

May 2014

Innovation in cancer care and implications for health systems

Global oncology trend report



Executive Summary

The intensifying global focus on oncology reflects its increasing impact on patients and expanding share of healthcare expenditure. The vast, growing market of oncology drugs is dynamic, with characteristics differing greatly across markets. While developers continue to innovate cancer therapeutics, greater scrutiny is placed on the price/benefit ratio of those innovations. Establishing the value of cancer treatments is challenging even with the most robust clinical data, and not surprisingly, payers have different approaches in determining which treatments to reimburse, in what circumstances, and at what levels. Amidst these dynamics, broader reforms in healthcare systems – such as those currently underway in the U.S. – bring additional sources of disruption as the intended and unintended consequences of change unfold.

Market dynamics

The global market for oncology drugs, including supportive care, reached \$91 billion in 2013, as measured at ex-manufacturer prices and not reflecting off-invoice discounts and rebates. Although this is up from \$71 billion in 2008, it represents a compound annual growth rate of 5.4%. The modest rate reflects a lack of breakthrough therapies for very large patient populations, patent expiries, reductions in the use of supportive care medicines and stronger payer management. This rate of growth is significantly lower than seen during the 2003-2008 period when growth each year exceeded 15%, driven by a small number of breakthrough therapies. Differences in incidence rates, access to medicines and treatment protocols are substantial between countries, but cancer is still a leading area of healthcare spend. In pharmerging markets, oncology is expected to be the fourth highest spend therapy class by 2017. While the U.S. and top five European markets have declined in their share of the global market, they still dominate it with 65% of total sales. Targeted therapies have dramatically increased their share of the oncology market, now accounting for 46% of total sales, up from 11% a decade ago.

Innovation

Developers have brought innovation across cancer types and therapeutic approaches, including preventive vaccines. Pharmaceutical company investments remain high and cancer therapies account for more than 30% of all preclinical and phase I clinical developments, with 22 new molecular entities being launched and reaching patients in the last two years alone. These new medicines have increased the complexity of treating cancer, leading to more combination therapies and additional lines of therapy. Clusters of innovation based on similar underlying science but separate development paths have transformed patient care in areas such as advanced melanoma and sub-populations of cancers with higher prevalence. Commercial returns for some recently launched oncology drugs have been as high as earlier benchmarks such as bevacizumab or imatinib. Many new drugs, however, are for small patient populations and face strong competition, lowering their level of sales and therefore returns to manufacturers. Investment in near-term future innovation has shifted toward biologics, mostly concentrated in targeted treatments, though preclinical products are mostly small molecule. While much of the pipeline is focused on lung and breast cancer, tumor types with lower prevalence such as ovarian, leukemia, stomach, and liver cancers are also being actively pursued. Immunology therapy has become a strong focus of investment recently based on current success in clinical trials and a promising outlook.

Value of treating cancer and pricing trends

The high number of new targeted therapies launched and available for cancer patients has also escalated payer scrutiny of their value relative to their incremental benefits compared to existing treatments. The average cost per month of branded oncology drug treatment in the U.S. is now about \$10,000, up from an average of \$5,000 a decade ago. Judging the incremental value of these treatments for individual patients is fraught with challenges due to the high level of variability of patient response, the frequent changes to protocol needed for patient care, and underlying issues of equity and patient care. The American Society of Clinical Oncology recently issued recommended targets for meaningful clinical trial outcomes, a useful step to guide those investing in innovation as well as those paying for patient care.

Concentrated payer systems and those with strong health technology assessment bodies tend to pay less for medicines than in the U.S. Pricing discount mechanisms in major European markets drive national net prices down by approximately 20 to 40% compared to U.S. list prices.

Biosimilars

The introduction of regulatory pathways for biosimilars and increased production capacity around the world are bringing a new competitive dynamic to the greater than \$40 billion biologics portion of the oncology market. The potential role of biosimilars in developed markets will be limited, however, if the expected flow of patent-protected innovative products continues to displace older off-patent products subjected to biosimilar competition. Biosimilars already play a role in the supportive care segment of the oncology market in Europe which can be expected to expand to the U.S. in the near-term. In low and middle-income countries, “non-original biologics” – which are based on original molecules never introduced in a particular country – are expected to play a significant role and already capture 60% or more of certain recombinant and synthesized biologics therapy areas. Their role in antineoplastics can also be expected to be significant by 2020. On a global basis, biosimilars – including non-original biologics – are expected to generate \$6-12 billion in oncology sales by 2020, increasing competition but accounting for less than 5% of the total biologics market at that time.

