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Introduction

Ernst R. Berndt, Dana P. Goldman, and John W. Rowe

Personalized and precision medicine (PPM)—that is, the targeting of therapies according to an individual’s biological, genetic, or clinical characteristics—is rapidly gaining prominence in health care. Reliable and affordable genetic analysis is now well within the reach of many patients and providers. Personalized and precision medicine has transformed care delivery in rare disease and oncology—especially cancer, where targeted therapies have improved treatment for breast cancer (Hudis 2007) and lung cancer (Gaughan and Costa 2011). Continued progress will involve new targeted therapies, but also the development of diagnostic tests and molecular assays to stratify disease or risk (Aspinall and Hamermesh 2007).

Personalized and precision medicine has also spawned a rapidly growing industry where genetic markers of disease and treatment are searched on a larger scale. Genetic tests already exist for nearly 2,500 different conditions, with several new tests added to the market monthly (UnitedHealth 2012). UnitedHealth Group estimated spending upward of \$500 million on genetic testing for its members in 2010 and projected total US annual expenditures on genetic and molecular testing of \$5 billion that year (UnitedHealth 2012). While spending could be substantial, so could the benefits, including dimin-

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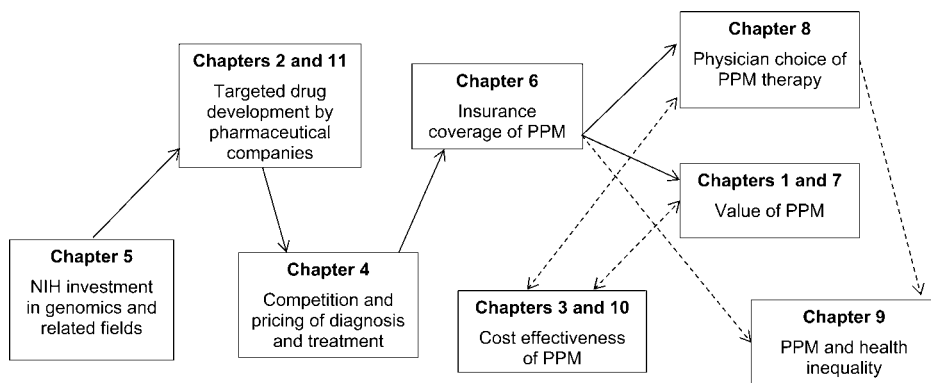


Fig. 0.1 Progress of personalized and precision medicine

ished side effects, fewer ineffective treatments, and reduced opportunity costs (Trusheim, Berndt, and Douglas 2007; Dzau et al. 2015). Personalized and precision medicine appears most valuable when the therapy being evaluated is expensive relative to alternatives, when side effects are frequent and severe (thereby making the empirical approach relatively less safe), and when delay from an alternate therapy can severely harm an individual's health (e.g., metastatic cancer, Davis et al. 2009).

It is clear that growth in PPM will depend not only on scientific and clinical progress, but also economic incentives inherent in the health care system. Economists have pointed out, for example, that cost-based reimbursement policies for diagnostic tests have limited development of tests for biomarkers (Goldman et al. 2013). Rectifying this deficiency will require a systematic approach to understanding the economics of this field (Institute of Medicine 2010), and hence our motive for producing this volume. The value of PPM arises not just because of its direct effect on a patient's health, but through the information it provides on a patient's likely response to a particular therapy. Personalized and precision medicine reduces the trial and error associated with empirical medicine, where physicians and their patients try an initial set of therapies and decide to continue or discontinue them on the basis of realized efficacy and side effects. In this manner, PPM transforms medical care from what economists call "experience goods," whose quality can only be determined through consumption, to "search goods," whose quality can be substantially (but frequently imperfectly) determined before consumption (Nelson 1970).

This volume explores various aspects of these PPM issues through an economic lens, tracing its progress from the bench to bedside, as noted in figure 0.1.¹ In the process, we explore issues related to public and private

1. We thank Jay Bhattacharya for this perspective.

investment, targeted drug development, competition and pricing, insurance coverage, physician decision-making, health inequality, and cost effectiveness.

