Alnylam's Use of Citeline Data

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About Me - Harrison Miller

- Machine learning scientist in research at Alnylam
  - Build predictive models for early-stage drug development
- M.S. in Applied Mathematics (2021) and B.S. in Chemical Engineering (2020)
- Starting at Harvard Business School in August (Class of 2026)

Background on Probability of Success Methodologies

Based on methodologies from *Estimation of clinical trial success rates and related parameters* by Wong et. Al.

In the *Wong* paper, path-by-path and phase-by-phase methodologies are introduced and compared

- Previous literature utilized phase-by-phase due to limitations in other data sets but due to the size of the Citeline data set, *Wong* was able to employ a path-by-path approach that we believe is a better way of viewing success rates of drug programs
- Path-by-path is more robust to missing data/incomplete data sets than phase-by-phase

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The Wong Methodology: Comparing Path-By-Path and Phase-By-Phase
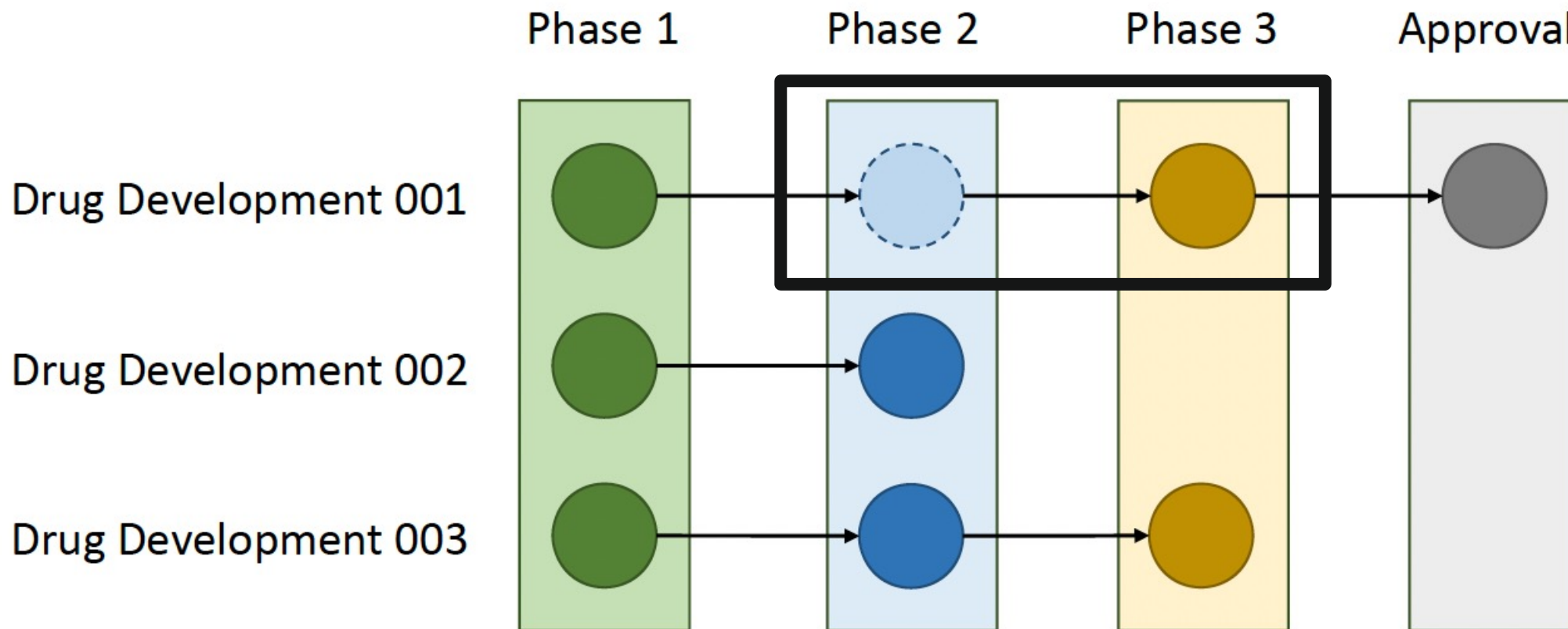
Method	$POS_{1,2}$	$POS_{2,3}$	$POS_{3,APP}$	$POS_{1,APP}$
Path-By-Path	1	2/3	1/2	1/3
Phase-By-Phase	1	1/2	1/2	1/4