U.S. specific oncology dynamics

The U.S. market accounts for 41% of total oncology drug sales but reforms are impacting cancer treatment site of care, reimbursed fees and patient out-of-pocket costs. While the number of medical oncologists has been rising steadily over the past decade, they are rapidly changing their practice profile. Over 40% of oncologists are now in practices with seven or more physicians, up from 29% in 2012, as smaller practices are aggregated and/or acquired by hospital systems. Oncologists themselves attribute this trend to financial pressures and the desire to alleviate risk.

At the same time, Accountable Care Organizations and healthcare organizations that are covered by the 340b Drug Discount Program have expanded their presence in oncology, moving more patient care from physician offices to hospital outpatient facilities. To reflect hospitals' higher costs and overheads, they receive higher reimbursement to administer drugs compared to physician offices. For typical therapies that are infused or injected by an oncologist, reimbursed costs for hospitals are at least double those for physician offices, sharply increasing costs to payers over the past two years. Patient out-of-pocket costs are then driven higher, depending on the patient's insurance plan and benefit design, which can trigger reduced levels of therapeutic persistence by the patient and higher overall cost of care.

The trends identified and described in this report will continue to evolve in rapid and unexpected ways. Relative to other parts of the healthcare system, oncology brings high levels of uncertainty – in terms of the nature and rate of innovative treatments, the willingness by payers to reimburse care at current levels, and the shifting composition of the cancer patient population from mature and developed markets to low- and middle-income countries. As the sales of cancer treatments rise to \$100 billion annually, more intensive scrutiny of this market can be expected and a deeper understanding of global oncology trends will be required by all stakeholders.

