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R&D in an Age of Multiplying Modalities and Targets

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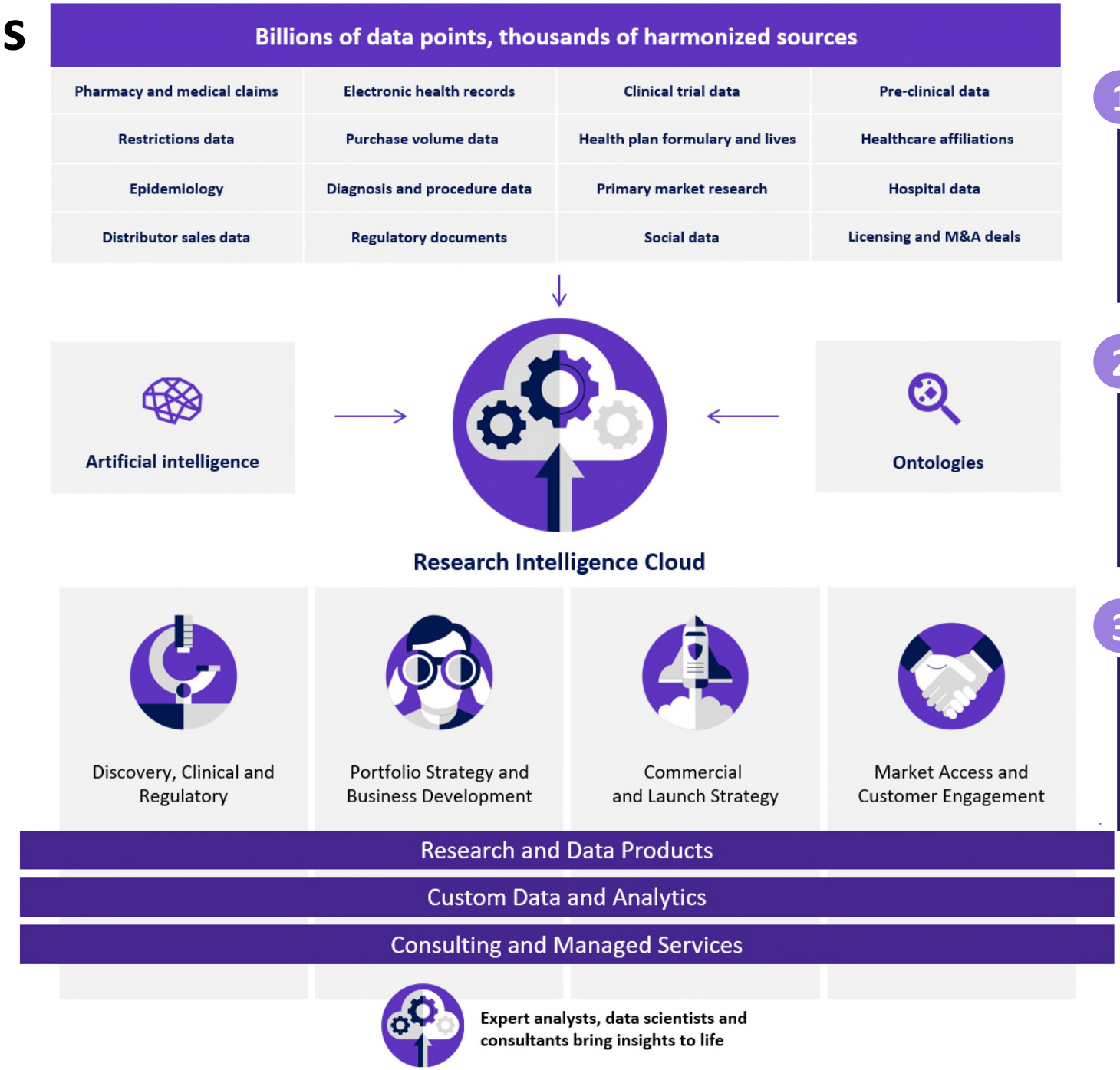
January 20, 2022

Our Focus



1. How is the R&D landscape expanding and becoming more complex?

2. What clinical and commercial challenges does this create?

3. How can we drive clinical success and ROIC?

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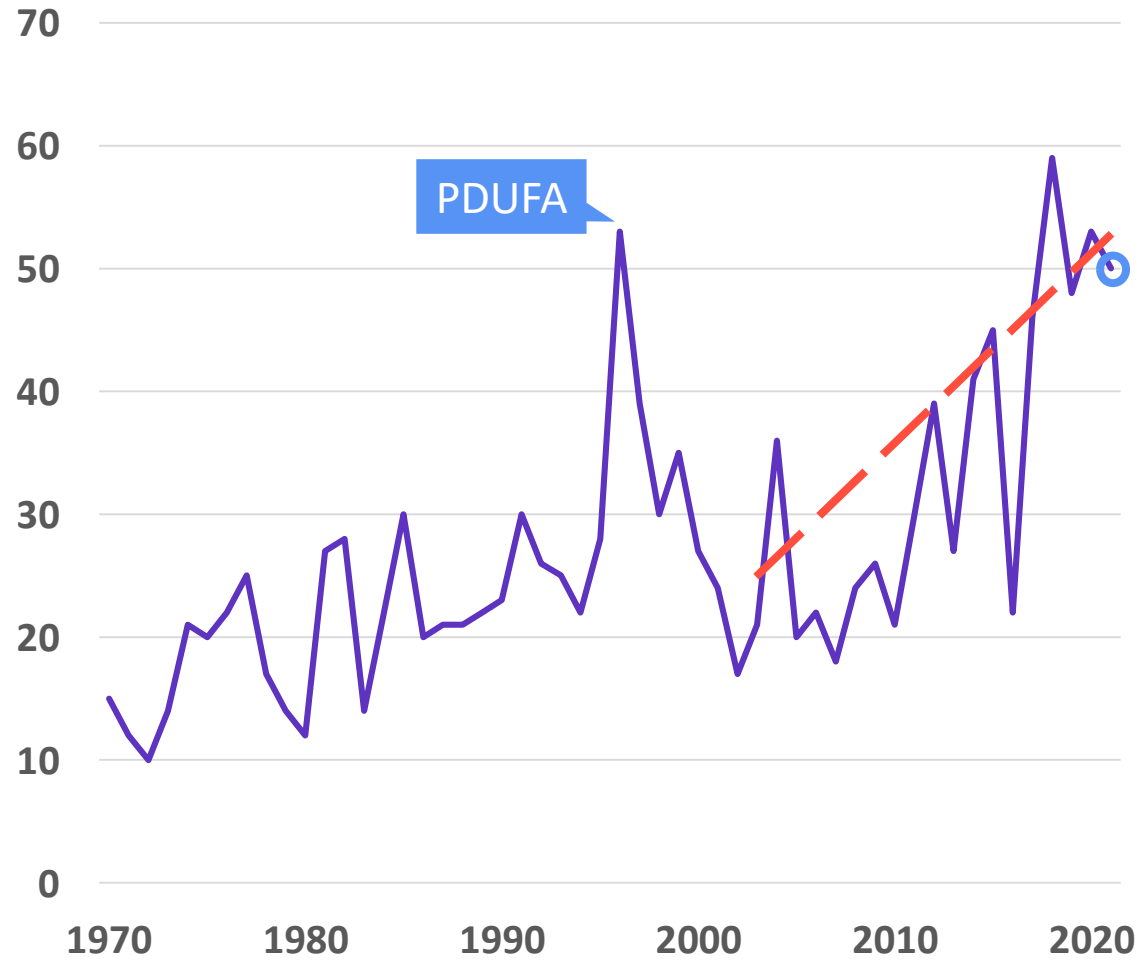
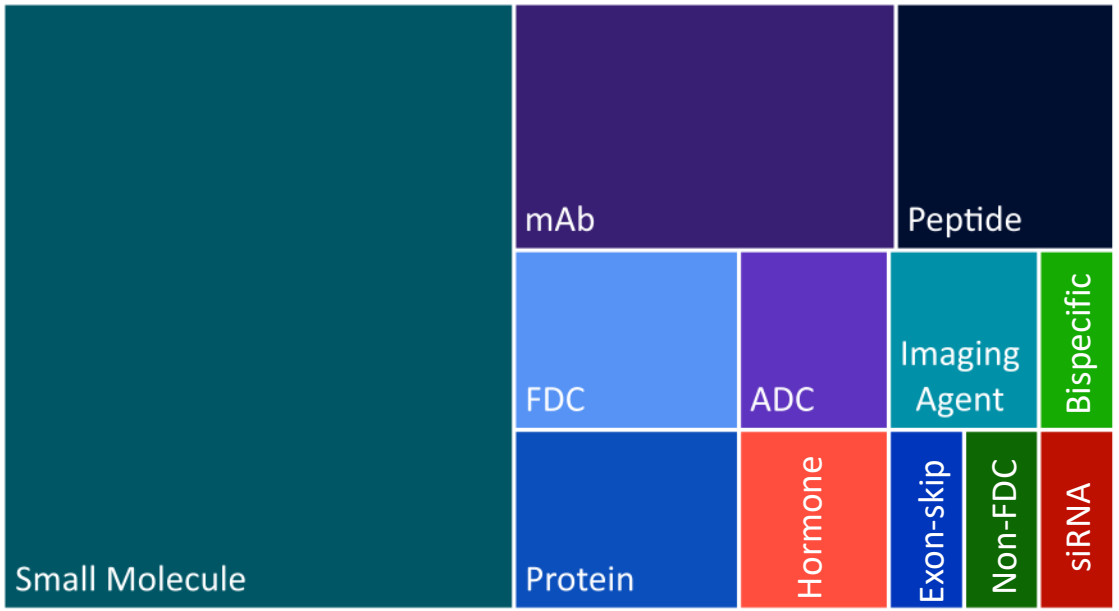
The pace of R&D has increased …

