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# The value proposition of molecular medicine.

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Individualized patient management is rapidly evolving, driven by the emergence of insights in discovery, development, regulatory, and comparative effectiveness sciences.<sup>1-4</sup> The pace of discovery is accelerating, enabled by platforms, including “omics”, stem cell biology, network medicine, and medical and biological informatics that provide unanticipated insights into pathophysiology.<sup>2, 4-6</sup> The integration of these paradigms has established a model for identifying the mechanistic underpinnings of disease, offering novel opportunities to individualize diagnostics that shape how modern therapies are deployed, including markers of disease prognosis, clinical predictors of therapeutic responses, and molecular determinants that optimize clinical management.<sup>7-</sup><sup>10</sup> Importantly, deconvolution of physiological circuits is producing a new vanguard of molecular therapies that target corrupted pathways at the center of disease pathogenesis, individualizing patient care algorithms that optimize benefits and minimize adverse effects.<sup>7-9, 11, 12</sup>

These technological achievements and innovations come at a price. In the United States, the market for biologic therapies will increase by 6.5% per year to >\$100 billion by 2015.<sup>13</sup> At that time, 8 of the top 10 drugs by cost will be biologics, and the current rate of growth predicts this class of agents will comprise 40% of drug spending by 2020.<sup>13</sup> Nowhere is this trend more evident than in oncology, in which discovery science has produced insights into the pathophysiology underlying neoplasia, yielding new diagnostic and therapeutic targets.<sup>14</sup> These discoveries have been translated into an array of patient management options molecularly targeted to corrupted circuits in tumorigenesis. However, the cost of these molecular modalities can approach \$100,000 annually.<sup>15</sup> They materially contribute to the doubling of the cost of treating cancer patients worldwide.<sup>15</sup> Moreover, the escalating price of molecular diagnostics and therapeutics is poised to be one dominant driver of the cost curve describing the rate of increase in healthcare expenditures in cancer care.<sup>15</sup> In that context, the aging of the population, associated with an increase in cancer incidence and prevalence, and the

cost of patient management will produce a 600% increase in the cost of cancer care in the 30 year period ending in 2020, reaching \$157 billion in the U.S.<sup>15</sup> In an environment of economic austerity demanding social responsibility, innovation in the form of molecular medicine must both improve the quality of patients' lives and the societal value proposition of healthcare management, each in an evidence-based affordable fashion. Absence of either element risks creating a healthcare system characterized by tiered access to innovation, limited only to a small group of the most economically advantaged, with rationing of the products of molecular medicine to other citizens. Technology and innovation in molecular medicine have created an imperative that patient management must be socially responsible, cost effective, and sustainable.<sup>15</sup>

While the revolution in technology is transforming diagnostic and therapeutic approaches for individual patients, the impact of this innovation on the societal healthcare value proposition is more ambiguous. This can best be appreciated by considering four recently approved molecularly targeted agents, in the context of their efficacy and cost. Sipuleucel-T (Provenge; Dendreon Corporation) is a therapeutic vaccine for metastatic hormone resistant prostate cancer. Dendritic cells isolated from patients are incubated with a fusion protein consisting of the prostatic acid phosphatase tumor antigen and granulocyte-macrophage colony stimulating factor ex vivo, followed by their re-infusion into patients.<sup>16</sup> A complete Sipuleucel-T treatment repeats three courses over one month. Regulatory approval of Sipuleucel-T was based on the IMPACT trial, which enrolled 512 patients with asymptomatic or minimally symptomatic metastatic hormone resistant prostate cancer. Median survival for patients treated with Sipuleucel-T was improved by ~4 months, to 25.8 months compared to 21.7 months for placebo-treated patients, reflecting a statistically significant improvement in overall survival (P=0.032).<sup>16</sup> A course of Sipuleucel-T treatment costs ~\$100,000.<sup>15</sup>

Abiraterone (Zytiga; Johnson & Johnson) also is a new molecularly targeted agent for hormone-resistant prostate cancer. Abiraterone inhibits CYP17A1, an enzyme

expressed in testicular, adrenal, and prostatic tumor tissues. CYP17 catalyzes two sequential reactions in the biosynthesis of androgens, including the conversion of pregnenolone and progesterone to their 17- $\alpha$ -hydroxy derivatives by its 17  $\alpha$ -hydroxylase activity, and the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by its C17,20 lyase activity.<sup>17</sup> DHEA and androstenedione are androgens and precursors of testosterone. Inhibition of CYP17 activity by abiraterone decreases circulating levels of testosterone.<sup>18</sup> In Phase III trials, it extended median survival almost 4 months, to 14.8 months compared to 11.2 months in placebo-treated, supporting its regulatory approval following an expedited six-month review.<sup>19</sup> Treatment costs for abiraterone are ~\$5,000 each month.<sup>19</sup>

