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Regulation and the Fate of Personalized Medicine?

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Personalized medicine can be succinctly described as the right dose of the right drug for the right indication for the right patient at the right time [1], the antithesis of the former blockbuster one-drug-fits-all approach. With more than 70 drugs that may be classified as “personalized” already on the market [2], this new paradigm in drug development may become a real force in the biopharmaceutical industry. That industry is eager to exit a particularly difficult innovation slump that also coincides with a “patent cliff,” i.e., the expiration of many patents for blockbuster drugs that heretofore limited generic competition in exceedingly lucrative markets [3].

The current bleak economic forecast for biopharm notwithstanding, there are powerful incentives drawing drug companies into this new method of drug development. Personalized medicine promises to increase efficacy in subpopulations of patients, providing opportunities to revive defunct or failed drugs with new, narrower indications and minimizing adverse drug reactions among those for whom the drug is no longer indicated.

A recent example of a personalized medicine drug passing FDA standards is Perjeta, approved for use in combination with Herceptin (itself a personalized treatment specifically approved for use on patients with overactive HER2 receptors) and docetaxel chemotherapy to create a comprehensive blockade of human-epidermal growth factor receptor (HER) signaling pathways for the treatment of HER2-positive metastatic breast cancer. Patients are required to take a genetic test to determine whether their cancer is HER2 positive before they can be prescribed the drug [4].

The concept of personalized medicine isn't novel; orphan drugs, those medicines with very narrow labeling that encompass only a sliver of the population, are in essence a form of personalized medicine, but without all the fancy recent “-omics” innovation driving current efforts in that direction.

This current incarnation of personalized medicine, however, may perhaps be best thought of as a third attempt to monetize the successful sequencing of the human genome. The first attempt entailed finding drug targets within what was largely an unannotated sequence of genetic code. The second, ongoing effort, still too young to evaluate [5], proposes using genome-wide association studies (GWAS) to investigate genetic sources of complex and often chronic diseases, or in some cases to suggest alternative or more specific uses of a drug [6]. The third, present effort aims to provide precise diagnoses and highly directed treatments based on genetic data [7].

This third wave comes as we are experiencing a precipitous drop in the price of both genetic sequencing and computing power and memory that has led to the nascent personalized genomics industry. This industry provides genetic data to the public relatively inexpensively. A phenomenal accomplishment: compare the current forecast of whole genome sequencing for \$1,000 or less with the \$3 billion price tag on the Human Genome Project completed in 2003 [8, 9].

Since personalized medicine often (but not always [10]) relies on knowledge of a particular genetic variant in a patient, it would be of great benefit if a large percentage of the public had easy access to their genomic make-ups, which could then be matched against a growing library of single nucleotide polymorphisms (SNPs), copy number variations (CNVs), other biomarkers, and proteomic, metabolomic, or epigenetic data associated with disease, drug metabolism, and other relevant indicators. Despite the exciting possibilities of personalized medicine, there remain substantial regulatory, legal, and social hurdles.

Regulation and the FDA

Many of the hurdles have to do with the Food and Drug Administration (FDA). While the FDA has indicated that it is interested in revising the regulatory structure to promote personalized medicine, the current regulatory uncertainties are likely to be a drag on financial investment in the field.

Changes will require up-to-date expertise in broad swaths of science and will necessitate significant shifts in the way the FDA does business—unprecedented cooperation across multiple centers and departments with different cultures, regulations, legal concerns, and foci. For example, personalized medicine often requires the integration of drugs and diagnostics, which are currently handled by least two separate FDA programs with different standards. This may cause logistical trouble. A given drug and its diagnostic companion may be produced by different corporations that would need to coordinate their distinct needs across multiple agencies and subfiefdoms within the FDA. Whether that means governing them by similar regulations, putting them through similar evaluation processes, or just reviewing the very different technologies at the same time remains to be seen.

Whereas previously a drug and its indications may have been thoroughly understood by a particular set of experts at the FDA, personalized medicine labeling may require several experts in nonoverlapping fields to develop a shared knowledge base. Similarly, the FDA will need to build additional capacity to define the optimal subpopulation for a particular drug, which is likely to require cooperation between a mix of clinical and research scientists. This cooperation is of particular importance since regulators are likely to overestimate the precision of genomic data when simpler biomarkers may be more efficient and more medically relevant.

Further, clinical trials will use smaller populations determined by relevant biomarkers in the clinical analysis of the drug, rather than being conducted in the

more random fashion of the past, when populations for trials were not determined by genomic information [11]. This, and the changing conception about the ethical usage of controls in trials where data strongly suggests that the drug will work with few adverse reactions, may change the way drug trials are conducted and evaluated. And, given the sometimes-controversial use of retrospective analysis (in which researchers, lacking genomic data on a new treatment, rely on, for example, data on race instead), the FDA will need to work toward better policing these analyses [12].

