KAISER ASSOCIATES

HOT INDICATIONS LIST

A global analysis of pharmaceutical investment intensity across 12,000+ R&D programs

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INTRODUCTION

ABOUT THE HOT INDICATIONS LIST

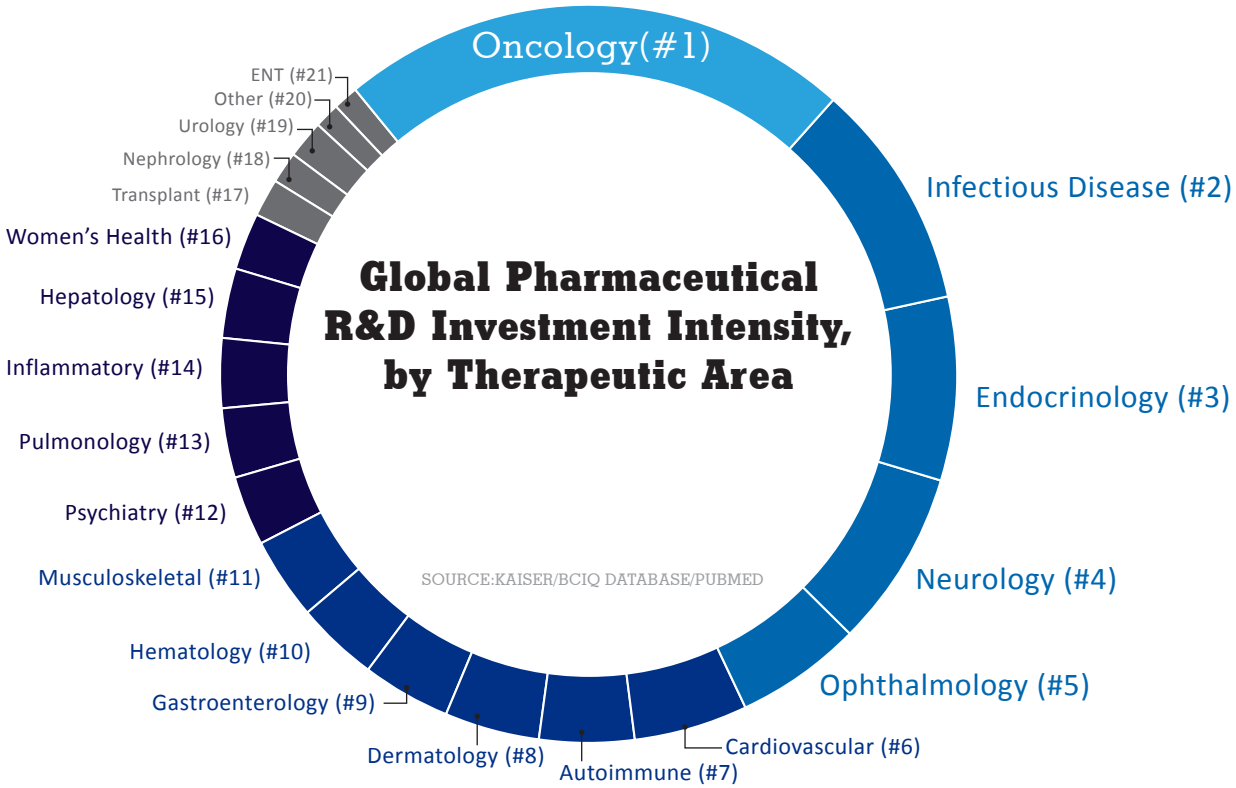
The pharmaceutical landscape is seeing unprecedented progress in the development of therapeutics for some of the most challenging diseases and disorders. In 2014, the FDA approved 41 new drugs, the highest recorded number since 1996. Throughout the year, Life Sciences publications were flooded with headlines about newly available drugs for hepatitis C, diabetes, and a variety of cancers, including melanoma, lymphoma, and lung cancer. There is no doubt that these indications were "hot" in 2014, and the companies bringing these novel treatments to market are well positioned to benefit from the momentum behind these diseases.

The ultimate question pharmaceutical companies will continue to ask themselves this year is **"What is the next big thing?"** More importantly, they will ask **"What is the next big thing for our company's portfolio?"**

To begin to answer these questions, Kaiser Associates conducted a comprehensive analysis of nearly **every pharma R&D program in the world**—over 12,000 programs across almost 600 indications. We developed a proprietary index that considers trends in development investment, fundraising, and scientific generation. The goal of our analysis is to predict which indications will be "hot" over the next 5+ years, based on the future indicators of therapeutics innovation.

Kaiser's Hot Indications List is the only global analysis of pharmaceutical investment intensity that considers new drug development investments from industry, financial markets, and the scientific community. We hope you find these insights useful and please, contact us to learn more about specific indications, or how this analysis can support your company's portfolio planning efforts.

THERAPEUTIC AREA RANKINGS



Throughout our analysis, high-ranking Therapeutic Areas (TAs) tend to have at least one thing in common—a focus on innovation for high burden diseases. The potential to introduce treatment options to highly underserved populations, along with demand supporting high prices, is attracting an unprecedented level of investment. This trend is common across the top 5 TAs, representing over half of the industry's overall efforts, and the top 12 that comprise 80%.

Oncology is the clear stand-out TA, and demonstrates a "king effect" in every evaluation category. Investment intensity for Oncology is twice as high as the next TA, and 26 of the Top 100 Hot Indications are cancers. The 979 companies developing Oncology drugs are represented by many big industry players and very well-funded smaller companies, with both groups investing fairly equally in treatments for both solid tumors and blood-borne cancers. These companies raised over $4B from venture capital (VC) and initial public offerings (IPOs) events in 2014 alone, which may suggest a trend towards over-investment and possibly over-valuation. This glut of investment will likely mean longer-term that prices will come down as more me-too products enter the market, and payers begin to push back with more options available. Regardless, Oncology will continue to be an exciting space for companies and investors to support the wide array of innovative treatments in development.

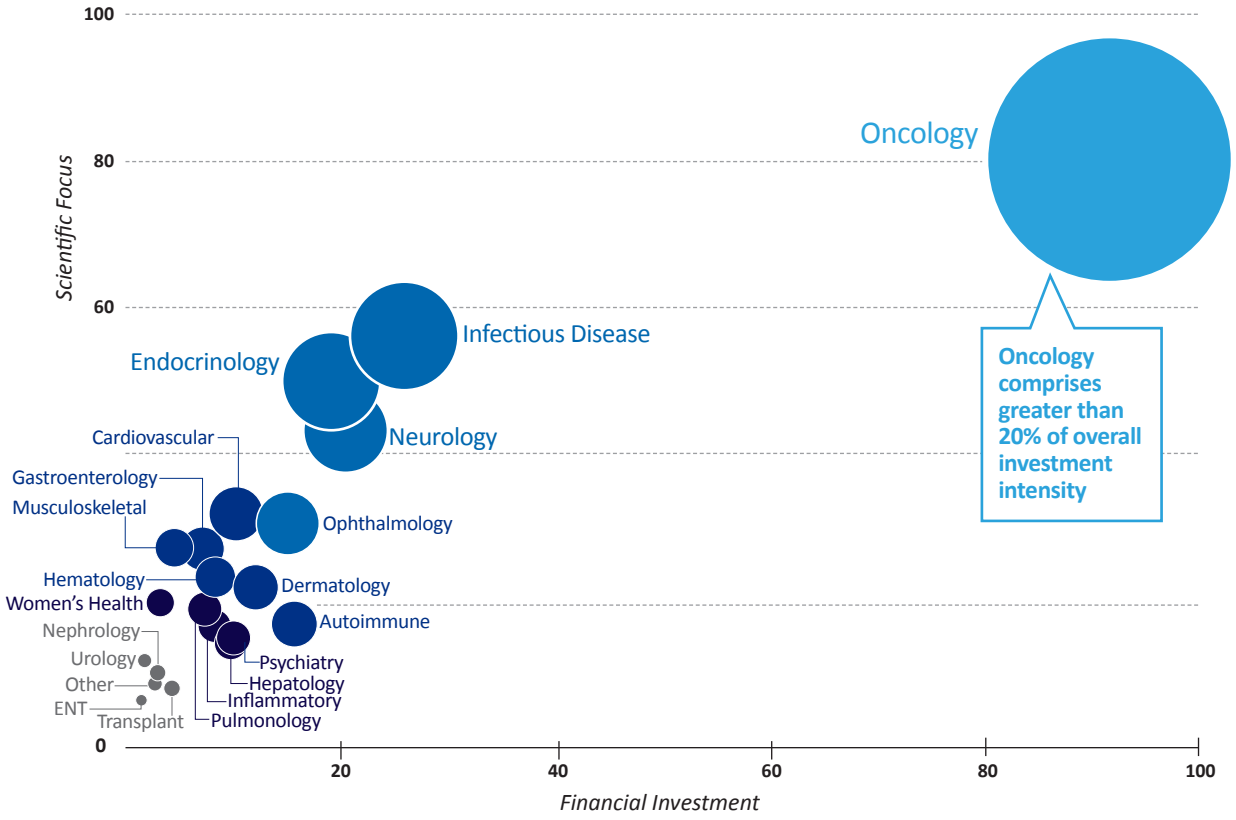
Infectious Disease is a surprising #2 in the TA ranking, especially given that the leading indication, **bacterial infections (#15)**, is a highly genericized market. Infectious Disease is strongly driven by viral indications, with GSK in particular providing much of the innovation through vaccines for **influenza (#18)**, **HIV / AIDs (#28)**, **dengue fever (#63)**, and **cytomegalovirus (#68)**, amongst others.

Endocrinology's #3 rank is due in large part to **diabetes (#4)**, which has the second highest number of overall programs, as well as **obesity (#30)**. Both indications received a significant amount of VC funding, over $200M each; however, the TA ranked unexpectedly low for IPOs at #11 overall. The Endocrinology pipeline is not without innovation, but investment seems to be driven more by growth in prevalence and global patient populations than by new technologies.

Cardiology, despite being the most prevalent category,

Therapeutic Area Drug Development Intensity, with Contributing Factors

Scientific Focus score includes clinical programs by stage, total publications and one-year growth in publications
Financial Investment score includes 2014 VC funding, 2014 IPO values, and historical number of FDA approvals by company
Bubble size represents the total R&D Investment Intensity for all indications in the Therapeutic Area



SOURCE: KAISER/BCIQ DATABASE/PUBMED

is towards the middle of the pack at #6. There are some mega-blockbusters on the near-term horizon in Cardiology, such as Novartis' *Entresto®* and Amgen's PCSK9 inhibitor *Repatha®*, which analysts project will each surpass $5B in global sales. However, lower investment activity from IPOs and VCs is likely due to the genericization of drugs for such common indications as **hypertension (#71)** and risk of **myocardial infarction (#76)**.

