



Paving the road to personalized medicine: recommendations on regulatory, intellectual property and reimbursement challenges

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ABSTRACT

Personalized medicine (PM) aims to harness a wave of ‘omics’ discoveries to facilitate research and discovery of targeted diagnostics and therapies and increase the efficiency of healthcare systems by predicting and treating individual predispositions to diseases or conditions. Despite significant investment, limited progress has been made bringing PM to market. We describe the major perceived regulatory, intellectual property, and reimbursement challenges to the development, translation, adoption, and implementation of PM products into clinical care. We conducted a scoping review to identify (i) primary challenges for the development and implementation of PM identified in the academic literature; (ii) solutions proposed in the academic literature to address these challenges; and (iii) gaps that exist in that literature. We identified regulatory barriers to PM development and recommendations in 344 academic papers. Regulatory uncertainty was a

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cross-cutting theme that appeared in conjunction with other themes including: reimbursement; clinical trial regulation; regulation of co-development; unclear evidentiary requirements; insufficient incentives for research and development; incompatible information systems; and different regulation of different diagnostics. To fully realize the benefits of PM for healthcare systems and patients, regulatory, intellectual property, and reimbursement challenges need to be addressed in lock step with scientific advances.

KEYWORDS: personalized medicine, precision medicine, device regulation, drug regulation, ‘omics’, diagnostics, biomarkers, intellectual property, reimbursement

INTRODUCTION

Personalized medicine (PM)¹ aims to harness a wave of ‘omics’² discoveries to tailor drug choices, dosages, and interventions to the biology of individual patients. Its goals are to target better healthcare, facilitate research and discovery of diagnostics and therapies, and predict individual predispositions to diseases or conditions.³ The Precision Medicine Initiative (PMI),⁴ announced by President Obama in January 2015 to ‘enable a new era of medicine through research, technology and policies that empower patients researchers and providers to work together toward development of individualized care’, fits within this broad definition of PM. The term precision medicine, however, is more mechanistic: its goal is to integrate individual-level molecular and clinical data to develop a more accurate taxonomy of diseases to enhance diagnosis, treatment, and disease management.⁵

The promise of PM is both therapeutic and economic. Many countries have invested financial, human, and infrastructure resources into the development and delivery of PM, hoping to provide better, more individualized healthcare and to use healthcare dollars more efficiently. High-throughput sequencing and bioinformatics infrastructure

¹ Other terms associated and often used interchangeably with personalized medicine include individualized medicine, molecular medicine, personalized genomic/genetic medicine, stratified medicine, tailored therapeutics, targeted therapeutics; *What is Personalized Medicine*, PACEOMICS, <http://paceomics.org/index.php/issues/> (accessed Aug. 2, 2016). Each of these terms has a slightly different meaning. A useful taxonomy of the terms, along with their definitions and first usages, is provided in Anna Pokorska-Bocci et al., ‘*Personalized Medicine: What’s in a name?*’, 11 *PERS. MED.* 197, 199–200 (2014). Despite the announcement of President Obama’s Precision Medicine Initiative, which likely increased the global usage of the term ‘Precision Medicine’, we used personalized medicine at the time we conducted the searches for our scoping review.

² “‘Omics’ is a term encompassing multiple molecular disciplines that involve the characterization of global sets of biological molecules such as DNAs, RNAs, proteins, and metabolites’. COMMITTEE ON THE REVIEW OF OMICS-BASED TESTS FOR PREDICTING PATIENT OUTCOMES IN CLINICAL TRIALS, INSTITUTE OF MEDICINE (U.S.), *EVOLUTION OF TRANSLATIONAL OMICS: LESSONS LEARNED AND THE PATH FORWARD 1*, 1 (Christine M. Micheel, Sharyl J. Nass & Gilbert S. Omenn eds., Nat’l Academies Press 2012).

³ Edward Abrahams et al., *The Personalized Medicine Coalition: Goals and Strategies*, 5 *AM. J. PHARMACOGONOMICS* 345, 345 (2005); Robert Langreth & Michael Waldholz, *New Era of Personalized Medicine: Targeting Drugs for Each Unique Genetic Profile*, 4 *ONCOLOGIST* 426, 426 (1999).

⁴ The Precision Medicine Initiative includes multiple components with efforts from the federal government and was budgeted at \$215 million in the fiscal year of 2016 by the President. NIH will lead efforts in cancer genomics, as well as the development of the large research participant cohort consisting of over one million participants; 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>.

⁵ COMMITTEE ON A FRAMEWORK FOR DEVELOPING A NEW TAXONOMY OF DISEASE, NATIONAL RESEARCH COUNCIL (U.S.), *TOWARD PRECISION MEDICINE: BUILDING A KNOWLEDGE NETWORK FOR BIOMEDICAL RESEARCH AND A NEW TAXONOMY OF DISEASE*, 12 (Steve Olson ed., Nat’l Academies Press 2011).

are facilitating PM research and development (R&D). However, while infrastructure costs are rapidly decreasing, human capacity to interpret and clinically apply ‘omics’ results remains a costly barrier to the widespread implementation of PM.⁶

A further goal of PM is to reinvigorate stagnating therapeutic R&D.⁷ Despite substantial increases in R&D investments to US\$50 billion per year, the number of new drugs approved annually in the USA has remained constant over the past 60 years.⁸ The high cost of many new therapies is in part driven by the cost of failures in clinical development: only 15.3% of drugs traverse the pipeline from phase I to market authorization for lead indications, a percentage that drops to 10.4% for all indications.⁹ The greatest rate of failure occurs due to a lack of evidence of efficacy in phase II. Specifically, for cancer R&D, a key target for PM, billions of dollars of investment have produced median gains in progression-free survival of only 2.1 months and median gains in overall survival of only 2.5 months for new cancer drugs developed between 2002 and 2014.¹⁰ PM promises to improve the current R&D environment with a more targeted approach. It will refine our understanding of disease taxonomy and thereby enable us to design clinical trials that enroll participants more likely to benefit from experimental interventions. This promises to improve efficacy and thus decrease clinical trial failure rates.

Despite significant investment, limited progress has been made to date in bringing PM products to the market.¹¹ While there have been some successes in precision medicine, notably in the field of oncology, its products are not currently in use for most diseases.¹² Challenges to progress in PM are both scientific and non-scientific. This paper focuses on the latter: we detail the major perceived non-science barriers to the creation, translation, and introduction of PM products into clinical care. We focus especially on those challenges that exist in the regulatory approvals arena, such as clinical trial design, the legal environment that impacts incentives for PM R&D, and the regulations that impact reimbursement of medical therapies, for example, a requirement for evidence of clinical utility. Despite harmonized rules for regular pharmaceutical clinical trials in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH),¹³ a significant challenge to the

⁶ William G. Feero, *Clinical Application of Whole-Genome Sequencing: Proceed with Care*, 311 J. AM. MED. ASS'N 1017, 1018 (2014).

⁷ Matthew Avery, *Personalized Medicine and Rescuing Unsafe Drugs with Pharmacogenomics: A Regulatory Perspective*, 65 FOOD & DRUG L.J. 37, 41 (2010).

⁸ Bernard Munos, *Lessons from 60 Years of Pharmaceutical Innovation*, 8 NAT. REV. DRUG DISCOV. 959, 961 (2009).

⁹ Michael Hay et al., *Clinical Development Success Rates for Investigational Drugs*, 32 NAT. BIOTECHNOL. 40, 41 (2014).

¹⁰ Tito Fojo et al., *Unintended Consequences of Expensive Cancer Therapeutics—The Pursuit of Marginal Indications and a Me-Too Mentality That Stifles Innovation and Creativity: The John Conley Lecture*, 140 JAMA OTOLARYNGOL. HEAD & NECK SURG. 122S, 122S (2014).

¹¹ The FDA approved a total of 22 therapeutics with companion diagnostic tests that are ‘essential for the therapeutic product’s safe and effective use’. Thirty-six products defined by their parent companies as companion diagnostics are marketed in the EU with approval.

¹² National Health Institute, *About the Precision Medicine Initiative Cohort Program*, <https://www.nih.gov/precision-medicine-initiative-cohort-program> (accessed July 20, 2016).

¹³ ICH HARMONISED TRIPARTITE GUIDELINE: GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1) (June 10, 1996), http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

international adoption of PM products is a lack of internationally accepted best practice standards, coupled with a lack of clear evidentiary standards for regulatory approval or reimbursement (in health insurance schemes). Existing standards are not harmonized across jurisdictions to facilitate cross-border movement or adoption of PM products. In large part, this reflects the confusion or inadequacy of regulatory and practice standards for PM within national borders.

Even though our research was international in scope, in this paper we focus on regulation of PM in the USA. This focus reflects the dominance in medical research with respect to funding and volume in that country. For example, President Obama's ambitious PMI includes the PMI Cohort Program, renamed under the current administration to All of Us, which will collect health and biospecimen data from over a million volunteers to facilitate research on individual variations in genetics, lifestyle, and environment. This research should facilitate delivery on the promise of PM. Furthermore, developments in the USA influence global norms for human subjects research through the ICH; and most PM products will seek approvals from the US Federal Drug Administration (FDA).¹⁴ Finally, there is considerable political will¹⁵ to create regulatory and policy incentives, including regulatory pathways to facilitate the introduction of PM products into American healthcare markets.

RESEARCH QUESTION AND METHODS

We used a scoping review to answer the following research questions: (i) What are the primary legal and regulatory challenges for the development and implementation of PM identified in the academic literature? and (ii) What solutions have been proposed in the academic literature to address these challenges? A scoping review provides a systematic overview of the type, extent, and quantity (but not the quality) of literature in a given research field.¹⁶ It also provides a mechanism to summarize and disseminate research findings to policy makers, practitioners, and consumers. We adapted the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement*¹⁷ to report the flow of information through the different phases of our scoping review (Figure 1).

We defined PM as seeking 'to improve stratification and timing of healthcare by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics as well as metabolomics'.¹⁸ We defined barrier as a regulatory structure identified by the study author as an impediment to PM development. We identified recommendations by looking for 'ought' statements about how regulatory

¹⁴ Rumiko Shimazawa & Masayuki Ikeda, *Are There Any Differences in the Regulations of Personalized Medicine Among the USA, EU and Japan?*, 75 BRIT. J. CLIN. PHARMACOL. 1365, 1365 (2013).

¹⁵ President Barack Obama, *Remarks at the East Room of the White House* (Jan. 30, 2015) (transcript <https://www.whitehouse.gov/the-press-office/2015/01/30/remarks-president-precision-medicine>); Julie Steenhuisen, *NIH Takes Next Steps in Obama's Precision Medicine Plan*, REUTERS (Sept. 17, 2015), <http://www.reuters.com/article/2015/09/17/us-health-precisionmedicine-idUSKCN0RH2K720150917>

¹⁶ Hilary Arksey & Lisa O'Malley, *Scoping Studies: Towards a Methodological Framework*, 8 INT'L J. SOC. RES. METHODOL. 19, 20 (2005).

¹⁷ David Moher et al., *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement*, 6 PLOS MED. (July 21, 2009), <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000097#s9>

¹⁸ Sebastian Schleidgen et al., *What is Personalized Medicine: Sharpening a Vague Term Based on a Systematic Literature Review*, 14 BMC MED. ETHICS 55, 64 (2013).

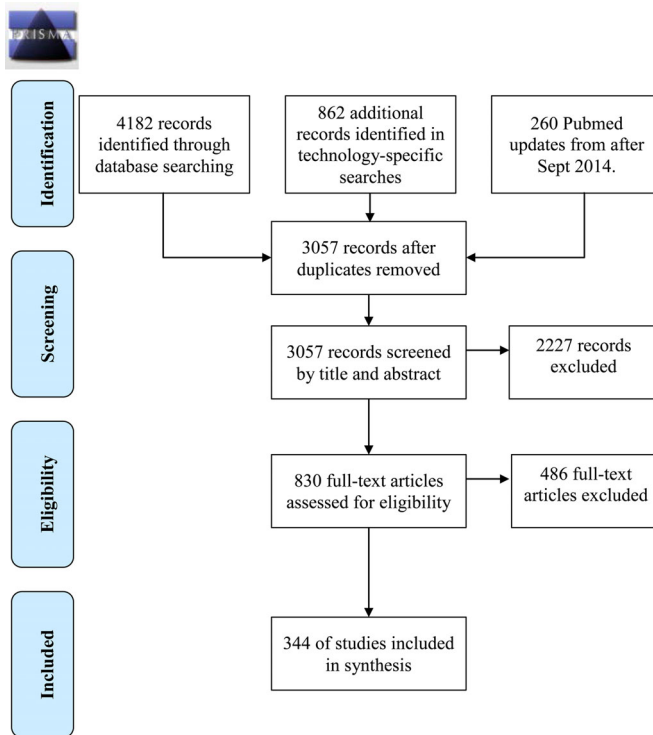


Figure 1. PRISMA diagram of personalized medicine scoping review method, illustrating inclusion/exclusion criteria. Adapted from Moher et al.¹⁷

systems could facilitate PM development. Based on this vocabulary and a list of synonyms for PM, developed with the input of a research librarian, we searched PubMed, Scopus, and LexisNexis for papers published between January 1, 2010 and April 1, 2014 (see Appendix). On September 30, 2014, the FDA published draft guidelines on a laboratory developed test (LDT) regulatory oversight framework. By then, LDT regulation had emerged as a topic of interest in our analysis. To capture responses to the proposed guidelines in the literature, we therefore extended our search period until February 6, 2015. For logistical reasons, we only conducted the extended search in PubMed. We imported all search results into Endnote 7 and removed duplicates. Of 5304 articles identified by our initial searches, 3057 remained. In consultation with economic and legal experts, we developed inclusion and exclusion standards to apply to our search results. We included English language papers that addressed both our definition of PM and regulatory challenges/barriers to PM development or proposed solutions to regulatory challenges/barriers to PM development. We included papers written on the regulatory systems affecting PM development in the European Union (EU), the USA, Canada, Japan, Singapore, and China.

Two researchers, WL and a research assistant, evaluated the titles and abstracts of search results for inclusion in the analysis. To ensure validity, the two researchers evaluated the same subset of titles and articles, and then compared their results. We cal-

culated a kappa score, a standard measure for intercoder reliability, of >0.9 , indicating consistent application of the inclusion and exclusion criteria.¹⁹ Eight hundred and thirty articles met our inclusion criteria. We retrieved full texts versions of these 830 articles, and two researchers (WL and LK) re-applied the inclusion and exclusion criteria to the full papers. They independently reviewed the same papers, representing 10% of the total dataset, and met to compare findings. Discrepancies were resolved through discussion to consensus. The authors then independently reviewed the remaining 746 papers for inclusion in the study, resulting in 344 articles that met our inclusion criteria.

We used NVivo¹⁰, a qualitative analysis software package, to assign relevant text from these 344 articles to subthemes and to organize subthemes into main themes. We constructed separate categories for barriers and recommendations. Using an inductive approach, WL and LK based their initial subthemes on the article text. We then organized these subthemes into main themes that minimized redundancy and overlap without losing important nuance. WL and LK assigned text to subthemes and main themes based on consensus discussion. When new subthemes emerged, we re-checked already analysed articles to apply the new subthemes. This iterative process is known in qualitative research as the constant comparison method.²⁰ We then summarized the features of the subthemes and main themes and provided these to experts in law and economics. We asked these experts to contextualize the barriers and recommended solutions we identified. This paper summarizes the themes for challenges and associated recommendations. Note that due to the time-consuming nature of a scoping review, we have added updated discussion of articles from targeted searches conducted after February 6, 2015.

OVERCOMING CHALLENGES FOR THE DEVELOPMENT AND IMPLEMENTATION OF PM

We identified eight main themes in our set of 344 articles related to challenges for the development and implementation of PM.²¹ These themes were unevenly represented across the literature set. Of the 344 articles, 40.1% discussed regulatory uncertainty; 25.3% discussed reimbursement; 20.1% discussed clinical trial regulations and design; 17.7% discussed regulations for co-development of pharmaceuticals and companion diagnostics (CDx); 16.0% discussed conflicting and unclear evidentiary standards in regulations; 14.0% discussed lack of or ineffective legal incentives for PM R&D; 12.5% discussed problematic or incompatible information systems and privacy concerns; and 11.3% discussed regulation of LDTs and direct-to-consumer (DTC) genetic tests. Table 1 lists the acronyms used in our discussion.

Regulatory uncertainty was the most discussed challenge for PM R&D and implementation. This was not surprising given that governments and healthcare systems were developing new regulations, guidance documents, and regulatory initiatives for PM. Because regulatory uncertainty was a cross-cutting theme, we discuss it in the context of each of the other themes, rather than in a stand-alone section. However, the key issue was that existing regulations appeared to be inapplicable to PM and suffered from a lack of harmonization, and thus interfered with PM development. Regulatory reform,

¹⁹ Mary L. McHugh, *Interrater Reliability: The Kappa Statistic*, 22 *BIOCHEM. MED.* 276, 279 (2012).

²⁰ KATHY CHARMAZ, *CONSTRUCTING GROUNDED THEORY* 54 (2d ed. 2014).

²¹ Note that articles could discuss more than one main theme.

Table 1. List of acronyms.

<i>Acronym</i>	<i>Term</i>
CDx	Companion diagnostics
CER	Comparative effectiveness research
CLIA	Clinical Laboratories Improvement Amendments
CMS	Center for Medicare and Medicaid Services
DTC	Direct to consumer
EHR	Electronic health records
EU	European Union
FDA	Food and Drug Administration
FTC	Federal Trade Commission
GINA	Genetic Information Non-Discrimination Act
HIPAA	Health Insurance Portability and Accountability Act
HTA	Health technology assessment
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug Application
IRB	Institutional review board
LDT	Laboratory developed test
NIH	National Institutes of Health
ODA	Orphan Drug Act
PHI	Protected health information
PM	Personalized medicine
PMA	Premarket approval
PMI	Personalized Medicine Initiative
PMR	Postmarket research studies
R&D	Research and development
RCT	Randomized controlled trial
SAE	Serious adverse events
SSRD	Single subject research design
USA	United States of America

whether to facilitate PM or to ensure greater safety and harmonization, created a climate of uncertainty, which created difficulties for research and approvals. There was a shared view that regulations were in flux, both in terms of frequent changes during the life cycle of drug or diagnostic development, and in terms of the flexibility with which those regulations might be applied for different PM products and services. For some stakeholders, changes to regulations were occurring too quickly,²² while for others a lack of clarity and transparency in applicable regulations created uncertainty.²³

An exemplar of regulatory reform that generated uncertainty in PM R&D and implementation is the 21st Century Cures Act²⁴ (the Act), passed by US Congress on December 7, 2016, and which President Obama signed into effect on December 13, 2016. The sweeping bipartisan legislation was widely supported by pharmaceutical industry and medical device manufacturers but was opposed by many consumer protection and patient safety groups.²⁵ The act provides increased funding of nearly \$ billion dollars for biomedical research through the NIH, the PMI, the BRAIN initiative (research into the human brain), and cancer research (referred to as the Cancer Moonshot).²⁶ Further, the act provides states with funding for opioid abuse prevention and funding at the federal level for increased research on and prevention of mental illness.²⁷

Central to the act's aim of facilitating the adoption of new therapies are controversial provisions that provide incentives for experimental therapies and faster and easier approvals for innovative drugs and medical devices.²⁸ In particular, the use of patient

²² Stuart Hogarth, *Regulatory Experiments and Transnational Networks: The Governance of Pharmacogenomics in Europe and the United States*, 25 *INNOVATION: EUR. J. SOC. SCI.* 441, 452 (2012); James Mittra & Joyce Tait, *Analysing Stratified Medicine Business Models and Value Systems: Innovation-Regulation Interactions*, 29 *NEW BIOTECHNOL.* 709, 717 (2012); Kate Traynor, *Targeted Drug Therapy Remains a Challenge*, 68 *AM. J. HEALTH-SYS. PHARMACY* 2320, 2324 (2011).

²³ James P. Evans & Michael S. Watson, *Genetic Testing and FDA Regulation Overregulation Threatens the Emergence of Genomic Medicine*, 313 *J. AM. MED. ASS'N* 669, 669 (2015); John D. Johnston & Peter Feldschreiber, *Challenges Posed to the European Pharmaceutical Regulatory System by Highly Personalized Medicines*, 77 *BRIT. J. CLIN. PHARMACOL.* 421, 425 (2014); Kelly A. McClellan et al., *Personalized Medicine and Access to Health Care: Potential for Inequitable Access?*, 21 *EUR. J. HUM. GENET.* 143, 145 (2013); Jessica E. Palmer, *Genetic Gatekeepers: Regulating Direct-to-Consumer Genomic Services in an Era of Participatory Medicine*, 67 *FOOD & DRUG L.J.* 475, 494 (2012); M. Pirmohamed, *Acceptance of Biomarker-Based Tests for Application in Clinical Practice: Criteria and Obstacles*, 88 *CLIN. PHARMACOL. & THER.* 862, 865 (2010); Randy J. Prebula, *The Promise and Personalized Medicine: Regulatory Controls and Tort Influences in the Context of Personalized Risks and Benefits*, 26 *J. CONTEMP. HEALTH L. & POL'Y* 343, 367 (2010); Agnese Querci, *Advanced Therapy Medicinal Products: The Regulation 1394/2007/CE, its Inurement in Italy and Connected Liability Regimes*, 12 *PHARMACEUTICALS POL'Y & L.* 259, 265 (2010); Rashmi R. Shah & Devron R. Shah, *Personalized Medicine: Is it a Pharmacogenetic Mirage?*, 74 *BRIT. J. CLIN. PHARMACOL.* 698, 710 (2012); L. Shahmirzadi et al., *Patient Decisions for Disclosure of Secondary Findings Among the First 200 Individuals Undergoing Clinical Diagnostic Exome Sequencing*, 16 *GENET. MED.* 395, 396 (2014); Kayte Spector-Bagdady & Elizabeth Pike, *Consuming Genomics: Regulating Direct-to-Consumer Genetic and Genomic Information*, 92 *NEB. L. REV.* 677, 731 (2014); Thomas Tursz & Rene Bernards, *Hurdles on the Road to Personalized Medicine*, 9 *MOL. ONCOL.* 935, 937 (2015); A. W. Warner et al., *Challenges in Obtaining Adequate Genetic Sample Sets in Clinical Trials: The Perspective of the Industry Pharmacogenomics Working Group*, 89 *CLIN. PHARMACOL. & THER.* 529, 532 (2010).

²⁴ 21st Century Cures Act, H.R. 34, 114th Cong. (2015).

²⁵ Mike DeBonis, *Congress Passes 21st Century Cures Act, Boosting Research and Easing Drug Approvals*, *THE WASHINGTON POST*, Dec. 7, 2016, https://www.washingtonpost.com/news/powerpost/wp/2016/12/07/congress-passes-21st-century-cures-act-boosting-research-and-easing-drug-approvals/?utm_term=.453cd4204838.

²⁶ H.R. 34, § 1001.

²⁷ H.R. 34, § 1003.

²⁸ H.R. 34.

experience data and ‘real-world evidence’ (including clinical experience data) in the approvals process, in addition to the standard data from randomized clinical trials, has raised concerns.²⁹ Primary among these concerns is that the loosening of evidentiary requirements for FDA approval will come at the cost of patient safety.³⁰

The act also facilitates a review pathway for biomarkers and other tools (such as animal model research) that help facilitate the development of new drugs.³¹ It provides regulatory clarity on the best path for approvals of combination products.³² The FDA has been directed to publish guidance on novel or adaptive clinical trial designs to ease burdens on companies submitting applications for approvals.³³

The ripple effects of broader regulatory changes also generate uncertainty for PM R&D and implementation by compounding the effects of other regulatory changes. Under the current administration of President Trump, the implementation of the 21st Century Cures Act faces uncertainty given both a hiring freeze for federal employees that will make it difficult for the FDA to hire the technicians and staff necessary to undertake the work of the act.³⁴ Additionally, in an effort to eliminate much of the federal regulatory bureaucracy, President Trump signed an executive order requiring the elimination of two regulations for each new regulation passed.³⁵ The order also applies to federal guidances of the kind used by the FDA to explain how companies can meet the requirements of the agency. To implement the act, the FDA would have to pass a number of regulations and publish several guidances. It remains unclear, therefore, whether President Trump will exempt the FDA from the executive order so that it can implement the act.

Further, the Trump administration has proposed cutting the budget of the NIH by approximately 18%, which puts in jeopardy research programs such as the Cancer Research Moonshot, and substance abuse (opioid abuse) programs.³⁶ In addition, the majority of the spending in the act was to have come from the Prevention and Public Health Fund, created under the Affordable Care Act (ACA).³⁷ With legislation proposed to repeal the ACA before the Senate at the time of writing,³⁸ it is unclear what impact such a repeal might have on the implementation of the act. What is clear is that both funding and implementation of the FDA initiatives and other biomedical research programs of the 21st Century Cures Act face increased uncertainty and delays in implementation.

In an environment of significant regulatory change, regulatory uncertainty is a barrier to realizing the potential of PM. PM developers weigh the risks posed by regulatory uncertainty when investing in PM R&D. And regulatory uncertainty hinders the implementation of PM, delaying potential benefits of PM to patients and healthcare systems.

