Proposal for NBER Project on Economic Dimensions of Personalized and Precision Medicine

"The Competitive Dynamics of Personalized and Precision Medicine: Insights from Game Theory"

Authors: Ernst R. Berndt, MIT and NBER

Mark R. Trusheim, MIT and Co-Bio Consulting

Over the last decade advances in our understanding of the human genome and biology more generally have facilitated the development and commercialization of therapies that, when combined with some form of biomarker diagnostic, are able to identify subpopulations of patients that are likely to respond differentially – either positively or negatively – to the therapy. This combination of biomarker and therapy has been given a variety of names – e.g., personalized medicine, precision medicine, tailored medicine, and stratified medicine. Although some truly personalized medicines have been launched, such as Provenge that extracts and harvests human tissues, exposes them to external treatment, and then infuses or injects them back into the patient[1], a more common approach involves probabilistically identifying subpopulations of patients who are likely to respond to the therapy with differential positive outcomes, or differentially negatively with adverse reactions. Because such a procedure involves identification of sub-strata of populations, we have dubbed this phenomenon stratified medicine ([1],[9]). Others, such as researchers at Eli Lilly and Company, have called attention to the fact that the combination of a companion diagnostic along with a therapeutic typically does not lead to mechanical, automaton-like decision making, but still involves physician choice and art, and therefore have called it tailored medicine. Policy advocates for more funding of the underlying scientific research have apparently chosen instead to emphasize the science, and have accordingly called it precision medicine.

Regardless of what one calls it, the combination of a therapy and a companion diagnostic relies critically on the ability *ex ante* to distinguish responders from non-responders to treatment. In practice, no diagnostic can perfectly identify the differential responders; the specificity and sensitivity performance of diagnostic tests are typically considerably less than 100%, yielding both false positives and false negatives.

After a brief review of the existing literature, in the first part of our proposed paper we will address the question, "What if precision medicine is not precise?" In practice, a cut-off value of the diagnostic test (typically yielding a continuous test score rather than a binomial zero or one value) must be chosen that balances including more of those patients who respond with including some of those who do not. Our previous work ([2], [3], [5], [6]) suggests that this choice involves more than scientific criteria since it also invokes ethical concerns of exposing patients unlikely to respond to risk of harm along with knowingly denying access to patients

[1] We are aware that while Dendreon launched Provenge to much public acclaim, it has been a commercial failure for Dendreon, who later in 2014 were acquired by Valeant. We do not know the current list price for Provenge.

who have a non-zero statistical chance of responding. The cut-off threshold decision also involves the economic interests of therapy and companion diagnostic innovators seeking to maximize their profits through premium pricing ([1], [8]), and the competing economic interests of payers/insurers attempting to reduce insurance premium costs and optimize the health impact per dollar spent. These economic considerations become more complex under dynamic competition among drug innovators, both during the initial race to be first and best in a novel drug class, and subsequently as new competitors enter, or are anticipated to enter the market for a drug class or therapeutic area.

The dynamics we propose to consider involve opportunities for prisoners' dilemma and similar game situations to emerge.[2] Game theory can rationalize seemingly paradoxical behavior among a small number of firms such as drug developers successively actively choosing a high companion diagnostic cut-off value that dramatically reduces the potential patient pool (and likely denies access to some potential responders) but which also results in a greater drug efficacy reported response rate leading to superiority labeling claims compared to incumbent competitors and potentially higher prices and mixed impacts on market shares. While none of the drug developers prefers this outcome, it is the best each can do given the behavior of their competitors, i.e. it is a Nash equilibrium.

In our proposed research, we will develop more completely these economic outcomes that may occur when stratified medicine is less than perfectly precise. We will characterize the choices created by stratified medicine for both developers and payers, the challenges faced by regulators, and the multi-round and dynamic game effects as the game structure evolves over time both naturally and due to the choices made by the players in the initial rounds. Consistent with the existing game theory literature in economics, we will also examine how a prisoners' dilemma-like Nash equilibrium can be disrupted such as by a change in the rules of the game. For example, suppose a savvy payer leveraged a lower-priced, low cut-off drug/companion diagnostic combination against a high priced drug by substituting/switching the low price drug while still using the high price cut-off value. In such a case, both the low- and high-priced drug developers will be harmed, and the payers/insurers will be able to capture the majority of the rents.