Urology and Women's Health are both surprisingly void of investment. Despite the big Urology markets for **overactive bladder / incontinence (#138)**, **benign prostatic hyperplasia (#197)**, and **erectile dysfunction (#245)**, there is virtually no drug innovation in Urology outside of **prostate cancer (#5)**, and to a lesser extent, **bladder cancer (#89)**. However, both of these indications are grouped in Oncology in our analysis. **Interstitial cystitis (#98)** is the only Women's Health-related indication in the Top 100, with 14 total programs that are all Phase II or earlier.

The final sections of this analysis include detailed Deep Dives into four Therapeutic Areas that we found to have particularly interesting pipeline technologies, investment trends, and market dynamics. As mentioned above, Oncology stands head and shoulders above the other TAs in virtually all aspects. Neurology includes an interesting mix of high-prevalence disorders, such as the top ranked indication **pain (#1)**, as well as a host of rare diseases like **Huntington's disease (#104)**, which is also profiled in the Ten Emerging Orphans section. Gastroenterology continues to mature, as the highest levels of investment intensity focus on rounding out treatment options for **ulcerative colitis (#27)** and **Crohn's disease (#43)**. And Ophthalmology draws high levels of VC and IPO investments to fund the development of innovative treatments for retina disorders like **age-related macular degeneration (#14)**, as well as other eye conditions.

THE HOT INDICATIONS LIST

Top 50 Hot Indications based on 2014 Investment Intensity: Pipeline Score, R&D Funding, and Academic Focus

RANK	INDICATION	THERAPEUTIC AREA	PROGRAMS
1	Pain	Neurology	343
2	Breast cancer	Oncology	307
3	Non-small cell lung cancer (NSCLC)	Oncology	197
4	Diabetes	Endocrinology	338
5	Prostate cancer	Oncology	198
6	Pancreatic cancer	Oncology	174
7	Colorectal cancer	Oncology	172
8	Rheumatoid arthritis (RA)	Autoimmune	223
9	Acute myelogenous leukemia (AML)	Oncology	137
10	Alzheimer's disease (AD)	Neurology	230
11	Liver cancer	Oncology	117
12	Depression	Psychiatry	64
13	Non-Hodgkin's lymphoma (NHL)	Oncology	93
14	Age-related macular degeneration (AMD)	Ophthalmology	92
15	Bacterial infections	Infectious	112
16	Schizophrenia	Psychiatry	65
17	Multiple sclerosis (MS)	Autoimmune	129
18	Influenza virus	Infectious Disease	148
19	Lupus	Autoimmune	58
20	Ovarian cancer	Oncology	159
21	Psoriasis	Dermatology	96
22	Acute lymphoblastic leukemia (ALL)	Oncology	33
23	Brain cancer	Oncology	156
24	Chronic lymphocytic leukemia (CLL)	Oncology	64
25	Multiple myeloma (MM)	Oncology	113

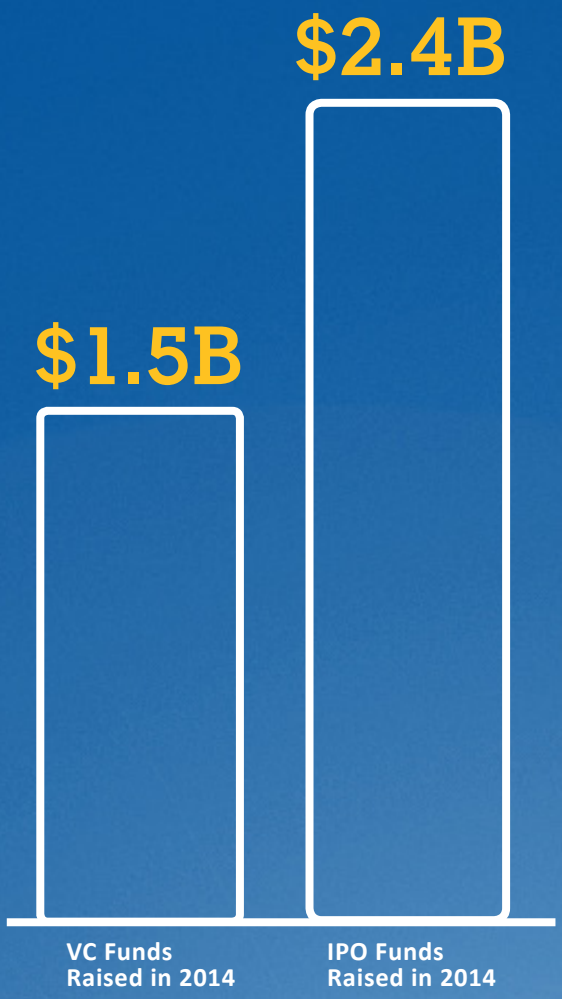
THE HOT INDICATIONS LIST

RANK	INDICATION	THERAPEUTIC AREA	PROGRAMS
26	Melanoma	Oncology	161
27	Ulcerative colitis	Gastroenterology	104
28	HIV / AIDS	Infectious Disease	131
29	Hepatitis C virus (HCV)	Hepatology	111
30	Obesity	Endocrinology	70
31	Diabetic macular edema (DME)	Ophthalmology	27
32	Neuroendocrine tumors	Oncology	34
33	Allergy	Inflammatory	52
34	Acne	Dermatology	36
35	Asthma	Inflammatory	141
36	Anemia	Hematology	43
37	B-cell lymphoma	Oncology	69
38	Graft-versus-host disease (GvHD)	Transplant	34
39	Parkinson's disease (PD)	Neurology	139
40	Gastric cancer	Oncology	68
41	Head and neck cancer	Oncology	71
42	Renal cancer	Oncology	73
43	Crohn's disease	Gastroenterology	61
44	Dermatitis	Dermatology	69
45	Liver disease	Hepatology	35
46	Pulmonary fibrosis	Pulmonology	45
47	Heart failure	Cardiovascular	65
48	Liver fibrosis	Hepatology	20
49	Ischemia / reperfusion injury	Cardiovascular	61
50	Glaucoma	Ophthalmology	61

SOURCE: KAISER/BCIQ DATABASE/PUBMED

TOP INDICATIONS TEN

PROGRAM **2014** HIGHLIGHTS



992
Companies with Top 10 indications

31
Initial Public Offerings

42
Companies Raised VC Funding

2,319
Drug Programs

SOURCE: KAISER/BCIQ DATABASE

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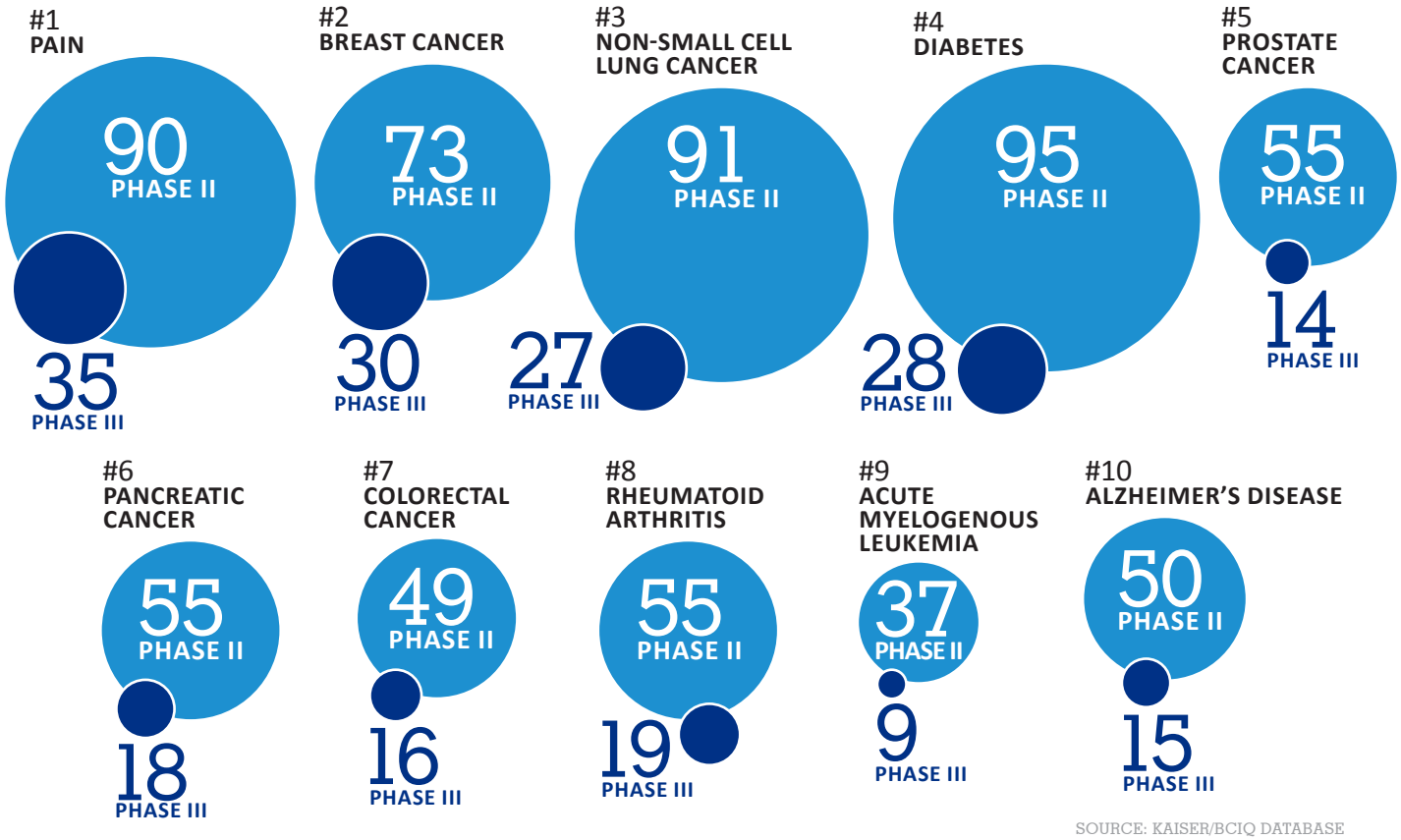
TOP TEN INDICATIONS

Late Stage Pipelines for Top Ten Indications, by Phase



SOURCE: KAISER/BCIQ DATABASE

The pipelines of the Top 10 Hot Indications tell an interesting story. Despite Oncology dominating the Top 10 overall, **pain (#1)** and **diabetes (#4)** lead the pack in late stage (Phases II and III) programs.

Amongst the 6 Oncology indications in the Top 10, companies with programs for **breast cancer (#2)** and **non-small cell lung cancer (#3)** have the most late-stage "shots on goal," and are being developed by a broad field of companies. Novartis, Bristol-Myers Squibb, Amgen, and Roche/Genentech are among the leading Large Cap companies developing late-stage Oncology drugs with indications in our Top 10. Pfizer and Eli Lilly have developed robust pipelines that span our Top 10, including late stage programs for pain, diabetes, **rheumatoid arthritis (#8)**, **Alzheimer's disease (#10)**, and a multitude of Oncology therapies for Top 10 Indications.