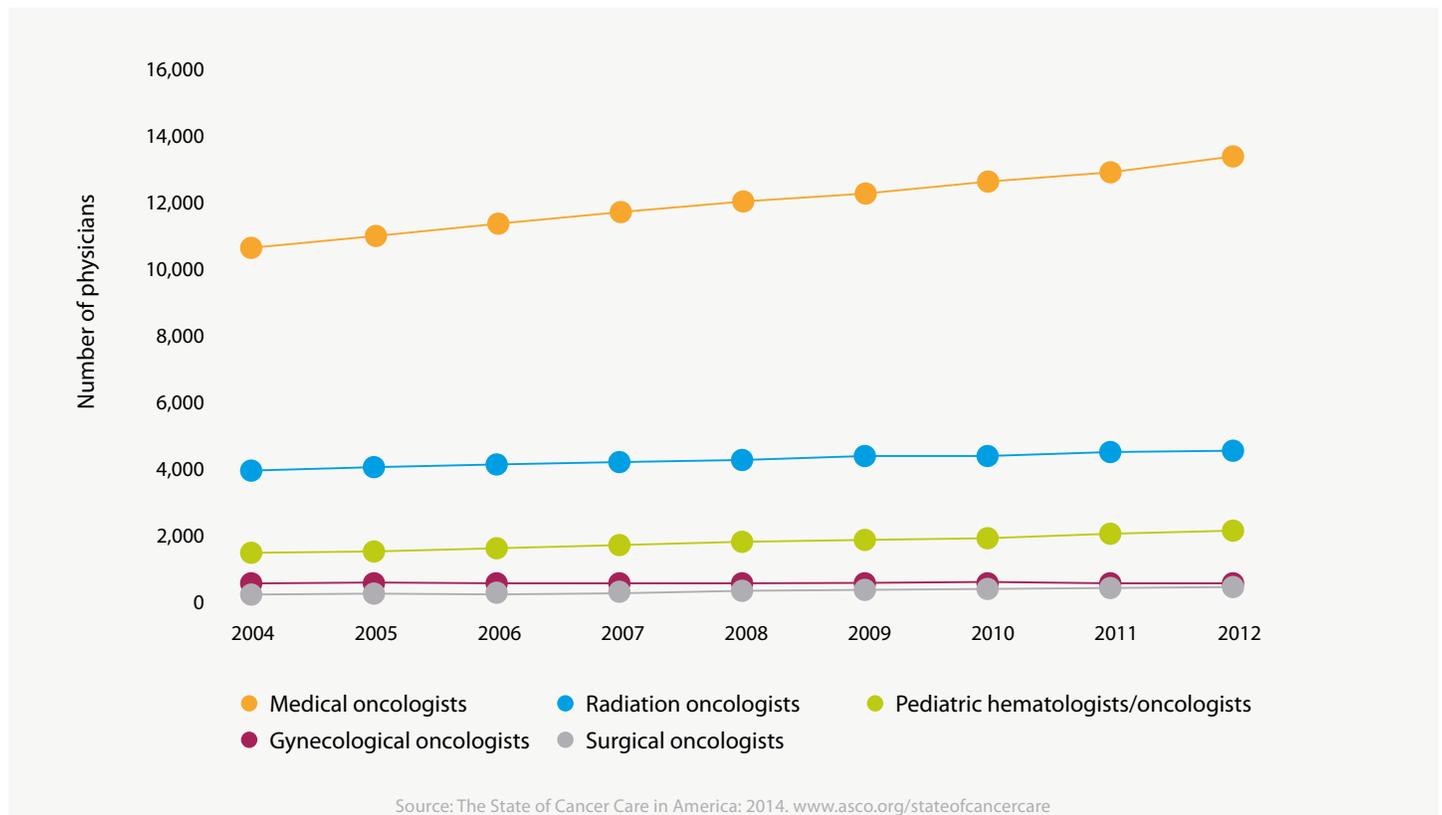
U.S. specific oncology dynamics

In the U.S., the delivery of cancer care is shifting. Physician practices are becoming larger and more cancer care is provided by Accountable Care Organizations and hospitals who enjoy increasingly favorable pricing under the ACA. Thus, some of the increases in cancer costs attributed to drug makers may actually be driven by the shift in setting of care. One unintended consequence is more cost is shifting to patients, potentially leading to reduced adherence.

- The U.S. has exhibited steady growth in the number of oncologists over the past decade although smaller physician practices have merged into larger ones or closed down completely, often driven by financial pressures felt by the oncologists.
- The change was driven in part by both the 2010 ACA, which encouraged the development of Accountable Care Organizations (ACOs) whose model required practice aggregation and hospital systems leveraging expanded 340B eligibility (340B Drug Pricing Program was created in 1992 to provide discounts to select “safety net” settings).
- Thus, more care is now provided in the hospital setting, whose reimbursement levels likely are passing more costs onto payers and subsequently passed patients via benefit design interventions and increased cost sharing.
- Increasing patient financial contribution is linked to declining therapeutic adherence, potentially resulting in drug discontinuation and higher overall total costs of care.

The number of oncologists in the U.S. continues to rise

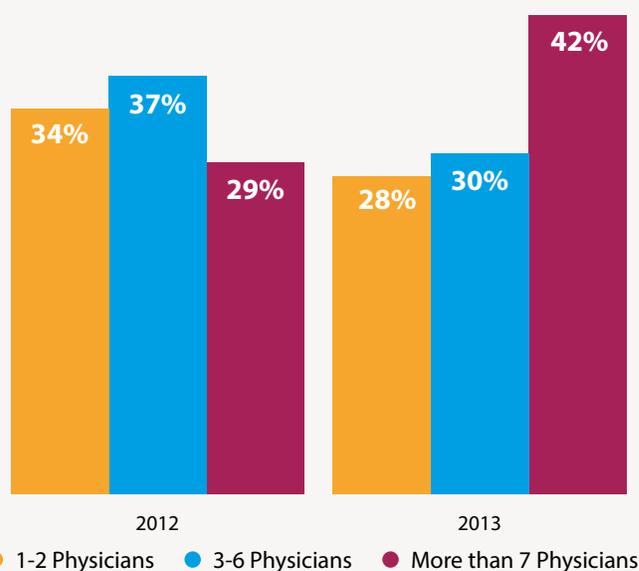
Growth in the number of oncologists in the U.S.