This is not to say that the FDA hasn't been trying [13]. In 2003, the FDA established the Voluntary Exploratory Data Submissions (VXDS) program, a repository for genetic data that the biopharmaceutical industry was keeping on its products [14]. Drug companies, however, were wary of submitting additional data that could potentially harm their applications for approval, and it took a number of years before they actually started providing the data, which will help the FDA, among other things, understand whether genomic data should be included in drug labels.

In 2011, the FDA issued a number of drafts for guidance that have implications for the regulation of personalized medicine [15-18]. These drafts typically deal with diagnostic tools and devices that may be necessary when determining whether a particular patient has a particular biomarker, for example, when developing drugs that can only be used with companion diagnostic tests. Some of the relevant parties felt that the FDA guidance actually indicated that the FDA did not yet have a good grasp on the nature of the personalized medicine industry, and particularly on how to promote innovation and investment [19].

FDA commissioner Margaret Hamburg has also voiced support for new science and innovation in general and personalized medicine and pharmacogenomics in particular [20, 21]. Further, earlier this year, Congress passed and the president signed FDA user-fee legislation that included provisions to develop the agency's capacity to review data on biomarkers and pharmacogenomics [22]. This apparent signal of confidence by Congress and the FDA as to the importance of the personalized medicine industry may provide additional confidence to the industry in the regulatory system that polices it.

The onus of revamping the regulatory climate is not borne by the FDA alone. Regulatory control of many diagnostic tests, including genetic tests, involves both the Clinical Laboratory Improvement Amendments (CLIA) program administered by the Centers for Medicare and Medicaid Services of the Department of Health and Human Services and the FDA's Office of In Vitro Diagnostics. CLIA typically regulates the technical accuracy of the test and the FDA typically regulates the test's medical applications.

Financial Incentives

In addition, regulatory and legal decisions may inhibit or discourage innovation. For example, it's unclear how recent efforts in reforming national health care [23] will affect the reimbursement process for diagnostic testing and other aspects of

personalized medicine. It's thought that payors who need evidence of the effectiveness and financial viability of a treatment will be able to obtain that data from, for example, the nongovernmental Patient-Centered Outcomes Research Institute (PCORI) established by health care reform. But cost-cutting measures created by the same reforms may prevent them from being able to do so [24, 25]. Contrast, for example, the position of Gregory Conko's and Henry I. Miller's *Forbes* editorial claiming that "ObamaCare threatens personalized medicine" [26] with law firm Foley and Lardner LLP's assessment that "the bill offers support for personalized medicine" [27].

Further, in the recent Supreme Court case *Mayo v. Prometheus* [28] the court reversed an appellate decision of the Federal Circuit by finding that specific patent claims that included a widely used method for titrating and optimizing the dosage of a drug were invalid. The court ruling, criticized by many for conflating basic concepts in patent law [29] but now nevertheless being followed in lower courts [30], deemed the method was unpatentable. The court, it appears, feared that patenting such tests might "interfere significantly with the ability of medical researchers to make valuable discoveries, particularly in the area of diagnostic research" [31].

However, given that the United States Patent Office has only just released their guidelines in light of the Supreme Court decision [32], it's unclear whether the end result will be the promotion of innovation, as anticipated by the courts, or more likely a chilling effect on the development and use of personalized-medicine diagnostic tests that rely on the protection of intellectual property to obtain funding from wary investors.

Furthermore, personalized medicine's tendency to move away from the one-size-fits-all blockbuster model for pharmaceuticals will result in a new drug paradigm involving substantially smaller markets with correspondingly smaller incentives for drug innovation and the likelihood that drug companies might invest in me-too drugs or generics [33].

The standard drugs for Alzheimer disease, cancers, asthma, and other chronic diseases can be ineffective on between a third and three-quarters of patients taking them [34]; many widely used drugs are ineffective for large swaths of the population. The ethics of selling those drugs notwithstanding, personalized medicine will effectively destroy the profits of that business model.

Regulations will also need to be updated to prevent pharmaceutical companies from abusing the Orphan Drug Act [35], which was enacted to promote pharmaceutical research for the portion of the population with rarer diseases that may be disenfranchised from drug development by the pharmaceutical industry. Such abuse might entail applying for funding that belongs to drugs for rare conditions, and salami slicing a broad target population into more specific populations to repurpose the drug as several drugs efficacious for smaller populations [36].