In chapter 1, Tomas J. Philipson shows that PPM is merely a continuation of a broader trend in medicine. There is not much conceptually different in PPM compared to the historical record of diagnostic testing and prescribing medicines conditional on the diagnosis. Testing cholesterol levels to determine which patients are appropriate for statins is in principle the same type of behavior as using gene tests to determine which breast cancer patients are appropriate for a given cancer drug. He argues there is a close link between rational nonadherence in health care and the value of personalized medicine. This stems from interpreting adherence as a simple learning problem about the individual value of a therapy. Although providers recommending treatments are likely more informed about the population-wide effects of these treatments, patients experiencing a treatment are more informed about the individual specific value of treatment. Nonadherence is thus inherently a dynamic demand behavior that requires an explanation of why people initiate but then discontinue therapy. Learning about treatment value provides one natural explanation. Personalized and precision medicine, in this view, is best interpreted as valuable technological change aimed at reducing such inefficiencies by reducing consumption for nonresponders and raising consumption for responders. This also has implications for the pricing of treatment and diagnostics, and the potential gains from bundling.

In chapter 2, Manuel Hermosilla and Jorge Lemus investigate the challenges of translating basic science to therapeutic innovation. In 2003, much optimism surrounded the completion of the Human Genome Project. Since then, progress has been slow. Hermosilla and Lemus focus on knowledge stemming from a leading type of genetic epidemiological science, the genome-wide association studies, and the ten years that followed the Human Genome Project. By constructing a measure of biological complexity—drawing on insights from networks—they show that for less complex diseases there is a strong and positive association between cumulative knowledge and the number of new therapies that enter the drug-development process. This association weakens as complexity increases, becoming statistically insignificant at the extreme. It appears that complexity mediates the relationship between discovery and therapeutic innovation.

In chapter 3, John A. Graves, Zilu Zhou, Shawn Garbett, and Josh F. Peterson consider the externalities of genetic testing for a particular disease. Their focus is pharmacogenomics, or the application of genetic testing to guide drug selection or dosing. With reduced costs of sequencing and improvements in clinical information systems, modern electronic health records can store genotypic data and return actionable drug-gene information through decision aides at the point of prescribing. Existing research on the value of pharmacogenomics has focused primarily on the short-term cost

effectiveness of single-gene tests—an approach that ignores the potential lifetime value of multiplexed genetic-testing strategies. Compared with single-gene testing, these strategies—which include whole genome sequencing, whole exome sequencing, and multiplexed genetic panel testing—facilitate the acquisition of wide swaths of genetic information all at once. Thus, a drug-gene pair for which single-gene testing is found to be cost ineffective could potentially improve overall value when integrated within a broader multiplexed testing strategy—assuming the information can be acted upon in a clinically relevant manner. They find that multiplexed genetic testing is not cost effective at the lower end of commonly used societal willingness-to-pay thresholds (e.g., \$50,000 per quality-adjusted life year [QALY]). However, at slightly higher thresholds (\$118,000/QALY or greater) a preemptive multiplexed testing strategy is optimal if the pharmacogenomic information is regularly utilized over a long time horizon. To the extent that physicians are no more likely to utilize genetic testing information that was obtained upstream as they are to order a new genetic test, then a serial single-gene testing strategy is preferred.

In chapter 4, Ernst R. Berndt and Mark R. Trusheim demonstrate how game theory can be used to frame the trade-offs inherent in the targeted treatment model. Personalized and precision medicine fragments the treatment populations, generating smaller markets that will attract only limited entry. The result is a series of “niche markets” where differentiated products compete with each manufacturer possessing market power. Economic models of behavior—including the prisoners’ dilemma and Bertrand competition—can help explain how drug developers set the cut-off value for companion diagnostics to define the precision medicine market niches and their payoffs. Precision medicine game situations may also involve payers and patients who attempt to change the rules of the game to their advantage or whose induced behaviors alter rewards to developers. They hypothesize that certain precision medicine areas such as inflammatory diseases are becoming complex simultaneous multigames in which distinct precision medicine niches compete. Those players that learn the most rapidly and apply their knowledge the most asymmetrically will be advantaged in this ongoing information race.

In chapter 5, Amitabh Chandra, Craig Garthwaite, and Ariel Dora Stern describe the drug-development pipeline for PPM over the past two decades for cancer and other diseases. They summarize the role of the National Institutes of Health (NIH) in supporting the existing pipeline of precision medicines by asking what share of pipeline precision medicines rely on research supported by NIH grants. They also consider the types of firms pursuing research and development (R&D) and how PPM R&D activities have evolved over recent years.