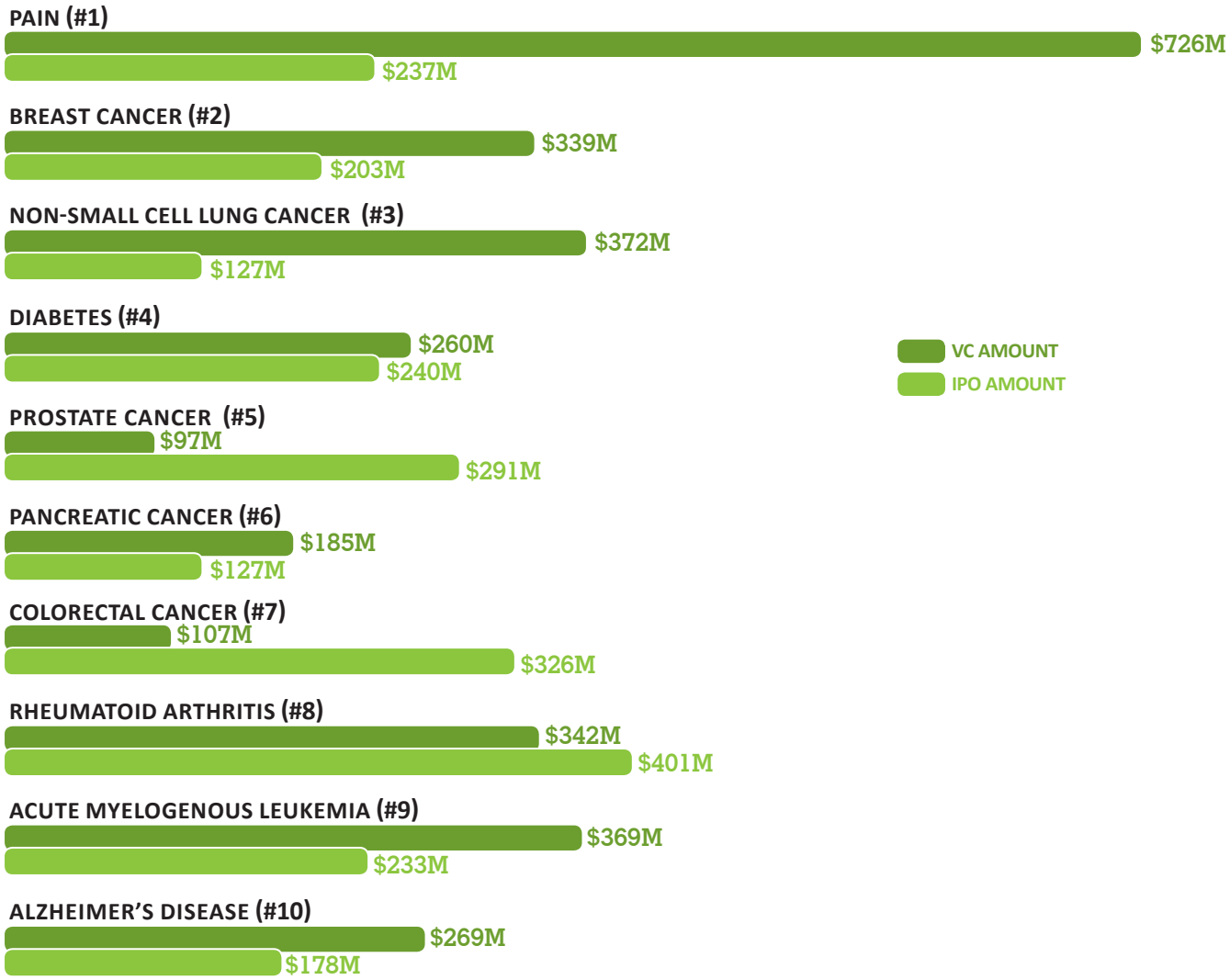
Clinical-stage companies are also providing meaningful Phase III candidates, which may offer big players additional opportunities to capture share and enter markets earlier through licensing and acquisition. For example, Northwest Biotherapeutics is awaiting partnership to enter Phase III trials for its *DCVax*® technology for **prostate cancer (#5)**, in addition to its ongoing Phase III trial for **brain cancer (#23)**. Other notable clinical-stage portfolios include Synta Pharmaceutical, which has Phase III for non-small cell lung cancer and **acute myelogenous leukemia (#9)**, and Nektar Therapeutics with several un-partnered candidates for complementary pain indications.

2014 was also a big year for investment in our Top 10 Indications. Across these indications, 42 companies received VC funding totaling nearly $1.5B in investments.

TOP TEN INDICATIONS

Funds Raised from IPOs and VC in 2014, for Top 10 Indications

Sum of funds raised by companies with at least one program



SOURCE: KAISER/BCIQ DATABASE

Moreover, many venture capitalists saw sizable liquidity events, with 31 IPOs representing nearly $2.4B.

The market is witnessing a tremendous amount of development investment intensity from clinical-stage portfolio companies with targeted pipelines, particularly in Oncology. These startups typically leverage a core platform technology for targeted therapeutic areas, and have garnered overwhelming, albeit highly speculative, attention from the investor community. For example, last year Juno Therapeutics raised over $614M from 2 rounds of VC funding and an IPO to support its early stage portfolio of CAR and TCR cancer-fighting technologies. Similarly, Intarcia Therapeutics landed $210M in VC, estimated to be the largest private biotech funding in 25 years, to fund its only program—a Phase III trial for ITCA 650 in type 2 diabetes.

Kaiser expects to see significant sustained drug development investment within these Top 10 Indications for the foreseeable future.

TEN EMERGING ORPHANS

PROGRAM **2014** HIGHLIGHTS

225
Companies with Programs for Emerging Orphans

12
Initial Public Offerings

14
Companies Raised VC Funding

278
Drug Programs

SOURCE: KAISER/BCIQ DATABASE/FDA OFFICE OF ORPHAN PRODUCTS DEVELOPMENT

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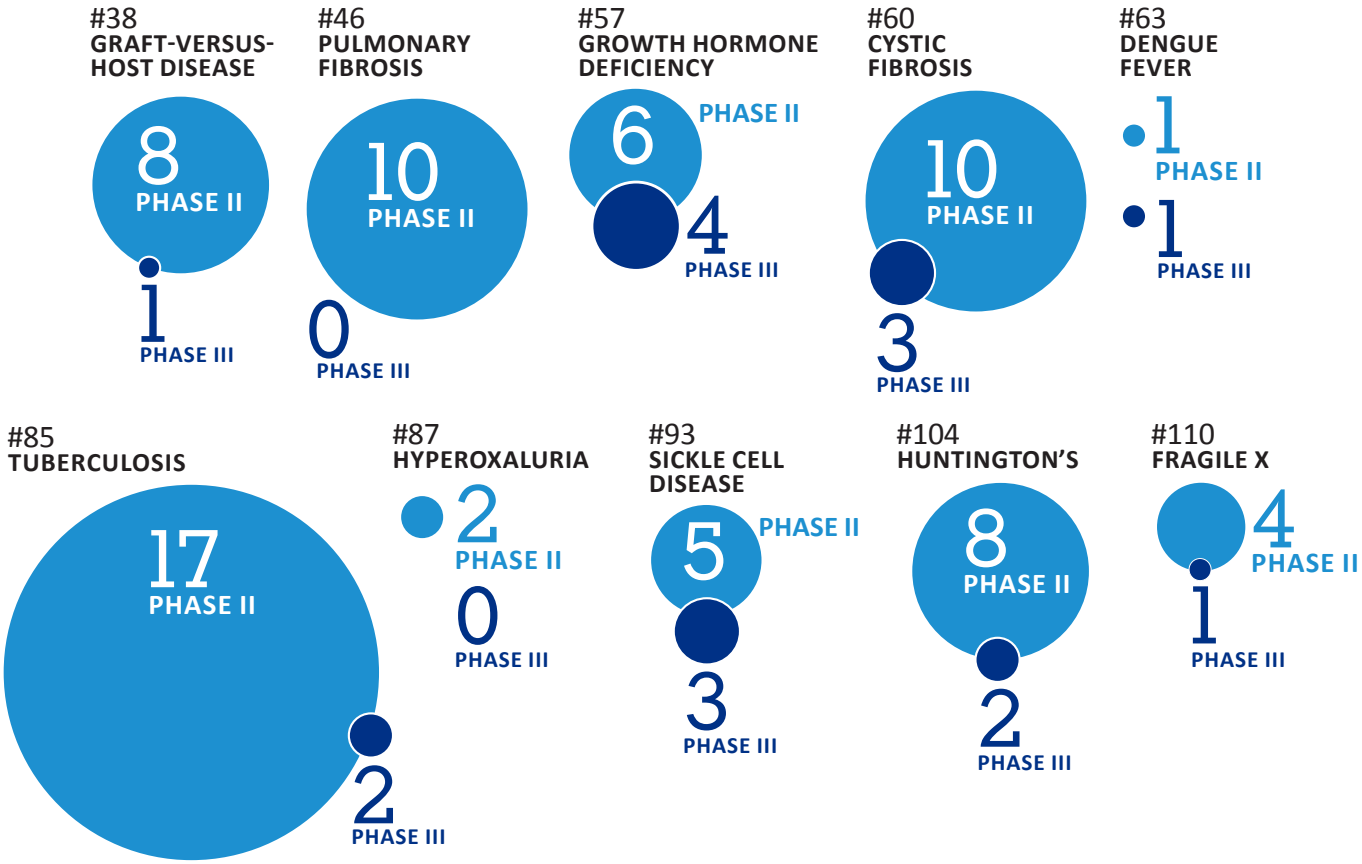
Late Stage Pipelines for 10 Emerging Orphan Indications, by Phase



SOURCE: KAISER/BCIQ DATABASE/FDA OFFICE OF ORPHAN PRODUCTS DEVELOPMENT

Over the past several years, the pharmaceutical market has seen a tidal shift in the interest from big industry players to pursue drugs for orphan diseases and disorders. Orphan designations not only offer financial and regulatory incentives, but they often represent lucrative opportunities to address some of the world's most debilitating diseases. Given this trend, it is not surprising that indications for orphan diseases are well represented in the Hot Indications List.

