Kx Advisors

HOT INDICATIONS LIST 2020

A global analysis of pharmaceutical investment intensity across R&D programs

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Innovation continues to drive progress in pharma and biotech in 2020. From the development of therapeutics for complex diseases to an industry-spanning effort to combat a pandemic, pharma investments and market focus are evolving quickly. Kx Advisors' 6th annual analysis of global R&D investment has identified the top indications for industry focus in 2019 across 20 therapeutic areas (TAs).

When we published our first Hot Indications List in 2015, we sought to answer the major question that pharmaceutical companies ask themselves, i.e., "what is the next big thing?" and, in the process, help identify the most strategic opportunities for growth. We conducted a comprehensive analysis of nearly every pharmaceutical R&D program in the world, developing a proprietary index that considers trends in development investment, fundraising, and scientific output. The goal then was to predict which indications would be "hot" over the next five years, based on where we observed investment intensity. This year, in addition to our annual analysis, we examine how our findings have changed over the past five years, assessing how TAs have progressed over time, and looking forward to future landscape evolution.

THERAPEUTIC AREA RANKINGS: THE LAST FIVE YEARS

Oncology (#1) continues to top the TA rankings with steady investment flow and increasing pipeline activity. Since 2015 it has led the other TAs in every category, including number of development programs, number of companies, VC & IPO funding, and number of publications. This continued lead highlights Oncology at the center of incredible commercial and academic interest, with the industry working to find the next cutting-edge cancer treatment. The TA will likely continue to dominate.

Similarly, **Infectious Diseases (#2)**, **Neurology (#3)**, and **Endocrinology (#4)** maintain their positions within the top five, unchanged since our 2015 analysis. In 2014, 27 companies with Neurology programs went public, demonstrating investors' appetite for investing in the TA's mix of highly prevalent conditions with significant unmet need and smaller orphan conditions offering substantial pricing power for truly effective therapeutics. Investment continues to be strong in Neurology; in 2019, 52 Neurology investment deals totaled $968 million.[1] Both **Immunology (#5)** and **Dermatology (#6)** moved up slightly in the TA ranking due to continued innovation for conditions such as psoriasis and rheumatoid arthritis, but also an increase in investment for dermatology therapies targeting underserved conditions such as alopecia areata and atopic dermatitis. **Gastroenterology (#7)** rose as the industry's understanding of gut immunology grew, and companies developed several innovative therapies for Ulcerative Colitis and Crohn's Disease. This change was also reflected in investor activity, which was fairly low in 2015, as demonstrated by the therapeutic area's rankings of 12th in venture capital and 18th in IPOs. Similarly, novel developments in retinal disorders with gene therapies and biologics keep **Ophthalmology (#9)** as a top TA. This drop from rank **#5** in 2015 could be attributed to unusually high fundraising activity in 2014, which our experts correctly predicted was not sustainable.

[1] *Healthcare Investments and Exits*. Silicon Valley Bank. https://www.svb.com/globalassets/library/uploadedfiles/reports/healthcare-report-2020-annual_full.pdf

The overall pipeline demonstrates markedly higher activity for COVID-19 than previous viral outbreaks,

including the Ebola & Zika virus epidemics, which saw 41 (Ebola) and 50 (Zika virus) Phase I-III programs in their outbreak years.

Any discussion about the pharmaceutical industry in 2020 must include the large-scale impact of COVID-19. As this analysis is based on 2019 data, we expect the effect to have significant implications for next year's Hot Indications analysis. Disruptions in clinical trial enrollment and delays in regulatory approval due to COVID-19 should impact most TAs and indications equally. Still, in 2020, we expect the Infectious Diseases TA to experience significantly higher investments and pipeline activity due to the new COVID-19 indication.