Alnylam's Thoughts and Experiences with Citeline Data

- While processing Citeline data, the amount of missing clinical trial data for a given drug/indication was noticeable
  - This was something *Wong* developed an algorithm for to fill out as much of the data set as possible
- We found the most robust information of the dataset was found in the Pharma Projects part of Citeline
- Citeline data does not differentiate well between certain indications

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How To Best Analyze and Process this Data (Big Data)

Historically, Excel has been an excellent tool to deal with data but there are more efficient tools

Citeline Drug ID	Generic Drug Name	Drug Names	Summary	Global Status	Development Status	Drug Disease	Drug Disease Group	Drug Disease: Rare	Company	Originator / Licensee	Company HQ Country
71236	177-Lu-DOTA-octreotate	[177Lu-DOTA0,Tyr3] octreotate; 177-Lu-DOTA-octreotate; 177-lutetium-DOTA0-Tyr3-octreotate; 177Lu-DOTATATE; AAA 601; AAA-601; AAA601; F 1515; F-1515; F1515; Lu-177 Dotatate; Lutate; Lutathera; lutetium (177Lu) oxodotreotide, Fujifilm; lutetium Lu 177 dotatate	Lutate is a lutetium-177 radiolabelled octreotate (AAA-601), a somatostatin analogue targeting somatostatin receptors, developed by Novartis (Advanced Accelerator Applications before acquisiton (BioSynthema before the acquisition)) for the treatment of metastatic gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs) (Press release, AAA, 18 May 2011, http://www.adacap.com/files/files_stampadwl/00022.doc; Company Web Page, AAA, 25 Jan 2018, http://www.adacap.com/press-room/; Company presentation, 1 Feb 2018, Fujifilm, Slide 16, https://www.fujifilmholdings.com/en/pdf/investors/other/ff_presentation_201802_001.pdf; Company pipeline, Fujifilm, May 2019 & 30 Mar 2021, http://fftc.fujifilm.co.jp/en/di/pipeline/index.html; 4th Qtr res, Novartis, 26 Jan 2021, Slide 56, https://www.novartis.com/sites/www.novartis.com/files/q4-2020-investor-presentation.pdf). It is also under development for extensive-stage small cell lung cancer (ClinicalTrials.gov, 2 Dec 2021 & 17 Dec 2021, https://clinicaltrials.gov/ct2/show/NCT05142696). It is also under development for glioblastma (ClinicalTrials.gov, 16 May 2022, https://clinicaltrials.gov/ct2/show/NCT05109728).	Launched	Active	Cancer, gastrointestinal, neuroendocrine	Anticancer	Rare	Novartis	Originator	Switzerland
						Cancer, gastrointestinal, neuroendocrine	Anticancer	Rare	Novartis	Originator	Switzerland
						Cancer, pancreatic, neuroendocrine	Anticancer	Rare	Novartis	Originator	Switzerland
						Cancer, pancreatic, neuroendocrine	Anticancer	Rare	Novartis	Originator	Switzerland
						Cancer, gastrointestinal, neuroendocrine	Anticancer	Rare	Novartis	Originator	Switzerland
						Cancer, gastrointestinal, neuroendocrine	Anticancer	Rare	Novartis	Originator	Switzerland
