Kx Advisors

# HOT INDICATIONS DEEP DIVE NEUROLOGY

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



PUBLISHED OCTOBER 2020

## For Kx Advisors' 6th annual Hot Indications List, we conducted a comprehensive analysis of nearly every pharmaceutical R&D program in the world, developing a proprietary index that considers trends in investment, fundraising, and scientific output.

This year, in addition to our annual analysis, we examine how our findings have changed over the past five years, assessing how Therapeutic Areas (TAs) have progressed over time, and looking forward to future landscape evolution.

Given the unmet need across many indications, it is no surprise that Neurology is within the top four TAs for the fifth year in the row. In our initial analysis in 2015, we projected a continued interest in the highly competitive TA, with a strong industry pipeline and small-player landscape. With 1,145 Phase II and III programs in development and generating $2B in VC funding, our initial analysis was correct, with continued growth in investment. In 2019, **Alzheimer's disease (#6)** and **Parkinson's disease (#12)** retained the top positions within Neurology. New developments in therapies for these top indications and emerging therapies keep overall interest in Neurology high.

### NEUROLOGY BY THE NUMBERS

**2019 Cumulative VC Funding**

**$1.95B**

**2019 Cumulative IPO Amount**

**$3.29B**

**61**
Indications

**81,206**
Companies

**1,145**
Phase 2 and Phase 3 programs

**173,010**
Publications





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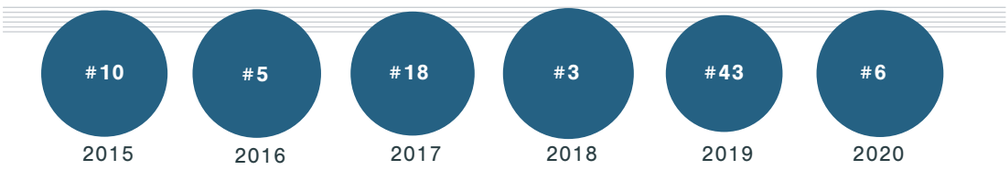
## ALZHEIMER'S DISEASE




**Alzheimer's disease (#6)** has been a top Neurology indication in the last five years due to the complex nature of the disease, the growing aging population, and the lack of a cure or effective therapies to slow disease progression. In the initial 2015 analysis, our team noted that investment in Neurology, particularly Alzheimer's, was already intense and predicted that it was likely to continue to grow over time. As companies have explored different MOAs, R&D intensity has varied over the past five years, but continued strong interest in development has kept the indication in the top 20.

As many companies have pursued amyloid beta-targeted drugs with unsatisfactory results, including Eli Lilly's recent Phase III solanumab failure, investment in the MOA has declined since 2017. The FDA's decision on Biogen's aducanumab (BIIB037) is expected in March 2021; if successful, it could be the first therapy to demonstrate that removing amyloid beta is the key to unlocking effective treatments. If it is not successful, further investment in the hypothesis that amyloid plaques drive disease pathology will diminish.

Conversely, Phase I and II programs targeting tau-fibrils have been rising steadily since 2017. Axon Neurosciences' tau vaccine, AADvac1, has presented positive Phase II trial data indicating that tau-fibrils may be a more promising option than amyloid-beta. There are several programs from large pharma players in Phase II programs targeting tau-fibrils, including ABBV-8E12 (AbbVie), LY3303560 (Eli Lilly), and RG6100 (Roche). Additionally, TauRx's second-generation tau aggregation inhibitor, LMTX, is in Phase III. If tau-fibrils are the root cause of Alzheimer's, there may be further investment in this MOA.

Additionally, the number of neuroprotection and anti-neuroinflammation therapies in development has started to increase, particularly in the early stages, further showcasing a large-scale shift to find alternative treatments to support patients living with Alzheimer's. The success of these programs, alongside tau-fibril-targeting programs, may determine the outlook in Alzheimer's disease; lack of progress is likely to lead to a drop in future rankings.