Conclusions

This list is not exhaustive; many legal, regulatory, social, and ethical obstacles to the development of a personalized genomic drug industry remain. For example, social concerns may be a sticking point. Thus, despite the efforts in developing the Genetic Information Non-Discrimination Act (GINA) [37], reasons remain for people to be wary of releasing their genetic data, including, but not limited to, the obvious loopholes that the act contains for providers of long-term care, disability insurance, and life insurance. New privacy regulations need to be in place before much of the population will be comfortable releasing genetic and genomic data, particularly to their insurance companies. The future of this promising nascent technology will be in large part determined by regulatory and legal changes.

References

1. Frueh F. Personalized medicine: what is it? How will it affect health care? Paper presented at: 11th Annual FDA Science Forum; April 26, 2005; Washington, DC.
<http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085716.pdf>. Accessed July 24, 2012.
2. Personalized Medicine Coalition. The case for personalized medicine; 2011. <http://www.personalizedmedicinecoalition.org/about/about-personalized-medicine/the-case-for-personalized-medicine>. Accessed July 23, 2012.
3. Greenbaum D. Patents and drug shortages: will the new congressional efforts save us from impending drug shortages? *Am J Bioeth.* 2012;12(1):18-20.
4. FDA approves Perjeta (pertuzumab) for people with HER2-positive metastatic breast cancer [news release]. South San Francisco, CA: Genentech; June 8, 2012. <http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=14007>. Accessed July 23, 2012.
5. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature.* 2007;447(7145):661-678.
6. Sanseau P, Agarwal P, Barnes MR, et al. Use of genome-wide association studies for drug repositioning. *Nat Biotechnol.* 2012;30(4):317-320.
7. Philippidis A. Harvard professor rides genomics' third wave: new firm aims to advance personalized medicine through precision diagnostics. *GEN: Genetic Engineering and Biotechnology News.* July 3, 2012. <http://www.genengnews.com/analysis-and-insight/harvard-professor-rides-genomics-third-wave/77899640/>. Accessed July 24, 2012.
8. Hamermesh RG, Andrews P, Aspinall MG. Gene sequencing: staking a position in an expanding industry. Harvard Business School Strategy Unit case no. 812-004. <http://ssrn.com/abstract=1998169>. Accessed July 24, 2012.
9. Mason CE, Elemento O. Faster sequencers, larger datasets, new challenges. *Genome Biol.* 2012;13(3):314.
10. BiDil website. <http://www.bidil.com/>. Accessed July 24, 2012.
11. Vaidyanathan G. Redefining clinical trials: the age of personalized medicine. *Cell.* 2012;148(6):1079-1080.

12. Greenbaum D. Incentivizing pharmacogenomic drug development: how the FDA can overcome early missteps in regulating personalized medicine. *Rutgers Law J.* 2008;40(1):97-158.
http://lawjournal.rutgers.edu/sites/lawjournal.rutgers.edu/files/issues/v40/1/02GreenbaumVol.40.1.r_1.pdf. Accessed July 24, 2012.
13. Mansfield E. Personalized medicine: what's new and interesting at the FDA. Paper presented at: the Genomic and Personalized Medicine Forum; April 26, 2012; Durham, NC. <http://www.genome.duke.edu/research/genomic-medicine/genomic-medicine-forum/documents/2012/Mansfield%20Duke%20Genomics%20and%20PM%20Forum%20042612.pdf>. Accessed July 24, 2012.
14. US Food and Drug Administration. Voluntary Exploratory Data Submissions (VXDS).
<http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083673.htm>. Accessed July 24, 2012.
15. Draft guidance for industry and food and drug administration staff - in vitro companion diagnostic devices: issued July 14, 2011.
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm262292.htm>. Accessed July 24, 2012.
16. US Food and Drug Administration. Draft guidance for industry, clinical investigators, and food and drug administration staff - design considerations for pivotal clinical investigations for medical devices: issued August 15, 2011.
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265553.htm>. Accessed July 24, 2012.
17. US Food and Drug Administration. Guidance for industry and food and drug administration staff - factors to consider when making benefit-risk determinations in medical device premarket approvals and de novo classifications: issued March 28, 2012.
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm>. Accessed July 24, 2012.
18. US Food and Drug Administration. Notice: draft guidance for industry and fda staff - commercially distributed in vitro diagnostic products labeled for research use only or investigational use only: frequently asked questions. *Federal Register.* June 1, 2011.
<https://www.federalregister.gov/articles/2011/06/01/2011-13390/draft-guidance-for-industry-and-fda-staff-commercially-distributed-in-vitro-diagnostic-products>. Accessed July 24, 2012.
19. See, e.g., Sheives P; Biotechnology Industry Organization. RE: Comments on draft guidance: commercially distributed in vitro diagnostic products labeled for research use only or investigational use only: frequently asked questions. http://www.bio.org/sites/default/files/BIO%20Comments%20to%20FDA%20on%20RUO_IUO%20Draft%20Guidance_Final.pdf. Accessed July 24, 2012.
20. Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med.* 2010;363(4):301-304.