Emerging movements in patient advocacy and clinical trial designs may also disrupt the historic stratified medicine game. Platform trials and clinical trial transparency efforts both serve to disrupt the game through standardization of protocols to increase drug comparability and so improve the payer bargaining position ([11] – [15]). 'Real world data' regarding patient treatments and outcomes gathered through formal patient registries or more informal social media reporting may similarly provide drug effectiveness evidence that could disrupt later stage game iterations ([16], [17], [18]). We will examine whether such information eliminates the

[2] For an introductory overview of game theory in economics, see the textbook treatment by Pindyck and Rubinfeld [10].

asymmetries that drive the current game and so resolves it in the payer's favor or simply changes the game.

Payers could also act more directly on their own behalf to create information for their advantage in the current game or to change the game. Payers could better mine the big data sets available to them, require drug developers to provide more information, or invest in collecting and analyzing more complete, comparable real world evidence themselves or in collaboration with patients, providers and researchers ([19]). Beyond simple data collection, payers could support the development of predictive diagnostics to independently stratify treatments. They could do this indirectly through higher reimbursement for diagnostics that aid them or directly by commissioning the clinical studies or even diagnostic research, as they did historically with mammograms ([5]).

Finally, we will examine how the game might change if payers behaved more like buyers who set explicit performance criteria and solicited bids or held auctions for products meeting those criteria. Developed country government payers routinely do this for military and space products they acquire, but rarely for the health products they reimburse. This approach has, however proven effective for vaccines in the US; and in developing countries through GAVI and advance market commitments ([20], [21]).

In terms of methodology, we envisage a chapter that lays out various possible scenarios of outcomes with dynamic competition among developers and rules of the game strongly influenced by payers/insurers and regulators. Although we plan to illustrate using some historical examples, we do not envisage employing either a highly formalized theoretical modeling effort nor a detailed econometric and data-intensive analysis.

REFERENCES

1. Trusheim, Mark R., Ernst R. Berndt and Frank L. Douglas, "Stratified Medicine: Strategic and Economic Implications of Combining Drugs and Clinical Biomarkers", Nature Reviews: Drug Discovery, April 2007, 6(4):287-293.

2. Trusheim, Mark R., Breon Burgess, Sean Xinghua Hu, Theresa Long, Steven D. Averbuch, Aiden A. Flynn, Alfons Lieftucht, Abhijit Mazumder, Judy Milloy, Peter Shaw, David Swank, Jian Wang, Ernst R. Berndt, Federico Goodsaid and Michael C. Palmer, "Quantifying Factors for the Success of Stratified Medicine," Nature Reviews: Drug Discovery 10:817-33, November 2011.

3. Trusheim, Mark R. and Ernst R. Berndt, "Economic Challenges and Possible Policy Actions to Advance Stratified Medicine", Personalized Medicine 9(4):413-27, 2012.

4. Trusheim, Mark R. and Ernst R. Berndt, "The Segmentation of Therapeutic

Populations in Oncology", Health Management, Policy and Innovation, 1(1):19-34, October 2012.

5. Trusheim, Mark R., and Ernst R. Berndt, "The clinical benefits, ethics, and economics of stratified medicine and companion diagnostics", *Drug Discovery Today* 20(12): 1439-1450, December 2015.

6. Trusheim, Mark R., M.J. Finley Austin, Carsten Rausch and Ernst R. Berndt, "Uncertain prognosis for high-quality diagnostics: clinical challenges, economic barriers and needed reforms", Pharmacogenomics (2013) 14(3):325-334.