- In the U.S., the number of oncologists in nearly every subspecialty has increased over the past decade, with the overall number of oncologists increasing faster than the growth in U.S. population.

The operating model and viability of the average U.S. oncology practice is changing

Oncology Practice Measure	Result (2012, 2011 % change)
Referring drug infusions elsewhere	47 v. 48, no change
Merged / acquired (non hospital)	132 v. 111, 19% increase
Closed	241 v. 199, 21% increase
Acquired by hospital	392 v. 314, 24% increase
Struggling financially	442 v. 369, 20% increase

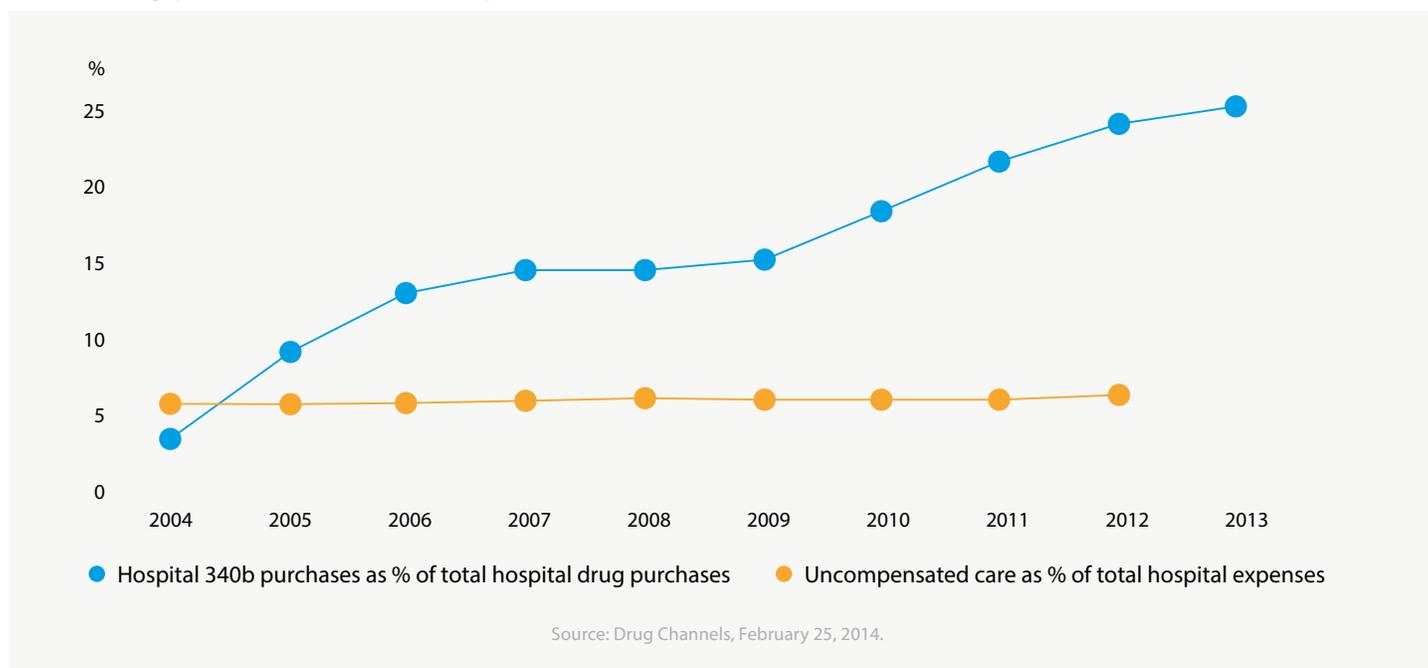


Source: Community Oncology Alliance (COA) Practice Impact Report, 2012, 2013
The State of Cancer Care in America: 2014. www.asco.org/stateofcancercaare

- Practice dynamics are changing in the U.S., demonstrating a clear trend toward the aggregation of smaller practices and the acquisition of practices by hospital systems.
- Many of these changes are viewed as unfavorable by practicing oncologists, with a tendency for practices to report financial troubles and even close their doors permanently.
- As a result of such financial struggles, the dwindling number of independent practices are likely feeling increased pressure to aggregate with other practices and alleviate risk.
- Underscoring this overall trend toward larger and/or hospital system-owned practices, the proportion of oncology practices comprising seven or more physicians increased from 29% in 2012 to 42% in 2013.