²⁹ H.R. 34, § 3001.

³⁰ Debonis, *supra* note 25.

³¹ H.R. 34, § 3011.

³² H.R. 34, § 3038.

³³ H.R. 34, § 3021.

³⁴ US Office of Management and Budget. M-17-22, *Comprehensive Plan for Reforming the Federal Government and Reducing the Federal Civilian Workforce* (Apr. 12, 2017).

³⁵ Exec. Order No. 13771, 82 Fed. Reg. 9339 (Jan. 30, 2017).

³⁶ *Id.*

³⁷ US OFFICE OF MANAGEMENT AND BUDGET, BUDGET OF THE U.S. GOVERNMENT: A NEW FOUNDATION FOR AMERICAN GREATNESS. FISCAL YEAR 2018 (2017).

³⁸ Better Care Reconciliation Act of 2017. H.R. 1628. 115th Cong. (2017).

Specific recommendations for creating certainty and clarity in specific regulatory areas are embedded in the sections below.

Challenge: Clinical Trials

Randomized controlled trials (RCTs) provide the evidentiary gold standard of safety and efficacy required for regulatory approvals in most jurisdictions, with some exceptions for rare diseases.³⁹ While differences exist, jurisdictions such as the USA, EU,⁴⁰ and Canada⁴¹ require similar evidence of safety and efficacy to satisfy regulators. While clinical trials are necessary to ensure patient safety, numerous commentators posited that they created a significant barrier to the timely and efficient translation of research to therapy,⁴² especially in the area of PM. There is a profound tension between the goals of PM to provide stratified, smaller populations of patients with tailored therapies and

³⁹ U.S. Food & Drug Administration, *FDA and Clinical Drug Trials: A Short History*, <http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm> (accessed Apr. 11, 2016).

⁴⁰ In the EU, medicinal products may only be marketed after receiving marketing authorization from the Union through the centralized market authorization process or from a competent authority in a member state. Certain medicines (medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, and viral diseases; medicines derived from biotechnology processes; advanced-therapy medicines, including gene-therapy, somatic cell-therapy or tissue-engineered medicines; orphan medicines) must be approved through a centralized marketing authorization application. Other medicines (new active substances not authorized in the European Community before May 20, 2004; medicinal products that contribute significant therapeutic, scientific, or technical innovation or are in the interests of patient health; generic copies of centrally authorized products) can be approved through the centralized approval procedure, or can be approved through national marketing authorizations and mutual recognition procedures. Through the centralized marketing procedure, companies submit their application to the EMA. The EMA strongly encourages prospective applicants to schedule a presubmission meeting to obtain regulatory, procedural, and legal advice. Once the application is submitted, it is subject to a scientific evaluation and after consultation with the Standing Committee for Medicinal Products for Human Use, the European Commission may grant a market authorization for the product. Applications submitted to a reference member state must include a draft assessment report, summary of product characteristics (SmPC), labeling and package leaflet. Identical applications must also be sent to concerned member state(s). If the national application is successful, a harmonized marketing approval will be issued in the reference member state and concerned member state(s). The regulatory agency involved may seek additional information or clarity from the sponsor during the application process, *Eudralex - Volume 2 - Pharmaceutical Legislation Notice to Applicants and Regulatory Guidelines Medicinal Products for Human Use*, EUROPA, http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm (accessed July 29, 2016).

⁴¹ Prior to filling out an application for a New Drug Submission, sponsors can submit a presubmission package and meet with the Health Canada review staff to discuss the presentation of the data in support of the submission. After submission, Health Canada may issue a Clarification Request to expand on, add precision, or re-analyze existing data, or a Notice of Noncompliance if the submission is deficient. The sponsor has these opportunities to submit the necessary additional information in order to complete their application. Health Canada issues a notice of compliance for successful applications, indicating that the product has met Health Canada's requirements for safety, efficacy and quality; *Guidance for Industry Management of Drug Submissions*, HEALTH CANADA, http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/mgmt-gest/mands_gespd-eng.php (accessed Dec. 19, 2013).

⁴² Alan Devlin, *Systemic Bias in Patent Law*, 61 DEPAUL L. REV. 57, 70 (2011); Anna B. Laakmann, *Collapsing the Distinction Between Experimentation and Treatment in the Regulation of New Drugs*, 62 ALA. L. REV. 305, 314 (2011); George A. Nayarapally, *A Review of Recent Federal Legislative and Policy Initiatives to Enhance the Development and Evaluation of High Value Drugs in the United States*, 14 DEPAUL J. HEALTH CARE L. 503, 510 (2013); Matthew Piehl, *Regulating Hype and Hope: A Business Ethics Model Approach to Potential Oversight of Direct-to-Consumer Genetic Tests*, 16 MICH. ST. U. J. MED. & L. 59, 70 (2011); Andrew S. Robertson, *The Role of DNA Patents in Genetic Test Innovation and Access*, 9 NW. J. TECH. & INTELL. PROP. 377, 392 (2011).

standard clinical trial designs, which examine efficacy in a large segment of the generalizable patient population.⁴³

Some concerns about clinical trials in the context of PM echoed general concerns about the regulation of clinical trials expressed by R&D firms in pharmaceutical and biotechnology sectors, researchers, and patient organizations. These concerns related to the long timelines (10–15 years) and high costs of clinical trials (\$2.87 billion dollars (in 2013 dollars)).⁴⁴ These debates highlighted tensions between the regulatory process, which legislatively mandated regulators to approve only safe and efficacious products, and the interests of R&D firms and patients, which wished to bring potential therapies to market quickly and at lower cost. In the following sections, we expand on the PM subthemes in the 69 articles that discussed clinical trials, namely expense and delay (21 articles); uncertainties in the approvals process (13 articles); the use of biomarkers in clinical trials (17 articles); and clinical trial design (26 articles).

Expense and Delay

Twenty-one articles discussed the time and expense required to generate both the pre-clinical and clinical data for FDA approval in the USA.⁴⁵ Regulatory requirements drive

⁴³ There are typically four or five phases to clinical testing of a new therapeutic. Phase 0 trials are exploratory studies with very limited human exposure to the therapeutic. Phase I is a safety trial to identify frequent and serious adverse events, as well as how the therapeutic is metabolized and excreted. The focus of phase II is preliminary effectiveness in the specific indication, with continuing collection of safety data and data collection on short-term adverse events. In phase III, the therapeutic is tested in different populations and at different dosages, as well as in conjunction with other therapeutics. Phase IV studies, or postmarket surveillance, occur after the regulator approves the therapeutic for marketing and generate data on safety, efficacy, and/or optimal use; *Glossary Definition: Phase*, CLINICAL TRIALS, <https://clinicaltrials.gov/ct2/help/glossary/phase> (accessed July 20, 2016).

⁴⁴ Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22, J. HEALTH ECON. 151, 164–5 (2003); Joseph A. DiMasi, *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 20 (2016).

⁴⁵ Jonathan J. Darrow, *Crowdsourcing Clinical Trials*, 98 MINN. L. REV. 805 (2014); Devlin, *supra* note 42, at 854; Avery, *supra* note 7, at 38; Rena Conti et al., *Personalized Medicine and Genomics: Challenges and Opportunities in Assessing Effectiveness, Cost-Effectiveness, and Future Research Priorities*, 30 MED. DEC. MAKING 328, 336 (2010); Evans & Watson, *supra* note 23, at 669; Jennifer S. Geetter, *Another Man's Treasure: The Promise and Pitfalls of Leveraging Existing Biomedical Assets for Future Use*, 4 J. HEALTH & LIFE SCI. 1, 39 (2011); John Hudson & Marta Orviska, *European Attitudes to Gene Therapy and Pharmacogenetics*, 16 DRUG DISCOV. TODAY 843, 844 (2011); K Ichimaru et al., *PMDA's Challenge to Accelerate Clinical Development and Review of New Drugs in Japan*, 88 CLIN. PHARMACOL. & THER. 454, 454 (2010); Robert Jones & Maria DeSantis, *Access to Targeted Therapies in Renal Cell Cancer*, 40 SEMIN. ONCOL. 521, 522 (2013); Gottfried E. Konecny, *The Path to Personalized Medicine in Women's Cancers: Challenges and Recent Advances*, 27 CURR. OPIN. OBSTET. & GYNECOL. 45, 46 (2015); Laakmann, *supra* note 42, at 314; Janet L. MacPherson & John E.J. Rasko, *Cellular Therapy in the Asia-Pacific Region. A Guide for the Future Pathologist*, 43 PATHOLOGY 616, 623 (2011); Michael McCarthy, *Obama Promises to Defend Health Law and Promote 'Precision Medicine'*, 350 BMJ 385, 385 (2015); Mittra & Tait, *supra* note 22, at 717; Richard A. Montagna, *Meeting the Technical Challenges of Personalized Medicine and Companion Diagnostics*, 44 MED. LAB. OBS. 16, 18 (2012); Bryn Nelson, *Ensuring Quality in Genomic Medicine: Amid the Rise in Complex Laboratory-Developed Tests, Regulatory Officials are Seeking the Right Balance on Quality Assurance*, 122 CANCER CYTOPATHOL. 855, 856 (2014); Neyarapally, *supra* note 42, at 510; Piehl, *supra* note 42, at 70; Scott D. Ramsey et al., *How Comparative Effectiveness Research Can Help Advance 'Personalized Medicine' in Cancer Treatment*, 30 HEALTH AFF. 2259, 2264 (2011); Robertson, *supra* note 42, at 392; Richard L. Schilsky et al., *Commentary: Tackling the Challenges of Developing Targeted Therapies for Cancer*, 15 ONCOLOGIST 484, 485 (2010).

up R&D costs, which are then reflected in the cost of approved therapeutics.⁴⁶ Where market size is reduced due to stratification of patients into small populations likely to benefit from a given therapy, the additional cost of running a clinical trial may create a financial disincentive. The high cost of clinical trials can also create barriers to physician and patient uptake in the form of higher prices, and difficulties with downstream reimbursement, for the same aforementioned reason.⁴⁷

Biomarkers

A major impediment for PM developers is the high cost and complexity of establishing and validating predictive biological markers (biomarkers). Biomarkers are objectively measurable biological characteristics, including genetic variants, or medical signs that indicate a pathogenic process or pharmacological response to a particular therapy.⁴⁸ Biomarkers may answer the following questions: ‘Does the drug reach the target? Does it have the desired biological effect? Does it have an influence on other expected or unexpected targets? Does the drug affect characteristics that predict desired or undesired effects?’⁴⁹ The presence or absence of a biomarker may predict whether and how a particular patient or subset of patients will respond to an experimental drug. Genetic biomarkers are particularly useful because genetic factors account for 15% to 30% of differences in drug metabolism and response between individuals.⁵⁰ Pharmacogenetic tests use genetic variations between individuals to determine drug absorption and disposition, or drug activity.⁵¹ The ability to predetermine, with the use of biomarkers,

⁴⁶ Avery, *supra* note 7, at 38; Evans & Watson, *supra* note 23, at 669; Hudson & Orviska, *supra* note 45, at 844; Ichimaru et al., *supra* note 45, at 454; Jones & DeSantis, *supra* note 45, at 522; Konecny, *supra* note 45, at 46; MacPherson & Rasko, *supra* note 45, at 623; Jeanette J. McCarthy et al., *Genomic Medicine: A Decade of Successes, Challenges, and Opportunities*, 5 SCI. TRANSL. MED. 189, 207 (2013); Mittra & Tait, *supra* note 22, at 710; Montagna, *supra* note 45 at 18; Nelson, *supra* note 45, at 856; Ramsey et al., *supra* note 45, at 2264; Schilsky et al., *supra* note 45, at 485.

⁴⁷ Joshua P. Cohen & Abigail E. Felix, *Personalized Medicine’s Bottleneck: Diagnostic Test Evidence and Reimbursement*, 4 J. PERS. MED. 163, 171 (2014); Leonard M. Fleck, *Just Caring: Assessing the Ethical and Economic Costs of Personalized Medicine*, 32 UROL. ONCOL. 202, 206 (2014); Shannon G. Gibson & Trudo Lemmens, *Niche Markets and Evidence Assessment in Transition: A Critical Review of Proposed Drug Reforms*, 22 MED. L. REV. 200, 211 (2014); Christof Koelsch et al., *Towards a Balanced Value Business Model for Personalized Medicine: An Outlook*, 14 PHARMACOGENOMICS 89, 92 (2013); Christophe Le Tourneau et al., *Designs and Challenges for Personalized Medicine Studies in Oncology: Focus on the SHIVA Trial*, 7 TARGET. ONCOL. 253, 264 (2012); Pierre Miossec et al., *Biomarkers and Personalised Medicine in Rheumatoid Arthritis: A Proposal for Interactions Between Academia, Industry and Regulatory Bodies*, 70 ANN. RHEUM. DIS. 1713, 1716 (2011); Katelin E. Petersen et al., *Personalized Medicine, Availability, and Group Disparity: An Inquiry into How Physicians Perceive and Rate the Elements and Barriers of Personalized Medicine*, 17 PUB. HEALTH GENOM. 209, 216 (2014); Mark R. Trusheim et al., *Quantifying Factors for the Success of Stratified Medicine*, 10 NAT. REV. DRUG DISCOV. 817, 823 (2011); Tursz & Bernards, *supra* note 23, at 938.

⁴⁸ ‘A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention’; U.S. Food & Drug Administration, *From our Perspective: Clinical Biomarker Qualification*, <http://www.fda.gov/Drugs/NewsEvents/ucm424545.htm> (accessed Jan. 5, 2015).

⁴⁹ Lasse Tengbjerg Hansen & Adam Heathfield, *Personalized Medicine: Translation of Concepts*, GENENGENEWS (Mar. 20, 2013), <http://www.genengnews.com/bioperspectives/personalized-medicine-translation-of-concepts/4783>.

⁵⁰ Giuseppe Novelli et al., *Genetic Tests and Genomic Biomarkers: Regulation, Qualification and Validation*, 5 CLIN. CASES MINER. & BONE METAB. 149, 152 (2008).

⁵¹ Lawrence J. Lesko & Janet Woodcock, *Translation of Pharmacogenomics and Pharmacogenetics: A Regulatory Perspective*, 3 NAT. REV. DRUG DISCOV. 763, 763 (2004).

the targeted patient population and therapeutic dosage should shorten drug development timelines, reduce expenses and provide a greater likelihood of bringing a drug successfully through the regulatory process. The development of appropriate biomarkers is therefore a major strategy for reinvigorating a lagging pharmaceutical business model focused on the development of blockbuster drugs that can be used in large portions of the population.⁵²

There are, however, problems with the identification and the validation of biomarkers that have undermined their utility thus far. First, scientifically identifying and establishing biomarkers is difficult.⁵³ Second, the regulatory criteria necessary to validate biomarkers are neither agreed upon nor clear. Third, there are difficulties in collecting high-quality data to show that the biomarker is clinically valid and useful, as biomarkers are often identified late in the drug development process when it becomes apparent that only a small subset of the patient population is reacting to the drug under development.⁵⁴ Indeed, PM has the potential to ‘rescue’ a drug that has failed to perform as expected in clinical trials by using a biomarker to identify the subset population in which the drug is effective. This ‘rebrands’ the drug as a PM for patients with that biomarker;⁵⁵ however, in this situation, where further investigation determines what biological or genetic factor is at work in the responding subpopulation, the drug is normally well along the drug validation and clinical development pipeline. Consequently, due to issues of timing, and difficulty generating adequate evidence, regulatory demands for biomarker validation data can often be greater than the evidence that emerges from the trials involving the biomarkers.

In the context of genetic biomarkers, differences exist between the evidentiary standards that are required to use a genetic test for a biomarker in a laboratory setting and those required by regulators before that test can be used in a clinical setting. Internal laboratory biomarker tests do not require independent validation and vary considerably from laboratory to laboratory and from jurisdiction to jurisdiction.⁵⁶ Regulatory standards for the use of biomarkers in a clinical setting are generally higher, requiring analytical validation that can be difficult to provide to the FDA without prior planning and early identification.⁵⁷

Finally, while PM developers see the opportunity to further reduce clinical trial sizes by identifying biomarker-positive participants, regulators are concerned with

⁵² The forerunner of this new generation of drugs is Herceptin, which the FDA approved, with a companion diagnostic to identify women with HER2 overexpression, as a treatment for metastatic HER2-overexpressing breast cancer. Genentech, the developer of Herceptin, has led the way in seeking approval for ever-broadening indications for its targeted therapeutics. This new generation of drugs begins its lifecycle in a small population with unmet medical needs, in which the developer can charge premium rates while also seeking evidence to expand into broader indications. While the growth rates of biologics have grown 20%, the growth rate of US pharmaceutical market grew only 6%–8%. Saurabh Aggarwal, *What’s fueling the biotech engine?*, 25 NAT. BIOTECH. 1097, 1098 (2007).

⁵³ Christopher-Paul Milne & Rachel Zuckerman, *Biopharmaceutical Industry Perspectives on the Business Prospects for Personalized Medicine*, 8 PERS. MED. 541, 544 (2011); Eric E. Walk, *Improving the Power of Diagnostics in the Era of Targeted Therapy and Personalized Healthcare*, 13 CURR. OPIN. DRUG DISCOV. & DEV. 226, 230 (2010).

⁵⁴ Hansen & Heathfield, *supra* note 49.

⁵⁵ Ignacio I. Wistuba et al., *Methodological and Practical Challenges for Personalized Cancer Therapies*, 8 NAT. REV. CLIN. ONCOL. 135, 140 (2011).

⁵⁶ Jean-Claude Libeer & Sharon Ehrmeyer, *ISO 15189: A Worldwide Standard for Medical Laboratories*, 3 POINT CARE 5, 6 (2004).

⁵⁷ Michael Nohaile, *The Biomarker is Not the End*, 16 DRUG DISCOV. TODAY 878, 881 (2011).

the risks posed to biomarker-negative patients. Regulators may therefore require both biomarker-positive and negative participants in clinical trials, thus reducing or nullifying any potential savings for the trial sponsor.⁵⁸ While regulatory approval is still possible without this evidence, the approval will limit clinical application to biomarker-positive patients,⁵⁹ unless physicians use it off-label.⁶⁰ The manufacturer may further have to undertake postmarketing studies or phase IV clinical trials in biomarker-negative populations, which raises costs and uncertainty from a manufacturer's perspective.⁶¹

Clinical Trial Design

Regulations require that clinical trials are designed with specific hypotheses and therapeutic targets in mind and proceed with prospective analysis to demonstrate safety and efficacy in a generalizable population. There are, therefore, significant tensions between standard clinical trial designs and designs adapted to the smaller patient subsets that are the hallmark of PM. First, smaller clinical trial designs provide inferior evidence of safety and efficacy due to the small numbers of patients involved.⁶² Small trials do not have the statistical power to detect efficacy, especially if the magnitude of the effect is predicted to be small. Second, without a large generalizable population study, it is difficult to fully understand the benefit/risk analysis of the drug.⁶³ This is concerning because any off-label⁶⁴ use by clinicians once the drug is approved can lead to unexpected and serious adverse events (SAE) not discovered in a phase III study. In addition, analysis of the subgroups enrolled in a clinical trial often comprises a retrospective analysis that takes place as the trial is ongoing or after a suboptimal or failed clinical trial.⁶⁵ Such post hoc analysis requires a mid-stream course correction with new patient targets and

⁵⁸ Koelsch et al., *supra* note 47, at 91; Yann Joly et al., *Regulatory Approval for New Pharmacogenomic Tests: A Comparative Overview*, 66 FOOD & DRUG L.J. 1, 4 (2011); Marie Loh & Richie Soong, *Challenges and Pitfalls in the Introduction of Pharmacogenetics for Cancer*, 40 ANN. ACAD. MED. 369, 369–70 (2011); Yasuto Otsubo et al., *Regulatory Perspective on Remaining Challenges for Utilization of Pharmacogenomics-Guided Drug Developments*, 14 PHARMACOGENOMICS 195, 198 (2013); M.A. Pacanowski, *Next-Generation Medicines: Past Regulatory Experience and Considerations for the Future*, 95 CLIN. PHARMACOL. & THER. 247, 248 (2013); Trusheim et al., *supra* note 47, at 824.

⁵⁹ Elizabeth A. Mansfield, *FDA Perspective on Companion Diagnostics: An Evolving Paradigm*, 20 CLIN. CANCER RES. 1453, 1455 (2014).

⁶⁰ Off-label use is defined as 'unapproved use of an approved drug'. The FDA approves drugs for specific indications; its approval indicates that the benefits of using the drug for that particular use outweigh the risks. Once a drug is approved, a healthcare provider may prescribe the drug for an unapproved use that they judge as medically appropriate for their patient; U.S Food & Drug Administration, *Understanding Unapproved Use of Approved Drugs 'Off Label'*, <http://www.fda.gov/ForPatients/Other/OffLabel/default.htm> (accessed June 2, 2016).

⁶¹ Francesco Pignatti et al., *Cancer Drug Development and the Evolving Regulatory Framework for Companion Diagnostics in the European Union*, 20 CLIN. CANCER RES. 1458, 1462 (2014).

⁶² Robert L. Cohen & Jeff Settleman, *From Cancer Genomics to Precision Oncology—Tissue's Still an Issue*, 157 CELL 1509, 1512 (2014); Sean A. McGhee, *How the Practice of Allergy Shows the Promise and Challenge of Personalized Medicine*, 104 MOL. GENET. & METAB. 3, 4 (2011); Henrik Winther & Jan Trøst Jørgensen, *Drug-Diagnostic Co-Development in Cancer*, 24 PHARMACEUTICAL MED. 363, 363 (2010).

⁶³ Efthimos Parasidis, *Patients over Politics: Addressing Legislative Failure in the Regulation of Medical Products*, 5 WIS. L. REV. 929, 931 (2011).

⁶⁴ See footnote 60.

⁶⁵ Anup Malani et al., *Accounting for Heterogeneous Treatment Effects in the FDA Approval Process*, 67 FOOD & DRUG L.J. 23, 28 (2012).

a different hypothesis during or after the clinical trial to ‘rescue’ the drug candidate, and ‘rebrand’ it as a stratified therapeutic for a specific, smaller population.⁶⁶ This type of post hoc analysis is not permitted under the current regulations, and it is not clear whether in all cases an entirely new clinical trial would be required.⁶⁷

Uncertainty in the Approval Process

In light of the preceding discussion, uncertainty about the clinical trial process for PM leads to uncertainty about the likelihood of regulatory approval. In addition to the high cost associated with the regulatory approval process, failure to gain approval means those costs cannot be recouped. Regulatory uncertainty in the clinical trial process exists with respect to the precise information companies must present to regulators for a successful application, and how that information will be used;⁶⁸ the use of biomarkers;⁶⁹ and the design of clinical trials that incorporate CDx.⁷⁰ PM developers desire better guidance on how best to design a successful clinical trial for a personalized therapy, because absent guidance, they risk presenting suboptimal evidence regarding stratification options. Designing clinical trials for differently responding subgroups (for example, biomarker-positive and biomarker-negative groups) requires additional time and resources.⁷¹ Companies are reluctant to make this investment without a commensurate increase in the certainty of regulatory approval.

Meanwhile, regulators struggle to make evidence-based risk and benefit decisions from clinical trials with very small sample sizes, which do not capture rare SAE.⁷² While existing standards for clinical trial design may be suboptimal for PM,⁷³ using novel clinical trial designs may not improve a therapeutic’s chance for approval.⁷⁴ In the absence of functional regulatory guidelines on clinical trial designs, PM developers and regulators will remain frustrated with the quality of evidence generated by clinical trials and the uncertain regulatory outcomes that follow.

⁶⁶ *Id.* at 29.

⁶⁷ *Id.*

⁶⁸ Gibson & Lemmens, *supra* note 47, at 208; Chiara Piana et al., *Integration of Pharmacogenetics and Pharmacogenomics in Drug Development: Implications for Regulatory and Medical Decision Making in Pediatric Diseases*, 52 J. CLIN. PHARMACOL. 704, 704 (2012); Francesco Pignatti et al., *Assessment of Benefits and Risks in Development of Targeted Therapies for Cancer – The View of Regulatory Authorities*, 9 MOL. ONCOL. 1034, 1037 (2015).

⁶⁹ Jane Fridlyand et al., *An Industry Statistician’s Perspective on PHC Drug Development*, 36 CONTEMP. CLIN. TRIALS 624, 744 (2013); Malani, *supra* note 65, at 29.

⁷⁰ Sarah Blankstein, *Pharmacogenomics- History, Barriers, and Regulatory Solutions*, 69 FOOD & DRUG L.J. 273, 283–4 (2014).

⁷¹ Avery, *supra* note 7, at 39; Gibson & Lemmens, *supra* note 47, at 204; Malani, *supra* note 65, at 28.

⁷² Blankstein, *supra* note 70, at 281; Cohen & Settleman, *supra* note 62, at 1512; McGhee, *supra* note 62, at 4; Parasidis, *supra* note 63, at 931; Winther & Jørgensen, *supra* note 62, at 363.

⁷³ Jaap Verweij et al., *Moving Molecular Targeted Drug Therapy Towards Personalized Medicine: Issues Related to Clinical Trial Design*, 6 MOL. ONCOL. 196, 201 (2012); J. S. de Bono & Alan Ashworth, *Translating Cancer Research into Targeted Therapeutics*, 467 NATURE 543, 543 (2010).