7. Baird, Lynn G., Mark R. Trusheim, Hans-Georg Eichler, Ernst R. Berndt and Gigi M. Hirsch, "Comparison of Stakeholder Metrics for Traditional and Adaptive Development and Licensing Approaches to Drug Development," Therapeutic Innovation & Regulatory Science, 47(4):474-483, July 2013.

8. Howard, David H., Peter B. Bach, Ernst R. Berndt and Rena M. Conti, "Pricing in the Market for Anticancer Drugs", *Journal of Economic Perspectives,* 29(1):139-162, Winter 2015.

9. Hu, Sean X., Murray L. Aitken, Arnold M. Epstein, Mark R. Trusheim and Ernst R. Berndt, "Defining and Quantifying the Use of Personalized Medicines", Nature Reviews: Drug Discovery, online version published 29 November 2013, http://www.nature.com/nrd/journal/v12/n12/full/nrd4177.html?WT.ec_id=NRD-201312. Hard copy version published December 2013.

10. Robert S. Pindyck and Daniel L. Rubinfeld, "Game Theory and Competitive Strategy", ch. 13 in Pindyck and Rubinfeld, *Microeconomics*, Eighth Edition, New York: Pearson Education, Inc., publishing as Prentice Hall, 2013, 487-528.

11. Bedard, Philippe L., Aaron R. Hansen, Mark J. Ratain, and Lillian L. Siu. "Tumour heterogeneity in the clinic." *Nature* 2013 501(7467): 355-364.

12. Eichler, Hans-Georg, Frank Pétavy, Francesco Pignatti, and Guido Rasi. "Access to patient-level trial data—a boon to drug developers." *New England Journal of Medicine* 2013 369(17): 1577-1579.

13. Nisen, Perry, and Frank Rockhold. "Access to patient-level data from GlaxoSmithKline clinical trials." *New England Journal of Medicine* 2013 369(5): 475-478.

14. Outterson, Kevin. "Clinical Trial Transparency—Antidote to Weaker Off-Label-Promotion Rules?." *New England Journal of Medicine* 2014 37(1): 1-3.

15. Strom, Brian L., Marc Buyse, John Hughes, and Bartha M. Knoppers. "Data sharing, year 1—access to data from industry-sponsored clinical trials." *New England Journal of Medicine* 2014 371(22): 2052-2054.

16. Gliklich, Richard E., Nancy A. Dreyer, and Michelle B. Leavy, eds. *Registries for evaluating patient outcomes: a user's guide*. No. 13. Washington DC: U.S. Government Printing Office, 2014.

17. Garrison, Louis P., Adrian Towse, Andrew Briggs, Gerard de Pouvourville, Jens Grueger, Penny E. Mohr, JL Hans Severens, Paolo Siviero, and Miguel Sleeper. "Performance-based risk-sharing arrangements—good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force." *Value in Health* 2013 16(5): 703-719.

18. Lavallee, Danielle C., Kate E. Chenok, Rebecca M. Love, Carolyn Petersen, Erin Holve, Courtney D. Segal, and Patricia D. Franklin. "Incorporating Patient-Reported Outcomes Into Health Care To Engage Patients And Enhance Care." *Health Affairs* 2016 35(4): 575-582.

19. Brennan, Niall, Allison Oelschlaeger, Christine Cox, and Marilyn Tavenner. "Leveraging the big-data revolution: CMS is expanding capabilities to spur health system transformation." *Health Affairs* 2014 33(7): 1195-1202.

20. Berndt, Ernst R., Denoncourt, Rena N., Warner*, U.S. Market for Vaccines: Characteristics, Case Studies and Controversies*, American Enterprise Institute for Public Policy Research, Washington DC. 2009.

21. Berndt, Ernst R., Rachel Glennerster, Michael R. Kremer, Jean Lee, Ruth Levine, Georg Weizsacker, and Heidi Williams. "Advance market commitments for vaccines against neglected diseases: estimating costs and effectiveness." *Health Economics* 2007 16 (5): 491-512.