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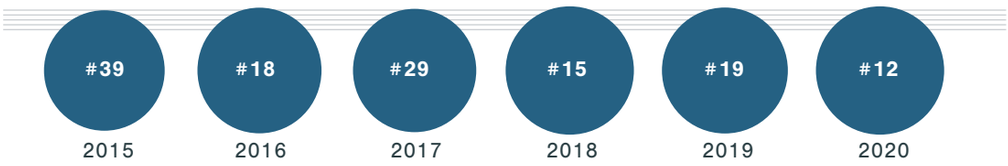
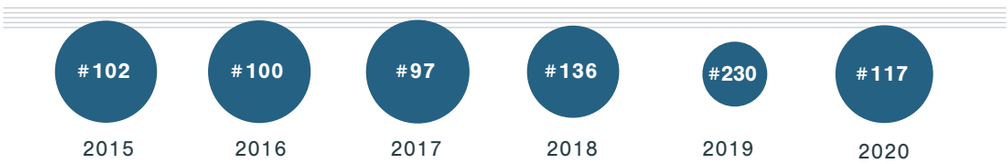
## PARKINSON'S DISEASE




With no cure and over 10 million people worldwide living with **Parkinson's disease (PD, #12)**, companies are funneling funding to innovative treatments, resulting in its jump in indication ranking from #39 in 2015. All current medications and therapies for PD aim to ease symptoms and improve quality of life for patients. Novel symptom management therapies focus on utilizing neuronal dopamine and controlling motor and non-motor symptoms. Novel gene therapies for dopamine production are gaining positive attention, including VY-AADC (NBIb-1817) from Voyager Therapeutics and Neurocrine Biosciences and Axovant Gene Therapies' AXO-LENTI-PD. Another area of focus is on supporting motor control and suppressing involuntary movement, empowering patients to regain control and enhance their day to day mobility. MeiraGTx's Phase I/II AAV-GAD is an investigational gene therapy designed to help patients with their motor-circuit modulation without impacting other brain regions.

Disease-modifying assets are the greatest unmet need in PD disease treatment, and thus are the driving force for investment in PD. Several large pharma companies are highly invested in alpha-synuclein targeted therapies, as can be seen in the Phase II PASADENA study of Roche's prasinezumab (PRX002), the Phase II trial of Biogen's cinpanemab (BIIB054), and Phase I studies by Lundbeck, AstraZeneca, Takeda, and AbbVie. These investments underline the urgency to find the first disease-modifying asset that effectively counteracts the progress of PD. Our experts expect a continued rise in funding and rankings moving forward for both symptom management and disease-modifying assets.

## HUNTINGTON'S DISEASE

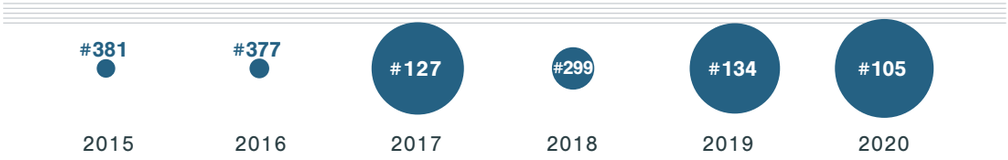



**Huntington's disease (#117)** is a complex disease with multiple symptoms, including motor function, depression, dementia, and others. These symptoms cannot all be targeted effectively at once by existing therapies. Therefore, novel disease-modifying strategies in development involve lowering huntingtin protein (encoded by the HTT gene) levels, and any disease-modifying treatment currently in development could be the first treatment of its kind for Huntington's disease. Potential disease-modifying therapies in development include ribonucleic acid interference (RNAi) and anti-sense oligonucleotide (ASO) therapies to knock down the disease-causing mutant (mHTT). RNAi programs include UniQure's Phase I/II AMT-130, a one-time administered gene therapy. ASO programs include Phase II RG6042 from Roche, which targets all forms of mHTT, and a Phase II WVE-120101 program from Wave Life Sciences and Takeda, which selectively targets SNP1. Our experts predict that Huntington's will likely continue to rise in rankings if RNAi therapies show success in early-stage clinical trials, given the explosion in number of treatments over the last few years.

## TOP MOVERS & EMERGING THERAPIES

Through our analysis, our experts identified indications that jumped significantly in investment and academic attention from 2015 to 2019. In previous years, renewed interest in previously static indications drove some top movers. This year, our analysis focused on emerging indications driven by new investment.