FDA New Molecular Entity Approvals, 1970-21



… as has the diversity of therapies

2021 FDA NMEs by Modality and Target



IL-13	ASBT	ROCK-2	EGFR/cMet	Alkylation
PCSK9	CRGP	Antiparasitic	C3	cPMP
FcRn	MMAE	MR	CD19	DMD
IgG2	HER2	ASPG	PD-1	CDK4/6
FR	hGH	APP	Contraceptive	ANGPTL3
CMV	KOR	Antifungal	sNRI	PI3Kd
CNP	HIF-2A	AAP	GLUC	HGF
INFa	rhGAA	FGFR	S1P1	CNI
BCR-Abl	INF1	KRAS	VEGF	HIV
C5a	IBAT	PSMA	DAT/NAT	sGC

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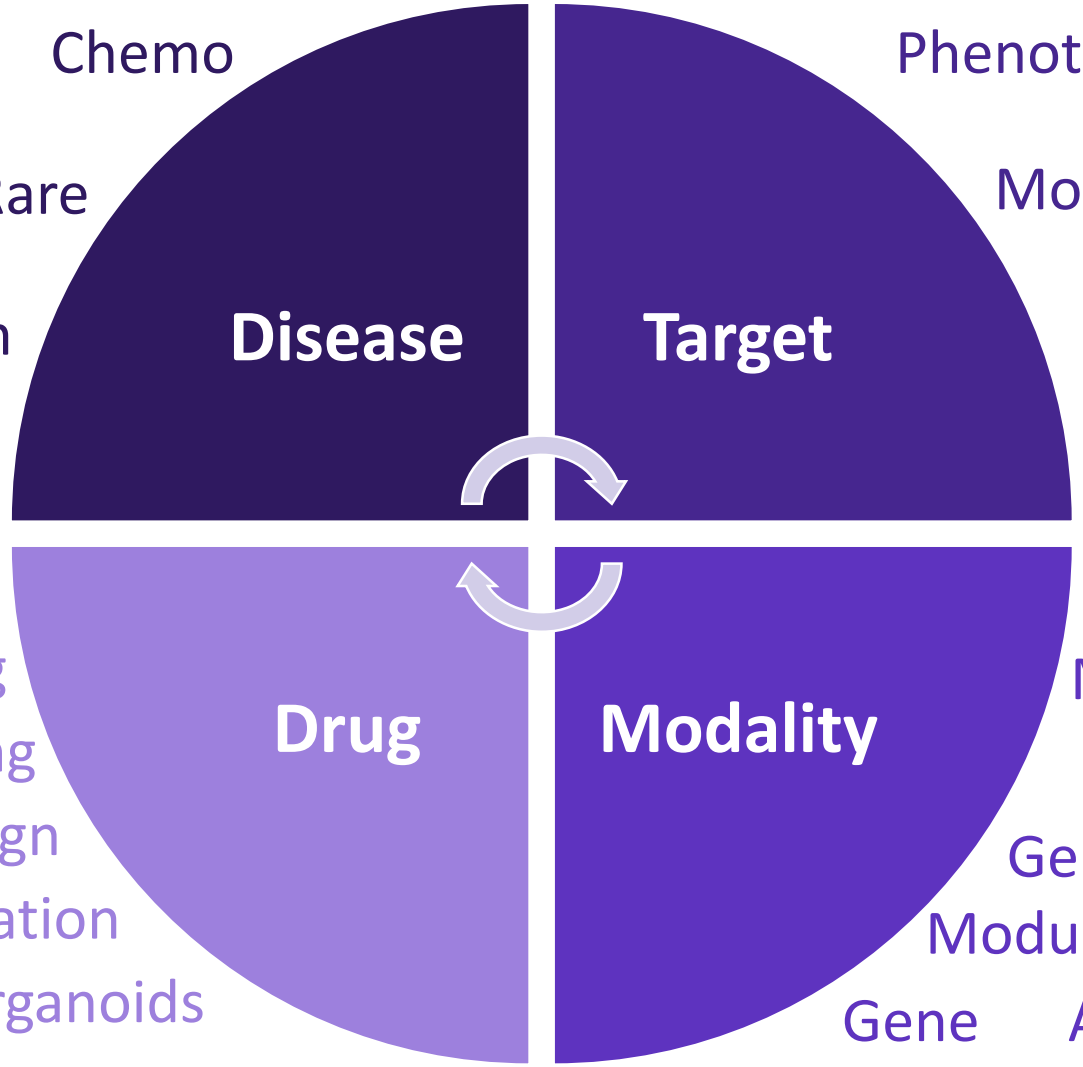
Waves of innovation in new modalities and our understanding of molecular biological have expanded the palette of drug discovery



Chronic
Infection
Chemo
Monogenic
Rare
Shared Mechanism
Personalized

Phenotype
Nature
Molecular Biology
Omics
Bioinformatics
Molecular Phenotype

Serendipity
Low-Throughput Screening
High-Throughput Screening
Rational Design
Biomarkers
Data Integration
Artificial Intelligence
Organoids

Small Molecule
Hormone
Natural Product
Enzyme
Antibody
Gene Modulators
siRNA
Autologous CAR-T
Gene Transfer
Allogeneic Cellular
mRNA
CRISPR

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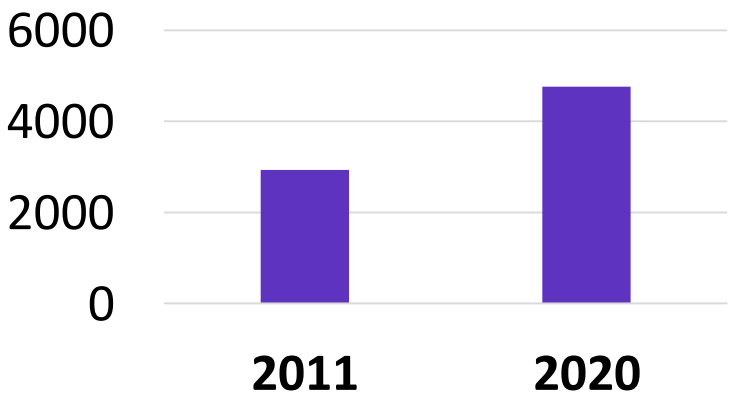
Novel modalities and technologies for target-based discovery have seen explosive growth in research and clinical activity since 2010

Publication volume 2011-22 and active mid/late-stage clinical trials (from POC onwards)

Cell & Gene Therapy

Publications

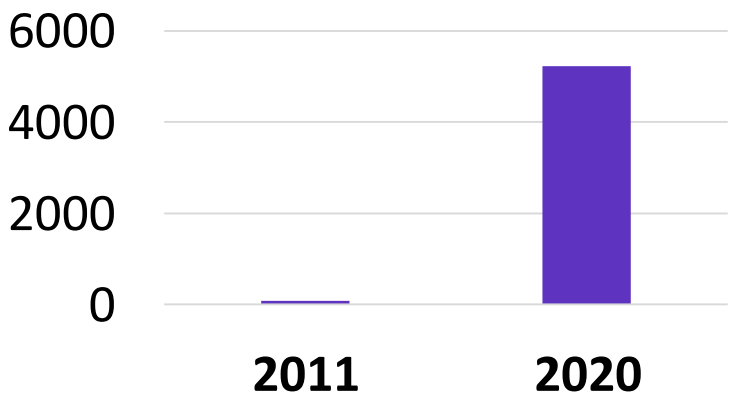


Mid/late-stage trials *(POC & later)*

Trials	4,539
Patients	~400K

CRISPR

Publications

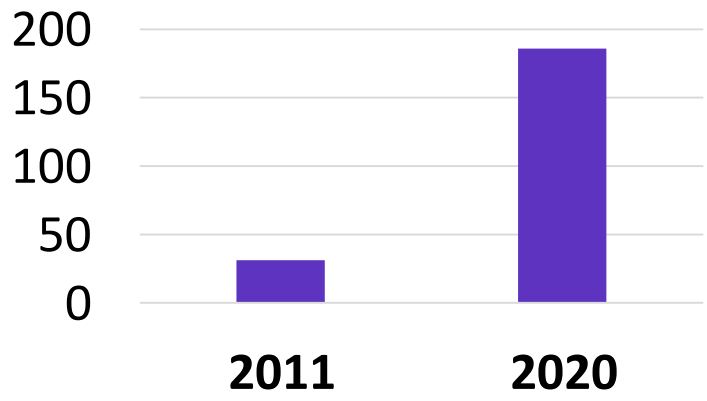


Mid/late-stage trials *(POC & later)*

Trials	62
Patients	~3,700

AI/ML for Drug R&D

Publications



Mid/late-stage trials *(POC & later)*

Trials	4,500
Patients	~400K

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Source: Clarivate 2022 Drugs-to-Watch Report