⁷⁴ Cohen & Settleman, *supra* note 62, at 1512; Jin Huang et al., *Emerging Trends in US Oncological Approvals: A 13-Year Review (1999-2011)*, 46 DRUG INFO. J. 344, 353 (2012); Le Tourneau et al., *supra* note 47, at 264; Nohaile, *supra* note 57, at 881; Manish R. Sharma & Richard L. Schilsky, *Role of Randomized Phase III Trials in an Era of Effective Targeted Therapies*, 9 NAT. REV. CLIN. ONCOL. 208, 211 (2011); Nigel Stallard et al., *Adaptive Designs for Confirmatory Clinical Trials with Subgroup Selection*, 24 J. BIOPHARM. STAT. 167, 183 (2014).

Recommendations to Overcome Clinical Trial Challenges

Given the numerous challenges posed by clinical trial regulations, many proponents of PM recommend changing or improving clinical trial design to aid PM development and clinical translation. In general, PM developers would like greater clarity and guidance about how information on biomarkers should be presented and how it will be used in the approvals process.⁷⁵ Strengthening postmarket study and surveillance (PMR) requirements,⁷⁶ using postmarketing authorization, encouraging phase IV clinical trials,⁷⁷ gathering ongoing evidence⁷⁸ and using limited or conditional approvals^{79,80} are all frequently mentioned recommendations. Recommendations involving PMR include the creation of an ‘approval with conditions’—a regulatory option that would fast track some approvals in combination with mandatory phase IV PMR and the creation of a centrally managed database for SAE reporting by physicians.⁸¹ It is thought that strengthening PMR could alleviate some of the difficulty companies have meeting evidentiary burdens, particularly with respect to bringing prospective population-segmented data to regulators.⁸² PMR might evaluate a drug’s effect in a specific patient population or identify new uses for the drug.

⁷⁵ Blankstein, *supra* note 70, at 277; Malcolm Rowland et al., *Impact of the Pharmaceutical Sciences on Health Care: A Reflection over the Past 50 Years*, 101 J. PHARM. SCI. 4075, 4089 (2012); Sharma & Schilsky, *supra* note 74, at 212 (2011); Takeki Uehara et al., *The Japanese Toxicogenomics Project: Application of Toxicogenomics*, 54 MOL. NUTR. & FOOD RES. 218, 226 (2010); F. Randy Vogenberg et al., *Personalized Medicine Part 2: Ethical, Legal, and Regulatory Issues*, 35 PHARM. & THER. 624, 631 (2010); Walk, *supra* note 53, at 230.

⁷⁶ Laakmann, *supra* note 42, at 334; Parasidis, *supra* note 63, at 935.

⁷⁷ Avery, *supra* note 7, at 39; Cohen & Settleman, *supra* note 62, 1512; Joly et al., *supra* note 58, at 4-5.

⁷⁸ Zeinab Awada & Nathalie Khoueiry Zgheib, *Pharmacogenovigilance: A Pharmacogenomics Pharmacovigilance Program*, 15 PHARMACOGENOMICS 845, 847 (2014); Gibson & Lemmens, *supra* note 47, at 208; J.W. Lee et al., *The Emerging Era of Pharmacogenomics: Current Successes, Future Potential, and Challenges*, 86 CLIN. GENET. 21, 25 (2014); N.A. Meadows et al., *An Evaluation of Regulatory and Commercial Barriers to Stratified Medicine Development and Adoption*, 15 PHARMACOGENOMICS J. 6, 8 (2015); Ramsey et al., *supra* note 45, at 2267-68; Renee Ahrens Thomas et al., *APhA 2010 House of Delegates: Paving the Way for the Profession’s Best Practices*, 50 J. AM. PHARM. ASS’N. 450, 452 (2010).

⁷⁹ Under provisions for limited, accelerated, or conditional approval, regulators may approve pharmaceutical products based on limited datasets while requiring the company to perform confirmatory tests post approval. Conditional approvals are a compromise between earlier patient access who suffer diseases with unmet medical needs and patient safety, Arna H. Arnardottir et al., *Additional Safety Risk to Exceptionally Approved Drugs in Europe?*, 72 BRIT. J. CLIN. PHARMACOL. 490, 491 (2011).

⁸⁰ Blankstein, *supra* note 70, at 313; Cohen & Felix, *supra* note 47, at 172; Cohen & Settleman, *supra* note 62, at 1513; William S. Dalton et al., *The 2010 Health Care Reform Act: A Potential Opportunity to Advance Cancer Research by Taking Cancer Personally*, 16 CLIN. CANCER RES. 5987, 5994 (2010); de Bono & Ashworth, *supra* note 73, at 545; Hans-Georg Eichler et al., *Bridging the Efficacy-Effectiveness Gap: A Regulator’s Perspective on Addressing Variability of Drug Response*, 10 NAT. REV. DRUG DISCOV. 495, 502 (2011); Gibson & Lemmens, *supra* note 47, at 208; Joly et al., *supra* note 58, at 4; Jan Tröst Jørgensen, *Companion Diagnostics in Oncology – Current Status and Future Aspects*, 85 ONCOLOGY 59, 65 (2013); Laakmann, *supra* note 42, at 334; D. O’Kane, *An Outsider’s Viewpoint: The FDA Should Regulate Clinical Pharmacogenetic/ Genomic Tests, But...*, 88 CLIN. PHARMACOL. & THER. 746, 747 (2010); George Poste et al., *Leveling the Playing Field: Bringing Development of Biomarkers and Molecular Diagnostics up to the Standards for Drug Development*, 18 CLIN. CANCER RES. 1515, 1520 (2012); Ramsey et al., *supra* note 45, at 2267-68; Schilsky et al., *supra* note 45, at 486; Carla G. van El & Martina C. Cornel, *Genetic Testing and Common Disorders in a Public Health Framework*, 19 EUR. J. HUM. GENET. 377, 380 (2011); S. J.H. Vijverberg et al., *Ethical and Social Issues in Pharmacogenomics Testing*, 16 CURR. PHARM. DES. 245, 250 (2010); Vogenberg et al., *supra* note 75, at 631; Wistuba et al., *supra* note 55, at 140.

⁸¹ Laakmann, *supra* note 42, at 340; Gibson & Lemmens, *supra* note 47, at 215; Schilsky et al., *supra* note 45, at 486; Poste et al., *supra* note 80, at 1521.

⁸² Laakmann, *supra* note 42, at 340.

Recommendations favoring mandatory PMR also reflect a general desire to capture SAE, and provide more rigorous feedback of clinical results into the regulatory process.⁸³ PMR might be used to identify the variability that underlies serious event rates in different patient groups.⁸⁴ To that end, recommendations range from using postmarketing data collection pilot projects created by the Center for Medicare and Medicaid Services (CMS) and Centers for Disease Controls and Prevention as models for the FDA's Sentinel program,⁸⁵ to standardizing reporting of SAE independent of pharmaceutical companies.⁸⁶ This would foster greater transparency, learning, and quicker turnover of innovation, which, while desirable, is foreign to a strong trade secret and confidentiality ethos in medical product development. There is little consensus, however, on how mandatory PMR should be instituted, as an FDA power through legislation,⁸⁷ or under a public/private funding partnership.⁸⁸ The latter option leaves all information publicly owned and appears to be at odds with existing data protection laws. In addition, recommendations aim to mitigate the difficulties, both scientific and evidentiary, with the validation of biomarkers.⁸⁹ Some propose the use of unvalidated biomarkers, so long as the sponsor commits to a phase IV clinical trial,⁹⁰ or the use of biomarkers that emerge during the early phases of the trial.⁹¹

Innovative Clinical Trial Design

Other recommendations relate to clinical trial design and several authors suggest a number of innovative or alternative trial designs to aid PM products through the regulatory approval stage. Several articles recommend that regulators work with PM manufacturers to create new models and provide greater guidance on permissible clinical trial design.⁹² Recommendations include innovations or alternatively designed studies that reduce costs,⁹³ do not rely on animal models,⁹⁴ or involve modified or conditional

⁸³ Awada & Zgheib, *supra* note 78, at 847; Gibson & Lemmens, *supra* note 47, at 215; Laakmann, *supra* note 42, at 343.

⁸⁴ Awada & Zgheib, *supra* note 78, at 847.

⁸⁵ Laakmann, *supra* note 42, at 340.

⁸⁶ Awada & Zgheib, *supra* note 78, at 847; Gibson & Lemmens, *supra* note 47, at 215.

⁸⁷ Parasidis, *supra* note 63, at 934-935.

⁸⁸ Cohen & Settleman, *supra* note 62, at 1512; Laakmann, *supra* note 42, at 344.

⁸⁹ Avery, *supra* note 7, at 51; Eichler et al., *supra* note 80, at 501; Federico M. Goodsaid, *Voluntary Exploratory Data Submissions to the US FDA and the EMA: Experience and Impact*, 9 NAT. REV. DRUG DISCOV. 435, 436 (2010); Otsubo et al., *supra* note 58, at 195; Mittra & Tait, *supra* note 22, at 716.

⁹⁰ Avery, *supra* note 7, at 54.

⁹¹ Mittra & Tait, *supra* note 22, at 716.

⁹² Lidia Becla et al., *Health Technology Assessment in the Era of Personalized Health Care*, 27 INT'L J. TECH. ASSESS. HEALTH CARE 118, 125 (2011); Cinnamon S. Bloss et al., *Genomics for Disease Treatment and Prevention*, 34 PSYCHIATR. CLIN. N. AM. 147, 154-55 (2011); Craig P. Carden et al., *Can Molecular Biomarker-Based Patient Selection in Phase I Trials Accelerate Anticancer Drug Development?*, 15 DRUG DISCOV. TODAY 88, 93-4 (2010); Zubin J. Eapen et al., *The Imperative of Overcoming Barriers to the Conduct of Large, Simple Trials*, 311 JAMA 1397, 1397 (2014); Eric Faulkner et al., *Challenges in the Development and Reimbursement of Personalized Medicine—Payer and Manufacturer Perspectives and Implications for Health Economics and Outcomes Research: A Report of the ISPOR Personalized Medicine Special Interest Group*, 15 VALUE HEALTH 1162, 1167 (2012); Judith M. Fontana et al., *Translational Research in Infectious Disease: Current Paradigms and Challenges Ahead*, 159 TRANSL. RES. J. LAB. & CLIN. MED. 430, 446 (2012).

⁹³ Blankstein, *supra* note 70, at 277; Fontana et al., *supra* note 92, at 446.

⁹⁴ Fontana et al., *supra* note 92, at 446.

approval paired with a postapproval requirement to develop additional evidence.⁹⁵ Adaptive trial design could reduce drug approval time and cost by recruiting only ‘likely responders’ based on biomarkers into clinical trials.⁹⁶ Alternatively, adopting an ‘adaptive group sequential design’ involving rolling admissions of sensitive subgroups could overcome some of the current clinical trial design barriers.⁹⁷

Authors also recommend regulatory acceptance of smaller clinical trial populations in lieu of prospective RCTs.⁹⁸ Reliance on prospective-only trial design invalidates the use of retrospective analysis or identification of biomarkers during the course of clinical trials. Adaptive trial design that involves contemporaneous biomarker identification would overcome this regulatory barrier.⁹⁹ Along with trial design that overcomes the difficulties with biomarker validation, several articles recommend moving from the traditional clinical trial group experimental design to Single Subject Research Design (SSRD) or ‘N of 1’ studies.¹⁰⁰ This move would be difficult and controversial as SSRD studies are not sufficient to satisfy current clinical trial information and design for regulatory approval.¹⁰¹ Despite the difficulty, SSRD would help identify highly reactive patients and speed up evidence collection to meet regulatory requirements.¹⁰²

Challenge: CDx and Co-Development

A second challenge facing PM development is the significant uncertainty that exists around the optimal, possible, and acceptable clinical trial design for therapeutics intended to be used with CDx. This uncertainty negatively impacts the advantages predicted for PM in the combination of tailored therapies and diagnostics that identifies the optimal patient population. Such CDx, commonly regulated as medical devices, are most often in vitro assays¹⁰³ or genetic tests. These assays and tests help identify

⁹⁵ Gibson & Lemmens, *supra* note 47, at 208.

⁹⁶ Blankstein, *supra* note 70, at 277.

⁹⁷ Cohen & Settleman, *supra* note 62, at 1512; Malani, *supra* note 65, at 25.

⁹⁸ Gibson & Lemmens, *supra* note 47, at 210; Tursz & Bernards, *supra* note 23, at 938.

⁹⁹ Eichler et al., *supra* note 80, at 502; Denis Horgan et al., *An Index of Barriers for the Implementation of Personalized Medicine and Pharmacogenomics in Europe*, 17 PUB. HEALTH GENOM. 287, 295 (2014).

¹⁰⁰ In general, ‘N of 1’ studies consist of a single patient as the whole trial who serves as his/her own control. In oncology, an ‘N of 1’ trial refers to the use of pathological and molecular characteristics to select an individualized therapeutic regimen. Michael J. Malinowski & Grant G. Gautreaux, *All that is Gold Does Not Glitter in Human Clinical Research: A Law– Policy Proposal to Brighten the Global ‘Gold Standard’ for Drug Research and Development*, 45 CORNELL INT’L L.J. 185, 197 (2012); Funda Meric-Bernstam & Gordon B. Mills, *Overcoming Implementation Challenges of Personalized Cancer Therapy*, 9 NAT. REV. CLIN. ONCOL. 542, 545 (2012).

¹⁰¹ Meric-Bernstam & Mills, *supra* note 100, at 545.

¹⁰² An in-depth discussion of SSRD is beyond the scope of this paper. See Malinowski & Gautreaux, *supra* note 100.

¹⁰³ In vitro diagnostic tests are 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 (1980). They are defined as any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body. The label of in vitro diagnostics must state that the product is ‘For In Vitro Diagnostic Use’, Council Directive 98/79, 1998 O.J. (L 331) (EC). Labels for in vitro diagnostics must also include the intended use or uses of the diagnostic and a statement of warnings or precautions and any other warnings appropriate to user hazards. Note that labels of in vitro diagnostics are not required to identify specific therapeutic products, unlike companion diagnostics (Food and Drug Administration (2014)), *In Vitro Diagnostic Device Labeling Requirements*, FDA,

the presence or absence of a biomarker, indicating the patient's suitability as the recipient of a particular therapy, such as a small-molecule drug, biologic, or gene/cell therapy. To fully exploit the therapeutic and economic advantages of the therapeutic–diagnostic partnership, ideally the CDx is marketed together and cross-labeled with its therapeutic to indicate paired use. Here, we expand on the subthemes related to co-development from 61 articles, namely issues with mandated co-development by regulators (32 articles); labeling issues (19 articles); lack of clarity on regulatory pathways (15 articles); the co-dependence of the therapeutic and the diagnostic threatens the success of both (8 articles); and the lack of appropriate business models for co-development (4 articles).

Regulatory preference to facilitate the pairing of a therapeutic and its CDx means that both should navigate the clinical trial and regulatory process at the same time. This will establish evidence that their use together is safe and effective. In a 2014 Guidance, the FDA indicated that co-development was preferred for CDx, including pharmacogenetic tests,¹⁰⁴ thereby making co-development all but mandated except for rare cases.¹⁰⁵ The regulatory preference for co-development, as well as ongoing uncertainty about how to achieve this, is a significant barrier in PM development. Relatively few concurrently developed therapeutics and CDx exist to date.¹⁰⁶

According to the FDA, a CDx should be identified and developed in parallel with a therapy. This is very difficult for developers, especially those in the private sector, to achieve, as R&D timelines for therapeutics and diagnostics do not support concurrent development.¹⁰⁷ Since biomarkers that form the basis of most in vitro assays and tests are normally identified retrospectively and late in the therapy's validation process,¹⁰⁸ developers that identify useful CDx for a therapy after phase II clinical trials face regulatory challenges that increase time and cost of development.¹⁰⁹ Additionally, achieving cooperation between different developers whose business interests may not be aligned is complicated and requires an unusual degree of transparency. Unlike large pharma-

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/InVitroDiagnosticDeviceLabelingRequirements/> (accessed July 16, 2014).

- ¹⁰⁴ Pharmacogenetics is the study of interindividual variations in whole-genome or candidate gene single-nucleotide polymorphism maps, haplotype markers, and alterations in gene expression or inactivation that might be correlated with pharmacological function and therapeutic response. A pharmacogenetic test is, therefore, a genetic test that predicts pharmacological function or therapeutic response in a patient, Lesko & Woodcock, *supra* note 51, at 763.
- ¹⁰⁵ U.S. Food & Drug Administration, *In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff* (Aug. 6, 2014), <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262327.pdf>.
- ¹⁰⁶ Amit Agarwal et al., *The Current and Future State of Companion Diagnostics*, 8 PHARMACOGENOMICS & PERS. MED. 99, 100 (2015).
- ¹⁰⁷ Blankstein, *supra* note 70, at 283; Abdel-Baset Halim, *The Biggest Challenges Currently Facing Companion Diagnostic Advancement*, 14 EXPERT REV. MOL. DIAGN. 27, 33 (2014); Horgan et al., *supra* note 99, at 289; Koelsch et al., *supra* note 47, at 92.
- ¹⁰⁸ Avery, *supra* note 7, at 56; Carden et al., *supra* note 92, at 90; Joshua P. Cohen, *Overcoming Regulatory and Economic Challenges Facing Pharmacogenomics*, 29 NEW BIOTECHNOL. 751, 753 (2012); de Bono & Ashworth, *supra* note 73, at 546; Patricia A. Deverka, *Economic Opportunities and Challenges for Pharmacogenomics*, 50 ANN. REV. PHARMACOL. & TOXICOL. 423, 427 (2010); Elizabeth Drucker & Kurt Krapfenbauer, *Pitfalls and Limitations in Translation from Biomarker Discovery to Clinical Utility in Predictive and Personalised Medicine*, 4 EMPA J. 7, 10 (2013); Eichler et al., *supra* note 80 at 502; Faulkner et al., *supra* note 92, at 1167; Joly et al., *supra* note 58, at 17.
- ¹⁰⁹ Mittra & Tait, *supra* note 22, at 714.

ceutical developers, diagnostic developers are commonly small biotechnology companies that tend to have leaner business models and marketing budgets.¹¹⁰ These differences make full cooperation difficult.

Co-development may threaten the success of each company's product. Where the diagnostic is tied to the use of a particular drug, the success or failure of that drug in clinical trials determines the success or failure of the diagnostic.¹¹¹ In situations in which the diagnostic might have multiple uses, co-development with a single drug may mean that the diagnostic will not clear regulatory hurdles for other uses. The converse occurs when rejection of the diagnostic leads to the rejection of the drug, which might otherwise be effective.¹¹² Co-development can also delay the introduction of the drug or diagnostic while the other remains in the approval process. This can have profound economic consequences for both companies.¹¹³ Furthermore, pairing the use of a drug with a diagnostic may reduce market size for drug development companies.¹¹⁴ Finally, it is less complicated for a company to develop a stand-alone diagnostic.¹¹⁵ Thus, a myriad of disincentives contribute to the lack of co-developed drugs and diagnostics.

In the USA, diagnostics and therapeutics have traditionally gone through different regulatory streams with different evidentiary standards. Moreover, regulatory streams at the FDA were designed well before the advent of PM. Two separate and distinct regulatory streams, therefore, exist for therapeutics and medical devices, respectively. Through the FDA, the Center for Drug Evaluation and Research¹¹⁶ and the Center for Biologics Evaluation and Research¹¹⁷ evaluate drugs, biologics, and combination products,¹¹⁸ whereas the Center for Devices and Radiological Health oversees medical de-

¹¹⁰ Koelsch et al., *supra* note 47, at 94.

¹¹¹ Joly et al., *supra* note 58, at 17; Jan Trost Jørgensen, *Companion Diagnostics and the Drug-Diagnostic Codevelopment Model*, 73 *DRUG DEV. RES.* 390 (2012); Jørgensen, *supra* note 80, at 65; Christine Leopold et al., *Personalised Medicine as a Challenge for Public Pricing and Reimbursement Authorities – A Survey Among 27 European Countries on the Example of Trastuzumab*, 113 *HEALTH POL'Y* 313, 314 (2013); Meadows et al., *supra* note 78, at 10; Tracy Merlin et al., *Assessing Personalized Medicines in Australia: A National Framework for Reviewing Codependent Technologies*, 33 *MED. DEC. MAKING* 333, 340 (2013); Krishna Prasad & Alasdair Breckenridge, *Pharmacogenomics: A New Clinical or Regulatory Paradigm? European Experiences of Pharmacogenomics in Drug Regulation and Regulatory Initiatives*, 16 *DRUG DISCOV. TODAY* 867, 870–71 (2011); Richard Simon, *Clinical Trial Designs for Evaluating the Medical Utility of Prognostic and Predictive Biomarkers in Oncology*, 7 *PERS. MED.* 33, 47 (2010).

¹¹² Jørgensen, *supra* note 80, at 65; Jørgensen, *supra* note 111, at 392.

¹¹³ Milne & Zuckerman, *supra* note 53, at 542; Adrian M. Senderowicz & Otmar Pfaff, *Similarities and Differences in the Oncology Drug Approval Process between FDA and European Union with Emphasis on In Vitro Companion Diagnostics*, 20 *CLIN. CANCER RES.* 1445, 1448 (2014).

¹¹⁴ Blankstein, *supra* note 70, at 283; *Special Report: Companion Diagnostics—Example of BRAF Gene Mutation Testing to Select Patients with Melanoma for Treatment with BRAF Kinase Inhibitors*, 26 *TECH. EVAL. CENTER ASSESS. PROGRAM EXEC. SUMM.* 1, 12 (2011).

¹¹⁵ Milne & Zuckerman, *supra* note 53, at 542; Mitra & Tait, *supra* note 22, at 716.

¹¹⁶ U.S. Food & Drug Administration, *About the Center for Drug Evaluation and Research* <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/> (accessed Dec. 9, 2014).

¹¹⁷ U.S. Food & Drug Administration, *About the Center for Biologics Evaluation and Research*, <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/> (accessed Dec. 9, 2014).

¹¹⁸ U.S. Food & Drug Administration, *Transfer of Therapeutic Products to the Center for Drug Evaluation and Research (CDER)*, <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133463.htm> (accessed Apr. 15, 2015).

vices.¹¹⁹ (see Figure 2). This separation creates uncertainty about how best to satisfy regulatory requirements for co-development, what data should be submitted and how best to time the submission of relevant regulatory requirements.¹²⁰ The existence of multiple paths for regulatory approval makes it confusing to determine which regulators approve CDx,¹²¹ especially if the test may have multiple intended uses.¹²² However, the appeal of having a paired therapeutic and diagnostic has led some companies engaged in the development of PM to attempt co-development, despite the myriad of difficulties they face.¹²³

Recommendations to Overcome Barriers for Co-development

Recommendations to overcome the barriers to co-development of therapeutics and diagnostics focus on implementing regulatory reforms that incentivize the co-development process, something the FDA attempted in its 2014 guidance.¹²⁴ In general, stakeholders seek the alignment of regulations between therapeutics and diagnostics,¹²⁵ greater regulatory clarity,¹²⁶ and recognition of the complications of the co-development process.¹²⁷ The creation of a single regulatory stream would ease the burden on companies seeking regulatory approvals in the PM space.¹²⁸ While co-development is strongly encouraged by the FDA, greater guidance on how to proceed

¹¹⁹ U.S. Food & Drug Administration, *Overview of Device Regulation*, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/> (accessed Aug. 14, 2015).

¹²⁰ Blankstein, *supra* note 70, at 283.

¹²¹ Eric Bender, *Catch-22 for Cancer Tests*, 3 *CANCER DISCOV.* 1090, 1090 (2013); *Id.*; F. Ciardiello et al., *Delivering Precision Medicine in Oncology Today and in Future—The Promise and Challenges of Personalised Cancer Medicine: A Position Paper by the European Society For Medical Oncology (ESMO)*, 25 *ANN. ONCOL.* 1673, 1676 (2014); Hudson & Orviska, *supra* note 45, at 844; Joly et al., *supra* note 58, at 20; Y.W. Francis Lam, *Scientific Challenges and Implementation Barriers to Translation of Pharmacogenomics in Clinical Practice*, 2013 *ISRN PHARMACOL.* 1, 7 (2013); Meric-Bernstam & Mills, *supra* note 100, at 547; Milne & Zuckerman, *supra* note 53 at 544; David R. Parkinson et al., *Making Personalized Cancer Medicine a Reality: Challenges and Opportunities in the Development of Biomarkers and Companion Diagnostics*, 18 *CLIN. CANCER RES.* 619, 620 (2012); Pignatti et al., *supra* note 61, at 1466; Elizabeth A. Punnoose & Mark R. Lackner, *Challenges and Opportunities in the Use of CTCs for Companion Diagnostic Development*, 195 *RECENT RESULTS CANCER RES.* 241, 248 (2012); Donald R.J. Singer & John Watkins, *Using Companion and Coupled Diagnostics Within Strategy to Personalize Targeted Medicines*, 9 *PERS. MED.* 751, 753 (2012); Janette Thomas et al., *Companion Diagnostics: Emerging Strategies and Issues in Pharmaceutical Development*, 12 *EXPERT REV. MOL. DIAGN.* 561, 561 (2014); Mark R. Trusheim et al., *Uncertain Prognosis for High-Quality Diagnostics: Clinical Challenges, Economic Barriers and Needed Reforms*, 14 *PHARMACOGENOMICS* 325, 327 (2013).