The Affordable Care Act expanded 340B eligibility and encouraged formations of ACOs, prompting these dynamics

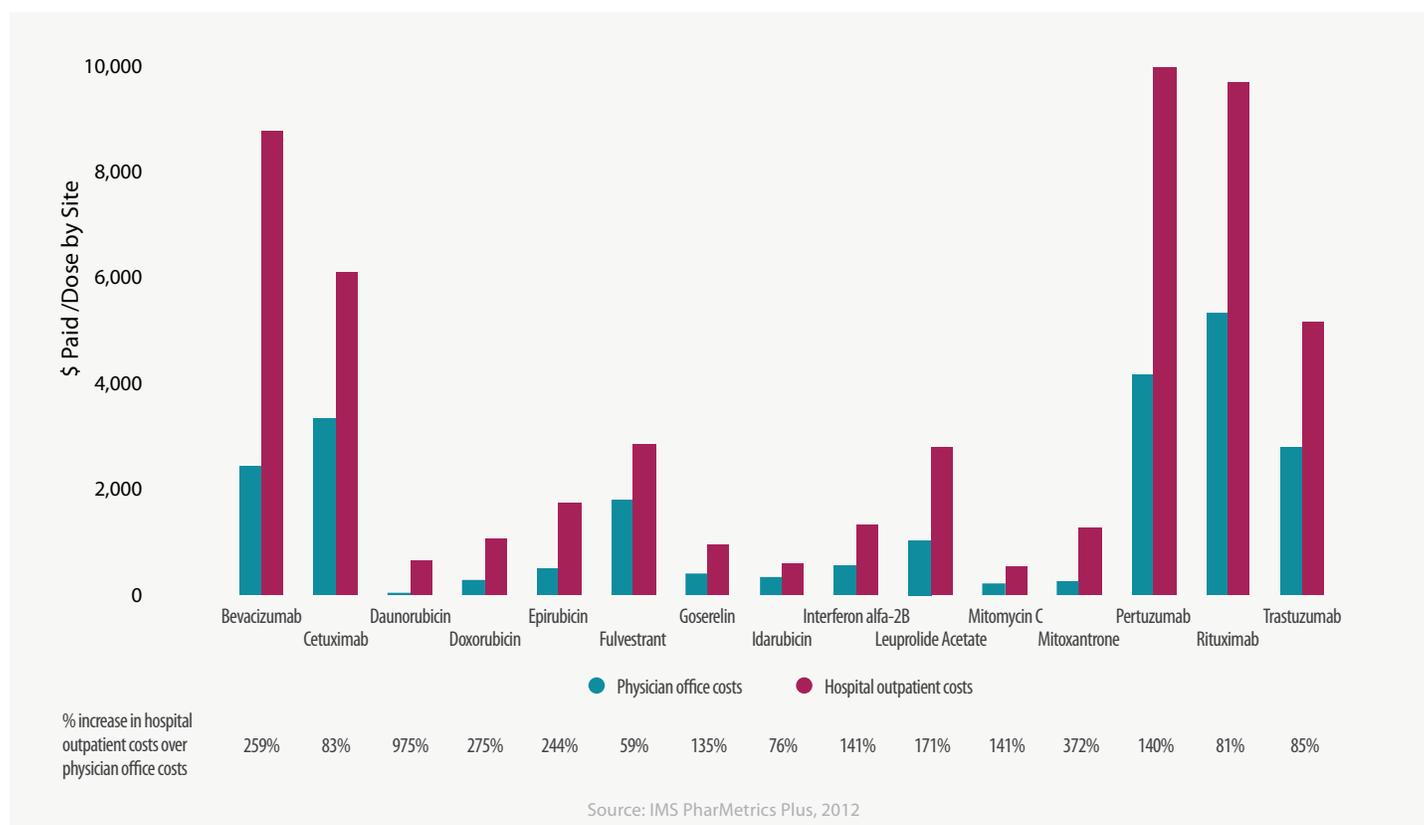
340B drug purchases vs. uncompensated care, 2004-2013