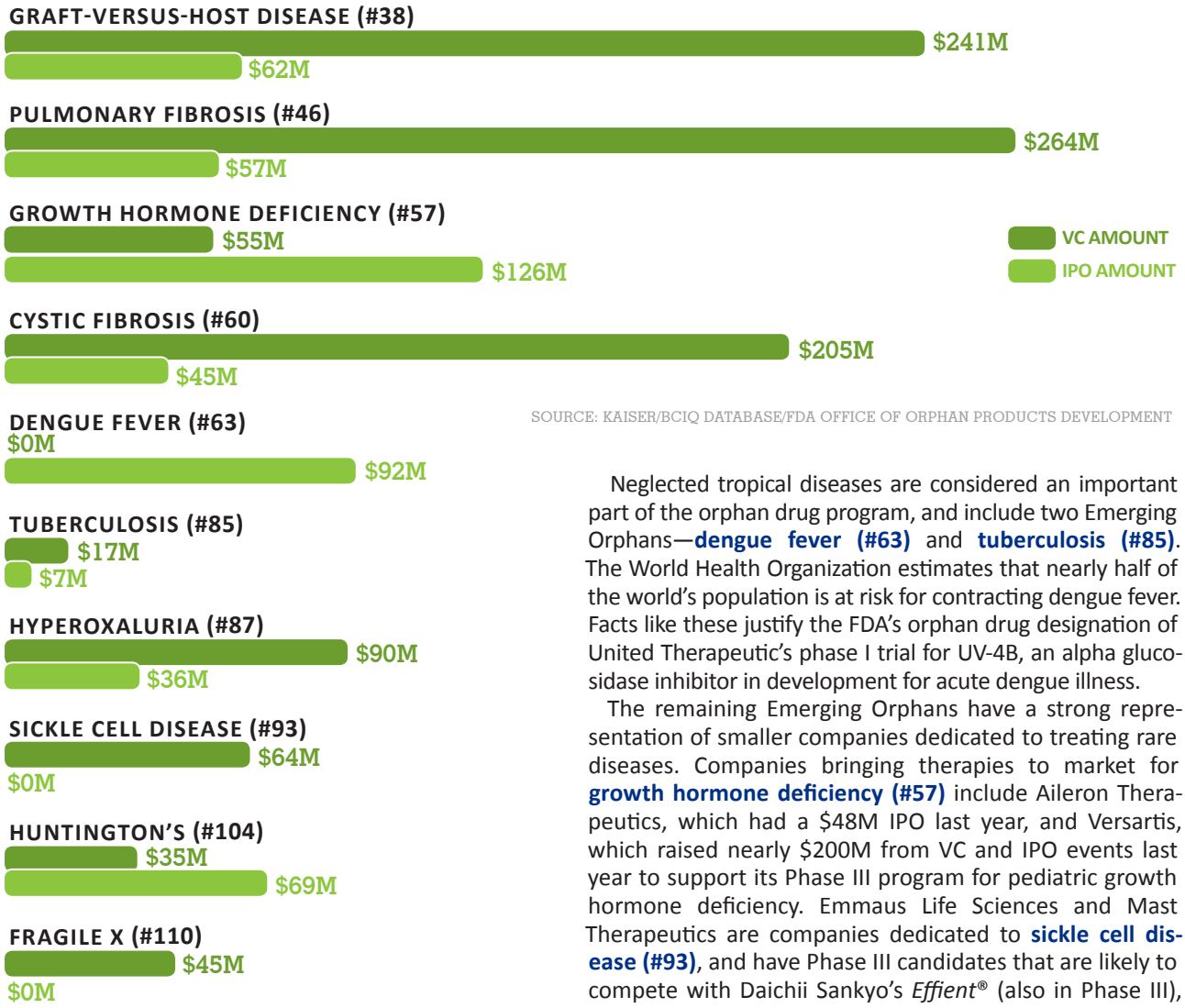
Kaiser's list of 10 Emerging Orphans focuses on *rare* diseases that meet the FDA prevalence threshold of 200,000 affected persons in the US, as well as *neglected tropical* diseases that affect large, often under-resourced populations outside the US. All indications included in this group have ongoing programs that have been given orphan designation by the FDA in the past few years. Oncology indications have been excluded from the 10 Emerging Orphans due to their strong representation in other sections of this analysis.

Closely related to Oncology, **graft-versus-host disease (GvHD) (#38)** is the highest ranking non-Oncology orphan indication. GvHD drug development has benefitted from recent scientific research focused on blood-borne cancers and the large financial investments this field has received. For example, Bellicum Pharmaceuticals raised $230M from two VC rounds and an IPO last year to support its 3 clinical-stage programs, 2 of which focus on GvHD risk mitigation. Kymab raised $40M in venture financing to fund its extensive early-stage Immunology and Oncology pipeline, including an anti-OX40L monoclonal antibody candidate for GvHD. Jazz Pharmaceuticals soon expects to announce the results of its Phase III European trials for *Leukotac*®, which is being developed for steroid refractory acute GvHD.

Pulmonology-related diseases also rank quite high amongst non-Oncology orphans, attributed to high-value

Funds Raised from IPOs and VC in 2014, for Emerging Orphan Indications

Sum of funds raised by companies with at least one program



SOURCE: KAISER/BCIQ DATABASE/FDA OFFICE OF ORPHAN PRODUCTS DEVELOPMENT

IPOs and strong Phase II pipelines for both **pulmonary fibrosis (#46)** and **cystic fibrosis (CF) (#60)**. Cystic fibrosis in particular may be better classified as a "re-emerging" orphan disease, as both *Pulmozyme*® (Genentech) and tobramycin were early beneficiaries of the Orphan Drug Act of 1983 and offered significant advancements in the treatment of CF. This trend of innovation in CF therapies continues today, led by Vertex Pharmaceuticals with two late-stage programs, and PTC Therapeutics with *Translarna*® in Phase III trials. Nivalis Therapeutics (formerly N30 Pharmaceuticals) is an intriguing clinical-stage company with four early-stage small molecule candidates, all in development for cystic fibrosis. The company raised $30M in VC funding in 2014, and recently held an IPO in June 2015 worth nearly $89M.

Neglected tropical diseases are considered an important part of the orphan drug program, and include two Emerging Orphans—**dengue fever (#63)** and **tuberculosis (#85)**. The World Health Organization estimates that nearly half of the world's population is at risk for contracting dengue fever. Facts like these justify the FDA's orphan drug designation of United Therapeutic's phase I trial for UV-4B, an alpha glucosidase inhibitor in development for acute dengue illness.

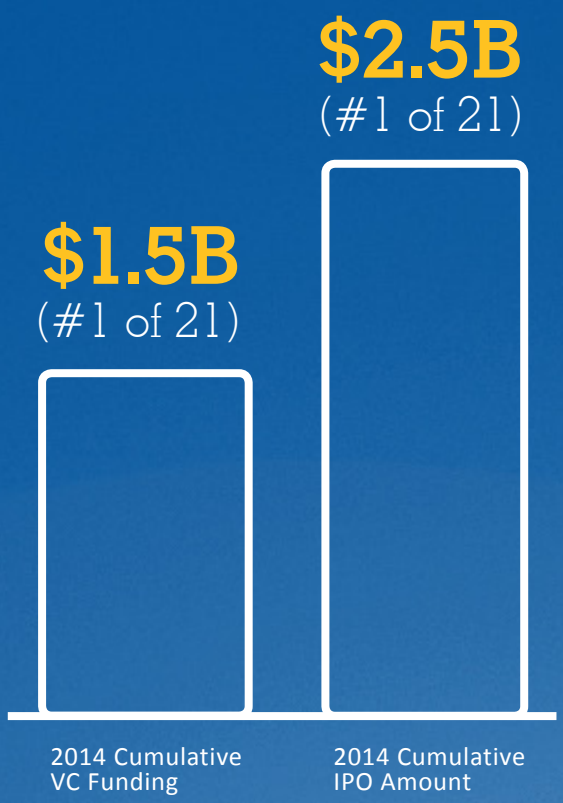
The remaining Emerging Orphans have a strong representation of smaller companies dedicated to treating rare diseases. Companies bringing therapies to market for **growth hormone deficiency (#57)** include Aileron Therapeutics, which had a $48M IPO last year, and Versartis, which raised nearly $200M from VC and IPO events last year to support its Phase III program for pediatric growth hormone deficiency. Emmaus Life Sciences and Mast Therapeutics are companies dedicated to **sickle cell disease (#93)**, and have Phase III candidates that are likely to compete with Daichii Sankyo's *Effient*® (also in Phase III), as well as GlycoMimetic's phase II rivipansel.

Huntington's disease (HD) (#104) is garnering notable investment intensity, largely due to increased public awareness driven by patient advocacy efforts. Auspex Pharmaceuticals' (recently acquired by Teva) lead candidate, a small molecule VMAT2 inhibitor, is in Phase III trials for chorea associated with Huntington's disease, and earned it $35M in private funding in 2014 prior to an IPO worth nearly $97M. Pfizer is developing an orphan-designated treatment for HD, a PDE10 inhibitor in Phase II trials. The **fragile X syndrome (#110)** pipeline is comprised of a similar mix of companies on a smaller scale. Seaside Therapeutics leads the way with two late-stage candidates that have been granted orphan status by the FDA, including the only Phase III program for fragile X.

DEEP ONCOLOGY DIVE

PROGRAM 2014 HIGHLIGHTS

(# OF 21) INDICATES TA RANK



979
COMPANIES
(#1 of 21)

319,352
PUBLICATIONS
(#1 of 21)

1,295
PHASE II &III PROGRAMS
(#1 of 21)

INDICATIONS IN TOP 100:

Breast cancer (#2)
Non-small cell lung cancer (#3)
Prostate cancer (#5)
Pancreatic cancer (#6)
Colorectal cancer (#7)
Acute myelogenous leukemia (#9)
Liver cancer (#11)
Non-Hodgkin's lymphoma (#13)
Ovarian cancer (#20)
Acute lymphoblastic leukemia (#22)
Brain cancer (#23)
Chronic lymphocytic leukemia (#24)
Multiple myeloma (#25)
Melanoma (#26)
Neuroendocrine tumors (#32)
B-cell lymphoma (#37)
Gastric cancer (#40)
Head and neck cancer (#41)
Renal cancer (#42)
Gastrointestinal stromal cancer (#54)
Small cell lung cancer (#61)
Cutaneous T-cell lymphoma (#65)
Chronic myelogenous leukemia (#70)
Thyroid cancer (#84)
Bladder cancer (#89)
Cervical cancer (#99)