New modalities like viral vectors for gene transfer face clinical uncertainties and commercial barriers, with few analogs and roadmaps

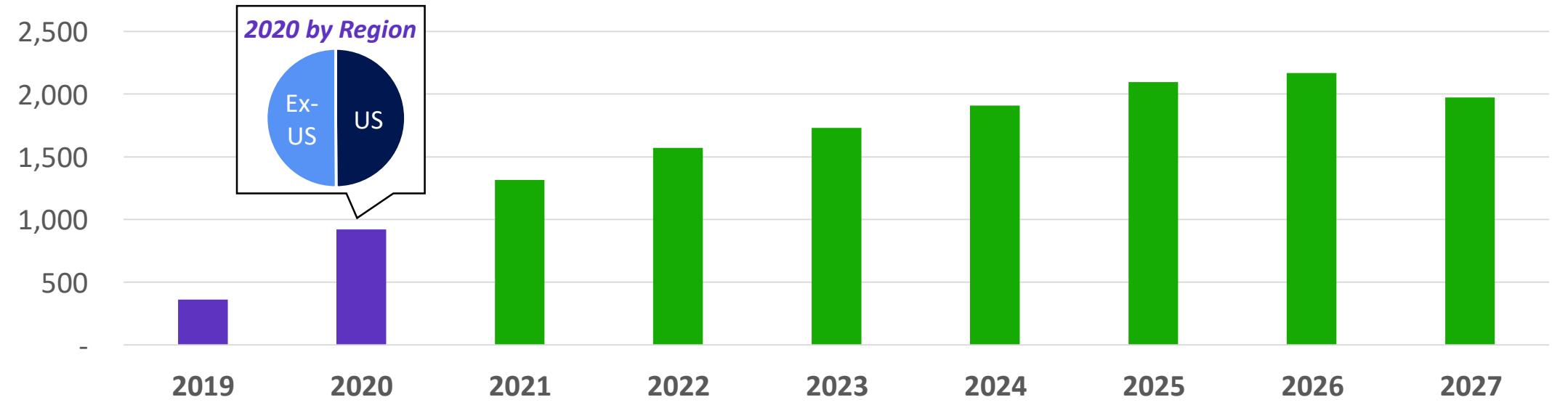
Novartis' ZOLGENSMA AAV9 SMN1 GTx for Spinal Muscular Atrophy

zolgensma®
(onasemnogene abeparvovec-xioi)
suspension for intravenous infusion

- Approved by FDA and EMA as IV administration in children age <2 *(Type 1)*
- Intrathecal in development for Type 2 (age > 2)

Global Sales, Actuals 2019-20 and Analyst Consensus (2021+)

USD Millions



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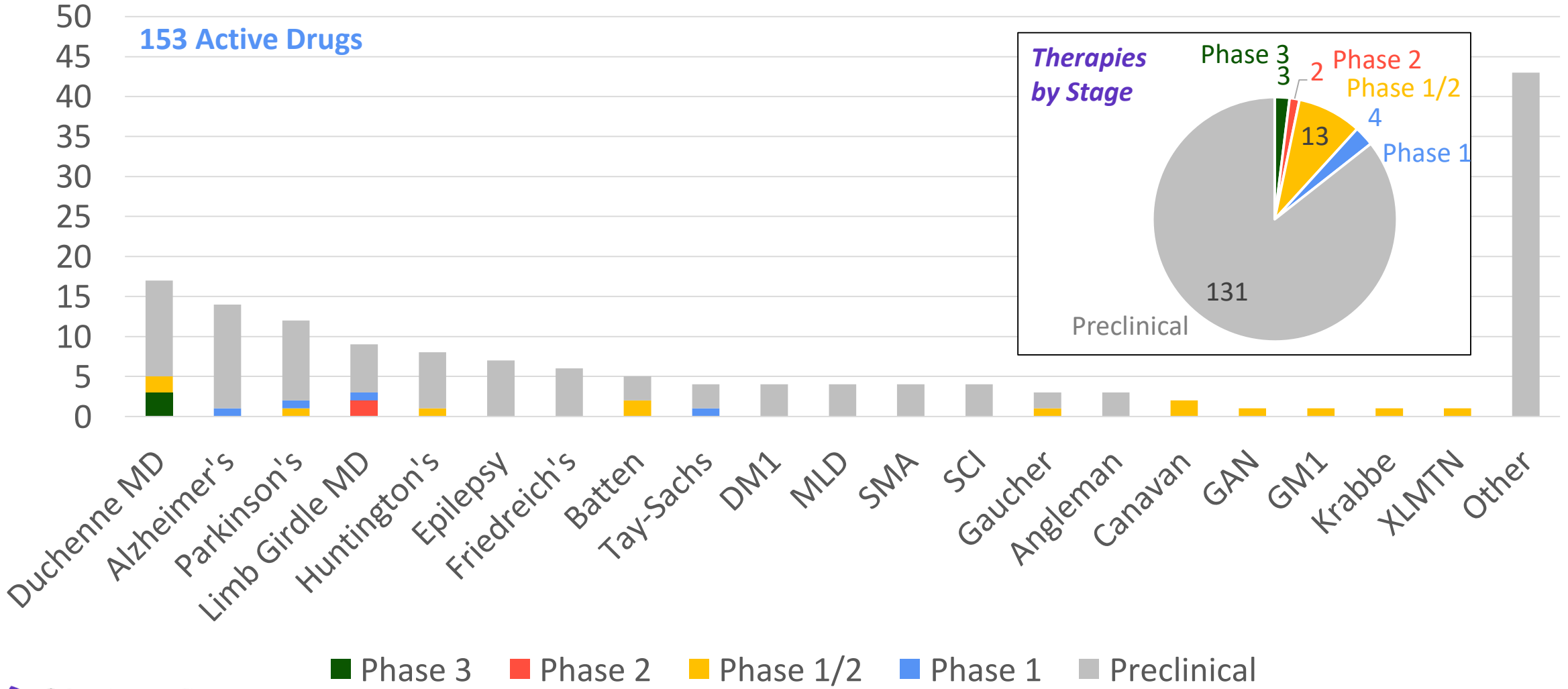
Source: Clarivate Cortellis Intelligence (Dec. 2021); DRG Market Research

Development activity is intense in emerging modalities, as seen for gene therapies to treat neurological diseases

Gene therapies in development by neurological indication and stage



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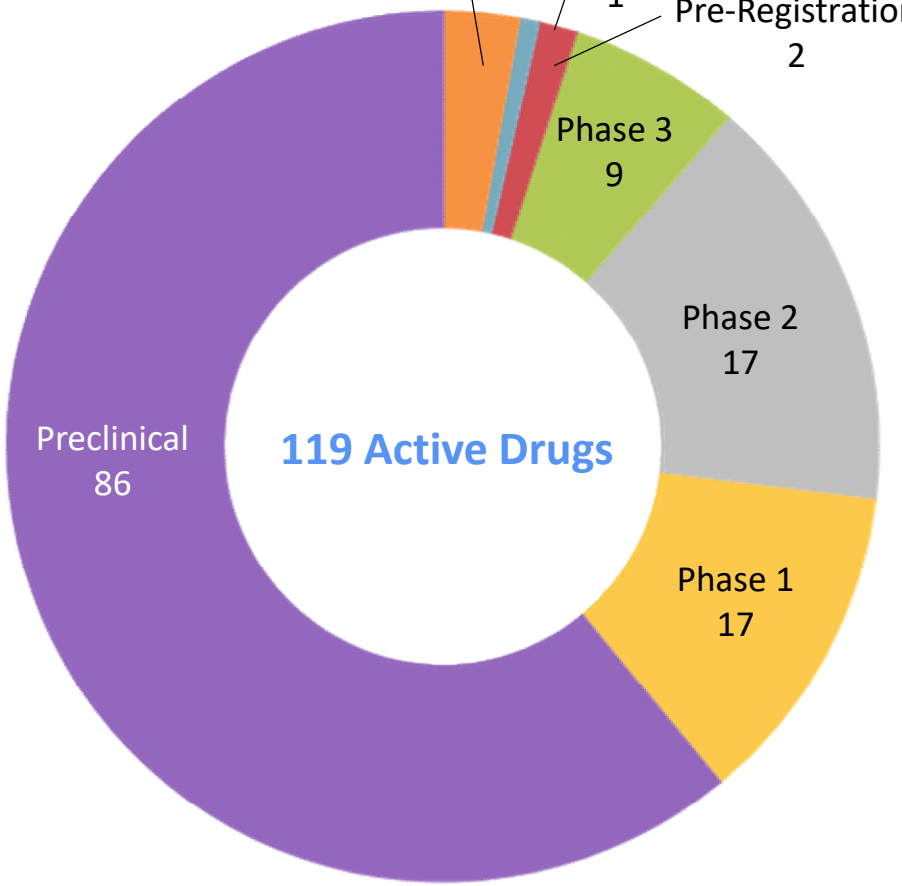
Source: Cortellis Clinical Trials Intelligence (Dec. 2021)