¹²² Pignatti et al., *supra* note 61, at 1466.

¹²³ For example: Talazoparib (BioMarin) and myChoice HRD (Myriad Genetics); PRAME ASCI (astuprotimut-r) (GlaxoSmithKline), and a qPCR-based diagnostic assay (Abbott Molecular); PC-MAB (Athera Biotechnologies/Boehringer Ingelheim) and CVDefine Kit (Electra-Box Diagnostica).

¹²⁴ *In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff*, *supra* note 105.

¹²⁵ Koelsch et al., *supra* note 47, at 96; Eunice Y. Lee & Hsin-Chieh Jennifer Shen, *Regulatory Considerations for Companion Diagnostic Devices*, 9 *BIOMARK. MED.* 67, 69 (2015); Yann Joly et al., *Diagnostic Testing for Vaccinomics: Is the Regulatory Approval Framework Adequate? A Comparison of Canada, the United States, and Europe*, 15 *OMIC5* 597, 604 (2011); Mittra & Tait, *supra* note 22, at 711; Adrian Thomas et al., *Comparative Effectiveness, Personalized Medicine and Innovation: The Path Forward*, 28 *PHARMACO-ECONOMICS* 923, 925 (2010).

¹²⁶ Blankstein, *supra* note 70, at 310; Cohen, *supra* note 108, at 755; Singer & Watkins, *supra* note 121, at 755.

¹²⁷ Avery, *supra* note 7, at 57; Cohen, *supra* note 108, at 753; Fridlyand et al., *supra* note 69, at 631; Mittra & Tait, *supra* note 22, at 716.

¹²⁸ Joly et al., *supra* note 125, at 604.

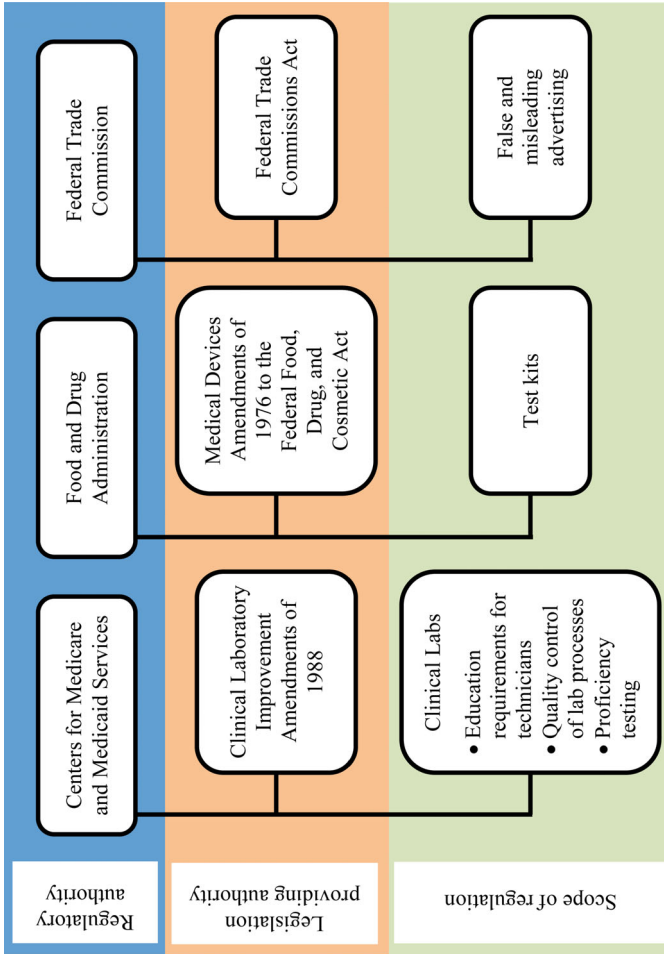


Figure 2. National Human Genome Research Institute (NHGR) Regulation of Genetic Tests. Adapted from <http://www.genome.gov/10002335> accessed July, 23, 2015.

with non-parallel development would aid the sizable majority of companies for which co-development is not possible.¹²⁹

Recommendations also focus on improving clarity on cross-labeling requirements.¹³⁰ Commentators note the lack of clear and common standards indicating what evidence is required to label drugs for a particular subgroup or for a particular genetic mutation.¹³¹ Greater clarity in labeling requirements would enhance patient care and the uptake of CDx (for example, pharmacogenetic tests).¹³² Clarity is needed on when cross-labeling is required and when it is simply recommended for informational purposes.¹³³ Greater flexibility in labeling or in making labeling changes could create a more responsive system in which additional tests or diagnostics could be added to labels as improvements and innovations in diagnostics appear.¹³⁴ Successful pairing of therapeutics and diagnostics could be enhanced through PMR to provide evidentiary support for labeling claims and by greater specificity in labeling requirements.¹³⁵ For example, labels could provide consumers and prescribers with further information and assessment on predictive claims,¹³⁶ the requirement for testing prior to taking a prescription,¹³⁷ and information on the actions required depending on the results of the CDx test.¹³⁸

Challenge: Regulation of Genetic Testing

As a subset of in vitro diagnostic tests, genetic tests may determine therapeutic choices or other personalized interventions.¹³⁹ Genetic tests fall into two categories: LDTs and genetic test kits. LDTs are the most common and are generally developed in a single laboratory to which patient samples must be sent for analysis.¹⁴⁰ LDTs can be thought of as ‘in-house’ genetic tests. Genetic test kits, on the other hand, comprise a set of reagents and analytical information sold together to multiple testing laboratories.¹⁴¹ Some genetic tests are marketed directly to consumers; such DTC genetic tests have been the subject of considerable controversy.¹⁴² In the following sections, we expand on the sub-

¹²⁹ Avery, *supra* note 7, at 57; Cohen, *supra* note 108, at 753.

¹³⁰ Blankstein, *supra* note 70, at 282; Rianne M.F. van Schie et al., *Implementation of Pharmacogenetics in Clinical Practice Is Challenging*, 12 PHARMACOGENOMICS 1231, 1232 (2011).

¹³¹ Blankstein, *supra* note 70, at 282; Prasad & Brekenridge, *supra* note 111, at 871; Samuya Pant et al., *Navigating the Rapids: The Development of Regulated Next-Generation Sequencing-Based Clinical Trial Assays and Companion Diagnostics*, 4 FRONT. ONCOL. 1, 13 (2014); Apostolia M. Tsimberidou et al., *Strategies to Overcome Clinical, Regulatory, and Financial Challenges in the Implementation of Personalized Medicine*, 2013 AM. SOC’Y CLIN. ONCOL. 118, 124 (2013); Charlie Schmidt, *Challenges Ahead for Companion Diagnostics*, 104 J. NAT’L CANCER INST. 14, 14 (2012).

¹³² Kathy L. Hudson, *Genomics, Health Care, and Society*, 365 NEW ENG. J. MED. 1033, 1036 (2011).

¹³³ Blankstein, *supra* note 70, at 310; Pant et al., *supra* note 131, at 13.

¹³⁴ Blankstein, *supra* note 70, at 307; Mansfield, *supra* note 59, at 1455.

¹³⁵ Mansfield, *supra* note 59, at 1455.

¹³⁶ *Id.*

¹³⁷ Singer & Watkins, *supra* note 121, at 751.

¹³⁸ *Id.*

¹³⁹ U.S. Food & Drug Administration, *Paving the Way for Personalized Medicine: FDA’s Role in a New Era of Medical Product Development* (Oct. 2013), <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf>.

¹⁴⁰ *Id.*

¹⁴¹ *Id.*

¹⁴² Palmer, *supra* note 23, at 476; Piehl, *supra* note 42, at 63-64; Serra J. Schlanger, *Putting Together the Pieces: Recent Proposals to Fill in the Genetic Testing Regulatory Puzzle*, 21 ANN. HEALTH L. 384, 388 (2012); Spector-

themes relevant to PM in 39 articles on genetic testing, namely: lack of regulations on LDTs (17 articles); lack of guidance on LDTs in the approvals process (9 articles); inadequate regulation of DTC genetic tests (6 articles); an underappreciation for the potential harms DTC genetic tests pose (6 articles); the problem of misleading advertising associated with DTC genetic tests (5 articles); the unsuitability of current regulations for DTC genetic tests (4 articles) and LDTs (2 articles); perceived difficulties with regulating LDTs (3 articles); a lack of clarity on how to regulate DTC genetic tests (3 articles); and the lack of clinical utility measures that hinder the uptake of LDTs (2 articles).

Three measures determine the validity and utility of genetic tests. Analytic validity determines whether and how well the test measures or determines the presence of the biomarker.¹⁴³ Clinical validity determines whether there is a correlation between the targeted clinical condition and the biomarker.¹⁴⁴ The third and more difficult measurement to determine is clinical utility. It asks: Does the test lead to increased human health, or a beneficial medical outcome?¹⁴⁵ Quality tests should therefore be analytically and clinically valid, as well as clinically useful.

These three measurements are applied differently and unequally to LDTs and to genetic test kits, due in part to the different regulatory regimes that govern the different types of tests.¹⁴⁶ This creates significant regulatory challenges.¹⁴⁷ In the USA, regulatory oversight of genetic testing is split between three federal government agencies: the FDA, the CMS, and the Federal Trade Commission (FTC), which is the federal consumer protection agency. Each of these agencies has a different mandate and applies different standards. This has led to numerous complaints of a lack of adequate, rigorous, and consistent regulation.¹⁴⁸ Despite the novel issues that genetic tests raise, no new regulatory system has been created for their approval. The existing regulatory structure creates false separations based on where and how genetic tests are used, rather than focusing on their validity and utility regardless of how they are applied.

Bagdady & Pike, *supra* note 23, at 691; Trevor Woodage, *Gatekeepers and Goalposts: The Need for a New Regulatory Paradigm for Whole Genome Sequence Results*, 11 NW. J. TECH & INTELL. PROP. 1, 3 (2012).

¹⁴³ National Human Genome Research Institute, *Regulation of Genetic Tests*, <http://www.genome.gov/10002335> (accessed June 21, 2016).

¹⁴⁴ *Id.*

¹⁴⁵ *Id.*

¹⁴⁶ *Id.*

¹⁴⁷ Blankstein, *supra* note 70, at 284; Joly et al., *supra* note 58, at 13-14; Meadows et al., *supra* note 78, at 9; McCarthy et al., *supra* note 46, at 199; O'Kane, *supra* note 80, at 746; Parkinson et al., *supra* note 121, at 621; Prebula, *supra* note 23, at 370; Charles Schmidt, *Larger Companies Dominate Cancer Companion Diagnostic Approvals*, 29 NAT. BIOTECHNOL. 955, 956 (2011); *Special Report: Companion Diagnostics—Example of BRAF Gene Mutation Testing to Select Patients with Melanoma for Treatment with BRAF Kinase Inhibitors*, 26 TECH EVAL. CENTER ASSESS. PROGRAM EXEC. SUMM. 1, 8 (2011).

¹⁴⁸ Joly et al., *supra* note 58, at 19; Jaimee Lee, *Missing the Target? Personalized Medicine Advances, but Questions Remain on Outcomes, Cost*, 43 MOD. HEALTHCARE 38, 40 (2013); Meadows et al., *supra* note 78, at 19; Conti et al., *supra* note 45, at 330; Faulkner et al., *supra* note 92, at 1164; Nelson, *supra* note 45, at 855; Pant et al., *supra* note 131, at 16; Piehl, *supra* note 42, at 71-73; Ramsey et al., *supra* note 45, at 2263; Charles L. Sawyers & Laura J. van 't Veer, *Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care: A Policy Statement from the American Association for Cancer Research*, 20 CLIN. CANCER RES. 4978, 4979 (2014); Schlanger, *supra* note 142, at 386-388; Schmidt, *supra* note 131, at 15; Yoshiaki Tazawa, *Perspective for the Development of Companion Diagnostics and Regulatory Landscape to Encourage Personalized Medicine in Japan*, 23 BREAST CANCER 19, 23 (2016); Winther & Jørgensen, *supra* note 62, at 373; Wistuba et al., *supra* note 55, at 140; Woodage, *supra* note 142, at 4-5.

The FDA has the authority to regulate genetic test kits as medical devices based on safety and efficacy under the Food, Drug and Cosmetic Act.¹⁴⁹ The regulations in that act create a stratified or tiered system of approval requirements based on the level of risk posed by the device to the patient or the user based on intended use and the indications for use. Class I devices are low risk and generally exempt from the requirement for a 510(k) premarket notification (a process establishing that the device is substantially equivalent to a device already marketed). As such, class I devices generally require only broad controls such as registration, labeling, and good manufacturing practices. Class II devices are classified as moderate risk and generally require a 510(k) premarket notification prior to marketing. Devices considered class III (highest risk classification) require a premarket approval (PMA) for clearance by the FDA to market the device. The PMA process is more complicated and requires the submission of clinical evidence to support the claims being made about the device.¹⁵⁰

With respect to genetic tests, FDA regulations require evidence that genetic test kits are analytically and clinically valid, although evidence of their clinical utility is not required.¹⁵¹ This is a point of concern, given that ensuring genetic testing leads to positive health outcomes (clinical utility) is critical for both patient welfare and reimbursement decisions. Until recently, the FDA has exercised its regulatory authority sparingly and only as it applies to genetic test kits—choosing to leave LDTs regulated only by the less stringent Clinical Laboratories Improvement Amendments (CLIA) regulations.¹⁵² The imposition of different standards on genetic test kits and LDTs is the most pressing issue for those who want to have equal, reliable testing for all genetic tests. Ongoing criticism of the differences between FDA and CLIA regulation has led to significant policy action at the federal level.

The CMS oversees clinical laboratories and regulates LDTs under the authority of CLIA.¹⁵³ The CMS ensures that LDTs are analytically valid but does not require evidence that LDTs meet the standards of either clinical validity or utility.¹⁵⁴ CLIA regulations categorize laboratory tests as either ‘waived’ or ‘non-waived’ according to whether they are low, moderate, or high complexity tests. Tests that are either moderate or high complexity are subject to additional requirements to ensure their safety. Higher complexity tests are generally grouped into specialty areas that are subject to more rigorous external proficiency testing to verify their ongoing analytic validity. While molecular and genetic tests are considered high complexity, they have not been designated as a subspecialty and, therefore, are not subjected to the most stringent testing available under CLIA.¹⁵⁵

In addition, significant concern exists about a lack of rigorous and consistent regulation of DTC genetic testing, which enables consumers or patients to access their ge-

¹⁴⁹ 21 U.S.C. § 301–92 (1976).

¹⁵⁰ *Overview of Device Regulation*, *supra* note 119.

¹⁵¹ U.S. Food & Drug Administration, *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* (Oct. 3, 2014), <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm416685.pdf>.

¹⁵² *Regulation of Genetic Tests*, *supra* note 143.

¹⁵³ Clinical Laboratory Improvement Amendments of 1988, Pub. L. No. 100-578, 102 Stat. 2903 (1988).

¹⁵⁴ *Regulation of Genetic Tests*, *supra* note 143.

¹⁵⁵ Bin Chen et al., *Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions*, 58 MMWR RECOMM. & REP. 1, 2 (2009).

netic information directly from a testing company.¹⁵⁶ For many years the FDA did not exercise its jurisdiction over DTC genetic tests, creating yet another group of genetic tests without rigorous regulatory oversight. This situation is changing as the technology advances and as the FDA asserts its authority over genetic testing. Whether the FDA regulatory approach is appropriate for DTC testing is an open question. Proponents claim that many of the risks associated with DTC genetic testing are speculative and that it has intangible benefits, including patient autonomy and privacy.¹⁵⁷ DTC genetic tests continue to create controversy, however, because they are advertised directly to consumers and the advertising may be fraudulent and/or may misrepresent the benefits for the consumer.¹⁵⁸ Misleading claims are under the regulatory purview of the FTC, which protects consumers from unfair and deceptive business practices and from false and misleading advertising claims.¹⁵⁹ Concerns about the claims made by DTC genetic testing providers have prompted calls for the FTC to exercise its authority to protect consumers, some of whom may make medical decisions to either forgo treatment, based on a false-negative test results, or undertake drastic medical procedures, such as prophylactic surgery, based on false-positive test results.¹⁶⁰ The FTC has largely ignored evaluating the truth of health marketing claims made by DTC genetic testing companies, which leaves the field open to fraudulent claims.¹⁶¹

Current perceptions persist that advertising of DTC genetic tests is false and/or misleading to such an extent as to undermine consumer and provider confidence in the veracity and utility of all genetic tests.¹⁶² The perception that the FTC is not taking action against DTC companies challenges the uptake of legitimate genetic tests.¹⁶³ Exacerbating this situation, there is a plethora of reasons for an individual to purchase a DTC test outside of health, including recreational, educational, and ancestry. This can be exploited by DTC companies in marketing and promotional materials.

¹⁵⁶ Stephanie Bair, *Direct-to-Consumer Credit Genetic Testing: Learning from the Past and Looking Toward the Future*, 67 FOOD & DRUG L.J. 413, 413 (2012); Michelle D. Irick, *Age of an Information Revolution: The Direct-to-Consumer Genetic Testing Industry and the Need for a Holistic Regulatory Approach*, 49 SAN DIEGO L. REV. 279, 284 (2012); McCarthy et al., *supra* note 46, at 199; Piehl, *supra* note 42, at 64; van El & Cornel, *supra* note 80, at 378; Vijverberg et al., *supra* note 80, at 251.

¹⁵⁷ Palmer, *supra* note 23, at 476; Kathryn Schleckser, *Physician Participation in Direct-to-Consumer Genetic Testing: Pragmatism or Paternalism*, 26 HARV. J.L. & TECH. 695, 719–20 (2013); Woodage, *supra* note 142, at 9.

¹⁵⁸ Palmer, *supra* note 23, at 489; Piehl, *supra* note 42, at 77; Schlanger, *supra* note 142, at 388; Spector-Bagdady & Pike, *supra* note 23, at 695; Woodage, *supra* note 142, at 6; UNITED STATES GOVERNMENT ACCOUNTABILITY OFFICE, NUTRIGENETIC TESTING TESTS PURCHASED FROM FOUR WEB SITES MISLEAD CONSUMERS (July 27, 2006), <http://www.gao.gov/assets/120/114612.pdf>.

¹⁵⁹ Federal Trade Commission, *Direct-to-Consumer Genetic Tests* (Jan. 2014), <http://www.consumer.ftc.gov/articles/0166-direct-consumer-genetic-tests>; 15 U.S.C. § 45a.

¹⁶⁰ Palmer, *supra* note 23, at 490; Piehl, *supra* note 42, at 84–85; Schleckser et al., *supra* note 157, at 720–22; Spector-Bagdady & Pike, *supra* note 23, at 705; Woodage, *supra* note 142, at 5.

¹⁶¹ In 2013, the FTC took its first actions to protect consumers of genetic tests. The FTC filed charges against two companies in January (Genelink, Inc. and its former subsidiary foru International Corporation) and against a third company in June (L'Oreal USA, Inc.) for 'purported personalized genomics products'. The charges were related to the marketing of nutrigenetic and dermagenetic products. The matters against the first two companies were resolved by settlement approved on May 12, 2014. The FTC announced a proposed settlement of the charges against L'Oreal on June 30, 2014.

¹⁶² Palmer, *supra* note 23, at 489; Piehl, *supra* note 42, at 77; Schlanger, *supra* note 142, at 388; Spector-Bagdady & Pike, *supra* note 23, at 691; Woodage, *supra* note 142, at 6.

¹⁶³ Irick, *supra* note 156, at 286; Schleckser et al., *supra* note 157, at 705–6; Palmer, *supra* note 23, at 476.

Recommendations for Regulation of Genetic Testing

Regulatory recommendations for improving genetic testing in PM include greater involvement of healthcare professionals,¹⁶⁴ greater regulation of both DTC¹⁶⁵ tests and LDT¹⁶⁶ at the federal level to ensure quality, and the creation of a comprehensive genetic test registry.¹⁶⁷

LDT Recommendations

The most common recommendations concerning LDT testing are to increase regulatory oversight¹⁶⁸ and evidentiary standards.¹⁶⁹ Recommendations include expanding FDA oversight to cover LDTs¹⁷⁰ (likely to occur in 2016); expanding evidentiary standards to include evidence of clinical validity and utility;¹⁷¹ and ensuring that LDT laboratories undergo proficiency testing, certification, or increased accreditation requirements.

Some critics who have complained that CLIA regulations are inadequate to ensure the quality of genetic tests advocate for the creation of a genetic subspecialty. This would involve an external review and a more rigorous examination of tests resulting in higher quality review.¹⁷² Furthermore, commentators over the last 15 years have criticized the FDA's unwillingness to hold DTC genetic tests¹⁷³ and LDTs¹⁷⁴ to the same standards it uses for test kits. After numerous studies and reports calling for increased

¹⁶⁴ Helen C. Dick, *Risk and Responsibility: State Regulation and Enforcement of the Direct-to-Consumer Genetic Testing Industry*, 6 ST. LOUIS U. J. HEALTH L. POL'Y 167, 177 (2012); Piehl, *supra* note 42, at 86; Spector-Bagdady & Pike, *supra* note 23, at 718.

¹⁶⁵ Bair, *supra* note 156, at 431–32; Dick, *supra* note 164, at 194; Irick, *supra* note 156, at 298; Palmer, *supra* note 23, at 523; Piehl, *supra* note 42, at 93; Schleckser et al., *supra* note 157, at 713; Spector-Bagdady & Pike, *supra* note 23, at 715; Woodage, *supra* note 142, at 5.

¹⁶⁶ Euan A. Ashley et al., *Genetics and Cardiovascular Disease: A Policy Statement from the American Heart Association*, 126 CIRCULATION 142, 145 (2012); Bair, *supra* note 156, at 413–14; Pascale Bourret et al., *Regulating Diagnosis in Post-Genomic Medicine: Re-Aligning Clinical Judgment?*, 73 SOC. SCI. & MED. 816, 822 (1982); Evans & Watson, *supra* note 23, at 669; Joseph D. Khoury & Daniel V. T. Catenacci, *Next-Generation Companion Diagnostics: Promises, Challenges, and Solutions*, 139 ARCH. PATHOL. & LAB. MED. 11, 12 (2015); Pant et al., *supra* note 131, at 15; Schlanger, *supra* note 142, at 398; Spector-Bagdady & Pike, *supra* note 23, at 703; Mark E. Robson et al., *American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility*, 28 J. CLIN. ONCOL. 893, 898 (2010); Mark A. Rothstein, *Currents in Contemporary Bioethics: The Case Against Precipitous, Population-Wide, Whole-Genome Sequencing*, 40 J. L. MED. & ETHICS 682, 684 (2012).

¹⁶⁷ Dick, *supra* note 164, at 198; Piehl, *supra* note 42, at 91; Spector-Bagdady & Pike, *supra* note 23, at 694.

¹⁶⁸ Bair, *supra* note 156, at 416; Lawrence J. Lesko & Issam Zineh, *DNA, Drugs and Chariots: On a Decade of Pharmacogenomics at the US FDA*, 11 PHARMACOGENOMICS 507, 510 (2010); Schlanger, *supra* note 142, at 398; Spector-Bagdady & Pike, *supra* note 23, at 703.

¹⁶⁹ Bair, *supra* note 156, at 429–30.

¹⁷⁰ Lesko & Zineh, *supra* note 168, at 510; Schlanger, *supra* note 142, at 398–99.

¹⁷¹ Bair, *supra* note 156, at 428; Spector-Bagdady & Pike, *supra* note 23, at 703.

¹⁷² Piehl, *supra* note 42, at 93; Schlanger, *supra* note 142, at 399; Spector-Bagdady & Pike, *supra* note 23, at 743; Woodage, *supra* note 142, at 7.

¹⁷³ Bair, *supra* note 156, at 427; Irick, *supra* note 156, at 286; McCarthy et al., *supra* note 46, at 199; Piehl, *supra* note 42, at 63; van El & Cornel, *supra* note 80, at 378; Vijverberg et al., *supra* note 80, at 251.

