Developments in Cancer Treatments, Market Dynamics, Patient Access and Value

Global Oncology Trend Report 2015
Introduction

A cluster of innovative medicines for patients with a wide variety of tumor types and based on promising new mechanisms of action has heightened excitement about prospects for major advances in cancer treatment. The large number of potential new medicines currently in clinical development or under regulatory review suggests breakthroughs will continue and bring not only more options but also competition among alternative treatments and increased movement toward more personalized medicines which, through the use of diagnostic testing, can be administered to those most likely to benefit from the drug. The increased prevalence of most cancers, earlier treatment initiation, and improved outcomes all contribute to growing use of oncology therapeutics as well as those medicines used for supportive care of the patient. Spending on medicines receives close scrutiny in all countries and oncology drugs are no exception to this. Issues of access, value and equity are the focus of global discussion and debate.

In this report, we share our updated perspective on the clinical landscape and what lies ahead; the dynamics of the market for oncology-related pharmaceuticals; and the current state of patient access to medicines and value considerations. The development of this report was guided by an External Advisory Board whose input on topics to cover and perspectives to develop was invaluable. The support of the entire global, multi-disciplinary IMS Health Global Oncology team was also critical to the report’s creation. We gratefully acknowledge Lee Blansett, Radha Mawrie, Rob Kotchie, Andy Wong, Natalia Balko, Saurabh Kumar, Jaime Thompson, Jennifer Lyle, Mohammed Muhsin, Melissa Pirolli, James Evans, Tanmay Saraykar, Kim Mehle, Paul Cariola, Marla Kessler, Pascal Le Francois and Donny Wong for their substantial contributions to this piece.

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Murray Aitken
Executive Director
IMS Institute for Healthcare Informatics

IMS Institute for Healthcare Informatics
100 IMS Drive, Parsippany, NJ 07054, USA
info@theimsinstitute.org www.theimsinstitute.org
Advisory Board Members

Joseph Bailes, MD
National Authority on Healthcare Policy

Christian Downs JD, MHA
Executive Director
Association of Community Cancer Centers, Rockville, MD

Mohammad Jahanzeb, MD, FACP
Professor of Clinical Medicine, Hematology-Oncology
Medical Director, USylvester Deerfield Campus
Sylvester Comprehensive Cancer Center
University of Miami, Miller School of Medicine

Rainer Lipp, MD
Internal Medicine Hematology and Oncology
Chief Executive Officer
German Oncology Holding
Hamburg, Germany

Jeff Patton, MD
Chief Executive Officer
Tennessee Oncology
Chief Medical Officer
RainTree Oncology Services
Executive summary

The pace of change in cancer care is accelerating. A cluster of innovative treatments, often combined with other new or existing medicines, and frequently associated with biomarkers, are emerging from the research and development pipeline. Many are for tumor types associated with low survival rates and where patients have limited options. The landscape is shifting rapidly, bringing new complexity to oncologists, payers and governments who all look to provide appropriate care to patients while ensuring the sustainability of healthcare systems. Earlier diagnosis, longer treatment duration and increased effectiveness of drug therapies are contributing to rising levels of spending on medicines for cancer care. Total global spending on such medicines reached the $100 billion threshold in 2014, even as their share of total medicine spending increased only modestly. Measures of value continue to be tested by payers and providers who, in some health systems, most notably the U.S., have growing concerns about the financial burden faced by cancer patients. These concerns are also reflected in activity on social media networks, which are increasingly turned to by patients for support throughout their cancer journeys.

Clinical landscape

Existing cancer treatments are incrementally improving patient outcomes, reflected in rising five-year relative survival rates for major cancers. A healthy pipeline of new drugs and combinations of drugs are bringing the promise of more rapid and significant patient benefits. New therapeutic classes and combination therapies will change the cancer landscape over the next several years: new “immuno-oncologics” hold out the promise of improved survival with lower toxicity for some patients, while combination therapies address multiple pathways in a tumor, potentially leading to substantial increases in survival.

The strong pipeline of medicines in clinical development also suggests that direct competition will increase in the next five years. Certain classes such as the Pi3K/mTOR/AKT inhibitors, will address multiple tumors but will inevitably become crowded. Certain tumors, such as non–small cell lung cancer, will also become battlegrounds, with multiple classes and multiple products within classes competing for the attention of oncologists and patients.
EXECUTIVE SUMMARY

Molecular diagnostics are rapidly transforming drug development and patient selection. Clinical trials with biomarkers have higher success rates than those without, and combining patients with a proven biomarker allows efficient trials to be conducted in rare cancers. New molecular diagnostics can simplify decision-making and reduce uncertainty. They can also complicate treatment selection since multiple tests may be used to identify markers, and their results are likely to vary in specificity and sensitivity.

These dynamics – more treatment options, more combinations, longer treatment times and improved survival rates – will increase the need to monitor and understand long-term outcomes and safety.

Market Dynamics

Global spending on oncology medicines – including therapeutic treatments and supportive care, and measured at ex-manufacturer prices not reflecting off-invoice discounts, rebates and patient access schemes – increased 10.3% in 2014 and reached $100 billion, up from $75 billion five years earlier. The compound average growth rate over the past five years was 6.5% globally on a constant exchange rate basis, though only 5.3% in the U.S. Targeted therapies now account for almost 50% of total spending and they have been growing at a compound average growth rate of 14.6% over the past five years.

In the major developed markets, a sharp increase in the volume of protected brands since 2011 and significant new product launches have been the primary drivers of spending growth, while the impact of patent expiries has moderated over the past few years. On a per capita basis, spending on therapeutic oncology medicines in the U.S. reached $99 in 2014, up from $71 in 2010, with similar levels of percentage increase occurring in other major markets with the exception of Spain where per capita spend has been flat.

Oncology drug spending has risen slightly as a percentage of total drug spending over the past five years in all regions, most notably in the EU5 countries where oncology now represents 14.7% of total drug spending, up from 13.3% in 2010. In the U.S., oncology has increased more modestly from 10.7% to 11.3% of total drug spending over the same period.

Future spending on oncology medicines through 2018 is expected to grow in the 6-8% range annually, compared to the 6.5% level seen over the past five years as growing demand and new therapy options are offset to some extent by new competition from biosimilars and small molecule generics following patent expiries.
EXECUTIVE SUMMARY

**Patient Access and Value**

Patient access to oncology medicines varies widely by country and closer scrutiny is being placed on value by payers and patients who may face a growing share of treatment costs. The availability of new medicines varies widely across the major developed countries with patients in Japan, Spain and South Korea having access in 2014 to less than half of the new cancer drugs launched globally in the prior five years. In pharmerging markets, the availability of newer targeted therapies remains low but is increasing. Even when available, however, the lack of reimbursement for drugs, particularly in countries employing formal cost effectiveness methodologies based upon cost per quality life year gained, constrains access for patients.

