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Cost-Consciousness Raising: Adding Value To Cancer Drug Development

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The revolution in cancer treatment driven by the molecular insights of genomics has moved decisively out of the lab and onto the market, but that R&D success is creating a new front in the age-old war on cancer: cost. The staggeringly high prices of the new generation of effective cancer drugs is spurring initiatives to add new ways to identify and measure the clinical value of new treatments to drug development, beyond the safety and efficacy standards FDA is charged to uphold.

In the last month, two major oncology associations – the American Society of Clinical Oncology and the American Association of Cancer Research – published reports highlighting the tension between the "extraordinary opportunities" offered by scientific advances and the "environment of intense pressure to contain rising health care costs," in the words of the group Turning the Tide Against Cancer.

"More frightening is the prospect that emerging targeted agents – many with staggering price tags – will need to be used in combinations in order to be effective," ASCO said.

ASCO's first "State Of Cancer Care In America" report was published by the Journal of Oncology Practice March 10, shortly after AACR's journal Clinical Cancer Research published "Turning the Tide Against Cancer Through Sustained Medical Innovation: The Pathway to Progress" in its March 1 issue.

"Assessing the comparative clinical benefit of cancer interventions … is essential to controlling costs in ways that sustain innovation," Turning the Tide Against Cancer said. Turning the Tide is an initiative sponsored by AACR, the Personalized Medicine Coalition, and Feinstein Kean Healthcare.

"Currently, traditional market forces are largely absent in pricing new cancer drugs, resulting in an artificial marketplace with few competitive pressures to limit prices," the ASCO report observed.

"Physicians must join with insurers, policymakers, pharmaceutical companies, providers and advocates to develop a more rational system for drug pricing," ASCO stated. "Solutions need to encompass pricing, insurance coverage, and evidence-based practice. … More rational pricing must be coupled with efforts to ensure that drug companies are still able to recoup their investments in high-risk, high-cost research programs in order to sustain innovation."

Cost and value of new drugs will be a challenge across the medical landscape given the concentration of novel drug development in high-cost areas like diabetes and autoimmune disease, but the problem is especially acute in oncology, where high-priced new agents are showing unprecedented efficacy, and are expected to be most effective in combination with other expensive new drugs – the so-called "stacked therapy" problem. ASCO described as "frightening" the "prospect that emerging targeted agents – many with staggering price tags – will need to be used in combinations in order to be effective."

After FDA approved combination use of **GlaxoSmithKline PLC**'s *Mekinist* and *Tafinlar* for melanoma in January, bearing a monthly price tag of over $17,000, Kantar Health executive Gordon Gochenauer predicted "a nightmare for payers" as "the accepted price of first-line therapies could reach up to $16,000 per month" (*"GSK's Mekinist/Tafinlar Combo Pushes The Price Bar" – "The Pink Sheet" DAILY, Jan. 9, 2014*).

FDA approved more than 25 new molecular and biological entities for cancer in just the past three years, with many more approvals for new indications and formulations of previously approved drugs (ASCO counted 18 cancer therapy approvals in 2013 alone). In 2014, FDA action is expected on high-profile pending agents like **Eli Lilly & Co.**'s ramucirumab, **Gilead Sciences Inc.**'s idelalisib, **Merck & Co. Inc.**'s

MK-3475, and **Novartis AG**'s ceritinib (*"Once More Unto The Breach: 2014 NME Candidates Crowd In Familiar Fields" – Pharmaceutical Approvals Monthly, February 2014*). The dominance of oncologics among the drugs awarded FDA's new "breakthrough therapy" designation holds the promise

of still more waves of innovative approvals to come (*"FDA "Breakthrough Therapy" Designations" – Pharmaceutical Approvals Monthly, March 2014*). And the greatest anticipation is for combinations with and between immunotherapies, like the checkpoint inhibitors.