In chapter 6, Mark V. Pauly considers how we should think about coverage for PPM. It may well be efficient to have some cost sharing to discourage low-

value uses of testing and treatment, but such potentially improved incentives trade off against less protection from financial risk. The economic theory of optimal insurance coverage shows how to characterize the ideal trade-off in simple cases, but what is ideal in this more complex case? He outlines some theoretical models of the ideal role of insurance in such settings with genetic testing and a specific treatment whose effectiveness is predicted by the test. Coverage of diagnostic tests is of particular salience because some testing is still experimental, some health plans do not cover purely diagnostic tests at all, and many insurance deductibles (including the most popular plans on exchanges) will leave tests uncovered until the deductible is exceeded. The pricing of tests, the alternatives to testing, and the effect of testing on the pricing of treatment all affect demand and optimal coverage. They also affect social welfare. Any financial gains from PPM—due to avoidance of futile therapy—may overstate the benefit to society since the avoided price is well above the value of the resources saved. Pricing of drugs above marginal cost can induce overuse of diagnostic tests even for treatments with minimal side effects, while overpricing of proprietary genetic tests can lead to underuse.

In chapter 7, Kristopher J. Hult demonstrates how PPM can help improve efficacy in a world where patient response is heterogeneous. As noted earlier, PPM increases the health benefit of existing treatments by better matching patients to treatments and by improving a patient's understanding of the risk of serious side effects. He finds that the impact of personalized medicine depends on the number of treatments, the correlation between treatment effects, and the amount of noise in a patient's individual treatment effect signal. For multiple sclerosis, PPM has the potential to increase the health impact of existing treatments by roughly 50 percent by informing patients of their individual treatment effect and risk of serious side effects.

In chapter 8, David H. Howard, Jason Hockenberry, and Guy David ask whether the introduction of an imperfect test will increase treatment rates due to induced demand. They study physicians' choice between conventional radiotherapy and intensity-modulated radiation therapy (IMRT) for breast cancer. Intensity-modulated radiation therapy is a costly form of radiotherapy and is unnecessary for most patients. Use of IMRT is 18 percentage points higher among patients treated in freestanding clinics, where physician-owners share in the lucrative fees generated by IMRT. Patients with left-side tumors, who are more likely to benefit from IMRT, are more likely to receive it regardless of treatment setting. However, patients with right-side tumors treated in freestanding clinics are more likely to receive IMRT than patients with left-side tumors treated in hospital-based clinics. These results highlight the challenge of optimizing the use of imperfect information regarding patients' ability to benefit from a treatment in an environment where physicians face incentives to provide it.

In chapter 9, Jui-fen Rachel Lu, Karen Eggleston, and Joseph Tung-Chieh Chang consider whether the high costs of PPM could exacerbate income-

related health disparities, especially in resource-poor settings. They study treatment of HER2-positive breast cancer in Taiwan between 2004 and 2015 and find that lower-income patients are more likely to be diagnosed with later stages of cancer, and this pattern renders coverage of target therapy pro-poor even before full coverage of the diagnostic tests. Moreover, the expansion of national health insurance coverage—including the fluorescence in situ hybridization (FISH) diagnostic test and trastuzumab for early stage breast cancer—strengthened the pro-poor distribution of genetic testing and target treatment, albeit only marginally. Taiwan's experience suggests that PPM can actually disproportionately benefit the poor, even in a national health insurance scheme, although other disparities may persist.

In chapter 10, Rebecca A. Pulk, Jove Graham, Frank R. Lichtenberg, Daniel Maeng, Marc S. Williams, and Eric Wright tell a cautionary tale about using pharmacogenomic data for outcomes research. They examine a large cohort of Geisinger patients with linked clinical and genetic information to describe the potential value of pharmacogenomic information for the prevention and treatment of cardiovascular disease. They show that genetic variations of two genes affecting the pharmacokinetics of commonly used cardiovascular medications are associated with higher cardiovascular risk and/or death. In theory, these events are potentially avoidable with pharmacogenomic testing and provide additional evidence support for routine pharmacogenomic testing in a generalized population. In practice, the results are sensitive to specifications and suggest some lessons for outcomes research with pharmacogenetic data.

In chapter 11, Philippe Gorry and Diego Useche consider how orphan drug (OD) legislation has impacted financing of innovation to treat rare diseases. They test whether OD designations (ODD) granted by the Food and Drug Administration (FDA) are relevant signals in attracting entrepreneurial finance and increasing the amount. They find that the signaling power of ODD is positively and statistically significant for initial public offering (IPO) investors in stock markets: an ODD prior to an IPO increases IPO proceeds by about 38 percent. The evidence also suggests ODDs are stronger than patent applications in attracting IPO investors and other valuable resources before companies go public.

Taken together, these chapters provide a broad view of the promise of PPM. The benefits extend beyond targeting therapies for patients who are already sick. It also includes the ability to identify healthy individuals at elevated risk of disease, enabling preventive measures to be targeted toward those who could benefit most, but perhaps at substantial additional cost. It is also clear that PPM may upend traditional models of health insurance, reimbursement, and regulation. While the volume does not provide all the answers, it does show the importance of viewing PPM through an economic lens.

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