Assessment of value for oncology products is becoming more complex as fewer new drugs have single indications and by 2020 it is expected most will have three or more indications. Divergence in clinical value by indication complicates assessments of appropriate pricing by payers since in many cases the majority of a drug’s clinical value may be in areas with small patient populations while most of its use is for indications with relatively less value.

Overall therapy treatment costs per month have increased 39% over the past ten years in inflation-adjusted terms, similar to the 42% increase in overall response rates and 45% increase in months that patients are on therapy, which also contribute to higher overall spending levels associated with improved survival rates. In the U.S., patient out of pocket costs associated with IV cancer drugs have risen steeply as consolidation of smaller group practices into larger hospital systems has triggered higher outpatient facility costs shared with patients. Patient concerns about the financial burden of living with cancer is a frequent topic of discussion on social media sites which are increasingly used by those with cancer – and their families and caregivers – as a source of information and for sharing experiences.
Clinical Landscape

Existing cancer treatments are incrementally improving patient outcomes, while new drugs and combinations of drugs are emerging with the promise of more rapid and profound patient benefits.

- Outcomes are improving: Five-year relative survival rates for major cancers are rising.
- The pipeline is healthy, and new options are being approved for cancer patients, providing more choices and frequently better outcomes than existing therapies.
- Despite successes, physicians’ satisfaction with their options varies across tumors, across products, and across countries; branded products’ cost/benefit relationship is a consistent source of debate.
- New therapeutic classes and combination therapies will change the cancer landscape over the next several years: new “immuno-oncologics” hold out the promise of improved survival with lower toxicity for some patients, while combination therapies address multiple pathways in a tumor, potentially leading to substantial increases in survival.
- The strong pipeline also suggests that direct competition will increase in the next five years: certain classes, e.g., Pi3K/mTOR/AKT inhibitors, will address multiple tumors but will inevitably become competitive; certain tumors, e.g., non–small cell lung cancer (NSCLC), will also become battlegrounds, with multiple classes and multiple products within classes competing for patients.
- Molecular diagnostics are rapidly transforming drug development and patient selection: trials with biomarkers have higher success rates than those without, and combining patients with a proven biomarker allows efficient trials to be conducted in rare cancers.
- New molecular diagnostics can simplify decision-making and reduce uncertainty, but can also complicate treatment selection: multiple tests may be used to identify markers, and their results are likely to vary in specificity and sensitivity.
Two-thirds of Americans diagnosed with cancer now live at least five years, compared to just over half in 1990. Although the changes are incremental year to year, cumulatively, more patients are gaining years of life.

Breakthroughs are rare and frequently apply to small subpopulations of a disease, e.g., ALK+ and EGFR+ NSCLC, or chronic myelogenous leukemia (CML). Most progress comes through continuous small improvements in detection and treatment, including refinements in using existing treatments as well as use of new treatments.

Survival gains also accrue from increased screening and earlier detection as well as advances in surgical and radiation oncology.

Within tumors, survival rates vary by age and ethnic group. For instance, between 1990–95 and 2005–10, five-year survival rates improved approximately 55% more for patients aged 50–64 than for patients aged 75–85.

Chart notes:
Relative survival is a net survival measure representing cancer survival in the absence of other causes of death. Relative survival is defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer free individuals.
Multiple tumor types are being treated with new medicines launched over the past five years

New Molecular Entity Launches 2010–14 by Indication

- Oncology pipelines have produced 45 new drugs launched in 2010–14 for more than 53 uses.
- In 2014, there were 10 new drugs launched globally, including five biologic therapies: two new immunotherapies, nivolumab and pembrolizumab, both checkpoint inhibitors; blinatumomab (first of a new class, bi-specific T-cell engagers [BiTEs]); ramucirumab; and siltuximab.
- Not all launches included all countries; for instance, alectinib for ALK+ NSCLC and mogamulizumab for ATCL were both launched in Japan but not in other markets.
- Many of the new agents will eventually be approved in multiple indications, providing new options for additional patients.

Chart notes: Molecules listed had initial global launch in the period 2010–14. Molecule indications based on approval by one or more regulatory bodies. Excludes sipuleucel-T, an autologous cell procedure not classified by IMS Health as a fully identifiable substance.

Source: IMS Health MIDAS Dec 2014, IMS Lifecycle “R&D Focus” Dec 2014
Despite continuing improvements in outcomes, physician satisfaction remains middling, even in HER2+ mBC

Physician Satisfaction with Existing Treatments (HER2+Breast cancer)

- HER2-positive cancer is diagnosed in 10%-20% of breast cancer patients. This cancer is particularly aggressive and more likely to spread rapidly than other types of breast cancer.
- Patients have seen dramatically improved outcomes from agents targeting the HER2 receptor, beginning with trastuzumab, which was approved in 1998 and is now used with both adjuvant (early-stage post-surgical) and metastatic patients.
- Three additional targeted therapies are now available globally; two can be used either as single agents or in combination.
- While Drug Treatment 1 has the highest satisfaction rating among surveyed cancer products, physicians continue to see room for improvement as metastatic patients gain survival but are not cured.
- Cost benefit is a concern for physicians across all countries and treatment options.
- Physicians in the U.S. and Brazil share similar perceptions of drug benefits, while Japanese physicians consistently rate current options lower.

Chart notes:
Surveys fielded to doctors in 3 countries to understand their satisfaction with 4 HER2+ drug treatment options in April 2014. Rating provided for each drug against 7 attributes on a scale of 1-7, with 1 being least satisfied to 7 being most satisfied. Scores were aggregated across all doctors in each of the 3 countries and for each of the 4 molecules.
Emerging classes, including immuno-oncologics, offer hope of further increases in options and potential breakthrough in outcomes for some patients

Immunology Oncology Evolution

- Immuno-oncology is seeing significant investment and experimentation and is likely nowhere near its potential clinical and commercial peak.

- Ipilimumab, a CTLA-4 approved in 2011 for metastatic melanoma, is leading the first surge of new therapies. Nivolumab and pembrolizumab, both PD-1 targeted agents approved in late 2014, are being rapidly adopted in melanoma and, like ipilimumab, are also being studied in multiple additional uses.