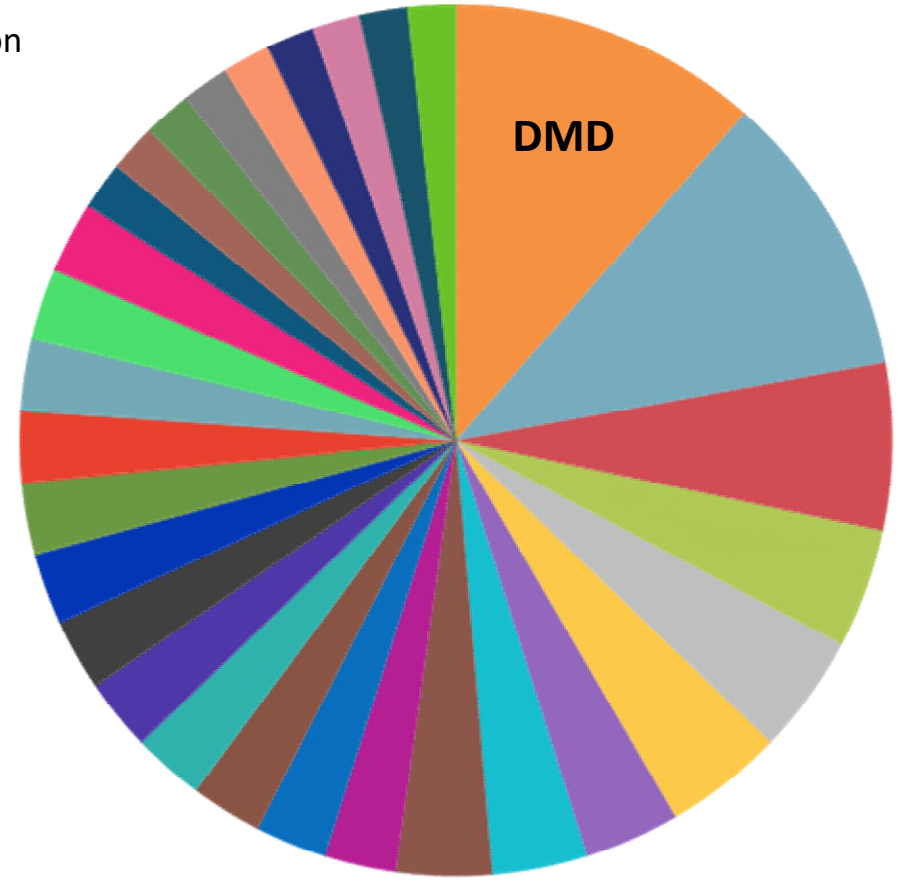
RNA antisense shows similarly high R&D activity and diversity

RNA antisense therapies by status and indication

By Stage



By Indication



Duchenne dystrophy	13
Cancer	12
Pancreas tumor	7
Cardiovascular disease	5
Lipid metabolism disorder	5
Parkinsons disease	5
Advanced solid tumor	4
Coronavirus disease 19 infection	4
Metastatic breast cancer	4
Alzheimers disease	3
Autoimmune disease	3
Head and neck tumor	3
Huntingtons chorea	3
Hyperlipidemia	3
Hyperlipoproteinemia type I	3
Hypertriglyceridemia	3
Idiopathic pulmonary fibrosis	3
Melanoma	3
Motor neurone disease	3
Scar tissue	3
Solid tumor	3
Alexander disease	2
Breast tumor	2
Cardiac failure	2
Cicatrix	2
Cystic fibrosis	2
Glioblastoma	2
Hepatitis B virus infection	2
Liver disease	2
Liver fibrosis	2

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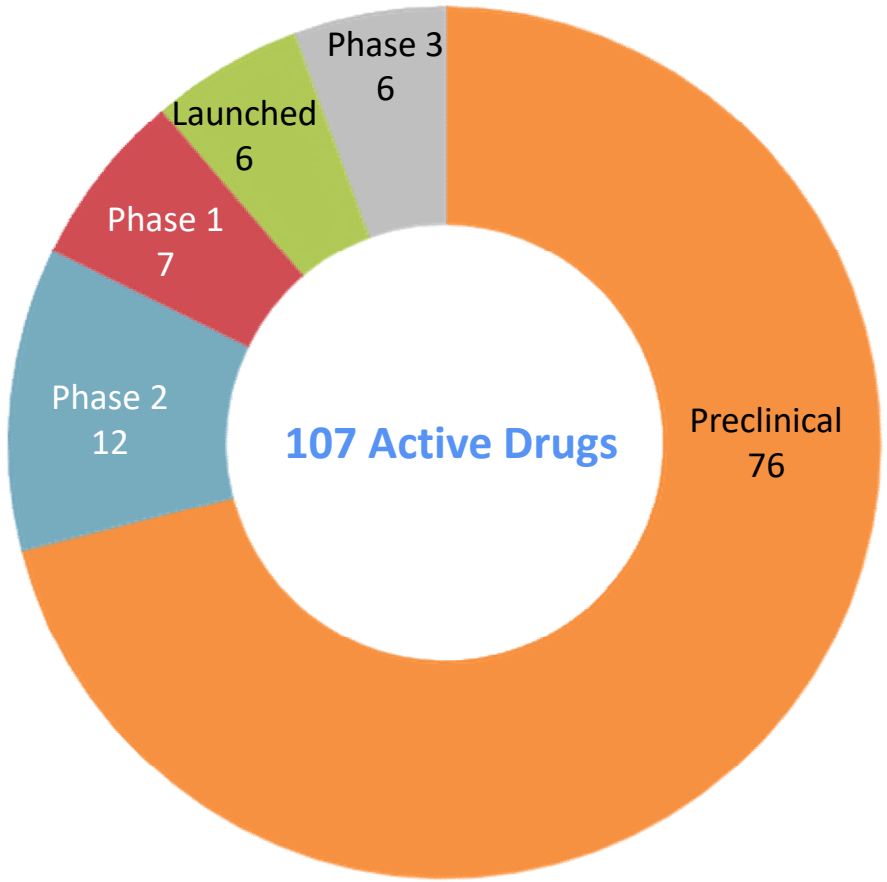
Source: Cortellis Competitive Intelligence (Dec. 2021)

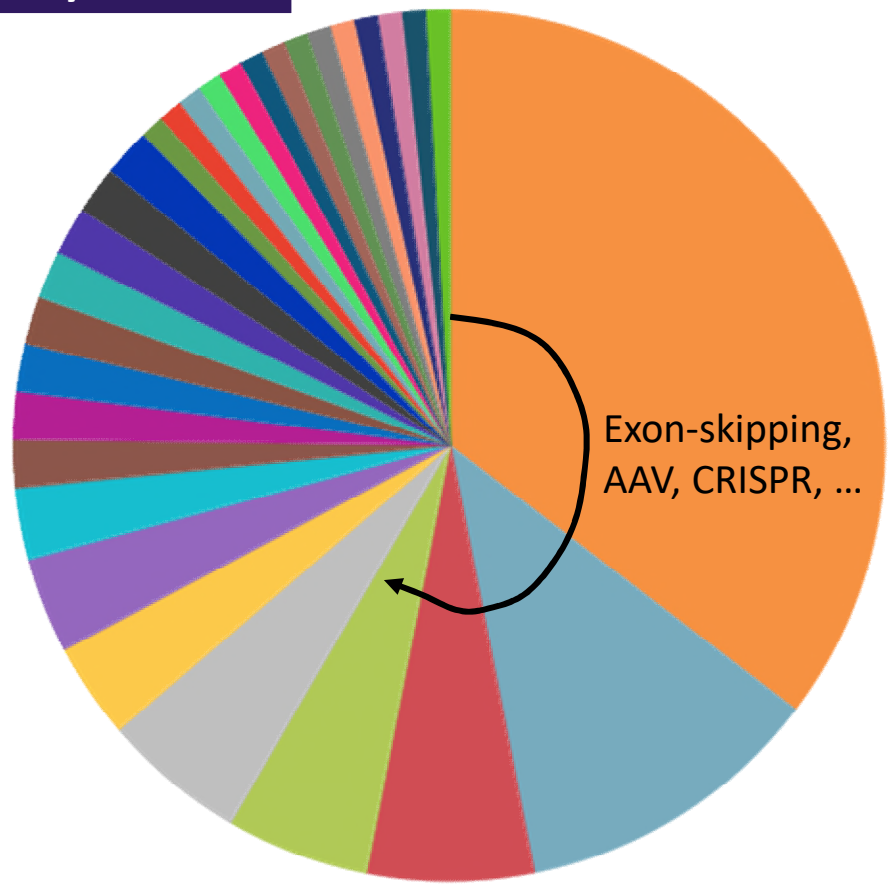
Expanding modalities and target actions are creating complex and crowded disease areas, as in Duchenne Muscular Dystrophy