						Cancer, gastrointestinal, neuroendocrine	Anticancer	Rare	Novartis	Originator	Switzerland
						(rows continue, Novartis / Originator / Switzerland)	Anticancer	Rare	Novartis	Originator	Switzerland
122827	3BP-227	177Lu-3BP-227; 177Lu-IPN01087; 3BP-227; 3BP227; IPN 01087; IPN 01087A; IPN 1087; IPN-01087; IPN-01087A; IPN-1087; IPN01087; IPN01087A; IPN1087	3BP-227 is a radio nuclear peptide based theranostic, targeting neurotensin receptor-1, which was under development by 3B Pharmaceuticals for the treatment of pancreatic cancer (Company pipeline, 3B Pharmaceuticals, 23 Feb 2016, http://www.3b-pharma.com/2_pipeline.php; Company Web Page, 3B Pharmaceuticals, 23 Feb 2016, http://www.3b-pharma.com/2_overview.php). It was previously developed for small-cell lung cancer (Company pipeline, Ipsen, 15 Apr 2017, https://www.ipsen.com/research-development/pipeline/; Company pipeline, 3B Pharmaceuticals, 21 Sep 2017, http://www.3b-pharma.com/2_pipeline.php). It had potential in glioblastoma multiforme (Company presentation, Ipsen, 27 May 2019, Slide 111, https://www.ipsen.com/websites/Ipsen_Online/wp-content/uploads/2019/05/15113433/Ipsen-Investor-Day-20191.pdf). It was also under development for melanoma (Company pipeline, 3B Pharmaceuticals, 8 Jul 2020, https://3b-pharma.com/targeted-radiotherapy/pipeline/pipeline-chart/). It was previously under development for solid cancer, gastric cancer, squamous cell carcinoma of the head and neck and bone cancer (Company presentation, Ipsen, 27 Jul 2018, Slide 9, https://www.ipsen.com/websites/IPSENCOM-PROD/wp-content/uploads/2018/07/26134036/H1-2018-Presentation-FINAL.pdf; ClinicalTrials.gov, 23 May 2018 & 7 Jun 2021, https://clinicaltrials.gov/ct2/show/NCT03525392).	No Development Reported	Ceased	Cancer, bone	Anticancer	Rare	3B Pharmaceuticals	Originator	Germany
						Cancer, bone	Anticancer	Rare	3B Pharmaceuticals	Originator	Germany
						Cancer, bone	Anticancer	Rare	Ipsen	Licensee	France
						Cancer, bone	Anticancer	Rare	Ipsen	Licensee	France
						Cancer, brain	Anticancer		3B Pharmaceuticals	Originator	Germany
						Cancer, brain	Anticancer		Ipsen	Licensee	France
						Cancer, colorectal	Anticancer		3B Pharmaceuticals	Originator	Germany
						Cancer, colorectal	Anticancer		3B Pharmaceuticals	Originator	Germany
						Cancer, colorectal	Anticancer		Ipsen	Licensee	France
						Cancer, colorectal	Anticancer		Ipsen	Licensee	France
						Cancer, gastrointestinal, stomach	Anticancer	Rare	3B Pharmaceuticals	Originator	Germany
						Cancer, gastrointestinal, stomach	Anticancer	Rare	3B Pharmaceuticals	Originator	Germany
						Cancer, gastrointestinal, stomach	Anticancer	Rare	Ipsen	Licensee	France
						Cancer, gastrointestinal, stomach	Anticancer	Rare	Ipsen	Licensee	France