- Chimeric Antigen Receptor–T cells (CARTs) are cell-based therapies which condition a patient’s T-cells to recognize a specific cancer. CARTs, like the PD-1/PD-L1 class are potential game-changers expected to find first use with hematologic cancers.

- New therapies and new classes will emerge in waves, with each wave building on the previous one; combinations of immuno-oncology products will increase the height of these waves.
Over the next 5+ years, combinations of targeted and immuno-oncology agents will account for many NME launches and line extensions

Expected Combination Regimen Launches in Oncology

- Chemotherapies are frequently used in combination as first- and second-line treatment for late-stage patients; while stakeholders are aware of the increased costs of these combinations, the individual agents are generally low cost and used for only four to six cycles of treatment.

- Newer combinations will incorporate targeted and immuno-oncology agents and have the potential to be used for a year or more.

- A large number of combinations will launch over the next six years, with an inflection point near 2020–21. Breast and hematology combos will predominate in the early years; after 2018, combos targeting solid tumors, especially lung cancer and melanoma, will increase dramatically.

- Budget impacts may result in new payer actions to address high per patient costs. Payers as yet lack an organized approach to evaluating combinations, instead largely focusing on the incremental costs and benefits of each new agent.

Chart notes:
Excludes some phase I/IB combos, non-US studies, certain early-stage trials that have been approved but not yet enrolled.
Combinations of targeted and immuno-oncology agents will improve outcomes, but complicate trial and commercialization strategies

Potential Combination Therapies Launching by 2021

- Roche is developing the largest number of combinations; most other manufacturers also have multiple combos in their pipelines.
- Most combinations include agents from two or more manufacturers; only Roche, BMS, AZ, and Janssen are studying combinations of an NME and an existing agent that are both produced by a single manufacturer.
- Combinations including new agents represent new levels of development and marketing complexity. Combining an NME with another manufacturer’s in-line product, for example, constrains pricing flexibility and complicates promotion.
- Combinations may create complex relationships among manufacturers in which two companies may collaborate in jointly developing a combination with two molecules in one indication, but compete in other indications.

Chart notes:
These are molecule combinations. Subject to change. Based on best available information
Validated pathways reduce clinical trial risk, facilitating “fast follower” strategies with rising competitive intensity

Pipeline by Number of Targeted Agents and Selected Pathways

- An analysis of pipeline agents for five specific mechanisms of action shows 100 phase II and phase III trials targeting eleven key tumors. These investigations include both NMEs and new indications for drugs currently on the market.

- Many molecules will fail to reach approval; however, the substantial number of NMEs in the classes with proven activity, e.g., VEGF and PD-1/PDL-1 inhibitors, suggests that direct competition can be expected to increase in multiple indications. This competition may lessen as products within a given class show differing levels of effectiveness in different cancers.
The NSCLC pipeline includes multiple options across therapy categories

Key In-Market and Investigational Agents for NSCLC

- GLOBOCAN estimates there were over 1.8 million new lung cancer cases and an additional 1.6 million deaths worldwide in 2012.
- NSCLC accounts for 85% of all lung cancer cases. Most patients are over the age of 65; however, substantial numbers of younger patients, including nonsmokers, are diagnosed each year. All patients share a generally poor outlook, with late-stage patients commonly surviving less than two years.
- Research into genetic subtypes is rapidly dividing NSCLC patients into groups defined by specific mutations. As mutations evolve and resistance to therapy develops, second- and third-generation targeted therapies now provide the potential for multiple years of treatment with good quality of life.
- Immuno-oncology agents are also proving valuable; nivolumab has been approved for squamous NSCLC, and data suggest it is also efficacious in non-squamous NSCLC.

Chart notes:
The chart includes globally marketed and emerging therapies in NSCLC as of Dec. 2014. Opdivo approval for NSCLC Mar.2015 * denotes: ALK +ve NSCLC, ^ denotes: EGFR +ve NSCLC pts., ** Phase II/III, ^^ denotes trial ongoing only in Israel, $ denotes Phase III planned.
The use of Real-World Evidence can demonstrate effectiveness in multiple subpopulations by linking biomarker data to treatment information

### Biomarker Durations of Therapy

#### Median Days on Erlotinib Therapy

<table>
<thead>
<tr>
<th></th>
<th>Median Days</th>
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<tbody>
<tr>
<td>EGFR neg n=62</td>
<td>135</td>
</tr>
<tr>
<td>EGFR pos n=90</td>
<td>358</td>
</tr>
<tr>
<td>KRAS pos n=15</td>
<td>115</td>
</tr>
<tr>
<td>KRAS neg n=137</td>
<td>312</td>
</tr>
</tbody>
</table>

Sources: IMS Health analysis of Foundation Medicine genomic profiling data linked to IMS Health Real-World Data

Targeting KRAS Mutations in Lung Cancer: No Longer Impossible By Caroline Helwick|September 1, 2014, Volume 5, Issue 14

- Even when biomarkers help show a drug’s clinical value by identifying strong-responding subpopulations in a trial, payers may demand evidence of their effectiveness in real-world settings.
- This Real-World Evidence (RWE) study, which matched IMS Real-World pharmacy claims to Foundation Medicine genomic profiling data for two mutations, demonstrated clinical value as measured by median duration of therapy.
- Patients with no identified EGFR mutations were on therapy for only 135 days on median, compared to 358 days for those with any EGFR mutation—who were also the strongest responders in clinical trials.
- KRAS mutations are present in 26% of NSCLC patients who are current or former smokers and 6% of those who have never smoked, and they are strongly associated with a lack of response to erlotinib and other EGFR-TKIs.
- RWE analysis confirms this: patients with a KRAS mutation had a median duration of therapy of just 115 days, compared to 312 for patients with wild-type KRAS.
- Use of biomarkers for better and more timely use of testing, combined with RWE assessments of outcomes, can inform future decisions.

\(^1\) Mao et al. 2010
Trials employing biomarkers for patient selection have a higher probability of success

Non-Small Cell Lung Clinical Trial Success for Molecules With and Without Biomarkers

- NSCLC has multiple genetically defined subpopulations. New therapies targeting molecular biomarkers are becoming standards of care in patient groups such as those with EGFR mutations and ALK-fusion genes.
- Drugs whose development strategies target a specific biomarker are much more likely to successfully progress through clinical trials than those without a biomarker.
- Most molecules appear to transition from phase I to phase II successfully; however, biomarker drugs have a significantly improved probability of transitioning from phase II to phase III.
- The overall success rate for non-biomarker drugs in the study was 11%, and the phase II transitional success rate of 67% suggests that biomarkers, especially when well validated, reduce technical risk.
New oncology therapeutics launched with either a companion diagnostic (CDx) or a biomarker continue to be a minority

Biomarker / CDx Status for Oncology Drugs Approved (U.S.)