Roche has acknowledged that the time has come to revise its approach to oncology pricing (*"Roche Experimenting With New Pricing Models In Oncology" – "The Pink Sheet," June 10, 2013*). The company has already grappled with the stacked biologics problem with its breast cancer drug *Perjeta* (pertuzumab), which is currently used in combination with *Herceptin* (trastuzumab) at a cost of about $11,000 a month, and is looking ahead towards combination of Perjeta with its trastuzumab-based antibody-drug conjugate *Kadcyla* (ado-trastuzumab emtansine), which would come in at around $15,700 a month.

Industry Cannot Act Alone

The cancer advocate reports are the latest products of an emerging "multi-stakeholder" approach to balancing innovation and cost containment in the oncology field. A "highly collaborative multidisciplinary ecosystem" will be needed to develop and support a continuous learning health care system in oncology, Turning the Tide said. "Policy incentives could stimulate the public-private partnerships and coalitions that are needed to create the foundations for implementation, address concerns associated with the integration of clinical research and clinical care, and facilitate data liquidity in preparation for such a system," it added.

Turning the Tide Against Cancer efforts kicked off with a June 2012 conference and discussion paper on "Sustaining Progress Against Cancer in an Era of Cost Containment" (*"Turning the Tide Against Cancer" – The RPM Report, June 2012*). The inclusion of the public affairs firm Feinstein Kean in the group's leadership underlines its consciousness-raising goal to "amplify the ongoing robust discussion and diverse perspectives brought to this issue … and to consider how to frame the research and regulatory policies necessary."

ASCO's "Value in Cancer Care Task Force" (previously the "Cost of Cancer Care Task Force") called for attention to "financial toxicity" of targeted cancer therapies when it published its second "Top 5" list of practices oncologists should avoid. At the Institute of Medicine's National Cancer Policy Summit Nov. 4 , the list's lead author, Beth Israel Deaconess Cancer Center Clinical Director Lowell Schnipper, called for development of a policy to tie drug prices to clinical value, with FDA and some third parties working to define the added value of any given therapy (*"ASCO "Top 5" List Turns Up Rhetorical Heat On Cancer Drug Prices" – The RPM Report, December 2013*).

Similar concerns about the cost/innovation tension are a theme of the association's 2014 State of Cancer Care report, which broadly examines challenges facing the oncology workforce.

Pricing and market access were also a hot topic at the annual Cancer Progress meeting in New York March 5. ASCO President Clifford Hudis (Memorial Sloan Kettering) described a new ASCO taskforce of stakeholders, including regulators, insurers, pharma, providers and academics, that will tackle the problem of defining good value in oncology; the group had its first meeting in February (*"Optimistic About Cancer Immunotherapy, Downbeat About Costs" – "The Pink Sheet," March 10, 2014*).

"A common method for assessing the relative value of cancer treatment options should drive treatment choices, insurance benefits, and research priorities," ASCO said in the State of Cancer Care report.

Start With Quality

Annual cancer care costs are estimated to rise from $104 billion in 2006 to more than $173 billion in 2020, ASCO notes, an increase "driven in part by a health care system that incentivizes the use of tests, treatments and services, some of which are unnecessary, ineffective or avoidable."

ASCO has repeatedly focused on quality improvements as a means of controlling cost, with initiatives like its Quality Oncology Practice Initiative (QOPI). The quality assessment and improvement program uses clinical guidelines, published studies and collective expert consensus to communicate emerging science and new clinical recommendations to participants; frequent updates ensure there is no significant research-to-practice delay, ASCO says. It reports noticeable improvements in areas like appropriate prescribing of anti-nausea medication, appropriate testing for genetic mutation and end-of-life care – all elements that contribute to the high cost of cancer care.

ASCO is not alone in its focus on quality improvement. The Institute of Medicine issued a report in September 2013 on "Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis," with recommendations focused on translating evidence into clinical practice, improving the performance of health care providers and measuring quality (*"Geriatric Exclusivity For Cancer Drugs Could Drive Needed Research – IoM Report" – "The Pink Sheet" DAILY, Sep. 13, 2013*).

The IoM panel echoed ASCO's calls for "evidence-based information about cancer care practices that are unnecessary or where the harm may outweigh the benefits."