- These shifting practice dynamics are driven by a number of factors, some of which are a result of the ACA .
- One predominant change, expanded 340B pricing eligibility, available to hospital outpatient settings.
 - 340B pricing provides an approximate 51% discount to AWP, encouraging eligible hospitals to pull drug administration services into the more costly hospital outpatient setting.
 - The ACA has expanded 340B eligibility such that designated cancer research centers can now qualify for these discounts.
- While the proportion of uncompensated care has remained steady over the past several years—essentially a proxy for the proportion patients that enable a hospital to qualify for these discounts—the percentage of total hospital drug purchases using these discounts is up nearly 20% from six years ago.
- Hospitals can use 340B purchasing discounts for oncology practices that they have acquired while still charging facility-level prices to commercial payers.
- The ACA has also facilitated the formation of ACOs, further encouraging hospitals to purchase oncology practices to infuse cancer drugs in the hospital outpatient setting.
- Separately, low reimbursement for cancer treatments administered in the oncologist’s office, by both government and commercial payers, leads the oncologist to “refer” the patient to the hospital for drug administration.

Hospitals have higher drug administration costs than physician offices

Hospital outpatient costs compared to physician office costs



- Reimbursement levels for drug administration costs in hospital outpatient facilities are on average an incremental 189% of the level of physician office reimbursed costs for commercially insured patients under the age of 65 years. These higher reimbursement levels are in part associated with higher costs incurred by hospitals and overheads related to their delivery of care.
- Higher costs in hospital outpatient facilities are incurred despite the increasing proportion of hospital systems that benefit from discounted drug pricing via 340B eligibility.
- Competitive advantages achieved through 340B pricing, in conjunction with the decline of independent oncology practices, suggest a trend toward hospital outpatient drug administration at a substantially elevated cost to payers and increase patient out of pocket expenses.

As the cost of chemotherapy increases by site of care, so does patient contribution

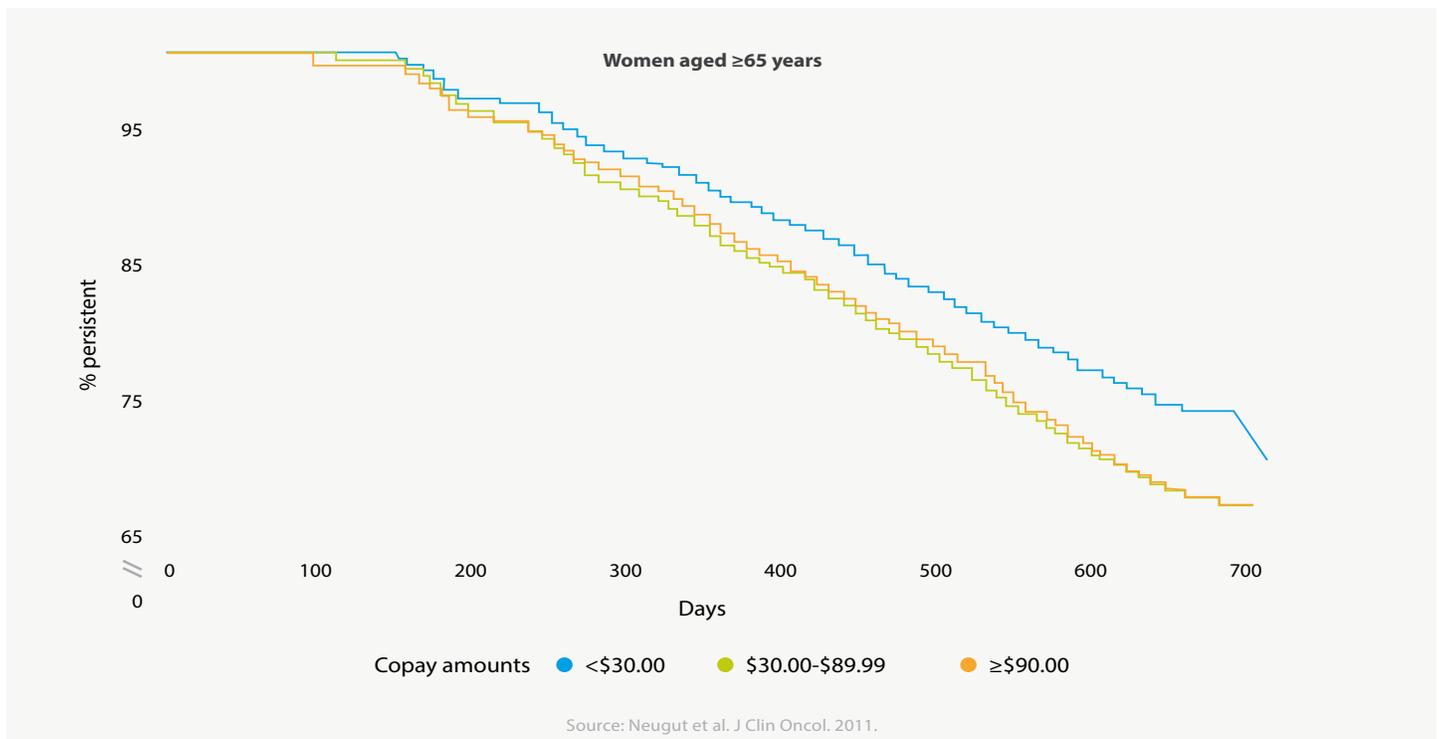
Therapy	\$ difference / dose paid by payor	\$ difference / dose paid by patient
	HOP v MD Office	HOP v MD Office
Alemtuzumab	6,251	-10
Bevacizumab	6,298	312
Cetuximab	2,764	374
Epirubicin	1,231	-2
Fulvestrant	1,054	-9
Leuprolide Acetate	1,756	121
Mitoxantrone	991	116
Pertuzumab	5,792	0
Rituximab	4,330	398
Trastuzumab	2,354	35