- Only one-third of the oncology therapeutics approved in the last 11 years had a biomarker or CDx on label for any indication.
- This share has remained relatively constant over the decade: of 10 approvals in 2014, one has a CDx, while three have biomarkers but no CDx.
- CDx could become “table stakes” in the next three to five years. Existing therapies have been able to launch with a biomarker but not a CDx if testing is well established in treatment (e.g., in many hematologic malignancies).
- The emerging plethora of tests will create additional complexity:
  - Manufacturers pursue differing CDx strategies during development, so multiple products in a class may be approved, each with its own CDx in specific tumors, as in the PD-1/PDL-1 class.
  - Many commercial labs in the U.S. develop their own lower-cost test kits, whose results may vary from those of a drug’s FDA-approved CDx due to use of different methods.
  - Some well-established drugs, most notably Herceptin, have multiple CDx tests approved, using different technologies—IHC, FISH, and CISH—though most have only one approved.
Biomarkers and companion diagnostics introduce complexity in part because of inconsistency in test results

Comparison of FISH and IHC Testing for ALK Rearrangements

- Many stakeholders expect molecular testing to provide a clear and accurate assessment of a tumor’s genetic mutations.
- However, this is not always the result. One study of 3,244 patients in two French cancer centers found that 150 patients were classified as ALK+ by either FISH or IHC, but only 80 by both.
- FISH has been established as standard for ALK testing and is the FDA-approved CDx for Xalkori (crizotinib). However, lab-developed tests have employed other techniques, such as IHC.

- Different results for the same population highlight the importance of test sequencing and validation.
- False negatives on biomarkers could represent a significant gap for patient outcomes as well as missed opportunity for manufacturers.
- With over 50% of pipeline therapies projected to have a biomarker, it is critical to validate differences in modalities, understand trade-offs of biomarkers and CDx in development, and help physicians and patients navigate this environment.

Chart Notes:
Parallel testing of 3244 NSCLC cases analyzed in two independent French centers. FISH-positive and/or IHC-positive reported in 4.6% of cases
Basket trials can efficiently demonstrate effectiveness in rare cancers by following mutations

Potential Applications of Histology Agnostic Approaches Across Rare Tumors

- While genetic subgroups reduce the size of markets, they also provide an opportunity to pursue multiple indications for targeted therapies in cancers with the same driver mutation.
- Patient populations with a specific mutation may inform a broader clinical development program. Small groups of patients, either in subpopulations of larger cancers or with rare cancers, can potentially be investigated in histology-independent trials, or “basket studies,” which pool patients with different cancers but common and well-established molecular signatures into a single trial.
- This approach saves time and development costs by reducing the number of patients with any given cancer required for a trial, and by focusing on overall response rate as evidence of effectiveness.
- These studies can provide cost-effective evidence for approval in rare indications and proof of concept for larger populations. A basket trial may be sufficient to gain approval for a rare indication where unmet need is high and the genetic target is well established.
- This strategy is most likely to succeed when pursuing follow-on indications where adequate safety data from previous studies help support the filing and adverse events reported in the basket study are consistent with those seen in earlier filings.
A basket study approach resulted in four follow-on indications using a single trial and published cases.

Response Rates to Imatinib Across Rare Tumors

- Novartis used a basket study to expand the indications for Glivec / Gleevec (imatinib), which inhibits BCR-ABL, c- KIT, ARG, and PDGFR tyrosine kinases. The company secured four additional indications through a single phase II trial demonstrating effectiveness in four rare cancers with these mutations.
- This study pooled 186 patients with over 40 rare indications with high unmet need, and the FDA application combined effectiveness data from the trial with published case studies supporting these outcomes and safety data.
- Glivec is now approved for 10 indications: two each in ALL, CML, and GIST, and one each in ASM, DFSP, HES/CEL, and MDS/MPD.
- Expanded use of Real-World Evidence could facilitate requirements for post-launch approvals.

*Response rate as cited in Gleevec Approval Package to FDA; includes data from Phase II histology-agnostic trial and independent case reports when applicable.

Reference: Center for Drug Evaluation and Research; Application Number: 21-588 / S-011, 012, 013, 014, 017 (162 of the HES patients were from 35 published case reports; 23 patients in 10 case studies for ASM, 24 in 12 case studies for MDS; 6 in 5 case studies for DFSP.)
Market Dynamics

Global spending on oncology reached $100 billion in 2014 as new treatments and increased demand drive steady growth.

- Global spending on oncology medicines – including therapeutic treatments and supportive care, and measured at ex-manufacturer prices not reflecting off-invoice discounts, rebates and patient access schemes – increased 10.3% in 2014 and reached $100 billion, up from $75 billion five years earlier.
- Targeted therapies now account for almost 50% of total spending and have been rising at a compound average growth rate of 14.6% over the past five years.
- In the major developed markets, a sharp increase in the volume of protected brands since 2011 and significant new product launches have been the primary drivers of spending growth, while the impact of patent expiries has moderated over the past few years.
- On a per capita basis, spending on therapeutic oncology medicines in the U.S. reached $99 in 2014, up from $71 in 2010, with similar levels of percentage increase occurring in other major markets with the exception of Spain where per capita spend has been flat.
- Oncology drug spending has risen slightly as a percentage of total drug spending over the past five years in all regions, most notably in the EU5 countries where oncology now represents 14.7% of total drug spending, up from 13.3% in 2010, while the U.S. has seen oncology increase more modestly from 10.7% to 11.3% of total drug spending over the same period.
- Future spending on oncology medicines through 2018 is expected to be in the 6–8% range, compared to 6.5% over the past five years as growing demand and new therapy options are offset to some extent by new competition from biosimilars and small molecule generics following patent expiries.
Global oncology spend has grown to $100 billion in 2014

Global Oncology Drug Spending 2010–14

- Pharmerging countries’ share of oncology drug spend for the period shows faster growth than that of other countries at 15.5%, while Japan’s at 4.3% is slower than others.
- U.S. continues to maintain its dominance of the oncology market, accounting for 42.2% of total spend followed by EU5.
- Global spending on oncology reached $100 Bn in 2014, up 10.3% over the prior year and bringing the compound annual growth rate to 6.5% over the past five years.
- Regional shares of total spending have remained steady except for pharmerging markets which increased from 9% to 13% while Japan has fallen from 12% to 9% over the past five years.