THERAPEUTIC AREA EVOLUTION: INFECTIOUS DISEASES

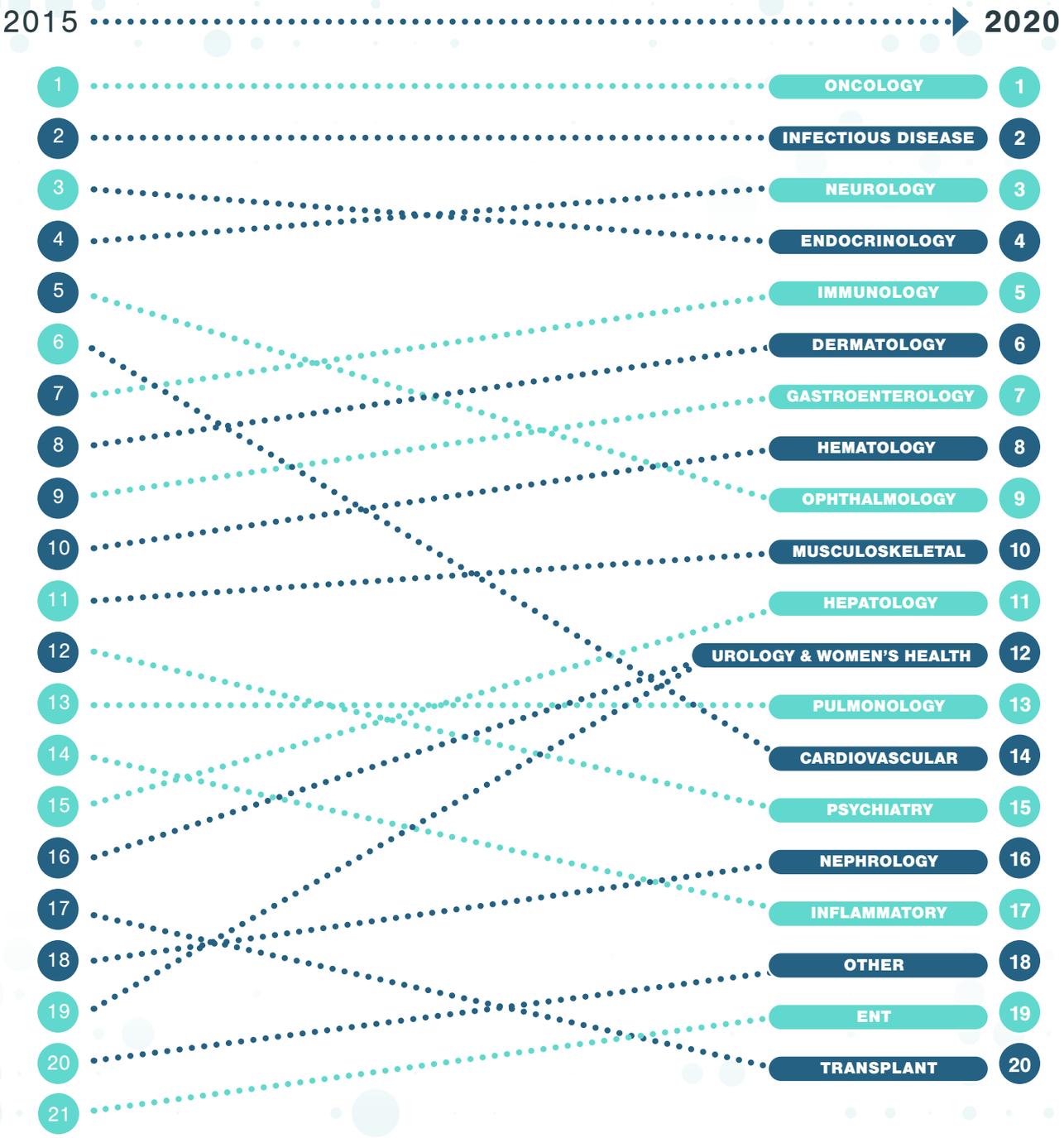
Sparked by the 2020 pandemic, worldwide investment, development, and research for COVID-19 skyrocketed. This focus on COVID-19 is exceptional; the overall pipeline demonstrates markedly higher activity for COVID-19 than previous viral outbreaks, including the Ebola and Zika virus epidemics, which saw 41 (Ebola) and 50 (Zika virus) Phase I-III programs in their outbreak years. With 233 companies pursuing clinical research for COVID-19 as of May 8, 2020, the scale of mobilization of the industry is unique. As part of this mobilization, numerous partnerships have formed to tackle the COVID-19 pandemic. For example, the Coalition for Epidemic Preparedness Innovation (CEPI) fund has raised over $1B to develop COVID-19 vaccines and entered collaborations with Novavax and Clover Biopharma. We can expect further partnership opportunities as pharmaceutical companies test their existing candidates to find novel treatments for COVID-19. For example, experts are testing psoriasis drugs like Otezla (Amgen) and rheumatoid arthritis IL-6 therapies like Actemra (Roche) to treat COVID-19-related pneumonia in hospitalized patients.

Outside of the novel coronavirus, the Infectious Diseases TA encompasses a range of notable conditions, including **HIV/AIDs (#38)**, **influenza (#42)**, and **Ebola (#119)**. Of 304 assets in the pipeline, 68% are therapeutic drugs, while 32% are vaccines.

BIG MARKET OPPORTUNITIES

Both the loss of exclusivity and the development of TNF-alpha biosimilars drove significant investments and pipeline activities over the last five years within the **Immunology**, **Dermatology**, and **Gastroenterology** TAs. The IL-17 class, led by Novartis' Cosentyx (first approved in 2015 for psoriasis), and the new IL-23 class, led by AbbVie's Skyrizi (approved in 2019 for psoriasis), are now driving these competitive markets. New MOAs, such as IL-6 therapies and JAK inhibitors, will continue to transform the landscape and set new expectations for both oral and biologic therapies.