DMD therapies by status and target action

By Stage



By Action



DMD gene modulator	40
DMD gene stimulator	13
CRISPR associated endonuclease Cas9 modulator	7
Dystrophin stimulator	6
Integrin alpha-7/beta-1 agonist	6
Dystrophin modulator	4
GDF-8 antagonist	4
Glucocorticoid receptor agonist	3
Androgen receptor modulator	2
Calcium channel modulator	2
Histone deacetylase inhibitor	2
Nuclear factor kappa B inhibitor	2
PPAR delta modulator	2
Proto-oncogene Mas agonist	2
Ryanodine receptor modulator	2
UTRN gene stimulator	2
ACTH receptor agonist	1
Adiponectin receptor agonist	1
Adrenocorticotrophic hormone ligand	1
Androgen receptor agonist	1
Angiotensin II receptor modulator	1
B4GALNT2 gene stimulator	1
BDNF gene stimulator	1
Biglycan modulator	1
Caveolin 3 modulator	1
CLK gene inhibitor	1
Connective tissue growth factor ligand inhibitor	1
Cytochrome P450 3A4 inhibitor	1
Dysferlin modulator	1
Endonuclease modulator	1

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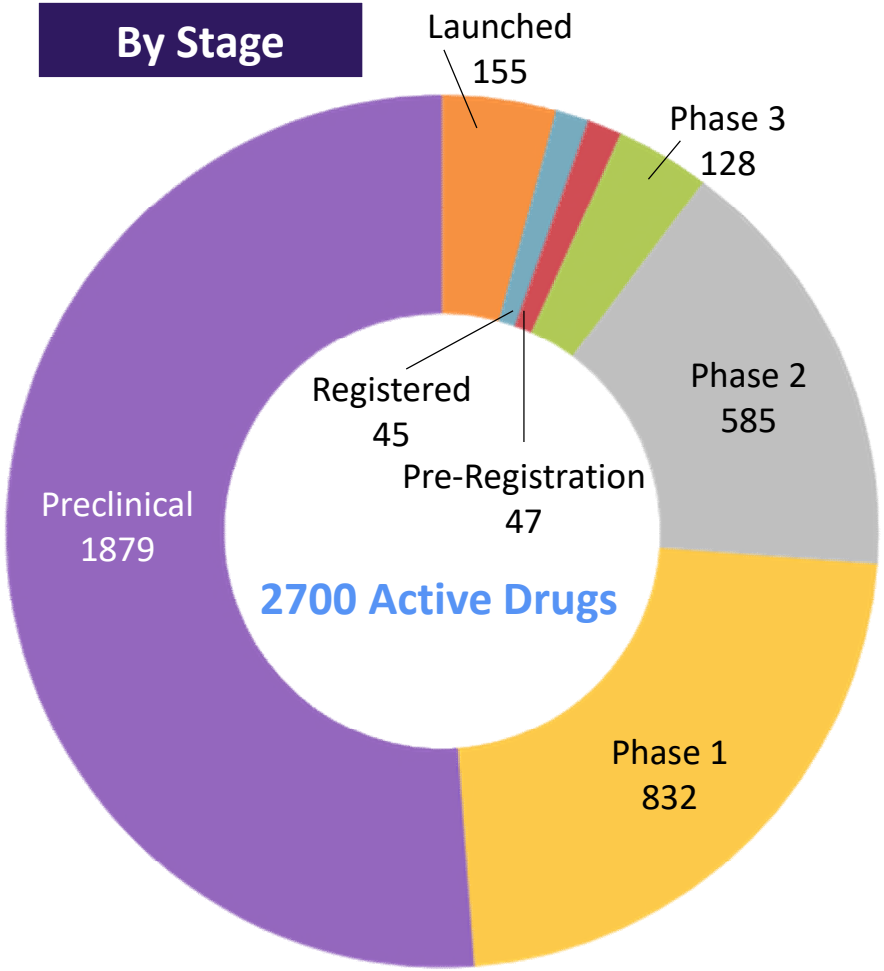
Source: Cortellis Competitive Intelligence (Dec. 2021)

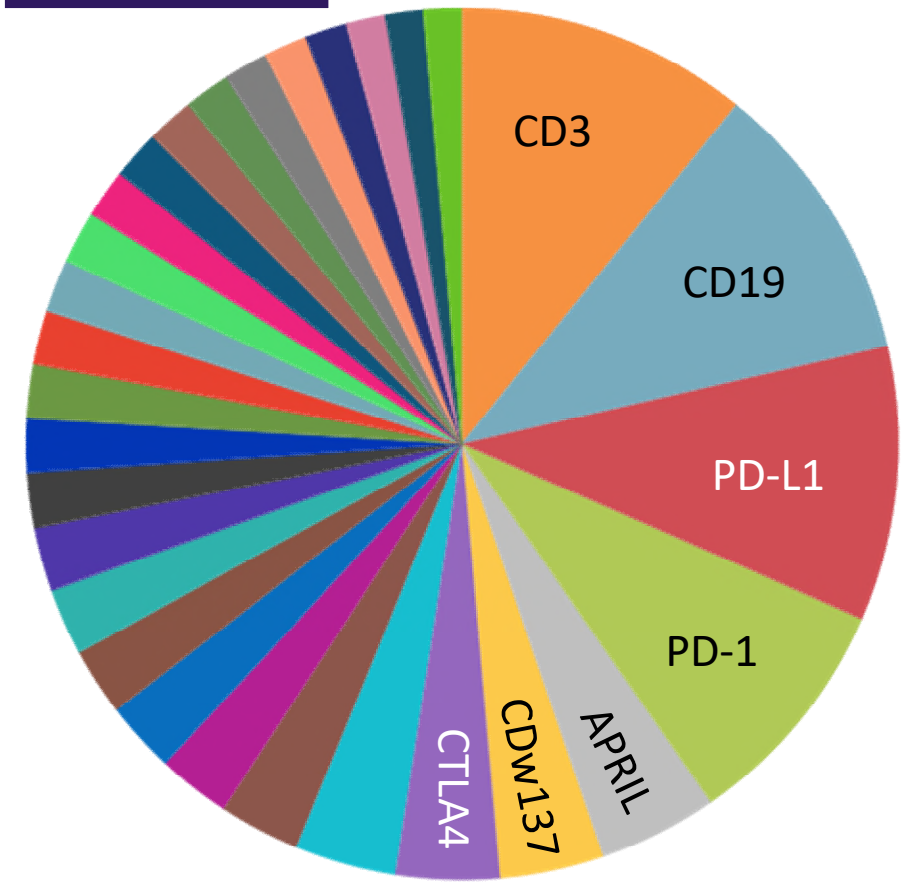
Crowded classes and diversity of targets are seen across many areas of R&D focus, as in immuno-oncology

Immuno-oncology therapies by stage and target action

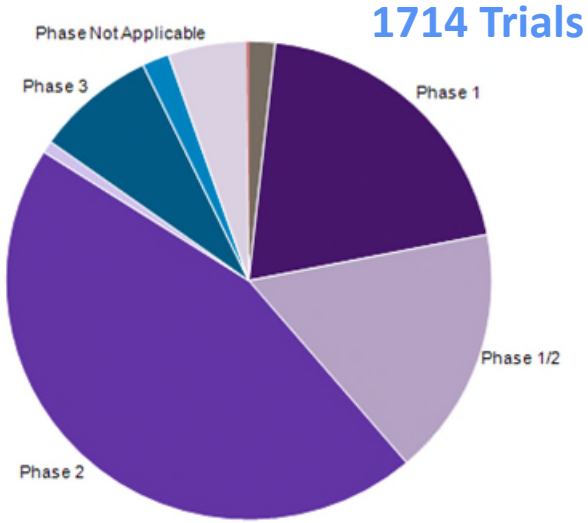
By Stage



By Action



Keytruda Clinical Trials by Phase



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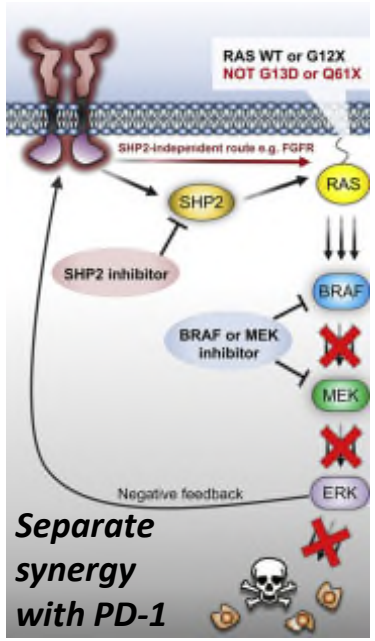
Source: Cortellis Competitive Intelligence (Dec. 2021)