Chart notes:
Oncology includes therapeutic treatments as well as supportive care, radiotherapy and immunotherapies. Spending in US$ with variable exchange rates. Growth in US$ with constant exchange rates.
Spending on targeted therapies continues to grow rapidly in all regions

Targeted Therapies Growth 2010–14

- For the 5 year period 2010–2014 targeted therapies have grown by 14.6% globally while cytotoxic, hormonal and supportive therapies have remained at about $52 Bn in annual sales.
- This pattern is also true for the Top 9 countries - US, EU5 and Japan, South Korea, Canada.
- Pharmerging countries have a lower share of targeted therapies, while their growth is higher than global markets.
- Targeted therapies now represent 48% of total oncology spending up from 36% in 2010.

Chart notes:
Oncology includes therapeutic treatments as well as supportive care, radiotherapy and immunotherapies.
In developed markets, most growth is from new brands and increased volume

Oncology Spending Growth Dynamics in Developed Markets 2010–14

- Within the nine major developed markets, growth has increased sharply in the past two years rising from $1.4 Bn growth in 2012 to $7.4 Bn in 2014.
- Most of the higher spending growth is due to increased volume demand for branded products in addition to newly launched products.
- The impact of patent expiries on reducing oncology drug spending has declined from about $2.9 Bn in 2011 to $1.3 Bn in 2014 as few molecules lost protection and faced competition from lower priced generics.
Per capita oncology drug spending increased in most developed countries

Therapeutic Oncology Drug Spend Per Capita 2010–14

- Between 2010 and 2014, therapeutic oncology spend, on a per capita basis, has increased in most developed nations, coinciding with the introduction of new biologics and targeted agents.
- U.S. continues to be the leader in per capita oncology spend, reaching almost $100 in 2014, up from $71 in 2010.
- The percentage increase in the 5-year period has been highest in UK at 67% while Spain has declined by 1% with its population growth exceeding therapeutic oncology spend.
- Population growth was negative in Germany (~1%) and flat in Japan (0%), while therapeutic oncology spend and per capita oncology has increased.
- Off-invoice discounts, rebates and patient access schemes may affect measures of per-capita spending and cross-country comparisons significantly.

Chart notes:
Oncology drug spend as a proportion of overall drug spend remains higher in EU5 and Japan than the U.S.

- Over the past five years, the share of country level spending on cancer drugs relative to other drugs has increased by about 1%, to 14.7% in the EU5, 11.6% in Japan, and 11.3% in the U.S.

- Spending on cancer drugs across pharmerging markets has increased from 5.8% to 6.7% over the past five years.

Source: IMS Health MIDAS, Dec 2014
The increase in spending on oncology drugs is expected in the 6-8% range through 2018

Global Oncology Market Forecast

• Increased spending levels are forecast through 2018 overall at a rate of 6–8% CAGR, bringing spending on oncology – including therapeutic treatments and those used for supportive care – to $117–147 Bn in 2018.

• The impact of patent expiries and biosimilar competition will be offset by higher levels of demand as prevalence, diagnosis and treatment rates increase.

• New product introductions will also trigger higher spending and longer durations of therapy, although much of this will be offset against existing treatments.

Chart notes:
Longer term growth in selected tumor types will remain modest as volume growth and new launches are offset by generic and biosimilar entities.

Forecast Growth in Select Tumors and Select Product Events US, EU5, Brazil, Japan 2013–2023 (Base Case)

- An increasingly sophisticated approach to patient subsetting will characterize growth in specific tumor markets during the forecast period.
- While overall global oncology drug spend is expected to rise, rates of growth for specific tumors will vary across countries.
- Overall drivers for growth include new product launches, the impact of therapeutic classes like immunotherapy, the expansion of drugs to earlier lines of therapy and epidemiological factors.
- Constraints include loss of exclusivity (LOE) for specific targeted agents, and competition to branded products from biosimilars and generics.
- While NSCLC has a high unmet need, and many agents in the development pipeline, LOE impact for Alimta, Tarceva, Gilotrif and Avastin is currently expected within the forecast period.
- Niche, incremental breakthroughs, in existing therapies and the launch of Palbociclib will be significant in breast cancer.
- The CRC landscape reflects the lack of any potential game-changers and domination of Erbitux and Avastin with expected LOE in the forecast period.
- Prostate cancer has high survival rates and growth drivers are mainly epidemiological factors.
Patient Access and Value

Patient access to oncology medicines varies widely by country and closer scrutiny is being placed on value by payers and patients who may face a growing share of treatment costs.

- The availability of new medicines varies widely across the major developed countries with patients in Japan, Spain and South Korea having access in 2014 to less than half of the new cancer drugs launched globally in the prior five years.
- In pharmerging markets, availability of newer targeted therapies remains low though increasing.
- Even when available, lack of reimbursement for drugs, particularly in countries employing formal cost effectiveness methodologies based upon cost per quality life year gained, constrains access for patients.
- Assessment of value for oncology products is becoming more complex as fewer new drugs have single indications and by 2020 it is expected most will have three or more indications.
- Divergence in clinical value by indication complicates assessments of appropriate pricing by payers since in many cases the majority of a drug’s clinical value may be in areas with small patient populations while most of its use is for indications with relatively less value.
- Overall therapy treatment costs per month have increased 39% over the past ten years in inflation-adjusted terms, similar to the 42% increase in overall response rates and 45% increase in months that patients are on therapy, which also contribute to higher overall spending levels associated with improved survival rates.
- In the U.S., patient out of pocket costs associated with IV cancer drugs have risen steeply as consolidation of smaller group practices into larger hospital systems has triggered higher outpatient facility costs shared with patients.
- Patient concerns about the financial burden of living with cancer is a frequent topic of discussion on social media sites which are increasingly used as a source of information and for sharing experiences.
The availability of new medicines varies widely across the major developed markets

Global New Molecular Entities 2009–13 – Availability as of 2014

- Access to cancer drugs varies widely across developed countries.
- Within countries, access may also vary, as some products may be available only to patients with the means to pay for the drugs themselves, or only for specific individuals through a highly selective process.