¹⁷⁴ Conti et al., *supra* note 45, at 330; Faulkner et al., *supra* note 92, at 1164; Joly et al., *supra* note 58, at 14; Lee, *supra* note 148, at 38; Meadows et al., *supra* note 78, at 9; Nelson, *supra* note 45, at 855; Pant et al., *supra* note 131, at 16; Piehl, *supra* note 42, at 72; Ramsey et al., *supra* note 45, at 2263; Sawyers & van't Veer, *supra* note 148, at 4979; Schlanger, *supra* note 142, at 387–389; Schmidt, *supra* note 131, at 15; Tazawa, *supra* note 148, at 24; Winther & Jørgensen, *supra* note 62, at 373; Wistuba et al., *supra* note 55, at 140; Woodage, *supra* note 142, at 19.

oversight action,¹⁷⁵ the FDA issued draft guidance on October 3, 2014, thus asserting its statutory authority and signaling its intention to exercise regulatory oversight over LDT. The draft guidance outlines the phasing in of a plan that extends the stratified risk-based framework applied to medical devices for premarket notifications and approvals to all genetic tests, regardless of where they are developed. Tests for rare diseases that meet the definition of a Humanitarian Use Device would be subject to discretionary authority regarding the need for PMA.¹⁷⁶ The new guidance requires notification to the FDA of LDTs as a no-fee alternative to registration and listing of LDTs. It further requires SAE reporting and a demonstration of clinical validity of LDTs.¹⁷⁷

The guidance has not been met with universal approval. Some articles express concern that increasing FDA oversight of LDTs will increase cost and delay for manufacturers. Others are concerned with the chilling effect on swift and ongoing improvement and innovation due to oversight bureaucracy, and some assert that the FDA lacks statutory authority to expand its oversight to LDT.¹⁷⁸ Statutory oversight aside, concerns about the FDA's workload and its ability to oversee the large number of LDTs will need to be weighed against the greater evidence of validity and utility derived from FDA oversight. Following a series of FDA workshops, several hearings before the House Energy and Commerce Committee Subcommittee on Health, and a lengthy public comment period, the FDA has indicated it will issue its final guidance in 2016.¹⁷⁹

On November 18, 2016, the FDA announced that it would not issue a final guidance for the oversight of LDTs.¹⁸⁰ This leaves the current uneven patchwork of oversight on DTC, LDT, and genetic test kits in place, and the concomitant problems discussed above. In January 2017, the FDA released a discussion paper laying out issues that could guide a legislative solution and signaling that the issue has not yet been put to rest.¹⁸¹ In particular, the FDA points to the need for 'well-curated databases' of scientific evidence on clinical validity and other measurements that could be used to establish the accuracy and validity of LDTs.¹⁸²

While backing away from guidance on LDTs, in July 2016, the FDA issued draft guidances on next generation sequencing (NGS) genetic tests as part of the PMI¹⁸³.

¹⁷⁵ National Institute of Health, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services* (Apr. 2008), http://osp.od.nih.gov/sites/default/files/SACGHS_oversight_report.pdf.

¹⁷⁶ 21 C.F.R. § 814.102a(5).

¹⁷⁷ *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*, *supra* note 151.

¹⁷⁸ Alan Mertz, *Re: Framework for Regulatory Oversight of Laboratory Developed Tests; Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories*, ACLA (Feb. 2, 2015), <http://www.acla.com/wp-content/uploads/2015/02/ACLA-Comments-to-FDA-on-LDT-Draft-Guidance-2015.02.021.pdf>.

¹⁷⁹ Jamie K. Wolszon & Jeffrey N. Gibbs, *FDA Plans to Issue Final LDT Framework in 2016; Subcommittee Members, CMS and FDA Officials Critique Proposed Legislative Approach that Would Give CMS LDT Premarket Review Authority*, FDA LAW BLOG (Dec. 20, 2015), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2015/12/fda-plans-to-issue-final-ldt-framework-in-2016-subcommittee-members-cms-and-fda-officials-critique-p.html.

¹⁸⁰ FDA, *DISCUSSION PAPER ON LABORATORY DEVELOPED TESTS (LDTs)* (2017), <https://www.fda.gov/downloads/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/laboratorydevelopedtests/ucm536965.pdf>.

¹⁸¹ *Id.*

¹⁸² *Id.*

¹⁸³ FDA, *DRAFT GUIDANCE: USE OF STANDARDS IN FDA REGULATORY OVERSIGHT OF NEXT GENERATION SEQUENCING (NGS)-BASED IN VITRO DIAGNOSTICS (IVD) USED FOR DIAGNOSING GERMLINE DISEASES* (2016),

While these guidances signal the FDA's intention to regulate IVD based on NGS as part of the PMI, the FDA has taken an approach aimed at facilitating the use of these tests and easing the scientific regulatory requirements.¹⁸⁴ The first guidance called for more public databases of genetic variants and their use in establishing clinical validity of NGS tests.¹⁸⁵ The second guidance discussed the need for standards in the designing, developing, and validating of NGS-based tests for germline diseases as part of the PMI.¹⁸⁶

In addition to greater quality assurances of LDTs, a number of authors advocate for the creation of a mandatory genetic test data registry.¹⁸⁷ Currently, there is a voluntary test registry hosted by the National Institutes of Health's (NIH) National Center for Biotechnology Information.¹⁸⁸ Despite recommendations by the Secretary's Advisory Committee on Genetics, Health, and Society to make registration mandatory for all genetic tests, it does not include all genetic tests. Additionally, the test registry may be more useful to consumers if standardized fields, such as the molecular basis of the tests and the methods used for testing, are included in the registry and uniformly entered to be easily searchable.¹⁸⁹

DTC Recommendations

Although there are a number of US states that currently either prohibit DTC testing or mandate professional involvement in ordering or interpreting genetic test results, many states do not regulate provision of DTC tests.¹⁹⁰ Recommendations include federal regulation of DTC tests through mandatory inclusion of professionals, including genetic counselors, in either the test ordering or the provision of test results.¹⁹¹ DTC companies should be responsible for providing greater quality assurances and more accurate information about their tests.¹⁹² Failing these changes, the numerous calls for increased comprehensive federal regulation by the FDA using its stratified risk-based approach¹⁹³ and FTC¹⁹⁴ oversight of DTC testing are likely to continue. In November 2013, the FDA signaled a new readiness to flex its authority over DTC tests in a way it had not done previously. It barred 23andMe, a DTC genetic testing company, from

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/fGuidanceDocuments/UCMS09838.pdf> (Accessed Feb. 5, 2017); FDA, DRAFT GUIDANCE: USE OF PUBLIC HUMAN GENETIC VARIANT DATABASES TO SUPPORT CLINICAL VALIDITY FOR NEXT GENERATION SEQUENCING (NGS)-BASED IN VITRO DIAGNOSTICS (2016), <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCMS09837.pdf>.

¹⁸⁴ *Id.*

¹⁸⁵ DRAFT GUIDANCE: USE OF STANDARDS IN FDA REGULATORY OVERSIGHT OF NEXT GENERATION SEQUENCING (NGS)-BASED IN VITRO DIAGNOSTICS (IVD) USED FOR DIAGNOSING GERMLINE DISEASES, *supra* note 183.

¹⁸⁶ DRAFT GUIDANCE: USE OF PUBLIC HUMAN GENETIC VARIANT DATABASES TO SUPPORT CLINICAL VALIDITY FOR NEXT GENERATION SEQUENCING (NGS)-BASED IN VITRO DIAGNOSTICS, *supra* note 183.

¹⁸⁷ Dick, *supra* note 164, at 198; Schlanger, *supra* note 142, at 396; Spector-Bagdady & Pike, *supra* note 23, at 694.

¹⁸⁸ GTR: GENETIC TEST REGISTRY, NCBI, <http://www.ncbi.nlm.nih.gov/gtr/> (accessed July 20, 2016).

¹⁸⁹ Schlanger, *supra* note 142, at 402.

¹⁹⁰ See, Dick, *supra* note 164.

¹⁹¹ *Id.* at 177; Piehl, *supra* note 42, at 83; Spector-Bagdady & Pike, *supra* note 23, at 718.

¹⁹² Piehl, *supra* note 42, at 81.

¹⁹³ Dick, *supra* note 164, at 194; Irick, *supra* note 156, at 298; Spector-Bagdady & Pike, *supra* note 23, at 743; Woodage, *supra* note 142, at 5.

¹⁹⁴ Dick, *supra* note 164, at 198; Schleckser et al., *supra* note 157, at 709.

using its broad-based genetic screen without regulatory approval.¹⁹⁵ In October 2015, 23andMe became the first DTC company to be granted FDA approval for its DTC test kits, a fact it heralded on its website.¹⁹⁶ Continuing the trend to greater scrutiny of DTC tests by the FDA, in November 2015 the FDA sent letters to three DTC genetic testing companies, DNA4Life, DNA-CardioCheck, and Interleukin Genetics, for marketing unapproved genetic tests.¹⁹⁷ However, on April 6, 2017, the FDA softened its initial decision, permitting 23andme to offer DTC genetic testing for 10 diseases or conditions, including Parkinson's disease, late-onset Alzheimer's disease, Celiac disease, and several hereditary conditions.¹⁹⁸ While paving the way for future genetic predisposition tests from 23andme and similar DTC companies, the FDA clarified its expectations with regard to the accuracy, reliability, and clinical relevance of such tests through special controls.¹⁹⁹ Further, the FDA has created a regulatory pathway for DTC genetic predisposition tests that will expedite approvals from premarket review after an initial de novo application.²⁰⁰ Despite relaxing its stance on some genetic tests, DTC diagnostic tests for conditions such as BRCA, for example, are not included in the authorization granted to 23andme.²⁰¹

In addition to FDA regulation of DTC testing, expansion of other federal protections such as privacy protections under The Genetic Information Non-Discrimination Act (GINA),²⁰² or the FDA Sentinel (postmarketing surveillance)²⁰³ program,²⁰⁴ could further bring DTC testing into the regulatory fold. Calls for additional oversight

¹⁹⁵ Alberto Gutierrez, *Warning Letter*, FDA, <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm> (accessed Sept. 24, 2015). On Feb. 19, 2015, the FDA announced that it had granted 23andMe permission to market its test for Bloom Syndrome (an autosomal recessive disease that can be passed on by asymptomatic carriers), but not the broader genetic screen, Robert Hof, *In Big Shift, FDA Plans To Let 23andMe Market Genetic Tests To Consumers*, FORBES (Feb. 19, 2015), <http://www.forbes.com/sites/roberthof/2015/02/19/in-big-shift-fda-plans-to-let-23andme-market-genetic-tests-to-consumers/>.

¹⁹⁶ 23ANDME, <http://mediacenter.23andme.com/en-ca/> (accessed Aug. 2, 2016).

¹⁹⁷ James L. Woods, Document Number GEN1500296, FDA (Nov. 2, 2015), <http://www.fda.gov/downloads/MedicalDevices/ResourcesforYou/Industry/UCM471784.pdf>; James L. Woods, Document Number GEN 1500806, FDA (Nov. 4, 2015), <http://www.fda.gov/downloads/MedicalDevices/ResourcesforYou/Industry/UCM471788.pdf>; James L. Woods, Document Number GEN1500800, FDA (Nov. 2, 2015), <http://www.fda.gov/downloads/MedicalDevices/ResourcesforYou/Industry/UCM471785.pdf>; Michael Mezher, *FDA Warns Three Companies Over DTC Genetic Tests*, RAPS (Nov. 9, 2015), <http://www.raps.org/Regulatory-Focus/News/2015/11/09/23563/FDA-Warns-Three-Companies-Over-DTC-Genetic-Tests/>.

¹⁹⁸ U.S. Food & Drug Administration, *FDA Allows Marketing of First Direct-to-Consumer Tests That Provide Genetic Risk Information for Certain Conditions* (Apr. 6, 2017) <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm551185.htm>.

¹⁹⁹ *Id.*

²⁰⁰ *Id.*

²⁰¹ *Id.*

²⁰² Irick, *supra* note 156, at 292.

²⁰³ Palmer, *supra* note 23, at 523.

²⁰⁴ In the fall of 2007, Congress passed the FDA Amendments Act, mandating FDA to establish an active surveillance system for monitoring drugs by using electronic data from healthcare information holders. The FDA's response to the mandate is the Sentinel Initiative. Its goal is to build and implement a new active surveillance system that will eventually be used to monitor all FDA-regulated products. The FDA has used administrative and insurance claims databases to investigate safety questions about agency-regulated products, but generally it has only worked with one particular healthcare system at a time to evaluate a given safety issue. Its current goal is to create a linked, sustainable system, which the FDA calls the Sentinel System, that will draw on existing automated healthcare data from multiple sources to actively monitor the safety of medical prod-

of DTC communications and advertising by the FTC are joined by calls to ‘regulate’ misleading or harmful claims on DTC tests by using a Tort law standard or reasonableness in negligence law,²⁰⁵ and by requiring DTC testing information and risk predictions to be harmonized with industry standards.²⁰⁶ The creation of uniform standards for risk predictions and other DTC communications could bring DTC genetic tests in line with other medical device regulation and hold riskier tests to a higher standard of examination.²⁰⁷

Finally, concerns about lax federal regulation and misleading advertising of DTC genetic testing has led several states to mandate that genetic test results be returned to a physician or learned intermediary with the skill to meaningfully interpret test results. The hope is that such meaningfully interpretation of genetic test results will lead to better healthcare decision making.²⁰⁸ While physicians have a duty, in many cases a legal duty, to impart incidental findings from genetic tests to a patient, the regulations are unclear regarding the duties of generators, providers, and interpreters of genetic test results.²⁰⁹ This confusion with respect to communication leads to quality control issues and inconsistent standards.

Challenge: Uncertain Regulations on Evidentiary Standards

In the following sections, we expand on the subthemes relevant to PM in 55 articles that discuss issues with evidence standards, namely existing standards that are unreasonable (11 articles) or unclear (11 articles) in a PM context; the failure of evidence produced by companies to meet regulatory requirements (12 articles), including the inability of many companies to carry out phase IV trials (8 articles); the increased cost associated with meeting regulatory data standards (7 articles); the inadequacy of data to expand applications to broader indications (4 articles); the delay that meeting evidentiary standards can cause (4 articles); and the unclear standards for clinical utility (2 articles).

PM developers find the data and evidentiary requirements for regulatory approval unclear.²¹⁰ Vague evidentiary standards and requirements act as a barrier to the trans-

acts continuously and in real-time. After a successful pilot program, Mini-Sentinel, the FDA activated the Sentinel System in February 2016; U.S. Food & Drug Administration, *FDA’s Sentinel Initiative – Background*, <http://www.fda.gov/Safety/FDASentinelInitiative/ucm149340.htm> (accessed June 27, 2016).

²⁰⁵ Piehl, *supra* note 42, at 90.

²⁰⁶ *Id.* at 81.

²⁰⁷ *Id.* at 93.

²⁰⁸ Judy G. Russell, *NY and MD Limits on 23andMe*, LEGAL GENEOL. (Dec. 23, 2012), <http://www.legalgenealogist.com/2012/12/23/ny-and-md-limits-on-23andme/#fn-4644-6>; Karen L. Nickel, *Notice to Cease and Desist Performing Genetic Testing Without Licensure or Physician Order*, STATE OF CALIFORNIA DEPARTMENT OF PUBLIC HEALTH (June 9, 2008), <http://www.wired.com/images/blogs/wiredscience/files/madrigal.PDF>. California Business and Professions Code Section 1288 provides that “[a]ny person conducting or operating a clinical laboratory may accept assignments for tests only from and make reports only to persons licensed under the provisions of law relating to the healing arts or their representatives’ CAL. BUS. & PROF. CODE § 1288 (2012); Dick, *supra* note 164, at 177.

²⁰⁹ Palmer, *supra* note 23, at 483; Rothstein, *supra* note 166, at 684; Rebecca Suarez, *Breaching Doctor-Patient Confidentiality: Confusion Among Physicians About Involuntary Disclosure of Genetic Information*, 21 S. CAL. INTERDISC. L.J. 491, 519 (2012); Susan M. Wolf, *The Role of Law in the Debate over Return of Research Results and Incidental Findings: The Challenge of Developing Law for Translational Science*, 13 MINN. J.L. SCI. & TECH. 435, 444 (2012).

²¹⁰ Blankstein, *supra* note 70, at 308; Bloss et al., *supra* note 92, at 159; Cohen, *supra* note 108, at 631; Lam, *supra* note 121, at 11; Pant et al., *supra* note 131, at 13; Schilsky et al., *supra* note 45, at 485; Thomas et al., *supra*

lation of PM products as companies struggle to develop appropriate evidence for approval and reimbursement.²¹¹ Whereas the FDA requires evidence of safety and efficacy, it does not require measures of clinical utility—that is, evidence that overall health outcomes are improved in a clinical setting. Payers, making choices about which therapies to cover, require this additional layer of evidence as a basis of payment decisions. In other words, what matters to a payer is whether a therapy is ultimately proven to be clinically useful and that it is a cost-effective alternative to existing therapies. These considerations are currently outside the evidence required for regulatory approval.

Lack of uniformity and clarity in data requirements between statutes, regulators, and payers poses challenges for developers. Not only is there lingering uncertainty about what data are required, but also when that data should be incorporated into the FDA investigational new drug application (IND) process.²¹² This is especially evident when data about a potential effect in a subpopulation or a relevant biomarker for that population emerge during a clinical trial. Further, it is not clear how the FDA will use the data that are submitted, and whether the data will be sufficient to validate a biomarker, or to permit the subpopulation effects to be generalized to the wider population. Manufacturers are concerned that evidence of subpopulation effects may be used to limit the application of a drug or device, rather than expand its application.

In addition to these concerns, the FDA can require companies to conduct PMR, otherwise known as phase IV studies, to collect evidence on how the therapeutic or device is working in clinical practice, and what SAE might have been reported with its use.²¹³ PMR are undertakings by companies to continue to collect evidence following regulatory approval; however, research shows that there is very low compliance with these commitments.²¹⁴ Such low compliance masks previously unknown SAE, but also does not reveal new uses for a drug or how the drug functions in different patient subgroups.²¹⁵ While regulators are reluctant to extrapolate from subpopulation data to other populations, groups, and ethnicities,²¹⁶ the expense involved in providing evidence on additional populations (and potentially undertaking an additional clinical

note 125, at 929; Debu Tripathy, *FDA and Avastin: Crossroads in an Era of Targeted Therapies*, 24 *ONCOLOGY* 989, 990 (2010); Tsimberidou et al., *supra* note 131, at 124; Vogenberg et al., *supra* note 75, at 630.

²¹¹ Varun Ahuja & Sharad Sharma, *Drug Safety Testing Paradigm, Current Progress and Future Challenges: An Overview*, 34 *J. APPL. TOXICOL.* 576, 586 (2014); Awada & Zgheib, *supra* note 78, at 845; George P. Brownman, *Special Series on Comparative Effectiveness Research Challenges to Real-World Solutions to Quality Improvement in Personalized Medicine*, 30 *J. CLIN. ONCOL.* 4188, 4188 (2012); Wylie Burke et al., *Essential Elements of Personalized Medicine*, 32 *UROL. ONCOL.* 193, 198 (2014); Carden et al., *supra* note 92, at 90; Jørgensen, *supra* note 80, at 63; Kenneth D. Levy et al., *Prerequisites to Implementing a Pharmacogenomics Program in a Large Health-Care System*, 96 *CLIN. PHARMACOL. & THER.* 307, 307 (2014); Haridarshan N. Patel et al., *Stakeholder Views on Pharmacogenomic Testing*, 34 *PHARMACOTHERAPY* 151, 163 (2014); Prasad & Brekenridge, *supra* note 111, at 869; Uehara et al., *supra* note 75, at 226.

²¹² Lam, *supra* note 121, at 11.

²¹³ *Glossary Definition: Phase*, *supra* note 43.

²¹⁴ Blankstein, *supra* note 70, at 284; Gibson & Lemmens, *supra* note 47, at 214; Laakmann, *supra* note 42, at 335; Malinowski et al., *supra* note 100, at 194; Milne & Zuckerman, *supra* note 53, at 542; W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy & Pharmaceutical Manufacturing*, 55 *B.C.L. REV.* 491, 517 (2014); Sharma & Schilsky, *supra* note 74, at 211; Verweij et al., *supra* note 73, at 201.

²¹⁵ Laakmann, *supra* note 42, at 337-38; Malinowski et al., *supra* note 100, at 194.

²¹⁶ Otsubo et al., *supra* note 58, at 198; Piana et al., *supra* note 68, at 706; Meenu Wadhwa et al., *WHO/KFDA Joint Workshop on Implementing WHO Guidelines on Evaluating Similar Biotherapeutic Products, Seoul, Republic of Korea 24–26 August, 2010*, 39 *BIOLOGICALS* 349, 353 (2011); Warner et al., *supra* note 23, at 533.

trial on the subgroup) may be prohibitive to developing PM products.²¹⁷ In the case of pharmacogenetic tests, developers remain uncertain whether they will be required to undertake phase IV studies, and whether that evidence might lead to restrictions on approvals in genetic subpopulations.²¹⁸

There are a number of reasons that companies do not fulfill their PMC and do not provide ongoing data to the regulators. First, PMR are expensive and time consuming.²¹⁹ Second, they are notoriously difficult to conduct, requiring data gathering of physician and patient reporting of SAE, which are widely underreported.²²⁰ Such detailed assessments of clinical efficacy are very difficult to provide.

Recommendations to Improve Evidentiary Requirements

Recommendations for bringing better quality evidence to regulators generally fall on the manufacturers. There is a call for submissions to regulators to provide higher quality evidence that is not only useful to payers and providers, but also that anticipates the need to show cost-effectiveness for reimbursement.²²¹ Additional recommendations for regulators include the use of less restrictive, more flexible, and innovative approaches to PM clinical trials and approvals.²²² This might be achieved by allowing alternative forms of evidence,²²³ initially using exploratory or modeling analysis combined with corroborative evidence,²²⁴ or permitting the use of comparison or equivalency data which relies on prior, similar submissions²²⁵ (as in follow on biologics). In particular, clear technical guidance on generation and submission of genomic data, clinical evidence standards, and the use of biomarkers in both drug development and pharmacogenetic studies is needed as an incentive to stimulate manufacturers to design their studies to capture these data.²²⁶ Pathways to make the generation of these

²¹⁷ Blankstein, *supra* note 70, at 284; Leopold et al., *supra* note 111, at 314; Milne & Zuckerman, *supra* note 53, at 543; O’Kane, *supra* note 80, at 747; Otsubo et al., *supra* note 58, at 195; Anup Patel, *Tissue Banking for Research—Bench to Bedside and Back—Myth, Reality or Fast Fading Reality at the Dawn of a Personalised Healthcare Era*, 12 CELL & TISSUE BANK. 19, 20 (2011); Trusheim et al., *supra* note 47, at 827.

²¹⁸ Blankstein, *supra* note 70, at 283.

²¹⁹ Laakmann, *supra* note 42, at 336.

²²⁰ Gibson & Lemmens, *supra* note 47, at 214; *Id.* at 337-8; Milne & Zuckerman, *supra* note 53, at 542; Sharma & Schilsky, *supra* note 74, at 211; Verweij et al., *supra* note 73, at 201.

²²¹ Meadows et al., *supra* note 78, at 11; Lisa M. Meckley & Peter J. Neumann, *Personalized Medicine: Factors Influencing Reimbursement*, 94 HEALTH POL’Y 91, 96 (2010); Merlin et al., *supra* note 111, at 339; Pirmohamed, *supra* note 23, at 864; Thomas et al., *supra* note 121, at 561.

²²² Pacanowski, *supra* note 58, at 294; Piana et al., *supra* note 68, 710; Pignatti et al., *supra* note 68, at 1037; Pirmohamed, *supra* note 23, at 864; Verweij et al., *supra* note 73, at 202.

²²³ Pacanowski, *supra* note 58, at 249.

²²⁴ Piana et al., *supra* note 68, at 710.

²²⁵ Chenggang Liang & Junzhi Wang, *China’s Perspective on Similar Biotherapeutic Products*, 39 BIOLOGICALS 312, 316 (2011); Meadows et al., *supra* note 78, at 12; Reza Mirnezami et al., *Preparing for Precision Medicine*, 366 NEW ENG. J. MED. 489, 490 (2012); Wistuba et al., *supra* note 55, at 140.

²²⁶ Blankstein, *supra* note 70, at 284; Adam Falconi et al., *Biomarkers and Receptor Targeted Therapies Reduce Clinical Trial Risk in Non-Small-Cell Lung Cancer*, 9 J. THORAC. ONCOL. 163, 168 (2014); Gibson & Lemmens, *supra* note 47, at 215; Joly et al., *supra* note 58, at 4; Myong-Jin Kim et al., *Pharmacogenomics: The Regulatory Environment and Labeling Implications*, in PHARMACOGENOMICS AND PERSONALIZED MEDICINE 55, 57 (Nadine Cohen ed., 2008); Mirnezami et al., *supra* note 225, at 490; Piana et al., *supra* note 68, at 709–10; Pignatti et al., *supra* note 68, at 1038 (2015); Tursz & Bernards, *supra* note 23, at 938; Zhiqun Zhang et al., *Systems Biology and Theranostic Approach to Drug Discovery and Development to Treat Traumatic Brain Injury*, 662 METHODS MOL. BIOL. 317, 325 (2010).

data less expensive and time consuming might include leveraging public–private partnerships and large cross-institutional studies involving non-industry actors as a means of validating biomarkers. Developing industry guidelines to create more accurate methods for predicting drug safety and pooling resources²²⁷ to address the costs associated with bringing PM products to market would help reduce the time and costs of evidence generation.