THERAPEUTIC AREA RANKINGS



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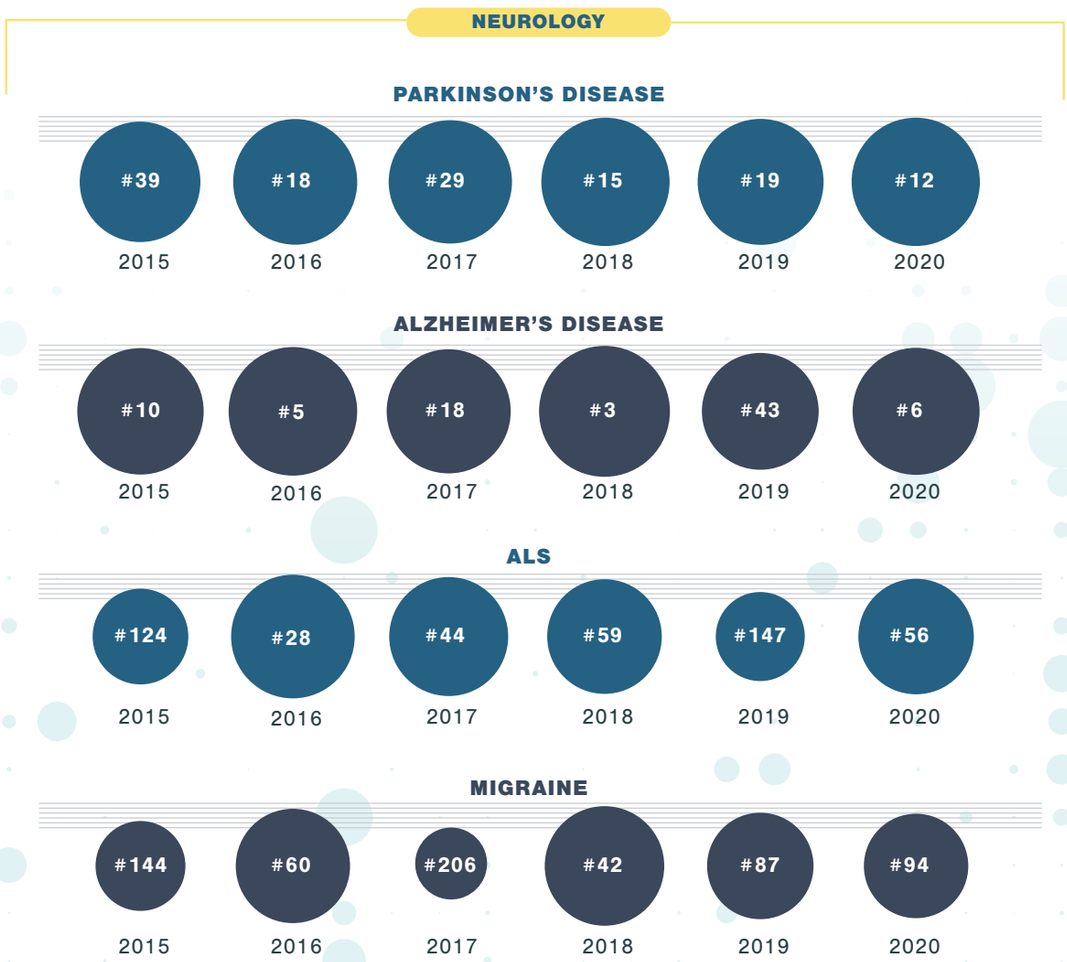
THERAPEUTIC AREA EVOLUTION: NEUROLOGY

Among indications driving change in the Neurology TA is **Alzheimer's disease (#6)**, which has been a top Neurology indication in the last five years. Due to the complex nature of the disease, the growing aging population, and lack of a cure or effective therapies to slow disease progression, the demand for solutions is high. Several countries adopted national policies to prioritize Alzheimer's disease drug development, propelling significant investments, like the UK's ~$300M Dementia Discovery Fund in 2015. While it has been a top indication, after its initial rise, it dropped in 2019 due to several clinical trial failures and subsequent lower investment.

Companies are funneling funding to innovative efforts for **Parkinson's disease (#12)**, which has moved up in the indication ranking since 2015. Novel therapies in Parkinson's, such as cell and gene therapies, aim to reverse disease progression, reduce dyskinesia, and control motor symptoms more effectively. 2019 FDA approvals, such as Nourianz (Kyowa Kirin), and developments in gene therapy, such as the Phase 1 trial results for Voyager Therapeutics' and Neurocrine Biosciences' VY-AADC01, further pushed Parkinson's up in the indication rankings.