## TOP MOVER: NEUROMYELITIS OPTICA




**Neuromyelitis optica (NMO, #105)**, a rare autoimmune process affecting the central nervous system, is one of the top movers within our five-year analysis. NMO has moved up by 276 spots since 2015, from 381 to 105 in 2020. The first approved therapies for NMO are responsible for this jump. Since June 2019, the FDA has approved three treatments: Alexion's Soliris (an anti-C5a/b antibody), an infusion-based therapy, was the first FDA-approved therapy for NMO spectrum disorder (NMOSD). The FDA recently approved Viela Bio's infusion-based Uplizna (anti-CD-19 mAb) and Roche and Chugai's Enspryng (anti-IL-6 mAb). Unlike the other two in-office infusions on the market, Enspyng is the first-ever at-home subcutaneous injection for NMO patients. This treatment improves the quality of care by allowing those living with NMO to administer it without needing to leave their homes.

Currently, the early-stage pipeline of Phase I and II assets in NMO is sparse with no novel MOAs in development. This shift indicates that investment intensity for NMO will likely decrease moving forward.

## EMERGING THERAPIES: CHARCOT-MARIE-TOOTH DISEASE


**Charcot-Marie-Tooth disease (CMT, #154)**, a group of conditions that damage the peripheral nerves, resulting in limited functionalities and pain, entered the Hot Indications ranking in 2017. There are no targeted drug therapies for CMT, and physicians manage the disease using a combination of adaptive devices, physical therapies, pain medication, and surgeries. CMT moved up 168 spots last year, driven by funding raised by early-stage companies developing novel treatments for neuropathies. One example is Regenacy Pharmaceuticals, a clinical-stage biopharma company that raised $30 million in series A investment in March 2020 to develop therapies for multiple neuropathies, including CMT. Regenacy is planning to test ricolinostat (ACY-1215), a selective histone deacetylase inhibitor, in a Phase II clinical trial.

Other companies developing therapies for CMT include Pharnext (PXT3003) for type 1 CMT, currently in Phase III clinical trials. PXT3003 is an inhibitor of PMP22 gene overexpression, associated with direct nerve protection and other positive effects on muscle cells, neuromuscular junctions, and immune cells. Following approval in adults, Pharnext plans to develop this therapy in children suffering from CMT. Similarly, Addex Therapeutics and the CMT Association are developing ADX71441, a pre-clinical asset with the potential to slow disease progression of CMT. Sarepta Therapeutics plans to progress NT-3 to clinical trials, for which it partnered with Aldevron in 2019 to provide a gene-transfer vehicle for the gene therapy. With no FDA-approved treatments or any existing cure, experts expect a continued focus on developing disease-modifying therapies that can slow down, reverse or prevent CMT progression.

## 2019 was a year of innovation within the Neurology TA, which generated 1,145 Phase II and III programs across

81,206 companies supported by 173,010 academic publications. We can expect new research to unlock new therapies in top indications, especially Parkinson's disease. The Neurology TA has been a top TA since our Hot Indications analysis began in 2015, and our experts predict investment and academic interest will ensure it retains that spot. Looking immediately ahead, 2020 is a unique year for clinical development across the industry, with the COVID-19 pandemic delaying clinical trials. While those delays will impact Neurology indications, we expect it will have little impact on continued investment.

### 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[1]:

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.

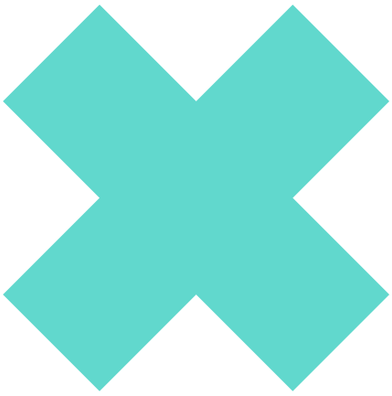
### HOT INDICATIONS RANKING:

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. 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.

[1]Sourced from *EvaluatePharma*



## 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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*Special thanks to Tarek Ahmed, Sam Eaton, and Shruti Sharma for their contributions to this analysis.*

*Design and Graphics by Kelly Martin Design*





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