But practice standards may just be the low-hanging fruit. ASCO asserts the rising costs of cancer care are also driven by the cost of new cancer therapies: "With newly approved drugs costing as much as $100,000 for a course of treatment, combination therapies are already becoming cost-prohibitive for many patients, even those with insurance," the report states.

The reality, acknowledged by both cancer research advocacy groups and the IoM, is that more attention should be on drug costs and payment reform.

Payment Reform Needed

The lack of competitive pressure on pricing has created "a rapid, unrelenting march toward drug costs that are unsustainable for the system," ASCO noted. It concludes that along with evidence-based practice, solutions need to include pricing and insurance coverage.

Payment reform is needed to shift practices from the traditional fee-for-service model, and the Center for Innovation within CMS is "poised to test various payment reform proposals." Some practices are already experimenting with reforms like prospective payment arrangements, shared savings programs, patient-centered medical homes and more efficient practice workflow, but "the overwhelming majority of practices (79%) ... remain in a fee-for-service environment," ASCO said.

IoM's recommendations on enhancing accessible, affordable cancer care task CMS and other payers with developing payment policies that reflect the evidence-based findings of professional societies, and with designing and evaluating new payment models that incentivize care based on the best available evidence and aligns with patient needs, values and preferences.

"If evaluations of specific payment models demonstrate increased quality and affordability, the Centers for Medicare and Medicaid Services and other payers should rapidly transition from traditional fee-for-service reimbursements to new payment models," the IoM concludes.

Linking Research And Care

Rapid learning health care systems are also being viewed as a solution. The promise of such systems is "to link research and care seamlessly, allowing for the aggregation and analysis of evidence-based knowledge and its subsequent application to patient care ... and for monitoring the evolution of value of a particular drug or diagnostic in the real-world setting over time," Turning the Tide said. "A continuous learning system will help reduce the cost and accelerate the process of drug development," the report predicts.

The group stressed the "current limitations in how we define value" as a hurdle to the development of continuous learning systems. "Stable point-in-time definitions of value may be unworkable in the new, rapidly advancing era of personalized cancer care," the Turning the Tide report stated.

"Oncology clinical trials, which are carefully designed to meet the FDA's rigorous premarket standards, are necessarily only a starting point for understanding value," the group said. "A more complete picture of clinical effectiveness and patient value does not emerge until the treatment enters real-world clinical use." Increasing use of electronic medical records and user-friendly digital tools makes it more feasible to track patients throughout their lifetimes, the group noted, which will allow clinicians to discern "true" value based on real-world evidence.

Turning the Tide Toward Continuous Learning

- **Accelerate the incorporation of research parameters into "meaningful use" guidelines for electronic health records**
- **Incentivize the consistent collection of outcomes data in standards-based form**
- **Develop a policy framework that supports the accessibility of clinical data for researchers and incentivizes data sharing**
- **Incentivize standards-based data collection and data exchange capabilities in research**
- **Enforce current provisions that mandate the sharing of data from government-funded research in a timely way**

ASCO has a major initiative underway to develop a "learning health system" in oncology through its CancerLinQ program, which aims to "support greater consistency and quality in practice and speed progress in developing new or better treatments." The program will cull data from electronic health records, initially to guide personalized treatment by identifying the best treatment options based on real-world experiences and real-time analysis of data captured in EHRs, but ASCO says researchers ultimately will be able to use the system to test hypotheses based on existing data as well as to use it prospectively in clinical trial settings (*"ASCO Linking E-Health Data To Promote Real-Time Personalized Cancer Care" – "The Pink Sheet," April 1, 2013*).

A CancerLinQ prototype program in 2013 gathered over 170,000 de-identified medical records "in any format" for breast cancer patients in the U.S., "overcoming the long-standing hurdle posed by inconsistent health data standards," the ASCO report noted. The association is proceeding with formal development of CancerLinQ; the first components should be available by early 2015. However, ASCO said, CancerLinQ "will require the support of policymakers to realize its full potential."