SOURCE: KAISER/BCIQ DATABASE/PUBMED

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THERAPEUTIC AREA SPOTLIGHT

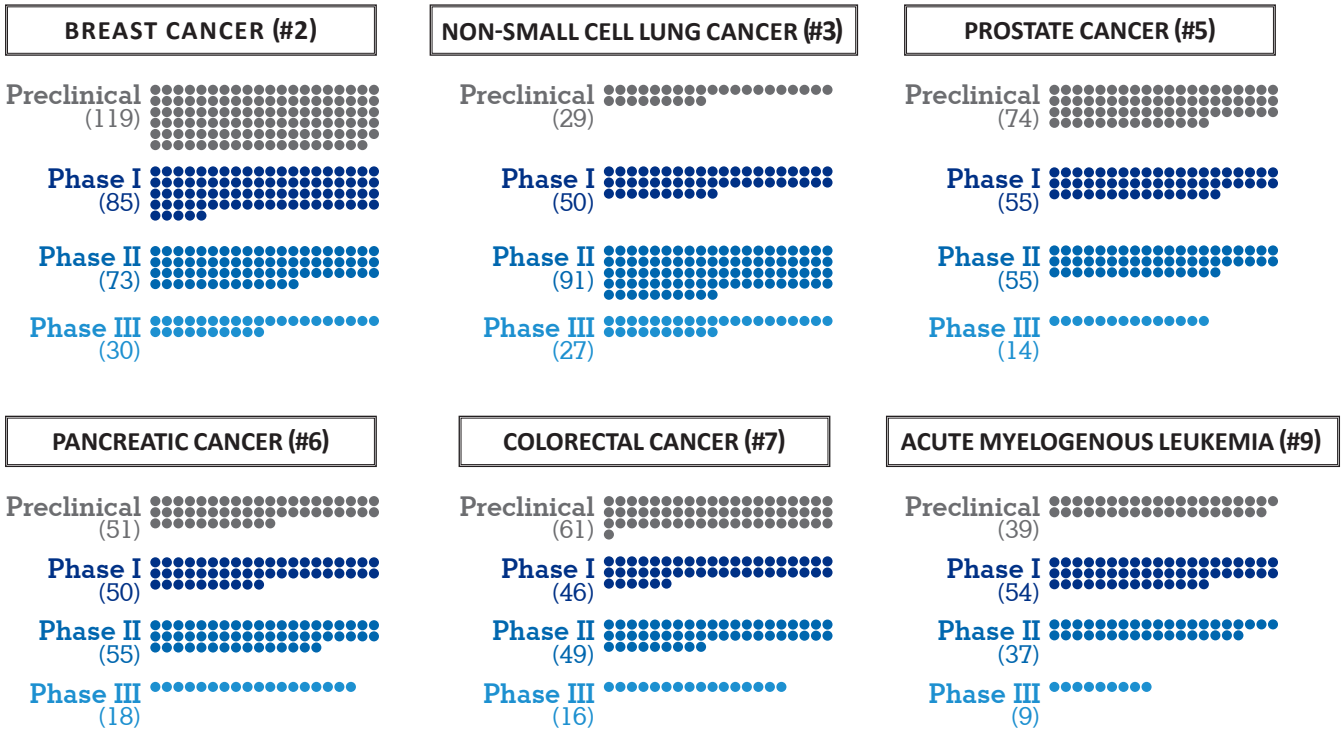
ONCOLOGY

Oncology encompasses a range of solid and blood-based cancer conditions. Oncology ranks first by a wide margin in the Therapeutic Area Rankings, and has 26 Hot Indications within the Top 100, including 6 of the top 10 indications.

Oncology leads all other TAs in every category, including a number of development programs; number of companies; VC & IPO funding; and number of publications—indicating it is at the center of incredible commercial *and* academic interest. While Oncology is the focus of a significant amount of investment, the Oncology pipeline also shows a high level of duplication, with more than 20% of pipeline Oncology programs addressing one of just 8 potential targets (e.g., mTor, VEGF/VEGFR, PDGF, HER2, etc.).

Industry investment in Oncology tends to focus on the subset of potential targets that have been validated with clinical data. Companies developing drugs against these targets benefit from some level of clinical de-risking, however, they face the challenge of "differentiation risk." The companies best equipped to overcome differentiation risk are those with the scale and resources to invest in additional studies and indications to drive better product labels over time. The industry focus on a limited number of targets also leaves broad white space opportunities further afield for companies with a greater appetite for risk.

Number of Programs by Stage of Development

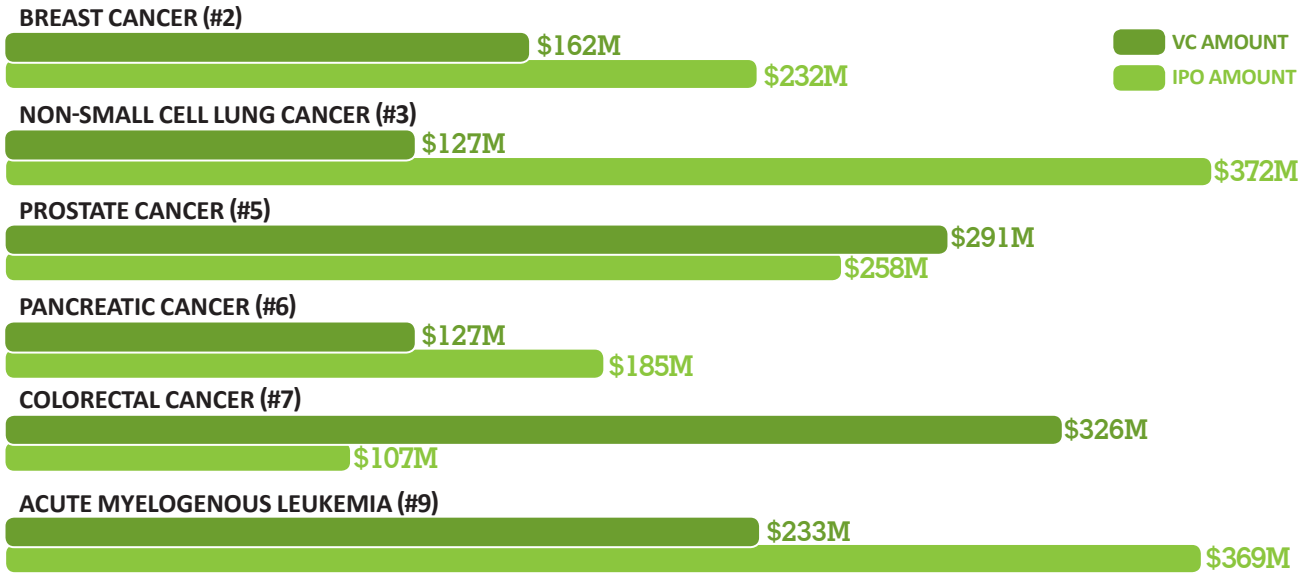


SOURCE: KAISER/BCIQ DATABASE

ONCOLOGY

Funds Raised from IPOs and VC in 2014, by Indication

Sum of funds raised by companies with at least one program



SOURCE: KAISER/BCIQ DATABASE

The hottest area of research in Oncology at the moment is the field of cancer immunotherapy—the use of the body's immune system to fight tumors. Cancer immunotherapy treatments fall into four broad categories: checkpoint inhibitors, TNF receptor agonists, cell therapies, and cancer vaccines. Several companies leading the charge in cancer immunotherapy were involved in notable 2014 funding events. Juno Therapeutics was involved in one of the largest Oncology-related IPOs in 2014, at $265M. Juno focuses on the cell therapy approach to cancer immunotherapy, with clinical and preclinical programs targeting **non-small cell lung cancer (#3)**, **acute myelogenous leukemia (#9)**, **non-Hodgkin's lymphoma (#13)**, **acute lymphoblastic leukemia (#23)**, and **B-cell lymphoma (#37)**. More recently, Juno struck a $1B deal with Celgene in June 2015 to partner on cancer and autoimmune research and drug development. The top Oncology indications identified by Kaiser correlate well with the largest cancer conditions (based on global incidence). Companies investing in Oncology hope to develop innovative and clinically differentiated treatments to gain access to the largest cancer patient populations. High disease severity and significant unmet need offer attractive pricing dynamics, even in the largest Oncology indications. With innovator companies retaining significant pricing power (for now) in the largest mass-market cancer indications, there is less incentive for these companies to invest in developing treatments for less-prevalent cancers.

The recent acquisition of Pharmacyclics by AbbVie provides an excellent example of market dynamics in Oncology today. AbbVie paid approximately $21B for a company with one approved $500M drug (for which it splits the revenue with J&J) and 2 Phase II programs in development. Many would argue that AbbVie drastically overpaid for this company, although given *Imbruvica's*® record-setting number of Breakthrough designations, its approval for **mantle cell lymphoma (#196)** based on Phase II data, and its impressive pipeline of Oncology indications, AbbVie and its supporters believe this is a bet worth taking.

Overall, Oncology emerges as the most heavily-competed therapeutic area, with a strong industry pipeline and small-player landscape supported by industry-leading VC and IPO investment. Many feel that Oncology is beginning to resemble a "gold rush," with a surplus of available capital chasing after every hot new opportunity until valuations bear little resemblance to reality of a company's pipeline. New technologies, such as immuno-oncology treatments, offer the potential to truly revolutionize patient outcomes. However, increasing payer and government pushback on pricing will demand a compelling "value story" in order to drive desired pricing. Oncology is a therapeutic area that almost every big player feels they have to be in. However, the potential pitfalls are as challenging as the potential rewards are large.

DEEP NEUROLOGY DIVE

PROGRAM 2014 HIGHLIGHTS

(# OF 21) INDICATES TA RANK

618
COMPANIES
(#2 of 21)

102,507
PUBLICATIONS
(#3 of 21)

429
PHASE II &III PROGRAMS
(#2 of 21)

INDICATIONS IN TOP 100:

Pain (#1)
Alzheimer's disease (#10)
Parkinson's disease (#39)
Epilepsy (#52)
Cognitive dysfunction (#73)
Stroke (#90)
Diabetic neuropathy (#94)