- Patients in no country had access in 2014 for all 37 new cancer drugs launched in the five year period 2009–13. The U.S., Germany, and the UK offer the broadest access, while South Korea, Spain and Japan have fewer than half of the new drugs available.
- Differences can result from regulatory requirements, health system priorities, and budget constraints.
Patients in pharmerging countries have less availability to newer targeted treatments

Global New Molecular Entities 2009–13 – Availability as of 2014

- Access is more limited in pharmerging countries than in developed countries.
- Across countries, a higher percentage of the new hormonal therapies are available than of the new cytotoxics or targeted therapies.
- In Brazil and Mexico, private insurers are more likely to reimburse new cancer drugs than public health systems, which remain less open to new products. Availability in China and India varies by region, and patients must frequently pay all or most of the cost for the newest drugs.
- The 2015 revision of the World Health Organization’s Essential Medicines List may result in the inclusion of targeted therapies and their increased availability across pharmerging countries.
Even when available, lack of reimbursement for drugs constrains access for patients

**National Reimbursement Status**

- Access to new cancer drugs is not universal even in developed countries, where national health systems’ priorities may result in their declining to reimburse some products.
- While they reimburse most non-cancer drugs, countries employing a formal cost-effectiveness methodology based upon cost per quality life year gained (cost per QALY, or CPQ) are much less likely to pay for new cancer drugs than countries employing other assessment approaches.
- Exclusion from access through normal health system channels does not universally mean that patients cannot arrange access: Australia, for example, operates a special fund to pay for trastuzumab for late-stage HER2+ breast cancer patients, while England’s Cancer Drug Fund (CDF) provides many products to individual patients who successfully apply for use outside the normal guidelines approved by the National Institute for Health and Care Excellence (NICE).

Chart notes:
*In Sweden, reimbursement at the county level was considered, as national level reimbursement decisions are not made for hospital drugs.
Assessment of value for oncology products is becoming more complex as most products have multiple indications.

Near-launch Oncology Pipeline Assets and Target Indications

- Of 88 cancer drugs marketed in 2014, 40 were for single indications and 48 for multiple indications.
- Currently, several of the single indication drugs are in clinical trials for Phase 2 and above and if approved, will be available to treat other indications.
- By 2020, most oncology drugs will carry multiple indications, reflecting developers’ pursuit of genetic targets across multiple tumors, and the rise of immuno-oncologics, which may have more than six indications.

Chart notes:
It includes compounds from Ph II to registration. It does not account for failures.
Divergence of clinical value by indication complicates assessments of appropriate pricing

Avastin CDF Scores vs. Cost Per Patient

- Most new drugs will be approved for multiple indications, but it is unlikely that any one will have similar effectiveness in all of them. Use of combinations may increase the variation in per patient costs across tumors.
- Avastin, for example, is approved for multiple indications in the U.S., and the English Cancer Drug Fund (CDF) has also covered it for some patients.
- Price and clinical value rarely match up across multiple indications. Using the CDF scores as a metric for clinical value demonstrates the lack of correlation between price and effectiveness.
- Avastin’s clinical value, as assessed by the CDF, differs across indications. Some indications, e.g. lung and renal cell cancers, have not been assessed and thus do not have scores.

Chart Notes:
Cost per patient is based upon U.S. price, ASP, and the duration of therapy reported in Avastin’s U.S. package insert.
Payment by use methodologies are required to match price with clinical value

Implications of Weighted Average Pricing

• Pricing a new cancer drug involves trading off a complex set of variables. The potential for multiple uses, with differing clinical value and numbers of patients, further complicates the process.

• Pricing based upon favorable clinical data in a small population may produce a price that is higher than optimal for one or more uses, and may lead to restricted access.

• Pricing based upon a weighted average of clinical values and expected patient volumes appears to offer a solution; however, this approach can threaten a product’s commercial viability where a low weighted average price is negotiated, but access then is restricted to small patient groups.

• Alternative pricing strategies that allow separate and distinct prices to be paid for individual patient groups, based upon the clinical value demonstrated by real world evidence, may be preferred by payers and manufacturers.
Cancer drug costs in the U.S. have increased both due to monthly prices and improving durations of therapy

Monthly and Total Patient Costs at Launch 2003-4 vs. 2013-15

- 2004 was a pivotal year in oncology, with the launch of three highly successful targeted agents (Avastin, Erbitux, and Tarceva) and Alimta, an important lung cancer drug. 2014 was equally important, with the first two PD-1 agents (Opdivo and Keytruda) approved, in addition to six targeted therapies.

- Comparing the two years in terms of clinical performance demonstrates the gains made during this decade of drug development. Overall response rates in 2014 exceeded those in 2004 by 12 percentage points, a relative gain of 42% in a critical measure of effectiveness. Patients also benefit from 2.9 additional months on therapy, a gain of nearly 45%.

- Price per month of therapy rose by $5,900, or 39% (3.4% CAGR), over the 10 years after adjusting for inflation. Individual monthly costs for eight of the new drugs ranged from $7,200 to $13,700, while two therapies indicated for very small populations of late-stage patients were priced higher. Total costs per patient ranged from $36,000 to $98,400 (except for blinatumumab), considerably less than the annualized costs sometimes cited.

Chart notes:
Prices are WAC or ASP. ASP for 2004 is Jan. 2005 inflated by 20.2%
Average yearly out of pockets costs for IV drugs have risen steeply in the U.S.

Average Yearly Out of Pocket Costs – Patients on Commercial Plans 2012–2013

- Between 2012 and 2013 out of pocket costs for IV cancer drugs grew by 71% and for orals by 16%.
- The period 2011–12 saw the launch of 20 new cancer drugs including 7 new biologics and the increases reflect the market uptake of these new launches.
- OOP costs have been impacted by plan designs and the increase in outpatient facility costs due to the consolidation of smaller group practices into larger hospital systems.

Chart notes:
OOP costs derived based on difference between allowed and paid. Costs include inpatient, outpatient and pharmacy costs.
Patients are actively gathering information about their disease online from a range of sources

Prostate Cancer Social Media Activity

- Social media and networking sites make a significant amount of rapidly evolving cancer-related content accessible to patients.
- Online communities like Wikipedia and information seeking through Google show varying volumes of activity, with views of the Wikipedia prostate cancer page at 4%–6% relative to Google searches for “prostate cancer.”
- Discussion boards, followed by Twitter, are the leading channels for brand conversations.
- Recognizing the growing role of social channels in dissemination of information in health care, in June 2014 the FDA issued best-practice guidances to pharma companies.
- These guidances cover presentation of risk and benefit information on drugs and correction of third-party information related to a company’s own drugs in social media.
- The guidances are a first step toward clear distinctions between patient- and pharma-generated content.