Non-compliance with PMR commitments has become such a problem that Congress mandated the FDA to work through the backlog of PMR commitments and provide annual reports on progress.²²⁸ To date, the backlog has been reduced, and the FDA is working to ensure greater compliance.²²⁹ In furtherance to fulfilling these obligations, the FDA has continued its commitment to the Sentinel program which tracks performance of medical products by accessing a number of data sources, including electronic health records (EHR), patient registries, and insurance datasets to better identify SAE and anticipates much better PMR of medical products.²³⁰

Challenge: Information Systems and Privacy

The literature on regulation of information systems reveals three main subthemes highlighting a tension between the interests of patients and developers of PM therapies and devices. In this section, we expand on privacy concerns (26 articles); sample storage and collection concerns (14 articles); and the heterogeneous nature of sample storage and collection regulations (9 articles). Issues of patient and research subject consent are mentioned in all three subthemes.

Human tissue samples, housed in hospital pathology laboratories and biobanks, support PM R&D. The samples are often used to determine genetic contributions to diseases when linked with phenotypic information and to test for biomarkers. The value of tissue samples is greatly enhanced when linked to medical health records or other data on disease histories and phenotypes. An ability to aggregate data across multiple national and international research facilities is crucial for scientific research, especially for rare disease phenotypes where information may be scarce. Consequently, pathological samples and EHR containing personal health information are simultaneously private patient information and valuable resources for drug companies and PM developers. Information systems that manage PM research data and samples are in tension, trying to balance the access and use requirements of researchers and developers with the autonomy and privacy interests of research participants.

²²⁷ McCarthy et al., *supra* note 46, at 197; Uehara et al., *supra* note 75, at 226.

²²⁸ U.S. Food & Drug Administration, *Postmarketing Requirements and Commitments: Reports*, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm064436.htm> (accessed Nov. 17, 2015).

²²⁹ FDA, REPORT TO THE SENATE COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS AND THE HOUSE COMMITTEE ON ENERGY AND COMMERCE (2014), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM472973.pdf>

²³⁰ Michael Mehzer, Woodcock: *Drug Safety Surveillance System Ready for Full Operation*, RAPS (Feb. 3, 2016), <http://raps.org/Regulatory-Focus/News/2016/02/03/24248/Woodcock-Drug-Safety-Surveillance-System-Ready-for-Full-Operation/>

Informed Consent and Privacy

Information and data management systems and the associated legal and ethical issues raised with respect to consent and privacy of personal or protected health information (PHI) are central to PM R&D. This is because much PM development involves use of biospecimens and knowledge of patient genetics or biomarkers. Since genetic information may reveal both personal and familial health or ancestry information, issues of consent and privacy are paramount in genetic studies and tests used in PM R&D. The legal requirement for researchers to obtain informed consent from research subjects is imbedded in US federal regulations that deal with human subjects research supported by the federal government.²³¹ The Common Rule governs human subjects research on products regulated by the FDA. These regulations also cover research on human tissues and associated information that can be linked to an identifiable individual.²³² In addition to the Common Rule, federal regulations governing the use of PHI were implemented in 2003 under the Health Insurance Portability and Accountability Act (HIPAA) of 1996.²³³ HIPAA applies to three categories of healthcare institutions, known as HIPAA covered entities: most healthcare providers, most health plans (insurers), and healthcare clearinghouses. HIPAA imposes limitations on the research uses and disclosures of identifiable patient information, requiring patient authorization for specific uses of certain PHI. HIPAA privacy rules do not apply to health information held by data brokers, websites, credit bureaus, disease registries, health researchers, disease advocacy organizations, law enforcement agencies, or others as defined under the act.²³⁴

The scope of informed consent as it relates to PM, in particular, is complex and important. Generally, consent to conduct research on a person or that person's tissues relates to a specific research activity that can be well described and for which consent can be meaningfully given or withheld based on knowledge of risks and alternatives. A problem for the PM research enterprise relates to whether a patient can give a non-specific consent to future research, without knowing what the nature and attendant risks of that research might be. Many argue that consent to research that is not yet defined cannot be informed and does not respect patient autonomy as required.²³⁵ While the acceptability of consent to future research is hotly debated, the ability to obtain consent to future undefined research is central to PM development. Much PM research comes from a retrospective analysis of clinical trials to determine what subpopulations might derive

²³¹ These are set out in Code of Federal Regulations at 45 C.F.R. § 46 (a) (2009) (known as the 'Common Rule'), and in 21 C.F.R. § 50, 56 (2015).

²³² According to HHS regulations at 45 C.F.R. § 46.101(b)(4) (2009), the study or collection of 'existing data' (including stored samples, records, pathological specimens, or diagnostic specimens) is deemed exempt from the requirements of the Common Rule, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, either directly or through identifiers linked to subjects, R. Hakimian et al., *50-State Survey of Laws Regulating the Collection, Storage, and Use of Human Tissue Specimens and Associated Data for Research*, NATIONAL CANCER INSTITUTE (2004), <http://m.acc.com/legalresources/resource.cfm?show=244011>

²³³ Health Insurance Portability and Accountability Act of 1996, Pub.L. No. 104–191, 110 Stat. 1936 (1996).

²³⁴ Robert Gellman & Pam Dixon, *The Precision Medicine Initiative and Privacy: Will Any Legal Protections Apply?*, WORLD PRIVACY FORUM (May 18, 2016), http://www.worldprivacyforum.org/wp-content/uploads/2016/05/WPF_PrecisionMedicineInitiative_May2016.fs.pdf

²³⁵ Timothy Caulfield, *Biobanks and Blanket Consent: The Proper Place of the Public Good and Public Perception Rationales*, 18 KING'S L.J. 209, 213 (2007).

a therapeutic effect. Consequently, the need to reexamine tissue samples for a different research outcome than originally described often arises. Re-consent of tissue donors for a different research objective may be neither feasible nor possible, and it is unclear whether it is required in all circumstances.

PM developers complain that the balance of regulations often emphasize individual autonomy and control over personal health information rather than the research enterprise and creation of a research platform of genetic information and resources, creating a barrier to PM development.²³⁶ Indeed, the regulations reflect a tension between balancing privacy and patient autonomy against a need for transparency, greater information gathering and sharing of research resources to advance PM.²³⁷

Complex layers of oversight from local institutional review boards (IRBs) to federal regulations protect individual autonomy and privacy, necessitating re-consent of research subjects, allowing subjects to withdraw from studies, and preferring anonymity and coded samples that make it more difficult to link PHI to tissue samples.²³⁸ Finding the right balance between researcher needs and subject protections is an ongoing regulatory exercise. In 2015, the Department of Health and Human Services proposed changes to the Common Rule²³⁹ that would require informed consent for research on biospecimens even if not linked to identifiable information. In addition, the changes would permit a broad consent to unspecified future research, heretofore not permitted. While the stated purpose for the changes includes increased simplicity and transparency for researchers, and additional protections for individual research subjects, the proposed rules are very controversial and some implicate individual privacy concerns. Some argue that they unduly favor researchers over patients, and ‘demand that patients accept a one-time grab at all data, for any purpose, in order to provide broad access to others with no promised informational or other return and no mechanism to reciprocate patients’ altruism.’²⁴⁰ On January 19, 2017, the final Common Rule was published²⁴¹. Changes that required consent for non-identifiable biospecimens were elim-

²³⁶ Bartha Maria Knoppers, *Lecture, Genomics: From Persons to Populations and Back Again*, 59 *GENOME* 537, 537 (2013); Michelle L. McGowan et al., *Integrating Genomics into Clinical Oncology: Ethical and Social Challenges from Proponents of Personalized Medicine*, 32 *UROL. ONCOL.* 187, 189 (2014); Charity Nofziger et al., *Comment, Policies to Aid the Adoption of Personalized Medicine*, 13 *NAT. REV. DRUG DISCOV.* 159, 160 (2014).

²³⁷ Gibson & Lemmens, *supra* note 47, at 216.

²³⁸ William K. Briggs, *Freeing Archival Research from the Accidental and Overbearing IRB Regulation that Costs Human Lives*, 14 *J. HEALTH TECH. L.* 237, 238–39 (2014); Geetter, *supra* note 45, at 49 (2011); Knoppers, *supra* note 236, at 537; Valerie Gutmann Koch, *PGTandME: Social Networking-Based Genetic Testing and the Evolving Research Model*, 22 *HEALTH MATRIX* 33, 63 (2012); McGowan et al., *supra* note 236, at 189; Meric-Bernstam & Mills, *supra* note 100, at 545; Nofziger et al., *supra* 236 210, at 160; Matthew J. Pielh, *The Brave New World of Genetic Biobanks: International Lessons for a Potential United States Biobank*, 46 *VAL. U. L. REV.* 69, 77 (2011); Pablo Villoslada & Sergio Baranzini, *Review, Data Integration and Systems Biology Approaches for Biomarker Discovery: Challenges and Opportunities for Multiple Sclerosis*, 248 *J. NEUROIMMUNOL.* 58, 59 (2012); Warner et al., *supra* note 23, at 533.

²³⁹ (NPRM) NOTICE OF PROPOSED RULEMAKING 2015 ffrSUMMARY, NATIONAL ARCHIVES AND RECORDS ADMINISTRATION (accessed Mar. 18, 2016), <https://www.gpo.gov/fdsys/pkg/FR-2015-09-08/pdf/2015-21756.pdf>

²⁴⁰ Patrick Taylor, *Henrietta Lacks and the Great Health Data Giveaway*, *HARV. L.: BILL HEALTH* (May 19, 2016), <http://blogs.harvard.edu/billofhealth/2016/05/19/henrietta-lacks-and-the-great-healthdata-giveaway/#more-18889> (accessed July 28, 2016).

²⁴¹ Federal Policy for the Protection of Human Subjects; Final Rule, 82 *Fed. Reg.* 12 (Jan. 19, 2017).

inated, but changes that provided the ability to use a broad consent for future research were retained²⁴².

A further regulatory barrier to PM is the heterogeneous and inconsistent regulations relating to human subjects research and biobanking, particularly the collection, sharing, and storage of data.²⁴³ There is a lack of harmonization both nationally and internationally between regulations covering the storage and use of biospecimens or use of PHI. PM developers and advocates argue that inconsistent regulations and conflicting standards create a climate of uncertainty that impedes the flow of both research materials and information between researchers and laboratories.²⁴⁴ Further barriers are created by inadequate and conflicting regulations to protect and use PHI, leading to improper use of that information and potential discrimination.²⁴⁵ Conflicting regulations exist not just between countries but within national systems.²⁴⁶ In the USA, federal regulations have differing definitions of and rules about what constitutes human subjects research, and whether and how informed consent for the use of tissue samples may be obtained. Adding to the complexity, both the federal Common Rule and HIPAA specifically leave room for individual states to create stricter standards on disclosure and use of biospecimens and PHI. State laws affecting the use of tissue and associated data in scientific research are found in a variety of sources, including medical records laws, privacy and health privacy laws, genetic testing/genetic information laws, and human subject protection laws. These laws are often different and inconsistent both among and within states. Regulations may impose different limits on uses of biospecimens and associated data and may offer different scopes of protection.²⁴⁷

The lack of regulatory clarity on how biospecimens and PHI can be shared and with whom has led to real concerns about individual privacy. This is particularly acute in genetic research since sensitive personal health information can now be revealed through genetic analysis of tissue samples using increasingly powerful sequencing tools that often reveal incidental health information. In the USA, despite the protections of the GINA, which forbids health insurers and employers from misuse of genetic information, patients continue to be fearful of discrimination after genetic testing. Where health

²⁴² *Id.*

²⁴³ Dalton et al., *supra* note 80, at 5992; Geetter, *supra* note 45, at 49; A. Harvey et al., *Scientific Committee for the ESF Forward Look on Personalised Medicine for the European Citizen, France*, 29 N. BIOTECHNOL. 625, 630–31; Koch, *supra* note 238, at 63; William McGeeveran et al., *Deidentification and Reidentification in Returning Individual Findings from Biobank and Secondary Research: Regulatory Challenges and Models for Management*, 13 MINN. J. L. SCI. & TECH. 485, 505–6 (2012); Sharon F. Terry, *The Tension Between Policy and Practice in Returning Research Results and Incidental Findings in Genomic Biobank Research*, 13 MINN. J. L. SCI. & TECH. 691, 699 (2012); Warner et al., *supra* note 23, 531; Wolf, *supra* note 205, at 442.

²⁴⁴ Mollie H. Ullman-Cullere & Jomol P. Mathew, *Emerging Landscape of Genomics in the Electronic Health Record for Personalized Medicine*, 32 HUM. MUTAT. 512, 514 (2011); Tsimberidou et al., *supra* note 131, at 122. See, Simon Oxenham, *Legal Confusion Threatens to Slow Data Science*, 536 NATURE 16, 16ffii 7 (2017).

²⁴⁵ Kate Crawford & Jason Schultz, *Big Data and Due Process: Toward a Framework to Redress Predictive Privacy Harms*, 55 B.C. L. REV. 93, 103 (2014); Geetter, *supra* note 45, at 43–4; Jonathan Kahn, *Privatizing Biomedical Citizenship: Risk, Duty, and Potential in Circle of Pharmaceutical Life*, 15 MINN. J. L. SCI. & TECH. 791, 814–5 (2014); McGeeveran et al., *supra* note 243, at 505–6; Palmer, *supra* note 23, at 492; Pielh, *supra* note 238, at 90; Rothstein, *supra* note 166, at 686–7.

²⁴⁶ Dalton et al., *supra* note 80, at 5992; Geetter, *supra* note 45, at 43ffii; Harvey et al., *supra* note 243, at 631; Koch, *supra* note 238, at 63; McGeeveran et al., *supra* note 243, at 505–6; Terry, *supra* note 243, at 699; Tsimberidou et al., *supra* note 131, at 122; Warner et al., *supra* note 23, at 533; Wolf, *supra* note 205, at 442.

²⁴⁷ Hakimian et al., *supra* note 232.

insurers control access to care and testing in the USA, concerns about improper use of genetic information have a chilling effect on research into genetics of diseases so critical to PM.²⁴⁸

Of continued concern is the lack of HIPAA protection for the medical and personal health information collected by the PMI. It is, as yet, unclear exactly how the biospecimens and associated data will be collected and stored, whether in a federal registry or in different states (each with different and sometimes conflicting regulations). Federal agencies including the NIH are not ‘covered entities’ under HIPAA and therefore the privacy rules do not apply, even if the PHI originated from a HIPAA covered entity. Once an HIPAA-covered entity shares PHI with a non-covered entity, the information generally passes outside the scope of the HIPAA privacy rule and beyond the jurisdiction of HIPAA oversight. The question of how the PHI of millions of volunteers will be adequately protected under the PMI is a pressing question.²⁴⁹

Recommendations on Management of Information

Recommendations to remove information management barriers include creating, improving, and harmonizing practices, guidelines, and policies for information sharing (4 articles). Most recommendations focus on improving biospecimen collection and storage (14 articles), and on creating stronger consent and privacy protections (7 articles). While some recommendations focus on systemic solutions, such as encrypting PHI between researchers and physicians (1 article), others focus on getting consent from patients to archive genetic data for future use (1 article), and moving toward the use of research advance directives (1 article). These recommendations support broader consents aimed at facilitating future research uses of biospecimens and PHI.

Collection procedures could be improved by ensuring samples are collected and sequenced in advance of clinical trial submissions. This should help with prospective biomarker identification, and ensure that enough genetic variants are represented and that samples from the intended patient population are available for submission in clinical trials. Strong protocols that include sample collection and storage procedures would also enable retrospective associations with safety and efficacy outcomes and retrospective identification of biomarkers.

In response to the PMI, the FDA created precisionFDA, an ‘online, cloud-based portal that will allow scientists from industry, academia, government and other partners to come together to foster innovation and develop the science behind a method of “reading” DNA known as next-generation sequencing’.²⁵⁰ Using NGS, precisionFDA aims to create a web platform to aid researchers in sharing and learning about individual genetic variations, with the hope that these actions will lead to PM knowledge and innovations. PrecisionFDA hopes to leverage tools for greater information sharing and to help with the validation of genetic sequences and ultimately biomarker identification. Tools include the creation of reference genomes that will be posted online.

²⁴⁸ Ashley et al., *supra* note 166, at 144; Conti et al., *supra* note 45, at 337; Kahn, *supra* note 245, at 813-4; Petersen et al., *supra* note 47, at 216; Thomas et al., *supra* note 125, at 926; Ullman-Cullere & Mathew, *supra* note 244, at 513; Vijverberg et al., *supra* note 80, at 247; Vogenberg et al., *supra* note 75, at 629.

²⁴⁹ Gellman & Dixon, *supra* note 234.

²⁵⁰ Taha A. Kass-Hout & Elaine Johanson, *FDA Launches precision FDA to Harness the Power of Scientific Collaboration*, FDA VOICE (Dec. 15, 2015) <http://blogs.fda.gov/fdavoices/index.php/2015/12/fda-launches-precisionfda-to-harness-the-power-of-scientific-collaboration/> (accessed July 28, 2016).

To address privacy concerns, authors recommend more transparent privacy laws with legal supports that protect individual interests in health information.²⁵¹ These might take the form of stronger federal regulations that cover more than just federally funded research (as in the Common Rule) and policies to handle genetic discrimination.²⁵² Recommendations to address the misuse of genetic information in contexts currently not covered by GINA, such as life, disability, and long-term care insurance or coverage of existing conditions with a genetic component, could strengthen PHI protections.²⁵³ Extending coverage to include full medical histories in the statutory definition of ‘genetic information’ and to misuse of that information to other contexts, like schools and biobanking, would provide patients with greater protections.²⁵⁴

In the context of the PMI, in November 2015 the White House published *Privacy and Trust Principles*, which recommended, inter alia, that ‘[m]ultiple tiers of data access—from open to controlled—based on data type, data use and user qualifications should be employed to ensure that a broad range of interested communities can utilize data while ensuring that privacy is safeguarded and public trust is maintained’.²⁵⁵ On May 25, 2016, the White House published its *PMI Data Security Policy Principles and Framework*.²⁵⁶ The recommendations require each organization involved in the PMI to create its own data security system, but call for ‘processes and controls to address both internal and external threats, and assure the confidentiality, integrity, and availability of data generated and contributed during precision medicine activities’.²⁵⁷ While requiring organizations embrace standard best practices, the *Data Security Policy Principles and Framework* does not create a harmonized system across the diverse set of organizations involved in the PMI. Instead, organizations must ensure that their security framework adequately addresses ‘the security risks they face and is consistent with the *PMI Data Security Policy Principles and Framework*’. The heterogeneous and myriad of organizations involved in the PMI are a particular challenge for data security in the PMI. With regard to a framework for data security, the report outlines a framework developed by the National Institute for Standards and Technology for *Improving Critical Infrastructure Cybersecurity, Version 1.0*, that enables five simultaneous and

²⁵¹ Ashley et al., *supra* note 166, at 144; Lynn G. Dressler, *Commentary, Integrating Personalized Genomic Medicine into Routine Clinical Care: Addressing the Social and Policy Issues of Pharmacogenomic Testing*, 74 N.C. MED. J. 509, 512 (2013); Andrew N. Freedman et al., *Cancer Pharmacogenomics and Pharmacoepidemiology: Setting a Research Agenda to Accelerate Translation*, 102 J. NAT’L CANCER INST. 1698, 1703 (2010); Jason H. Karnes et al., *Using Systems Approaches to Address Challenges for Clinical Implementation of Pharmacogenomics*, 6 WILEY INTERDISC. REV. SYS. BIOL. MED. 125, 126 (2014); Mirnezami et al., *supra* note 225, at 490.

²⁵² Amal Alzu’bi, et al., *Personal Genomic Information Management and Personalized Medicine Challenges, Current Solutions, and Roles of HIM Professionals*, 11 PERSP. HEALTH INFO. MGMT. 1, 9 (2014); van El & Cornel, *supra* note 80, at 380; Vogenberg et al., *supra* note 75, at 629; Warner et al., *supra* note 23, at 535.

²⁵³ Anya E.R. Prince, *Comprehensive Protection of Genetic Information: One Size Privacy or Property Models May Not Fit All*, 79 BROOK. L. REV 175, 193 (2013).

²⁵⁴ *Id.*

²⁵⁵ White House, *Precision Medicine Initiative: Privacy and Trust Principles* (Nov. 9, 2015), <https://www.whitehouse.gov/sites/default/files/microsites/finalpmiprivacyandtrustprinciples.pdf>

²⁵⁶ White House, *Precision Medicine Initiative: Data Security Policy Principles and Framework* (May 25, 2016), https://www.whitehouse.gov/sites/whitehouse.gov/files/documents/PMI_Security_Principles_Framework_v2.pdf (accessed July 28, 2016).

²⁵⁷ *Id.*

continuous functions—Identify, Protect, Detect, Respond and Recover—to assess cybersecurity and data security performance.²⁵⁸

In addition, articles recommend increasing federal funding of biobanks as a means to achieving higher standards and more harmonization of rules and practices relating to data management and security. With regard to the PMI, on May 26, 2016 the NIH awarded \$142 million over five years to the Mayo Clinic in Minnesota to establish the world's largest research-cohort biobank. The PMI cohort biobank will collect, store, and distribute biospecimens for research.²⁵⁹ Finally, numerous articles recommend greater adoption and use of EHR and of systems to facilitate protected transfer and storage of those EHR.²⁶⁰ Use of EHR is a cornerstone of the PMI as well.

Challenge: Incentives to Enter PM space and IP barriers

According to the literature, intellectual property rights, particularly patents, create barriers to PM innovation, investment, and development in two distinct ways. First, PM developers argue that the patent system does not provide certain, predictable, strong rights that protect the substantial investment in PM drug and device development.²⁶¹ PM developers call for stronger incentives where the market may not provide adequate financial reward. In contrast, patients, healthcare providers, and those unable to innovate due to blocking patents argue for a more open system, because existing patents on drugs and diagnostics stifle innovation, investment, and development of PM drugs and devices. These stakeholders argue that strong patent rights block further innovation,²⁶² create patent thickets,²⁶³ and function as barriers to provider and patient access to drugs

²⁵⁸ National Institute of Standards and Technology, *Framework for Improving Critical Infrastructure Cybersecurity* (June 9, 2016), <http://www.nist.gov/cyberframework/upload/cybersecurity-framework-021214.pdf>

²⁵⁹ National Institutes for Health, *NIH funds biobank to support Precision Medicine Initiative Cohort Program* (May 26, 2016) <https://www.nih.gov/news-events/news-releases/nih-funds-biobank-support-precision-medicine-initiative-cohort-program> (accessed July 28, 2016).

²⁶⁰ Eichler et al., *supra* note 80, at 504; Sean X. Hu et al., *Market Watch: Defining and Quantifying the Use of Personalized Medicines*, 12 NAT. REV. DRUG DISCOV. 896, 897 (2013); Frank Pasquale, *Grand Bargains for Big Data: The Emerging Law of Health Information*, 72 MD. L. REV. 382, 743 (2013).

²⁶¹ Roger D. Klein, *Opinion, Legal Developments and Practical Implications of Gene Patenting on Targeted Drug Discovery and Development*, 87 CLIN. PHARMACOL. & THER. 633, 633 (2010); Scott Parker & Ben Hall, *Review, Patenting Personalized Medicines in the UK, Europe and USA*, 3 PHARM. PAT. ANAL. 163, 164 (2014); Price II, *supra* note 214, at 523.

²⁶² Aura Bertoni, *Open Source Models in Biomedicine: Workable Complementary Flexibilities Within the Patent System*, 14 WAKE FOR. J. BUS. & INTEL. PROP. L. 126 (2013); Devlin, *supra* note 42, at 132; Kahn, *supra* note 245, at 877 (2014); Mini Kapoor, *Comment, Proposal for Resolution to Challenges Posed by DNA Sequence Patents on the Development of Multiplex Genetic Tests*, 49 HOUS. L. REV. 131, 133–4 (2012); Sapna Kumar, *Life, Liberty and the Pursuit of Genetic Information*, 65 ALA. L. REV. 625, 629 (2013); William Lesser, *Myriad & Prometheus, Laws & Products of Nature: Are the Courts Considering an Economic Non-Statutory Subject Matter Exclusion?*, 53 IDEA: INTEL. PROP. L. REV. 173, 218 (2013); Yahong Li, *Intellectual Property and Innovation: A Case Study of High-Tech Industries in China*, 13 OR. L. REV. 263, 275 (2011); Kali N. Murray & Esther van Zimmeren, *Dynamic Patent Governance in Europe and the United States: The Myriad Example*, 19 CARDOZO J INT'L & COMP. L. 287, 291 (2011); W. Nicholson Price II, *Unblocked Future: Why Gene Patents Won't Hinder Whole-Genome Sequencing and Personalized Medicine*, 33 CARDOZO L. REV. 1691, 1727 (2012); Robertson, *supra* note 42, at 388; Tiana Leia Russell, *Unlocking the Genome: The Legal Case Against Genetic Diagnostic Patents*, 16 MARQ. INTEL. PROP. L. REV. 81, 111 (2012); Spector-Bagdady & Pike, *supra* note 23, 723–4 (2014); Melissa F. Wasserman, *The PTO's Asymmetric Incentives: Pressure to Expand Substantive Patent Law*, 72 OHIO ST. L.J. 1, 11 (2011).

²⁶³ Murray & van Zimmeren, *supra* note 262, at 291.

and devices.²⁶⁴ Limited empirical evidence supports either side of the patent debate.²⁶⁵ Here, we expand on the subthemes related to intellectual property (32 articles) and a lack of incentives for developers (20 articles).