ALS (#56) has been climbing in rankings steadily in the last five years with the continued flow of investments and pipeline assets. Even though ALS comprises the most complex spectrum of pathologies amongst all neurodegenerative disorders, with a high rate of clinical trial failure, the FDA approval of Radicava (Mitsubishi Tanabe) in 2017 provided a much-needed boost to continue investment in ALS. ALS has been a significant area of interest for small to mid-cap biotechs, creating partnerships like Ionis and Biogen.

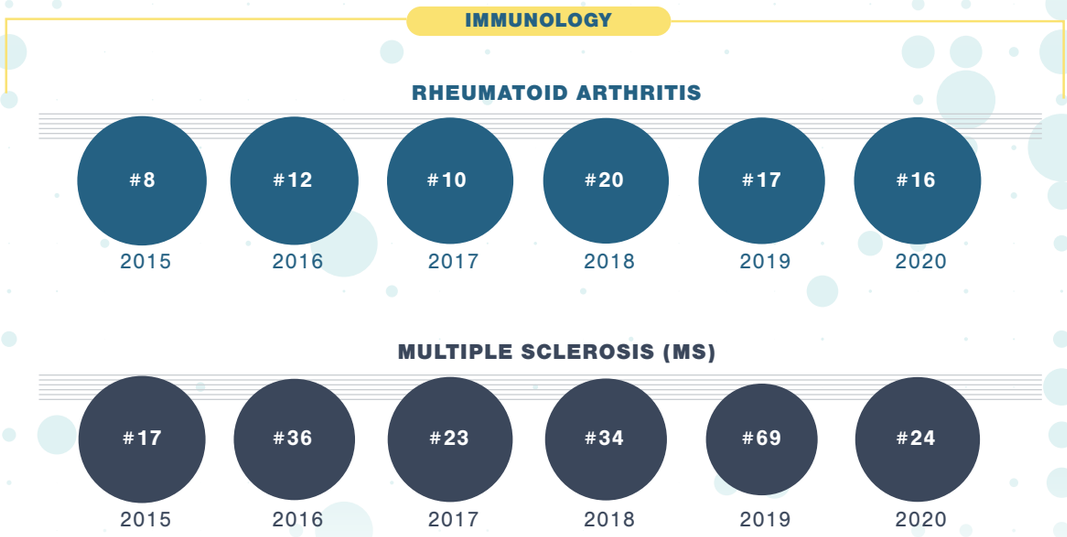
After an initial rise in 2018, **Migraine (#94)** has dropped in the rankings from 2018 **(#42)** to 2020 **(#94)**. The high investment in 2017 may have been due to major trials for monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway. The first therapy of this class, Aimovig (Novartis / Amgen), was approved in 2018. There have been three other CGRP mAbs approved since: Ajovy (Teva), Emgality (Eli Lilly), and Vyepti (Lundbeck), and the market continues to grow, led in 2020 by approval of Biohaven's oral CGRP antagonist, Nurtec ODT.



THERAPEUTIC AREA EVOLUTION: IMMUNOLOGY

While there were large-scale changes across the TA, **Rheumatoid Arthritis (RA, #16)** kept its top position within immunology for the last five years. However, its overall indication ranking has slipped. Apart from TNF-alpha and Rituxan biosimilars, IL-6 therapies, like R-Pharm's olokizumab, are high-potential candidates in Phase III. Novel oral therapies, like JAK inhibitors, are starting to compete with biologics. After AbbVie's Rinvoq approval in August 2019, experts expect Gilead's filgotinib to be the next major entrant in the RA market. Looking forward, disease-modifying and locally delivered gene therapies are leading the next wave of innovation in RA. The trend is likely to grow with investors like 4BIO, who raised a dedicated VC fund to develop RA gene therapies.

Formerly a major focus of investment, ranking **#17** in 2015, **Multiple Sclerosis (MS, #24)** slipped in the overall ranking. Despite the fall, MS returned to the top 25 in our 2020 analysis, mainly due to continued high pipeline activity. Small molecules and monoclonal antibodies with a range of MOAs (e.g., CD-20 mAbs and next-gen S1P receptor modulators) are pushing for earlier and more aggressive therapy. A principal future goal is identifying innovative MOAs that address the underlying neurologic deterioration, rather than just suppressing systemic inflammation.