Source: IMS Pharmedics Plus, 2012

- Looking at a list of ten routinely prescribed chemotherapies, the covered cost per dose increased by 189% in the hospital outpatient setting when compared to the oncologist's office.
- Dollars allowed represents the amount that the payers will cover or reimburse and include the portion paid by the patient and the reimbursement to the provider. Amounts paid by the patient are the difference between the allowed amount and the amount reimbursed to the administering provider.
- In many of these cases, these higher allowed costs in the hospital outpatient setting lead to increased patient costs, since patient costs are commonly a percent of the overall payment amount.
- Lower or no differences in patient cost in the hospital outpatient setting are likely explained by benefit design – some legacy benefits contain no patient costs for hospital infusions; such benefits are now being phased out. Also, if a patient reaches their OOP maximum for the year by the time they receive a particular therapy, the patient contribution would be \$0 regardless of the site of care at which the drug is administered. This phenomenon is most commonly observed for later-line therapies, such as those indicated for metastatic disease, since the patient will have already satisfied their maximum yearly OOP obligation during earlier treatments.
- For these commonly used oncology drugs, the average increased cost to the patient is \$134 per dose received in the hospital as an outpatient when compared to the oncologist's office. Of note is that multiple therapies may be given per treatment cycle when both combination and chemotherapy support drugs are considered, leading to significant increases in member financial burden.

Increases in patient financial burden are associated with reductions in therapeutic persistence