						Cancer, head and neck	Anticancer		3B Pharmaceuticals	Originator	Germany
						Cancer, head and neck	Anticancer		3B Pharmaceuticals	Originator	Germany
						Cancer, head and neck	Anticancer		Ipsen	Licensee	France
						Cancer, head and neck	Anticancer		Ipsen	Licensee	France
						Cancer, lung, small cell	Anticancer	Rare	3B Pharmaceuticals	Originator	Germany
						Cancer, lung, small cell	Anticancer	Rare	Ipsen	Licensee	France
						Cancer, melanoma	Anticancer		3B Pharmaceuticals	Originator	Germany
						Cancer, pancreatic	Anticancer	Rare	3B Pharmaceuticals	Originator	Germany
						Cancer, pancreatic	Anticancer	Rare	3B Pharmaceuticals	Originator	Germany
						Cancer, pancreatic	Anticancer	Rare	Ipsen	Licensee	France
						Cancer, pancreatic	Anticancer	Rare	Ipsen	Licensee	France
						Cancer, sarcoma, Ewing's	Anticancer	Rare	3B Pharmaceuticals	Originator	Germany
						Cancer, sarcoma, Ewing's	Anticancer	Rare	3B Pharmaceuticals	Originator	Germany
						Cancer, sarcoma, Ewing's	Anticancer	Rare	Ipsen	Licensee	France
						Cancer, sarcoma, Ewing's	Anticancer	Rare	Ipsen	Licensee	France
						Cancer, solid, unspecified	Anticancer		3B Pharmaceuticals	Originator	Germany
						Cancer, solid, unspecified	Anticancer		3B Pharmaceuticals	Originator	Germany
215126	3rd generation AR N-terminal domain inhibitor, Essa Pharma	3rd generation AR N-terminal domain inhibitor, Essa Pharma; prostate cancer therapy, Essa Pharma	Essa Pharma is developing a 3rd generation small molecule inhibitor of the androgen receptor (AR) N-terminal domain for the treatment of prostate cancer (Company pipeline, ESSA Pharma, 31 May 2022, https://www.essapharma.com/product-candidates/pipeline/; Company Web Page, ESSA Pharma, 31 May 2022, https://www.essapharma.com/science/androgen-receptor-pathway/).	Preclinical	Active	Cancer, prostate	Anticancer		Essa Pharma	Originator	Canada
113809	4D-110	4D 110; 4D-110; 4D-R 100; 4D-R100; 4D110; 4DR100; opthamological gene therapy, 4D Molecular Therapeutics; RG 6247; RG-6247; RG6247	4D-110 (RG-6247; 4D-R100) is AAV-mediated retinal gene therapy, under development by 4D Molecular Therapeutics for ophthalmologic and other monogenic diseases including choroideremia (Company Web Page, 4D, 26 May 2015; Company pipeline; 4D, 7 May 2018 & 18 Jun 2022, https://4dmoleculartherapeutics.com/product-pipeline/pipeline-overview/; Company pipeline, Roche, 23 Jul 2020,	Phase II Clinical Trial	Active	Choroideremia	Sensory	Rare	4D Molecular Therapeutics	Originator	USA
						Choroideremia	Sensory	Rare	Astellas Pharma	Licensee	Japan
						Ocular disorder, unspecified	Sensory		Astellas Pharma	Licensee	Japan
						Choroideremia	Sensory	Rare	Roche	Licensee	Switzerland
						Ocular disorder, unspecified	Sensory		4D Molecular Therapeutics	Originator	USA
						Ocular disorder, unspecified	Sensory		Roche	Licensee	Switzerland