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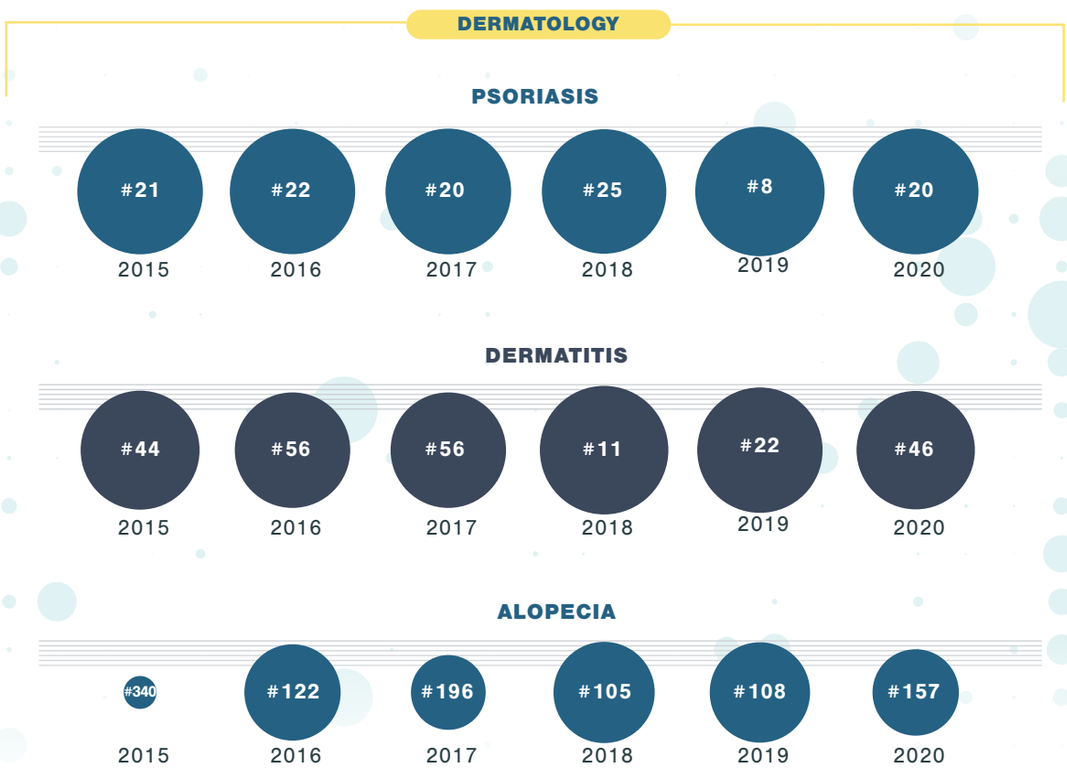
THERAPEUTIC AREA EVOLUTION: DERMATOLOGY

Over the past five years, the pharmaceutical market has seen a massive shift in investment across dermatology indications. In 2019 **psoriasis (#20)** became a top 10 indication, ranked eighth. It has retained its position as the top dermatology indication since 2015 due to increasing pipeline activity backed up by steady investment flow, sustained by high-profile approvals for Janssen's Tremfya in 2017 and AbbVie's Skyrizi in 2019. The major $13.4 B acquisition of Celgene's Otezla by Amgen in 2018 highlights the continued interest in the indication. Additional novel MOAs for psoriasis are in the pipeline, including IL-17A/F (bimekizumab, UCB) and TYK2 (BMS-986165, Bristol-Myers Squibb).

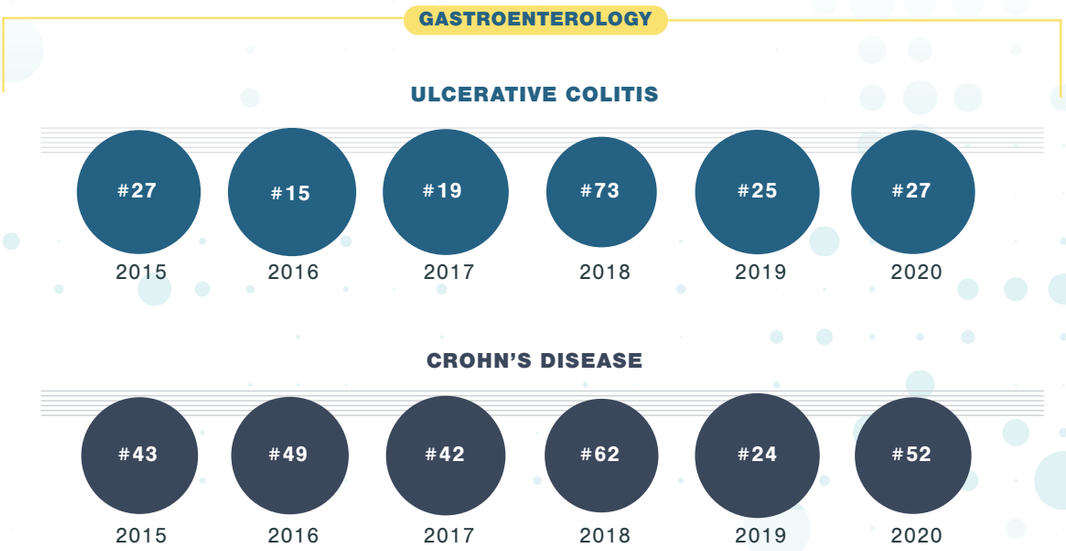
Dermatitis (#46) drove a substantial increase in TA investment in 2017. While investment declined in 2018, dermatitis remained a significant driver of VC investment in 2019. The atopic dermatitis (AD) pipeline has expanded significantly, as new classes of therapeutics undergo investigation. In 2017, Regeneron's Dupixent, an IL-4/13 inhibitor, was the first biologic approved for treating moderate-to-severe AD. There are several other biologics in Phase III trials for moderate-severe AD, namely IL-13 and IL-31 inhibitors, with LEO Pharma's tralokinumab expected to launch next, in 2021. There is also a range of JAK inhibitors currently in Phase III trials for moderate-to-severe AD. Lilly's Olumiant (already approved for RA) is expected to launch in 2020 and has reported favorable top-line Phase III results. At the same time, topical JAK inhibitors such as Incyte's topical ruxolitinib seek to make their mark with strong efficacy and better safety profiles.