SOURCE: KAISER/BCIQ DATABASE/PUBMED

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THERAPEUTIC AREA SPOTLIGHT

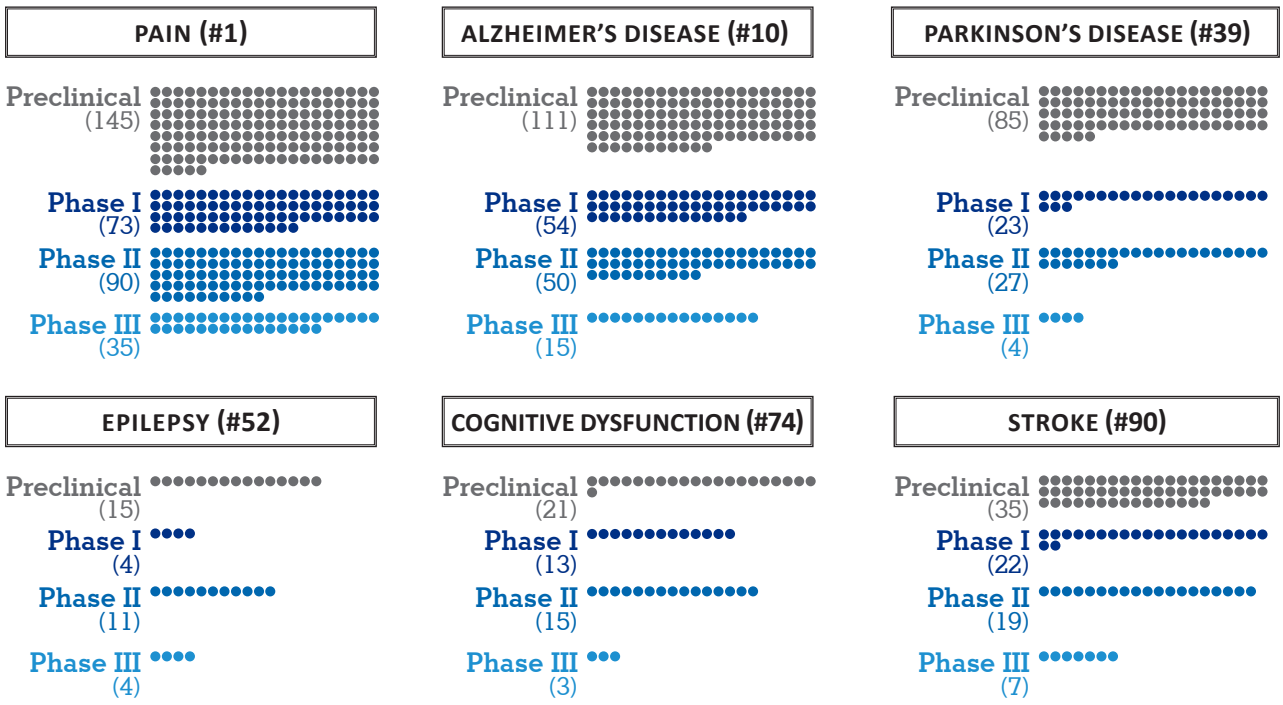
NEUROLOGY

Neurology encompasses a range of common CNS conditions, including top ranked **pain (#1)**, **Alzheimer's disease (#10)**, and **epilepsy (#52)**, as well as less prevalent indications like **neuralgia (#102)** and **Huntington's disease (#104)**. This TA would be even larger with the inclusion of **multiple sclerosis (#17).** MS can be classified as a Neurological disorder or an Autoimmune disorder; for the purposes of this analysis, we have placed it in Autoimmune. Neurology ranks third overall in the Therapeutic Area Rankings, and offers an attractive mix of highly-prevalent conditions with significant unmet need and smaller orphan conditions offering substantial pricing power for truly effective therapeutics. Based on this opportunity landscape, Kaiser expects continued strong investment in this therapeutic area despite widespread generic utilization and a challenging development environment.

Neurology's ranking is driven largely by its sizeable industry pipeline, especially for Phase II and III programs. Relatively low VC funding reduces Neurology's overall score compared to Endocrine and Infectious Disease, but also indicates a large potential opportunity for future VC-driven investment in early-stage Neurology pipeline programs.

Generic erosion of several major branded pain drugs (e.g., *Celebrex®*, *Lyrica®*, and *Cymbalta®*) is expected to drive near-term stagnation and decline of the pain therapeutic market. Further out, the pain pipeline programs drawing the greatest attention include mirogabalin, a Phase III asset under development by Daiichi Sankyo, and tanezumab, a Phase III asset under development by Pfizer and Eli Lilly. Tanezumab, an anti-NGF antibody, is generating particular excitement by patients and physicians as potentially one of the first biologic pain therapies. Although the class of anti-NGF antibodies was previously pulled from development by the FDA in 2011 due to safety concerns, Pfizer and Eli Lilly were recently able to provide preclinical data indicating that tanezumab is not subject to the same safety risk, clearing the way for these companies to advance the product through the development

Number of Programs by Stage of Development

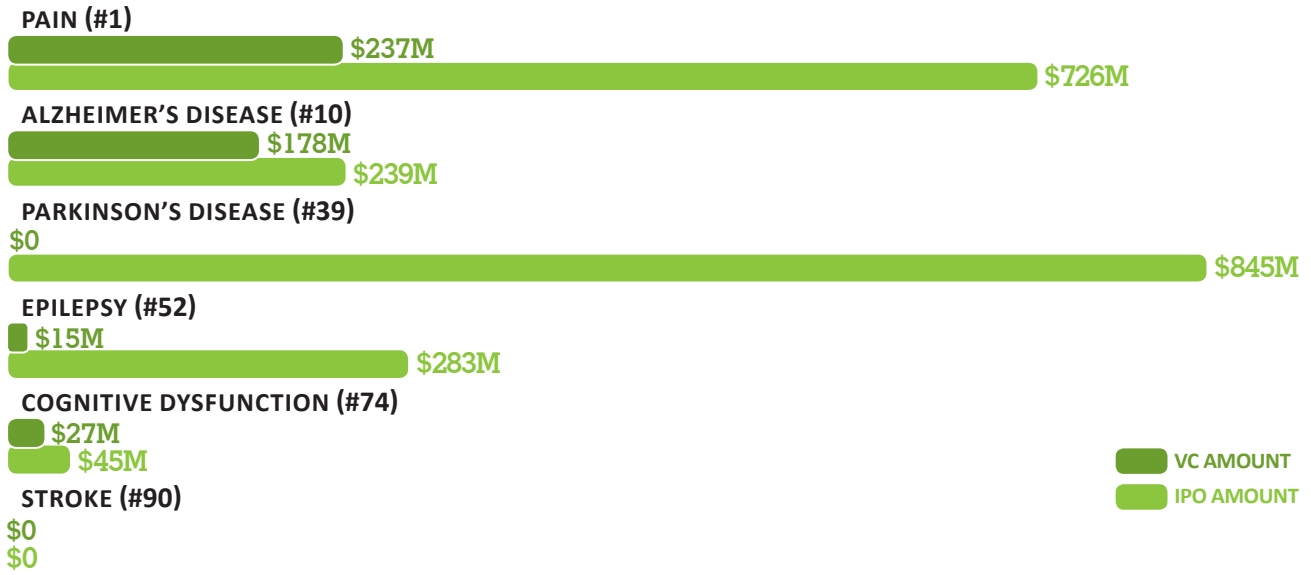


SOURCE: KAISER/BCIQ DATABASE

NEUROLOGY

Funds Raised from IPOs and VC in 2014, by Indication

Sum of funds raised by companies with at least one program



SOURCE: KAISER/BCIQ DATABASE

pathway. 2014 VC funding in Neurology was somewhat concentrated, with four companies accounting for almost 70% of total 2014 funding. Companies at the top of the Neurology 2014 VC funding list include Spinifex, with Phase II programs in **diabetic neuropathy (#94)**, neuralgia, and pain, and Annexon Bioscience, with a preclinical program in Huntington's disease. Spinifex has recently been acquired by Novartis, while Annexon remains independent.

2014 IPO funding was more widely distributed among a broader set of companies—27 companies with Neurology programs went public in 2014. The Neurology IPO landscape clearly demonstrates investors' appetite for companies investing in major categories that are expected to grow as populations age across major markets. Top 2014 Neurology IPOs included Sage Therapeutics, with programs in preclinicals through Phase II, including **epilepsy (#52)**, **essential tremor (#547)**, as well as Auspex Pharmaceuticals (since then acquired by Teva), with preclinical through Phase III programs including pain, **Parkinson's disease (#39)**, and Huntington's disease. One notable 2015 funding event is the Axovant IPO. At $315M, it is the largest biotech IPO ever, based on amount of capital raised. Axovant is a single-product company, working to commercialize a castoff Alzheimer's product originated by GSK. The Axovant IPO is emblematic of the intense investment in Alzheimer's disease, including some of the biggest companies competing in Neurology. Success in Alzheimer's drug development has been elusive, as recent disappointing readouts from Biogen, Eli Lilly, and Roche have cast further doubt on the hypothesized "amyloid plaque" mechanism for Alzheimer's treatment. As the industry retrenches from this setback, focus is likely to shift to drugs targeting specific Alzheimer's symptoms, rather than disease-modification treatments. However, the market potential for a truly effective disease-modifying Alzheimer's treatment dictates that companies will continue to pursue these drugs. Eli Lilly, Roche, Merck, Johnson & Johnson, and a number of other companies continue to work on plaque-clearing medications.

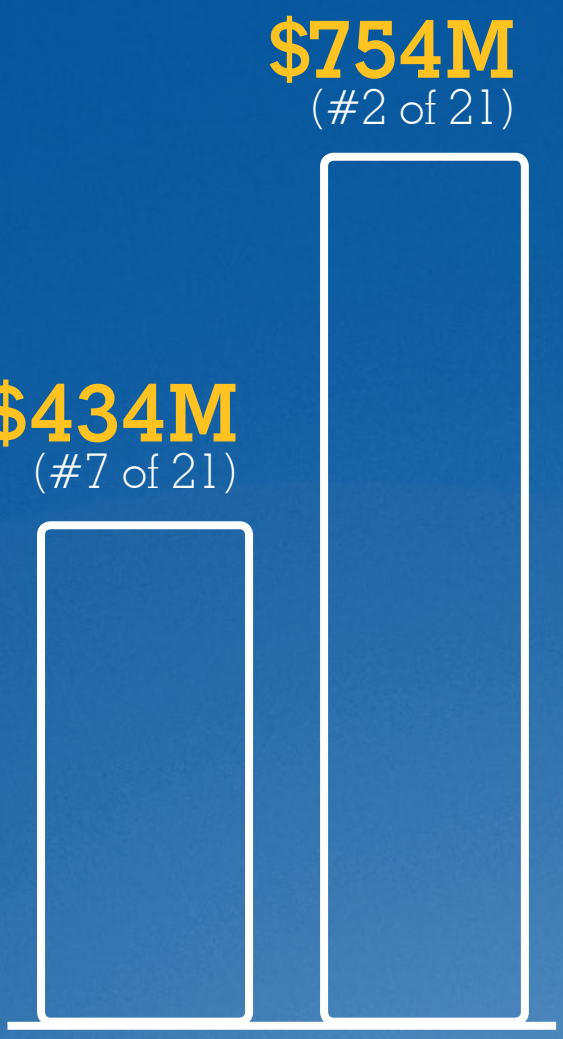
Increasing genericization of the largest Neurology disease areas, such as pain management, demands meaningful innovation and differentiation on safety and efficacy to drive premium pricing and reimbursement. Clinical challenges, such as poorly defined drug targets and a lack of reliable biomarkers for many CNS diseases (including Alzheimer's disease), increase development risk and drive a high rate of late-stage failures in this therapeutic area.

Overall, Neurology emerges as a highly competitive therapeutic area with a strong industry pipeline and small-player landscape despite relatively low VC and IPO funding. Investment in Hot Indications in Neurology, particularly pain, Alzheimer's, and Parkinson's, is already intense and likely to continue to grow over time.