The Progression of PTRS

Ancient History

- Small data sets
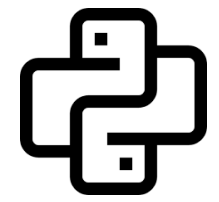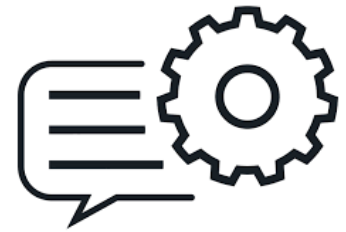- Simple homegrown analytics

Yesterday's news

KMR GROUP

Tufts Center for the Study of Drug Development
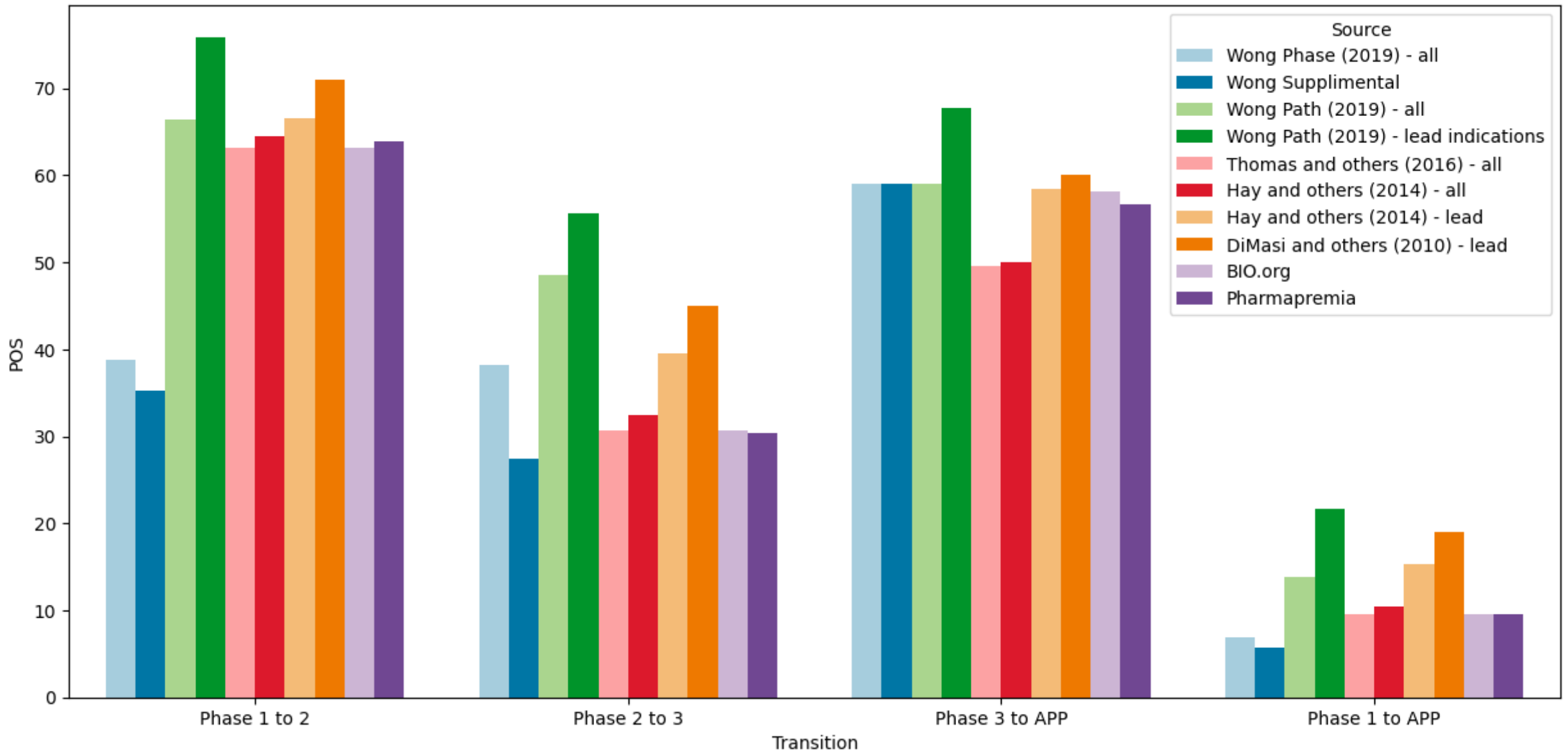**TUFTS UNIVERSITY**