Alopecia (#157) had the most considerable leap within Dermatology over the last five years and saw a peak in VC related investment in 2018. The rise in the ranking of alopecia coincides with alopecia areata's (AA's) selection by the FDA as an indication in its Patient Focused Drug Development Initiative in 2016-2017. Investment is driven primarily by JAK inhibitors; investigation of the effect of JAK inhibitors on hair growth started in 2014 when a Columbia University study reported near-complete hair regrowth in patients receiving ruxolitinib (Incyte). Now, notable pipeline therapies include Pfizer's oral JAK3 inhibitor PF-06651600, which received breakthrough designation by the FDA in 2018 and is currently in Phase IIb / III trials. There is continued interest in developing a JAK inhibitor with the right efficacy for AA, without the full range of potential side effects. As the race to develop a suitable JAK inhibitor carries on, we expect further investment.



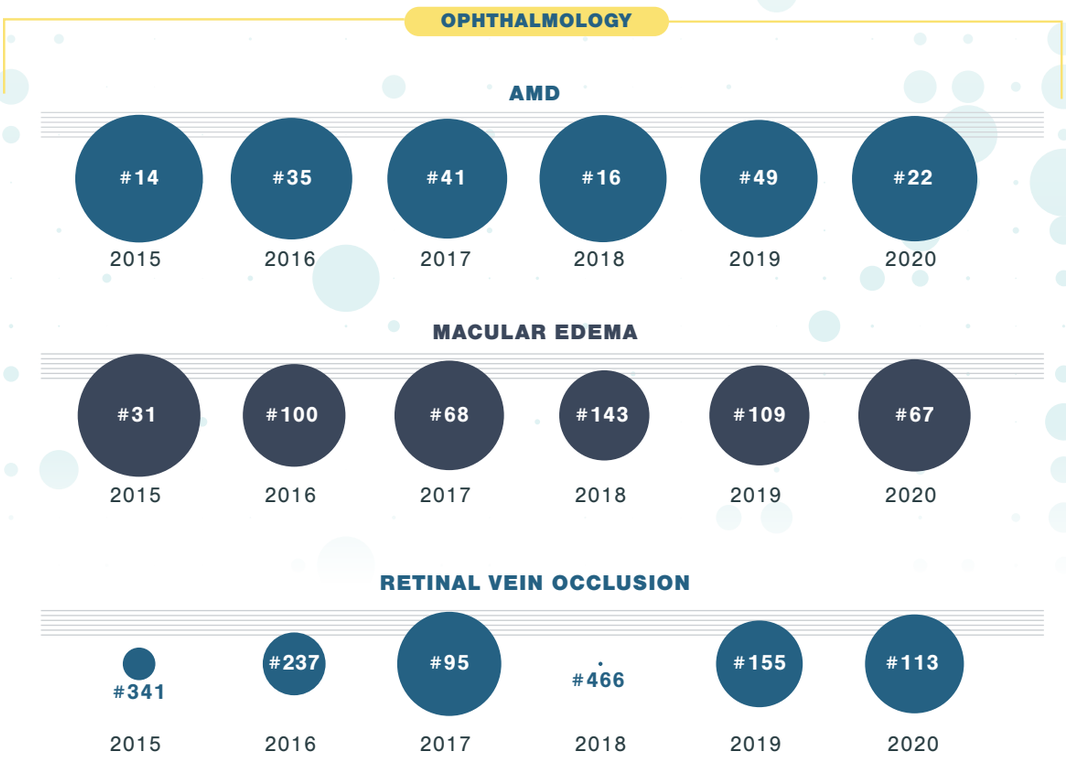
THERAPEUTIC AREA EVOLUTION: GASTROENTEROLOGY

Driven by considerable changes in the Gastroenterology landscape over the last five years, the TA rose from ninth in 2015 to seventh this year. This rise can be attributed to indications like **Ulcerative Colitis (#27)** and **Crohn's disease (#52)** coming into the R&D spotlight. Due to increased disease awareness and scientific research, the current Crohn's disease and Ulcerative Colitis pipelines include innovative approaches like regenerative therapy, immune cell modulation, and microbiome targeting. Despite the development of several biologics for Crohn's disease, low efficacy and ineffective symptom management of the condition are critical obstacles in the field.