While full-scale continuous learning systems are in the early stages, insurers, researchers and industry are working with insurance claims databases to evaluate outcomes and comparative effectiveness. For example, Pfizer recently joined the Optum Labs collaboration between **UnitedHealth Group Co.** and the **Mayo Clinic**, which aims to analyze claims data with EHRs, to inform the company's development of personalized medicine (*"Pfizer Seeks Insights Into Big Data Analysis, Personalized Medicine Through Optum Labs" – "The Pink Sheet," Feb. 24, 2014*).

But getting payers and pharma companies to agree on the terms for collaborations on new approaches to payment can

be tricky. UnitedHealth tried to put together pilot program for four pharmas, three payers and one genetics company to test experimental cancer treatments and share information on outcomes, but that remains a work in progress. When first discussing the idea, UHC Senior VP-Oncology, Genetics and Women's Health Lee Newcomer said "We need to provide pharma an environment where they can supply those early testable drugs to patients anywhere with the right set of complex system biology" while payers cover patient care; treatment results will be collected in registries that would be accessible to participating payers so "we can learn and learn exceedingly quickly" (*"UnitedHealth Pursuing Payer/Pharma Collaboration To Evaluate Novel Cancer Treatments" – "The Pink Sheet," Nov. 25, 2013*).

The ASCO report sees encouragement in the early results of some payer-driven progams to apply HIT to oncology, like "cancer pathway" programs (*"Cancer Pathways Will Help Inform Drug Performance Measures, Payers Say" – "The Pink Sheet," April 2, 2012*). The report cites an **Aetna Inc.** program using U.S. Oncology's treatment algorithms and software, which showed a 12% reduction in overall costs for lung, breast and colon cancer treatment in the course of one year. However, ASCO cautioned, "there are also risks associated with having disparate and uncoordinated payer-driven quality initiatives, including the potential for such programs to focus primarily on cost rather than improving outcomes."

Irreducible Complexity?

Personalized cancer therapies, especially in combination, present challenges to the health care market beyond their high price tags. More effective treatment strategies for individual patients will "significantly increase the complexity of cancer care," ASCO noted. "As cancer becomes segmented into more and more 'rare' genetically defined diseases, it will be increasingly difficult for physicians to assimilate and apply the volume of available information in the care of their patients."

Guidance provided by "big data" approaches like CancerLinQ "will be vital" in the increasingly complex care environment, ASCO said, but the promise of "big data" is predicated upon improvements in health information technology – an area that is still emerging. "The adoption of HIT systems in oncology is complicated by the unique data requirements of modern oncology practices," ASCO adds.

The role of companion diagnostics adds another degree of difficulty. Personalized cancer medicine will "require support of coverage and payment policies that provide adequate reimbursement for novel, evidence-based molecular diagnostics and targeted therapies," Turning the Tide said. The group noted that "the current absence of a rational reimbursement approach represents a significant challenge for the development of the molecular diagnostics pipeline."

Companion diagnostics development occupies a tricky niche in the cancer ecosystem. During R&D, most diagnostic companies appear to be paid by their pharma partners to develop tests in fee-for-service style arrangements or through fixed milestone payments. To receive a return on investment, diagnostics firms must obtain solid pricing and reimbursement – a difficult task, thanks to the limited intellectual property protections and easy reproducibility of many tests, although FDA-approved companion diagnostics aim to secure better reimbursement than tests that don't go through the process.

Ultimately, diagnostic companies would like to receive royalties on sales of the drug or sales-based milestones as a way to share some of the long-term value of the product, Myriad Genetics Laboratories President Mark Capone said recently, but as of yet such conversations are "theoretical in nature" (*"Deals Of The Week Wonders: Will Pharma Ever Pay More For Companion Diagnostics?" – "The Pink Sheet," Nov. 25, 2013*).

The challenge of adapting oncology development, regulation, reimbursement and practice in the era of high-priced targeted cancer therapy will be one of the chief challenges facing medicine in coming years – the inevitable consequence of the tremendous gains in efficacy of the new generation of cancer treatments.

As the ASCO and Turning the Tide Against Cancer reports emphasize, the problem of sustaining innovation while containing costs will require the involvement of all of the stakeholders, a daunting prospect. The reports highlight both the importance of the task and its nascent state – the organizations are calling for a conversation, not presenting solutions. Change will not be simple.