DEEP DIVE
OPHTHALMOLOGY

PROGRAM **2014** HIGHLIGHTS

(# OF 21) INDICATES TA RANK



386
COMPANIES
(#7 of 21)

22,775
PUBLICATIONS
(#14 of 21)

136
PHASE II &III PROGRAMS
(#8 of 21)

INDICATIONS IN TOP 100:

Age-related macular degeneration (#14)
Diabetic macular edema (#31)
Glaucoma (#50)
Dry eye (#64)
Diabetic retinopathy (#78)

SOURCE: KAISER/BCIQ DATABASE/PUBMED

KAISER ASSOCIATES

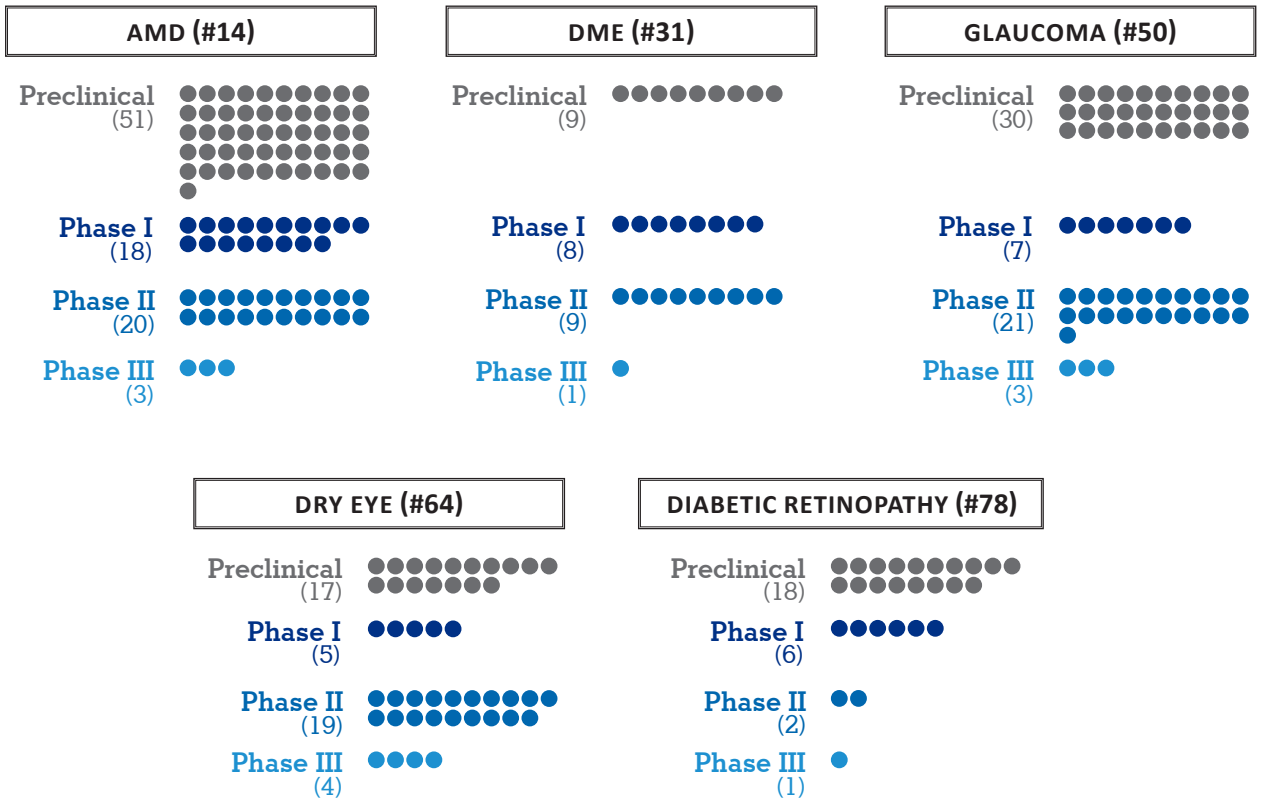
THERAPEUTIC AREA SPOTLIGHT

OPHTHALMOLOGY

Ophthalmology, despite being a relatively smaller therapeutic market, ranked fifth among all Therapeutic Areas in our investment intensity index. Ophthalmology's high ranking was due in large part to an extremely successful year in fund raising, particularly via IPO. All told, 10 companies with eye care development programs went public in 2014, and raised a total of $754M in initial public offerings. Ophthalmology's total IPOs ranked second among all therapeutic areas, behind only Oncology. Ophthalmology also performed well in venture fundraising, with the TA's largest fundraising event going to PanOptica ($45M Series B) for its topical anti-VEGF program.

From a development standpoint, two retina conditions—**age-related macular degeneration (#14)** and **diabetic macular edema (DME) (#31)**—are driving the high investment levels in Ophthalmology. The success of anti-VEGF therapies *Lucentis®* (Genentech) and *Eyelea®* (Regeneron), which both surpass $1B in worldwide sales, continues to attract a broad base of investors. More than 70 companies are pursuing AMD programs, which include both wet and dry / atrophic

Number of Programs by Stage of Development



SOURCE: KAISER/BCIQ DATABASE

OPHTHALMOLOGY

indication pursuits. New anti-VEGF treatments with longer durations and novel VEGF and PDGF combinations (including those from Ophthotech, Regeneron and Allergan) dominate the later stage pipeline. Many earlier stage programs are focused on dry / atrophic AMD, which is widely considered to be the next blockbuster category due to its high prevalence and unmet need.

Diabetic macular edema and **diabetic retinopathy (#78)**, together, account for over 50 preclinical and clinical stage programs. Due to the amount of investment in AMD and diabetic disorders, we expect the retina category to dominate innovation and growth in the next 10 years. We also expect the balance of power to become more distributed. Today, Genentech, Regeneron, Allergan, and Novartis Alcon dominate worldwide ophthalmic drug sales. Going forward, however, successful development-stage companies will likely seek to "go it alone" due to greater access to capital and the relatively small commercial investment required to succeed with the concentrated group of retina specialists (less than 3,000) in the US.

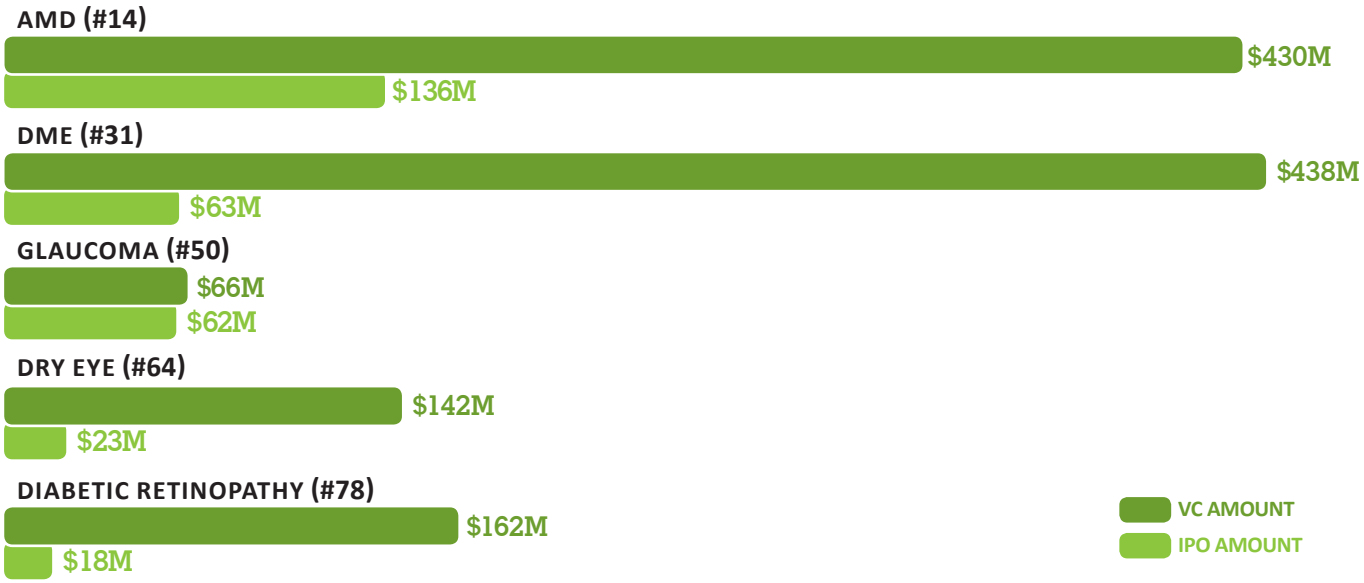
Outside of retinal disorders, **glaucoma (#50)** continues to receive significant early and late-stage investment despite the genericization of first-line gold-standard *Xalatan®* (latanprost). The latest innovation in glaucoma appears more focused on new delivery platforms than new molecular entities. Drug companies are developing sustained release formulations of existing prostaglandin analogs (latanaprost, bimatoprost, and travoprost) in an effort to improve the traditionally poor patient compliance associated with eye drops. Outside of new delivery systems, Rho Kinase inhibitors represent the most anticipated emerging treatment in glaucoma.

Dry eye (#64), which has a notoriously difficult FDA approval pathway due to the requirement to meet sign and symptom endpoints, continues to see high development activity despite a long list of recent failures. Shire's *Lifitegrast®* seeks to become the first challenger to Allergan's $1B+ *Restasis®*, expecting its FDA decision in October 2015. Regardless of approval or rejection, the FDA decision will be an important signal to the 30+ dry eye programs in development.

Overall, Ophthalmology continues to excite investors with the promise of emerging sight-saving therapies and new delivery systems. Although Ophthalmology may not sustain its high level of IPO and VC events, we expect the category to "fight above its weight" and continue its meaningful contribution to drug innovation in the coming years.