- Larger, curated data sets (Dimasi, KMR, others)
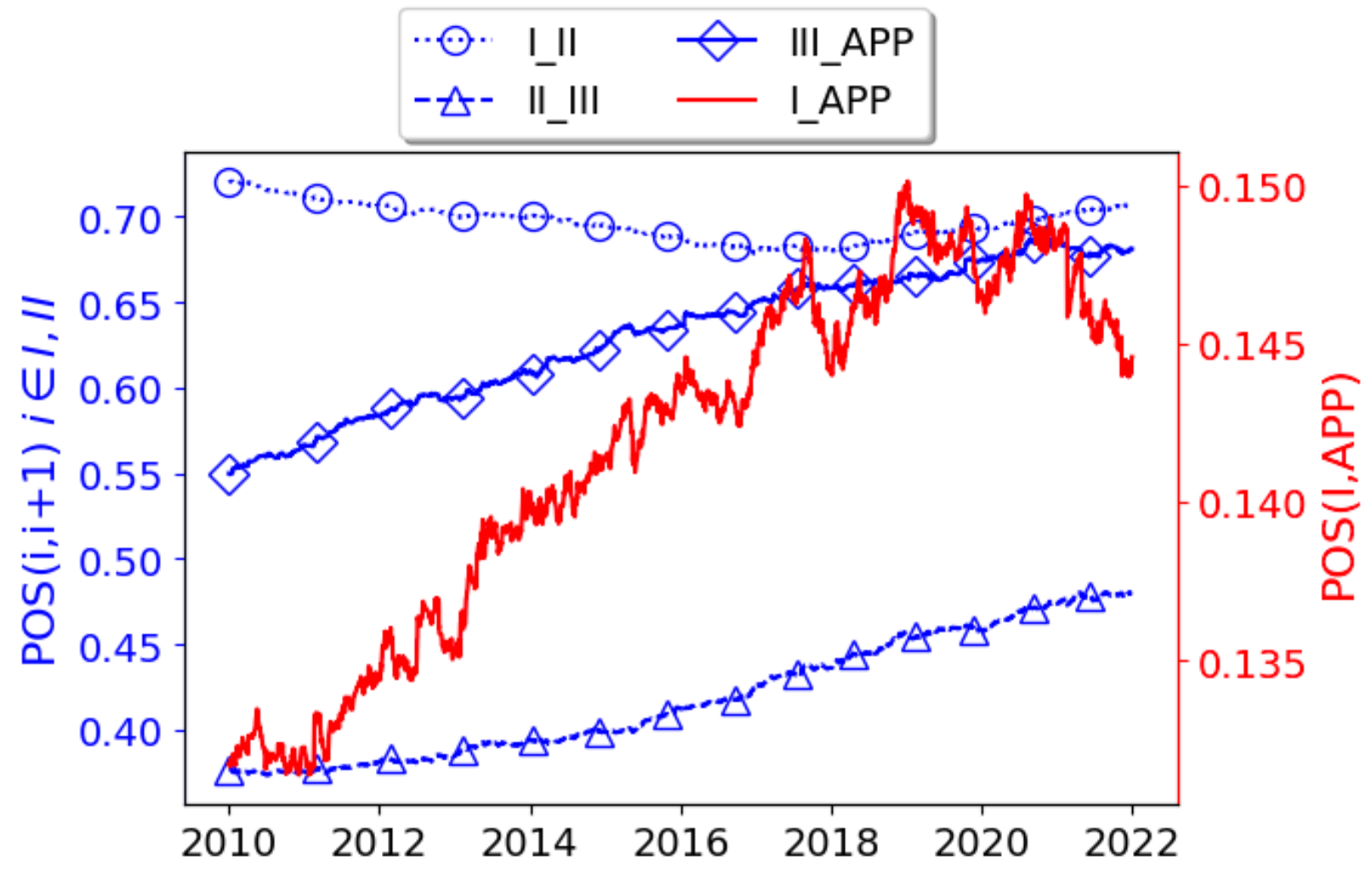- Proprietary analytics for fee or publication

Today / Tomorrow

GitHub

- Large, public cloud-based data
- Server-based analytics that can handle large data sets
- Natural language processing / AI
- Shared code via git hub

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POS going up over time

How Can Clinical Trial Data be Used in Research

- Clinical trial data can be filtered to show drugs that have failed for some reason
  - Can you succeed where someone else failed because you have a safer, more potent technology?
    - Alnylam's platform is more specific and potent than many antibodies or small molecules
- By filtering on preclinical data, can you be a fast follower?
  - Companies like EQRx and Checkpoint Therapeutics have used fast following to proliferate while limiting clinical trial costs
    - Being first in class or first in any area is always harder (there are more hurdles to clear)
- By looking at approvals, you can identify drug targets that are not worth going after due to competition issues (how soon will you be competing with generics?)

Too Far Behind

Fast Follower

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Other Business Implications

- Benchmarking – comparing our performance versus others
- Identifying outlier performance and understanding drivers
- This can help inform the organization where we need to be more efficient and where we have an edge
  - This can help inform the organization where we need to be more efficient and where we have an edge
  - This can help us show external parties why Alnylam is a company you want to be associated with
- Specific areas of relevance:
  - Success rates for specific drug MoAs, disease areas, modalities, etc.
  - Cycle times (i.e., will programs be more or less expensive?)