THERAPEUTIC AREA EVOLUTION: OPHTHALMOLOGY

Ophthalmology has dropped from fifth amongst all TAs in 2015, to ninth this year. In 2015, the TA's high ranking was a result of a successful year in fundraising in 2014, mainly in IPOs, like Avalanche Bio (now Adverum Biotechnologies), closing its initial public offering at $102 million. Retinal disorders like **AMD (#22)** have dropped slightly in ranking since 2015, but managed to return to the top 25 indications due to high pipeline activity and fundraising events to develop novel MOAs beyond anti-VEGF inhibitors. In the last decade, scientific research has exposed a complex interplay of several molecular mechanisms that companies are now trying to target, either via multiple pathways (e.g., Kodiac Sciences' KSI 501, IL-6/VEGF dual inhibitor) or new targets (e.g., Santen's carotuximab for refractory wet age-related macular degeneration). Dry AMD has also been a target for complement biology, e.g., IVERIC bio's Zimura. All these therapies seek to delay retinal disease progression and extend the time between treatments, a key pain point for AMD, **macular edema (#67)**, and **retinal vein occlusion (#113)** patients.



LOOKING FORWARD

The most significant impact on investment and innovation in pharma and biotech is COVID-19; massive investment has been diverted to address the crisis. Early-stage efforts may be the most impacted in the pipeline, whereas later stage developments may fare better, with many companies and investors staying the course. However, clinical trials for non-COVID indications may be delayed. Next year's Hot Indications will reveal the degree of impact COVID-19 has had on the healthcare industry.

METHODOLOGY

Our Hot Indications analysis framework considers the volume of ongoing scientific investigation, as well as the types of companies and levels of funding supporting these trials. Our analysis evaluated 43,440 drug programs ongoing in 2019, categorized them into 598 unique indications, and compared available data for these indications across three main criteria[2]:

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:** 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. In contrast, for others, it will be discontinuation in pre-clinicals or Phase I. The score measures availability of funds and willingness to invest based on two 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 2019 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 589 indications, we calculate the overall ranking score by a weighted average of Pipeline Score (50%), R&D Funding (40%) and Academic Focus (10%).

THERAPEUTIC AREAS:

Each indication is categorized into one of 20 TAs, including an Other category. In general, indications are categorized based on the medical specialty most likely to treat patients with a disease or disorder. Systemic diseases, such as autoimmune 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 immunology, whereas MS is included in immunology due to the variety of symptoms it presents.

