. Who and what we regulate clearly needs to be in scope—is it tests and healthcare products or is it professional and research practice, or all of these? This affects what is

[128] Thomas Murray, *Genetic Exceptionalism and 'Future Diaries': Is Genetic Information Different From Other Medical Information?* in GENETIC SECRETS: PROTECTING PRIVACY AND CONFIDENTIALITY IN THE GENETIC ERA 60 (M Rothstein ed., 1997).

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regulated and who the regulator will be. The question is not how to regulate, but how to regulate well.[129] In this regard, Stuart Hogarth points to the central role played by regulatory agencies in the production of new healthcare technologies, like pharmacogenomics, and in the creation of new regulatory spaces.[130] Hogarth and others emphasize the importance of developing agreed sets of standards, whether internationally,[131] or nationally.[132] Those proposing new regulatory structures or approaches must be cognizant of the governance and cultural contexts in which they are to be introduced.

Precision medicine and society

In light of the increasing translation of genomic research results into clinical practice, there have been grander calls for a recasting of science's contract with society, in a way that emphasizes reciprocity and meeting public needs. This should not simply entail dissemination of information to educate members of the public about the role precision medicine in modern healthcare, but genuinely engaging with them to understand how they view the promises and problems of these technological developments.[133]

While education is one of the softer regulatory tools, sitting firmly at the base of Ayers and Braithwaite's responsive regulatory pyramid,[134] it seems clear that educational tools need to be improved. This should preferably occur 'before' an individual is sitting in a doctor's office facing a potentially serious or traumatic medical decision about himself/herself or a loved one. How do we improve genetic education so that all eventual patients, prospective research participants, and consumers of DTC services have a reasonable, minimum understanding of human genetics and the potential capacity and limits of precision medicine to facilitate autonomous decision-making? What role does or should genetic education play in managing risks of genomic medicine and research? One tool that school and university educators are adopting to assist students with their understanding of the complexities of genetics and genomics is the adoption of participatory or 'experiential' approaches.[135] There are a growing number of examples of high schools and universities offering students the opportunity to provide their DNA for genomic analysis. One empirical study has shown that many university students find it an exciting and easier way to learn.[136]

Medical practitioners continue to play a dominant role at the interface between the healthcare system and the public. Their effectiveness in advising their patients about diagnostic and treatment options presupposes that they have the appropriate skills and understanding to provide requisite advice. Studies undertaken in the US suggest that many medical practitioners have large gaps in their genomic knowledge, and that they

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129 Barbara J. Evans, Wylie Burke & Gail Jarvik, *The FDA and Genomic Tests—Getting Regulation Right*, 372 New Eng. J. Med. 2258, 2258 (2015).

130 Stuart Hogarth, *Regulatory Experiments and Transnational Networks: the Governance of Pharmacogenomics in Europe and the United States*, 25 Innovation—Eur. J. Soc. Sci. Res. 1 (2012).

131 *Id.*

132 Isaac Chan & Geoffrey S. Ginsburg, *Personalized Medicine: Progress and Promise*, 12 Ann. Rev. Genom. & Hum. Genet. 217, 231–2 (2001).

133 Joly et al., *supra* note 63, at 407.

134 Ian Ayres & John Braithwaite, Responsive Regulation (1992).

135 Lori-Ann A. Daley et al., *Personal DNA Testing in College Classrooms: Perspectives of Students and Professors*, 17 Genet. Testing & Molecular Biomarkers 1 (2014).

136 *Id.* at 1.

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'lack the requisite knowledge … to provide adequate genomic testing and counseling'.[137] Specialists, too, need 'genomic' training.[138]

Over-medicalization

There is a real risk that without appropriate safeguards, precision medicine may drive defensive medical practices, shift standards of care to expect more rather than less intervention, and produce extraneous information of uncertain clinical utility. In turn, this could lead to a growing cohort of the 'worried well'.[139] Amy McGuire and Wylie Burke refer to this problem in the context of DTC genomic analysis as 'raiding the medical commons'. They argue that the time a medical practitioner spends with a patient discussing their personal health genomic analysis reports, which continue to be of dubious clinical value, detracts from the time that could be spent discussing other more relevant matters.[140] Another term that has been coined to refer to those individuals who sit in the twilight zone between sickness and health is 'patients in waiting'.[141]

These scenarios raise further questions as to the kinds of information that patients and other consumers need to make informed decisions about clinical care. There is already a growing movement in healthcare questioning 'over-medicalization'. For example, in Australia, the USA and Canada, the 'Choosing Wisely' initiative involves over fifty medical organizations developing evidence-based recommendations for practices or procedures that should be reconsidered or discontinued because they fail to benefit, and may even harm, patients. In the UK, the *British Medical Journal's* 'Too Much Medicine' project focuses on the harms of over-diagnosis and unnecessary healthcare interventions. It is timely to reflect on whether precision medicine will promote 'appropriate healthcare', recognizing that 'too much medicine is harming both the sick and the well'.[142]

CONCLUSION

This essay has shown that responding to President Obama's call to modernizing the current regulatory landscape for precision medicine will be no simple task. In this era of rapid technological change, the need for appropriate regulatory oversight is acute to ensure that available technologies are safe and that people receive the best-indicated treatment. There is, however, more to regulation than the (at times) blunt instrument of the law. Softer regulatory and educative tools also need to be brought into the mix.

The key regulatory challenge is how to effectively facilitate the practice of precision medicine, so that we maximize the potential benefits, while avoiding excessive and inappropriate utilization that could harm patients, drive up healthcare costs, and draw funding away from other needs. Whether regulation—either existing or tailor-made for precision medicine—can be effective remains to be seen. The analysis presented in this

137 Ribhi Hazin et al., *Ethical, Legal and Social Implications of Incorporating Genomic Information into Electronic Health Records*, 15 GENET. MED. 810, 812 (2013); See also Chan & Ginsburg, *supra* note 132, at 230.

138 Dietel et al., *supra* note 26, at 418.

139 Paul Glasziou et al., *Too Much Medicine; Too Little Care*, 347 BRIT. MED. J. 4247 (2013).

140 Amy L. McGuire & Wylie Burke, *Raiding the Medical Commons: An Unwelcome Side Effect of Direct-to-Consumer Personal Genome Testing*, 300 J. AM. MED. ASSOC. 2669 (2008).

141 Stefan Timmermans & Mara Buchbinder, *Patients-in-Waiting: Living between Sickness and Health in the Genomics Era*, 51 J. HEALTH & SOC. BEHAV. 408 (2010).

142 Glasziou et al., *supra* note 139, at 4247.

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essay identifies five key recurring elements that must be taken into account in the development of any regulatory framework for precision medicine:

(i) appropriate consideration of safety, efficacy, and patient need;
(ii) cost effectiveness;
(iii) consistency/equivalency across geographical, technological, and institutional borders;
(iv) respect for cultural differences; and
(v) genuine engagement with all relevant stakeholders.

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