21. US Food and Drug Administration. Driving biomedical innovation: initiatives for improving products for patients; October 2011.
<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm274333.htm>. Accessed July 24, 2012.
22. Baker S. Obama signs bipartisan FDA bill. *The Hill*. July 9, 2012.
<http://thehill.com/blogs/healthwatch/medical-devices-and-prescription-drug-policy-/236773-obama-signs-bipartisan-fda-bill>. Accessed July 24, 2012.
23. Patient Protection and Affordable Care Act (PPACA), Pub L No. 111-148, 124 Stat 119 (2010). <http://www.gpo.gov/fdsys/pkg/PLAW-111publ148/pdf/PLAW-111publ148.pdf>. Accessed July 24, 2012.
24. Ofili E, Sproles D. Conference scene: the healthcare reform act, comparative effectiveness research and personalized medicine. *Per Med*. 2011;8(2):133-135.
25. Zaorsky N, Showalter T. How will comparative effectiveness research influence clinical decision making? *Med Forum*. 2012;13:22.
<http://jdc.jefferson.edu/tmf/vol13/iss1/22>. Accessed July 24, 2012.
26. Conko G, Miller HI. ObamaCare threatens personalized medicine. *Forbes*.
<http://www.forbes.com/2009/12/21/health-care-reform-personalized-medicine-opinions-contributors-gregory-conko-henry-i-miller.html>. Accessed July 24, 2012.
27. Foley and Lardner LLP. Legal news: life sciences health care reform bill offers support for personalized medicine. April 6, 2010.
<http://www.foley.com/health-care-reform-bill-offers-support-for-personalized-medicine-04-06-2010/>. Accessed July 24, 2012.
28. Supreme Court of the United States. *Mayo Collaborative Services, DBA Mayo Laboratories, et al. v. Prometheus Laboratories, Inc.*, No. 10-1150.
<http://www.supremecourt.gov/opinions/11pdf/10-1150.pdf>. Accessed July 24, 2012.
29. Wegner HC. *Mayo v Prometheus*: implications for “composition[s] of matter.”
http://www.grayonclaims.com/storage/Wegner_Mayo_v_Prometheus_April27REV.pdf. Accessed July 24, 2012.
30. *SmartGene v Advanced Biological Laboratories*, SA No. 08 00642 (D. DC March 30, 2012). http://www.gpo.gov/fdsys/pkg/USCOURTS-dcd-1_08-cv-00642/pdf/USCOURTS-dcd-1_08-cv-00642-0.pdf. Accessed July 24, 2012.
31. *Mayo v. Prometheus*, 1304.
32. Hirshfeld AH. Memorandum: 2012 interim procedure for subject matter eligibility analysis of process claims involving laws of nature; July 3, 2012. United States Patent and Trademark Office.
http://www.uspto.gov/patents/law/exam/2012_interim_guidance.pdf. Accessed July 24, 2012.
33. Greenbaum D. New rules, different risk: the changing freedom to operate analysis for biotechnology. *North Carolina J Law Tech*. 2010;11(1):139-160.
<http://www.ncjolt.org/sites/default/files/Greenbaum%20v11%20139-160.pdf>. Accessed July 24, 2012.

34. Mushiroda T. Advancing personalized medicine: tailoring drugs to fit a patient's genetic predisposition. *RIKEN Research*. 2012;7(2). <http://www.rikenresearch.riken.jp/eng/frontline/6945>. Accessed July 24, 2012.
35. Pub L No. 97-414 (1983). <http://history.nih.gov/research/downloads/PL97-414.pdf>. Accessed July 24, 2012.
36. Friedman Y. Will personalized medicine be a driver for widespread price controls? *J Commercial Biotechnol*. 2012;18(3):3-4. <http://commercialbiotechnology.com/article/view/559/526>. Accessed July 24, 2012.
37. Genetic Information Nondiscrimination Act of 2008, Pub L No. 110-233, 122 Stat 881 (2008). <http://www.gpo.gov/fdsys/pkg/PLAW-110publ233/pdf/PLAW-110publ233.pdf>. Accessed July 24, 2012.

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