Vemurafenib (Zelboraf; Daiichi Sankyo and Hoffmann–La Roche) is a new targeted agent for the treatment of late stage melanoma.<sup>20</sup> Vemurafenib induces programmed cell death in melanoma cell lines by inhibiting B-Raf common V600E mutation.<sup>21</sup> Indeed, vemurafenib only works in melanoma patients whose tumor carries the V600E BRAF mutation, in which the amino acid at position 600 on the B-Raf protein is glutamate, rather than the normal valine. Of patients with melanoma, ~60% carry this mutation. In striking contrast, melanoma cells without this mutation are not inhibited by vemurafenib, and the drug paradoxically stimulates normal BRAF and may promote tumor growth in such cases.<sup>22</sup> Vemurafenib was approved for the treatment of unresectable or metastatic BRAF V600E-positive melanoma, based on a phase III study of 675 patients who were randomized to either vemurafenib or dacarbazine.<sup>23</sup> Progression free survival was improved nearly 4 months, from 1.6 months in dacarbazine-treated patients to 5.3 months in those treated with vemurafenib, and objective response rate (48% vs. 4%) were all significantly better on the vemurafenib arm.<sup>19</sup> Treatment costs for vemurafenib are ~\$10,000 each month.<sup>19</sup>

Ipilimumab (Yervoy; Bristol-Myers Squibb) is a fully human monoclonal antibody that also has been approved for late stage melanoma. Ipilimumab targets cytotoxic T-

lymphocyte-associated antigen 4 (CTLA-4), which is a negative regulator of T cell-dependent immune responses.<sup>19</sup> Ipilimumab blocks CTLA-4, enhancing T-cell mediated anti-tumor activity.<sup>19</sup> Approval of ipilimumab was based on a phase III trial of 676 patients with unresectable or metastatic disease demonstrating an improvement of survival of ~4 months, from 6.4 months for control-treated patients, to 10 months for those treated with ipilimumab.<sup>24</sup> Treatment costs for ipilimumab are ~\$30,000 per dose.<sup>19</sup>

These recently approved targeted agents highlight a common theme of molecular therapies emanating from the new biology: modest clinical improvement, here measured in months of survival, with relatively high costs, approaching ~\$100,000. Modest benefit for high cost establishes an ambiguous value proposition for these innovations in the context of individual patients, the healthcare system and society. For patients and their families, the opportunity to gain months of survival can be a miracle for those with a terminal disease facing imminent death, with a value that is beyond quantification. This philosophy aligns closely with those who consider decisions about individual resource allocation to be the strict province of patients and their families, rather than governments and societies. Moreover, in the U.S., this philosophy has been facilitated by policies surrounding healthcare financing, which consider safety and efficacy, but not the cost-benefit ratio. This system creates a moral hazard in which consumers (patients) insulated from the financial burden of the product are incented to utilize marginally effective resources.<sup>15</sup>

The value proposition of molecular innovations for individual patients contrasts with that for healthcare systems and societies. The over-arching objective of societal policies generally is to achieve the greatest good for the greatest number of citizens. With respect to healthcare policies, this translates into balancing access, quality, equity and cost.<sup>15</sup> For example, the UK guarantees access to healthcare to all citizens, but the availability of specific interventions in the marketplace is defined by formulaic

quantification of costs and benefits. At the other end of the spectrum, the U.S. guarantees the availability in the marketplace of all interventions that are safe and effective, regardless of cost, but patient access to those interventions is not universal. These differences in approaches to healthcare finance underscore the imperative that policies concerning the value of innovation are ultimately shaped by societal concepts of the value of health and specific clinical outcomes.<sup>15</sup> Regardless of the healthcare model, each operates in an environment of limited resources, requiring cost-benefit analyses of the value of innovation and the anticipated improvements in health. Importantly, they must consider an inherent choice required by constrained resources: whether those improvements are worth the trade-off in healthcare benefits lost by other modalities displaced by the added cost of innovation.<sup>15</sup>

These observations highlight the imminent challenge of deploying the advancing wave of innovation in molecularly medicine to manage patients. They underscore the importance of establishing the evidence base for the value of new therapeutics by not only qualifying their ability to improve patient outcomes, but also quantifying that improvement (how much) and the likelihood of its achievement.<sup>1, 15</sup> They recognize that the value of these improvements in clinical outcomes is not a universal construct with global applicability but, rather, society-specific, in part, defined by relative economies and models of healthcare finance. They consider whether the deployment of these modalities improves the overall value proposition of the healthcare system. Indeed, molecularly targeted agents that prevent recurrent cancer relieve the economic burden of treating future advanced disease. Moreover, they consider the value of molecular therapies in the context of whether their quantitative outcomes are worth the healthcare benefits lost by economic displacement of other healthcare initiatives.