Development Trends

Multi-Target Strategies in Oncology

SHP2 Inhibition



- Cross-tumor combo regimens (2, 3+)
- Multiplying options
- Fragmented markets
- Cost to payers
- Unmet need and mechanistic rationale vs. Evidence-Based Medicine

Rare Disease Specialists

1. Target orphans with high unmet need for favorable regulatory and reimbursement pathways
2. Ensure mechanism is well understood and that the drug directly addresses it to de-risk POC trials
3. Surrogate endpoints and accelerated approval to gain approval with limited Phase 3 expense
4. Multiple programs with de-coupled risks to raise odds of winners funding the rest

bridgebio

Rallybio

healx

Technology Specialists and Alliances

- Modality specialists
- AI specialists

Alnylam PHARMACEUTICALS
moderna
REGENXBIO
mesoblast
IONIS
BIONTECH
Exscientia
Atomwise
insitro
Generate
Valo
Isomorphic Laboratories

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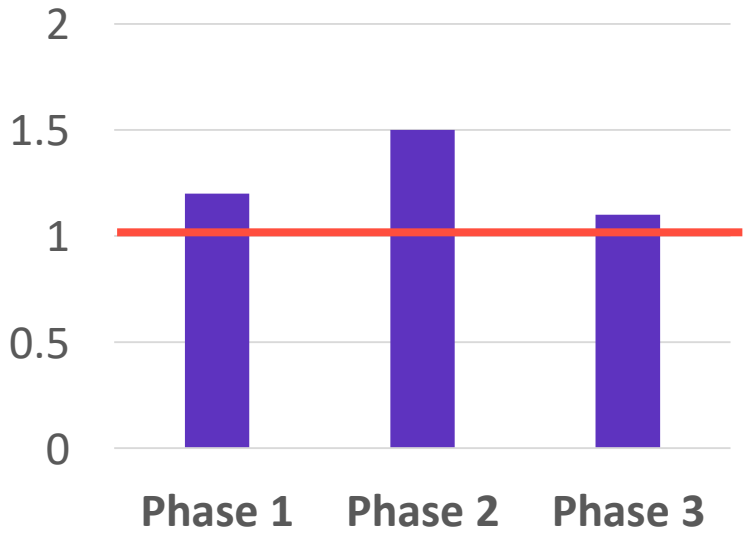
Sources: Ahmed et al., Cell Reports (2019)26:65-78

Bioinformatics and AI are not just accelerating target-based discovery, they can guide our portfolio and programs to improve ROIC

Odds Ratio for Progression with Genetic Support of the Target-Indication Pair

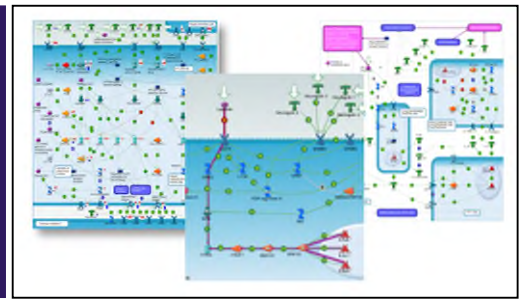


Genetic support doubles pTRS from Phase 1 to Approval

+18% gain in pTRS from Phase 2 onwards with genetic support *[CMR data]*

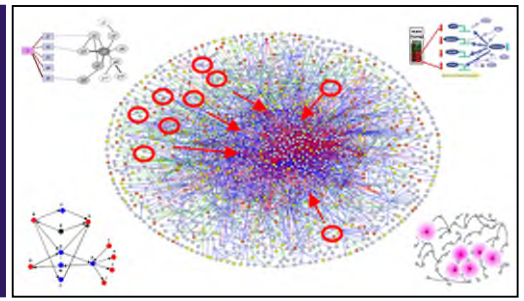
Mechanistic Support of Drug Target to Disease is Strongest when Consistent Across Multiple Sources

Pathway



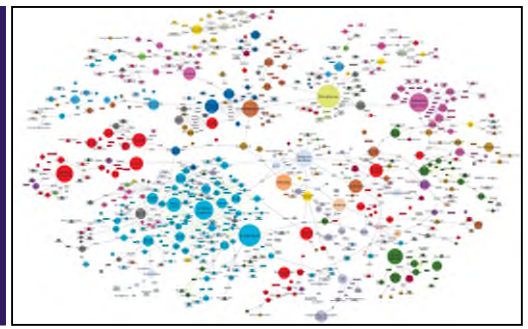
Are the target and disease linked through clinical/biological studies, GWAS data, or pathways?

Network



What is the connectivity of the target to disease genes within the tissue-specific network?

Disease Similarity



What is the network similarity between the disease and those for which the target is validated?

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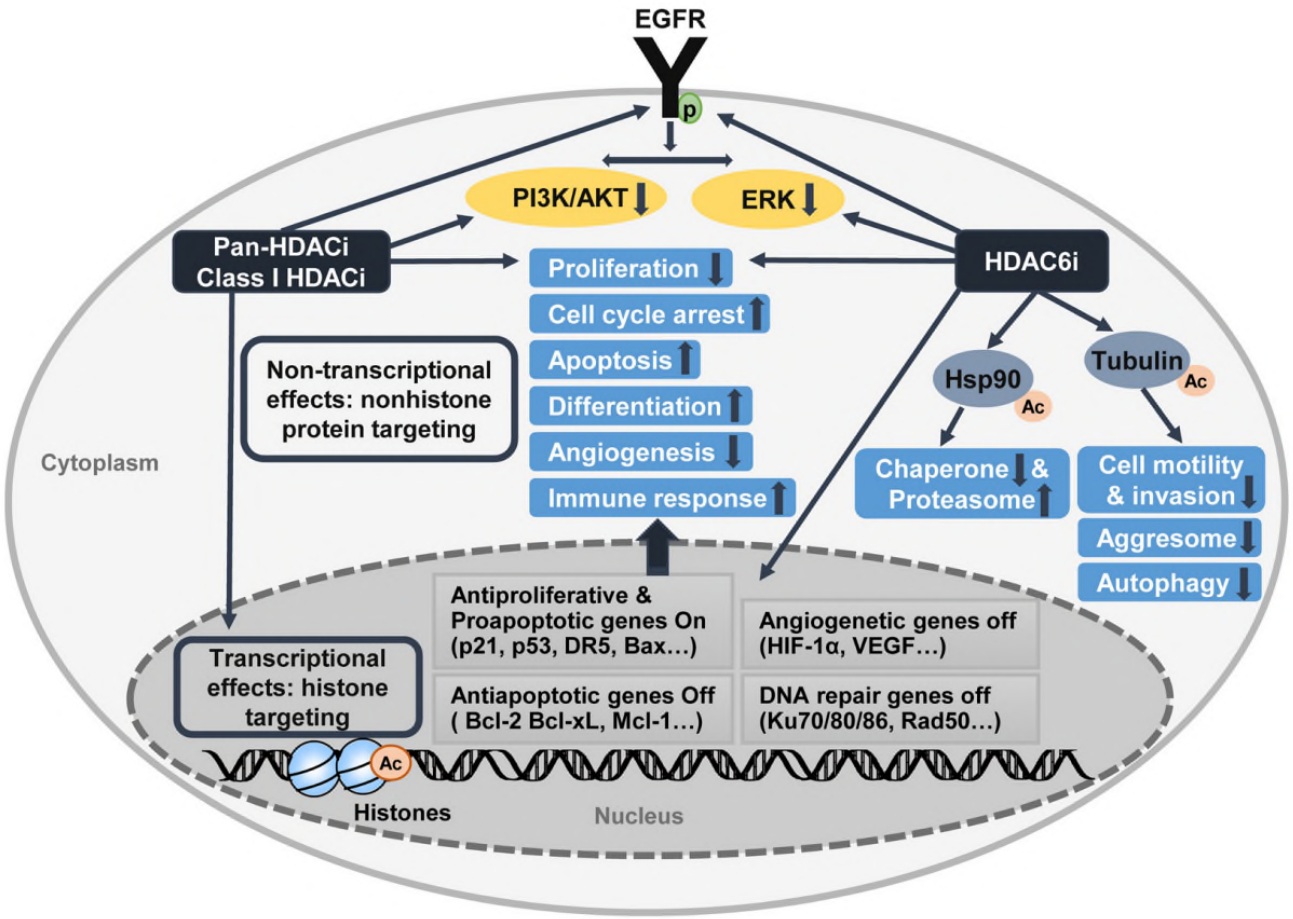
Sources: Nelson et al. Nature Genetics (2015) 47(8):856-860; Centre for Medicines Research (CMR); Clarivate bioinformatics