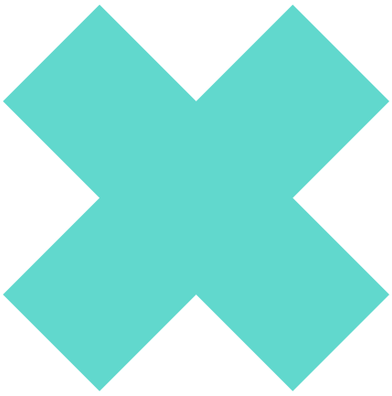
[2]Sourced from *EvaluatePharma*

TOP 100 HOT INDICATIONS

2020 RANK	INDICATION	THERAPEUTIC AREA	2015 RANK
1	**Breast cancer**	**Oncology**	2
2	**Diabetes**	**Endocrinology**	4
3	**Non-small cell lung cancer (NSCLC)**	**Oncology**	3
4	**Non-Hodgkin's lymphoma (NHL)**	**Oncology**	13
5	**Colorectal cancer**	**Oncology**	7
6	**Alzheimer's disease (AD)**	**Neurology**	10
7	**Pancreatic cancer**	**Oncology**	6
8	**Acute myelogenous leukemia (AML)**	**Oncology**	9
9	**Prostate cancer**	**Oncology**	5
10	**Ovarian cancer**	**Oncology**	20
11	Melanoma	Oncology	26
12	Parkinson's disease (PD)	Neurology	39
13	Multiple myeloma (MM)	Oncology	25
14	Head & neck cancers	Oncology	41
15	Liver cancer	Oncology	11
16	Rheumatoid arthritis (RA)	Immunology	8
17	Gastric cancer	Oncology	40
18	Pain	Neurology	1
19	Bladder cancer	Oncology	89
20	Psoriasis	Dermatology	21
21	Non-alcoholic steatohepatitis (NASH)	Hepatology	112
22	Age-related macular degeneration (AMD)	Ophthalmology	14
23	Glioblastoma multiforme (GBM)	Oncology	496
24	Multiple sclerosis (MS)	Immunology	17
25	Myelodysplastic syndrome (MDS)	Oncology	133
26	Acute lymphoblastic leukemia (ALL)	Oncology	22
27	Ulcerative colitis	Gastroenterology	27
28	Renal cancer	Oncology	42
29	Sarcoma	Oncology	121
30	Asthma	Inflammatory	35
31	Small cell lung cancer	Oncology	61
32	Anemia	Hematology	36
33	Cervical cancer	Oncology	99
34	Biliary cancer	Oncology	171
35	Esophageal cancer	Oncology	181
36	Inflammatory bowel disease (IBD)	Gastroenterology	27
37	Uterine cancer	Oncology	N/A
38	HIV / AIDS	Infectious Disease	28
39	Hodgkin's disease	Oncology	142
40	Cancer-related bone loss	Oncology	303
41	Skin cancer	Oncology	147
42	Influenza virus	Infectious Disease	18
43	Amyloidosis	Endocrinology	227
44	Epidermolysis bullosa	Dermatology	131
45	Basal cell carcinoma (BCC)	Oncology	331
46	Dermatitis	Dermatology	44
47	Obesity	Endocrinology	30
48	Kidney transplant	Nephrology	83
49	Sickle cell disease	Hematology	93
50	Lupus	Immunology	19

TOP 100 HOT INDICATIONS

2020 RANK	INDICATION	THERAPEUTIC AREA	2015 RANK
51	Hepatitis B virus (HBV)	Hepatology	67
52	Crohn's disease	Gastroenterology	43
53	Gastric ulcers	Gastroenterology	417
54	Chronic lymphocytic leukemia (CLL)	Oncology	24
55	Glioma	Oncology	N/A
56	Amyotrophic lateral sclerosis (ALS)	Neurology	124
57	Dry eye	Ophthalmology	64
58	Nonalcoholic fatty liver disease (NAFLD)	Hepatology	370
59	Wounds	Dermatology	80
60	Gastroesophageal reflux disease (GERD)	Gastroenterology	217
61	Depression	Psychiatry	12
62	Respiratory infection	Pulmonology	195
63	Infertility	Endocrinology	88
64	Pulmonary fibrosis	Pulmonology	46
65	Hyperlipidemia	Endocrinology	178
66	Epilepsy	Neurology	52
67	Macular edema	Ophthalmology	31
68	Scleroderma	Immunology	148
69	Cytomegalovirus (CMV)	Infectious Disease	68
70	Schizophrenia	Psychiatry	16
71	Mesothelioma	Oncology	149
72	Hearing loss	ENT	184
73	Dermal ulcers	Dermatology	62
74	Sjogren's syndrome	Immunology	255
75	Stroke	Neurology	90
76	Pulmonary hypertension	Pulmonology	N/A
77	Fallopian tube cancer	Oncology	513
78	Vasculitis	Inflammatory	265
79	Hemophilia	Hematology	79
80	Polymyositis	Musculoskeletal	444
81	Respiratory syncytial virus (RSV)	Infectious Disease	158
82	Diabetic retinopathy	Ophthalmology	78
83	Myositis	Musculoskeletal	286
84	Eye infection	Ophthalmology	287
85	Thyroid cancer	Oncology	84
86	Duchenne muscular dystrophy	Musculoskeletal	N/A
87	Autism	Psychiatry	58
88	Acute kidney injury	Nephrology	N/A
89	Psoriatic arthritis	Immunology	132
90	Ataxia	Neurology	119
91	Lung cancer, general	Oncology	N/A
92	Heart failure	Cardiovascular	47
93	Myelofibrosis	Hematology	N/A
94	Migraine	Neurology	144
95	Hemorrhagic conditions	Hematology	106
96	Clostridium	Infectious Disease	108
97	Glomerulonephritis	Nephrology	387
98	Pompe's disease	Endocrinology	111
99	Hypercholesterolemia	Endocrinology	170
100	Celiac disease	Immunology	320



ABOUT Kx

For more than 30 years, Kx Advisors (operating as Kaiser Associates' healthcare practice) has provided strategy consulting services to help healthcare executives achieve critical business growth goals. With a highly collaborative approach they have developed pragmatic solutions for leading pharmaceutical, biotechnology, medical device, health IT, and digital health clients, with data-driven insights to give those clients the tools to compete and win across the healthcare industry.

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