Funds Raised from IPOs and VC in 2014, by Indication

Sum of funds raised by companies with at least one program



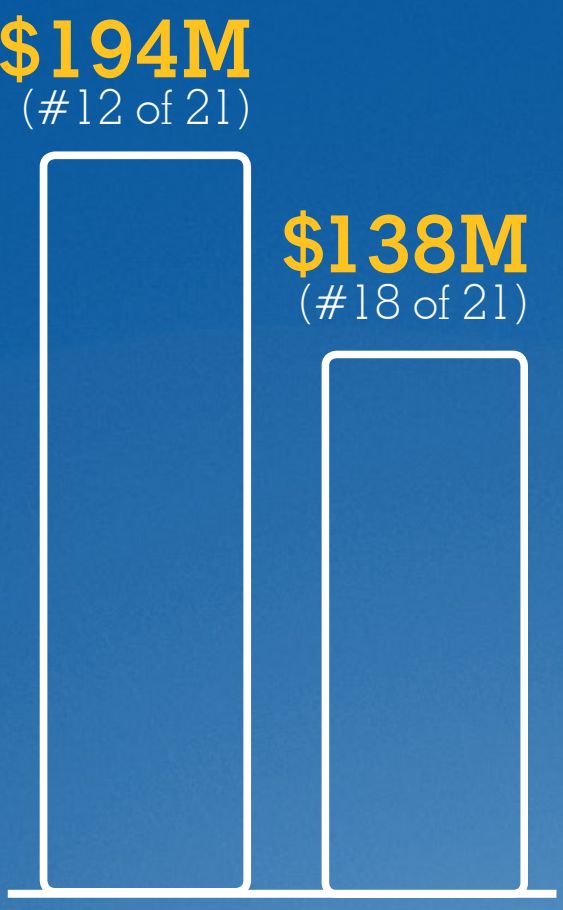
SOURCE: KAISER/BCIQ DATABASE

DEEP DIVE

GASTROENTEROLOGY

PROGRAM **2014** HIGHLIGHTS

(# OF 21) INDICATES TA RANK



205
COMPANIES
(#9 of 21)

25,335
PUBLICATIONS
(#13 of 21)

170
PHASE II &III PROGRAMS
(#7 of 21)

INDICATIONS IN TOP 100:

Ulcerative colitis (#26)
Crohn's disease (#42)
Irritable bowel syndrome (IBS) (#97)

SOURCE: KAISER/BCIQ DATABASE/PUBMED

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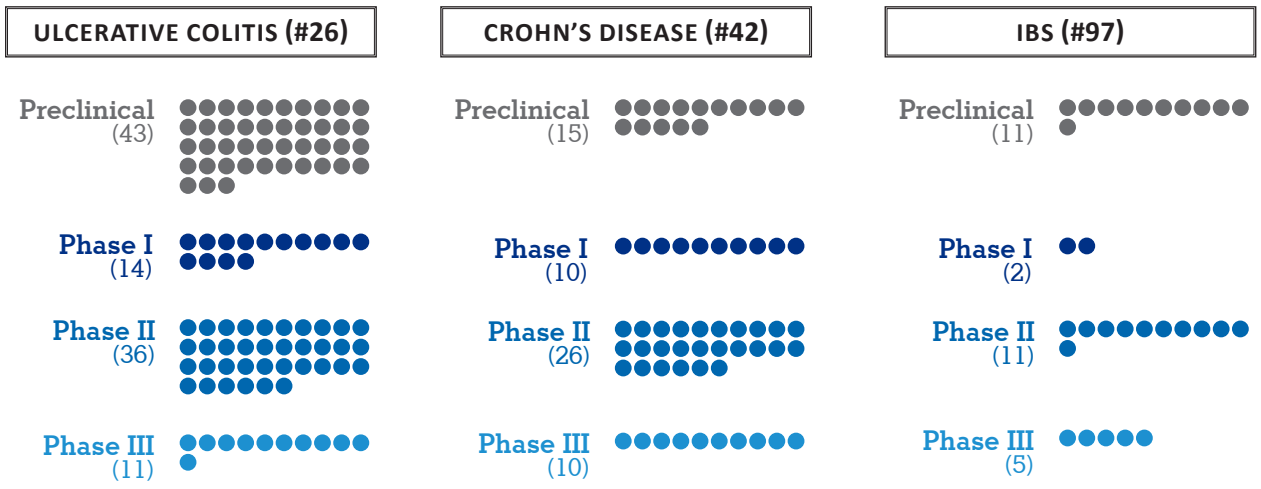
THERAPEUTIC AREA SPOTLIGHT

GASTROENTEROLOGY

Gastroenterology (GI) ranks in the middle of the pack at ninth among all Therapeutic Areas. The GI pipeline is comprised of drugs in development for 30 indications, however only 3 indications are included in the top 100: **ulcerative colitis (#27)**, **Crohn's disease (#43)**, and **irritable bowel syndrome (IBS) (#97)**. Kaiser expects drug development investment intensity to continue at a steady state for GI for the foreseeable future. Next-generation treatments for inflammatory bowel disease, such Roche's promising anti-adhesion molecule, etrolizumab, will continue to address the under-treated patient market, while of anti-TNF biosimilars will capture already well-treated patient populations.

Industry players entering GI markets tend to approach with one of two pipeline strategies—portfolios for autoimmune diseases, and portfolios addressing broader unmet needs in Gastroenterology. Pfizer leads the former group with several ongoing programs, including trials for *Xeljanz*® and other molecules to treat both ulcerative colitis and Crohn's disease, as well as a Phase II trial studying *Lyrica*® for IBS. In the latter group, Eli Lilly and Theravance Biopharma have promising GI pipelines, with late-stage

Number of Programs by Stage of Development



SOURCE: KAISER/BCIQ DATABASE

GASTROENTEROLOGY

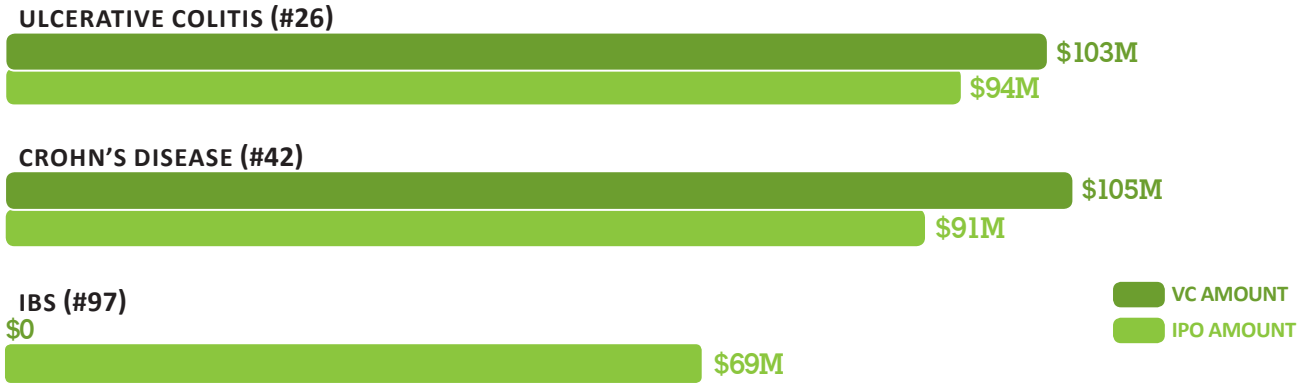
programs for opioid-induced **constipation (#173)** and other emerging indications.

Finally, there is a fairly low level of investor activity in Gastroenterology, reflected by the therapeutic area's rankings of 12th in venture capital and 18th in IPOs. Venture capital amounts raised in 2014 were fairly small, with the median series at ~$14M. Most notably, Novimmune secured $66M in series B funding to support its pipeline of monoclonal antibodies, including a CD3ε molecule in phase II development for Crohn's disease. Overall IPO activity was very low, with nearly half of the total amount for the TA raised by Ardelyx's IPO of $60M. The company has a Phase III trial of *Tenapanor*® (NHE3 inhibitor) for constipation-predominant IBS, as well as early-stage studies in ulcerative colitis and Crohn's disease for their TGR5 agonist candidate.

Overall, Gastroenterology is garnering less investment from companies and investors than it did a decade ago, when drugs for disorders like **GERD (#225)** and **dyspepsia (#266)** dominated commercial activities. Following the successes of biologic treatments for Crohn's disease, ulcerative colitis appears to be eliciting the most investment intensity, making an already competitive market even more competitive.

Funds Raised from IPOs and VC in 2014, by Indication

Sum of funds raised by companies with at least one program



SOURCE: KAISER/BCIQ DATABASE

METHODOLOGY

Kaiser Associates' methodology is designed to assess investment intensity of drug development for each indication through a comprehensive and balanced analysis of the key drivers and metrics.

Our Hot Indications analysis framework considers the volume of ongoing scientific investigation, as well as the types of companies and level of funding supporting these trials. Kaiser's analysis evaluated 12,101 drug programs ongoing in 2014, categorized them into 582 unique indications, and compared available data for these indications across 3 main criteria:

1. PIPELINE SCORE

The Pipeline Score measures the overall level of drug development activity for an indication. The score gives greater value to later-stage programs, higher volumes of programs overall, and indications with greater numbers of companies with programs.

2. R&D FUNDING

R&D Funding estimates the availability of financing to support the development of each drug program to its reasonable endpoint. For some programs, this endpoint will be FDA approval, while for others it will be discontinuation in preclinicals or Phase I.

The score measures availability of funds and willingness to invest based on 2 main inputs for each indication. First, the R&D Funding Score quantifies the historical track record of sponsor companies, based on the number of drugs each company has successfully developed. Second, the score measures initial public offering and venture capital investment fundraising activity in 2014 for each indication, with the expectation that the financing from such events will be major contributors in supporting ongoing R&D programs.

3. ACADEMIC FOCUS

Academic Focus measures the overall publication activity for each indication, based on the absolute number and the one-year change in publications citing the indication for the evaluation period.

Hot Indications Ranking

For each of the 582 indications, the overall ranking score is calculated by a weighted average of Pipeline Score (50%), R&D Funding (40%) and Academic Focus (10%). Throughout this analysis, the rank number from the final Hot Indications List is denoted in parentheses immediately following first mention of the indication in each section.

Therapeutic Areas & Ranking

The Therapeutic Area Ranking is an index of R&D investment intensity that synthesizes and normalizes the Hot Indications Ranking scores for all indications within a Therapeutic Area.

Each indication is categorized into one of 21 TAs, which include 20 major fields of medicine and an "Other" group. The assignment of indications into TA plays a meaningful role in the Therapeutic Area Ranking. In general, indications are categorized based on the medical specialty most likely to treat patients with a disease or disorder.

Systemic diseases, such as automimmune disorders, or TAs representing a variety of medical specialties, such as Musculoskeletal, are grouped on a case-by-case basis. For example, Crohn's disease and ulcerative colitis are included in Gastroenterology rather than Autoimmune, whereas Multiple Sclerosis is included in Autoimmune due to the variety of symptoms it presents.

Sources

- BCIQ database, accessed May, 8 2015
- FDA, *Novel New Drugs 2014 Summary*, January 2014
- FDA Office of Orphan Products Development
- PubMed Health, US National Library of Medicine
- Company press releases and corporate websites

ABOUT KAISER ASSOCIATES

ABOUT KAISER

Founded in 1981, Kaiser Associates is an international strategy consulting firm that serves as a key advisor to the world's leading companies. We provide our clients with the unique insight to drive critical decision-making and solve their most pressing problems.

Kaiser's Healthcare Practice engages with executives at leading Life Sciences companies, including pharmaceutical, medical device, clinical diagnostics, consumer health, and health IT. We work with our clients to identify new growth markets, develop long-term portfolio strategies, and maximize commercial success.

The foundation of Kaiser's service offering is its world-class "outside-in" methodology, which involves delivering critical facts and insights from the complex external environment to drive strategic decision making. Kaiser possesses the unique ability to generate insights across physicians, thought leaders, patients, competitors, partners, regulators, suppliers, and payers. Kaiser uses its deep industry experience and analytical tools to synthesize this diverse set of insights and develop high-impact solutions.

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