Numerous articles assert that the high cost of drug development generally coupled with smaller financial returns for niche or personalized therapies necessitates strong and certain incentives to develop PM products. PM developers, in particular, decry a lack of certainty in scope and strength of patent protection.²⁶⁶ Industry stakeholders assert that consistent moves to amend and reform patent law have led to unpredictability in patent application and protections,²⁶⁷ which in turn undermine investment and innovation in PM.²⁶⁸

However, not all commentators favor stronger patent rights for PM therapeutics. Several authors argue that patents hinder innovation in the PM space and can create barriers to patient access of drugs and genetic testing. Patent holders may block development of better tests, can prevent second opinion testing (especially through licensing practices, granting overly broad or exclusive license to underlying technology), may cover gene sequences such that development of genetic tests is hindered, and may create lack of innovation space through overly broad patent claims. In other words, broadly drafted or multiple overlapping patents can create an anticommon that stifles innovation because follow-on developers fear liability for patent infringement.²⁶⁹ What is clear from the literature is a lack of consensus on whether (i) patents act as necessary incentives to PM investment, innovation, and development such that they should be strengthened, or (ii) patents stifle innovation and investment, particularly in the device space, such that novel incentives are needed and patent rights should be curtailed. This tension runs through the literature and through the recommendations.

Some see the use of patents on subpopulations as a means of ‘evergreening’ or extending patent protection over a drug that has been repackaged as a PM for a smaller patient population. Even novel regulatory initiatives to entice innovation in the event of market failures may have an ‘evergreening’ effect such that they encourage unnecessary patient stratification (known as ‘salami-slicing’) in drug development without scientific justification²⁷⁰ and, thereby, stifle innovation in the PM space.

Unlike in pharmaceuticals, stronger and clearer patent law is not seen as the most significant incentive needed to support innovation and investment in PM tests and de-

²⁶⁴ Kapoor, *supra* note 262, at 133; Kumar, *supra* note 262, at 637; Robertson, *supra* note 42, at 386; Adriane Scola, *Uncommon Genes, Unpatentable Subject Matter*, 34 SEATTLE U. L. REV. 909, 919 (2011).

²⁶⁵ Christopher M. Holman, *Unpredictability in Patent Law and its Effect on Pharmaceutical Innovation*, 76 MO. L. REV. 645, 651 (2011); Julia Carbone et al., *Commentary, DNA patents and Diagnostics: Not a Pretty Picture*, 28 NAT. BIOTECHNOL. 784, 785 (2010).

²⁶⁶ Holman, *supra* note 265, at 645; Klein, *supra* note 261, at 635; Parker & Hall, *supra* note 261, at 168.

²⁶⁷ Holman, *supra* note 265, at 645.

²⁶⁸ Klein, *supra* note 261, at 633; Parker & Hall, *supra* note 261, at 164.

²⁶⁹ Bertoni, *supra* note 262, at 132; Devlin, *supra* note 42, at 70; Kahn, *supra* note 245, at 877; Kapoor, *supra* note 262, at 147; Kumar, *supra* note 262, at 629; Lesser, *supra* note 262, at 217-8; Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 699 (1998); Li, *supra* note 262, at 275; Murray & van Zimmeren, *supra* note 262, at 291; Price II, *supra* note 262, at 1727; Robertson, *supra* note 42, at 386; Russell, *supra* note 262, at 111; Spector-Bagdady & Pike, *supra* note 23, at 723; Wasserman, *supra* note 262, at 11.

²⁷⁰ Gibson & Lemmens, *supra* note 47, at 206; Milne & Zuckerman, *supra* note 53, at 543; Miossec et al., *supra* note 47, at 1717.

vices.²⁷¹ One of the greatest barriers to PM device development with respect to intellectual property is general uncertainty about the applicability, strength, scope, and enforceability of patents on medical devices due to shifting patent law. The validity of many diagnostic patents has recently been called into question; therefore, it is unclear whether novel genetic tests will encounter patent thickets or infringe existing gene patents.²⁷² Recent judicial rulings by the Supreme Court of the United States have created uncertainty as to the status of patents on both diagnostic and medical methods.²⁷³ Patents on gene-based molecular diagnostics may be problematic and fall afoul of recent rulings invalidating patent claims on naturally occurring molecules, including DNA sequences, and biomarker associations with drug dosing.²⁷⁴ Given the uncertainty in patent incentives, other forms of incentives may be needed to support the business model for device and diagnostic makers, which is leaner than that of pharmaceutical companies.²⁷⁵ Nevertheless, the current curtailing of the scope of PM-relevant patents serves as a natural experiment on the role of patent incentives in the diagnostics industry.

Recommendations on Incentive Systems and Patent Regulation

Where the market fails to provide adequate financial incentives for investment and development of PM drugs and devices, authors recommend stimulating entry into the PM device market via additional incentives. Articles recommend economic and regulatory incentives, ranging from using existing statutes and regulations in innovative ways²⁷⁶ to creating entirely new incentive structures.²⁷⁷

Incentivizing PM development using existing patent systems is a recommendation many favor.²⁷⁸ Increased market exclusivity or extended patent periods for drugs mar-

²⁷¹ Munir Pirmohamed & Dyfrig A. Hughes, *Comment, Pharmacogenetic Tests: The Need for a Level Playing Field*, 12 NAT. REV. DRUG DISCOV. 3, 4 (2013).

²⁷² Ashley et al., *supra* note 166, at 143; Wylie Burke, et al., *Commentary, Extending the Reach of Public Health Genomics: What Should be the Agenda for Public Health in an Era of Genome-Based and 'Personalized' Medicine?*, 12 GENET. MED. 785, 788 (2010); Ava Caffarini, *Directed to or Encompassing a Human Organism: How Section 33 of the America Invents Act May Threaten the Future of Biotechnology*, 12 J. MARSHALL REV. INTELL. PROP. L. 768, 784 (2013); Faulkner et al., *supra* note 92, at 1164; E. Richard Gold, Robert Cook-Deegan & Tania Bubela, *Editorial, AMP v. Myriad: A Surgical Strike on Blockbuster Business Models*, 5 SCI. TRANSL. MED. 192ed9, 2 (2013); Lesser, *supra* note 262, at 218; Price II, *supra* note 262, at 1727.

²⁷³ Caffarini, *supra* note 272, at 784; Lesser, *supra* note 262, at 175; Price II, *supra* note 262, at 1727. Note: in Canada, see *Novartis Pharmaceuticals Canada Inc. v. Cobalt Pharmaceuticals Co.*, 236 A.C.W.S. (3d) 1001, 2014 FCA 17 (Can.), and Europe, The European Patent Convention art. 54 (Oct. 5, 1973), [http://documents.epo.org/projects/babylon/eponet.nsf/0/00E0CD7FD461C0D5C1257C060050C376/\\$File/EPC.15th.edition.2013.pdf](http://documents.epo.org/projects/babylon/eponet.nsf/0/00E0CD7FD461C0D5C1257C060050C376/$File/EPC.15th.edition.2013.pdf), medical methods are non-patentable.

²⁷⁴ *Mayo Collaborative Servs. v. Prometheus Labs. Inc.*, 566 U.S. ___ (2012) (naturally occurring molecules); *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. ___ (2013) (methods for determining biomarker-drug dose associations).

²⁷⁵ Koelsch et al., *supra* note 47, at 97.

²⁷⁶ Gibson & Lemmens, *supra* note 47, at 206; Avery, *supra* note 7, at 63; Holman, *supra* note 26, at 693.

²⁷⁷ Michael Abramowicz, *Orphan Business Models: Towards a New Form of Intellectual Property*, 124 HARV. L. REV. 1362, 1387 (2011); David C. Babiian, *Adopting Pharmacogenomics and Parenting Repurposed Molecules Under the Orphan Drug Act: A Cost Dilemma*, 13 MARSHALL REV. INTELL. PROP. L. 668, 671 (2014); Price II, *supra* note 214, 496-7; Robertson, *supra* note 42, at 397.

²⁷⁸ Blankstein, *supra* note 70, at 283; Cynthia Hathaway, *A Patent Extension Proposal to End Underrepresentation of Women in Clinical Trials and Secure Meaningful Drug Guidance for Women*, 67 FOOD & DRUG L.J. 143, 172 (2012); Meadows et al., *supra* note 78, at 11; Mittra & Tait, *supra* note 22, at 717; Parker & Hall, *supra* note

keted with a CDx could incentivize PM co-development.²⁷⁹ Other authors advocate for additional market exclusivity for diagnostics and novel manufacturing innovations.

However, recommendations for using patent incentives reflect the tension between proprietary rights and freedom to operate and access. Recommendations therefore range from calls for stronger, clearer patent laws²⁸⁰ to calls for limits on patent protection.²⁸¹ Recommended mechanisms to enhance freedom to operate include the creation of gene-patent clearinghouses²⁸² and patent pools.²⁸³ For genetic testing in particular, advocates for accessibility recommend using compulsory licensing,²⁸⁴ requiring reasonable royalties,²⁸⁵ or instituting march-in rights to overcome patent barriers on genetic test development.²⁸⁶ Several authors recommend the creation of a research exemption in the Patent Act²⁸⁷ that would insulate physicians and researchers from patent infringement liability, which could stimulate R&D in academic centers.²⁸⁸ Other exemptions such as protections from patent infringement suits for all diagnostic use²⁸⁹ or genetic testing for patient care purposes²⁹⁰ would likewise ease fears of infringement liability. Recent developments in case law, specifically *Alice Corp v. CLS Bank* on the application of patent protections on abstract ideas,²⁹¹ continue to contribute to a lack of clarity about the applicability of patent protection for diagnostic tests. This continued uncertainty undermines patent protections as incentives on genetic diagnostics.

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- 261, at 164; Price II, *supra* note 262, at 698; Price II, *supra* note 214, at 527–8; Trusheim et al., *supra* note 121, at 328; van El & Cornel, *supra* note 80, at 380; Michael M. Ward, *Personalized Therapeutics: A Potential Threat to Health Equity*, 27 J. GEN. INTERN. MED. 868, 870 (2010).
- 279 Blankstein, *supra* note 70, at 283; Meadows et al., *supra* note 78, at 11; Mitra & Tait, *supra* note 22, at 717; Parker & Hall, *supra* note 261, at 164; Trusheim et al., *supra* note 121, at 328; van El & Cornel, *supra* note 80, at 380; Ward, *supra* note 278, at 870.
- 280 Trusheim et al., *supra* note 121, at 328.
- 281 Kumar, *supra* note 262, at 669–70; Li, *supra* note 262, at 227; Price II, *supra* note 262, at 1727; John L. Ryan, *Unlikely Splicing - the Myriad Decision, the Genomic Research and Accessibility Act, Orphan Diseases and the Future of Antisense Drugs*, 28 J. CONTEMP. HEALTH L. & POL'Y 144, 175 (2011).
- 282 A clearinghouse is 'any agency that brings together seekers and providers of goods, services or information, thus matching demand and supply', Lori Sheremeta & E. Richard Gold, *Creating a Patent Clearinghouse in Canada: A Solution to Problems of Equity and Access*, 11 HEALTH L. REV. 17, 18–9 (2003), <http://www.hli.ualberta.ca/HealthLawJournals/~media/hli/Publications/HLR/11-3-04sheremetpstrfrm.pdf>. A patent clearinghouse 'would administer the rights of several patent owners; authority would be granted by the patent owner to the collective to set license terms to others who would be permitted to work the patent', *Id.* at 17; Price II, *supra* note 262, at 1727.
- 283 A patent pool is 'the aggregation of IP rights that are the subject of cross licensing arrangements, whether transferred directly by the patentee to a licensee or through some medium, such as a joint venture set up specifically to administer the patent pool', Sheremeta & Gold, *supra* note 282, at 18, <http://www.hli.ualberta.ca/HealthLawJournals/~media/hli/Publications/HLR/11-3-04sheremetpstrfrm.pdf>.
- Kapoor, *supra* note 262, at 152.
- 284 Kumar, *supra* note 262, at 668.
- 285 Li, *supra* note 262, at 276; Simone A. Rose, *Semiconductor Chips, Genes and Stem Cells: New Wine for New Bottles?* 38 AM. J. L. & MED. 113, 152 (2012).
- 286 Ryan, *supra* note 281, at 175.
- 287 U.S. Patent Law, 35 U.S.C. §§ 1 et seq.
- 288 Kumar, *supra* note 262, at 637; Li, *supra* note 262, at 277; Price II, *supra* note 262, at 1727; Ryan, *supra* note 281, at 175.
- 289 Price II, *supra* note 262, at 1727.
- 290 Kumar, *supra* note 262, at 627.
- 291 *Alice Corp. Pty. Ltd. v. CLS Bank International*, 134 S. Ct. 2347 (2014).

Several authors point to incentives for the development of pharmaceuticals for rare diseases under the US Orphan Drug Act²⁹² (ODA)²⁹³ as a model. Incentives under the ODA have led to the development of drugs for smaller or less-lucrative markets; more than 400 drugs for rare diseases have been developed since 1983.²⁹⁴ Recommendations include repurposing the ODA for PM to incentivize market entry and provide market exclusivity while avoiding the uncertainties of the patent system.²⁹⁵ Others caution regulators to revisit provisions of the ODA to ensure that incentives are not misappropriated as science advances and disease categories shift.²⁹⁶ Additional recommendations include creating either an ODA-like regulatory pathway for PM-based drugs²⁹⁷ or a sui generis framework for PM products.²⁹⁸

Initiatives like the Humanitarian Device Exemption²⁹⁹ also provide a mechanism for device manufacturers to short-cut some evidentiary requirements normally associated with PMA from the FDA. However, some authors note that no period of market exclusivity is provided under the Exemption and suggest that market exclusivity is a necessary incentive for PM device development. Others recommend implementing incentive programs like the Priority Review Voucher Program,³⁰⁰ which provides incentives for R&D in drugs and biologics for rare pediatric diseases. The Voucher Program does not currently apply to medical devices.³⁰¹

However, the 21st Century Cures Act provides medical device manufacturers in the PM space with additional incentives in the form of a quicker pathway through FDA approvals. Building on the priority review device pathway, the FDA will have a fast track for breakthrough medical technologies aimed at patients with life-threatening or irreversibly debilitating diseases or conditions, and limited alternatives.³⁰² In addition, the Humanitarian Device Exemption has been expanded to include devices that treat conditions that affect up to 8000 people, up from the previous level of 4000 people.³⁰³

There was also support for more predictable funding for PM, for example, from a centralized fund or government funding of studies for smaller or underserved populations.³⁰⁴ President Obama's PMI is intended to create this kind of incentive. Other au-

²⁹² Orphan Drug Regulations, 21 C.F.R. § 316 (2013).

²⁹³ U.S. Food and Drug Administration, *Humanitarian Device Exemption*, <http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket submissions/humanitariandeviceexemption/default.htm> (accessed July 27, 2016).

²⁹⁴ U.S. Food and Drug Administration, *Developing Products for Rare Diseases & Conditions*, <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm> (accessed July 27, 2016).

²⁹⁵ Avery, *supra* note 7, at 63.

²⁹⁶ Gibson & Lemmens, *supra* note 47, at 207.

²⁹⁷ Babaian, *supra* note 277, at 671.

²⁹⁸ Rose, *supra* note 285, at 121.

²⁹⁹ *Developing Products for Rare Diseases & Conditions*, *supra* note 294.

³⁰⁰ U.S. Food and Drug Administration, *Rare Pediatric Disease Priority Review Voucher Program* (Section 529), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm375479.htm> (accessed July 27, 2016).

³⁰¹ Food and Drug 126 Stat. 1094 21 U.S.C. 360ff. <https://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf>

³⁰² H.R. 34, § 3051.

³⁰³ H.R. 34, § 3052.

³⁰⁴ Blankstein, *supra* note 70, at 296; Hathaway, *supra* note 278, at 173; Lam, *supra* note 121, at 11; Trusheim et al., *supra* note 121, at 329.

thors call on the FDA to create incentives for PM developers, including reduced FDA user fees for pharmaceutical companies that work with device manufacturers to incentivize co-development.³⁰⁵ Tax breaks and other incentives for investment in diagnostic companies to ‘rescue’ drugs that fail in phase II trials might stimulate creation of PGx data for smaller groups of patients³⁰⁶ and boost overall investment in PM. Finally, one author suggests forgoing incentive schemes in favor of increasing drug prices to reflect the costs involved in drug development and allowing the market to create incentives.³⁰⁷ Noting the current political climate in the USA regarding high drug prices³⁰⁸ and the need to keep drugs affordable in the CMS and in other national healthcare systems,³⁰⁹ this seems an unworkable policy recommendation.

Challenge: Reimbursement

Uncertain or inadequate reimbursement by public and private payers of diagnostics and therapeutics creates one of the greatest barriers to the development and adoption of PM.³¹⁰ PM developers and their investors already face a high chance of failure either in proof of concept or regulatory approval.³¹¹ However, following regulatory approval, additional uncertainty exists as to whether a PM product will be reimbursed. Lack of a positive reimbursement decision disincentivizes investment and creates barriers to use by prescribing and authorizing clinicians and patients.³¹² Clinicians may account for the financial state of a patient in recommending an expensive therapy, and, if no billing mechanism for a service (eg to order a specific PM diagnostic test) exists, clinicians have no financial incentive to perform that service.³¹³ In public health systems, like those in Canada and the UK, the government is the payer and simply does not pur-

³⁰⁵ Blankstein, *supra* note 70, at 296.

³⁰⁶ Trusheim et al., *supra* note 121, at 329.

³⁰⁷ Khrisna Chinthapalli, *Higher Drug Prices Will Boost Development of Personalised Medicine, Says New Report*, 347 *BMJ*, 4549, 4549 (2013); Rana Foroohar, *Why Hillary Is Right To Take On Pharma’s Price Gouging*, *TIME*, Sept. 23, 2015, <http://time.com/4046041/hillary-clinton-martin-shkreli/>; Andrew Pollack & Sabrina Tavernise, *Valeant’s Drug Price Strategy Enriches It, but Infuriates Patients and Lawmakers*, *NEW YORK TIMES*, Oct. 4, 2015, http://www.nytimes.com/2015/10/05/business/valeants-drug-price-strategy-enriches-it-but-infuriates-patients-and-lawmakers.html?_r=0 (accessed July 27, 2016).

³⁰⁸ Bianca DiJulio et al., *Kaiser Health Tracking Poll: October 2015*, HENRY J. KISSINGER FOUND. Oct. 28, 2015 <http://kff.org/health-costs/poll-finding/kaiser-health-tracking-poll-october-2015/>

³⁰⁹ Juliette Cubanski & Tricia Neuman, *The Facts on Medicare Spending and Financing*, HENRY J. KISSINGER FOUND. July 20, 2016 <http://kff.org/medicare/issue-brief/the-facts-on-medicare-spending-and-financing/>

³¹⁰ Blankstein, *supra* note 70, at 282; Cohen & Felix, *supra* note 47, at 171; Louis D, Fiore & Leonard William D’Avolio, *Commentary, Detours on the Road to Personalized Medicine: Barriers to Biomarker Validation and Implementation*, 306 *JAMA*, 1914, 1914 (2011); Fleck, *supra* note 47, at 202; Hans-Joerg Fugel et al., *Stratified Medicine and Reimbursement Issues*, 3 *FRONT. PHARMACOL.* 1, 2–3 (2012); Halim, *supra* note 107, at 34; Le Tourneau et al., *supra* note 47, at 264; J. Steven Leeder et al., *Conference Scene: Pediatric Pharmacogenomics and Personalized Medicine*, 11 *PHARMACOGENOMICS* 1691, 1692 (2010); Miossec et al., *supra* note 47, at 1716; Petersen et al., *supra* note 47, at 217; Parkinson et al., *supra* note 121, at 622; Carrie Printz, *Healthcare Reform Affects Cancer on Many Fronts: More Coverage for Treatment and Prevention Planned*, 116 *CANCER* 3525, 3526 (2010); Rothstein, *supra* note 166, at 684; Trusheim et al., *supra* note 47, at 823; Tursz & Bernards, *supra* note 23, at 938; Walk, *supra* note 53, at 230; Wistuba et al., *supra* note 55, at 140.

³¹¹ Montagna, *supra* note 45, at 18.

³¹² Babaian, *supra* note 277, at 675; Evans & Watson, *supra* note 23, at 670; Daniel Hayes et al., *Personalized Medicine: Risk Prediction, Targeted Therapies and Mobile Health Technology*, 12 *BMC MED* 1, 3 (2014); Holman, *supra* note 265, at 650.

³¹³ Rothstein, *supra* note 166, at 684.

chase or provide access to all existing therapies.³¹⁴ The same is true in the USA, where health insurance plans are determinative of which treatments will be reimbursed. At a federal level, the CMS makes similar decisions with regard to Medicare and Medicaid. Here, we expand on the subthemes related to reimbursement from 87 articles, including diagnostics and drugs are reimbursed separately (22 articles); insufficient reimbursement (17 articles); the ineffectiveness of current health technology assessment (HTA) for evaluating PM (14 articles); clinical utility is not required for reimbursement decisions (13 articles); the mismatch between evidence required by payers and regulators (13 articles); a general lack of data (10 articles), more specifically, a lack of evidence on clinical utility (6 articles); a sense of uncertainty about the reimbursement of PM (6 articles); fixed reimbursement for technologies treating some diseases (5 articles); an unwillingness on developers' parts to invest without assured reimbursement (3 articles); a mismatch between evidence produced by companies and the payers' expectations (2 articles); and uncertainty over reimbursement for predictive genotyping (2 articles).

Ideally, health system payers, in making coverage decisions, require evidence that a therapy or test is clinically useful—that evidence demonstrates measurable increases in health or well-being in clinical application.³¹⁵ This evidentiary issue is at the crux of the reimbursement barrier. Evidence of clinical utility is not required for regulatory approvals and yet it is necessary to meet the threshold for reimbursement.³¹⁶ As mentioned above, CLIA regulations require that genetic tests meet a threshold of analytic validity³¹⁷ and FDA regulations require evidence of safety and effectiveness in comparison with existing standard therapies, which includes data of analytical and clinical validity.³¹⁸ Neither set of approval regulations requires evidence of clinical utility.

The same problems of inadequate data and insufficient evidence for successful navigation of the regulatory approvals system create difficulties for the reimbursement process. Evidence of clinical utility is often forthcoming only after PMR and longitudinal studies and is generally lacking in the field of PM.³¹⁹ Data on clinical utility of genetic tests are particularly hard to develop, in part due to the difficulties correlating genetic tests and therapies with positive medical outcomes resulting from the underlying limitations of genetic predictors.³²⁰ Since all genetic variants are not directly associated with a disease or clinical condition, it is difficult to make clear medical predictions based on genetic information.³²¹ Absent a clearer relationship between biomarkers, CDx, and improved health outcomes, payers remain skeptical and reimbursement remains uncertain.³²²

³¹⁴ Blankstein, *supra* note 70, at 282; Le Tourneau et al., *supra* note 47, at 264.

³¹⁵ Parkinson et al., *supra* note 121, at 620; Poste et al., *supra* note 80, at 1518–9.

³¹⁶ Pignatti et al., *supra* note 68, at 1035; Parkinson et al., *supra* note 121, at 622; Poste et al., *supra* note 80, at 511.

³¹⁷ Piehl, *supra* note 42, at 76; Schlanger, *supra* note 142, at 389.

³¹⁸ Ramsey et al., *supra* note 45, at 2262.

³¹⁹ Conti et al., *supra* note 45, at 333; Faulkner et al., *supra* note 92, at 1164.

³²⁰ Deverka, *supra* note 108, at 434.

³²¹ *Id.* Merlin et al., *supra* note 111, at 338.

³²² Cohen, *supra* note 108, at 754; Conti et al., *supra* note 45, at 333; Faulkner et al., *supra* note 92, at 1167; Lam, *supra* note 121, at 9.

Questions remain about the level of evidence that is required to demonstrate clinical utility. Data required for regulatory approval differ not only in kind (analytical and clinical validity compared to clinical utility), but also in application of standards required for reimbursement decisions.³²³ There is no standardized method of preparing evidence of clinical utility, and uncertainty about what technical standards will be used creates confusion for test and drug manufacturers. This adds to the general uncertainty about the financial viability of PM therapies³²⁴ that already results from the expense of R&D and clinical trials, uncertain success of pharmaceuticals, and the smaller markets to which PM may be targeted.