Chart notes: Average monthly searches, Geography – US, Language – English
Social media networks are used by patients throughout their cancer journey

Share of Social Media Discussion Topics by Patient Journey Stage

- Patient narratives unfold in social media throughout the cancer journey and there are key themes that dominate each stage of these journeys.
- In the diagnosis and pre-treatment stage for prostate cancer, tumor markers dominate 33% of conversations; and 26% of patients express disbelief and skepticism about their diagnosis.
- During treatment, 67% of conversations are about available options and 20% about preparation and information gathering for HCP visits.
- As survival rates improve and the numbers of patients living with prostate cancer increase, financial concerns (43%), active surveillance (25%) and emotional concerns (14%) are the key conversation topics.
- In view of this, resources like ASCO’s Compendium of practice tools for high-quality survivorship care to manage the psychosocial effects of cancer and financial or insurance concerns, are much-needed and timely.
Patients are discussing drug treatment options across multiple channels

Drug Treatments Discussion Channels

- Brand conversations occur across platforms but mostly on discussion boards and Twitter.
- Casodex, Eligard, Firmagon, Lupron and Zoladex brands are brands that lead on Discussion Boards.
- Twitter is the leading platform for Jevtana, Provenge, Taxotere, Xtandi and Zytiga.
- News sites, blogs, and publications are also channels for brand discussion but play a much smaller role than discussion boards and Twitter.
- Facebook and clinical trial sites contribute minimally to brand-related conversations.
Both positive and negative sentiments are expressed about specific drug options

Prostate Cancer Brand Sentiment on Social Media

- Patients express positive, neutral and negative sentiment about prostate cancer drug treatments.
- While sentiment varies for brands, sentiment scores aggregated across social platforms reveal a predominantly negative pattern.
- In prostate cancer, positive sentiment for the following brands Jevtana, Provenge and Zytiga is higher than for others.
- Patient conversations provide an important lens for tracking real-world data related to brand performance.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKT</td>
<td>Protein kinase B, an enzyme involved in cell signaling</td>
</tr>
<tr>
<td>ALK+</td>
<td>Possessing a mutation of the gene for production of anaplastic lymphoma kinase, a protein involved in cell growth</td>
</tr>
<tr>
<td>ALL</td>
<td>Acute lymphoblastic or acute lymphocytic leukemia, an aggressive form of blood cancer</td>
</tr>
<tr>
<td>ARG</td>
<td>Advanced and recurrent gastric cancer</td>
</tr>
<tr>
<td>BCR-ABL</td>
<td>A gene formed by fusion between parts of two chromosomes; associated with leukemia</td>
</tr>
<tr>
<td>BRAF</td>
<td>A protein involved in cell signaling and cell growth</td>
</tr>
<tr>
<td>CD40</td>
<td>A receptor protein on the surface of immune cells</td>
</tr>
<tr>
<td>CEL</td>
<td>Chronic eosinophilic leukemia</td>
</tr>
<tr>
<td>CISH</td>
<td>Chromogenic in situ hybridization, a technique for testing for biomarkers</td>
</tr>
<tr>
<td>c-KIT</td>
<td>A receptor protein on the surface of many cells; a tumor marker</td>
</tr>
<tr>
<td>CLL</td>
<td>Chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>CML</td>
<td>Chronic myeloid leukemia</td>
</tr>
<tr>
<td>CRC</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>CSF1R</td>
<td>Colony stimulating factor 1 receptor; a cell surface receptor; mutations associated with certain cancers</td>
</tr>
<tr>
<td>CTCL</td>
<td>Cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>Cytotoxic T-lymphocyte-associated protein 4</td>
</tr>
<tr>
<td>DFSP</td>
<td>Dermatofibrosarcoma protuberans, a soft tissue sarcoma in deep layers of skin</td>
</tr>
<tr>
<td>EGFR+</td>
<td>Possessing a mutation of the gene for production of epidermal growth factor receptor</td>
</tr>
<tr>
<td>EML4-ALK</td>
<td>A protein coded by an abnormal gene fusion; promotes lung cancer</td>
</tr>
<tr>
<td>FISH</td>
<td>Fluorescence in situ hybridization, a technique for testing for biomarkers</td>
</tr>
<tr>
<td>GIST</td>
<td>Gastrointestinal stromal tumor</td>
</tr>
<tr>
<td>HER2+</td>
<td>Possessing a gene for overexpression of human epidermal growth factor receptor 2, a cause of breast cancer</td>
</tr>
<tr>
<td>HES</td>
<td>Hypereosinophilic syndrome</td>
</tr>
<tr>
<td>IHC</td>
<td>Immunohistochemistry, a technique for testing for biomarkers</td>
</tr>
<tr>
<td>iNHL</td>
<td>Indolent non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>KIT</td>
<td>A cell surface receptor protein; mutations in the KIT gene are associated with various cancers</td>
</tr>
<tr>
<td>KRAS</td>
<td>A protein involved in cell signaling pathways, cell growth, and cell death; mutations of the KRAS gene can cause cancer</td>
</tr>
<tr>
<td>LAG3</td>
<td>A T-cell inhibitory receptor preventing T cells from being effective against tumor cells</td>
</tr>
<tr>
<td>MCL</td>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>MEK</td>
<td>A protein involved in cell signaling pathways; mutations of the MEK gene can cause cancer</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>MOA</td>
<td>Mechanism of action</td>
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<tr>
<td>MPD</td>
<td>Myeloproliferative disorder</td>
</tr>
<tr>
<td>MPS</td>
<td>Myelodysplastic syndrome</td>
</tr>
<tr>
<td>mTOR</td>
<td>Mechanistic target of rapamycin; a protein that helps control several cell functions, including cell division and survival, and binds to rapamycin and other drugs</td>
</tr>
<tr>
<td>NME</td>
<td>Necrolytic migratory erythema, a rash associated with pancreatic cancer</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Non–small cell lung cancer</td>
</tr>
<tr>
<td>ORR</td>
<td>Overall response rate</td>
</tr>
<tr>
<td>PD1</td>
<td>Programmed death 1</td>
</tr>
<tr>
<td>PDGFR</td>
<td>Platelet–derived growth factor receptor</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Programmed death ligand 1</td>
</tr>
<tr>
<td>Pi3K</td>
<td>A protein involved in cell signaling</td>
</tr>
<tr>
<td>PTCL</td>
<td>Peripheral T-cell lymphoma</td>
</tr>
<tr>
<td>TIM3</td>
<td>A T-cell inhibitory receptor</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor, a substance made by cells that stimulates new blood vessel formation</td>
</tr>
</tbody>
</table>
Notes on Sources

**IMS Real-World Data (RWD)** is the fit-for-purpose, broadest global set of Real-World Data available. It is de-identified patient level data from over 500 million patients across more than 25 countries. IMS RWD incorporates over 10 data types and provides the ability to examine nearly every disease. The most widely collected sources include electronic medical records, claims, longitudinal prescriptions, hospital encounters, and cross-sectional surveys with deep patient history.