We are in the midst of a revolution in disease management established by emerging innovations in platform technologies, where clinical outcomes are resolved by targeted molecular diagnostics and therapeutics. This evolving paradigm has already



yielded products that have advanced into the healthcare marketplace. In the context of worldwide economic realities and constrained healthcare resources, it is essential to establish the value proposition of targeted diagnostics and therapeutics, to ensure their benefits are maximized for patients, populations and societies.<sup>3</sup>

## References

1. Honig PK. Comparative effectiveness: the fourth hurdle in drug development and a role for clinical pharmacology. *Clin Pharmacol Ther.* 2011;89:151-6.
2. Terzic A, Waldman SA. Translational medicine: path to personalized and public health. *Biomark Med.* 2010;4:787-90.
3. Waldman SA, Hohl RJ, Kearns GL, Swan SJ, Terzic A. Clinical pharmacology as a foundation for translational science. *Clin Pharmacol Ther.* 2011;90:10-3.
4. Waldman SA, Terzic A. Patient-centric clinical pharmacology advances the path to personalized medicine. *Biomark Med.* 2011;5:697-700.
5. Nelson TJ, Terzic A. Induced pluripotent stem cells: an emerging theranostics platform. *Clin Pharmacol Ther.* 2011;89:648-50.
6. Roden DM, Tyndale RF. Pharmacogenomics at the tipping point: challenges and opportunities. *Clin Pharmacol Ther.* 2011;89:323-7.
7. Waldman SA, Kraft WK, Nelson TJ, Terzic A. Clinical pharmacology: a paradigm for individualized medicine. *Biomark Med.* 2009;3:679-84.
8. Waldman SA, Kraft WK, Nelson TJ, Terzic A. Experimental therapeutics: a paradigm for personalized medicine. *Clin Transl Sci.* 2009;2:436-8.
9. Waldman SA, Terzic A. Clinical and translational sciences: at the intersection of molecular and individualized medicine. *Clin Transl Sci.* 2008;1:6-8.
10. Waldman SA, Terzic A. Translational medicine in the era of health care reform. *Clin Transl Sci.* 2009;2:96-7.
11. Waldman SA, Terzic A. Molecular therapy drives patient-centric health care paradigms. *Clin Transl Sci.* 2010;3:170-1.

12. Waldman SA, Terzic A. The roadmap to personalized medicine. *Clin Transl Sci.* 2008;1:93.
13. Adams K. The business of biologics. *Biotechnology Healthcare.* 2011;8:1.
14. Zahedi P, De Souza R, Piquette-Miller M. Optimizing cancer care: is the future bright? *Clin Pharmacol Ther.* 2011;90:347-50.
15. Sullivan R, Peppercorn J, Sikora K, Zalcborg J, Meropol NJ, Amir E, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol.* 2011;12:933-80.
16. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010;363:411-22.
17. O'Donnell A, Judson I, Dowsett M, Raynaud F, Dearnaley D, Mason M, et al. Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. *Br J Cancer.* 2004;90:2317-25.
18. Attard G, Reid AH, Yap TA, Raynaud F, Dowsett M, Settattree S, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol.* 2008;26:4563-71.
19. Holstein S, Hohl R. 2011 Therapeutic additions and possible deletions in oncology. *Clinical Pharmacology and Therapeutics.* 2012;In press.
20. Bollag G, Hirth P, Tsai J, Zhang J, Ibrahim PN, Cho H, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. *Nature.* 2010;467:596-9.

21. Sala E, Mologni L, Truffa S, Gaetano C, Bollag GE, Gambacorti-Passerini C. BRAF silencing by short hairpin RNA or chemical blockade by PLX4032 leads to different responses in melanoma and thyroid carcinoma cells. *Mol Cancer Res.* 2008;6:751-9.
22. Hatzivassiliou G, Song K, Yen I, Brandhuber BJ, Anderson DJ, Alvarado R, et al. RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature.* 2010;464:431-5.
23. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *New Engl J Med.* 2011;364:2507-16.
24. Robert NJ, Dieras V, Glaspy J, Brufsky AM, Bondarenko I, Lipatov ON, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol.* 2011;29:1252-60.