Once a medical intervention is proven to be clinically useful, determining its reimbursement value is another barrier, one that is particularly troublesome with respect to CDx.³²⁵ First, the value of genetic information to overall health outcomes is indeterminate, let alone the value of tests that uncover that information.³²⁶ There is no agreed-upon set of parameters used to evaluate the reimbursement rate of CDx and little transparency in the reimbursement process.³²⁷ As a nascent field, it is unclear how to economically evaluate the worth of predictive testing for drug response.³²⁸

HTA and economic evaluation are traditionally used to evaluate the value of new pharmaceuticals and medical technologies relative to existing standards of care. HTA bodies have little experience with CDx and uses cost-effectiveness (a measure of the improvement in health outcomes relative to cost) and clinical utility measures, which may not be directly applicable.³²⁹ The interrelationship between PM therapy and CDx

³²³ Matthew Herder, *Choice Patents*, 52 IDEA: INTELL. PROP. L. REV. 309, 377–8 (2011); Jones & DeSantis, *supra* note 45, at 525; Meckley & Neumann, *supra* note 221, at 94; Parkinson et al., *supra* note 121, at 620; Pignatti et al., *supra* note 61, at 1466; Poste et al., *supra* note 80, at 1518–9; Rumiko Shimazawa & Masayuki Ikeda, *Letter to the Editor, Approval gap of Pharmacogenomic Biomarkers and in Vitro Companion Diagnostics Between the United States and Japan*, 39 BRIT. J. CLIN. PHARMACOL. 210, 210 (2014); Cheryl A. Thompson, *Regulations, Economics Hindering Adoption of Personalized Medicine*, 68 AM. J. HEALTH-SYS. PHARMACY 372, 374 (2011); Issam Zineh & Shiew-Mei Huang, *Biomarkers in Drug Development and Regulation: A Paradigm for Clinical Implementation of Personalized Medicine*, 5 BIOMARK. MED. 705, 706 (2011).

³²⁴ Bender, *supra* note 121, at 1090; Meadows et al., *supra* note 78, at 10; Parker & Hall, *supra* note 261, at 164; Parkinson et al., *supra* note 121, at 622; Trusheim et al., *supra* note 47, at 823; Walk, *supra* note 53, at 230; Rachel Zuckerman & Christopher-Paul Milne, *Market Watch: Industry Perspectives on Personalized Medicine*, 11 NAT. REV. DRUG DISCOV. 178, 181 (2012).

³²⁵ Sarah K. Byron et al., *The Health Technology Assessment of Companion Diagnostics: Experience of NICE*, 20 CLIN. CANCER RES. 1469, 1475 (2014); Ciardiello et al., *supra* note 121, at 1676; Merlin et al., *supra* note 111, at 334.

³²⁶ Ashley et al., *supra* note 166, at 150; Cohen, *supra* note 108, at 752; Conti et al., *supra* note 45, at 333; Dressler, *supra* note 251, at 511; Faulkner et al., *supra* note 92, at 1163; Merlin et al., *supra* note 111, at 338; Nelson, *supra* note 45, at 856.

³²⁷ Cohen & Felix, *supra* note 47, at 171.

³²⁸ Byron et al., *supra* note 325, at 1475; Bengt Jönsson, *Technology Assessment for New Oncology Drugs*, 19 CLIN. CANCER RES. 6, 8 (2013).

³²⁹ Byron et al., *supra* note 325, at 1475; Conti et al., *supra* note 45, at 333; Faulkner et al., *supra* note 92, at 1164; Maggie H. Francis, *Beyond Safe and Effective: The Role of the Federal Government in Supporting and Disseminating Comparative-Effectiveness Research*, 21 ANN. HEALTH L. 329, 335–6 (2012); Lam, *supra* note 121, at 9; Lesko & Zineh, *supra* note 168, at 510; Meadows et al., *supra* note 78, at 9; Merlin et al., *supra* note 111, at 334; Tibor van Rooij et al., *Personalized Medicine Policy Challenges: Measuring Clinical Utility at Point of Care*, 12 EXPERT REV. PHARMACOECON. OUTCOMES RES. 289, 291 (2012); Richard S. Saver, *Health Care Reform's Wild Card: The Uncertain Effectiveness of Comparative Effectiveness Research*, 159 U. PA. L. REV. 2147, 2193 (2011); Thomas et al., *supra* note 121, at 561; Julia R. Trosman et al., *Health Technology Assessment and Private Payers' Coverage of Personalized Medicine*, 7 AM. J. MANAGED CARE. 18s, 22s (2011); Ioannis S. Vizerianakis,

means the tests often follow the therapies, resulting in different timelines, different evidence, and interdependence, all of which complicate HTA and reimbursement decisions.³³⁰ Complicating the valuation exercises are multiple potential CDx, whose value may be linked to, or differ from, the value of the therapy.³³¹ Traditionally reimbursement rates for diagnostics are much lower than pharmaceuticals, and are based on cost, as low as \$50 to \$100 per test, rather than value.³³² Reimbursement policies based on cost do not recognize the clinical value or development costs of CDx³³³ thus, the CDx reimbursement rate is magnitudes lower than for its therapy. This is a major barrier to independent investment in the development of new and innovative CDx.³³⁴ In addition, the development of value-based analysis for reimbursement for PM is being developed on an ad hoc, case by case basis, leading to inconsistencies.³³⁵

Comparative Effectiveness Research in Healthcare

Comparative effectiveness research (CER) compares the relative effectiveness of different therapies at improving health outcomes. It is particularly useful in identifying ineffective therapies. By contrast, cost-effectiveness measures the improvement in health outcomes relative to cost.³³⁶ CER has become an important part of the US healthcare industry. This follows the authorization of \$1.1 billion in The American Recovery and Reinvestment Act of 2009³³⁷ to conduct research comparing ‘clinical outcomes, effectiveness, and appropriateness of items, services, and procedures that are used to prevent, diagnose, or treat diseases, disorders, and other health conditions’.³³⁸ Competing needs for scarce healthcare dollars has increased government and healthcare purchaser initiatives to determine the most effective use of those resources. CER compares the effectiveness as well as benefits and harms of existing healthcare interventions, including tests, surgeries, and drugs. As such, its objective is to find the most effective interventions between medical alternatives. Purchasers, governments, and consumers can then determine which treatments are most effective and least expensive between competing options. Cost-effectiveness measures remain controversial in the USA, because they are the basis for decisions about rationing of healthcare expenses.³³⁹

Nanomedicine and Personalized Medicine Toward the Application of Pharmacotyping in Clinical Practice to Improve Drug-Delivery Outcomes, 7 *NANOMED. NANOTECHNOL. BIOL. & MED.* 11, 14 (2011); Edie E. Zusman, *Review, Comparative Effectiveness Research: Policy and Politics*, 33 *NEUROSURG. FOCUS* 6, 10 (2012).

³³⁰ Singer & Watkins, *supra* note 121, at 754.

³³¹ Byron et al., *supra* note 325, at 1470.

³³² Bender, *supra* note 121, at 1090; Byron et al., *supra* note 325, at 1475; Ciardiello et al., *supra* note 121, at 1676; Fiore & D’Avolio, *supra* note 310, at 1914; Meadows et al., *supra* note 78, at 10; Parker & Hall, *supra* note 261, at 164.

³³³ Bender, *supra* note 121, at 1090; Byron et al., *supra* note 325, at 1475; Ciardiello et al., *supra* note 121, at 1676; Fiore & D’Avolio, *supra* note 310, at 1914; Meadows et al., *supra* note 78, at 10; Parker & Hall, *supra* note 261, at 164.

³³⁴ Bender, *supra* note 121, at 1090; Pirmohamed & Hughes, *supra* note 271, at 4.

³³⁵ Cohen & Felix, *supra* note 47, at 171.

³³⁶ Jason Shafrin, *Comparative Effectiveness vs. Cost Effectiveness Research*, *HEALTHCARE ECONOMIST*, Mar. 11, 2010, <http://healthcare-economist.com/2010/03/11/comparative-effectiveness-vs-cost-effectiveness-research/>

³³⁷ American Recovery and Reinvestment Act, H.R. 1, 111th Cong. (2009).

³³⁸ Milton C. Weinstein & Jonathan A. Skinner, *Comparative Effectiveness and Health Care Spending — Implications for Reform*, 362 *NEW ENG. J. MED.* 460, 460 (2010).

³³⁹ *Id.*

Since CER uses aggregate outcomes data to determine whether one treatment option is less effective than another, it can be very difficult for advocates of PM interventions with smaller groups of patients to contribute data for CER comparisons.³⁴⁰ Outcomes data for a particular condition may overwhelm a smaller subgroup of patients, unless the subgroup becomes the basis for comparative analysis.³⁴¹ While CER can use different subgroups for analysis, doing so would require validating the subgroup as appropriate and looking at different data research tools.³⁴² Exacerbating this research difficulty is the extremely high price of some PM drugs and tests, which, coupled with a small patient population, disadvantages them in CER. Those making reimbursement decisions are faced with questions about whether a test, drug, or treatment is worth purchasing. To justify higher prices, developers of PM will be required to provide more evidence than is required to support regulatory approval, which excludes considerations of cost.³⁴³

Companion Diagnostic Reimbursement

Historical structures for reimbursement of diagnostics pose a barrier to investment in and adoption of CDx. In part, this barrier is the result of the different reimbursement structures, payers, and codes that exist for drugs and diagnostics.³⁴⁴ Twenty-two articles raise the disparate treatment of drugs and diagnostics at the payer level; however, these articles do not discuss the role of hospitals in decision making about diagnostics. Traditionally, diagnostic tests have been developed in hospital laboratories and the addition of tests has been under the purview of the director of the laboratory. As such, tests were part of the hospital budget with no explicit or formal process for their development or reimbursement. Thus, a non-transparent adoption process for diagnostics evolved. As more diagnostics are developed outside the hospital laboratory and sold as kits to hospitals, they become part of the formal budgeting process and must compete for those dollars. The prices for commercialized genetic tests and CDx are very expensive, compared to in-house developed diagnostics, even though diagnostic tests cost less than drugs. This makes it very difficult for a hospital diagnostic budget to absorb a CDx and puts pressures on laboratory directors to expand their budgets to accommodate new CDx.

Where insurance plans are concerned, pharmaceuticals often have a separate plan from medical services and are generally reimbursed at a higher rate than diagnostics.³⁴⁵ Drugs are reimbursed according to their value, whereas diagnostics are reimbursed ac-

³⁴⁰ Francis, *supra* note 329, at 335-6; Pirmohamed & Hughes, *supra* note 271, at 4; Saver, *supra* note 329, at 2181-2; Zusman, *supra* note 329, at 10.

³⁴¹ Saver, *supra* note 329, at 2180.

³⁴² *Id.*

³⁴³ George Poste, *Comment, Bring on the Biomarkers*, 469 NATURE 156, 157 (2011); Shimazawa & Ikeda, *supra* note 323, at 210.

³⁴⁴ Avery, *supra* note 7, at 38; Cohen, *supra* note 108, at 754; Dressler, *supra* note 251, at 511; Faulkner et al., *supra* note 92, at 1164; Fugel et al., *supra* note 310, at 2-3.

³⁴⁵ Bender, *supra* note 121, at 1090; Byron et al., *supra* note 325, at 1475; Ciardiello et al., *supra* note 121, at 1676; Fiore & D'Avolio, *supra* note 310, at 1914; Meadows et al., *supra* note 78, at 10; Parker & Hall, *supra* note 261, at 164.

ording to their cost, depending on the materials and type of test.³⁴⁶ Pricing of drugs presents a balance between volume and price; in other words, the lower the volume, the higher the price that may be charged to make a profit. However, if the patient population is small, different incentives must be found or the cost to patients will be high and hospital formulary restrictions may reduce access.³⁴⁷ Medical diagnostics on the other hand are generally reimbursed according to Current Procedural Terminology codes managed by the American Medical Association, and the reimbursement rates established by the CMS.³⁴⁸ The existing reimbursement system has established codes with fixed rates for certain disease states that would need to be changed for all types of PM diagnostics to be reimbursed according to their value based on evidence.³⁴⁹ In addition, Medicare, the American government's largest health insurance plan, has declared that it will not pay for most preventative genetic testing.³⁵⁰ Under statute, CMS cannot reimburse for preventative services without Congressional approval. It is therefore unclear what evidence or reimbursement changes will spur additional coverage of CDx at the federal level.³⁵¹

Recommendations for Reimbursement of PM

Realizing the potential of PM by overcoming reimbursement barriers requires the creation of closer working relationships and clearer communications between drug and device manufacturers, regulators, and reimbursement authorities earlier in the drug development process.³⁵² This would ensure that manufacturers understand what kind of evidence is necessary for reimbursement decisions.³⁵³ While earlier involvement of reimbursement agencies requires a shift in traditional timelines, it would enable HTA and cost-effectiveness considerations to be incorporated earlier in the design of clinical programs.³⁵⁴ Increasing the predictability of reimbursement for PM products should facilitate the development of PM.³⁵⁵ Clarifying current reimbursement guidelines and the basis on which risk-benefit and effectiveness determinations are made would illuminate decision criteria and valuation interpretations,³⁵⁶ thereby facilitating business decisions and preparation for regulatory and reimbursement submissions.

³⁴⁶ Byron et al., *supra* note 325 at 1475; Ciardiello et al., *supra* note 121, at 1676; Fiore & D'Avolio, *supra* note 310, at 1914; Fugel et al., *supra* note 310, at 3; Leeder et al., *supra* note 310, at 1692; Meadows et al., *supra* note 78, at 10; Parkinson et al., *supra* note 121, at 622; Trusheim et al., *supra* note 121, 818.

³⁴⁷ Cohen & Felix, *supra* note 47, at 167.

³⁴⁸ Fugel et al., *supra* note 310, at 3.

³⁴⁹ Cohen, *supra* note 108, at 754; Dressler, *supra* note 251, at 511; Faulkner et al., *supra* note 92, at 1169; Fugel et al., *supra* note 310, at 3.

³⁵⁰ Blankstein, *supra* note 70, at 282.

³⁵¹ Dressler, *supra* note 251, at 511.

³⁵² Cohen & Felix, *supra* note 47, at 172; Deverka, *supra* note 108, at 434; Faulkner et al., *supra* note 92, at 1167; Thomas et al., *supra* note 121, at 561; Tsimberidou et al., *supra* note 131, at 123; Verweij et al., *supra* note 73, at 202.

³⁵³ Cohen & Felix, *supra* note 47, at 172.

³⁵⁴ Thomas et al., *supra* note 121, at 561.

³⁵⁵ Trusheim et al., *supra* note 121, at 329; Vogenberg et al., *supra* note 75, at 630; Walk, *supra* note 53, at 230.

³⁵⁶ Sinead Cuffe et al., *Cancer Patients' Acceptance, Understanding, and Willingness-to-Pay for Pharmacogenomic Testing*, 24 PHARMACOGENET. GENOMICS 348, 353; Fleck, *supra* note 47, at 205; Horgan et al., *supra* note 99, at 291; Joly et al., *supra* note 58, at 24; Pignatti et al., *supra* note 68, at 1040; Tazawa, *supra* note 148, at 22; Thomas et al., *supra* note 125, at 929.

Some articles recommend greater alignment between safety regulators and reimbursement authorities.³⁵⁷ In the USA, such alignment would broaden the remit of the FDA beyond safety and efficacy concerns to include considerations of comparative effectiveness and clinical utility. Numerous commentators consider this reform not as a wholesale change but as a novel approach to regulatory approvals specifically aimed at assessing PM drugs and their CDx. Many stakeholders believe that regulators and researchers should consider clinical utility and cost-effectiveness data in the development of drugs, biomarkers, and diagnostics.³⁵⁸

The creation of shared models of valuation between regulatory and reimbursement authorities, coupled with adoption of complementary evidentiary standards that include data on clinical utility,³⁵⁹ would facilitate a more predictable return on investment for PM developers. If regulators require effectiveness data to be generated in clinical trials, these data could create an evidence base for PM to satisfy reimbursement authorities. Pathways for these data to be passed on to hospitals, clinicians, and payers could further facilitate adoption of PM products. In addition, where complete effectiveness evidence is not available, conditional reimbursement could be granted contingent on generation of additional effectiveness evidence and ongoing CER.³⁶⁰ This would require alignment between conditional regulatory approvals and conditional reimbursement, both of which would be reliant on postmarket data collection. Reimbursement authorities might require submission of a strategy for how postmarket evidence will be generated prior to unconditional approval.³⁶¹ Consequently, drug and device manufacturers need to develop standardized methods to assess validity and utility. This will provide data to reimbursement authorities in a standardized fashion.³⁶² Developing and harmonizing clinical best practices and practices for modeling economic outcomes of PM will be an important part of this exercise.

Other recommendations advocate greater change to reimbursement policies, including a move away from cost-based reimbursement of diagnostics to value-based reimbursement.³⁶³ Focusing on value rather than on technology or process will create incentives for investment in CDx and move diagnostics onto a more level playing field with drug reimbursement.³⁶⁴ While this would certainly create incentives to invest in diagnostics, it is unclear what the overall impact of such a change would be on healthcare costs and resource allocation. Keeping costs under control in this scenario might

³⁵⁷ Eichler et al., *supra* note 80, at 502; Nofziger et al., *supra* note 236, at 160; Pacanowski, *supra* note 58, at 249; Pirmohamed, *supra* note 23, at 864; Thomas et al., *supra* note 125, at 929; Walk, *supra* note 53, at 230.

³⁵⁸ Dick, *supra* note 164, at 195-6; Pignatti et al., *supra* note 61, at 1466; Thomas et al., *supra* note 125, at 929; Woodage, *supra* note 142, at 15-6.

³⁵⁹ Dick, *supra* note 164, at 195-196; Eichler et al., *supra* note 80, at 503; Faulkner et al., *supra* note 92, at 1164; Fugel et al., *supra* note 310, at 4; Nofziger et al., *supra* note 236, at 160; Pacanowski, *supra* note 58, at 249; Pirmohamed, *supra* note 23, at 864; Thomas et al., *supra* note 125, at 929; Walk, *supra* note 53, at 230; Woodage, *supra* note 142, at 13-4.

³⁶⁰ Conti et al., *supra* note 45, at 336; Horgan et al., *supra* note 99, at 291; Nelson, *supra* note 45, at 856; Ramsey et al., *supra* note 45, at 2268; Robertson, *supra* note 42, at 396-7; Trusheim et al., *supra* note 121, at 330; Tursz & Bernards, *supra* note 23, at 939.

³⁶¹ Robertson, *supra* note 42, at 397.

³⁶² Ramsey et al., *supra* note 45, at 2266.

³⁶³ Blankstein, *supra* note 70, at 283; Gibson & Lemmens, *supra* note 47, at 213; Lesko & Zineh, *supra* note 168, at 511; Meadows et al., *supra* note 78, at 11; Sawyers & van 't Veer, *supra* note 148, at 4979.

³⁶⁴ Cohen & Felix, *supra* note 47, at 172; Khoury, *supra* note 166, at 1213; Meckley & Neumann, *supra* note 221, at 97.

involve federal price controls on patented tests and pharmaceuticals.³⁶⁵ Other systemic changes include changing the reimbursement codes that are used by clinicians, hospitals, and insurance companies to keep up with new advances in diagnostics.³⁶⁶ This would enable reimbursement of precision therapeutics and incentivize next-generation diagnostics that may be more cost-effective than standard treatments that do not segment the population. However, as whole genome sequencing increases in use for diagnosis, greater evidence of its analytic and clinical validity as well as clinical utility should be required.³⁶⁷ Finally, a number of authors underline the need for the HTA system to be changed to respond to PM.³⁶⁸ HTA needs to be adapted for the evaluation of combination products and those diagnostics aimed at smaller segments of the patient population.

CONCLUSION

PM promises to be at the forefront of government and scientific agendas for the foreseeable future. Since beginning our research, the PMI has motivated significant US health research and policy action; there will be continued spending, development of infrastructure, and data-sharing systems. The FDA final guidance on LDTs is expected at any time. Revisions to the federal Common Rule will continue to be debated. The open reference platform of precision FDA will generate information that will help inform future regulatory directions and decision making. Pharmaceutical and biotechnology companies will continue to work toward developing personalized treatments and diagnostics, not just in the USA but around the globe.³⁶⁹ While the reviewed articles express concern about barriers to PM, they all assume that PM would bring tangible benefits to patients and/or healthcare systems (a limitation of our study).

Our research revealed the significant regulatory and non-regulatory barriers to the realization of PM, which will need to be addressed in tandem. In the first instance, while PM R&D has focused almost exclusively on genetics, it has become clear that genes are not as predictive as once believed. Indeed, highly prevalent and predictive genetic mutations are uncommon. Thus, the science of PM requires broadening to include fields such as proteomics, metabolomics, and cell therapies. In addition, there is a lack of clinical uptake of PM by healthcare providers resulting from both structural and human fac-

³⁶⁵ Alzu'bi et al., *supra* note 252, at 9.

³⁶⁶ Cohen & Felix, *supra* note 47, at 172.

³⁶⁷ Woodage, *supra* note 142, at 15–16.

³⁶⁸ Byron et al., *supra* note 325, at 1475; Ciardiello et al., *supra* note 121, at 1676; Gibson & Lemmens, *supra* note 47, at 213; Jönsson, *supra* 328 297, at 8; van Rooij, *supra* note 329, at 292.

³⁶⁹ For example, in Europe the Innovative Medicines Initiative is a public–private partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations, in order to encourage biopharmaceutical innovation in Europe. It supports projects like the Diabetes Research on Patient Stratification project and other personalized medicine projects. See DIRECT, *DIRECT—Innovative Medicines Initiative: Diabetes Research on Patient Stratification*, <http://www.direct-diabetes.org/imi/index.php> (accessed on July 25, 2016). In Canada, another public–private partnership, the Exactis Innovation initiative ‘Personalized my Treatment’, targets barriers in clinical trial design. This initiative will create a comprehensive database of tissue samples, genomic data, and clinical data from cancer patients to match patients with PM clinical trials. See Merck Canada, *\$4 Million Partnership to Reduce Barriers to the Development of Personalized Medicine in Oncology*, MCGILL FAC. MED. ELECTRONIC NEWSLETTER (Apr. 20, 2016) <http://publications.mcgill.ca/medenews/2016/04/20/4-million-partnership-to-reduce-barriers-to-the-development-of-personalized-medicine-in-oncology/> (accessed July 25, 2016).

tors. The structural barriers include the traditional focus on treatment of disease rather than its prevention in the current US healthcare system.³⁷⁰ PM tests will require greater resources and expertise for interpretation and explanation of the meaning of test results for patients.³⁷¹ Human factors include inadequate clinician education and/or training in PM, especially genetics, and, therefore, lack of expertise and comfort with interpretation of test results³⁷² and how best to counsel patients. Lack of training inhibits clinical uptake, which, in turn, will impede the generation of data on clinical utility of PM products and services.

Addressing the structural, financial, and regulatory barriers to PM needs to proceed in lock-step with scientific advances if PM is to reach its promised potential. Indicators are that reforms will be propelled by the scientific community, industry, political will, and, most importantly, the patient advocacy community—the ultimate beneficiary of PM technologies and services.

Personalized medicine search terms: theranostic* OR personalized medicine* OR personalised medicine* OR individualized medicine* OR individualised medicine* OR pharmacogenetic* OR targeted therap* OR pharmacogenomic* OR companion diagnostic* OR genomic test* OR stratified medicine* OR precision medicine* OR biotherap* OR co-dependent technolog* OR co-dependent technolog* OR codependent technolog* OR hybrid technolog* OR genomic medicine* OR customized medicine* OR customised medicine* OR integrated diagnostic* OR integrated therapeutic* OR molecular targeted therap* OR P4 medicine* OR patient specific therap* OR personalized molecular cancer therap* OR personalised molecular cancer therap* OR personalised molecular cancer therap* OR personalized cancer therap* OR personalised cancer therap* OR individualized cell therap* OR individualised cell therap* OR PGX OR pharmacoproteomic* OR pharmacometabolomic* OR stratified therap* OR tailored therap* OR targeted drug therap* OR (diagnosti* OR prognosti* AND personalized OR personalised OR companion OR codependent OR stratified OR genomic OR individual* OR pharmacogenomic*).

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³⁷⁰ Geoffrey S. Ginsburg, *Viewpoint, Realizing the Opportunities of Genomics in Health Care*, 309 JAMA 1463, 1464 (2013).

³⁷¹ Woodage, *supra* note 142, at 8.

³⁷² Amy P. Abernethy et al., *Rapid-Learning System for Cancer Care*, 28 J. CLIN. ONCOL. 4268, 4273 (2010); Blankstein, *supra* note 70, at 274; Mafalda. M. Dias et al., *Exploration of the Perceptions, Barriers and Drivers of Pharmacogenomics Practice Among Hospital Pharmacists in Adelaide, South Australia*, 14 PHARMACOGENOMICS J. 235, 238 (2014); Halim, *supra* note 107, at 31; Maxwell J. Mehlman, *Professional Power and the Standard of Care in Medicine*, 44 ARIZ. ST. L.J. 1109, 1218 (2012); Neyarapally, *supra* note 42, at 506; Palmer, *supra* note 23, at 482-3; Pasquale, *supra* note 260, at 742; Piehl, *supra* note 238, at 93; Piehl, *supra* note 42, at 79; Elizabeth R. Pike et al., *Finding Fault? Exploring Legal Duties to Return Incidental Findings in Genomic Research*, 102 GEO. L.J. 795, 811 (2014); Pirmohamed, *supra* note 23, at 864; Rothstein, *supra* note 166, at 684; Suarez, *supra* note 205, at 499; Eric J. Topol, *Commentary, Pharmacy Benefit Managers, Pharmacies, and Pharmacogenomic Testing: Prescription for Progress?* 2 SCI. TRANSL. MED. 44cm22, 2 (2010); Wolf, *supra* note 205, at 445; Woodage, *supra* note 142, at 11–2.

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