For a single target, we find increasing diversity of indications with clinical potential, that may be hard to merge in a single program

Potential indications for HDAC6 inhibition



Oncology

- Glioblastoma Multiforme
- Ovarian Cancer
- Breast Cancer

Neurology

- Alzheimer's Disease
- Peripheral Neuropathy
- ALS
- Huntington's Disease

Cardiology

- Aetherosclerosis

Renal/Rare

- Polycystic Kidney Disease

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Sources: Lee et al., Oncotarget (2017) v8n11, 18577-18599; Krukowski et al., Pain (2017) 158(6):1126-1137; Mazzeltti, Front. Neurosci. (2020)14:624; Nomura et al., Front. Physiology, (2021), 12:675724; Cebotaru et al., Kidney Int. (2016)90(1):90-99; Ke et al., Molecular Medicine (2018)24L33

The expanded R&D landscape benefits patients and opens new areas of investment, but poses clinical and commercial challenges

Opportunities

- ✓ Disease modifying therapies
- ✓ Synergistic combinations
- ✓ Personalized regimens
- ✓ Secular growth in drug R&D

Challenges

- ⊗ Market fragmentation
- ⊗ Complex/evolving positioning
- ⊗ Evidence through RCTs alone
- ⊗ Maintaining and growing ROIC

Driving ROIC in Today's R&D Landscape

1. **Pick the right bets in complex and uncertain markets (odds ↑, table stakes ↓)**
2. **Leverage innovative designs and technologies to streamline and speed trials**
3. **Realize asset value across a diverse set of indications and patients**

Levers

Portfolio & Program Design	Trial Efficiency	Evidence & Contracting
Time-to-market ↓ pTRS ↑	Reach ↑ *(sites, decentralized)*	Real World Evidence ↑
Label breadth ↑ Cost ↓	Velocity ↑ *(EHR, RT monitoring)*	Outcomes Contracting ↑
	Count ↓ *(synthetic arms, adaptive)*	

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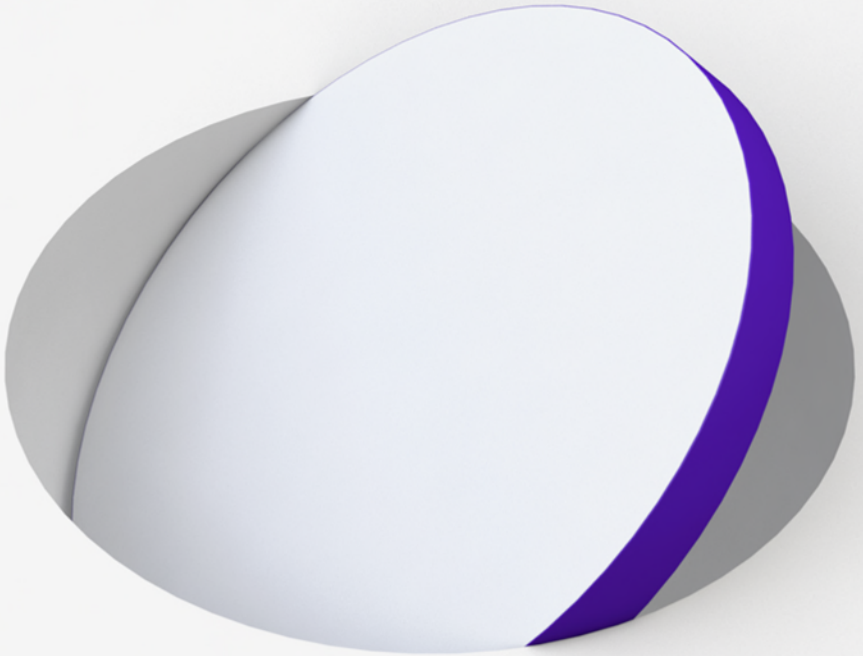
Questions?



For more information, please contact:

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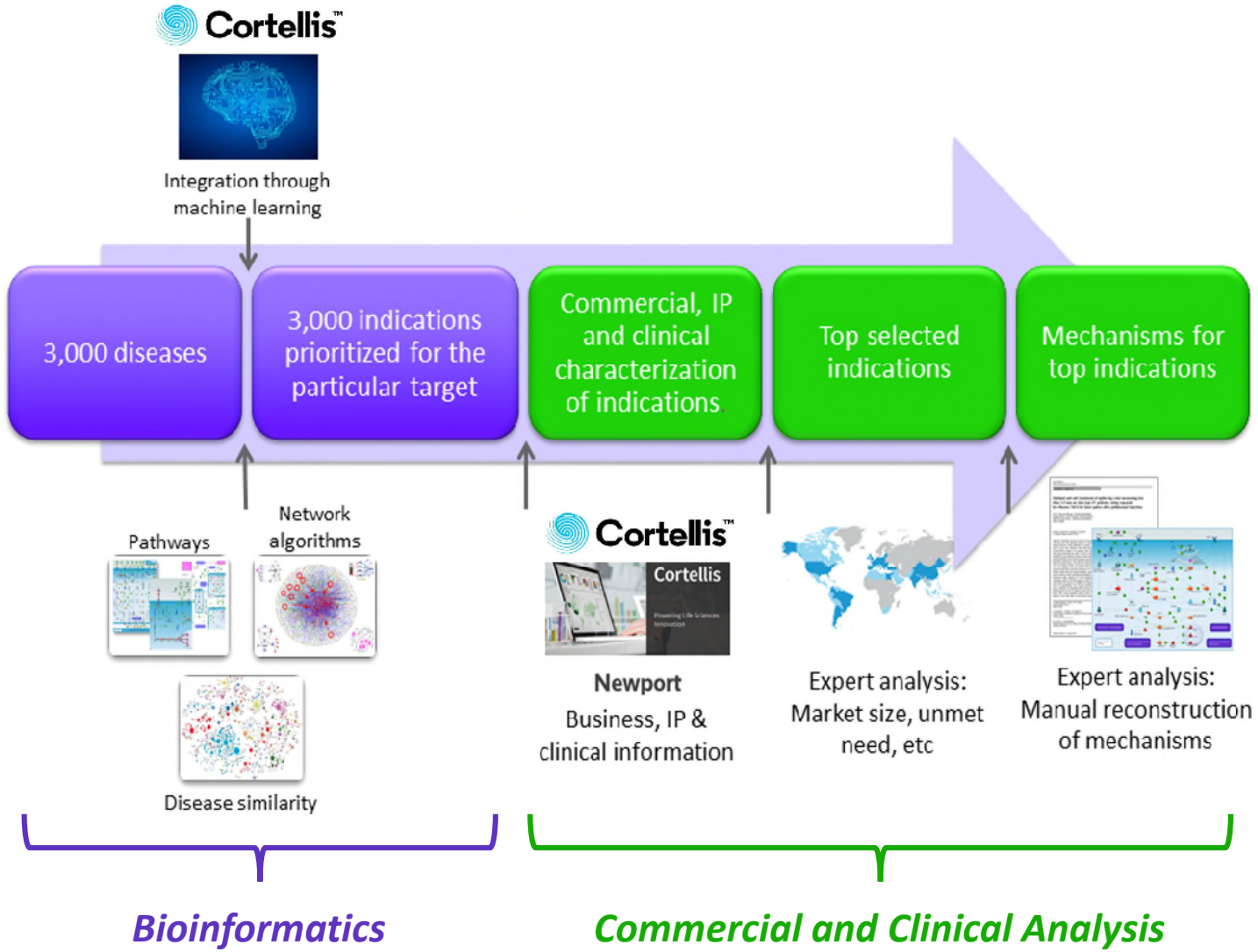
Our Approach to Bioinformatics-Driven Indication Prioritization