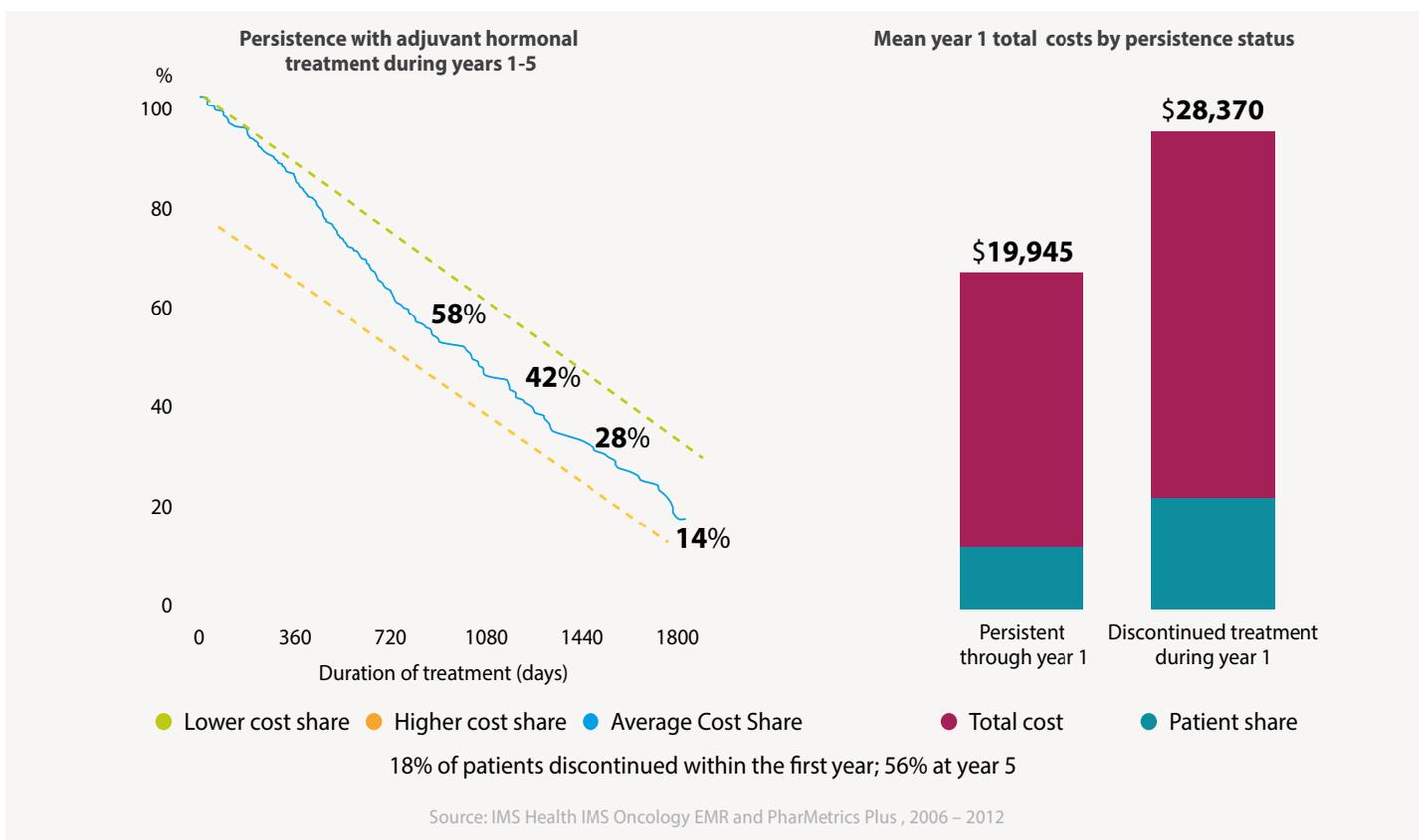
Adjuvant hormonal therapy persistence in breast cancer patients



- Looking specifically at adjuvant hormonal therapy for breast cancer demonstrates an inverse relationship between patient OOP cost and drug persistence.
 - As copay amounts increased, persistence fell with more than a \$30 copay. This suggests even small changes in patient contribution can lead to measurable changes in drug compliance.
- Even copays as modest as \$30 - \$90 appear to have an effect on therapy persistence, and the effect becomes more pronounced as copays increase.
- While copays are a function of the payer's benefit design, co-insurance is a function of both the benefit design (% of drug price that is charged to the patient) and the manufacturer's drug price, each of which can lead to unsustainable patient financial burden.

In certain scenarios, a reduction in therapeutic adherence can drive up the total cost of care

Early-stage ER+/PR+ breast cancer patients who discontinued adjuvant hormonal treatment



- Reduced therapeutic persistence is a key consideration because adherence can directly impact outcomes and, ultimately, the total cost of care.
- Again, focusing on adjuvant hormonal therapy in breast cancer, persistence levels declined over a 5 year time span and declined to an even greater extent among patients with a higher cost share.
- A \$9000 savings was associated with improved therapeutic persistence through the first year of therapy.
- Taking these findings into consideration, sites of care that increase patient contribution and cost sharing may actually lead to a significant increase in the total cost of care. Stakeholders are questioning the sustainability of rapid growth among hospital outpatient facility settings for oncology drug administration.