**IMS MIDAS™** is an analytics platform used to assess worldwide healthcare markets. It aggregates IMS’s global audits and normalizes to international standards of product naming, company ownership, currency exchange rates, volume metrics and product segmentations, and estimates of price levels at different points in the supply chain. Price levels do not reflect off-invoice discounts, rebates, and patient access schemes. Segmentations include therapy classes, forms, dosages, and those related to brands, generics and patent protection.

**IMS LifeCycle™R&D Focus™** is a global database for evaluating the market for medicines, covering more than 31,000 drugs in R&D and over 8,900 drugs in active development worldwide. It includes information about the commercial, scientific and clinical features of the products, analyst predictions of future performance, and reference information on their regulatory stage globally.

**IMS Disease Insights™** draws on multiple IMS Health data sources and extensive primary market research to create patient-based insights and sales forecasts.

**Nexxus Social Media** provides Listening capabilities through healthcare-specific ontologies that make social media engagement possible and support healthcare organizations in the areas of market assessment, competitive intelligence, brand performance, risk management and consumer/healthcare professional engagement.
Authors

Murray Aitken  
Executive Director, IMS Institute for Healthcare Informatics

Murray Aitken is Executive Director, IMS Institute for Healthcare Informatics, which provides policy setters and decision makers in the global health sector with objective insights into healthcare dynamics. He assumed this role in January 2011. Murray previously was Senior Vice President, Healthcare Insight, leading IMS Health’s thought leadership initiatives worldwide. Before that, he served as Senior Vice President, Corporate Strategy, from 2004 to 2007. Murray joined IMS Health in 2001 with responsibility for developing the company’s consulting and services businesses. Prior to IMS Health, Murray had a 14-year career with McKinsey & Company, where he was a leader in the Pharmaceutical and Medical Products practice from 1997 to 2001. Murray writes and speaks regularly on the challenges facing the healthcare industry. He is editor of Health IQ, a publication focused on the value of information in advancing evidence-based healthcare, and also serves on the editorial advisory board of Pharmaceutical Executive. Murray holds a Master of Commerce degree from the University of Auckland in New Zealand, and received an M.B.A. degree with distinction from Harvard University.

Lee Blansett  
Senior Principal P&MA Consulting, IMS Health

Lee is a Senior Principal in P&MA Consulting in the U.S. He currently serves as the IMS Consulting Group’s representative to IMS Health’s Global Oncology Initiatives.

Lee has twenty years of experience working with, consulting to, and studying providers and payers in the U.S. and EU. He has extensive experience with hospital and community oncology providers, with commercial and public reimbursement, and with managed care, including contracting and medical management.

Prior to IMS, he led research and analysis for DaVinci’s publications Oncology Market Access—U.S., and Oncology Market Access—EU. Lee has an M.B.A. in Entrepreneurial Studies at The Wharton School, University of Pennsylvania. and a B.Sc. in Finance at Santa Clara University, where he was a National Merit Scholar.
Radha Mawrie
Senior Manager, IMS Health

Radha Mawrie is a Senior Manager at IMS Health and works on new product development in the global oncology business. Radha’s prior experience is in healthcare information services and includes launching evidence-based decision support tools to meet the needs of healthcare stakeholders, including hospitals and physicians across multiple specialties. She previously worked at Reed Elsevier and Wolters Kluwer Health.

Radha holds an MBA from the Indian Institute of Management, Bangalore.
About the Institute

The IMS Institute for Healthcare Informatics leverages collaborative relationships in the public and private sectors to strengthen the vital role of information in advancing healthcare globally. Its mission is to provide key policy setters and decision makers in the global health sector with unique and transformational insights into healthcare dynamics derived from granular analysis of information.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved patient care. With access to IMS Health’s extensive global data assets and analytics, the Institute works in tandem with a broad set of healthcare stakeholders, including government agencies, academic institutions, the life sciences industry and payers, to drive a research agenda dedicated to addressing today’s healthcare challenges.

By collaborating on research of common interest, it builds on a long-standing and extensive tradition of using IMS Health information and expertise to support the advancement of evidence-based healthcare around the world.
### Research Agenda

The research agenda for the Institute centers on five areas considered vital to the advancement of healthcare globally:

- The effective use of information by healthcare stakeholders globally to improve health outcomes, reduce costs and increase access to available treatments.
- Optimizing the performance of medical care through better understanding of disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.
- Understanding the future global role for biopharmaceuticals, the dynamics that shape the market and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.
- Researching the role of innovation in health system products, processes and delivery systems, and the business and policy systems that drive innovation.
- Informing and advancing the healthcare agendas in developing nations through information and analysis.

### Guiding Principles

The Institute operates from a set of Guiding Principles:

- The advancement of healthcare globally is a vital, continuous process.
- Timely, high-quality and relevant information is critical to sound healthcare decision making.
- Insights gained from information and analysis should be made widely available to healthcare stakeholders.
- Effective use of information is often complex, requiring unique knowledge and expertise.
- The ongoing innovation and reform in all aspects of healthcare require a dynamic approach to understanding the entire healthcare system.
- Personal health information is confidential and patient privacy must be protected.
- The private sector has a valuable role to play in collaborating with the public sector related to the use of healthcare data.
The IMS Institute for Healthcare Informatics
100 IMS Drive, Parsippany, NJ 07054, USA

About IMS Health
IMS Health is a leading global information and technology services company providing clients in the healthcare industry with comprehensive solutions to measure and improve their performance. End-to-end proprietary applications and configurable solutions connect 10+ petabytes of complex healthcare data through the IMS One™ cloud-based master data management platform, providing comprehensive insights into diseases, treatments, costs and outcomes. The company’s 15,000 employees blend global consistency and local market knowledge across 100 countries to help clients run their operations more efficiently. Customers include pharmaceutical, consumer health and medical device manufacturers and distributors, providers, payers, government agencies, policymakers, researchers and the financial community.

As a global leader in protecting individual patient privacy, IMS Health uses anonymous healthcare data to deliver critical, real-world disease and treatment insights. These insights help biotech and pharmaceutical companies, medical researchers, government agencies, payers and other healthcare stakeholders to identify unmet treatment needs and understand the effectiveness and value of pharmaceutical products in improving overall health outcomes. Additional information is available at www.imshealth.com.

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