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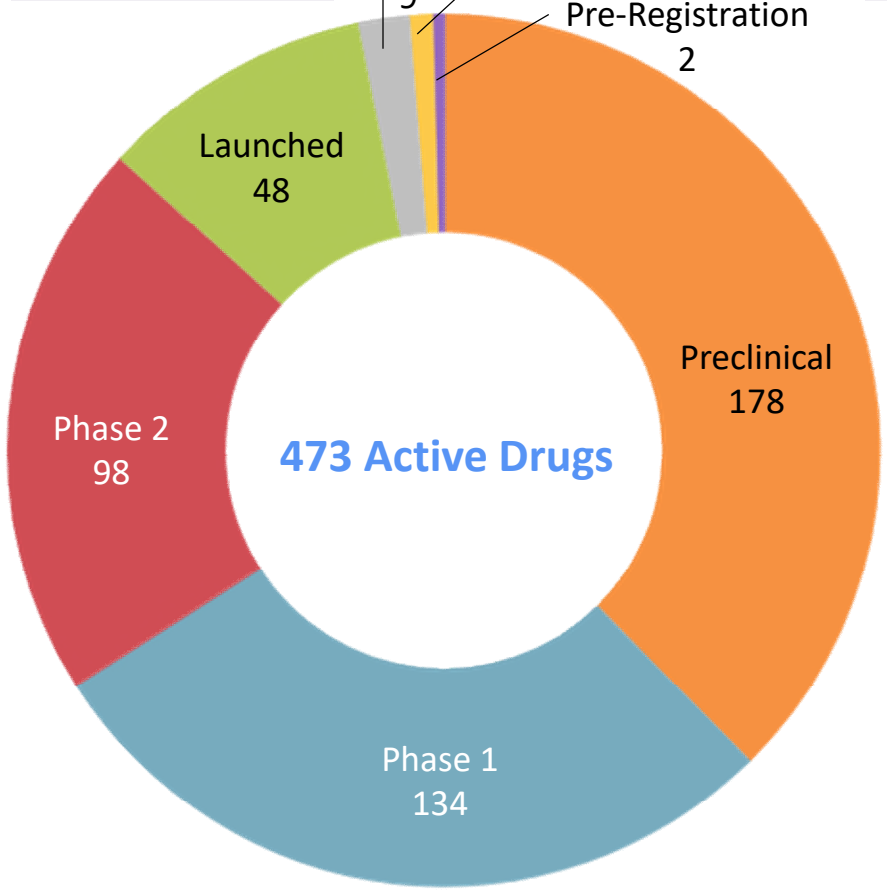
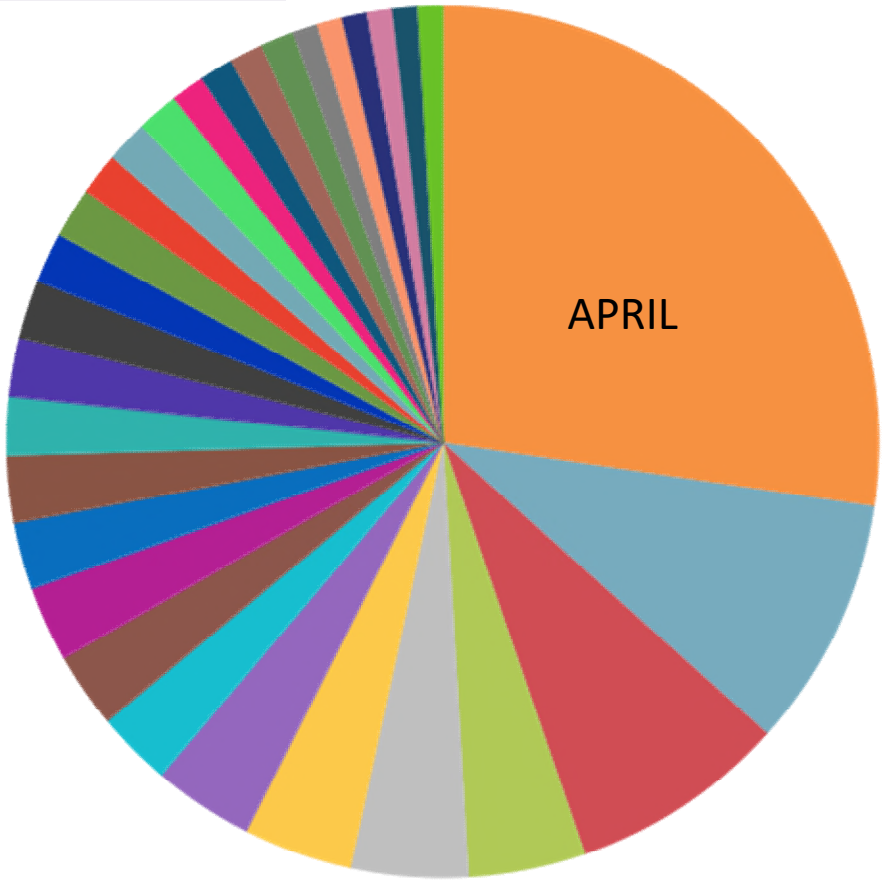
Across many diseases we see a similar story… the first 2 APRIL drugs launched in MM in 2020 & 2021, but another 86 are in development

Multiple myeloma therapies by stage and target action

By Stage



By Action



APRIL receptor modulator	88
CD3 modulator	30
ADP ribosyl cyclase-1 modulator	26
ADP ribosyl cyclase-1 inhibitor	14
Interferon alpha 2 ligand	14
Protein cereblon modulator	13
SLAM family member 7 modulator	12
APRIL receptor antagonist	9
B-lymphocyte antigen CD19 modulator	9
CD47 antagonist	9
Bcl-2 protein inhibitor	8
Mcl-1 differentiation protein inhibitor	8
Cancer testis antigen NY-ESO-1 modulator	7
HLA class I antigen A-2 alpha modulator	7
Proteasome inhibitor	7
Programmed cell death protein 1 inhibitor	6
T cell immunoreceptor Ig ITIM protein inhibitor	6
G protein coupled receptor C 5D modulator	5
Histone deacetylase inhibitor	5
Histone deacetylase-6 inhibitor	5
DNA polymerase inhibitor	4
Exportin 1 inhibitor	4
Syndecan-1 modulator	4
Topoisomerase II inhibitor	4
Bcl-xL Bcl-2 associated death promotor inhibitor	3
Bromodomain containing protein inhibitor	3
Btk tyrosine kinase inhibitor	3
Gamma-secretase inhibitor	3
Histone deacetylase-1 inhibitor	3
Histone deacetylase-2 inhibitor	3

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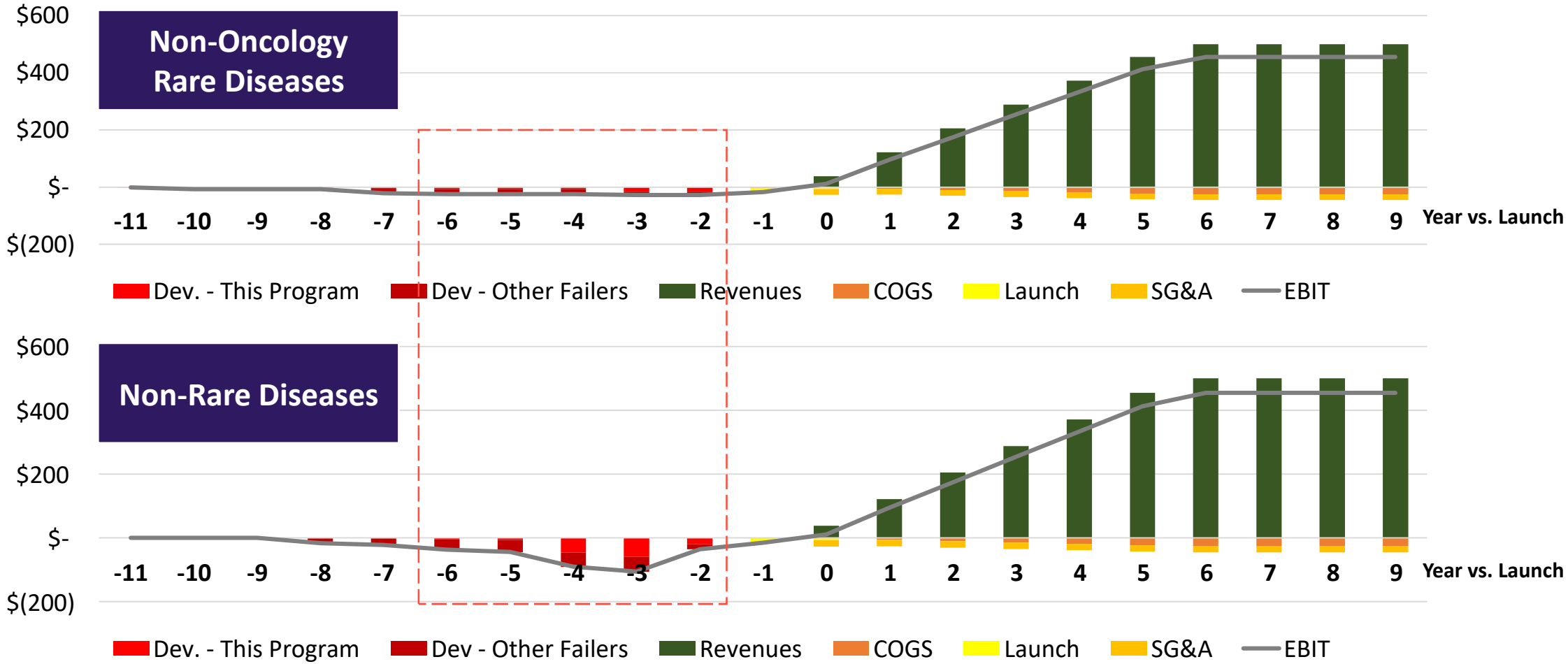
Source: Cortellis Competitive Intelligence (Dec. 2021)

Monogenic rare diseases enjoy a ROIC advantage from de-risked POC trials and cheaper Phase 3… can we achieve this more broadly?

Risk-adjusted EBIT impact per approved drug in a large, de-coupled portfolio ($ Millions)



Includes only clinical development cost, not discovery and preclinical

Source: Clarivate Analysis